Diseases of the poor: the socioeconomic impact of neglected tropical diseases

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ISBN 978-94-6332-588-2

Cover design Anita Lenk

Printed by GVO drukkers & vormgevers, Ede

Diseases of the Poor:

the Socioeconomic Impact of

Neglected Tropical Diseases

Ziekten van de armen: de sociaaleconomische impact van vergeten tropische ziekten

Thesis

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
rector magnificus

Prof.dr. R.C.M.E. Engels

and in accordance with the decision of the Doctorate Board.

The public defence shall be held on

Thursday 19th December 2019 at 11:30hrs

by

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'No human being is to find peace
in the enjoyment of happiness
if others beside him are unhappy.'
Rudolf Steiner

Content

Chapter 1

Introduction

Health is with no doubt one of the most important - if not the most important- good in a person's life. Not only is health a direct constituent of a person's well-being, it also enables one to follow goals and carry out projects, functioning as an agent. It encompasses and goes beyond the utility theory concept of health as the means to increasing one's human capital or income. Health allows a person to choose the life she wants to live. [1]

1.1 Health and welfare

Economic welfare theory considers that what individuals and populations value the most is to maximize utility. This is done through the best possible combination of the consumption of goods and services: some that can be bought and sold and some that cannot, but that nevertheless have discernable value. Besides consuming goods and services, utility might also be generated via leisure, including spending time with family and friends or taking care of others.[2] There are three ways through which health contributes to individual utility or social welfare: people prefer to be more healthy than less; health influences the enjoyment of consumption of other goods and services; the absence of health compromises other economic objectives that allow people to consume market goods (e.g. generating income). One reservation that has to be made is that consumption of health goods and services does not yield welfare directly, as the consumption of most types of goods and services. Despite people's preference for not incurring these kind of expenses, they pay them believing it will protect or promote their health. Therefore, it can be said that health status, leisure and the consumption of 'non-health' goods and services are the main determinants of economic welfare. [2]

1.2 Economic consequences of disease

There are several ways of defining categories of health-related costs. We used the same terminology as in the 'WHO guide to identifying the economic consequences of disease and injury', but instead of using direct/indirect costs (they can have other meanings, for instance indirect costs mean overhead costs in a company's perspective), we used out-of-pocket payments (OPPs) and productivity loss (for the sake of clarity). Economic impact of ill-health can be investigated from a macroeconomic perspective (societal or population-level) or a microeconomic one, concentrating in the economic effects that ill-health can have on households (including impoverishment). The types of costs included in an economic impact study will depend on the question being asked, the chosen scope or perspective (for instance, if only market losses - quantifiable – or if non-market losses will also be included). [2]

Out-of-pocket payments - OPPs

Out-of-pocket payments can be described as the expenses attributable to a specific illness. They can be directly related to medical costs (e.g. consultation, diagnostic tests and other emergency, ambulatory or inpatient interventions, medication, nursing care, rehabilitation) or to non-medical costs (e.g. transportation costs, caregiver time and subsistence costs while attending a hospitalized household member, special food needs, changes to the household structure to accommodate disease consequences – such as wheel chair access). In developing countries, individuals or households often have to pay for the costs themselves when illness occurs, since they cannot rely much on universal/social insurance schemes. At the household level, costs incurred in the acquisition of health services to enhance and restore the health of individuals or population groups should represent the resources that could have been used for other types of consumption had the disease or illness not occurred, including the costs of health insurance borne by households. If not paid by the individuals/households, they can be sometimes paid by firms (depending on the working agreements). [2,3]

Productivity loss

Productivity loss here refers to the short-term or long-term productivity loss resulting from morbidity, disability and mortality related to a disease. It be estimated from an

individual, household, firms or societal perspective. It usually considers absenteeism (work absence due to sickness), presenteeism (the person is present at work, but not fully functioning due to sickness) and/or mortality (present value of future earnings lost by individuals who die prematurely from the disease). It can be particularly important in developing countries, where employment opportunities tend to depend more on physical endurance and strength. Productivity loss can be calculated using the human capital approach (which involves multiplication of the total number of absent days by the wage rate of the absent worker) or the friction cost method (which restricts the estimation of the potential production losses to the 'friction period' needed to find a replacement worker, providing a level of correction in the short term). [2,4,5]

Social consequences

Besides economic losses, disease also imposes social consequences, affecting people's feelings, thoughts, behavior and ultimately wellbeing. These consequences might come from the symptoms and suffering of the particular disease, but also from the economic hardship/impoverishment imposed by it. For instance, households might reduce expenditures on education in the short-term, a child might not go to school due to disease symptoms, or the child might show suboptimal school achievements due to inadequate nutrition from reduced available resources. This might lead to potentially long-term consequences to a child being out of school, impacting human/social capital formation. Also, time spent seeking health care and time spent by a household member taking care of a sick person could have been spent on leisure activities. In short, besides economic losses, disease also has a negative impact on households' repository of knowledge, experiences, and social networks, plus its stock of health and wellbeing. [2]

Economic hardship due to disease and poverty

Illness-related economic losses can have an important impact on the amount of resources available for consumption, forcing the reduction of basic expenditures (such as food and shelter) or children's education. Furthermore, they can cause or accentuate household poverty. When OPPs are especially large compared to a household's total income (or consumption), they are considered to be catastrophic. Using a definition of large expenditures as 10% of total household expenditure, the global incidence of people incurring catastrophic health expenditures in 2010 was 808 million. [6] In the same year,

the estimated worldwide incidence of impoverishment due to health related OPPs was 97 million people. [7]

Economic hardship due to disease and poverty (from disease and from other causes) are unfortunately still so relevant that two of the Sustainable Development Goals are devoted to these causes. The first SDG is 'To end poverty in all its forms everywhere by 2030' and SDG 3 'Good health and well-being - Ensure healthy lives and promote well-being for all' has a specific goal to 'Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all'. [8,9]

Socioeconomic

The term 'socioeconomic' is widely used and has no consensual definition. Some of the various interpretations include 'the use of economics in the study of society', or 'how economic activity interferes and is influenced by social processes'. [10] In this context, socioeconomic refers to the interaction of both economic and social consequences of NTDs on individuals, households and countries/societies, which can also include how social processes related to the disease might interfere with economic activity.

1.3 Neglected Tropical Diseases (NTDs)

NTDs are a group of communicable diseases diverse in biological and transmission characteristics. They are associated with chronic, disabling and disfiguring morbidity, but also death. Most of them affect forgotten people, the extreme poor with little political capital, living in slums or in rural areas, frequently also affected by conflict, predominantly in low–and middle-income countries (LMIC). Almost everyone in the poorest bottom billion in the world has at least one NTD, which also contributes to keep them trapped in poverty. The number of prioritized NTDs by the WHO is currently 20, although other organizations might define them differently. The public health importance of 13 parasitic and bacterial infections (that are the highest burden NTDs) together (in disability-adjusted life years) was considered to rank closely with HIV/AIDS, malaria, ischemic heart disease, among the most important health problems in the developing world. [11-14]

NTD control or elimination targets for the year 2020 were set out in the World Health Organization (WHO) Roadmap of 2012 and endorsed by partners of the London Declaration in the same year. This declaration included the ten following diseases: Guinea worm disease, lymphatic filariasis (LF), leprosy, sleeping sickness (human African trypanosomiasis - HAT), blinding trachoma, schistosomiasis, soil-transmitted helminthiases (STH), Chagas disease, visceral leishmaniasis (VL) and river blindness (onchocerciasis). [15-17]

The WHO recommends five interventions to reach the NTDs targets: preventive chemotherapy (PCT) by mass drug administration (MDA); innovative and intensified disease management (IDM); vector ecology and management; veterinary public health services; and the provision of safe water, sanitation, and hygiene. [17,18]

PCT is used for LF, onchocerciasis, schistosomiasis, STH and blinding trachoma. It involves largescale delivery of safe, single-dose medicines to eligible populations at regular intervals, donated to and distributed by the WHO. In the many areas where the diseases treated with PCT are coendemic, integrated delivery of treatment is recommended. Since the side effects of PCT medications are relatively mild, treatment is delivered without the need for specific diagnosis. [17]

IDM is the strategy for Chagas, HAT, leprosy, and VL. It involves caring for infected individuals and those at risk of infection by diagnosing as early as possible, providing treatment to reduce infection and morbidity, and managing complications. This intervention is the main strategy for controlling and preventing NTDs for which there are no medicines available for preventive chemotherapy. Due to the relative toxicity of medicines, diagnostic confirmation is needed before treatment. [17,18]

Table 1 briefly describes the NTDs that will be mentioned in the subsequent thesis chapters.

Table 1. Brief description of the NTDs mentioned in the subsequent thesis chapters *[14,19,20]*

Disease	Agent	Transmission	Geographical distribution and estimated numbers	Pathogenesis	Physical signs and symptoms	Treatment	WHO current recommended target and strategy
Lymphatic filariasis (LF)[1] (elephantiasis)	Three species of thread-like nematode worms, known as filariae: *Wuchereria bancrofti, Brugia malayi* and *Brugia timori*.	Transmitted through mosquitoes.	120 million people in several tropical and subtropical areas of the world.	Male and female worms form "nests" in the human lymphatic system, obstructing the flow of lymphatic fluids.	-Acute: local inflammation involving skin, lymph nodes, lymphatic vessels, extremely painful and accompanied by fever. -Chronic: lymphoedema of the limbsand hydrocele, kidney damage.	Albendazole with ivermectin or with diethylcarbamazine citrate, or triple drug therapy with all three drugs (IDA) in specific settings.	Elimination[3] through interruption of the transmission cycle, provision of preventive chemotherapy through mass drug administration (MDA), vector control in some areas.
Onchocerciasis[1] (river blindness)	Filarial worm - *Onchocerca volvulus*.	Transmitted through blackflies.	17 million people. More than 99% of infected people live in 31 countries in sub-Saharan Africa.	Female adult worms produce embryonic larvae (microfilariae) that migrate to the skin, eyes and other organs.	-severe inflammation, itching and various skin lesions -nodules under skin -visual impairment and blindness.	Ivermectin.	Elimination[3] through distribution of ivermectin via MDA, and together with vector control in some areas.
Schistosomiasis[1] (bilharzia)	Parasitic worms: urogenital schistosomiasis by *Schistosoma haematobium* and intestinal schistosomiasis by *S. guineensis, S. intercalatum, S. mansoni,*	Transmitted through contact with fresh water contaminated with snails that release larval forms (cercariae) of schistosomes, which penetrate the skin.	240 million people worldwide in tropical and sub-tropical areas.	The microscopic adult worms live in the veins, the urinary tract and intestines. The eggs they lay are trapped in the tissues and the body's reaction to them can cause massive damage.	-symptomatic acute infection -anemia -cognitive impairment -diarrhea -abdominal pain -fatigue -hepatosplenomegaly (enlargement of both the liver and the spleen)	Praziquantel.	Control[4] through regular treatment with praziquantel of school children and adults at risk in endemic areas, provision of potable water, adequate sanitation, hygiene

table continues

	S. japonicum, or *S. mekongi.*				-hematemesis (blood vomiting) -ascites (abnormal accumulation of fluid in the abdomen) -haematuria (blood in urine) -dysuria (painful urination) -obstruction of ureters - kidney damage - bladder cancer.		education, and snail control.
Soil-transmitted helminthiases (STH): Ascariasis, trichuriasis, hookworm disease[1]	Intestinal worms: *Ascaris lumbricoides*, *Trichuris trichiura* and the hookworms (*Necator americanus* and *Ancylostoma duodenale*).	From soil contaminated with parasite eggs from human faeces in areas where sanitation is poor. Ascariasis and trichuriasis are transmitted through oral infection with eggs; and hookworm is transmitted via penetration of larvae (from hatched eggs) through the skin.	880 million children are in need of treatment for these parasites in tropical and subtropical areas.	Impaired nutritional status leading to anemia and even death via intestinal bleeding, loss of appetite, diarrhoea or dysentery, and reducing absorption of micronutrients.	Ascariasis -abdominal pain -diarrhea -wasting -cognitive impairment -inflamation of the lungs -visceral damage Hookworm -intestinal inflammation -anemia -wasting -cognitive impairment Trichuriasis -abdominal pain -diarrhea -anemia -wasting -cognitive impairment.	Albendazole or mebendazole.	Control[4] through periodic mass administration of anthelminthic drugs to children at risk (MDA), improvement in provision of potable water, adequate sanitation, hygiene education.
(Blinding) trachoma[1]	Bacterium *Chlamydia trachomatis*.	Transmitted through direct or indirect personal contact (also flies).	232 million people at risk; 7.3 million require surgery for trachomatous trichiasis; 1.9	The cumulative effect of many inflammatory episodes may cause the upper eyelid to	-eye discharge -swollen eyelids -trichiasis (eye lashes turned inwards) -blindness.	Oral azithromycin and topical tetracycline, eventually surgery to correct the	Elimination[3] through provision of antibiotics to clear ocular infection,

table continues

			million are visually impaired (of whom 1.2 million are blind). Endemic in 51 countries in Africa, Asia, Central and South America, Australia and the Middle East.	turn inwards, so that the eyelashes rub on the eyeball, resulting in intense pain and scarring of the front of the eye, ultimately leading to irreversible blindness.		position of the eyelashes and prevent blindness.	facial cleanliness to reduce transmission, improvement in provision of potable water, adequate sanitation, hygiene education.
Chagas disease (American trypanosomiasis)[2]	Protozoan parasite *Trypanosoma cruzi*.	Transmitted through the contact of infected faeces of a blood-sucking triatomine bug with its bite; through consumption of food contaminated with *T. cruzi*; blood transfusion or organ transplants from infected donors; mother-to-child (passage from infected mother to newborn during pregnancy or childbirth).	7 million people are infected worldwide, mostly in Latin America.	Symptoms acute phase: caused by the immunological response to parasites in the blood circulation. Chronic phase: parasites stay hidden in the heart and digestive muscles, causing neurological alterations that can lead to heart failure by the destruction of the heart muscle and its nervous system.	- Acute: mostly asymptomatic or non-specific symptoms (fever, headache, muscle pain). - Chronic: may also be symptom-free but may progress to clinical forms of the disease (cardiac, digestive and/or neurological), which can be life threatening if left undiagnosed and untreated.	Benznidazole or nifurtimox to kill the parasite in acute, reactivated cases or early chronic phase. Specific symptomatic treatment for cardiac, digestive or neurological manifestations.	Control[4] through blood screenings to avoid infection through transfusion and organ transplantation, screening and diagnosis in pregnant women and their children, vector control.
Human African trypanosomiasis (HAT) [2]	Protozoan parasites: *Trypanosoma brucei*	Transmitted by vector: tse tse fly;	65 million people at risk and 1,442 reported cases in	First stage: trypanosomes multiply in	- First stage: bouts of fever, headaches, joint pains and itching.	First stage: pentamidine or suramin.	Elimination[3] through vector control,

table continues

(sleeping sickness)	*gambiense -98%* or *Trypanosoma brucei rhodeniense – 2%*).	mother-to-child (less common).	2017 in 36 sub-Saharan Africa countries.	subcutaneous tissues, blood and lymph. Second stage: parasites infect the central nervous system.	- Second stage: changes of behaviour, confusion, sensory disturbances, poor coordination, disturbance of the sleep cycle. Fatal if not treated.	Second stage: melarsoprol, eflornithine with nifurtimox. Treatment guidelines are being updated by the WHO, fexnidazole in phase 2 and 3 trials.	surveillance systems, and accessibility for people at risk to diagnosis and treatment.
Leprosy (Hansen's disease) [2]	Bacterium *Mycobacterium leprae.*	Transmitted via frequent contacts with untreated cases (person to person).	215,000 new cases in 2015: 60% in India, 13% in Brazil and 8% in Indonesia, but present in all WHO regions.	Bacteria enter Schwann cells of the peripheral nervous system. Damage is caused by cell destruction by the bacilli and by the immunological reaction of the person against the bacilli, leading to irreversible impairment of nerve function.	- skin lesions -disfigurement - sensory loss, with or without thickened nerves - muscle weakness - vision impairment Sensory loss can lead to the loss of parts of extremities due to repeated injuries or infection due to unnoticed wounds.	Multidrug therapy (MDT) combining rifampicin, clofazimine and dapsone.	Elimination[3] through early case detection - with a special focus on children to reduce disabilities and reduce transmission, detection campaigns in highly endemic areas or communities, improvement of health care coverage and access for marginalized populations.
Visceral leishmaniasis (VL) [2]	Protozoan parasites: *Leishmania donovani, Leishmania infantum,* and *Leishmania chagasi.*	Transmitted by the bites of over 90 species of sandflies.	50,000 to 90,000 new cases of VL occur worldwide each year, 95% of them in 10 countries:	Parasites invade liver, spleen, lymphatic system and bone marrow cells.	- irregular bouts of fever - weight loss - swelling of the spleen and liver - anaemia.	Sodium stibogluconate with or without paromomycin; Liposomal amphotericin B;	Control[4] through early diagnosis and effective prompt treatment, effective disease surveillance, vector

table continues

	Bangladesh, Brazil, China, Ethiopia, India, Kenya, Nepal, Somalia, South Sudan and Sudan.	High fatality rate if untreated (75 to 95%).	miltefosine; meglumine antimoniate. Scheme depends on the health conditions of the patient and the available infrastructure by the health system.	control and control of animal reservoir hosts.

1. Lymphatic filariasis (LF), onchocerciasis, schistosomiasis, soil-transmitted helminthiases (STH) and trachoma can be controlled or eliminated by means of PCT delivered through MDA programs.

2. Chagas disease, human African trypanosomiasis (HAT), leprosy, and visceral leishmaniasis (VL) are controlled or eliminated by innovative and intensified disease management (IDM).

3. Elimination – reduction of incidence of infection by a specific pathogen in a defined geographical area to 0, as a result of efforts, with minimal risk of reintroduction, as a result of deliberate efforts; continued actions to prevent re-establishment of transmission may be required.[21]

4. Control – reduction of disease incidence, prevalence, intensity, morbidity or mortality (or a combination) as a result of efforts. The term "elimination as a public-health problem" should be used only upon achievement of measurable targets in relation to a specific disease. Continued intervention measures may be required to maintain this reduction.'[21]

Guinea worm has not been included in Table 1 or in the analyses shown in the subsequent chapters, since it is already close to reaching eradication (i.e. permanent reduction to zero cases, with no more risk of reintroduction).

London Declaration targets and Sustainable Development Goals

NTD control or elimination targets for the year 2020 were set out in the WHO Roadmap of 2012 and endorsed by partners in the London Declaration of the same year. [15-17]

According to the London Declaration, Guinea worm should be eradicated by 2020; LF, HAT, leprosy and trachoma should be eliminated; schistosomiasis, STH, Chagas disease, VL and onchocerciasis should be controlled, as shown in Table 1. The partners signing the declaration commit to provide drugs, technical support, funding to implement programs, collaboration for more efficiency, research of new treatments and interventions in order to achieve these targets. [16]

To reach the London Declaration targets, each disease poses its particular challenges. For the diseases treated with ivermectin (LF and onchocerciasis), one of them is co-endemicity with loiasis (another disease endemic in Central Africa caused by the filarial parasite *Loa loa*), which offers the possibility of severe adverse reaction (even death) following ivermectin treatment. Therefore, new strategies to diagnose loiasis before treatment are needed, so that treatment for LF and onchocerciasis can be offered in the regions also facing loiasis. [22-24] Diseases treated via MDA still need more research to ensure effective MDA coverage and evaluation of programs' effectiveness and efficiency. Vector transmitted diseases need more monitoring of and research on insecticide resistance. In general, improved access to and affordable diagnostics and treatment is needed (especially drugs for IDM diseases), one of the reasons for many partners to defend universal health coverage (UHC) guaranteed at least for NTDs.[25,26] WHO's new NTD roadmap for the years 2021-2030 sets a target of '100% of the population at risk protected against out-of-pocket health payments due to NTDs by 2030'.[20] Improvement of the delivery of existing products/strategies through responsive and resilient health systems is essential to reach the London Declaration targets. This is also needed to meet the aspiration of NTD 'endgame' as mentioned by SDG 3.3: "By 2030, end the epidemics of AIDS, tuberculosis, malaria, and neglected tropical diseases and combat hepatitis, water-borne diseases, and other communicable diseases." and to meet the specific 3.3.5 goal for NTDs 'a 90% reduction in the number of people requiring interventions against NTDs by 2030'. [14,25-28]

Not only increased investments directly aimed at NTDs, but improvements in education, water sanitation and hygiene are fundamental to reaching NTDs targets. Since populations endemic for NTDs are the less likely to access these services, many SDGs may be reached once they do: 1-No poverty, 2-Zero hunger, 3-Good Health and Wellbeing, 4-Quality education, 6-Clean Water and Sanitation, 8- Decent Work and Economic Growth, 10- Reduced Inequalities, 11-Sustainable Cities and Communities, improving the wellbeing of vulnerable groups and equity.[14,28,29]

Economic aspects of NTDs

The disease burden of NTDs has been estimated in DALYs (Disability-Adjusted Life Years, expressed as the number of years lost due to ill-health, disability or early death). Although DALYs tend to underestimate the burden of NTDs due to underreporting or missing data from LMICs, in 2012 NTDs accounted for approximately 22 million globally (about 1% of the global total). [18]

In addition to the disease burden, the economic burden that NTDs inflict on patients and their families is also heavy. Compared to studies of the epidemiology and health consequences of NTDs, relatively few studies have investigated the impact of NTDs on OPPs and productivity loss for individuals, households, and societies. An improved understanding of the economic effect of NTDs on individuals, households and countries is important to forecast economic implications of any changes in effective and equitable implementation strategies and to better estimate the benefits of addressing NTDs. These advances in estimating economic costs could help in the advocacy for prevention and control actions, in increasing health policy dialogue, and in convincing funders and policymakers that investments in these actions are worth making. [30,31]

1.4 Objectives and research questions

The main objective of this thesis is to study the socioeconomic effects of NTDs on individuals and society by answering the following four specific research questions:

a. How (far) has productivity loss related to NTDs / disease been described in the literature?

b. How much economic benefit can be expected from reaching the targets for the 10 London Declaration NTDs?
c. What are the costs and cost drivers related to a new strategy aimed at reaching the targets? The example of *Loa loa*
d. What are the effects of combining OPPs and productivity loss in the assessment of illness-related impoverishment?

1.5 Structure of the thesis

This thesis contains 6 more chapters. Chapter 2 describes a systematic literature review to identify and examine publications describing the impact of lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminths (ascariasis, trichuriasis, and hookworm infection) and trachoma on productivity loss in adults. Chapters 3 and 4 report on the estimation of economic benefit (to individuals) of meeting the 2020 WHO targets for PCT and IDM NTDs respectively. This meant estimating how much of the economic loss faced by affected individuals due to productivity loss and out-of-pocket payments secondary to these diseases would be avoided by reaching these targets. Chapter 5 presents the costs of a pilot round in Cameroon for a new strategy to treat onchocerciasis in areas where *Loa loa* is coendemic. Chapter 6 examines the joint impact of OPPs and productivity loss on the likelihood of illness-related impoverishment, using Chagas disease as an example. Chapter 7 concludes this thesis with a discussion of the relevance of these findings, describing possible areas for future research, conclusions and recommendations.

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Chapter 2

Productivity Loss Related to Neglected Tropical Diseases Eligible for Preventive Chemotherapy: a Systematic Literature Review

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2016

PLoS Neglected Tropical Diseases 10(2): e0004397.

https://doi.org/10.1371/journal.pntd.0004397

Abstract

Background

Neglected Tropical Diseases (NTDs) not only cause health and life expectancy loss, but can also lead to economic consequences including reduced ability to work. This article describes a systematic literature review of the effect on the economic productivity of individuals affected by one of the five worldwide most prevalent NTDs: lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminths (ascariasis, trichuriasis, and hookworm infection) and trachoma. These diseases are eligible to preventive chemotherapy (PCT).

Methodology/Principal Findings

Eleven bibliographic databases were searched using different names of all NTDs and various keywords relating to productivity. Additional references were identified through reference lists from relevant papers. Of the 5316 unique publications found in the database searches, thirteen papers were identified for lymphatic filariasis, ten for onchocerciasis, eleven for schistosomiasis, six for soil-transmitted helminths and three for trachoma. Besides the scarcity in publications reporting the degree of productivity loss, this review revealed large variation in the estimated productivity loss related to these NTDs.

Conclusions

It is clear that productivity is affected by NTDs, although the actual impact depends on the type and severity of the NTD as well as on the context where the disease occurs. The largest impact on productivity loss of individuals affected by one of these diseases seems to be due to blindness from onchocerciasis and severe schistosomiasis manifestations; productivity loss due to trachoma-related blindness has never been studied directly. However, productivity loss at an individual level might differ from productivity loss at a population level because of differences in the prevalence of NTDs. Variation in estimated productivity loss between and within diseases is caused by differences in research methods and setting. Publications should provide enough information to enable readers to assess the quality and relevance of the study for their purposes.

Author Summary

Neglected Tropical Diseases (NTDs) not only have impact on health and life expectancy of mostly disadvantaged populations, but can also lead to economic consequences, including reduced ability to work. Investments in health improvement of the populations affected by NTDs would also help to increase economic growth of the affected regions, since healthier populations are more economically productive. We performed a systematic literature review to better understand how much NTDs affect people's economic welfare. Here we present the results for the NTDs that are controlled with preventive chemotherapy (PCT): lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminths (ascariasis, trichuriasis, and hookworm infection) and trachoma. Our findings show that PCT NTDs clearly affect productivity, although the actual impact depends on the type and severity of the NTD as well as on the context where the disease occurs. Variation in estimated productivity loss is also caused by differences in research methods. Publications should provide enough information to enable readers to assess the quality and relevance of the study for their purposes.

Introduction

Most of the people affected by Neglected Tropical Diseases (NTDs) are impoverished and marginalized populations, with low visibility and little political voice. They are not considered a priority market for pharmaceutical manufacturers or a health risk for the wealthier parts of the world. [1-3] Nevertheless, NTDs have an important impact on child development, school attendance, learning, nutritional status, pregnancy outcomes, and worker productivity, especially in poor rural settings, where physical labor is the major subsistence mode. As any other disease, they can lead to productivity loss in many ways, including reduced productivity at work (presenteeism), absence from work (absenteeism) or even job loss, depending on the type, severity and duration of the disease. [2-12]

Many publications in the literature describe the epidemiological and physical aspects of NTDs. In contrast, the impact of NTDs on paid and unpaid work and the productivity of individual men and women has been less frequently studied. Most of the data about the economic burden of NTDs come from small studies in restricted geographical areas.[13]

The costs of treatment, mainly long-term ones, can inflict further economic difficulties in populations already struggling to live with less than US$ 1 a day. Besides the obvious advantages of decreasing the healthcare costs due to lack of care or delayed care, investments in health improvement would also help to increase economic growth of the affected regions since healthier populations are more economically productive. [14-16]

As part of the movement to increase the attention given to NTDs, a coalition of many stakeholders gathered in January 2012 to discuss the importance of reaching the 2020 WHO goals for this group of diseases. As a result, the London Declaration was signed by many partners, committed to eradicate Guinea worm disease, eliminate three NTDs (lymphatic filariasis, leprosy, African sleeping sickness (human African trypanosomiasis) and blinding trachoma) and control the others (schistosomiasis, soil-transmitted helminths, Chagas disease, visceral leishmaniasis and river blindness (onchocerciasis)). [17,18]

A better understanding of the effect that NTD have on people's economic livelihood would be an additional argument in favor of controlling or eliminating them. With this in mind, we performed a systematic literature review to identify and examine publications describing the impact of the London Declaration NTDs. Here we present the results for the five most prevalent ones, which are the ones eligible for preventive chemotherapy (PCT diseases): lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminths (ascariasis, trichuriasis, and hookworm infection) and trachoma on productivity loss in adults. [7,19,20]

Methods

We performed a comprehensive search of the literature relating to the economic impact of all of the NTDs included in the London Declaration. Databases searched included Embase, Medline (OvidSp), Web of Science, Scopus, CINAHL, PubMed publisher, Cochrane, Popline, Lilacs, Scielo and Google Scholar. The search terms aimed at identifying articles about direct costs of treatment (such as consultation fees, medication, transport, food, assistance, accommodation), as well as indirect labor costs arising from decreased working hours and reduced economic activity attributable to morbidity. The search strategy included the names of the ten London Declaration NTDs (since many articles mention more than one) and words such as: 'economic', 'financ', 'cost', 'productivity', 'absenteeism', 'employment', and 'cost'. A detailed list of the keywords used for each database is found in Supporting Information (S1 File). The search only considered title and abstracts, did not use any time restriction, and was restricted to the English language. The main database search was conducted in November 2013. There is no review protocol registered. This search included not only productivity loss, but also direct costs for all 10 London Declaration NTDs for a larger project. The results found in this article are limited to the results of the literature search regarding productivity loss from PCT NTDs.

The databases were merged according to the order shown in Table 1. Duplicates were removed automatically using Endnote and the remaining articles were then compared manually using author, year, title, journal, volume and pages to identify any additional duplicates. [21] After duplicates were excluded, we selected the articles that were related

to each particular disease and screened the abstract and title of all papers to identify the ones that might provide information on productivity or indirect costs. The full-text versions of all remaining articles were then examined. Articles that did not contain any information on productivity, or only qualitative information on productivity loss (without any quantitative measures) were excluded, as well as articles that investigated productivity loss in children. Since the number of relevant publications was expected to be small, no restrictions were made regarding populations (participants), interventions, comparisons, outcomes, study design, or length of follow-up. Articles that could not be retrieved through their respective journals, contacting libraries, or after contacting the authors were classified as 'not available' and excluded from the selection. Any additional relevant articles identified when reading the full-text articles or checking their reference lists (i.e., the 'snowball' search strategy) were screened using abstract and title and then examined in more detail if they were considered potentially relevant.

In addition to searches using databases relating to the 'white' literature, we also searched the grey literature by screening websites of relevant organizations (i.e. World Health Organization, the Centre for Neglected Tropical Diseases, the Carter Center) (see S2 File). The list of selected articles for each disease was sent to disease experts identified in the literature and from institutions researching/combating NTDs, to check if the selection was comprehensive.

Data were extracted from selected articles independently, using a standardized Excel sheet, for the variables: author, year, study design, population, sample size, follow-up period, country, region, disease sequela, definition of productivity loss and results. Disease sequelae are disease manifestations, which for this review were defined by the Global Burden of Disease 2010 study (see S1 Table). [22] No summary measure was chosen beforehand. Instead, the results were presented separately per disease and study and described as they were reported in the articles; results were not statistically combined.

If the productivity loss was not already described in percentages of annual productivity in the articles, we calculated it whenever the unit of measurement made it possible, for the sake of comparability between studies and diseases. A working year was assumed to consist of 300 working days. [23]

Since the outcome of interest was productivity loss, various study designs were expected. The studies were therefore critically appraised regarding general criteria of selection, performance, attrition, detection, and reporting biases, as specified in the Cochrane Handbook for Systematic Reviews of Interventions. [24,25] Therefore, each article was given a rating regarding the risk of bias (possible options: low, high or unclear) for each criterion as well as a summary rating. [24,25] We added an extra criterion about the degree of relevance that the study outcomes defined as productivity loss had in terms of quantifying productivity loss in adults due to an NTD. This 'relevance' criterion was also rated as low or high. This review was conducted according to the PRISMA checklist for systematic reviews.

Results

Results of the database searches

Table 1 provides an overview of the databases searched and the number of articles identified through each of them. In total, 11,449 articles regarding all 10 NTDs were identified using the database searches. Of these, 5,316 articles remained after duplicates were removed. There was no duplication across the various NTDs.

Table 1. Results of database searches

Database	Hits	After exclusion of duplicates
Embase.com	2913	2854
Medline (OvidSP)	2887	682
Web-of-science	1224	478
Scopus	3339	660
CINAHL	282	126
PubMed publisher	175	150
Cochrane	60	7
Popline	176	147
Lilacs	257	100
Scielo	36	26
Google Scholar	100	87
Total	11449	5316

Lymphatic filariasis

From the main database, 281 peer reviewed papers were related to lymphatic filariasis (LF). The grey literature search and snowballing method added 24 more articles, resulting in 305 articles being screened by title and abstract. Of the 72 full-text publications that were examined, 13 quantitatively described productivity loss related to LF (S1 Fig).

Lymphedema and hydrocele due to lymphatic filariasis are the two sequelae considered by the GBD study for this disease. Acute dermatolymphangioadenitis (ADLA) is part of these sequelae as acute inflammatory attacks suffered by most of the chronic patients, sometimes many times a year.[23]

An overview of the studies that used a quantitative method to describe productivity loss from lymphatic filariasis can be seen in Table 2, together with the calculated percentages of productivity loss.

Table 2. Description of studies investigating productivity loss due to lymphatic filariasis

Author	Year	Country	Study design	Population	Sample size	Definition of productivity loss	Sequela	Results	Adjusted percentage of prod. loss [1]
Babu	2002	India	Case vs control	Small farmers, daily wage laborers	377	Working hours/day	a) chronic filariasis (both sequelae)	a) 4.94 ± 3.33 vs 6.06 ± 3.22 controls	a) 18.48% (annual)
							b) lymphedema	b) male 4.45 ± 3.52 vs. 5.26 ± 3.21 controls (not significant) / female 5.45 ± 3.3 vs.7.12 ± 3.07 controls	b) male 15.40% (annual) / female 23.45% (annual)
							c) hydrocele	c) 4.98 ± 3.00 vs. 5.78 ± 2.84 controls	c) 13.84% (annual)
Babu	2003	India	Case vs control	Small farmers, daily wage laborers	1329	Hours spent in economic activity	ADLA	0.81 ± 2.31 h/day ADLA vs. 3.50 ± 3.74 h/day controls	76.85% (during ADLA episode) 1.58% (annual)
Babu	2006	India	Case vs control	Weavers	136	Hours spent in productive work/day	a) lymphedema	a) 8.02 ± 2.67 vs. 9.13 ± 1.61 controls	a) 10% (annual)
							b) hydrocele	b) 8.71 ± 1.86 vs. 10.08 ± 1.70 controls	b) 18.9% (annual)
Budge	2013	India	Pre/post-intervention	Homemakers/ Housekeepers	375	Working days lost to disability in the previous 30 days	Lymphedema	6.4 days	21.3% (annual)
Chandrasena	2004	Sri Lanka	Cohort	Patients attending morbidity control clinics	31	Capacity to perform any domestic or economic activity	ADLA	52% totally / 31.3% moderately incapacitated during ADLA episode	1.53% (annual)[2]

table continues

Chu	2010	Review	Review	Review	Review	Reduced work hours and economic activity	a) ADLA	a) 75% during ADLA episode	Idem
							b) lymphedema	b) 20%	b) 22.56% (annual)[3]
							c) hydrocele	c) 15%	c) 20.41% (annual)[3]
Gasarasi	2000	Tanzania	Cohort	Three villages in Rufiji district	65	Total incapacitation due to ADLA	ADLA	72.5% of the episodes, mean duration of 3.7 days	0.9% (annual)
Gyapong	1996	Ghana	Case vs control	Subsistence farmers	572	Ability to perform activities (vs others with similar diseases)	ADLA	at least 3 full days of incapacitation	at least 1% (annual)
Ramaiah	2000	India	Case vs control	Agricultural workers, carpenters, weavers	263 ADLA 478 Lym	Time spent on economic activity/day	a) ADLA	a) 0.97 ± 2.36 h/day vs. 4.48 ± 3.82 controls during attacks	a) 78.34% during ADLA episode
							b) lymphedema	b) 4.40 ± 3.79 h/day vs. 5.13 ± 3.83 controls	b)14.23% (annual), 24.3% (annual)[3]
Ramaiah	1999	India	Case vs control	Agricultural workers, carpenters, weavers	150	Time spent on economic activity/day	a) lymphedema	a) 3.93 h vs. 4.64 h controls	a) 15.3% (annual)
							b) hydrocele	b) 5.10 h vs 6.19 h controls	b) 17.6% (annual)
Ramaiah	1998	India	Case vs control	Two villages (south India)	124	Working hours	ADLA	0.68 ± 1.91h vs 4.40 ± 3.74 h controls / 3.58	84.54% during ADLA episode / 1% (annual)

table continues

								± 1.95 days duration/attack	
Ramaiah	1997	India	Case vs control	Agricultural workers, weavers	372	Working hours	ADLA, lymphedema, hydrocele	28% worked fewer hours, 5% gave up work	[4]
Sabesan	1992	India	Case vs control	Patients attending filariasis clinics	528	Working days	ADLA	a) 23.4 days/year Bancroftian filariasis	a) 7.8% (annual)
								b) 26.5 days/year Brugian filariasis	b) 8.8% (annual)

ADLA - acute dermatolymphangioadenitis

1. Translation into percentage of productivity loss as described in the cited source, assuming 300 working days a year, for the ADLA episodes alone, for chronic sequelae alone, or for the weighted average of both, when applicable.
2. Totally incapacitated assumed 100% productivity loss, moderately incapacitated assumed 50% productivity loss during ADLA episodes
3. Weighted average including productivity loss from ADLA episodes and chronic symptoms
4. Only qualitative data, impossible to calculate annual productivity loss

Productivity loss in LF patients can occur because of ADLA or the chronic sequelae of the disease (lymphedema and hydrocele). Our search identified six studies that examined only the acute attacks (ADLA), five articles that described the impact of chronic sequelae, and two that measured both.

The range in estimated productivity loss during ADLA attacks was 77-100% during the days of the attacks. The ranges in annual productivity loss reported in the literature were 10-26% for lymphedema and 15-19% for hydrocele (only the chronic sequelae). However, studies of productivity loss due to lymphedema and hydrocele rarely considered the different stages and varying severity of these symptoms. Most of the studies describing productivity loss due to LF measured it by comparing lost working hours or days amongst workers with LF with those seen amongst healthy workers.

Onchocerciasis

Of the 5316 articles in the source database, only 167 articles were related to onchocerciasis. In addition, 52 articles were found through the 'snowball' search and grey literature sources, which meant that a total of 219 articles were screened on abstract and title. Of these, 57 articles remained for full-text examination; from which only 10 contained quantitative information on productivity losses related to onchocerciasis (S2 Fig).

The GBD sequelae (disease manifestations) considered for onchocerciasis were skin disease and vision loss.

Table 3 provides an overview of studies that have quantitatively examined productivity loss resulting from onchocerciasis. Only one study - by Thomson - reported productivity loss due to onchocerciasis in general, of 20%.[26] The other papers focused on the effects of the specific sequelae of onchocerciasis on productivity.

Table 3. Description of studies investigating productivity loss due to onchocerciasis

Author	Year	Country	Study design	Population	Sample size	Sequela	Definition of productivity loss	Results [1]
Benton	1990	World	CBA/model	n/a	n/a	Blindness	Assumption	100%
Evans	1995	Guinea - OCP area	Observational (survey)	Household members in a highly endemic area	319	a) visual impairment	Self-reported 'inactive' occupational status	a) 38%
						b) blindness		b) 79%
Kim	1995	West Africa	CBA/model	n/a	n/a	Blindness	a) Productive years gained by preventing onchocerciasis blindness	a) 20 years
							b) Potential productivity loss	b) 100%
Kim	1997	Ethiopia	Case vs. control	Coffee plantation workers	235	a) OSD - intermediate	Daily wages (individuals infected with OSD vs. those without)	a) 10%
						b) OSD - severe	Daily wages (individuals infected with OSD vs. those without)	b) 15%
Okeibunor	2011	Cameroon, DRC, Nigeria, Uganda	Observational (cross sectional)	Primarily residents from villages where ivermectin distribution was ongoing	1600	General onchocerciasis	a) Increase in productivity from ivermectin treatment	a) 76%
							b) Percentage of respondents that referred ability to work better after ivermectin treatment	b) (75.6%)

table continues

Oladepo	1993	Nigeria	Case vs. control	Male farmers	102	OSD	Farm size that a men can keep satisfactorily weeded (workers with vs. without OSD)	9,117 vs 13,850 m^2 (34% loss)
Thomson	1971	Cameroon	Case vs. control	Estate workers in an onchocerciasis endemic area	420	Unspecified (general)	Working days (workers with vs. without onchocerciasis)	20%
Wogu	2008	Nigeria	Observational (survey)	Rural farming community in a meso-endemic area	200	a) OSD - itching	a) Percentage of respondents that referred reduction in strength and concentration at work	a) 13.5%
						b) OSD - nodules	b) Percentage of respondents that referred decline in sales in business/trading	b) 11%
						c) visual impairment – ocular lesions	c) Percentage of respondents that reported giving up jobs (Productivity loss not specified)	c)14%
Workneh	1993	Ethiopia	Case vs. control	Male permanent coffee plantation workers	196	OSD	Absenteeism/sick leave and net monthly pay (workers with vs. without OSD)	25%
World Bank	1997	Nigeria, Ethiopia, Sudan	Case vs. control	Households in hyperendemic communities	824	OSD	Time spent on productive activities (individuals with vs. without OSD signs and symptoms)	not significant

CBA - cost-benefit analysis; OSD - onchocerciasis skin disease; n/a - not applicable

1.Percentage of annual productivity loss already calculated in the original publication

Four studies examined productivity loss related to onchocerciasis skin disease (OSD) [27-30]. Two of these studies compared Ethiopian coffee plantation workers with OSD to uninfected workers at the same plantation: Workneh et al.[28] concluded that workers with OSD had a one-year income that was 25% lower than that of healthy workers while Kim et al. [28] found 10-15% lower daily wages of individuals with OSD compared to those without. The study by Oladepo et al. [27] focused on the utilization of land and found that men with OSD had a significantly smaller (34%) amount of land than men without OSD. The study by the World Bank [30] found that individuals with onchocerciasis spent less time per day performing productive activities (farming and non-farming) and household activities than healthy individuals. However, these differences were not statistically significant.

Evans (1995) discussed the economic impact of blinding onchocerciasis [30], and found that visual acuity was strongly associated with occupational status. Approximately 80% of people that were blind due to onchocerciasis did not work, compared to 60% of the visually impaired (due to onchocerciasis) and 2% of the sighted.

Three studies (Thomson [26]; Wogu et al. [32] and Okeibunor et al. [33]) described in more general terms the socioeconomic consequences of onchocerciasis. For instance, Wogu et al. [32] reported that 13.5% of individuals with onchocerciasis-related itching experienced reduced concentration at work. In addition, 14% of the individuals with ocular lesion reported that they gave up their jobs because of visual impairment. Similarly, Okeibunor et al. [33] found that 76% of their subjects reporting increased productivity after (community based) treatment with ivermectin.

In addition to the observational studies of onchocerciasis-related productivity loss, we also identified several economic evaluations that considered productivity loss in their analyses. Two cost-benefit analyses, one by Benton and another by Kim, included productivity gains due to prevention of onchocerciasis blindness as part of the benefits of prevention. [34,35]. However, these gains were not actually observed in a patient population but based on the assumption that blind individuals are not productive at all. Kim et al. [35] assumed that each prevented case of blindness would result in 20 years of extra productivity.

Schistosomiasis

From the main search database, 670 articles referred to schistosomiasis, including publications identified through 'snowball' searching and grey literature sources. Of these, 26 articles were retrieved for full-text examination and eleven of them contained quantitative information on productivity losses caused by schistosomiasis (S3 Fig).

Three different worms of the genus Schistosoma can cause schistosomiasis: *Schistosoma haematobium, Schistosoma mansoni, and Schistosoma japonicum*. Ten sequelae were included for schistosomiasis in the GBD study: mild diarrhea, mild anemia, moderate anemia, severe anemia, hepatomegaly, hematemesis, ascites, dysuria, bladder pathology, and hydronephrosis due to schistosomiasis.

Table 4 provides a list of the studies investigating productivity loss attributable to schistosomiasis and the calculated percentages of annual productivity loss.

Table 4. Description of studies investigating productivity loss due to schistosomiasis

Author	Year	Country	Study design	Population	Sample size	Sequela	Definition of productivity loss	Results	Percentage of annual prod. loss [1]
Audibert	1998	Mali	Case vs. control	Families cultivating paddy in endemic region treated and not treated with praziquantel	412 households	infection by *S. haematobium; S. mansoni*	a) man-days worked/ha	a) 69 man-days per family worker	a) 23%
							b) farm size	b) additional 0.47 ha	b) 8.7%
Barbosa	1981	Brazil	Retrospective study + prospective study (both observational; matched case-control)	Sugarcane cutters; uninfected and stages I and 3 of a 3-stage clinical gradient (light, moderate, severe) for infected workers	94 (retrospective); 36 (prospective)	infection by *S. mansoni*	Reduced earnings compared to controls	Retrospective: no significant difference; Prospective: Stage III 31.9% to 38.4% less productivity vs. stage I	Idem [2]
Blas	2006	Philippines	Observational study	Municipalities with relatively high endemicity	801	infection by *S. japonicum*	Loss of working capacity	Assumed loss: 25% (mild), 50% (moderate),	Idem [2]

table continues

								75% (severe), 100% (very severe)	
Fenwick	1972	Tanzania	Observational study	Cane-cutters; men (uninfected, infected, treated)	approx. 300	*S. mansoni*	Mean bonus earnings, increase in cane cut	3% significant difference in productivity between uninfected and infected workers; true difference might be 5%	Idem [2]
Kamel	2002	Egypt	Case vs. control	Textile company workers (infected vs healthy)	340 (170 vs 170)	infection by *S. haematobium; S. mansoni*	a) productivity score	a) 1059 vs 1113 (non-significant)	a) 4.8%
							b) additional hours/month	b) 26.5 vs 32.6 hours (significant)	b) 18.7%
							c) total incentives/ month	c) 46.3 vs 56.2 incentives (significant)	c) 17.6%
Leshem	2008	Tanzania	Observational study	Israeli travelers	27	Acute schistosomiasis	# missed workdays	Average 7.8 days	2.6%

table continues

Leslie	2011	Niger	Cost effectiveness analysis	Schistosomiasis control programs (school-based vs community distributed MDA)	484	infection by *S. haematobium*	potential economic gain from adult treatment	$4.30, equal to 3 days of labor (based on agricultural day rate of $1.40 in 2005) or 2.3 days (based on rate of $1.90 in a normal year)	1%
Umeh	2004	Nigeria	Observational study	315 households from 4 communities	1763	Urinary Schistosomiasis	Average # of work-days lost due to urinary schistosomiasis	a) 4.7 days (head of household)	a) 1.5%
								b) 27.7 (adult male)	b) 9.2%
								c) 17.6 (wife)	c) 5.8%
								d) 24.7 (adult female)	d) 8.2%
								e) 19.09 weighted average	e) 6.3%
Wright	1972	Africa, Mauritius, Southwest	Economic impact assessment	various	n/a	infection by *S. haematobium; S.*	Reduced productive capacity	Assumed loss: 100% (severe), 10%	Idem [2]

table continues

		Asia, Southeast Asia, America, World				*mansoni; S. japonicum*		(moderately severe)	
Wu	2002	China	Case vs. control (matched)	Patients with advanced S. japonicum vs healthy individuals	48 cases, 56 controls	Advanced *S. japonicum*	Average workdays lost	Case vs. control: 4.11 vs. 0.86 days ($p<0.01$)	1%

n/a - not applicable; S. haematobium - *Schistosoma haematobium*; S. japonicum - *Schistosoma japonicum*; S. mansoni - *Schistosoma mansoni*, # - number of

1. Translation into percentage of annual productivity loss assuming 300 working days a year

2. Percentage of annual productivity loss already calculated in the original publication

The studies vary regarding schistosomiasis being caused by *S. haematobium, S. mansoni* or *S. japonica* and also regarding the sequela they focused on. Most of the studies we identified compared productivity loss between infected and uninfected workers in a company or municipality, whereas Blas et al. and Wright et al. calculated the costs of productivity loss based on assumptions and not on empirical data. [36,37] Productivity loss was also measured using different units: lost man-days/work days [38-41], reduced earnings/bonus/incentives [42-44], cane cut [45], and lost working hours [43].

Soil-transmitted helminths

In total, 538 articles in the source database were related to soil-transmitted helminths (STH) -ascariasis, trichuriasis and hookworm disease. The snowballing method and the gray literature search yielded an additional 48 articles, which meant that 586 articles were screened by title and abstract. Of the 72 publications that were fully read, only 6 had information related to productivity loss and STH (S4 Fig).

The GBD study lists the following sequelae related to each of the STH diseases: infestation, severe wasting, and mild abdominopelvic problems, as well as anemia only for hookworm disease.

Table 5 shows the list of studies, the summary of their findings regarding productivity loss as a consequence of STH, and the yearly percentages that were calculated wherever needed.

Table 5. Description of studies investigating productivity loss due to soil-transmitted helminths

Author	Year	Country	Study design	Population	Sample size	Sequela	Definition of productivity loss	Results	Percentage of annual prod. loss [1]
Basta	1979	Indonesia	Case vs control	Rubber plantation workers (male)	302	Anemia	a) collection of wet latex by tappers	a) 18.7% more	Idem [2]
							b) removal of roots and weeds	b) 20% more	Idem [2]
							c) physical capacity test (HST)	c) 15% higher HST scores in non-anemic group	Idem [2]
Gilgen	2001	Bangladesh	RCT of iron-folic acid supplement & regular deworming	Tea pluckers (female) randomized to different treatment arms	553	Anemia	a) volume of green leaves plucked per day (kg/pld)	a) 1.8 less kg plucked (anemic vs. non-anemic)	a) 6.3%
							b) average wages earned per day	b) $1.1 less	b) 4%

table continues

							c) sick leave (# days)	c) 0.3 days more	c) 0.1%
							d) absenteeism (# days)	d) 0.9 days more	d) 0.3%
Selvaratnam	2003	Sri Lanka	Before-after	Tea pluckers (2500 m above sea level) (female)	304	Anemia	Volume of leaves plucked (per increase in hemoglobin of 1g/dL)	26% increase	Idem [2]
Wolgemuth	1982	Kenya	Case vs control	Road construction workers (male, female)	47	Infection /Anemia	Volume of earth moved (m^3/hour)	6% loss; Hb increase of 1.30 g/dL associated with a 5.6% increase in productivity	Idem [2]
Casey	2011	Vietnam	Before-after (CEA)	Women in reproductive age in rural area	349	Anemia	Individual productivity gain after improvement of anemic state	5% in manual and 17% in heavy occupation (used values by Horton and Ross 2003)	Idem [2]

table continues

Tanner	2013	Bolivia	Case vs control	Indigenous group of hunter-horticulturalists	86	Infection	Yield in agricultural and hunting/fishing (24h period)	(uninfected 6.8 kg vs. infected 4.4 kg; nonsignificant)	35.29%

CEA - Cost effectiveness analysis; RCT - randomized controlled trial, # - number of

1. Translation into percentage of annual productivity loss assuming 300 working days a year

2. Percentage of annual productivity loss already calculated in the original publication

Productivity loss from STH infection was generally measured by comparing infected to uninfected controls. Wolgemuth et al. observed that road construction workers with infection showed 6% less productivity (measured using volume of earth moved) than other workers. [46] Tanner et al. compared the agricultural and hunting or fishing yields reported in a 24-hour period among an indigenous Amazonian group of hunter–horticulturalists. There was a negative association of hookworm infection for both women and men, with hookworm-infected people reporting an average quantity of crops that was 35.29% less than uninfected people (no statistical significance). [47]

Productivity loss associated with anemia was mostly measured in women with three studies, by Casey et al., Gilgen et al., and Selvaratnam et al. [48-50] One study by Basta et al. investigated men [51] and one by Wolgemuth et al. investigated both women and men.[46] Two studies compared anemic versus non-anemic workers - Basta, and Gilgen [51,52], while three studies examined the productivity of the same individual twice, once while anemic and infected by STH and once after an intervention to increase the hemoglobin level - Casey, Selvaratnam, Wolgemuth [46,48,50], with or without deworming. The only randomized controlled trial was performed by Gilgen et al., assessing iron supplementation with and without deworming, with a significant negative association between hookworm infection and ferritin levels. Furthermore, anemic workers had a poorer performance regarding kilograms of leaves plucked and wages earned by day, as well as more sick and absent days compared to non-anemic workers. [52] There were two studies describing a positive linear association between hemoglobin and productivity. Selvaratnam et al found that an increase in 1g/dL in hemoglobin corresponded with an increase in 26% in a worker's productivity. [50] Wolgemuth et al. described a linear increase in productivity ranging from 3.5% to 5.6% (depending on the formula used in the study) for each 1g/L in hemoglobin gain.[46]

Trachoma

In total, 538 articles from the initial search were related to trachoma and 11 articles were found through the 'snowball' search and grey literature sources, which led to a sum of 549 articles that were screened on title and abstract. Of these, 22 articles remained for full-text examination (S5 Fig).

The only sequela considered by the GBD study for trachoma was vision loss (from low vision to blindness).

A summary of the main features of the studies that investigated productivity loss due to trachoma quantitatively is shown in Table 6.

Table 6. Description of studies investigating productivity loss due to trachoma

Author	Year	Country	Study design	Population	Sample Size	Sequela	Definition of productivity loss	Productivity loss [1]
Frick	2001	The Gambia	Model	n/a	n/a	Low vision	Based on disability weight (GBD, 1996)	24.5%
Frick	2003a	Global	Model	n/a	n/a	a) blindness	Based on disability weight (GBD, 1996)	a) 60%
						b) low vision	Based on disability weight (GBD, 1996)	b) 24.5%
Frick	2003b	Global	Model	n/a	n/a	a) blindness	Assumptions based on disability weights (GBD, 1996), also assumed that 10% of blind persons required a caregiver who lost productivity completely	a) 60%/100%
						b) low vision	Assumptions based on disability weights (GBD, 1996), also assumed that 10% of blind persons required a caregiver who lost productivity completely	b) 24.5%

n/a - not applicable

1. Percentage of annual productivity loss actually used in the original publication

Of the studies we identified, none of them directly observed the extent of productivity loss caused by trachoma in a population. The three studies that examined this topic made assumptions about productivity loss in order to calculate the costs. [53-55] These studies assumed a productivity loss of either 60% or 100% for blindness and 24.5% for visual impairment and these percentages were based on the disability weights that existed at the time of the studies.

Risk of bias

Sixty percent of the selected articles had a high overall risk of bias (26 articles of 42), mostly due to detection bias (24 of 42 articles), selection bias (21 articles of 42), and attrition bias (10 of 42 articles). Twenty-two articles were rated as relevant, and of these studies, two-thirds (14/21) had a high overall risk of bias, 2 had a low overall risk of bias and 6 had an unclear overall risk. Only 6 articles had a low overall risk of bias, of which only 2 were relevant, and 9 had an unclear summary rating, of which 6 were relevant (as described before). No particular trend was observed, regarding over- or underestimation of results due to bias. For the complete risk of bias assessment table, please refer to S3 Table.

Discussion

Neglected tropical diseases can have a profound effect on the health and economic livelihood of the individuals suffering from them as well as that of their families. We examined what has been published in the literature regarding the loss in productivity seen amongst patients with the NTDs that are eligible for preventive chemotherapy: lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminths (ascariasis, trichuriasis, and hookworm infection) and trachoma. In general, our systematic literature review revealed that few studies have actually examined the degree of productivity loss related to these NTDs, which to some extent might have been influenced by the focus on literature written in English. Table 7 shows a summary of the flowcharts for all PCT NTDs, which shows the relatively small numbers of articles containing quantitative information on productivity loss related to PCT NTDs compared to the number of the publications screened by title and abstract.

Table 7 : Summary of flowcharts for all PCT NTDs

	Lymphatic filariasis	Onchocerciasis	Schistosomiasis	STH	Trachoma
Papers screened on title and abstract	305	219	670	586	549
Assessed full text	72	57	26	72	22
Studies with quantitative info on productivity losses	13	10	10	6	3

We also found large variation in the definition of productivity loss as well as the estimated productivity loss as reflected in percentage productivity loss over a one-year period. This is not surprising given the diversity in the methods chosen to quantify absolute and relative productivity loss, the many symptoms that these NTDs can cause, and the many different contexts of the different countries and regions where these diseases are endemic.

Many of these studies were performed many years ago and involved very specific populations in specific countries. However, besides biological reasons, there are methodological reasons for this variation. One explanation is simply random variation, where the results of two studies with the very same study design simply differ due to chance. A more important issue relates to the fact that studies varied in their approach when examining productivity loss. First of all, studies varied in their selection of the study population. Many studies focused on workers on large plantations, while others observed road workers, and the different studies were performed in different settings and countries, which might differ in important ways from other professions and other populations suffering from the same NTD elsewhere. The generalizability of the results from one study to another population must therefore be carefully considered.

The second type of variation in study design relates to the choice of comparison group. Most studies chose workers who did not have the NTD as the comparison group (only one, Gyapong 1996, compared patients with lymphatic filariasis with patients with other febrile diseases). The sometimes tacit assumption made with this comparison is that any difference in productivity can be attributed to the NTD and its symptoms. However, the

validity of this comparison can be questioned, certainly if no correction is made for background characteristics such as age, sex, job experience, diet, height, and BMI (body mass index), which can affect productivity. Fortunately, some but not all studies included these factors when analyzing and reporting their results. Other studies did not compare two different populations but used a before-after study design to see how much productivity improved after treatment. This approach focuses directly on the productivity gain that can be achieved using available treatments.

The third type of variation relates to the actual measure of productivity. Many studies used the number of hours or days to quantify productivity. In contrast, some studies used other, arguably more accurate, methods which involved examining the volumes that were actually collected or processed per day (i.e. how many kilograms of tea were plucked per day). [47] Some studies even used multiple outcomes to study productivity loss. Ultimately, one could argue that the choice of outcome measure should be based on what a decision-maker considers important. For example, an employer might be particularly interested in volume outcomes since workers with an NTD who never miss a day at work may nevertheless be less productive than other workers. Another point worth considering when measuring productivity loss is that the adjustment of worker behavior and the associations between nutrition, body composition, and work productivity may be more complex. Workers might adapt work pace or intensity, allowing them to minimize the effects of poor health on work productivity. [47]

The fourth type of variation relates to the length of time that productivity loss is measured. Most studies used a fixed length of time (e.g., year) when measuring productivity, also to account for seasonality, which could also influence productivity along the year. In some instances, however, the length of time was disease-based (e.g., length of an episode). This approach may reveal that productivity loss is very high (>50%) if the symptoms are extreme, but the impact of disease on productivity over a longer period (e.g., one year) may be small if these episodes last just a few days and only occur a couple of times per year.

Other limitations of the studies are worth mentioning. Firstly, many studies did not check for other concomitant NTDs prevalent in the same region. One possible reason for this could be the assumption that the control group has the same risk to be affected by the

non-investigated disease as the case group. Secondly, measurement of productivity loss in working populations may lead to an underestimation of impact due to the 'healthy worker effect', since people who had to stop working because of the disease are excluded from the study [38]. Thirdly, most of the studies that diagnosed NTDs using stool examination took only one sample, which resulted in a high probability of false negatives and a possible underestimation of productivity loss due to the NTD. [56-58] Lastly, correction of hemoglobin levels for altitude or for smoking status of the patients was not mentioned by any of the anemia studies, which could also lead to an underestimation of the productivity loss. [59]

Based on the literature, the NTDs with the greatest impact on an individual's productivity loss are onchocerciasis and trachoma, because both of them can lead to blindness. The studies of actual patients revealed an increased likelihood of stopping with work or a substantial decrease in productivity. However, other studies simply assumed that productivity loss would be high.

It is important to distinguish between productivity loss at an individual level from productivity loss at a population level. For example, while the individual productivity loss from an NTD like STH may be much less than loss from another NTD like onchocerciasis, the overall impact of STH at a population level may be greater than that of onchocerciasis as a result of its higher prevalence. Therefore, what we consider important depends on the perspective we are taking (either that of the individual or that of the population).

The extent to which productivity is affected by diseases – in this case NTDs – can also help to understand the economic burden of diseases for affected individuals, countries, regions, and even globally. If we take the example of STH in India, around 50 million cases of hookworm (in adults older than 15 years) would be expected in 2020 if the epidemiological situation in 1990 had continued unabated. If we assume an annual income of US$1333 (which equals the annual income of an individual in the lowest GDP quintile in India in 2005) and an average productivity loss due to hookworm anemia of 6%, we could estimate an economic burden from productivity loss of roughly US$ 4 billion just in that one year. Obviously, the impact is much more pronounced when other

years or countries are considered. These estimates can help to estimate the impact on productivity of achieving the targets described in the 2012 London Declaration. [18]

Some recommendations regarding future studies of productivity loss can also be made. The assessment of productivity loss secondary to NTDs should be further researched to enable a better understanding of the economic burden it generates. Additional research is needed to develop standard methods to describe absolute and relative productivity loss. However, this will not be an easy task, given the diverse symptoms caused by these diseases and the variety of countries and cultures where these diseases are endemic; with some NTDs such as lymphatic filariasis, a distinction between treated and untreated patients will have to be made as well. As described above, there are some factors that should be considered when designing future studies: the choice of the comparison group (preferably a comparable assuredly non-infected group), the outcome measure assessing productivity (preferably quantitative), the length of the assessment (not only during acute attacks, accounting for seasonal variation), and confounders of the disease effect on the productivity/work performance (for instance nutrition, BMI, type of work/profession). These elements should be transparently described and their (missing) values discussed, to determine how much they might have influenced the results. In particular, researchers should provide sufficiently detailed information to enable readers to assess the quality and relevance of the study.

Conclusion

Various studies have examined productivity loss in patient populations having one of the five most prevalent NTDs. While is clear that these diseases reduce productivity, the actual impact depends on the type, severity and duration of the NTD as well as on the setting. Variation in estimated productivity loss between and within diseases is caused by differences in the different definition of productivity loss, research methods and setting. It is therefore important to examine the literature carefully to understand what was actually observed in order to draw conclusions about the generalizability of the studies. Since productivity loss is an important aspect of the burden of diseases, further research on better estimates of the magnitude of the productivity loss caused by NTDs would

enable a more complete picture of their economic burden to individuals, countries, and globally, adding an additional persuasive argument in favor of their control.

This review already contributes to a better perception of the magnitude of the effect of an NTD on people's working and economic situation, and can already offer additional arguments in favor of controlling and eliminating them. However, there is still much room for further research in this field to improve the understanding on NTDs' effects on individuals' productivity loss.

Acknowledgments

We would like to express our gratitude to Tanja Houweling, Margarete Kulik, who contributed to the development of this work with valuable comments and insights.

We are especially grateful to Wichor Bramer, whose work as a biomedical information specialist was crucial in designing the most comprehensive possible syntaxes for our literature reviews.

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Supporting Information

S1 File. Literature Search Syntax

Embase.com

('African trypanosomiasis'/de OR 'Chagas disease'/de OR 'trypanosomatid infection'/exp OR leprosy/exp OR 'Helminthiasis'/de OR 'Ascariasis'/de OR 'Trichuriasis'/de OR 'Hookworm infection'/exp OR 'Schistosomiasis'/exp OR 'Trachoma'/de OR 'Chlamydiasis'/de OR 'Chlamydiaceae infection'/de OR 'Dracunculiasis'/de OR 'Lymphatic filariasis'/exp OR 'Elephantiasis'/de OR 'Filariasis'/de OR 'Onchocerciasis'/de OR (((sleeping OR Hansen* OR neglected OR Robles) NEAR/3 (disease* OR sickness)) OR ((NTD* OR GWD) AND disease*) OR Chagas* OR leishmaniasis OR trypanosomiasis OR ((leishmania OR trypanosom* OR schizotrypanum OR worm* OR hookworm* OR whipworm* OR ancylostoma* OR Euglenoz* OR kinetoplast*) AND (infect* OR infestat* OR disease* OR transmiss*)) OR 'black fever' OR 'kala azar' OR lepros* OR lepra* OR helminth* OR ascari* OR trichuria* OR trichocephal* OR bunostomias* OR schistosom* OR bilharzi* OR 'Katayama fever' OR Trachoma* OR 'Egyptian ophthalmia' OR (chlamydia NEAR/3 conjunctiv*) OR dracuncul* OR draconti* OR filari* OR philar* OR wucher* OR brugia* OR elephantias* OR onchocerc* OR (river NEXT/1 blindness)):ab,ti) AND (productivity/de OR absenteeism/de OR 'job performance'/de OR 'return to work'/de OR 'work capacity'/de OR 'working time'/de OR 'cost of illness'/de OR 'patient transport'/de OR income/de OR salary/de OR 'medical leave'/de OR workload/de OR retirement/de OR employment/exp OR unemployment/de OR (((economic* OR financ* OR cost* OR pharmacoeconomic* OR expend* OR expens*) NEAR/3 (patient* OR individual* OR personal* OR household)) OR fee OR fees OR productivit* OR unproductivit* OR absenteeis* OR presenteeis* OR ((job OR work* OR profession* OR occupation* OR labour) NEAR/3 (perform* OR efficien* OR return* OR back OR capacit* OR abilit* OR disabilit* OR unab* OR limit* OR impair* OR loss OR losing OR restrict* OR reduct* OR input*)) OR (work* NEXT/1 (time OR week* OR day* OR load*)) OR workweek* OR workday* OR ((caregiver* OR illness* OR disease*) NEAR/3 burden) OR (distan* NEAR/3 (hospital* OR facilit* OR doctor* OR physician* OR 'health care')) OR 'patient transport' OR 'health shock' OR income* OR

salary OR salaries OR payment* OR ((medical OR sick) NEXT/1 leave) OR workload* OR 'time off work' OR retire* OR employment* OR employed* OR unemploy* OR 'societal perspective' OR 'human capital' OR 'friction cost' OR 'lost time'):ab,ti) NOT ([animals]/lim NOT [humans]/lim)

Medline (OvidSP)

("Trypanosomiasis, African"/ OR exp "Chagas disease"/ OR exp "Euglenozoa Infections"/ OR exp leprosy/ OR "Helminthiasis"/ OR "Ascariasis"/ OR "Trichuriasis"/ OR exp "Hookworm infection"/ OR exp "Schistosomiasis"/ OR "Trachoma"/ OR "Chlamydiaceae Infections"/ OR "Chlamydia Infections"/ OR "Dracunculiasis"/ OR "Elephantiasis, Filarial"/ OR "Elephantiasis"/ OR "Filariasis"/ OR exp "Onchocerciasis"/ OR (((sleeping OR Hansen* OR neglected OR Robles) ADJ3 (disease* OR sickness)) OR ((NTD* OR GWD) AND disease*) OR Chagas* OR leishmaniasis OR trypanosomiasis OR ((leishmania OR trypanosom* OR schizotrypanum OR worm* OR hookworm* OR whipworm* OR ancylostoma* OR Euglenoz* OR kinetoplast*) AND (infect* OR infestat* OR disease* OR transmiss*)) OR "black fever" OR "kala azar" OR lepros* OR lepra* OR helminth* OR ascari* OR trichuria* OR trichocephal* OR bunostomias* OR schistosom* OR bilharzi* OR "Katayama fever" OR Trachoma* OR "Egyptian ophthalmia" OR (chlamydia ADJ3 conjunctiv*) OR dracuncul* OR draconti* OR filari* OR philar* OR wucher* OR brugia* OR elephantias* OR onchocerc* OR (river ADJ blindness)).ab,ti.) AND ("Psychology, Industrial"/ OR absenteeism/ OR exp "Task Performance and Analysis"/ OR "underachievement"/ OR "return to work"/ OR "Work Capacity Evaluation"/ OR "cost of illness"/ OR exp "Transportation of Patients"/ OR exp income/ OR workload/ OR retirement/ OR employment/ OR unemployment/ OR "Health Services Accessibility"/ OR (((economic* OR financ* OR cost* OR pharmacoeconomic* OR expend* OR expens*) ADJ3 (patient* OR individual* OR personal* OR household)) OR fee OR fees OR productivit* OR unproductivit* OR absenteeis* OR presenteeis* OR ((job OR work* OR profession* OR occupation* OR labour) ADJ3 (perform* OR efficien* OR return* OR back OR capacit* OR abilit* OR disabilit* OR unab* OR limit* OR impair* OR loss OR losing OR restrict* OR reduct* OR input*)) OR (work* ADJ (time OR week* OR day* OR load*)) OR workweek* OR workday* OR ((caregiver* OR illness* OR disease*) ADJ3 burden) OR (distan* ADJ3 (hospital* OR facilit* OR doctor*

OR physician* OR "health care")) OR "patient transport" OR "health shock" OR income* OR salary OR salaries OR payment* OR ((medical OR sick) ADJ leave) OR workload* OR "time off work" OR retire* OR employment* OR employed* OR unemploy* OR "societal perspective" OR "human capital" OR "friction cost" OR "lost time").ab,ti.) NOT (exp animals/ NOT humans/)

Cochrane

((((sleeping OR Hansen* OR neglected OR Robles) NEAR/3 (disease* OR sickness)) OR ((NTD* OR GWD) AND disease*) OR Chagas* OR leishmaniasis OR trypanosomiasis OR ((leishmania OR trypanosom* OR schizotrypanum OR worm* OR hookworm* OR whipworm* OR ancylostoma* OR Euglenoz* OR kinetoplast*) AND (infect* OR infestat* OR disease* OR transmiss*)) OR 'black fever' OR 'kala azar' OR lepros* OR lepra* OR helminth* OR ascari* OR trichuria* OR trichocephal* OR bunostomias* OR schistosom* OR bilharzi* OR 'Katayama fever' OR Trachoma* OR 'Egyptian ophthalmia' OR (chlamydia NEAR/3 conjunctiv*) OR dracuncul* OR draconti* OR filari* OR philar* OR wucher* OR brugia* OR elephantias* OR onchocerc* OR (river NEXT/1 blindness)):ab,ti) AND ((((economic* OR financ* OR cost* OR pharmacoeconomic* OR expend* OR expens*) NEAR/3 (patient* OR individual* OR personal* OR household)) OR fee OR fees OR productivit* OR unproductivit* OR absenteeis* OR presenteeis* OR ((job OR work* OR profession* OR occupation* OR labour) NEAR/3 (perform* OR efficien* OR return* OR back OR capacit* OR abilit* OR disabilit* OR unab* OR limit* OR impair* OR loss OR losing OR restrict* OR reduct* OR input*)) OR (work* NEXT/1 (time OR week* OR day* OR load*)) OR workweek* OR workday* OR ((caregiver* OR illness* OR disease*) NEAR/3 burden) OR (distan* NEAR/3 (hospital* OR facilit* OR doctor* OR physician* OR 'health care')) OR 'patient transport' OR 'health shock' OR income* OR salary OR salaries OR payment* OR ((medical OR sick) NEXT/1 leave) OR workload* OR 'time off work' OR retire* OR employment* OR employed* OR unemploy* OR 'societal perspective' OR 'human capital' OR 'friction cost' OR 'lost time'):ab,ti)

Web-of-science

TS=(((((sleeping OR Hansen* OR neglected OR Robles) NEAR/3 (disease* OR sickness)) OR ((NTD* OR GWD) AND disease*) OR Chagas* OR leishmaniasis OR trypanosomiasis OR ((leishmania OR trypanosom* OR schizotrypanum OR worm* OR hookworm* OR whipworm* OR ancylostoma* OR Euglenoz* OR kinetoplast*) AND (infect* OR infestat* OR disease* OR transmiss*)) OR "black fever" OR "kala azar" OR lepros* OR lepra* OR helminth* OR ascari* OR trichuria* OR trichocephal* OR bunostomias* OR schistosom* OR bilharzi* OR "Katayama fever" OR Trachoma* OR "Egyptian ophthalmia" OR (chlamydia NEAR/3 conjunctiv*) OR dracuncul* OR draconti* OR filari* OR philar* OR wucher* OR brugia* OR elephantias* OR onchocerc* OR (river NEAR/1 blindness))) AND ((((economic* OR financ* OR cost* OR pharmacoeconomic* OR expend* OR expens*) NEAR/3 (patient* OR individual* OR personal* OR household)) OR fee OR fees OR productivit* OR unproductivit* OR absenteeis* OR presenteeis* OR ((job OR work* OR profession* OR occupation* OR labour) NEAR/3 (perform* OR efficien* OR return* OR back OR capacit* OR abilit* OR disabilit* OR unab* OR limit* OR impair* OR loss OR losing OR restrict* OR reduct* OR input*)) OR (work* NEAR/1 (time OR week* OR day* OR load*)) OR workweek* OR workday* OR ((caregiver* OR illness* OR disease*) NEAR/3 burden) OR (distan* NEAR/3 (hospital* OR facilit* OR doctor* OR physician* OR "health care")) OR "patient transport" OR "health shock" OR income* OR salary OR salaries OR payment* OR ((medical OR sick) NEAR/1 leave) OR workload* OR "time off work" OR retire* OR employment* OR employed* OR unemploy* OR "societal perspective" OR "human capital" OR "friction cost" OR "lost time")) AND (human* OR patient*))

Scopus

TITLE-ABS-KEY(((((sleeping OR Hansen* OR neglected OR Robles) W/3 (disease* OR sickness)) OR ((NTD* OR GWD) AND disease*) OR Chagas* OR leishmaniasis OR trypanosomiasis OR ((leishmania OR trypanosom* OR schizotrypanum OR worm* OR hookworm* OR whipworm* OR ancylostoma* OR Euglenoz* OR kinetoplast*) AND (infect* OR infestat* OR disease* OR transmiss*)) OR "black fever" OR "kala azar" OR lepros* OR lepra* OR helminth* OR ascari* OR trichuria* OR trichocephal*

OR bunostomias* OR schistosom* OR bilharzi* OR "Katayama fever" OR Trachoma* OR "Egyptian ophthalmia" OR (chlamydia W/3 conjunctiv*) OR dracuncul* OR draconti* OR filari* OR philar* OR wucher* OR brugia* OR elephantias* OR onchocerc* OR (river W/1 blindness))) AND ((((economic* OR financ* OR cost* OR pharmacoeconomic* OR expend* OR expens*) W/3 (patient* OR individual* OR personal* OR household)) OR fee OR fees OR productivit* OR unproductivit* OR absenteeis* OR presenteeis* OR ((job OR work* OR profession* OR occupation* OR labour) W/3 (perform* OR efficien* OR return* OR back OR capacit* OR abilit* OR disabilit* OR unab* OR limit* OR impair* OR loss OR losing OR restrict* OR reduct* OR input*)) OR (work* W/1 (time OR week* OR day* OR load*)) OR workweek* OR workday* OR ((caregiver* OR illness* OR disease*) W/3 burden) OR (distan* W/3 (hospital* OR facilit* OR doctor* OR physician* OR "health care")) OR "patient transport" OR "health shock" OR income* OR salary OR salaries OR payment* OR ((medical OR sick) W/1 leave) OR workload* OR "time off work" OR retire* OR employment* OR employed* OR unemploy* OR "societal perspective" OR "human capital" OR "friction cost" OR "lost time")) AND (human* OR patient*))

CINAHL

(MH "Trypanosomiasis" OR MH Leishmaniasis OR MH leprosy OR MH "Helminthiasis+" OR MH "Ascariasis" OR MH "Hookworm infections" OR MH "Schistosomiasis+" OR MH "Trachoma+" OR MH "Chlamydiaceae Infections+" OR MH "Chlamydia Infections+" OR MH "Dracunculiasis" OR MH "Elephantiasis, Filarial+" OR MH "Elephantiasis" OR MH "Filariasis" OR MH "Onchocerciasis+" OR (((sleeping OR Hansen* OR neglected OR Robles) N3 (disease* OR sickness)) OR ((NTD* OR GWD) AND disease*) OR Chagas* OR leishmaniasis OR trypanosomiasis OR ((leishmania OR trypanosom* OR schizotrypanum OR worm* OR hookworm* OR whipworm* OR ancylostoma* OR Euglenoz* OR kinetoplast*) AND (infect* OR infestat* OR disease* OR transmiss*)) OR "black fever" OR "kala azar" OR lepros* OR lepra* OR helminth* OR ascari* OR trichuria* OR trichocephal* OR bunostomias* OR schistosom* OR bilharzi* OR "Katayama fever" OR Trachoma* OR "Egyptian ophthalmia" OR (chlamydia N3 conjunctiv*) OR dracuncul* OR draconti* OR filari* OR philar* OR wucher* OR brugia* OR elephantias* OR onchocerc* OR (river N1 blindness))) AND (MH "Psychology, Occupational+" OR MH absenteeism+ OR MH

"Task Performance and Analysis+" OR MH "Job Re-Entry+" OR MH "Job Performance" OR MH "Work Capacity Evaluation+" OR MH "Economic Aspects of Illness+" OR MH "Transportation of Patients+" OR MH income+ OR MH workload+ OR MH retirement+ OR MH employment+ OR MH unemployment+ OR MH "Health Services Accessibility+" OR (((economic* OR financ* OR cost* OR pharmacoeconomic* OR expend* OR expens*) N3 (patient* OR individual* OR personal* OR household)) OR fee OR fees OR productivit* OR unproductivit* OR absenteeis* OR presenteeis* OR ((job OR work* OR profession* OR occupation* OR labour) N3 (perform* OR efficien* OR return* OR back OR capacit* OR abilit* OR disabilit* OR unab* OR limit* OR impair* OR loss OR losing OR restrict* OR reduct* OR input*)) OR (work* N1 (time OR week* OR day* OR load*)) OR workweek* OR workday* OR ((caregiver* OR illness* OR disease*) N3 burden) OR (distan* N3 (hospital* OR facilit* OR doctor* OR physician* OR "health care")) OR "patient transport" OR "health shock" OR income* OR salary OR salaries OR payment* OR ((medical OR sick) N1 leave) OR workload* OR "time off work" OR retire* OR employment* OR employed* OR unemploy* OR "societal perspective" OR "human capital" OR "friction cost" OR "lost time")) NOT (MH animals+ NOT humans+)

PubMed publisher

((((sleeping[tiab] OR Hansen*[tiab] OR neglected[tiab] OR Robles[tiab]) AND (disease*[tiab] OR sickness[tiab])) OR ((NTD*[tiab] OR GWD[tiab]) AND disease*[tiab]) OR Chagas*[tiab] OR leishmaniasis[tiab] OR trypanosomiasis[tiab] OR ((leishmania[tiab] OR trypanosom*[tiab] OR schizotrypanum[tiab] OR worm*[tiab] OR hookworm*[tiab] OR whipworm*[tiab] OR ancylostoma*[tiab] OR Euglenoz*[tiab] OR kinetoplast*[tiab]) AND (infect*[tiab] OR infestat*[tiab] OR disease*[tiab] OR transmiss*[tiab])) OR black fever[tiab] OR kala azar[tiab] OR lepros*[tiab] OR lepra*[tiab] OR helminth*[tiab] OR ascari*[tiab] OR trichuria*[tiab] OR trichocephal*[tiab] OR bunostomias*[tiab] OR schistosom*[tiab] OR bilharzi*[tiab] OR Katayama fever[tiab] OR Trachoma*[tiab] OR Egyptian ophthalmia[tiab] OR (chlamydia[tiab] AND conjunctiv*[tiab]) OR dracuncul*[tiab] OR draconti*[tiab] OR filari*[tiab] OR philar*[tiab] OR wucher*[tiab] OR brugia*[tiab] OR elephantias*[tiab] OR onchocerc*[tiab] OR (river blindness[tiab]))) AND ((((economic*[tiab] OR financ*[tiab] OR cost*[tiab] OR pharmacoeconomic*[tiab] OR expend*[tiab] OR

expens*[tiab]) AND (patient*[tiab] OR individual*[tiab] OR personal*[tiab] OR household[tiab])) OR fee[tiab] OR fees[tiab] OR productivit*[tiab] OR unproductivit*[tiab] OR absenteeis*[tiab] OR presenteeis*[tiab] OR ((job[tiab] OR work*[tiab] OR profession*[tiab] OR occupation*[tiab] OR labour[tiab]) AND (perform*[tiab] OR efficien*[tiab] OR return*[tiab] OR back[tiab] OR capacit*[tiab] OR abilit*[tiab] OR disabilit*[tiab] OR unab*[tiab] OR limit*[tiab] OR impair*[tiab] OR loss[tiab] OR losing[tiab] OR restrict*[tiab] OR reduct*[tiab] OR input*[tiab])) OR working time*[tiab] OR work week*[tiab] OR work day*[tiab] OR work load*[tiab] OR workweek*[tiab] OR workday*[tiab] OR ((caregiver*[tiab] OR illness*[tiab] OR disease*[tiab]) AND burden[tiab]) OR (distan*[tiab] AND (hospital*[tiab] OR facilit*[tiab] OR doctor*[tiab] OR physician*[tiab] OR health care[tiab])) OR patient transport[tiab] OR health shock[tiab] OR income*[tiab] OR salary[tiab] OR salaries[tiab] OR payment*[tiab] OR medical leave[tiab] OR sick leave[tiab] OR workload*[tiab] OR time off work[tiab] OR retire*[tiab] OR employment*[tiab] OR employed*[tiab] OR unemploy*[tiab] OR societal perspective[tiab] OR human capital[tiab] OR friction cost[tiab] OR lost time[tiab])) AND publisher[sb]

Google Scholar

(trypanosomiasis | Chagas | leprosy | Helminthiasis | Ascariasis | Trichuriasis | Hookworm | Schistosomiasis | Trachoma | Chlamydiasis | Dracunculiasis | filariasis | Onchocerciasis | "neglected disease") "(individual | personal | household)
(cost | costs | economic | expenses | financial)"

Popline / Lilacs / Scielo

(trypanosomiasis OR Chagas OR leprosy OR Helminthiasis OR Ascariasis OR Trichuriasis OR Hookworm OR Schistosomiasis OR Trachoma OR Chlamydiasis OR Dracunculiasis OR filariasis OR Onchocerciasis OR "neglected disease") (productivity OR absenteeism OR "sick leave" OR unemployment OR "individual costs" OR "personal costs")

Google

(trypanosomiasis | Chagas | leprosy | Helminthiasis | Ascariasis | Trichuriasis | Hookworm | Schistosomiasis | Trachoma | Chlamydiasis | Dracunculiasis | filariasis | Onchocerciasis | "n

eglected disease") "(individual|personal|household) (cost|costs|economic|expenses|financial)" filetype:PDF

https://www.google.com.br/search?output=search&sclient=psy-ab&q=(trypanosomiasis%7CChagas%7Cleprosy%7CHelminthiasis%7CAscariasis%7CTrichuriasis%7CHookworm%7CSchistosomiasis%7CTrachoma%7CChlamydiasis%7CDracunculiasis%7Cfilariasis%7COnchocerciasis%7C%22neglected+disease%22)+%22(individual%7Cpersonal%7Chousehold)+(cost%7Ccosts%7Ceconomic%7Cexpenses%7Cfinancial)%22&oq=(trypanosomiasis%7CChagas%7Cleprosy%7CHelminthiasis%7CAscariasis%7CTrichuriasis%7CHookworm%7CSchistosomiasis%7CTrachoma%7CChlamydiasis%7CDracunculiasis%7Cfilariasis%7COnchocerciasis%7C%22neglected+disease%22)+%22(individual%7Cpersonal%7Chousehold)+(cost%7Ccosts%7Ceconomic%7Cexpenses%7Cfinancial)%22&gs_l=hp.3...27394.27394.0.27768.1.1.0.0.0.0.0.0..0.0.ernk_timecombined...1...1.1.32.psy-ab..1.0.0.lh0asBa9CXo&pbx=1&bav=on.2,or.r_qf.&bvm=bv.56988011,d.cWc,pv.xjs.s.en_US.dtklyhSMdi0.O&biw=1280&bih=671&dpr=1#newwindow=1&q=(trypanosomiasis%7CChagas%7Cleprosy%7CHelminthiasis%7CAscariasis%7CTrichuriasis%7CHookworm%7CSchistosomiasis%7CTrachoma%7CChlamydiasis%7CDracunculiasis%7Cfilariasis%7COnchocerciasis%7C%22neglected+disease%22)+%22(individual%7Cpersonal%7Chousehold)+(cost%7Ccosts%7Ceconomic%7Cexpenses%7Cfinancial)%22+filetype%3APDF

S2 File. Grey Literature Search

The publications of the following organizations were searched: BMGF, Carter Center, CBM International (Christian Blind Mission), CDC Centers for Disease Control and Prevention, Centre for Neglected Tropical Diseases (Liverpool School of Tropical Medicine), Drug for Neglected Diseases Initiative, Global Alliance to Eliminate Lymphatic Filariasis, Global Network - NTD (Sabin Vaccine Institute), Hellen Keller International, Hollows, IDA Foundation, IDB - Interamerican Development Bank, IMA World Health, IMF, Imperial College London, International Trachoma Initiative, Lepra, Liverpool Associates in Tropical Health, PLOS NTD x economic, Research Triangle Institute – RTI, Sightsavers, The Task Force for Global Health, UN, USAID, WHO, World Bank, World Vision.

S1 Table. List of disease sequelae according to the 2010 GBD study

Disease	Sequelae GBD	Sequalae
Onchocerciasis	Skin disease due to Onchocerciasis	Mild skin disease due to Onchocerciasis
		Moderate skin disease due to Onchocerciasis
	Vision loss due to Onchocerciasis	Blindness due to Onchocerciasis
		Low vision due to Onchocerciasis
		Visual field impairment due to Onchocerciasis
		Visual field blindness due to Onchocerciasis
Lymphatic Filariasis	idem	Lymphedema
	idem	Hydrocele due to lymphatic filariasis
STH - Ascariasis	idem	Ascariasis infestation
	idem	Severe wasting due to ascariasis
	idem	Mild abdominopelvic problems due to ascariasis
STH -Trichuriasis	idem	Trichuriasis infestation
	idem	Severe wasting due to trichuriasis
	idem	Mild abdominopelvic problems due to trichuriasis
STH - Hookworm disease	idem	Hookworm infestation
	idem	Severe wasting due to hookworm disease
	idem	Mild abdominopelvic problems due to hookworm disease
	Anemia due to hookworm disease	Mild anemia due to hookworm disease
		Moderate anemia due to hookworm disease
		Severe anemia due to hookworm disease

table continues

Schistosomiasis	idem	Schistosomiasis
	idem	Mild diarrhea due to Schistosomiasis
	Anemia due to Schistosomiasis	Mild anemia due to Schistosomiasis
		Moderate anemia due to Schistosomiasis
		Severe anemia due to Schistosomiasis
	idem	Hepatomegaly due to Schistosomiasis
	idem	Haematemesis due to Schistosomiasis
	idem	Ascites due to Schistosomiasis
	idem	Dysuria due to Schistosomiasis
	idem	Bladder pathology due to Schistosomiasis
	idem	Hydronephrosis due to Schistosomiasis
Trachoma	Trachoma	Low vision due to trachoma
		Blindness due to trachoma
HAT	idem	African trypanosomiasis
Chagas disease	idem	Acute chagas disease
	idem	Chronic heart disease due to chagas disease
	idem	Chronic digestive disease due to chagas disease
	idem	Heart failure due to chagas disease
Leishmaniasis	idem	Visceral leishmaniasis
	idem	Cutaneous leishmaniasis
Leprosy	idem	Disfigurement due to leprosy

table continues

S2 Table. Risk of bias assessment table

Author	Year	Study design	Selection bias	Performance bias	Attrition bias	Detection bias	Reporting bias	Summary risk	Relevance[1]
Lymphatic filariasis									
Babu	2002	OBS	Unclear	Low	Low	High	Unclear	High	High
Babu	2003	OBS	High	Low	Low	High	Low	High	High
Babu	2006	OBS	High	Low	Low	High	Low	High	High
Budge	2013	OBS	Unclear	Low	Low	Low	Low	Low	Low
Chandrasena	2004	OBS	High	Low	Low	High	Low	High	Low
Gasarasi	2000	OBS	Unclear	Low	Low	High	Low	High	Low
Gyapong	1996	OBS	High	Unclear	Low	High	Unclear	High	Low
Ramaiah	2000	OBS	High	Low	High	High	Low	High	High
Ramaiah	1999	OBS	High	Low	Low	High	Low	High	High
Ramaiah	1998	OBS	High	Low	Unclear	High	Low	High	High
Ramaiah	1997	OBS	High	Unclear	Unclear	High	High	High	Low
Sabesan	1992	OBS	High	Unclear	High	High	Unclear	High	High
Onchocerciasis									
Benton	1990	CBA/model	Low	Unclear	Unclear	High	Low	High	Low

table continues

Evans	1995	Survey	Low	Low	Unclear	Unclear	Low	Unclear	Low
Kim	1995	CBA/model	Low	Low	Unclear	High	Low	High	Low
Kim	1997	OBS	High	Low	Low	Unclear	Unclear	Unclear	High
Okeibunor	2011	OBS	Low	Low	Unclear	Low	Low	Low	Low
Oladepo	1993	OBS	Low	Unclear	Unclear	Unclear	Low	Unclear	High
Thomson	1971	OBS	High	Unclear	High	High	High	High	High
Wogu	2008	Survey	Low	Unclear	Low	Unclear	Low	Unclear	Low
Workneh	1993	OBS	High	Low	Unclear	Unclear	Low	Unclear	High
World Bank	1997	OBS	High	Unclear	Unclear	Unclear	Unclear	Unclear	High
Schistosomiasis									
Audibert	**1998**	OBS	Low	Low	Low	Unclear	High	Unclear	High
Barbosa	**1981**	OBS	Low	Low	Low	High	High	High	High
Blas	2006	OBS	High	Unclear	High	Unclear	Unclear	High	Low
Fenwick	1972	OBS	High	Unclear	High	Unclear	Low	High	High
Kamel	2002	OBS	High	Unclear	High	High	Unclear	High	High
Leshem	2008	OBS	Low	Low	Low	Low	Low	Low	Low
Leslie	2011	CEA	High	Unclear	High	High	High	High	Low

table continues

Umeh	2002	OBS	Low	Low	Unclear	low	low	Low	Low
Wright	1972	Economic impact	High	Unclear	Unclear	High	Low	High	Low
Wu	2002	OBS	Unclear	Low	Unclear	Low	Low	Low	High
Soil-transmitted helminths									
Basta	1979	OBS	High	Unclear	High	Unclear	High	High	High
Gilgen	2001	RCT	Unclear	Unclear	Unclear	Unclear	High	Unclear	High
Selvaratnam	2003	OBS	Unclear	Low	Low	Unclear	Low	Low	High
Wolgemuth	1982	OBS	Unclear	High	High	High	Unclear	High	High
Casey	2011	CEA	High	Low	High	High	High	High	Low
Tanner	2013	OBS	High	Unclear	Unclear	High	Low	High	High
Trachoma									
Frick	2001	Model	Low	Low	Unclear	High	Low	High	Low
Frick	2003a	Model	Unclear	Unclear	Unclear	High	Low	High	Low
Frick	2003b	Model	Unclear	High	Unclear	High	Low	Unclear	Low

1. to which extent it measured productivity loss caused by NTD quantitatively

CBA - Cost-benefit analysis
CEA – Cost-effectiveness analysis
OBS – Observational study
RCT – Randomized controlled trial

S3 Table. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Pages 3 and 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. 'There is no review protocol registered.'	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. 'Since the number of relevant publications was expected to be small, no restrictions were made regarding populations (participants), interventions, comparisons, outcomes, study design, or length of follow-up.'	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. The list of selected articles for each disease was sent to disease experts identified in the literature and from institutions	4 and 5

table continues

		researching/combating NTDs, to check if the selection was comprehensive.'	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. (all search strategies are fully presented in the Supporting Information)	S1.Literature Search Syntax
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). 'Articles that did not contain any information on productivity, or only qualitative information on productivity loss were excluded, as well as articles that investigated productivity loss in children.(…) Articles that could not be retrieved through their respective journals, contacting libraries, or after contacting the authors were classified as 'not available' and excluded from the selection.'	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. 'Since the outcome of interest was productivity loss, various study designs were expected. The studies were therefore critically appraised regarding general criteria of selection, performance, attrition, detection, and reporting biases. Each article was given a rating for low, high or unclear risk of bias for each criterion and a summary rating. (1,2) We added an extra criterion to assess to which extent the study outcomes defined as productivity loss were relevant when describing quantitative work productivity loss in adults due to an NTD. This 'relevance' criterion was also rated as low or high.'	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). 'No summary measure was chosen, the results were presented separately per disease and per study, descriptively (results were not statistically combined).'	5

table continues

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis. (see item 13)	5

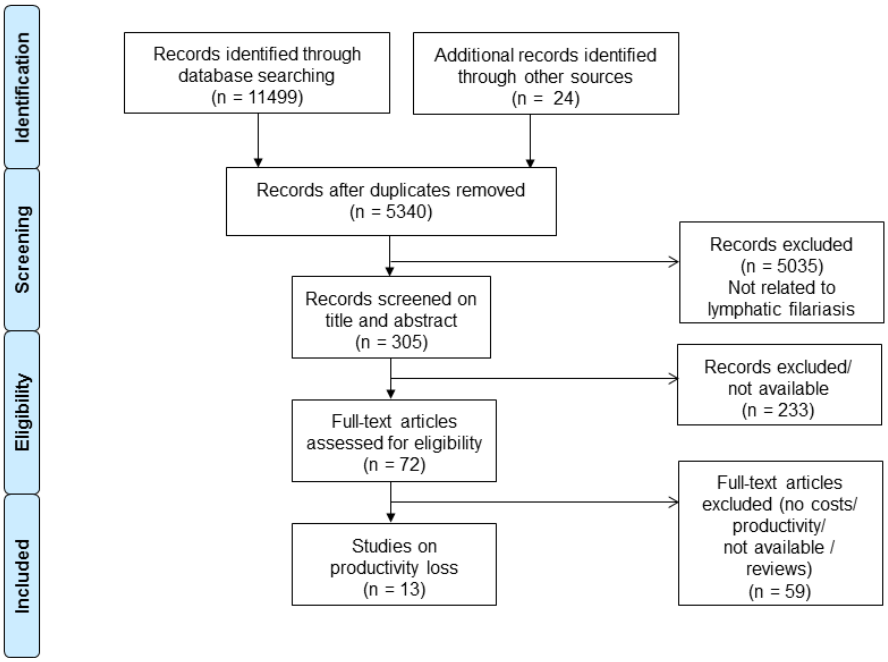
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not applicable
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5 to 18 (flow diagrams per disease shown in Supporting Information)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	18 and Supporting Information 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable

table continues

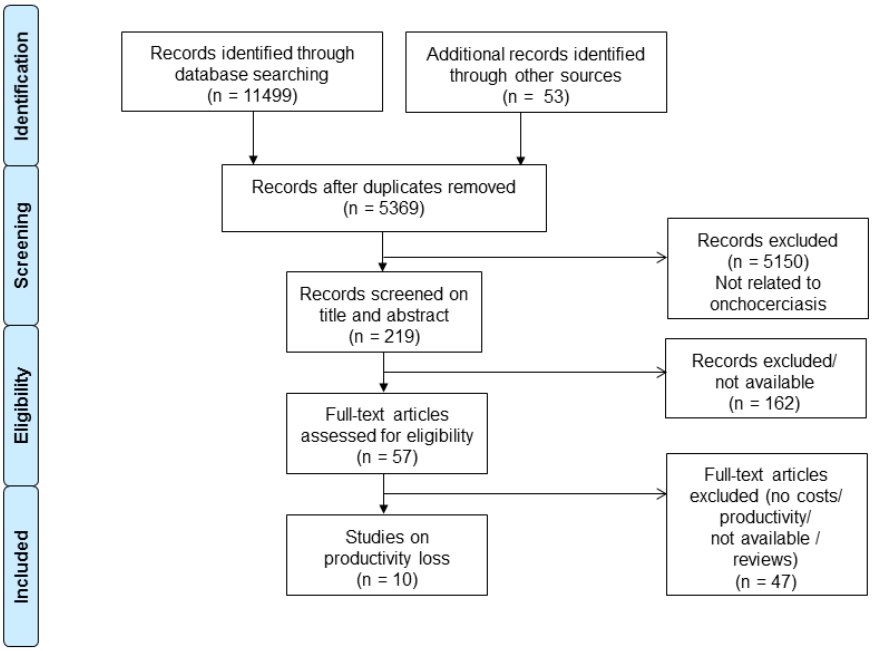
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Not applicable
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18 and 19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19 to 21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Described during submission

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

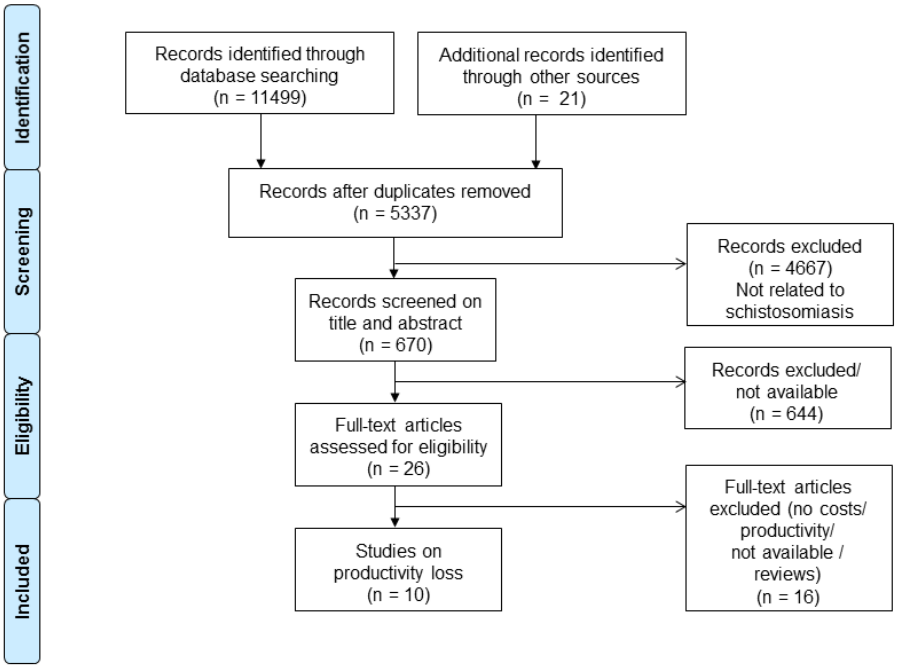
S1 Fig. Flowchart describing the literature search for lymphatic filariasis



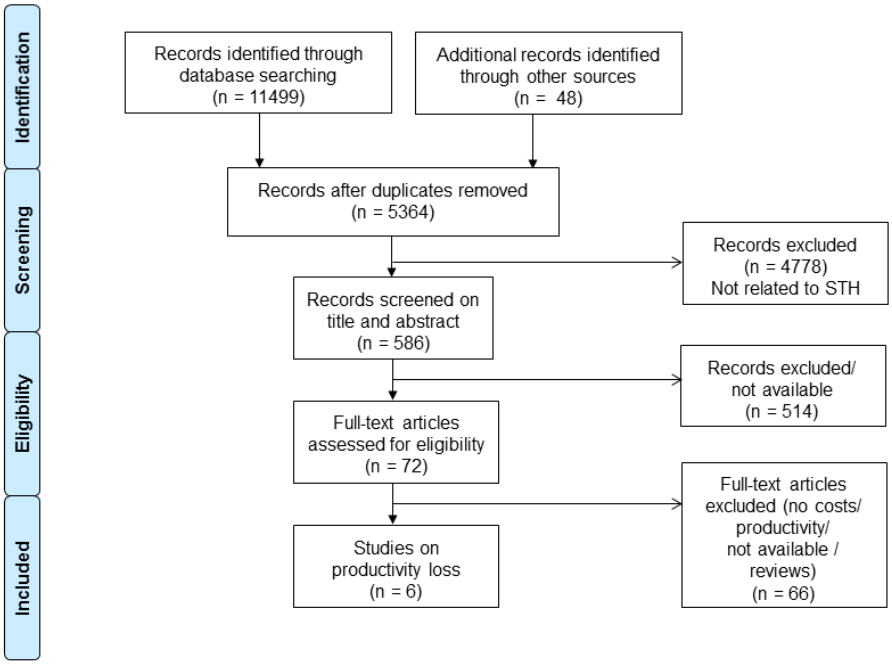
S2 Fig. Flowchart describing the literature search for onchocerciasis



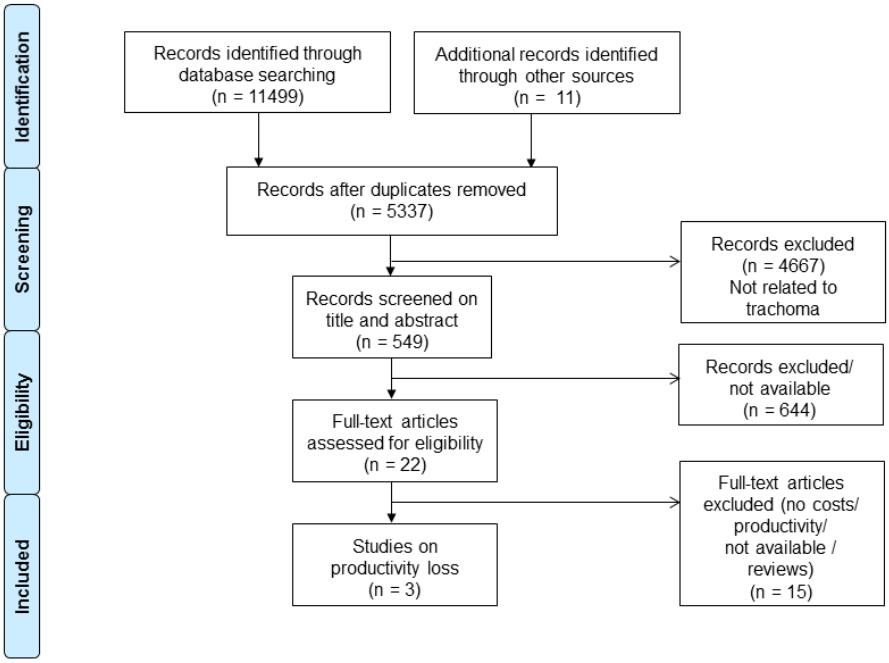
S3 Fig. Flowchart describing the literature search for schistosomiasis



S4 Fig. Flowchart describing the literature search for soil-transmitted helminths



S5 Fig. Flowchart describing the literature search for trachoma



Chapter 3

The Socioeconomic Benefit to Individuals of Achieving the 2020 Targets for Five Preventive Chemotherapy Neglected Tropical Diseases

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2017

PLoS Neglected Tropical Diseases 11(1): e0005289.

https://doi.org/10.1371/journal.pntd.0005289

Abstract

Background

Lymphatic filariasis (LF), onchocerciasis, schistosomiasis, soil-transmitted helminths (STH) and trachoma represent the five most prevalent neglected tropical diseases (NTDs). They can be controlled or eliminated by means of safe and cost-effective interventions delivered through programs of Mass Drug Administration (MDA)—also named Preventive Chemotherapy (PCT). The WHO defined targets for NTD control/elimination by 2020, reinforced by the 2012 London Declaration, which, if achieved, would result in dramatic health gains. We estimated the potential economic benefit of achieving these targets, focusing specifically on productivity and out-of-pocket payments.

Methods

Productivity loss was calculated by combining disease frequency with productivity loss from the disease, from the perspective of affected individuals. Productivity gain was calculated by deducting the total loss expected in the target achievement scenario from the loss in a counterfactual scenario where it was assumed the pre-intervention situation in 1990 regarding NTDs would continue unabated until 2030. Economic benefits from out-of-pocket payments (OPPs) were calculated similarly. Benefits are reported in 2005 US$ (purchasing power parity-adjusted and discounted at 3% per annum from 2010). Sensitivity analyses were used to assess the influence of changes in input parameters.

Results

The economic benefit from productivity gain was estimated to be I$251 billion in 2011–2020 and I$313 billion in 2021–2030, considerably greater than the total OPPs averted of I$0.72 billion and I$0.96 billion in the same periods. The net benefit is expected to be US$ 27.4 and US$ 42.8 for every dollar invested during the same periods. Impact varies between NTDs and regions, since it is determined by disease prevalence and extent of disease-related productivity loss.

Conclusion

Achieving the PCT-NTD targets for 2020 will yield significant economic benefits to affected individuals. Despite large uncertainty, these benefits far exceed the investment required by governments and their development partners within all reasonable scenarios.

Given the concentration of the NTDs among the poorest households, these investments represent good value for money in efforts to share the world's prosperity and reduce inequity.

Author Summary

The five most prevalent neglected tropical diseases (NTDs) are lymphatic filariasis (LF), onchocerciasis, schistosomiasis, soil-transmitted helminths (STH) and trachoma. They can be controlled or eliminated by means of safe and cost-effective interventions delivered through programs of Mass Drug Administration (MDA) - also named Preventive Chemotherapy (PCT).The WHO defined targets for NTD control/elimination by 2020, reinforced by the 2012 London Declaration, which, if achieved, would result in benefits not limited to health gains. We estimated the potential economic benefit of achieving these targets for these NTDs. Economic benefit was calculated by combining the estimated disease frequency with productivity loss resulting from the disease, from the perspective of a person affected by each of the NTDs. The same was done for the healthcare costs paid by the affected individuals. The economic benefit to individuals from productivity gain was estimated to be I$ 251 billion in 2011-2020 (before achieving the targets) and I$ 313 billion in 2021-2030 (after achieving the targets). The estimated total healthcare costs averted are substantial though lower than productivity costs: $0.72 billion in 2011-2020, $0.96 billion in 2021-2030. This would mean a return of US$ 27.4 for each dollar spent between 2015-2020 to reach the targets and US$ 42.8 between 2021-2030. The economic impact varies between NTDs and regions, since it is determined by disease prevalence and the degree of productivity loss caused by the disease.

Introduction

Neglected tropical diseases (NTDs) are a group of debilitating infectious diseases that can result in death, but are more often associated with chronic, disabling and disfiguring morbidity [1]. Most of them affect forgotten people, with little political or financial capital, living in slums or in rural areas (predominantly in low – and middle-income countries), away from cities where policymakers live and work. [2-5]

Besides having devastating consequences for one's health, NTDs also have an important effect on the economic welfare of patients and their families, imposing additional economic difficulties for populations struggling to live below the poverty line of 1US$ a day [2-4,7-11,59]. In this sense, NTDs are an additional obstacle to sustainable development, which can be achieved only in the absence of high prevalence of debilitating communicable and non-communicable diseases. [14]

NTD control or elimination targets for the year 2020 were set out in the WHO Roadmap of 2011 and endorsed by partners in the London Declaration of 2012 [15-17]. Among these 10 NTDs, the most prevalent globally are: onchocerciasis, lymphatic filariasis (LF), schistosomiasis, soil-transmitted helminths (STH), and trachoma. [9,18,19] Even though they can be controlled or eliminated by means of safe and cost-effective interventions delivered through programs of Mass Drug Administration (MDA) - also named Preventive Chemotherapy (PCT) - NTD programs still face many obstacles [7]. Some of them are closely related to the degree of awareness that policymakers and the global health communities have of the health and socioeconomic importance of NTDs [13]. To bring more light onto this issue, de Vlas et al. estimated the health gains of achieving the 2020 targets. [16,17]. Their findings suggest that roughly 300 million disability-adjusted life-years (DALYs) can be averted for the five PCT-NTDs over the period 2010-2030. [20]

An improved understanding of the economic impact that NTDs have on individuals, households, and countries would help in informing the scale-up of effective and equitable interventions to address them [59]. Therefore, robust and clear estimates of the cost of NTDs to patients, households and broader societal costs are needed. Combining these cost estimates with the already existing estimates of disease burden and comparing the

result to the estimated cost of intervention could bolster the case for increased investment.

The aim of the study described in this article was to estimate the socioeconomic benefit (to individuals) of controlling or eliminating PCT-NTDs. More specifically, we examined the productivity loss and out-of-pocket payments (OPPs) that can be prevented globally, assuming the 2020 WHO targets for these diseases will be met.

Methods

Study design

The estimate of economic benefit was based on the health benefit calculated by De Vlas et al.[20] Briefly, De Vlas et al used 2010 GBD data of prevalent cases of the NTDs included in the London Declaration for the years 1990 and 2010 as the starting point in their calculations, with estimates for other years obtained by interpolating between 1990 and 2010, and further extrapolated until 2030, under the assumption that the 2020 WHO Roadmap targets were met and sustained beyond 2020. They first created a "counterfactual scenario", which assumed that the epidemiological situation from 1990 regarding NTDs would continue unabated and that the number of cases would increase as a function of overall population growth. They estimated the numbers of disease cases that would be expected if the 2020 targets mentioned by the 2012 London Declaration and described by the WHO were to be achieved (target achievement scenario). Disease cases averted by achieving the targets were calculated for each GBD disease manifestation (or "sequela"), country, sex and age group. For a complete list of the GBD sequela per NTD, refer to Salomon et al (2012).[21] Guinea worm (dracunculiasis) was not included in this study, since it was targeted to eradication in 2015. [22]

De Vlas et al. used a time period of 2011-2030 that extended beyond 2020 since some of the benefits of achieving the targets will only arise after that year. That is, the benefits of preventing permanent sequelae like blindness will appear much later than the benefits of better treatment of other sequelae. [20]

General Approach to Estimate the Economic Benefits

This economic study builds on the approach used by de Vlas et al. to assess the health benefits of achieving the 2020 targets. Namely, for each GBD disease sequela a comparison is made between the counterfactual scenario and the target achievement scenario, calculating the benefit for the period between 2011 and 2030 (ten years before and then years after the target achievement) instead of the entire period from 1990 to 2030. The economic benefit was calculated by subtracting the costs calculated for the target achievement scenario from the costs of the counterfactual scenario. [20]

All economic benefit estimates were expressed in international dollars (constant 2005 I$), a hypothetical unit of currency that has the same purchasing power as the U.S. dollar has in the United States at a given point in time (in this case, 2005). It is calculated using purchasing power parity (PPP) exchange rate, defined as the amount of a country's currency required to buy the same amounts of goods and services in the domestic market as U.S. dollar would buy in the United States. It is regarded as a more valid measure to compare estimates between countries. [23,24]

Economic benefits from productivity gain and out-of-pocket payments were reported separately, as recommended by the WHO. Intangible costs and leisure time were not included.[12,67,68] Discounting at 3% was applied using the base year of 2010. All calculations were performed using Microsoft Excel (version 2010). [28]

Time frame

The estimated economic benefits are presented for 2011-2020 and 2021-2030 separately to show how much of the benefits can be expected before the 2020 targets are met compared to after 2020.

Perspective

We used a microeconomic perspective to analyze the economic costs per GBD sequela, sex and country. Only the most important costs that individuals in low- and middle-income countries incur during illness were included in the analysis, namely indirect costs due to lost productivity and the direct costs of obtaining health goods and services [25].

Countries

The countries included in the analysis were the ones with disease cases for each sequela according to the GBD study. The list of countries differs according to disease and sequela. The list of countries per disease can be accessed by using the open-access web-based dissemination tool available here: https://erasmusmcmgz.shinyapps.io/dissemination/. [20]

Productivity loss

The annual productivity loss per NTD was calculated using the formula shown below (Fig.1). The costs per country and NTD were calculated independently for both counterfactual and target achievement scenarios. The economic benefit was obtained by comparing the target achievement scenario to the counterfactual scenario. Global and region-specific benefits were estimated by adding up the benefits of all countries or the countries within a specific region.

Figure 1. General formula for calculating productivity loss

$$TPC_{cNTD} = \sum_{y} \frac{\left(PS1_{c\,y} * PLs1_{c\,y} * I_{c\,y}\right) + \left(PS2_{c\,y} * PLs2_{c\,y} * I_{c\,y}\right) + \cdots}{(1+D)^{t}}$$

TPC	=	Total productivity costs (in US$ 2005)
NTD	=	Neglected Tropical Disease
c	=	Country
y	=	Year
PS1	=	Number of prevalent cases aged 15+ years with sequela 1
PS2	=	Number of prevalent cases aged 15+ years with sequela 2
PLs1	=	% productivity loss related to sequela 1 of NTD
PLs2	=	% productivity loss related to sequela 2 of NTD
I	=	GDP per capita in the lowest quintile
D	=	Annual discount rate (%)
t	=	Time (years beyond 2010)

Prevalent cases

The number of prevalent cases refers to the average number of cases per country, age group, and sex with a specific disease sequela in any particular moment in a year. The numbers of disease cases of each year in the period 2011-2030 for both the counterfactual and the target achievement scenarios were calculated by de Vlas et al. and used in our analyses [20].

Only individuals older than 15 years were included in the calculation of productivity loss. The lower age limit of 15 was chosen since it is often used by the International Labour Organization (ILO) [29], even though we know that a significant percentage of children aged 5-14 years works in developing countries (sometimes as high as 27%), especially in rural settings. [30,31] All cases older than 65 years were included in the calculations, assuming they would continue to work after this age, since only a small proportion of people effectively receive a pension in developing countries (median: 7%); people living below the US$ 2/day poverty line are even considered not to have any effective basic social protection. [32,33].

Productivity loss associated with disease

Productivity loss refers to the amount of time spent on economic activity that is lost due to a specific disease sequela. Economic activity includes time spent in the formal labor market but also time spent on self-sufficient farming, time spent on domestic chores or other unpaid activities. [34,35]

Estimates of the productive time lost due to a specific NTD sequela were not easily obtained, since published literature of population-based studies on this topic is scarce. [36] To address this issue, previous studies have used disability weights as a proxy for extent of productivity loss, assuming a linear relationship between productivity and the disability weight [37,38]. However, there are many reasons to believe that disability weights are not appropriate indicators for productivity loss, since a variety of different health states have almost the same disability weights even though they may result in differing degrees of productivity loss. For example, in the most recent set of disability weights (GBD 2010), blindness has a weight of 0.195, severe anemia has a weight of 0.164 and disfigurement (level 2 with itch or pain) has a weight of (0.187). [21] It seems rather implausible that these various health states lead to the same amount of productivity

loss. Perhaps more importantly, the latest published disability weights from 2010 sometimes differ dramatically from previous values. For instance, the most recent weight for blindness is 0.195, much lower than the previous weight of 0.60 [39].

We therefore performed a comprehensive search of the literature to determine the most appropriate estimates of productivity loss related to NTDs. [36] Results were translated into annual proportions of productivity loss per sequela, assuming 300 working days per year [40]. If several estimates of productivity loss were identified in the literature review, we used the lowest value found as the base-case value to keep the estimates conservative. One exception was lymphatic filariasis, where we chose to use the values reported by an earlier review [40]. If no estimates of productivity losses were available in the literature, assumptions were made based on the productivity loss of similar sequelae caused by other diseases.

Table 1 shows the percentage of annual productivity loss per sequela, which ranges from 0% for sequela like mild onchocerciasis skin disease to 79% for blindness. The table shows additional information for onchocerciasis and trachoma since the GBD study only reported the number of cases per disease sequela and not the number in each level of severity. For example, for vision loss due to onchocerciasis, only the numbers of cases with vision loss were reported and not the numbers with blindness, severe vision loss and moderate vision loss. Therefore, in order to calculate an overall estimate of productivity loss, we had to combine our estimates of productivity loss per severity level with the estimated frequencies of the different severity levels (i.e., the 'case mix'). Table 1 therefore shows the productivity loss according to severity and case mix regarding severity for onchocerciasis and trachoma. The minimum and maximum estimates of productivity loss are shown in the sensitivity analysis section.

Productivity losses associated with long-term cognitive impairment due to helminthic infections and productivity compensation mechanisms were not calculated in our analyses. This is discussed later in the Discussion section.

Income

In this study, income refers to annual income losses to patients as a consequence of NTD sequela. As in earlier economic impact studies of NTDs, productivity loss was calculated

by using the human capital approach, which uses income to place monetary terms on healthy time [25,40,41]. The human capital approach has been criticized for its use in the estimation of productivity losses experienced by society as a whole, in part because it assumes full employment (i.e. that there are no unemployed individuals to replace the sick ones). [25] We limit our analysis to the productivity loss of affected individuals.

Estimating the income of individuals with NTDs is difficult, since these diseases are mainly prevalent in rural areas where self-sufficient farming is one of the most – and sometimes the most - important sources of revenue [9]. Previous economic analyses of NTDs have applied different methods to estimate the rural wage, including use of GDP per capita, average agricultural value added per worker and the lowest wage estimate from different predefined wage sources [37,38,40].

We compared the GDP per capita of the lowest quintile with the minimum nominal annual wage (both 2010 PPP), for the endemic countries with the highest number of prevalent cases (which would have the highest impact on the final results), showing that the minimum wage would still be higher. Since NTDs are generally known as diseases of the poorest, we decided to use the GDP per capita of the lowest income quintile for the calculations of this study, and use only one data source for income instead of several (this parameter was varied with the lowest decile and the second lowest quintile in the sensitivity analysis). The World Bank Development Indicators website provided the data needed to calculate the average GDP per capita in the different quintiles since this website reports the GDP per capita (PPP) in international dollars of the year 2005 and income shares of the population in the different quintiles [42]. In the rare cases where information about GDP per capita or income shares of the year 2010 for a country was missing, we used data from preceding years; if no information from any year was available, we used the average of surrounding countries. In order to keep estimates conservative, we assumed that income and income shares remained constant over time, and we did not adjust income for labor force participation or age-related income patterns.

Table 1. Estimates of productivity loss used in the calculations of economic benefit

Disease & Sequela	Severity	Base case Annual productivity loss	Sources	Case[1] Mix	Sources	Remarks	Weighted productivity loss per sequela
Lymphatic filariasis							
Lymphedema		16%	[43-50]	N.A.			N.A.
Hydrocele		15%	[44,47,49,51,52]	N.A.			N.A.
Onchocerciasis							
Vision loss	Blindness	79%	[53]	29%	4	5	49.8%
	Severe	38%	Idem [54]	12%	4	5	49.8%
	Moderate	38%	Idem [54]	59%	4	5	49.8%
Skin disease	Moderate	10%	[55]	32%	4		3.2%
	Mild	0%	Assumption	68%	4	6	3.2%
Schistosomiasis							
Acute episode		0%	[21]	N.A.		2	N.A.
Mild diarrhea		3%	[54]	N.A.			N.A.
Hepatomegaly		3%	Idem [54]	N.A.		7	N.A.
Dysuria		1.6%	[56]	N.A.		7	N.A.
Bladder pathology		1.6%	Idem [54]	N.A.		7	N.A.
Hydronephrosis		1.6%	Idem [54]	N.A.		7	N.A.
Hematemesis		100%	[54,57,58]	N.A.			N.A.
Ascites		100%	Idem [54]	N.A.			N.A.

table continues

Anemia		7%	[59-65]	N.A.		[3]	N.A.
Soil-transmitted helminths							
Ascariasis	Infestation	6%	[64,65]	N.A.		[6]	N.A.
Trichuriasis	Infestation	6%	Idem	N.A.		[6]	N.A.
Hookworm	Infestation	6%	Idem	N.A.		[6]	N.A.
Hookworm	Anemia	6%	[59-65]	N.A.		[6]	N.A.
Ascariasis	Mild abdominopelvic problems	0%	[21]	N.A.		[2]	N.A.
Trichuriasis	Mild abdominopelvic problems	0%	Idem	N.A.		[2]	N.A.
Hookworm	Mild abdominopelvic problems	0%	Idem	N.A.		[2]	N.A.
Ascariasis	Severe wasting	0%	[21]	N.A.		[8]	N.A.
Trichuriasis	Severe wasting	0%	Idem	N.A.		[8]	N.A.
Hookworm	Severe wasting	0%	Idem	N.A.		[8]	N.A.
Trachoma							
Vision Loss	Blindness	79%	[53]	35%	[4]	[9]	32%
	Severe Visual Impairment	38%	[53]	10%	[4]	[9]	32%
	Moderate Visual Impairment	0%	Assumption	55%	[4]	[9]	32%

table continues

1. Case mix represents the distribution of the different degrees of severity within a disease sequela. Since the prevalent case estimates were only available per disease sequela and not severity, productivity loss values of the different degrees of severity were combined with the case mix to calculate a frequency-weighted value of productivity loss for that sequela. For sequelae with only one level of severity, the productivity loss value was applied to all prevalent cases.

2. The lay description used in the GBD study to describe some sequelae indicated that the sequela "did not interfere / did not impose difficulties with daily activities", therefore productivity loss assumed 0%.

3. Even though productivity loss due to schistosomiasis and STH-related anemia was based on the same studies, the actual degree of productivity loss differed between the diseases. The GBD documentation describes a higher mean hemoglobin loss due to schistosomiasis (2.8 g/L) than the loss due to hookworm (2.08 g/L). Since the literature showed a linear relationship between hemoglobin loss and productivity loss, this proportion was kept in the calculations of the productivity loss due to schistosomiasis and hookworm anemia (higher percentage of productivity loss due to schistosomiasis anemia than to hookworm anemia).[48,49]

4. Case-mix values from the GBD study documentation and from the assumptions used by de Vlas et al.[62]

5. Evans et al. made no distinction between moderate and severe visual impairment. We assumed that Evans considered the productivity loss from low vision a weighted average of moderate and severe impairment and that the distribution of moderately and severely impaired persons was equal to the distribution used in the GBD study.

6. To ensure a conservative estimate.

7. According to the GBD study, the sequela "did not interfere/did not impose difficulties with daily activities". Since clinical experience and literature have shown that they interfere with daily activities, productivity loss was not assumed to be 0%.

8. GBD data reported only cases amongst children younger than 5 years, which fell outside the scope of our definition of economically active population of 15+ years.

9. Productivity loss estimates were based on the study of onchocerciasis by Evans et al. since no studies of trachoma-related productivity loss were found and since the GBD descriptions of visual impairment from onchocerciasis and trachoma are similar. Average productivity loss from trachoma differed from that of onchocerciasis because of differences in case mix regarding severity. 0% productivity loss was attributed to moderate visual impairment caused by trachoma to ensure a conservative estimate.

Out-of-Pocket Payments

We used one general formula to estimate the total out-of-pocket payments (OPPs) (Figure 2). This formula was applied for each country and NTD separately, for both the counterfactual and the target achievement scenarios (Fig.2). The economic benefit was calculated by taking the difference between the results using the target achievement scenario and the results using the counterfactual scenario. Global and region-specific benefits were estimated by adding up the benefits of all countries or the countries within a specific region. In contrast to the estimation of the productivity loss that was calculated for individuals older than 15 years, OPPs were calculated for all prevalent cases, including children, since these costs are unrelated to the ability to work.

Figure 2. General formula for calculating out-of-pocket payments

$$TDC_{cNTD} = \sum_{y} \frac{\left(PS1_{c\,y} * DCS1_{c\,y} * H_{c\,y}\right) + \left(PS2_{c\,y} * DCS2_{c\,y} * H_{c\,y}\right) + \cdots}{(1+D)^{t}}$$

TDC	=	Total Direct Costs (in US$ 2005)
NTD	=	Neglected Tropical Disease
c	=	Country
y	=	Year
PS1	=	Number of prevalent cases with sequela 1
PS2	=	Number of prevalent cases with sequela 2
DCS1	=	Annual direct costs sequela 1
DCS2	=	Annual direct costs sequela 2
H	=	percentage of individuals seeking health care
D	=	Annual discount rate (%)
t	=	Time (years beyond 2010)

Prevalence of NTDs and their sequelae

The same prevalence estimates used to calculate the productivity loss were used to calculate the OPPs.

Annual direct costs

Direct costs for health care refer to the costs that arise from seeking treatment to enhance or restore health and are paid for by the patient himself (e.g. payments made to health practitioners or suppliers of pharmaceuticals) [25]. Our literature review showed that relatively few studies have quantified direct costs for the five PCT diseases. This is not surprising considering that many drugs to cure these five diseases are donated for free by several international partnerships. [16,17] In this case, costs to the individual were assumed to be zero (except for LF, as explained below) even though individuals receiving free treatment might bear travel, escort, accommodation, food and other costs themselves. Another reason for the scarcity of information on direct costs is that initial complaints are often not considered important enough to seek health care, and once chronic sequelae have developed, only palliative measures can be taken, for instance onchocerciasis, trachoma, or lymphatic filariasis. [43-50,55]

We assumed that blindness and skin disease due to onchocerciasis do not lead to any substantial out-of-pocket payments. First, there is no treatment for blindness, which is irreversible. Second, in the absence of a control program, skin disease is often not considered important enough for patients to seek health care. [66] We therefore ignored any additional costs since we did not expect any substantial additional costs for skin disease and since no publications describe additional OSD-related OPPs.

Soil-transmitted helminthiasis and schistosomiasis were assumed to be cured with the anti-parasitic medication, resulting in minimal chronic sequelae and costs. [67,68]

Just as with blindness due to onchocerciasis, blindness and low vision due to trachoma were assumed not to lead to any OPPs. This is not to say that no OPPs are expected, since previous studies have shown that patients with trichiasis can be treated surgically, which can result in additional spending for patients despite the fact that surgery is often provided for free.[98-103] However, since prevalence estimates of trichiasis were not

included in the GBD database, trichiasis-related OPPs (and productivity costs) could not be included in this study.

Previous studies on lymphatic filariasis have shown that the expenditures of patients seeking treatment due to LF sequelae are not negligible, even after they are treated with anti-parasitic drugs. [40,43,44,46,47,52,75-83] Therefore, we calculated the direct costs arising from lymphedema and hydrocele. Annual out-of-pocket payment costs were calculated for each WHO region separately since treatment type and costs can vary between regions. Table 2 shows the values used to estimate the OPPs for LF, which were kept constant over time. These values, used in the study by Chu et al., included costs for medicines, consultation fees, transport, food, accommodation and others. They were not only divided according to sequela, but also by WHO region, with the exception of India, for which country-specific estimates were available. [40]

Percentage of patients seeking care

Percentage of patients seeking care refers to the percentage of patients who seek treatment for that NTD sequela (shown in Table 2).

Table 2. Direct costs used for lymphatic filariasis with lower and upper limits [between brackets]

LF Sequela	WHO region	Annual Direct Costs[2] (int US$)	Patients Seeking Treatment	Patients that have ADLA	Source
ADLA[1] Lymphedema	WHO AFRO[3]	0.36 [0.6 – 1.25]	65% [55% - 70%]	95% [90 – 95%]	[40]
	WHO SEARO[4]	5.60 [0.93 – 19.43]			
	WHO WPRO[5]	19.60 [3.27 – 68.1]			
	WHO AMRO[6]	6.00[9] [1.0 – 20.82]			
	WHO EMRO[7]	0.36 [0.06 – 1.25]			
	All GPELF countries[8]	6.00 [1.0 – 20.82]			
	India[11]	(same as SEARO)	85% [65% - 98%]	95% [90 – 95%]	[40,43,44,80]
ADLA Hydrocele	WHO AFRO	0.18 [0.3 – 0.62]	65% [55% - 70%]	70% [45% - 90%]	[40]
	WHO SEARO	2.80 [0.47 – 9.72]			
	WHO WPRO	9.80 [1.63 – 34.01]			
	WHO AMRO	0.18 [0.03 – 0.62]			
	WHO EMRO	0.18 [0.03 – 0.62]			
	All GPELF countries	3.00 [0.50 – 10.41]			
	India[11]	(same as SEARO)	85% [65% - 98%]	70% [45% - 90%]	[40,43,44,80]
Chronic Lymphedema	All regions	4.3 [0.85 – 15.0]	50% [30 – 55%]	-	[40]
	India[11]		65% [49 - 74%]	-	[40,43,80]

table continues

Chronic Hydrocele [10]	All regions	2.9 [0.55 – 10.05]	40% [20 – 50%]	-	[40]
	India[11]		60% [49 - 74%]	-	

1. ADLA - acute dermatolymphangioadenitis
2. Based on an average of two ADLA episodes a year for hydrocele and four ADLA episodes a year for lymphedema [23]
3. WHO AFRO - World Health Organization African Region
4. WHO SEARO - World Health Organization Region South-East Asia
5. WHO WPRO - World Health Organization Western Pacific Region
6. WHO AMRO - World Health Organization Americas Region
7. WHO EMRO - World Health Organization Eastern Mediterranean Region
8. GPELF – Global Programme to Eliminate Lymphatic Filariasis
9. Since the region-specific estimate was not mentioned, the global average was used [23]
10. Hydrocelectomy already included in the chronic cost of hydrocele
11. Different estimates were used for India due to more primary data available suggesting estimates differ from other regions. [23]

Productivity gain of premature mortality averted

The number of productive years lost due to NTD-related premature mortality was estimated using country-, age-, and sex-specific mortality data for every year in the 1990-2030 period. The number of lost work-years was determined for the two scenarios (counterfactual scenario and target achievement scenario). The productive years lost per person were estimated by comparing the year in which the person died due to an NTD (e.g., ascariasis) and the year in which the person would otherwise have died according to country-specific life expectancies. The difference between these two years reflected the total number of productive years lost due to an NTD. We then restricted these lost productive years to the time period used in our analyses (i.e., 2011-2030). Economic benefit in the 2011-2030 period was calculated by combining the lost productive years with income per person.

Sensitivity analysis

Economic benefit was calculated by combining various base-case values for disease prevalence, income, and productivity loss. This raised the question of how much the estimate of benefit would change if the values of the different input parameters were to change. Probabilistic sensitivity analyses were therefore performed to determine how much the statistical uncertainty about the values of input parameters influenced the estimated economic impact. In these analyses the values of three input parameters were allowed to vary simultaneously, assuming that there was no correlation between the values of the different parameters.

The input parameters in our analysis included: 1) the GBD estimates of disease prevalence in 2010; 2) percentage of productivity loss and OPP per individual, and 3) income. The values of these parameters were varied using a beta PERT distribution in combination with the point estimate and the upper and lower limits for each input parameter. The limits used were based on different data sources or unavoidable assumptions. Table 3 shows the upper and lower limits used for the uncertainty regarding prevalence, productivity loss and income, per disease, while table 2 shows the upper and lower limits used for the calculations related to OPPs.

Table 3. Lower and upper limits used in the sensitivity analyses

	Relative uncertainty in global prevalence in 2010			Estimates of productivity loss [1]			Estimates of income		
	Lower limit	**Point estimate**	**Upper limit**	**Lower limit**	**Point estimate**	**Upper limit**	**Lower limit**	**Point estimate**	**Upper limit**
Lymphatic filariasis	0.886	1.000	1.136	10%	15%	20%	0.871	1.000	1.424
Onchocerciasis	0.936	1.000	1.103	14%	17%	30%	0.836	1.000	1.673
Schistosomiasis	0.987	1.000	1.027	2.5%	4%	18%	0.815	1.000	2.352
STH (anemia)	0.861	1.000	1.228	3%	6%	12%	0.766	1.000	2.106
STH (infestation)				3%	6%	9%			
Trachoma	0.694	1.000	1.421	16%	32%	63%	0.871	1.000	1.424

1. The productivity loss estimates seen in Table 1 are here shown as frequency-weighted estimates per sequela and per disease with their respective upper and lower limits used in the sensitivity analysis.

The importance of uncertainty about the prevalence in 2010 and the years thereafter was examined by applying the country-specific upper and lower confidence intervals of the GBD estimates for 2010 to all the years in the 2010-2030 period.

Uncertainty about the actual productivity loss and OPP from having one of the five diseases was addressed by using the highest and lowest values from studies with sufficient quality found through the literature review and estimating a frequency-weighted estimate of productivity loss and OPP per disease.

The variation in the income estimates was based on the variation of income of the country with the highest number of prevalent cases for each disease. The lower limit was the average income in the lowest decile, while the upper limit was the average income in the second-highest quintile of these countries. The ratio between the income in the lowest quintile (point estimate) and the income in the lowest decile and second-highest quintile (limits) in these countries was then applied to the general income variation.

Since the sensitivity analysis was performed varying these three variables simultaneously, the actual lower and upper limits in the sensitivity analysis were broader than the individual ones shown by Table 3.

Return on Investment

We calculated a rough estimate of the net return on investment (ROI) from 1990 to 2020 (NTD Roadmap targets) and to 2030 (the SDG target). Net ROI is the present value of the benefit to affected individuals minus the present value of the cost to public and philanthropic funders, divided by the present value of the cost to public and philanthropic funders. We used the economic benefit to affected individuals of averted OPP and productivity loss calculated in this study, and the investment costs based on recent WHO estimates from the Third Report on Neglected Tropical Diseases. [22]

We converted the I$ 2010 benefits to US$ 2015, for direct comparison to the investment targets. Evidently, part of these benefits is attributable to investments made before 2011; in calculating benefits net of costs we therefore had to estimate investments in the period 1990-2010. We conservatively assumed that investments in the period 1990-2010 were at

the same level of those in 2011 (in real terms). 1990 is assumed to mark the beginning of concerted global efforts to control most NTDs and 2011 is assumed to mark the beginning of the recent scale-up in investment to eliminate them. In reality, investments before 2011 were probably lower than this in most countries. Investments in improving housing and water and sanitation that occurred over the same period were not considered, since these were not targeted at the NTDs but nonetheless contributed to their control. We did not estimate the ROI for middle and low income settings separately due to lack of the necessary data on investments. We applied a discount rate of 3% per annum for both costs and benefits. [84]

Results

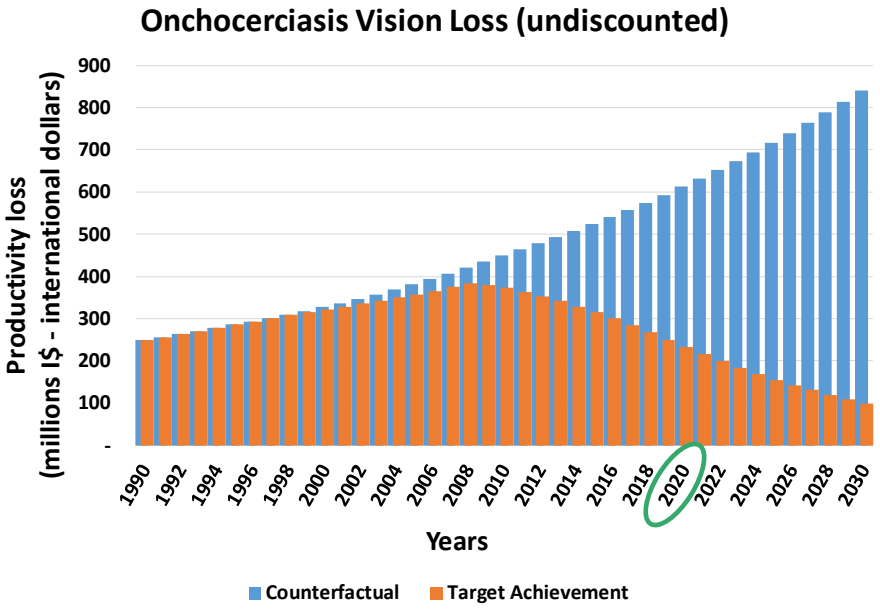
Timing of economic benefits

Figure 3 shows the pattern of the global productivity loss over time (1990-2030) of onchocerciasis skin disease. Onchocerciasis skin disease serves as an example; however for other diseases similar patterns can be seen.

Total global loss per year in the counterfactual scenario (blue) and target achievement scenario (orange). The economic benefit is the difference between both scenarios.

The blue bars in Figure 3 represent the total global loss per year in the counterfactual scenario. The increase in loss over time is simply a result of population growth. The orange bars represent the global loss in the target achievement scenario, which gradually reduces over time. The difference between the blue and the orange bars is the economic benefit.

Figure 3: Productivity loss due to skin disease from onchocerciasis according to the counterfactual and target achievement scenarios (millions I$ - international dollars)



As a result of fewer cases after the targets are achieved in 2020, the benefits for the period 2021-2030 will be higher than for the period 2011-2020 (table 4). For some disease sequelae the differences between the two periods will be significant (e.g. trachoma-related blindness) whereas for other diseases the difference is small (e.g. onchocerciasis skin disease). This can partly be explained by the differences in the targets between the diseases, which will affect the numbers of cases expected in 2020 when the targets are achieved. [16,17] More importantly, some disease sequelae are reversible whereas others are irreversible. Reversible sequelae can be cured or prevented (e.g. skin disease) whereas irreversible sequelae (e.g. blindness) can only be prevented. As a result, it is expected that the number of patients with reversible sequelae will decrease quickly and few patients will persist after 2020. In contrast, the prevalence of irreversible sequelae will decline more gradually and will persist for many years after 2020.

Total global overview of the economic benefit from averted productivity loss

As a result of achieving the London Declaration targets for the five PCT diseases many individuals will be cured or prevented from having one of these diseases. This can lead to economic benefits for individuals by averting direct treatment costs in terms of OPPs and indirect productivity losses. This can result in billions of dollars of benefit per disease on a global scale, with a total of I$ 250.6 billion (US$ 102 billion) productivity costs averted for the period 2011-2020 and I$ 312.8 billion (US$ 127 billion) for 2021-2030 for the five PCT diseases together (Table 4). The 2.5th and 97.5th percentile values calculated through the sensitivity analyses are I$ 186.6 – 346.3 billion and I$ 233.0 – 432.4 billion respectively (US$ 76.2 – 141.4 billion and US$ 86.1 – 203.4 billion), for the same periods.

Table 4 shows the global base case economic gain per disease sequela, for the periods 2011-2020 (before target achievement) and 2021-2030 (after target achievement) and the totals, with the 2.5th and 97.5th percentile calculated in the sensitivity analysis. Figure 4 shows the total values per disease (in I$) together with the sensitivity analysis diagram of the calculations of the total economic benefit of achieving the 2020 targets for the PCT diseases.

Table 4: Total economic benefit from productivity loss averted, base case estimates and 2.5th and 97.5th percentiles (billions I$ - international dollars and US$ - US dollars, discounting 3% from 2010)

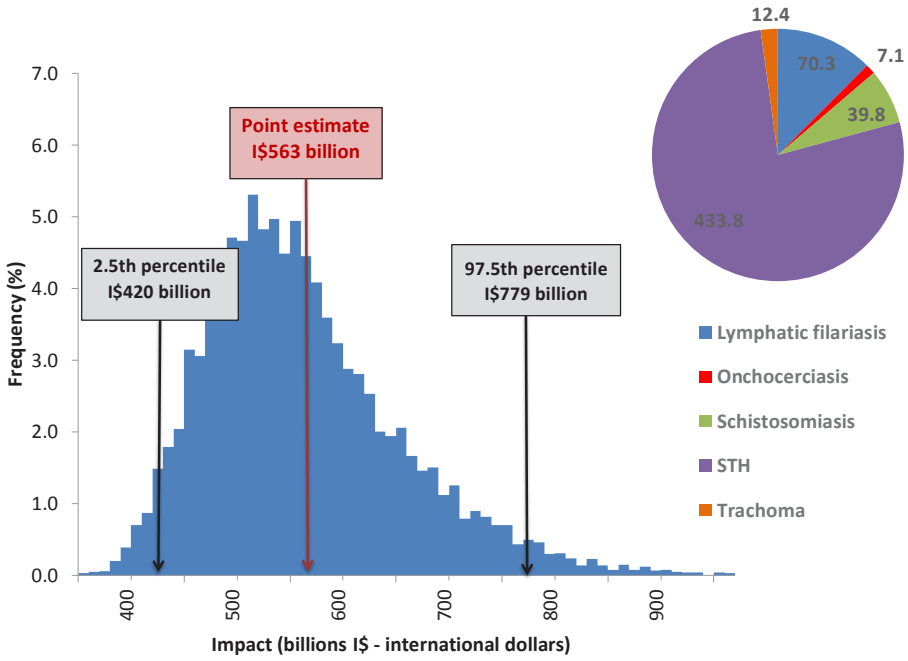
Disease	Sequelae	Base Case Estimates I$ - International dollars		Base Case Estimates US$ - US dollars	
		2011-2020	**2021-2030**	**2011-2020**	**2021-2030**
Lymphatic filariasis	Lymphedema	$ 12.7	$ 16.7	$ 4.4	$ 5.9
	Hydrocele	$ 18.1	$ 22.8	$ 6.1	$ 7.9
	Total	$ 30.8 [22.6 – 41.1][1]	$ 39.5 [28.9 – 52.8][1]	$ 10.5 [7.7 – 14.0][1]	13.8 [10.1 – 18.4][1]
Onchocerciasis	Skin disease	$ 0.68	$ 0.86	$ 0.32	$ 0.41
	Vision loss	$ 1.9	$ 3.6	$ 0.87	$ 1.7
	Total	$ 2.6 [1.9 – 4.0][1]	$ 4.4 [3.2 – 6.9][1]	$ 1.19 [0.88 – 1.84][1]	$ 2.11 [1.52 – 3.27][1]
Schistosomiasis	Anemia	$ 8.7	$ 17.7	$ 3.7	$ 7.5
	Ascites	$ 0.38	$ 1.4	$ 0.2	$ 0.7
	Bladder pathology	$ 0.17	$ 0.63	$ 0.1	$ 0.3
	Dysuria	$ 0.62	$ 1.5	$ 0.3	$ 0.7
	Hematemesis	$ 0.18	$ 0.66	$ 0.1	$ 0.3
	Hepatomegaly	$ 0.96	$ 2.3	$ 0.4	$ 1.1
	Hydronephrosis	$ 0.56	$ 1.37	$ 0.3	$ 0.6
	Mild diarrhea	$ 0.6 [2]	$ 1.5 [2]	$ 0.3 [2]	$ 0.7 [2]
	Schistosomiasis deaths	$ 0.85	$ 1.7	$ 0.37	$ 0.74
	Total	$ 12.4 [6.2 – 35.0][1]	$ 27.4 [13.6 – 77.2][1]	$ 5.5 [2.7 – 15.4][1]	$ 11.9 [5.9 – 33.7][1]

table continues

STH	Ascariasis deaths	$ 0.03	$ 0.1	$ 0.01	$ 0.04
	Ascariasis infestation	$ 47.1	$ 43.5	$ 19.8	$ 18.2
	Hookworm anemia	$ 116.8	$ 142.8	$ 48.3	$ 58.7
	Hookworm infestation	$ 25.1	$ 28.0	$ 10.4	$ 11.5
	Trichuriasis infestation	$ 13.6	$ 16.5	$ 5.9	$ 7.3
	Total	$ 202.8 [141.0 – 303.4][1]	$ 231.0 [160.5 – 345.6][1]	$ 84.4 [58.7 – 126.4][1]	95.7 [66.6 – 143.4][1]
Trachoma	Vision loss	$ 1.9	$ 10.4	$ 0.71	$ 3.6
	Total	$ 1.9 [1.0 – 3.3]	$ 10.4 [5.5 – 17.8]	$ 0.71 [0.37 – 1.23][1]	$ 3.6 [1.25 – 6.16]1
Total (all diseases)		**$ 250.6 [186.6 – 346.3][1]**	**$ 312.8 [233.0 – 432.4][1]**	**$ 102.3 [76.2 – 141.4][1]**	**127.2 [86.1 – 203.4][1]**

1. Sensitivity analyses' 2.5th and 97.5th percentiles between brackets
2. Reported in millions International (I$) and US Dollars (US$) due to the comparatively small numbers.

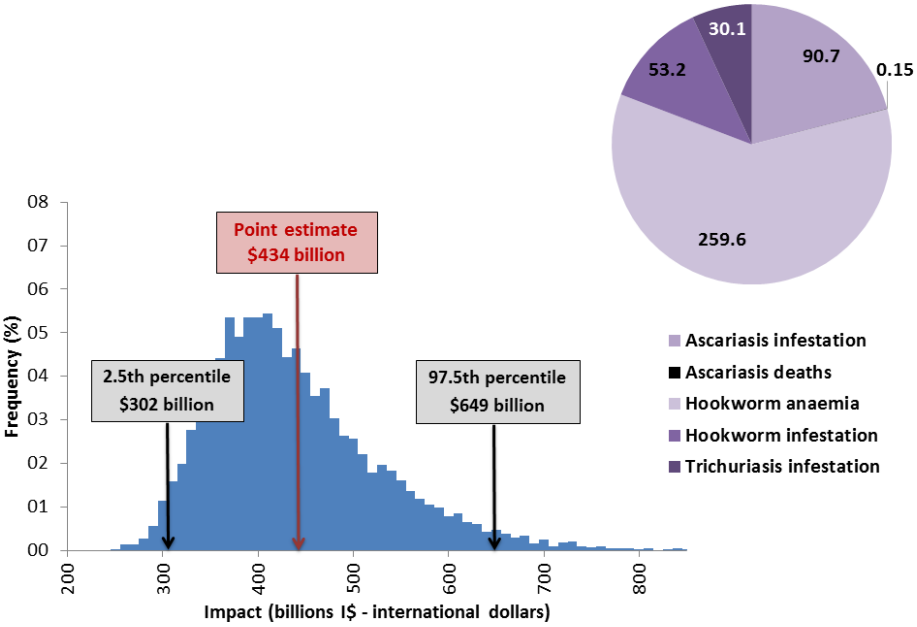
Figure 4. Global economic benefit (productivity loss prevented) for the period 2011-2030 (billions I$ - international dollars)



Global economic benefit from reaching the targets for 5 PCT diseases, lower and upper estimates from sensitivity analysis.

The disease that is responsible for the largest economic benefits is clearly STH, especially the anemia sequela (Figures 4 and 5), accounting for almost 60% of the benefits from reaching the targets for STH. Even though it causes a relatively low productivity loss, this finding can be explained by the widespread distribution of STH.

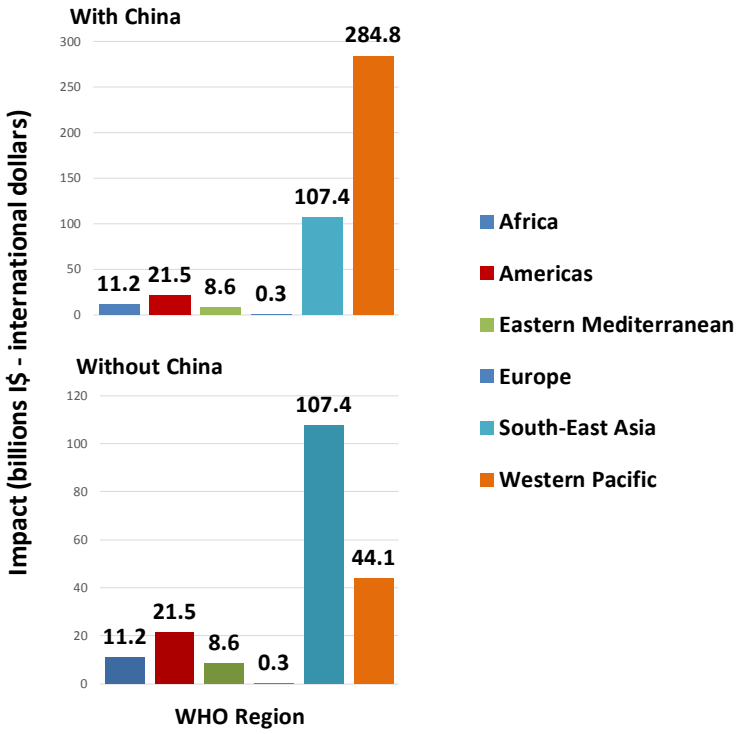
Figure 5. Global economic benefit or reaching the targets for STH (point estimates), per disease sequela for the period 2011-2030 (billions I$ - international dollars)



STH is the disease responsible for the largest economic impact, especially the anemia sequela. The 2.5 and 97.5 percentiles calculated in the sensitivity analysis are shown in the diagram.

Figure 6 highlights the regional variation in the economic benefit, per WHO region. [85] Unsurprisingly, when China is included, the Western Pacific region clearly outweighs the benefits of all the other regions, mainly due to the control of STH. The South East Asia region has the highest benefits when China is not included, which is due to the impact in India.

Figure 6. Economic benefit of reaching the PCT targets per WHO region, with and without China



Regional variation in the economic benefit, per WHO region, where the Western Pacific region outweighs the benefits of all the other regions when China is included, mainly due to the control of STH. The South East Asia region has the highest benefits when China is not included, due to the impact in India.

Out-of-Pocket Payments versus productivity loss

Economic benefit due to prevention of lost working time is considerably higher compared to the benefit due to the prevention of direct OPP (I$ 31 billion vs I$ 0.72 billion in 2011-2020 and I$ 40 billion vs I$ 0.96 billion in 2021-2030, corresponding to US$ 11 billion vs US$ 0.25 billion and US$ 14 billion vs US$ 0.33 billion in the same periods). This is attributable to relatively inexpensive medicines compared to income.

Economic benefit of averted premature mortality

The economic benefit from averted premature mortality was rather small compared to the benefit of averted morbidity, amounting to just 0.48% of the total economic benefit for the period 2011-2030. Within the diseases that presented death cases, it corresponded to 0.03% of the STH benefit and 6.41% of the schistosomiasis benefit.

Return on Investment

The ROI was calculated considering a benefit to individuals of US$ 119.7 billion in the period 2015-2020 and US$ 399 billion in the period 2015-2030, if the 2020 targets for PCT diseases were to be met and considering costs to funders of US$ 2.8 billion and US$ 6.2 billion in the same periods.

The net benefit is US$ 27.4 for every dollar invested during the period 1990-2020 and US$ 42.8 for every dollar invested in the period 1990-2030 (best estimates). More detailed information on the ROI and the internal rate of return per WHO region, as well as other considerations on the investment case of ending/controlling NTD can be found in a forthcoming publication. [113]

The health benefits calculated by De Vlas et al and the economic benefits shown here will be publicly available through the open access website: https://erasmusmcmgz.shinyapps.io/dissemination/.

Discussion

This is the first study estimating the global economic benefits of achieving WHO Roadmap targets endorsed by the London Declaration for the five PCT diseases. Prevalence estimates based on the GBD study, productivity loss and OPP values based on published literature and income estimates based on World Development Indicators data were used. The productivity costs were calculated using the human capital approach and reported separately from the OPPs [25]. Averted costs were calculated by comparing expected costs of the target achievement scenario with a counterfactual scenario.

Our findings suggest that by averting the five PCT disease, a total of I$ 563 billion (US$ 229 billion) of productivity loss and I$1.7 billion (US$ 0.58 billion) OPPs can be averted over the 20 year time period 2010-2030. This implies that roughly I$ 28 billion (US$ 11 billion) on productivity loss only can be averted annually.

General Approach

We used the human capital approach to calculate the productivity loss. Although this method is generally used and therefore increases comparability with previous studies, some would argue that it overestimates the actual productivity loss from the societal perspective [86]. Since we focused on the economic loss to individuals affected by NTDs, the alternative approach of the friction cost method (which focuses only on the lost productivity until a replacement can be found) was not considered. The consequences of the five PCT diseases are often chronic in nature, which mostly leads to reduced productivity while working (presenteeism) rather than lost work days (absenteeism). For instance, someone with itching due to onchocerciasis will still be able to work but will be less productive at work due to the distracting itching and constant scratching, or a tea plucker with hookworm anemia will not be absent from work, but will earn less due to fewer kilograms of tea plucked. [87,88] While these workers could also be replaced with healthier workers, this is less likely since they are still showing up for work. Therefore, use of the friction method is not expected to have a substantial effect on the estimated economic benefit. This means that the aggregation of individual costs does not exactly represent the total societal cost, since individuals' productivity losses are still compensated by a variety of mechanisms in the societal level. Some of these mechanisms, for instance household coping strategies and work compensation will be discussed later in this section.

The link between income and productivity depends on more factors than only labor. In the systematic literature review we performed for this study [36], most publications reported productivity in terms of days/hours of work although some publications reported it in terms of output (as kilograms of tea plucked a day, or square meters of constructed road a day). A linear relationship between health and productivity was not always seen and most of the time there was not enough information on this issue. Therefore, and also because of using conservative values for productivity loss, we

assumed that average productivity gain would equal marginal productivity gain. The lack of information in the literature prevents us from knowing if this would have under- or overestimated the results.

The impact of NTDs on productivity amongst agricultural families is worth commenting on in more detail since NTDs can lead to productivity loss in different ways. To start with, affected families might own less land than unaffected families as a direct result of NTD-related productivity loss. Oladepo et al reported that 'farmers with OSD (Onchocercal Skin Disease) had significantly less farmland under cultivation (9,117 m^2) than those with no OSD (13,850 m^2)'. But even with a fixed amount of land, healthy farmers could be able to increase their productivity in different ways, including: harvesting more than once a year (enabling them to quickly harvest one crop and plant another); investing more energy in site preparation, which requires more physical strength (e.g., to remove stones and dead trees); working in steep areas that would otherwise be underutilized; and being capable of investing more energy in ameliorating compaction, aeration, soil moisture status, and weeding. It is worth noting that land preparation is by far the most time-consuming activity for the farmer and family, and that weeding accounts for more than 60 percent of the time a peasant farmer spends on the land. [89-92]

Household coping strategies and social security were not included in the calculations. However, household coping strategies can have several effects on the total costs that the illness of a family member can cause for the household. Coping strategies can reduce the impact of lost productivity because another household member can take over the work. For the individual patient these costs are still onerous and may lead to overwhelming effects. Patients may need to borrow money to pay for the treatment or forgo treatment if they cannot afford it. [40] On the other hand, when, for example, children step in and take over the work of their ill parents, they cannot go to school and may therefore have more limited career opportunities later in life. [25]

Productivity loss due to subtle morbidities (for schistosomiasis and STH) as well as productivity loss by informal care were not included in this analysis. The reason for not including the subtle morbidities is that these are not part of the GBD study. However, previous research has shown that subtle morbidity affects people later in life since they

may often become trapped in poverty due to low-salary jobs and poorer school performance. [93-96] The productivity loss of caregivers of the blind due to trachoma or onchocerciasis or the severely affected by lymphedema or hydrocele is also not negligible although very little data is currently available.[97] Excluding the effects of subtle morbidity and informal care on productivity loss leads to an underestimation of the economic benefit.

Large differences in economic benefit can be seen between diseases and countries/regions, since economic benefit clearly depends on disease prevalence in a country, the impact that the disease has on productivity and OPPs and income. Comparisons between diseases can only be made with caution. For one, the data limitations and potential biases in the methodology affect the different diseases differently. Furthermore, when multiple diseases can be treated in one single visit, it does not make sense to look at the economic returns from just one disease at a time. Integrated delivery of medicines and preventive efforts means that these returns are in fact complementary. The economic returns from investments in NTDs also depend on how productivity is valued in monetary terms, but the gains are not restricted to them. Physical and mental health of billions of people will be gained with the control/elimination and eradication of NTDs, and attributing exclusively monetary value to these domains in terms of productivity gain underestimates this much bigger gain, of which increased productivity is only a by-product. Therefore, the economic benefit of controlling NTDs (as calculated here) should not be the only argument driving policymaking.

Productivity loss is often minimized by compensating mechanisms, which from the perspective of the individual could be for instance cancelling or postponing work, working extra hours to compensate, or having colleagues compensate for the lost productivity. [98,99] To our knowledge, there is no description in the literature of compensating mechanisms in Low- and Middle-Income Countries (LMIC), and the ones described for firms in developed countries do not necessarily reflect the reality of agricultural families/workers in developing countries. [100] Also, the more chronic nature of sequelae of NTDs leaves less room for work compensation, and some do not even enable people to work due to their severity, such as hepatomegaly or splenomegaly in schistosomiasis, heart failure in Chagas disease, blindness in onchocerciasis and others.

Therefore, we do not know the extent to which work compensating mechanisms would have changed the results, but for the reasons just mentioned, probably the results would not change much. [101-103]

Technical validity

R scripts were written to construct technical validity/calibration of our Excel calculations. The R scripts are completely independent of the Excel calculations and use the same original data (GBD, UNPOP, GDP, productivity loss) as the Excel sheets (though transformed). The few differences we found lead to the improvement of the formulae for some of the diseases and later matching of the results, but the general programming in Excel did not change. R scripts and example Excel sheets can be found in the Supporting Information.

Data sources

Prevalent cases

The numbers of prevalent cases were drawn from the 1990 and 2010 GBD estimates and the calculations made by De Vlas et al. [20] The GBD data on which prevalence estimates were based already contained uncertainty ranges, varying in relative terms from 10% less to 40% more compared to the mean (Table 3), depending on availability of country and disease-specific epidemiological data. [20] This uncertainty increased as the GBD numbers were extrapolated over time to estimate the annual prevalence estimates for the period 2010-2030.

In this sense, the extrapolation of the counterfactual estimates may be questioned for several countries that have experienced rapid and large economic growth since 1990, and consequently have not maintained the same epidemiological situation for NTDs as in 1990, as De Vlas et al. have argued. [20] This would mean that the difference between the prevalent cases of the two scenarios would be somewhat smaller. If we take the disease with the biggest economic impact, STH, we would see that more than half of the STH benefits are gained in China due to the possibly overestimated difference between the two scenarios [104]. Nevertheless, if we present the economic benefits excluding the

results for China, we would have a lower but still substantial total productivity gain of I$ 126.1 billion for 2011-2020 and I$ 195.8 billion for 2021-2030.

Productivity loss and Out-of-Pocket Payments

Literature on productivity loss and out-of-pocket payments was scarce and not available at all for some diseases. [36] As a result, a general global estimate of productivity loss was used for each sequela, which was sometimes based on only one study. When no OPP or productivity loss values were available, other methods were required to estimate productivity loss (e.g. use studies of other diseases with similar sequelae). The few available studies were also often liable to several types of risk of bias, generating large uncertainty around the productivity loss estimates. [36] For instance, the productivity loss estimate used for four schistosomiasis disease sequelae was derived from one article by Fenwick and Figenschou published in 1972, who assessed the difference in productivity of cane cutters uninfected and infected with *Schistosoma mansoni* in Tanzania. [105] In fact, the values of productivity loss used were based on studies performed in very specific contexts, i.e. with tea pluckers, road workers, rubber tappers, farmers, in different countries. The generalizability of these studies to all persons with an NTD may be limited. First, by measuring the productivity loss in working populations, the results will suffer from the 'healthy worker effect', since the productivity loss was measured in affected persons that are still able to work, not considering the ones too sick to work [106]. This would underestimate the productivity loss each disease would cause. Second, the productivity loss estimated in the specific regional and working contexts is not necessarily the same for other professions (more or less strenuous, for instance) or for other contexts. Extrapolation of the data from one specific context to others was done due to lack of data, and, depending on the disease sequela, the profession and the working environment, it might have over- or underestimated the extent of productivity loss.

The same productivity loss estimate was used for men and women, despite the fact that this might not always be the case. First, cultural factors may restrict women's activities to domestic ones, which differ from farming and other occupations that men might have in the same culture; these differences could lead to different productivity losses. [44,46,48,96,107] Second, when performing the same tasks, women can perform differently from men. [64] Third, the same sequela can affect men and women differently. One example is anemia, which might be more frequent and even more severe in women,

aggravated by menstrual and birth blood loss, breastfeeding depletion, [62] but might impact the productivity of men even more, since they have more muscle mass and may perform more strenuous tasks than women and are therefore more affected by less efficient blood oxygen transport. Many of the studies investigating productivity loss due to hookworm anemia in men found higher values (18.7–20%) than the ones investigating women (5.4-6.32%). Others showed a bigger impact of anemia on people who perform heavy work compared to those who do light work, so both the difference in severity and the different nature of the jobs could lead to different estimates in productivity loss due to anemia for both women and men.[59-64,108-110] At the same time, a recent systematic review on the impact of hookworm infection and deworming on anemia did also not report gender differences regarding this subject. [111]

As described in the methods, we assumed out-of-pocket payments for onchocerciasis, schistosomiasis, STH, and trachoma to be zero. We know that there are other costs that individuals would have to bear besides transportation costs, such as food, accommodation, escort, diagnostic investigations or procedures (i.e. laboratory) and treatment. Since we did not have enough information on all of these different costs for all PCT diseases and countries included in this study, we assigned a zero value to the direct costs of PCTs (except for LF, as explained before), which led to a conservative estimate of the OPPs.

Income

We used the GDP per capita of the lowest income quintile as a proxy for income for the calculations of this study. Compared to the data sources used by other authors described above, the GDP per capita of the lowest quintile seems to be the most conservative estimate without having to combine multiple data sources for income. For instance, when comparing the GDP per capita of the lowest quintile with the minimum nominal annual wage (both 2010 PPP) we would have $ 1592 versus $3453 for China, and $ 1333 versus $2288 for India. [112-113] One could argue that the lowest quintile can refer either to the share of income or of consumption, and that the lower quintile of the population is likely the recipient of considerable transfers, so only part of the income would be earned, and therefore dependent on the worker's productivity. Hence, since NTDs are generally known as diseases of the poorest, using the GDP per capita of the lowest quintile would still overestimate the annual productivity loss of the affected populations. We therefore

allowed income to vary to the GDP per capita of the lowest decile in the sensitivity analysis.

Comparisons with the literature

To our knowledge only a small number of other studies have assessed economic benefits of preventing or treating NTDs. However, these studies did not include all five PCT diseases but examined one specific NTD per study, and most of them one specific country. Comprehensive global assessments were not identified so far.

Frick et al. examined the economic impact of trachomatous visual loss in the year 2000. They estimated an annual productivity cost of $2.9 billion (US$ 1995). This significantly differs from our findings, with an annual average of $620 million for trachoma in the period 2011-2030. Frick used a productivity loss based on disability weights (0.40 for low vision and 0.60 for blindness). We used 79% for blindness but split low vision into severe visual impairment with 35% productivity loss and moderate visual impairment 0% productivity loss. Since trachomatous moderate impairment (55%) is far more common than severe impairment (10%) this together resulted in a much lower productivity loss for low vision compared to what Frick used, namely 6%.

Chu et al. (2010) examined the economic benefits resulting from a global program to eliminate LF. Chu et al. estimated productivity costs and OPP, but they used a different approach to estimate the benefits. They quantified the clinical manifestations that would be averted, while we used GBD sequelae; the health system, was included in their costs calculations, while our approach was focused on the costs of the disease paid by the individual; they calculated the economic benefit for a fixed cohort population, which led to lifetime economic benefits that cannot be compared with our results for a 20-year period.

Limitations

The comprehensiveness of this economic analysis is limited by the paucity of country/regional data regarding productivity loss and OPPs related to the different NTDs and their sequelae, as well as the characteristics of the affected populations (e.g. income). In addition, assumptions had to be made regarding the predictions of the prevalent cases of each NTD. Even though sensitivity analyses were performed to

estimate lower and upper limits of economic benefit, better knowledge and understanding about the abovementioned parameters would improve the estimates. Further research is needed to derive more accurate measures of productivity loss due to NTDs. Furthermore, studies that provide a more accurate characterization of the affected populations would allow a more realistic calculation of economic benefits, due to better information on their socioeconomic context (i.e., details about income, professions, and type of work performed). Future research should also be performed in as many affected countries as possible to shed more light on the socioeconomic differences between the different affected populations in the different countries and enable the consideration of each particular setting in future economic calculations.

Considering that the 2020 targets for the 10 London Declaration NTDs described by the WHO [16,17] will be met of course implies a natural uncertainty about the future. The actual economic benefit will evidently depend on the extent that each country will reach those targets. In this sense, our results do advocate in favor of directing policies that invest in reaching these goals, but our results cannot help deciding on the instruments to reach them.

Conclusions

The robust findings of our study show that investing in achieving the 2020 WHO targets for the London Declaration NTDs will certainly result in substantial economic gain. The economic benefit to individuals from productivity gain was estimated to be I$ 251 (I$ 187 – I$ 346) billion in 2011-2020 and I$ 313 (I$ 233 – I$ 432) billion in 2021-2030, corresponding to US$ 102 (US$ 76 – US$141) and US$ 127 (US$ 86 – US$ 203) respectively (2.5th and 97.5th percentiles from sensitivity analyses between brackets). Total OPPs averted were I$0.72 (US$ 0.25) billion and I$0.96 (US$ 0.33) billion in the same periods. The best estimates for the net benefit (return on investment) is US$ 27.4 for every dollar invested during the period 1990-2020 and US$ 42.8 for every dollar invested in the period 1990-2030. The impact varies between NTDs and regions, since it is determined by disease prevalence and productivity loss caused by each disease manifestation.

Although the results of this study should be interpreted with care because of the different factors of uncertainty discussed above, we can conclude that economic benefits to

individuals will greatly exceed the investments required in interventions. We hope that these results help advocating in favor of addressing the social and environmental determinants of health, especially for the poor and vulnerable, aiming at more equity, inclusion, productivity and health in societies.

Initiatives for joint collection of better socioeconomic and epidemiological data would enable more accurate and complete estimates, leading to better planning and decision-making.

Acknowledgments

We would like to express our true gratitude to the following individuals whose valuable comments and insights contributed to the development of this work: Donald Bundy, and Deborah McFarland.

We are especially grateful to Wichor Bramer, whose work as a biomedical information specialist was crucial in designing the most comprehensive possible syntaxes for our literature reviews.

The content of this paper is solely the responsibility of the authors and does not represent the official views of WHO.

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Supporting Information

S1 File. Excel example of calculations of the counterfactual scenario for Onchocerciasis Skin Disease

S2 File. Excel example of calculations of the remaining case scenario for Onchocerciasis Skin Disease

S3 File. R scripts for the calculations of the counterfactual and remaining case scenarios for Onchocerciasis

Chapter 4

Socioeconomic benefit to individuals of achieving 2020 targets for four neglected tropical diseases controlled/eliminated by innovative and intensified disease management: Human African trypanosomiasis, leprosy, visceral leishmaniasis, Chagas disease

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2018

PLoS Neglected Tropical Diseases 12(3): e0006250.

https://doi.org/10.1371/journal.pntd.0006250

Abstract

Background

The control or elimination of neglected tropical diseases (NTDs) has targets defined by the WHO for 2020, reinforced by the 2012 London Declaration. We estimated the economic impact to individuals of meeting these targets for human African trypanosomiasis, leprosy, visceral leishmaniasis and Chagas disease, NTDs controlled or eliminated by innovative and intensified disease management (IDM).

Methods

A systematic literature review identified information on productivity loss and out-of-pocket payments (OPPs) related to these NTDs, which were combined with projections of the number of people suffering from each NTD, country and year for 2011–2020 and 2021–2030. The ideal scenario in which the WHO's 2020 targets are met was compared with a counterfactual scenario that assumed the situation of 1990 stayed unaltered. Economic benefit equaled the difference between the two scenarios. Values are reported in 2005 US$, purchasing power parity-adjusted, discounted at 3% per annum from 2010. Probabilistic sensitivity analyses were used to quantify the degree of uncertainty around the base-case impact estimate.

Results

The total global productivity gained for the four IDM-NTDs was I$ 23.1 (I$ 15.9 –I$ 34.0) billion in 2011–2020 and I$ 35.9 (I$ 25.0 –I$ 51.9) billion in 2021–2030 (2.5th and 97.5th percentiles in brackets), corresponding to US$ 10.7 billion (US$ 7.4 –US$ 15.7) and US$ 16.6 billion (US$ 11.6 –US$ 24.0). Reduction in OPPs was I$ 14 billion (US$ 6.7 billion) and I$ 18 billion (US$ 10.4 billion) for the same periods.

Conclusion

We faced important limitations to our work, such as finding no OPPs for leprosy. We had to combine limited data from various sources, heterogeneous background, and of variable quality. Nevertheless, based on conservative assumptions and subsequent uncertainty analyses, we estimate that the benefits of achieving the targets are considerable. Under plausible scenarios, the economic benefits far exceed the necessary investments by endemic country governments and their development partners. Given the higher frequency of NTDs among the poorest households, these investments

represent good value for money in the effort to improve well-being, distribute the world's prosperity more equitably and reduce inequity.

Author Summary

Human African trypanosomiasis, leprosy, visceral leishmaniasis and Chagas disease are neglected tropical diseases (NTDs) controlled or eliminated by innovative and intensified disease management (IDM). We estimated the economic impact of meeting the 2020 targets defined by the WHO for NTD control/elimination, reinforced by the 2012 London Declaration. A systematic literature review identified information on productivity loss and out-of-pocket payments (OPPs) relating to these NTDs. The economic benefit was calculated by combining the estimated disease cases with estimated productivity losses and OPPs resulting from the diseases, from the perspective of affected individuals. Very little information about OPPs and productivity loss due to NTDs was found in the literature. The total global productivity gained by reaching the goals for the four IDM-NTDs was I$ 23.1 billion in the period 2011-2020 and I$ 35.9 billion in the period 2021-2030. The reduction in OPPs was I$ 14 billion and I$ 18 billion for the same periods. In order to estimate the economic impact of meeting the London declaration targets regarding four IDM-NTDs, we had to combine data from various sources, heterogeneous background, and variable quality. Nevertheless, based on conservative assumptions and subsequent uncertainty analyses, we estimate that the benefits of achieving the targets are nearly double the required investments by endemic country governments and their development partners to reach the 2020 targets.

Introduction

Disadvantaged populations from low- and middle-income countries (LMICs) often have to deal with the health and economic consequences of neglected tropical diseases (NTDs), which can often aggravate their struggles to avoid poverty.[1-12] Chagas disease, human African trypanosomiasis (HAT), leprosy and visceral leishmaniasis (VL) are still difficult and costly to manage and available tools are unsuitable for use in large-scale preventive control programmes. They should be controlled or eliminated by "innovative and intensified disease management" (IDM), as promoted by the World Health Organization (WHO). [13,14] The populations affected by them frequently live in rural or remote areas, thereby limiting access to diagnosis and treatment of both the disease as well as the disabilities they cause.[15]

Efforts of many private and public sector organizations have aimed at increasing the attention, as well as research and funding, given to NTDs. One of the results was the 2012 London Declaration, based on targets set out in the WHO Roadmap for the control and elimination of 10 NTDs by the year 2020.[15-17]

Compared to studies of the epidemiology and health consequences of NTDs, relatively few studies have examined the impact of NTDs on the productivity and out-of-pocket payments (OPPs) of individuals, households, communities and countries.[13,57] There is clear evidence that health improvements positively influence economic welfare and vice-versa. In this sense, apart from addressing the human fundamental right to the highest attainable standard of health, controlling and eliminating NTDs would also have a direct and sustainable effect on the economic growth and financial welfare of the affected populations, and consequently lead to greater national and global prosperity.[9,12,20-22]

Advances in understanding the economic consequences of NTDs could help to further encourage prevention and control actions, assuring funders and policymakers that resources committed to these efforts are a good investment, or at least resulting in increased health policy dialogue.[18,23]

We estimated the economic benefits of reaching the 2020 WHO targets for four IDM diseases: Chagas disease, human African trypanosomiasis, leprosy and visceral

leishmaniasis, which meant estimating how much of the economic loss faced by affected individuals due to productivity loss and out-of-pocket payments secondary to these diseases would be avoided by reaching these targets.

Methods

General approach and study design

The general approach to estimate the economic benefits is the same as the one used to calculate the benefits of achieving the 2020 WHO targets for NTDs controlled or eliminated by preventive chemotherapy (PCT) described by Redekop et al. [140] This approach follows the concepts used by Chu et al., and a conceptual framework can be seen as Supporting Information 1 (S1 Figure. Conceptual framework). [25]

The Global Burden of Disease Study (GBD) is the most extensive worldwide observational epidemiological study up to now. Mortality and morbidity from major diseases, injuries and risk factors to health are described at the global, national and regional levels. The GBD-2010 data of prevalent cases of the NTDs included in the London Declaration for the years 1990 and 2010 were used as starting points for the calculation of the estimates for other years. They were obtained by interpolating between 1990 and 2010, as presented by de Vlas et al. The prevalent cases until 2030 were estimated by extrapolation under the assumption that the 2020 WHO Roadmap targets would be met and sustained beyond 2020. For each GBD disease sequela, a comparison is made between a counterfactual scenario (which assumed that the epidemiological situation from 1990 regarding NTDs would continue unabated and that the number of cases would increase as a function of overall population growth) and a target achievement scenario (that considers the 2020 targets described in the 2012 London Declaration and described by the WHO being achieved). [26]

We calculated the base case estimates of the benefit for the period between 2011 and 2030 (i.e., the period between ten years before and ten years after the target achievement) instead of the entire period from 1990 to 2030. The economic benefit was calculated by subtracting the costs for the target achievement scenario from the costs of the

counterfactual scenario. The economic benefit of each country was combined in order to provide region and global estimates of the economic benefit.

International US$ (constant 2005 dollars) were used to express all estimates in this study. It is a hypothetical unit of currency that has the same purchasing power as the U.S. dollar has in the United States at a given point in time (in this case 2005). It is estimated using purchasing power parity (PPP) exchange rate, defined as the amount of a country's currency needed to purchase the same amounts of goods and services in the domestic market as one U.S. dollar would buy in the United States. It is a valid measure frequently used to compare estimates between countries. [27,28]

Constant discounting at 3% was applied to both productivity loss and OPPs, using the base year of 2010. Discounting is a mathematical operation to adjust future costs and effects of health-care interventions to the "present value". When calculating for discounting, for each year (n) in the future the value of costs or benefits is multiplied by $(1/(1 + D)^{n})$, D being the discount rate. [24,29,30]

Following WHO's recommendations, the economic benefits from prevented productivity loss and out-of-pocket payments were reported separately. [12] All calculations were performed using Microsoft Excel (version 2010). [31]

Perspective

Like previous NTD economic impact studies, we used the human capital approach in our study with the perspective of the individual affected by an NTD to analyze the economic costs per GBD sequela, sex and country.

The WHO Guide to Identifying the Economic Consequences of Disease and Injury distinguishes the following cost categories when calculating the microeconomic impact of disease and injury: expenditures on health; labour and productivity losses; effects on human, physical and financial capital formation; non-market impacts such as leisure or caregiver time. We only included the first two in our analyses, incurred by affected individuals during illness in low- and middle-income countries. [23,32-35]

Countries

All countries referred by the GBD study as endemic for IDM NTDs were included in the analyses [23]. The list of countries per disease can be found using the open-access web-based dissemination tool available at https://erasmusmcmgz.shinyapps.io/dissemination/.

Literature review

We performed a systematic review of the literature to identify general and country-specific information on productivity loss (indirect labor costs resulting from reduced working hours and economic activity attributable to morbidity) and direct costs incurred by individuals (such as consultation fees, medication, transport, food, assistance, accommodation) due to the 10 NTDs included in the London Declaration. Although in this paper we report on four IDM NTDs, we combined the 10 NTDs in the review, since many papers often refer to several NTDs and describe the economic impact of the related sequelae. Details about the methodology applied to all NTDs and the results regarding the findings on productivity loss related to the NTDs eligible for PC can be found in the review by Lenk et al.[36] In summary, the searched databases included Embase, Medline (OvidSp), Web of Science, Scopus, CINAHL, PubMed publisher, Cochrane, Popline, Lilacs, Scielo and Google Scholar. Websites of relevant organizations (i.e. World Health Organization, the Centre for Neglected Tropical Diseases, the Carter Center) were also screened for relevant grey literature. The search syntax used for each database can be found in the Supporting Information (S1 File. Literature Search Syntax), and the complete list of institutions searched for grey literature can be found in Supporting Information 3 (S2 File. Grey Literature Search). A total of 11,449 articles concerning all 10 NTDs were identified using the database searches. Of these, 5,316 articles remained after duplicates were removed (S1 Table. Results of database searches). We sorted the articles that were related to each particular disease and screened the abstract and title of all papers, examining the full-text version of all articles that provided information on productivity loss or indirect costs. The paucity of studies that provide quantitative estimates of productivity loss and OPPs from NTDs can be seen in Supporting Information 5 (S2 Table. Literature review – results per disease). [36]

Productivity loss

The formula below was used to calculate the annual productivity loss for each NTD and country, using the prevalence estimates for the counterfactual and target achievement scenarios independently (Fig.1).

Figure 1. General formula for calculating productivity loss

$$TPC_{cNTD} = \sum_{y} \frac{\left(PS1_{c\,y} * PLs1_{c\,y} * I_{c\,y}\right) + \left(PS2_{c\,y} * PLs2_{c\,y} * I_{c\,y}\right) + \cdots}{(1+D)^{t}}$$

TPC	=	Total productivity costs (in US$ 2005)
NTD	=	Neglected Tropical Disease
c	=	Country
y	=	Year
PS1	=	Number of prevalent cases aged 15+ years with sequela 1
PS2	=	Number of prevalent cases aged 15+ years with sequela 2
PLs1	=	% productivity loss related to sequela 1 of NTD
PLs2	=	% productivity loss related to sequela 2 of NTD
I	=	GDP per capita in the lowest quintile
D	=	Annual discount rate
t	=	Time (years beyond 2010)

Prevalent cases

We used the estimates relative to both the counterfactual and the target achievement scenarios calculated by de Vlas et al, as described in the general approach. [26] The population older than 15 years was used for the calculation of productivity loss. [24]

Productivity loss from disease manifestations

Disease can lead to productivity loss in many ways, including reduced productivity at work (presenteeism), absence from work (absenteeism) or even job loss, which were translated into each infected individual's annual loss of income due to the effects of each NTD sequela. [23,25]

Unless otherwise specified, we converted the least biased value of productivity loss found in the literature into annual percentages per sequela, assuming 300 working days per year, as seen in Table1. [25] In every year of the interval we assumed that there were no differences in productivity loss between men and women, between younger and older persons, and between countries. We also assumed that all persons older than 15 years are equally productive. If no estimates for productivity loss were found in the literature, assumptions were made as described in Table 1.

Table 1 shows the estimates of annual productivity loss for each sequela included in the GBD study for IDM NTDs. Sequelae related to poor mental illness due to IDM diseases were not included in the GBD study and cutaneous leishmaniasis is not included in the London Declaration. Please refer to S3 Table. Publications reporting productivity loss for Chagas Disease and S4 Table. Publications reporting productivity loss for Visceral Leishmaniasis for a more detailed description of the sources. It shows mostly the productivity loss from absenteeism, due to lack of data on presenteeism. The table also shows additional information for chronic digestive disease and heart failure due to Chagas disease since the GBD study only reported the number of cases per disease sequela and not according to severity level. For example, regarding heart disease, only the numbers of cases with heart disease were reported and not the numbers per severity level (i.e. mild, moderate, severe). Therefore, in order to calculate an overall estimate of productivity loss, we had to combine our estimates of productivity loss per severity level with the estimated frequencies of the different severity levels (i.e., the 'case mix'). Table 1 therefore shows the productivity loss according to severity and case mix regarding severity for chronic digestive disease and heart failure. Upper and lower limits for the estimates of productivity loss are shown in the sensitivity analysis section.

Table 1. Annual percentages of productivity loss used in the calculations of economic benefit

Disease & Sequela	Severity	Base case - Annual productivity loss[1]	Case Mix[2]	Source	Remarks
Chagas					
Acute		2.33%	N.A.	[37]	7 of 300 working days
Chronic heart disease		4.67%	N.A.	[37]	14 of 300 working days
Chronic digestive disease	Normal bowel function	0%	30%	[37,38]	1% of the individuals with abnormal bowel function are assumed to undergo surgery, with a productivity loss of 45% (135 days of 100% productivity loss). Weighted average of prod loss of 3.8%.
	Abnormal bowel function	5%	70%	[37,39]	
Heart failure	Mild	0%	10%	[37,40]	14/300 working days and disability weight. Weighted average of prod loss of 61%.
	Moderate	4%	30%		
	Severe	100%	60%		
Human African trypanosomiasis					
Cognitive impairment	Severe	100% (Assumption)	52.5%[4]	[7]	Weighted average of productivity loss of 57%.[4]
Disfigurement	Level 2	10%[3]	47.5%[4]	[7]	
Leprosy					
Disfigurement due to leprosy	Level 2	28%	N.A.	[41]	
Visceral leishmaniasis					

table continues

Visceral leishmaniasis	100% (if untreated)[5] 6-30% (if treated)[6]	N.A.	[42-45]	Country-specific values were used to reflect differences in diagnosis and/or treatment patterns.

N.A. – Not applicable

1. If the original source did not provide the percentage of productivity loss, this was calculated based on the measurement unit used in the original source.
2. The case mix represents the distribution of the different degrees of severity within a disease sequela. Since the prevalent case estimates were only available per disease sequela and not severity, for sequelae with heterogeneous levels of severity (i.e., mix of milder and more severe forms), the productivity loss values (of the different degrees of severity) were combined with the case mix frequency to calculate a frequency-weighted value of productivity loss for that sequela. For sequelae with a more homogeneous level of severity, the productivity loss value was applied to all prevalent cases.
3. Used the same as onchocerciasis moderate skin disease [30].
4. The case mix in 2010 consisted of 47.5% mild cases and 52.5% severe cases, which changed linearly to 100% mild cases and 0% severe cases in 2020. Consequently, the weighted productivity loss of 57% in 2010 decreased linearly to 10% in 2020, which was represented solely by the productivity loss due to mild cases.".
5. The global estimate for the productivity loss of untreated patients is 50% (assuming 100% productivity loss over duration of illness, and assumed duration from symptoms to death is 6 months).
6. Productivity loss for treated patients in India, Sudan, Bangladesh, and Nepal is 20%, 30%, 6% and 20% respectively, which was extrapolated to the respective WHO region.
7. Case-mix values from the GBD study documentation and from the assumptions used by de Vlas et al.

Productivity loss due to premature mortality

The number of productive years lost due to NTD-related premature mortality per person was estimated using the country-, age-, and sex-specific data on years-of-life lost (YLL) as provided by the GBD study. The GBD calculations used uniform Japanese life-expectancies attributed to the year of death, but for our study we preferred to use country-specific life expectancies and only for the study period 1990-2030. We have therefore divided the YLL values by the Japanese age-specific life-expectancies to arrive at the number of deaths per country, age and sex, and treated them as incident cases for 'absent persons' due to death by an NTD (e.g., visceral leishmaniasis). The prevalence of such 'absent persons' was then calculated similar to the procedure for irreversible disease manifestations. Work-years lost were now calculated by the difference between the number of absent persons for the counterfactual scenario and target achievement scenario over the 1990-2030 period. Economic benefit from averted premature mortality in the 2011-2030 period was calculated by combining the lost productive years with income per person, for the 15+ age group. Discounting at 3% was applied to the results using the base year of 2010. [24]

Income

IDM-NTDs are highly prevalent in countries that are no longer regarded as low-income countries. Nevertheless, most NTDs continue to affect poor populations that do not experience the welfare and health benefits of the economic growth seen in these countries. [47,48]

Different methods were applied in previous economic analyses of NTDs to estimate the rural wage, including use of GDP per capita, average agricultural value added per worker and the lowest wage estimate from distinct predefined wage sources. [37,38,40]

We compared the GDP per capita of the lowest income quintile with the minimum nominal annual wage (both 2010 PPP) for the endemic countries with the highest number of prevalent cases (which would have the highest impact on the final results) and found that the minimum wage was higher than the GDP per capita of the lowest income quintile. Considering the characteristics of the populations affected by NTDs regarding welfare mentioned above, we decided to use the GDP per capita of the lowest income

quintile as a proxy for income when calculating the base-case impact estimate, and use only one data source for income instead of several.

GDP per capita for each country (purchase power parity-PPP, 2005 international $) and income shares of the five income quintiles were obtained from the World Development Indicators of the World Bank's website.[49] In the rare cases where information about GDP per capita or income shares of the year 2010 for a country was lacking, we used data from previous years; if no information from any year was available, we used the average of surrounding countries.

Since many of the countries included in this study have shown an increase in the GDP per capita of the lowest quintile in the last decade, we assumed that the income shares and the GDP per capita remained constant over the assessed period of 2011-2030, to keep estimates conservative. Income was not adjusted for labor force participation (people employed or actively looking for work) or age-related income patterns.

Out-of-pocket payments (OPPs)

The annual economic burden related to out-of-pocket payments was calculated using the formula below for each country and NTD independently (Fig.2). Despite the limited number of studies of OPPs from IDM-NTDs, it was possible to use country-specific values for Brazil, Argentina and Mexico, currently the countries with the highest prevalence of Chagas disease (based on GBD estimates). Their values for OPPs and productivity loss were therefore calculated separately. They serve as examples of how the economic impact of Chagas disease could be calculated for each country, if sufficient country-specific data are available.

Costs were calculated by multiplying four values: the total number of cases in each year; annual direct costs per sequela; percentage of cases treated each year, and percentage of patients paying for treatment each year. Since OPPs are not related to the ability to work, they were calculated for all prevalent cases, including children. We assumed no change in prices for the period 2011-2030 to keep estimates conservative.

Figure 2. General formula for calculating out-of-pocket payments

$$TDC_{cntd}=\sum_{y}\frac{\left(PS1_y * DCS1_y * PT_y * PP_y\right)+\left(PS2_y * DCS2_y * PT_y * PP_y\right)+\cdots}{(1+D)^t}$$

TDC = Total out-of-pocket payments (in US$ 2005)

NTD = Neglected tropical disease

c = Country

y = Year

PS1 = Number of persons with sequela 1 of NTD

PS2 = Number of persons with sequela 2 of NTD

DCS1 = Annual out-of-pocket payments relating to sequela 1 (per WHO region or country)

DCS2 = Annual out-of-pocket payments relating to sequela 2 (per WHO region or country)

PT = Percentage of patients treated

PP = Percentage of patients paying for the treatment

D = Annual discount rate

t = Time (years)

Prevalence estimates

The same prevalence estimates used to calculate the productivity loss were used to calculate the OPPs.

Annual out-of-pocket payments

OPPs relate to expenses usually incurred by an affected individual due to the illness, including consultation fees, medication, diagnostic tests, travel and escort costs, food, accommodation, etc. Whenever the information was available, the cost of the drug was excluded from the OPPs in case it is donated for free or reimbursed, as well as consultation or laboratory exams if they are also covered by the local health system. Depending on the data identified in the literature, country- or region-specific values were used. The same treatment value per sequela was used for all individuals in each country and sequela, and prices were adjusted to 2005 values using Consumer Price Index (CPI) and purchase power parity (PPP).[49]

In our calculations, the amount paid by patients varied depending on which direct costs patients have to pay per disease sequela and country. OPPs for HAT, for instance, included consultation fees, cost of travel, laboratory costs, all expenses for hospitalization as well as food for the patient and the caregiver. If the OPP described in the literature did not include non-medical payments, since estimates for these costs were lacking in the literature, we opted not to include them, also to keep our results conservative. If the medication was not included in the list of reimbursed drugs or the NTD was not included in the health insurance package, we assumed that all patients had to pay for treatment. This was the case for the three countries for which we could find specific information in the literature about Chagas disease. [38,50-68]

Percentage of cases treated and paying for treatment

The Sustainable Development Goals (SDGs) emphasize the need to address inequity and provide health for all. The goal of universal health coverage (UHC) means financial risk protection, access to quality healthcare services, and access to safe, effective, quality, and affordable essential medicines and vaccines for all. [69] In line with these concepts, a joint WHO/World Bank framework for monitoring progress towards UHC proposed a target of a minimum of 80% essential health services coverage and 100% financial protection from out-of-pocket payments in 2030, which would mean 100% of the population at risk protected against out-of-pocket payments due to NTDs by 2030. [70]

Parallel to the assumption that the London Declaration targets would be met, we therefore assumed a scenario where 80% of health coverage and 100% of financial protection would be achieved in 2030, instead of only assuming that people seeking care 'do not suffer financial hardship when using health services.' [71] We assumed that the percentage of patients currently paying for the treatment corresponds to the percentage of persons not covered by health systems or insurance, since, by definition, out-of-pocket payments are direct payments made by individuals to healthcare providers at the time of service use. [72]

In the counterfactual scenario, the percentage of cases that were treated in 2010 was kept constant at that level until 2030, to simulate a situation where nothing would be done. Similarly, the percentage of cases that paid for their treatment in 2010 was kept constant until 2030. In the target achievement scenario, we assumed that the percentage of cases

treated in 2010 would linearly increase to 80% in 2030, and we assumed that the percentage of patients who paid for their treatment in 2010 would linearly decrease to 0% in 2030.

For these percentages, the literature review provided country-specific data for the three most prevalent countries for Chagas disease: Argentina, Brazil and Mexico. [145,156,159,161,163-168,175-177] A general average price for Latin America from Wilson et al was used for all other endemic countries, after correction for PPP for each endemic country (Table 2). [51]

Table 2. Out-of-Pocket Payments, percentage of patients being treated and percentage of patients paying for treatment according to the literature, used in the calculations for Chagas disease (I$ - international dollars)

Out-of-pocket payments					
	Acute	**Chronic Heart Disease**	**Chronic Digestive Disease**	**Heart failure**	**Source**
Argentina	$ 32.35	$ 3,505.46	$ 4,275.12	$ 3,505.46	[36,37]
Brazil	No costs	$ 2,574.21	$ 902.71	$ 8,231.06	[56,58]
Mexico	$ 112.54	$ 267.69	$ 875.90	$ 19,351.39	[68]
General [1]	$ 15.98 - 46.94	$ 390.1 - 1115.83	$ 390.1 - 1115.83	$ 296.2 - 1564.03	[38,51]
Percentage being treated					
All countries	10%	35%	35%	35%	[38,39,51]
Percentage paying for treatment					
Argentina	100%	38%	38%	38%	[54,55,57,77,78]
Brazil	0%	25%	25%	25%	[57,79,80]
Mexico	100%	100%	100%	100%	[50,57,81,82]
General [2]	100%	25%	25%	25%	[57,79,80]

1. Between country variation.
2. For conservative reasons, we assumed the same situation as in Brazil for all other endemic countries, since Brazil has the lowest percentage
3. of people paying: 75% of the population has free access to its health system. [79]

Like Chagas, some country-specific OPPs for visceral leishmaniasis were found for India, Bangladesh, Nepal, and Sudan, which were used to calculate the annual OPPs for these countries (sources listed in S5 Table. Publications reporting Out-of-Pocket Payments for Chagas disease and S6 Table. Publications reporting Out-of-Pocket Payments for Visceral Leishmaniasis). A general average price available from the literature was used for all other endemic countries. Percentages for treated patients (successfully and unsuccessfully), untreated patients and patients paying for treatment were also derived from the literature and were assumed to linearly reach 80% treatment (keeping the same proportion between the three treatment categories) and 100% not paying for treatment in 2030, considering UHC as previously mentioned (Table3).

Table 3. Values used to calculate Out-of-pocket payments (OPPs) for visceral leishmaniasis (I$ - international dollars)

Out-of-pocket payments		**Reference**
India	$ 354.75	[43]
Sudan	$ 488.89	[43,83,84]
Bangladesh	$ 286.84	[45]
Nepal	$ 364.00	[42]
General	$ 160.00	[84,85]
Percentage being treated		
India	80%	[86-88]
Sudan		
treated successfully	50%	[89]
treated unsuccessfully	5%	
untreated (undetected)	45%	
Nepal/Bangladesh	80%	[87,90]

All drugs currently used for the treatment of human African trypanosomiasis are donated to WHO for free distribution by the manufacturers (Sanofi and Bayer). Nevertheless, individuals affected by HAT still bear other costs than medication costs when seeking treatment, which is one of the reasons for many of them either not to seek treatment, or only do so long after their diagnosis or when their symptoms become more acute. [193] The OPPs described for HAT in the study by Lutumba et al. included these costs, i.e

consultation fees, cost of travel, laboratory/diagnostic costs, food for the patient and caregiver during hospitalization, and material such as syringes and needles. These costs were used for all endemic countries, after correction (Consumer Price Index – CPI and purchase power parity – PPP (Table 4). [27,91-93]

We assumed no OPPs for leprosy since no information was available from the literature at the time the literature review was performed and to keep the estimates of OPP conservative. This assumption is supported by the fact that multidrug therapy (MDT) has been made available free of charge through the WHO for the past 20 years. The costs of palliative treatment of the incurable sequelae were not included for the same reasons.[70]

Table 4. Values used to calculate Out-of-Pocket Payments (OPPs) for human African trypanosomiasis (I$ - international dollars)

OPPs		**Reference**
Annual prices per HAT case	$ 156.77	[193]
Percentage being treated		
General	24%	[195] (7,200 reported, 30,000 estimated)
Patients paying		
General	100%	Assumption

Return on Investment

We calculated the net return on investment (ROI) by obtaining a crude estimate of the relationship between the economic benefit and the necessary investments to reach the 2020 NTD Roadmap targets and the 2030 SDG targets. The net ROI is the current value of the benefit to affected individuals minus the current value of the cost to public and philanthropic funders, divided by the current value of the cost to public and philanthropic funders. The economic benefit to affected individuals of averted OPP and productivity loss calculated in this study and the investment costs based on recent WHO estimates published in the Third Report on Neglected Tropical Diseases were used in these calculations.

In the case of IDM NTDs, only investments in individual management of HAT, leprosy, and visceral leishmaniasis were included, as well as active case finding for HAT, leprosy and VL, and vector control for VL (only in areas of the Indian subcontinent that are not co-endemic with malaria), plus the cost of integrated surveillance in HAT-endemic areas. Investments and benefits related to Chagas disease were not included. [70]

For comparison to the disease-specific investment targets published by WHO in the Third Report on Neglected Tropical Diseases, the I$ 2010 benefits were converted to US$ 2015. Since part of these benefits can clearly be credited to investments made before 2011, we conservatively assumed the investments to be equal to those in 2011 (adjusted for inflation). We assumed 1990 to mark the beginning of concerted global efforts to control most NTDs and 2011 to mark the beginning of the recent scale-up in investment to eliminate them. In reality, investments before 2011 were probably lower than this in most countries. We did not consider investments in improving housing and water and sanitation that occurred over the same period, since these were not targeted at the NTDs but contributed to their control nonetheless. The ROI for middle and low income settings was not calculated separately due to lack of the necessary data on investments. Since investments estimates are given in US$, ROI is presented in US$ only. A discount rate of 3% per annum was applied for both costs and benefits. More detailed information on the ROI and the internal rate of return per WHO region, as well as other considerations on the investment case of ending/controlling NTD, can be found in the recently published DCP3/World Bank volume on infectious diseases by Fitzpatrick et al. [95]

Sensitivity analysis

The economic benefit was calculated using base-case values for the components of the formulae described above. We examined how much effect changes in four input parameters used in our calculations had on the estimated economic benefit: 1) the prevalence estimates, 2) the productivity loss percentages and out-of-pocket payments, 3) income, and 4) percentage of patients seeking and paying for treatment.

We performed a probabilistic sensitivity analysis, where the values of all input parameters are varied simultaneously to obtain the overall uncertainty regarding the economic

benefit. Beta PERT distributions were used in combination with values shown in table 5; the values of the different parameters were assumed to be independent of each other.

By applying the country-specific upper and lower confidence limits of the GBD - 2010 estimates, we examined the relevance of uncertainty about the prevalence in all the years in the 2010–2030 period. Productivity loss and OPP values were varied by using the highest and lowest values found in articles with sufficient quality retrieved in the literature review. If no estimates were available from the literature, assumptions were made, as described in Table 1. For each disease, we varied income using data from the country with the most prevalent cases in the world. The lower limit of income equalled the average income in the lowest income decile in that country, while the upper limit equalled the average income in the second-lowest income quintile. For OPPs, we varied the uncertainty regarding out-of-pocket payments (per person) by a factor of 2 (i.e., from 50% to 200%). [24]

The rough estimates of the return on investment calculated in this study were not subject to sensitivity analysis, following the original publication by Fitzpatrick et al. [95]

Table 5. Upper and lower limits used in the sensitivity analyses

	Chagas disease			HAT			Leprosy			Visceral leishmaniasis		
	Lower limit	**Point estimate**	**Upper limit**	**Lower limit**	**Point estimate**	**Upper limit**	**Lower limit**	**Point estimate**	**Upper limit**	**Lower limit**	**Point estimate**	**Upper limit**
Relative uncertainty in global prevalence in 2010	0.226	1.000	1.90	0.190	1.000	2.90	0.689	1.000	1.41	0.569	1.000	1.57
Estimates of productivity loss [1]	50%	57%	100%	2%	5%	10%	14%	28%	55%	6%	19%	100%
Estimates of income	0.836	1.000	1.673	0.588	1.000	2.265	0.871	1.000	1.424	0.871	1.000	1.424
Out-of-Pocket Payments per person	0.50	1.00	2.00	115	700	11,954	N.A.[6]	N.A.[6]	N.A.[6]	1.00	1.00	1.00
Probability of being treated (counterfactual scenario)	0%	6.7%[2] 35%[3,4,5]	100%	0%	24%	100%	N.A.[6]	N.A.[6]	N.A.[6]	0%	55%	100%
Probability of paying for healthcare (counterfactual scenario)	0%	67%[2] 69.4%[3,4] 34.2%[5]	100%	0%	80%	100%	N.A.[6]	N.A.[6]	N.A.[6]	0%	80%	100%
Probability of being treated	0%	80[2,3,4,5]	100%	0%	80%	100%	N.A.[6]	N.A.[6]	N.A.[6]	0%	80%	100%

table continues

(target achievement scenario)												
Probability of paying for healthcare	0%	0%	100%	0%	0%	100%	N.A. [6]	N.A. [6]	N.A. [6]	0%	0%	100%
(target achievement scenario)												

1. The productivity loss estimates seen in Table 1 are here shown as frequency-weighted estimates per disease with their respective upper and lower limits used in the sensitivity analysis

2. Value for acute Chagas disease sequela (weighted average of three most prevalent countries).
3. Value for chronic heart disease sequela (weighted average of three most prevalent countries).
4. Value for chronic digestive disease sequela (weighted average of three most prevalent countries).
5. Value for heart failure sequela (weighted average of three most prevalent countries).
6. N.A. – not applicable

Technical validity

R scripts were written to examine the technical validity of our Excel-based calculations. They used the same original data (GBD, UNPOP (United Nations Population Division), GDP, productivity loss) as the Excel files (though transformed), but were completely independent of the Excel calculations. The small number of differences were found led to the improvement of the formulae for some of the diseases and subsequent matching (or calibration) of the results, although the general programming in Excel did not change. R scripts and sample Excel sheets can be found in the Supporting Information section.

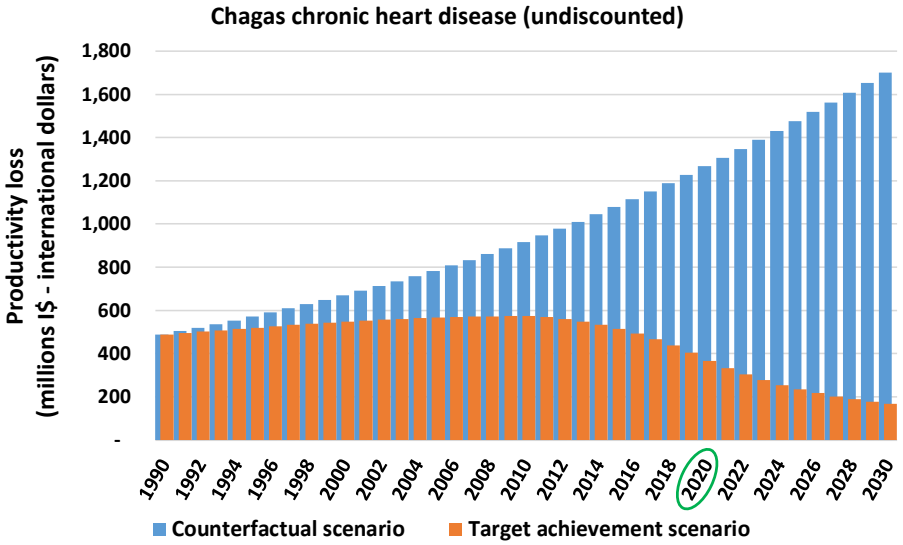
The health benefits calculated by De Vlas et al. and the economic benefits shown here will be publicly available through the open access website: https://erasmusmcmgz.shinyapps.io/dissemination/.

Results

Productivity loss

Figure 3 provides a graphical demonstration of the different cost estimates and their trend over time in the counterfactual and target achievement scenarios. The difference between the rising productivity costs in the counterfactual scenario and the decreasing costs in the target achievement scenario represents the total economic benefit of achieving the targets, which is highly dependent on the estimated prevalence of the IDM-NTDs over time. Since the same pattern can be seen for all IDM diseases and related sequelae, we provide the example of productivity costs from the Chagas chronic heart disease sequela (the sequela with the biggest impact).

Figure 3: Productivity loss due to Chagas chronic heart disease according to the counterfactual and target achievement scenarios (millions I$ - international dollars).



Total global loss per year in the counterfactual scenario (blue) and target achievement scenario (orange). The economic benefit is the difference between both scenarios.

Overview of the global estimates of the economic benefit from averted productivity loss

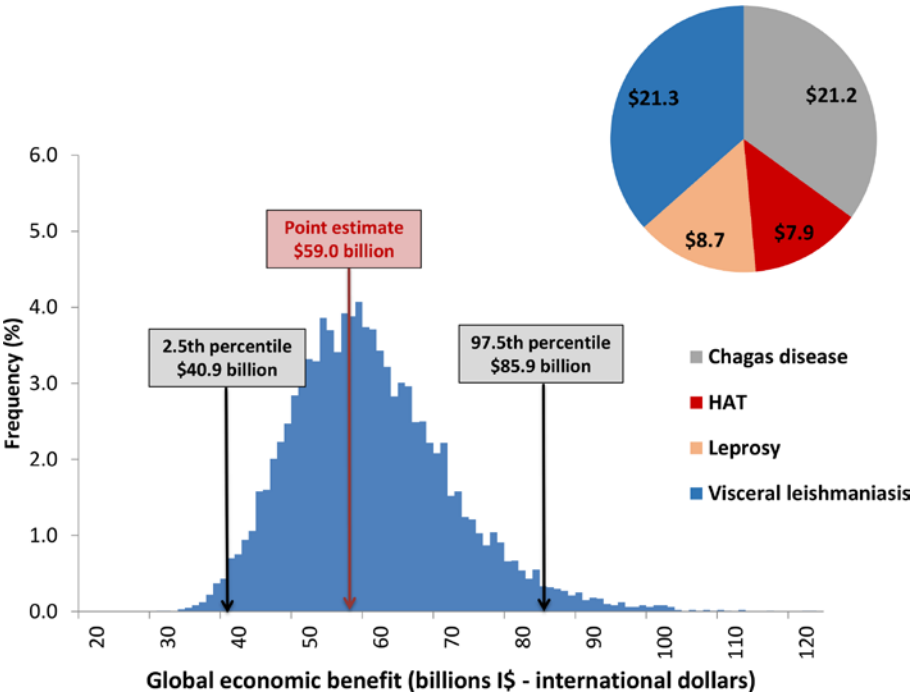
Table 6 shows the total economic benefits in productivity gain for each of the IDM-NTDs and their sequelae. The total benefits of achieving the targets for all four IDM diseases were estimated at I$ 23.1 billion (I$ 15.9 – 34.0 billion) or US$ 10.7 billion (US$ 7.4 – 15.7 billion) in 2011-2020 and I$ 35.9 billion (I$ 25.0 – 51.9 billion) or US$ 16.6 billion (US$ 11.6 – 24.0 billion) dollars in 2021-2030 (base case estimates and 2.5th and 97.5th percentile values from the sensitivity analysis).

Table 6: Total economic benefit from productivity loss averted, base case estimates and 2.5th and 97.5th percentiles (billions I$ - international dollars and US$ - US dollars 3% discounting from 2010)

Disease	Sequelae	Economic benefit (productivity loss averted)		Economic benefit (productivity loss averted)	
		I$ - International dollars		US$ - US dollars	
		2011-2020	2021-2030	2011-2020	2021-2030
Chagas disease	Acute	$ 0.4	$ 0.5	$ 0.2	$ 0.3
	Chronic heart disease	$ 5.1	$ 7.9	$ 2.9	$ 4.6
	Chronic digestive disease	$ 0.8	$ 1.1	$ 0.5	$ 0.6
	Heart failure	$ 0.3	$ 0.8	$ 0.2	$ 0.5
	Chagas deaths	$ 1.6	$ 2.7	$ 0.9	$ 1.5
	Total	$ 8.2 [3.0 – 17.2]	$ 13.0 [4.9 – 27.6]	$ 4.7 [1.7 – 9.8]	$ 7.5 [2.83 – 15.9]
HAT	African trypanosomiasis	$ 0.5	$ 0.6	$ 0.3	$ 0.3
	African trypanosomiasis deaths	$ 2.7	$ 4.1	$ 1.5	$ 2.3
	Total	$ 3.2 [2.6 – 16.6]	$ 4.7 [1.5 – 9.8]	$ 1.8 [1.5 – 9.3]	$ 2.6 [0.9 – 5.5]
Leprosy	Disfigurement	$ 3.7	$ 5.0	$ 1.5	$ 2.0
	Total	$ 3.7 [2.0 – 6.2]	$ 5.0 [2.7 – 8.4]	$ 1.5 [0.8 – 2.5]	$ 2.0 [1.1 – 3.4]
Visceral leishmaniasis	Visceral leishmaniasis	$ 0.1	$ 0.1	$ 0.03	$ 0.04
	Visceral leishmaniasis deaths	$ 7.9	$ 13.2	$ 2.7	$ 4.5
	Total	$ 8.0 [5.1 – 11.7]	$ 13.3 [8.5 – 19.4]	$ 2.7 [1.7 – 3.9]	$ 4.5 [2.9 – 6.6]
Total (all diseases)		**$ 23.1 [15.9 – 34.0]**	**$ 35.9 [25.0 – 51.9]**	**$ 10.7 [7.4 – 15.7]**	**$ 16.6 [11.6 – 24.0]**

Figure 4 shows the total values per disease (in I$) together with the sensitivity analysis diagram of the calculations of the total economic benefit of achieving the 2020 targets for the IDM diseases. The total economic benefit calculated for the entire period was $59.0 billion, with the 2.5th and 97.5th percentile values of I$ 40.9 and I$ 85.9 billion calculated in the sensitivity analysis.

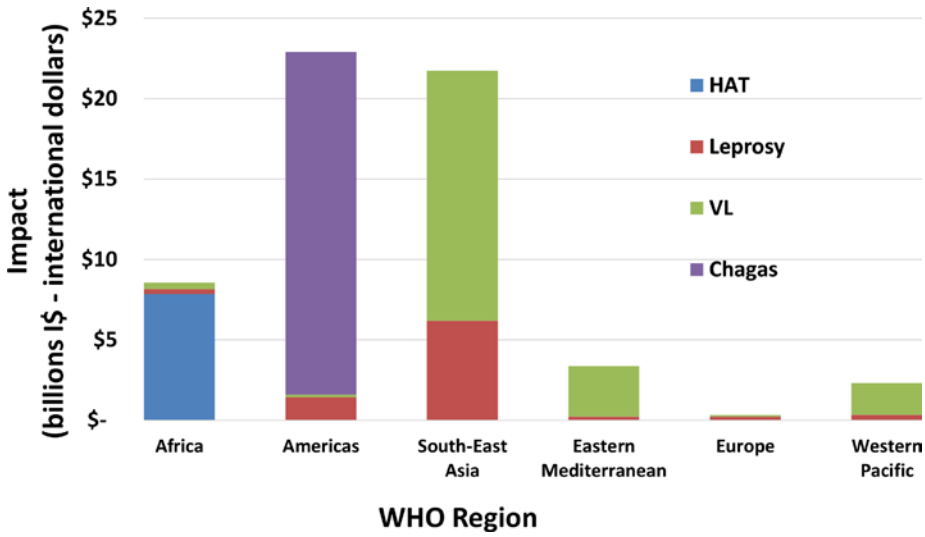
Figure 4. Global economic benefit (productivity loss averted) for IDM NTDs, for the period 2011-2030 (billions I$ - international dollars).



Global economic benefit from reaching the targets for IDM NTDs, lower and upper estimates from sensitivity analysis. Global economic benefit per disease.

Figure 5 shows the regional variation in the economic benefit, with the Americas and South-East Asia outweighing over the other regions due to Chagas disease and visceral leishmaniasis, respectively. More productivity loss prevented can be expected in the Americas and South-East Asia regions due to Chagas disease and visceral leishmaniasis, respectively.

Figure 5. Regional economic benefit (productivity loss averted) for IDM NTDs, for the period 2011-2030 (billions I$ - international dollars) per WHO region.



Regional economic benefit from reaching the targets for IDM NTDs, for the period 2011-2030 per WHO region.

Out-of-Pocket Payments

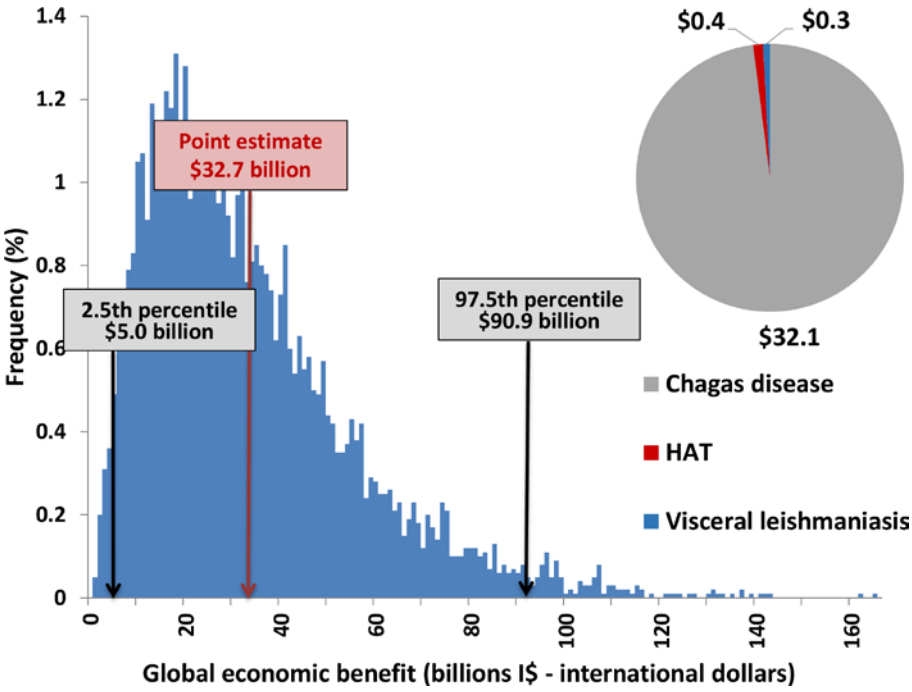
IDM-NTDs impose a considerable burden on patients, mostly due to their incurable sequelae, and often compel patients to seek and pay for treatment. [13,96] Table 7 shows the economic gains regarding out-of-pocket payments that could be expected by reaching the 2020 targets for IDM-NTDs. Chagas chronic heart disease is the main reason for the OPPs among all sequelae.

Table 7: Total economic benefit from out-of-pocket payments averted, base case estimates and 2.5th and 97.5th percentiles (billions I$ - international dollars and US$ - US dollars) discounting 3% from 2010

Disease	Sequelae	Economic benefit (OPPs averted) I$ - International dollars		Economic benefit (OPPs averted) US$ - US dollars	
		2011-2020	2021-2030	2011-2020	2021-2030
Chagas disease	Acute	$ 0.02	$ 0.05	$ 0.01	$ 0.03
	Chronic heart disease	$ 12.52	$ 14.50	$ 5.70	$ 8.20
	Chronic digestive disease	$ 1.41	$ 2.95	$ 0.81	$ 1.74
	Heart failure	$ 0.15	$ 0.48	$ 0.08	$ 0.26
	Total	$ 14.10 [2.2 – 41.7]	$ 17.97 [2.5 – 48.6]	$ 6.57 [1.2 – 21.9]	$ 10.24 [1.3 – 25.5]
HAT	African trypanosomiasis	$ 0.19 [0.001 – 1.5]	$ 0.20 [0.001 – 1.6]	$ 0.10 [0.0005 – 0.75]	$ 0.10 [0.0005 – 0.80]
Visceral leishmaniasis	Visceral leishmaniasis	$ 0.13 [0.06 – 0.19]	$ 0.14 [0.06 – 0.22]	$ 0.05 [0.02 – 0.07]	$ 0.05 [0.02 – 0.08]
Total (all diseases)		$ 14.42 [2.4 – 42.0]	$ 18.31 [2.6 – 48.9]	$ 6.72 [1.12 – 19.55]	$ 10.39 [1.48 – 27.75]

Figure 6 shows the total values per disease together with the sensitivity analysis diagram. The total economic benefit calculated for the entire period was I$ 33 billion, with the 2.5th and 97.5th percentile values of I$ 5 and I$ 90 billion calculated in the sensitivity analysis.

Figure 6. Global economic benefit (out-of-pocket payments averted) for IDM NTDs, for the period 2011-2030 (billions I$ - international dollars).



Total economic benefit from out-of-pocket payments averted, base case estimates and 2.5th and 97.5th percentiles (billions I$ - international dollars), discounting 3% from 2010.

Return on Investment

The ROI was calculated based on an estimated benefit of US$ 5.4 billion (in 2015-2020) and US$ 20.9 billion (in 2015-2030), assuming the 2020 targets for IDM diseases were to be met, and considering costs to funders of US$ 1.1 billion and US$ 2.2 billion in 2015-2020 and 2015-2030, respectively.

The net benefit was estimated to be US$ 0.9 [0.62 – 1.32] for every dollar invested during the period 1990-2020 and US$ 2.8 [1.94 – 4.05] for every dollar invested in the period 1990-2030 (best estimates and 2.5th and 97.5th percentiles related only to the benefits). A net benefit of US$ 0.9 per dollar means every dollar invested yielded US$ 1.9 in benefits, or benefits nearly double the investment in the period 1990-2020. [95]

Discussion

This study is a first attempt to estimate the global economic benefits of achieving the London declaration targets for four IDM NTDs (Chagas disease, human African trypanosomiasis, leprosy, and visceral leishmaniasis).

General approach

Scarce and heterogeneous data available on country- or regional-specific productivity loss and OPPs related to the different NTDs and their sequelae limits the comprehensiveness of this economic analysis to some extent. The same can be said about the paucity of information regarding the characteristics of the affected populations (e.g. income) and the impact of assumptions regarding the future frequencies of each NTD. More accurate measures of productivity loss caused by NTDs and better descriptions of the affected populations (e.g., type of work, income) in the different affected countries would greatly improve the quality of any estimates of the economic burden of NTDs and the economic benefits of controlling NTDs.

The economic benefits of reaching the 2020 targets for IDM-NTDs were estimated using the human capital approach, which increases comparability with other studies. However, critics may argue that it overestimates the extent of productivity loss from the societal perspective. [97] Nevertheless, the perspective from the individuals affected by these diseases, rather than a societal one, was chosen for this study. The first reason for this choice was to maintain comparability with the recently published results regarding the economic benefit of reaching the 2020 London Declaration targets for PCT NTDs (i.e., the ones controlled or eliminated through preventive chemotherapy).[24] Secondly, the friction cost method focuses only on lost productivity until a replacement can be found.

Use of the friction cost method is likely to have a limited effect on the results for leprosy and Chagas since these diseases can lead to reduced productivity while working (presenteeism) rather than simply lost work days (absenteeism) and presenteeism will not necessarily lead to replacement of the worker. Therefore, the use of the friction method is not expected to have a substantial effect on the estimated economic benefit for these diseases. In contrast, the biggest economic impact for HAT and VL is through avoiding premature deaths. Therefore, the friction cost method might have been a better choice, since premature death would lead to worker replacement. We also acknowledge that the aggregation of individual costs does not exactly correspond to the total societal cost, since individuals' productivity losses can be compensated by a variety of mechanisms at the societal level. Some of these mechanisms are discussed later in this section (e.g., household coping strategies).

Labor is not the only factor that influences the link between income and productivity. In all retrieved papers there was not enough information on whether there is a linear relationship between health and productivity. Therefore, and also because of using conservative values for productivity loss, we assumed that average productivity gain would equal marginal productivity gain. The lack of information in the literature prevents us from knowing if this would have under- or overestimated the results.

Household coping strategies, social security, productivity loss of caregivers of people with IDM-NTDs, and work compensation mechanisms were not included in the calculations. However, household coping strategies can mediate the effects that an illness of a family member can have on household finances in several ways; for example, another member might start working to reduce the loss of household income. However, even if coping strategies are able to maintain the household income, they may reduce future opportunities for children who suspend their education and start working. [23] The productivity loss due to psychosocial consequences of the diseases (i.e.stigma and discrimination) was also not included, since these types of sequelae are not included in the GBD study; their omission may have led to an underestimation of the economic benefit.

The basis for the diseases (and their sequelae) included in the GBD study was a set of brief lay descriptions emphasizing the main functional consequences and symptoms

associated with each health state. For the sake of simplicity, comprehensibility, and feasibility, some aspects of health states were inevitably omitted in the GBD study, which means that it might not encompass all disease consequences. [40] For instance, erythema nodosum leprosum, a complication of leprosy that is known to result in direct costs by affected individuals, was not included. [197] Inclusion of other health states would lead to a higher estimate of the productivity loss and OPPs, and consequently, of the economic benefit.

The large differences in the magnitude of the economic gain between the different diseases and sequelae and the affected countries/regions are a direct consequence of the prevalence of each disease in each country, the consequences of each sequela, the chosen proxy for income and the percentages of patients being treated and paying for treatment for these diseases in each country or region.[34] One should be careful when making comparisons between diseases. First, the results for each disease are affected differently by the data limitations and potential biases in the methodology mentioned in the 'Limitations' section. The estimated economic benefit from investments in NTDs also relies on the way productivity is valued in monetary terms. Assigning exclusively monetary value to these domains in terms of productivity gain undervalues the much bigger gain in physical and mental health that will lead to the increase in productivity. Therefore, policymaking should consider the health impact of controlling NTDs and not simply the economic benefit (as calculated here).

The expected benefits in 2021-2030 are greater than that in 2011-2020, which is not surprising, since the difference in disease frequency between the counterfactual scenario and target achievement scenario will be greater in 2021-2030 (after the targets are met).

The gains of achieving the 2020 targets for IDM diseases are not restricted to the economic benefits, with billions of people gaining physical and mental health, increased mobility, improved performance in school, access to care, structural improvement of health care services, community participation, and democracy with the control/elimination and eradication of NTDs. [198] Therefore the economic benefits estimated in this study represent just one part of the benefits that society could experience by achieving the London Declaration goals.

Comparisons with the literature

As far as we are aware of, this is the first reported attempt to estimate the economic burden of IDM diseases per endemic country and globally, from an individual's perspective. We know of only one other global cost-of-illness study of an IDM disease. Specifically, Lee at al. estimated a global annual burden from Chagas disease of US$ 0.5 ($0.2 – 1) billion in healthcare costs (corrected to US$2005 values for comparison) and US$ 6 (4 - 8) billion including lost productivity for Latin America related to disease-induced early mortality, using a societal perspective. Their estimate of healthcare costs is approximately 30% less than our estimate of annual OPPs of US$ 0.85 (0.1 – 2.4) billion (2011-2030) while their estimate of lost productivity related to mortality is two times greater than our annual general productivity loss average of US$ 1.4 (0.9 – 2.0) billion using an individual's perspective. However, it is difficult to make meaningful comparisons between our estimates and their estimates because of differences in methodology. For example, Lee et al grouped countries into quartiles based on GDP per capita (low/low-middle/high-middle/high income) and estimated the healthcare costs by quartile, assuming a linear correlation between costs and GDP per capita. With the exception of the three most prevalent countries (for which we had country-specific estimates), we converted one general Latin American estimate to local currencies of each of the other endemic countries. Lee et al included treatment-seeking probability in their model that was much higher than the percentage that we used (78% versus 35%). Also, they did not mention what they used regarding percentage of people paying for the treatment. [100]

NTDs and poverty

Paying for treatment – especially for IDM-NTDs treatment – can be catastrophic for individuals and even for households.[35] This is one of the reasons why the Sustainable Development Goals (SDGs) are more difficult to achieve without addressing NTDs (and vice-versa). This is especially true for goal 3.3: 'By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases.' [7,101] Furthermore, NTDs constitute an obstacle to achieving wider human development outcomes (for instance, food and

nutritional security, and improved maternal and child health). So, undoubtedly, achieving universal health coverage for NTDs will support progress in various interdependent development areas, such as poverty, education, sanitation, nutrition, water and gender equality. [9,70]

Limitations

Prevalent cases

Due to the scarcity of data on NTD spread and control, the prevalence estimates from the GBD study show very wide confidence intervals. These wide CIs affect the predictions by De Vlas et al. of the health impact of achieving the targets described in the London Declaration. Substantial uncertainty regarding the frequency of IDM diseases also existed, where the variation ranged from five times less to up to three times greater than the mean values (Table 7), dependent on availability of country and disease-specific epidemiological data [26]. This uncertainty only increased as the GBD numbers were extrapolated to estimate the prevalence in the period of 2010-2030. Given the influence of disease frequency on our estimates of economic impact, we included uncertainty about disease frequency in our sensitivity analyses. The results of these analyses show that even if the true prevalence values were close to the lower limits of the ranges used in our analyses, the economic impact would still be substantial**.**

Productivity loss and Out-of-Pocket Payments

In general, limited data was found on productivity loss and out-of-pocket payments, as well as the percentages of patients getting treatment or having to pay for it. As described in the Methods section, the OPP estimates available in the literature regarding IDM-NTDs varied, partly because some sources included only drugs, while others included other medical and non-medical costs. This means that the values used might have been overestimated for some diseases but underestimated for other diseases. For instance, the variability in OPP prices for Chagas disease between Argentina and Brazil is due to their differences regarding the organization of the health system, the approaches to treating Chagas disease and its manifestations, and the infrastructure to treat Chagas manifestations. As an example, the digestive form of Chagas disease frequently needs

surgery, but the direct costs related to it depend on access to hospital care and whether treatment is insured. [38,50-68]

We also assumed that the percentage of patients paying for treatment equals the percentage of uninsured persons. This could lead to an overestimation of the costs, since not all individuals affected by NTDs might want treatment or be able to pay for it. However, it could also be an underestimation of the costs, since in many countries insured patients pay for treatment out-of-pocket in order to be treated faster.

When no OPP or productivity loss values could be found, assumptions were made. In some cases, data from other diseases with similar sequelae were used. For instance, the productivity loss from disfigurement due to HAT was estimated using the estimate for onchocerciasis moderate scriot disease since they have the same GBD sequela category. [102]

Most of the studies described lost productivity in working days missed because of the disease sequelae (absenteeism), especially for visceral leishmaniasis and Chagas digestive disease, where treatment itself requires a long hospitalization.[41-43,88,103-106] Only a few studies provided quantitative estimates of the decreased productivity loss at work due to presenteeism, something that can occur because of problems such as disfigurement or the early stages of Chagas disease.[38,62]

Several assumptions regarding the generalizability of data had to be made due to lack of data. First, the same estimate for productivity loss was applied to men and women, even though the degree of productivity loss may differ between the two. [107-112] Secondly, for each sequela, the same estimate for productivity loss was applied to all individuals and countries, even though it differs between professions and settings. A similar situation was seen with OPPs, since sometimes only one estimate for one country was available (i.e. HAT), although the values used in the different countries were adjusted using CPI and PPP. Transferring the data from one country to another might have led to over- or underestimates of productivity loss estimates, as well as OPPs, depending on the disease sequela, the profession and the working environment, and the characteristics of each health care system.[34,113]

The achievement of 80% essential health services coverage and 100% financial protection from out-of-pocket payments in 2030, will surely happen in various ways and paces in the 191 countries included in this study. Most countries might want to invest sooner to gain more efficiency by reducing the vectors and prevalent cases and thereby reducing the number of infected individuals and disease transmission. This approach would probably follow a curve of 'economies of scale', which would mean more investments than the linear approach we followed. This would probably result in less economic benefit, but it would be difficult to estimate how much less, given the many possibilities and scenarios each country faces. In this sense, we calculated an ideal scenario that included reaching both the London Declaration targets and the WHO/World Bank recommendations for universal coverage and financial protection regarding NTDs aiming to provide extra arguments in favor of pursuing them.

Income

Different methods have been used in previous economic analyses of NTDs to approximate the rural adult wage, including use of GDP per capita, average agricultural value added per worker and the lowest wage rate from different predefined wage sources.[25,114,115]

The GDP per capita of the lowest income quintile was used as a proxy for income for our calculations, since it provided the lowest - and therefore most conservative - estimates possible without having to combine multiple data sources. This approach could be criticized as an overestimation of the annual productivity loss of the affected populations, since NTDs are typically known as diseases of the poorest. We consequently varied income to the GDP per capita of the lowest decile in the sensitivity analysis.

Sensitivity analyses

A good estimate of the uncertainty around the economic impact shown in this paper is an impossible task, since the uncertainty regarding the impact on prevalence over the years cannot be reliably estimated Although sensitivity analyses were carried out to estimate the degree of uncertainty surrounding our estimates of economic benefit, greater knowledge of the variables used would improve the quality of the analyses.

Despite the effort to account for many of the differences between diseases (sequela, productivity loss, OPP per disease, etc), our analyses represent a simplification of reality. In case more empirical data become available, more detailed studies could be done for each disease. Moreover, individual countries are encouraged to perform similar analyses to gather and use local data wherever possible to derive better local estimates of economic benefit.

Reaching the 2020 targets for the 10 London Declaration NTDs described by the WHO [15,17] will depend on continued and sufficient efforts to achieve them, so especulating that they will be met of course implies a natural uncertainty about the future. The real economic benefit will certainly depend on local data, local circumstances, and the degree that each country will reach those targets. In this sense, our results support the implementation of efforts to reach these goals, but our results cannot help in deciding on how to reach them.

Conclusions

While the different factors of uncertainty described in the Discussion suggest that the results of this study should be interpreted with care, we can safely conclude that the economic benefits to individuals are at least equal to the investments required by governments and their development partners to reach the London Declaration 2020 targets. It is more likely that the economic benefits will far exceed the necessary investments. Given the higher frequency of NTDs among the poorest households, these investments represent good value for money in efforts to increase human well-being and freedom, to better share the world's prosperity and reduce inequity. We hope that these results can help policymakers in affected countries to choose to add NTDs to their public health, medical and scientific priority lists. A concerted effort is needed to collect better epidemiological and economic data to enable more accurate and complete estimates, which can be a better basis for planning and decision making.

Acknowledgments

We would like to express our sincere gratitude to the following individuals whose valuable comments and insights contributed to the development of this work: Donald Bundy, Deborah McFarland, Anna Righetti, and Danique Roodnat.

We are especially grateful to Wichor Bramer, whose work as a biomedical information specialist was crucial in designing the most comprehensive possible syntaxes for our literature reviews.

The authors alone are responsible for the views expressed in this article, which do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

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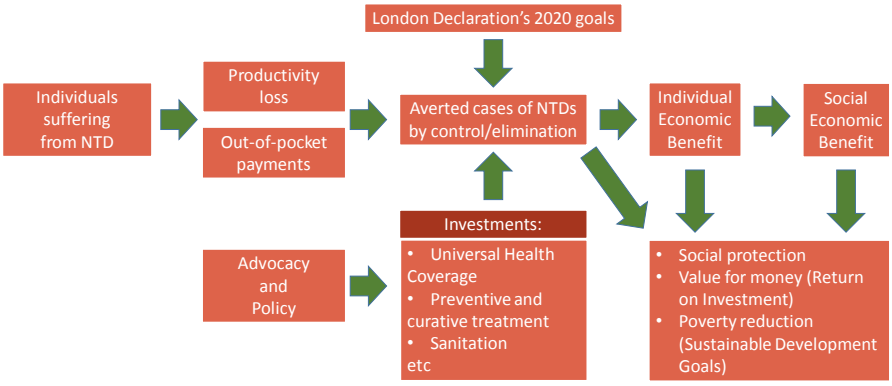
Supporting Information

S1 Figure. Conceptual framework



S1 File. Literature Search Syntax

(please refer to file S1 in Chaper 2)

S2 File. Grey Literature Search

(please refer to file S2 in Chaper 2)

S1 Table. Results of database searches.

Database	Hits	After exclusion of duplicates
Embase.com	2913	2854
Medline (OvidSP)	2887	682
Web-of-science	1224	478
Scopus	3339	660
CINAHL	282	126
PubMed publisher	175	150
Cochrane	60	7
Popline	176	147
Lilacs	257	100
Scielo	36	26
Google Scholar	100	87
Total	11449	5316

The literature review yielded 11449 hits, 5316 after duplicates were excluded, for the 10 NTDs cited in the London Declaration.

S2 Table. Literature review – results per disease.

	Human African Trypanosomiasis	Chagas Disease	Visceral Leishmaniasis	Leprosy
Papers screened on title and abstract	95	355	497	709
Assessed full text	25	95	54	97
Studies with quantitative data on productivity losses	3	12	10	4
Studies with quantitative data on out-of-pocket payments	1	19	14	6

The paucity of studies that provide quantitative estimates of productivity loss and OPPs from NTDs can be seen in the table above.

S3 Table. Publications reporting productivity loss for Chagas Disease

Author	Year	Country	Study design	Population	Sample size	Sequela	Definition of productivity loss	Results
Arata et al.	1994	Bolivia	Report	NA	NA	b.chronic heart disease c.heart failure d.digestive disease	production lost due to chagas morbidity	b, c, d. conservative estimate of 25% incapacity is used for chronic Chagas cases in Bolivia 1-3% of chronic cases require surgery or sophisticated interventions
Basombrío et al.	1998	Argentina	Cost-benefit analysis	Inhabitants of the province of Salta	NR	a.acute b.chronic heart disease c.heart failure d.digestive disease	inability to work	a.average 7 days/year b.mild cardiopathy cannot perform physically demanding jobs but can undertake light tasks, only partial incapacity - 14 days/year c.patients with severe cardiopathy are incapable of working d.full working ability for many years, partial incapacity only in advanced stages - 15 days/year 5% digestive cases need surgery

table continues

da Silva et al.	1995	Brazil	Cross sectional	Ambulatory patients	284	all	Percentage economically active per sex and phase of disease	Women Phase I - 22% Phase II - 27.6% Phase III - 5.8% Men Phase I - 22% Phase II - 15.2% Phase III - 7.2%
Luquetti et al.	1997	Brazil	Expert report	Cases under evaluation for Disability benefit	NA	a.acute b.chronic heart disease c.heart failure d.digestive disease	inability to work	b. mild/moderate cardiopathy cases can work in any activity that does not require physical effort and assuming this does not present a risk to themselves or others c. severe cardiac cases are entitled to disability benefit and disability retirement d. Digestive forms in principle do not contraindicate any work, only very severe cases or during recovery from eventual surgery
PAHO	2010	Global	Report	NA	NA	d. digestive disease	NR	d. 30% have normal bowel function

NA – Not applicable

NR – Not reported

PAHO – Panamerican Health Organization

S4 Table. Publications reporting productivity loss for Visceral Leishmaniasis

Author	Year	Country	Study design	Population	Sample size	Sequela	Definition of productivity loss	Productivity loss
Adhikari et al.	2005	Nepal (Danusha and Mahottari districts)	Observational	Economically active age group (15-59 years) and children below 15	18	VL	a. Days lost by patients & caregivers (incl. school days lost) b. Days lost by patients (including school days lost) c. Days lost by children and caregivers d. Days lost by children e. Opportunity costs	a. 178 days b. 117 days c. 67 days d. 62 days e. 8913.50 Rs
Adhikari et al.	2009	Nepal (Siraha and Saptari)	Observational	KA patients	61	VL	Total indirect costs of an episode of KA treatment	10910 (mean) 7800 (median)
Adhikari et al.	2010	Nepal	CBA	N/A	N/A	VL	a. Total opportunity cost of household (from Adhikari et al. 2009) b. Productivity gains from KA interventions	a. 11000 Nepalese rupees b. 26484 million Nepalese rupees (40%

table continues

								of total benefits)
Meheus et al.	2006	India (Bihar)	Observational	VL patients (including inpatients)	77	VL	a. Total indirect costs b. Income loss (patient) c. Income loss (attendant) d. Monthly interest on loans e. Days absent from school f. Duration of illness	a. 5500 (median, rupees) b. 4400 (median, rupees) c. 900 (median, rupees) d. 200 e. 67 days (25% were students) f. 70 days (median)
Meheus et al.	2010	Indian subcontinent	CEA	N/A	N/A	VL	a. Productivity loss during VL treatment b. Income loss during VL treatment	a. Assumed 100% productivity loss b. Assumed an income loss of 1.48 US$/day.

table continues

Meheus et al.	2013	Sudan	Observational	Patients from two hospitals[1]	75 (incl 45 under 15)	VL	a. Working days lost during a VL episode (patients) b. Working days lost during a VL episode (caregivers) c. Income loss, working individuals (n=22) d. Income loss, all patients (n=75) e. Income loss, all caregivers (n=99)	a. 51 (median) b. 39 (median)(from 20/99 caregivers) c. 101 US$ (median) d. 41 US$ (mean) e. 44 US$ (mean)
Ozaki et al.	2011	Bangladesh	Observational	Past and current patients with PKDL[2,3]	134 (56 patients treated, 78 untreated)	PKDL	a. Missed work days per PKDL treatment course b. Missed work days per PKDL treatment (patients, caregivers)	a. 43 (median) b. 123 (median)
Sarnoff et al.	2010	India (Bihar)	Observational	Households (HH) with a member currently with VL	194 HHs, 227 persons	VL	a. Annual number of working days lost b. Annual income loss c. Restricted daily activities	a. 120 days (amongst the 36% who worked) b. 146 US$ (median) c. 30 days (average) (all patients)

table continues

Sharma et al.	2006	Bangladesh	Observational	VL patients	113	VL	Income loss during VL episode	40 US$ (median)
Shreshta et al.	2008	Nepal (Kathmandu)	Observational	VL patients	60	VL	Working days lost due to the disease	100 (average, min 14 max 210)
Sundar et al.	2010	India (Bihar)	Observational	Patients who received VL treatment	183 patients, 171 HHs	KA	a. Duration of illness (symptoms to cure) b. Monthly work loss after illness c. Monthly work loss during illness d. Median time loss during illness (the 15 weeks)	a. 15 weeks (median) b. 1.08 weeks (before illness 4.29 weeks/month; after illness 3.21 weeks/month) c. 2.14 weeks/month d. 2.14

KA – Kala Azar (Visceral Leishmaniasis); VL – Visceral leishmaniasis; CBA - cost-benefit analysis; CEA - cost-effectiveness analysis; N/A - not applicable; HH - household

1) Three hospitals initially selected but 1 did not have any patients at time of treatment.

2) PKDL Post–kala-azar dermal leishmaniasis, is a complication of visceral Leishmaniasis characterized by a macular, papular, or nodular rash, PKDL develops months to years after apparently successful treatment of kala-azar or in rare cases, in the absence of clinical visceral leishmaniasis.

3) Definition of past and current patients: past PKDL case patient was defined as an individual with a macular, papular, or nodular rash for at least 1 month that was diagnosed by a physician and treated with SAG with resolution. A current PKDL case patient was defined as an individual with a macular, popular, or nodular rash for at least 1 month that was diagnosed by the study physician who was experienced in the clinical diagnosis of the disease.

4) Excluded: pt kala-azar treatment failure or post-kala-azar-dermal leishmaniasis.

S5 Table. Publications reporting Out-of-Pocket Payments for Chagas disease

Author	Year	Country	Study design	Population	Sample size	Sequela	Definition of costs	OPPs
Abuhab et al.	2013	Brazil	Prospective trial	Adult patients high complexity cardiology university hospital in the city of São Paulo	58 Chagas and 519 other etiologies	Severe heart failure	Costs of units spent during admission by each patient, including all fixed and variable costs of care at local costs, given the institutional division within which care was given. That methodology was used for accounting supplies (pharmacy, blood bank, and disposablematerial), procedures and surgeries, and diagnostic tests (imaging and blood)	Mean cost per day US$ 467 (323–815)
Arata et al.	1994	Bolivia	Report	N/A	N/A	a. acute b. chronic heart disease c. heart failure d. digestive disease	Annual costs of medical attention during the acute and the chronic phases and for some aspects of congenital Chagas	a. average cost about 100 Bolivianos b. overall average: 200 Bolivianos c. Severe cardiac cases: up to US$ 4000

table continues

								d. 300 to 500 Bolivianos
Basombrío et al.	1998	Argentina	CBA	Population of the departmen t of Anta, province of Salta	39,213	a.acute b.chronic heart disease c.heart failure d.digestive disease	Annual costs based on market prices and official standard fees for examination and basic treatment of patients.	a. US$ 591.8 b and c. US$ 603.62 d. US$ 736.15
Castillo - Riquelme et al.	2008	Colombia	Cost of illness, with Delphi consensus estimates	Chagas patients from	63	b. chronic heart disease c. heart failure d. digestive disease	Services consumed by the patients grouped into ambulatory care, visits to emergency services, in-patient bed-days, clinical and other diagnostic investigations or procedures, surgical procedures, and other medical procedures (e.g. rehabilitation if applicable). Basic,	b. basic US$46.4, intermediate US$ 188, high level care US$ 3651.5 c. basic US$ 51.4, intermediate US$ 259.3, high level care US$ 7980.9

table continues

							intermediate and high level of care.	
Castillo - Riquelme et al.	2013	Chile	CEA (model)	Discharges between 2005 and 2009 with ICD-10 of chronic Chagas disease	49	b. chronic heart disease c. heart failure d. digestive disease	Public annual costs and prices reported by the study of verification costs 2009 Chilean pesos June 2009	b. $6730 (pesos chilenos) c. $470670 (pesos chilenos) d. $733230 (pesos chilenos)
Lee et al.	2013	Latin America	Simulation model (Markov)	N/A	1000 individuals	Not specified	Annual health care cost with an individual with T. cruzi infection	US$ 2600 ($1966 - 3034)

table continues

Medici et al.	2001	Bolivia	Report	Children under 5 years old, pregnant women and births in the infected areas	NR	Acute	Annual treatment for the target population	US$ 31
Moncayo et al.	1999	Latin America	Report	N/A	N/A	Not specified	Direct costs due to ambulatory medical care per patient per year in the countries of the Southern Cone Initiative	Argentina US$ 406 Brazil US$1,250 Bolivia US$227 Uruguay US$ 877 Weighted average cost six countries US$ 559
PAHO	1997	Chile	Report	N/A	N/A	b. chronic heart disease c. heart failure	Annual costs of treatment chronic chagasic cardiomyopathy	Consultation US$ 411.5 - 549.5 Hospitalization US$ 170 (average 20 days) Drugs US$ 168 - 906

table continues

								Laboratory tests US$ 48.5
PAHO and others	2010	Latin America	Report	N/A	N/A	Acute	Costs of Benzonidazol treatment	US$ 10
Ramsey et al.	2014	Mexico	Markov decision model	N/A	One million patients were simulated	a. acute b. chronic heart disease c. heart failure d. digestive disease	Direct medical costs for CD include those for hospitalization, outpatient consultations, laboratory tests, annual screening, clinical procedures, and medications.	Consultation/hospital/drugs/lab tests a. US$ 17/6.5/61.2/12.4 b. US$ 98.1/21.4/162.8/36+25.4 c. US$ 481.2/151.2/162.8/254.4+179.9 d. US$ 296.6/93.2/162.8/156.8+110.9
Remme et al.	2006	Brasil and Argentina	Book	N/A	N/A	Not specified	Annual costs of consultations, care, and supportive treatment for chronic chagasic patients.	US$ 1000

table continues

Schofield et al.	1991	Argentina, Brazil, Boilivia, Chile, Paraguay, Peru, Uruguay	CBA (model)	N/A	N/A	b. chronic heart disease c. heart failure d. digestive disease	Average cost of consultation, care and supportive treatment for chrinic Chagas disease patients.	c/d. hospitalization US$ 30.00 per patient per day (average of 25 days/year) c.US$ 2500 for pacemaker and US$185.00/year antiarrythmic drug (amiodarone) d.US$ 1750 grade III megaesophagus or mega-colon corrective surgery
Wilson et al.	2005	Latin America	CEA (model)	N/A	N/A	a. acute b. chronic heart disease c. heart failure d. digestive disease	annual costs from diagnosis and supportive treatment according to the type and severity	a. US$ 486 b. US$ 250 c. US$ 350.42 d. US$ 250

CBA - cost-benefit analysis; CEA - cost-effectiveness analysis; N/A - not applicable; NR – Not reported

S6 Table. Publications reporting Out-of-Pocket Payments for Visceral Leishmaniasis

Author	Year	Country	Study design	Population	Sample size	Sequela	Defenition of costs	Direct Costs
Meheus et al.	2013	Sudan	Survey	Patients 2 hospitals	75	VL	a.Direct medical costs in health-seeking phase of VL episode (consultation, drugs, laboratory investigations). b.Direct non medical costs in healthseeking phase of VL episode (transportation, food and other).	a. 24.2 US$ (median), 45,9 US$ (mean) b. 2,6 US$ (median), 15 US$ (mean)
							a.Direct medical costs of admission and treatment of VL episode. b.Direct non-medical of admission and treatment of VL episode; 85% caused by food costs of pt caretakers in the hospital.	a.14 US$ (median), 18,5 US$ (mean) b. 126,5 US$ (median) and 133 US$ (mean) 185 US$

table continues

							Total median direct expenditure by HH (incl health seeking phase and treatment facility).	
Griekspoor et al.	1999	Sudan	CEA and case study	Patients with VL	3067	VL	a. Costs per patient for recommended treament (pentavalent antimonium salt).	a. 100 US$ (on average)
Mannocci et al.	2007	Italy	Observarional (accessed hospital discharge data and mean length of stay)	patients with Leishmaniasis and Visceral Leishmaniasis who visited a hospital	N/A	Leishmaniasis	Total hospitalisation costs for Leishmaniasis (ordinary hospitalization 3343,54 and daily hospitalization 329,50 multiplied with the respective number of discharges and added ordinary hospital costs to day-hospital ones).	a. 7,497,579.20 Euros (1,561,218.50 + 1,637,256.40 + 1,459,892.90 +1,468,983.60 + 1,370,227.80 for years 1999-2003)
Ozaki et al.	2011	Bangladesh	Observational (structured questionaires)	Past and current patients with PKDL	134 (55 patient treated, 78 untreated)	PKDL	a. total direct costs per treated patient because of treatement with SAG (inlc. diagnosis, provider fee, test, treatment, SAG, other medication, Syringe, informal payments to provider,	a. 179 US$ (median) 218 (mean) b. no direct expenditures

table continues

							transportation, miscellaneous, special food) b. total direct costs per untreated patient (n=78).	
Sharma et al.	2006	Bangladesh	Observational (structured questionaires)	Patients with VL in two villages in Mymensingh District (the most highly endemic district in Bangladesh)	113 VL patients	VL	Total direct costs for care for a VL patient (inl. Provider, SAG, informal payments miscellaneous costs).	87 US$ (median)
Ahluwalia et al.	2003	Bangladesh (Fulbaria Thana)	Observational (focus group discussions, qualitative)	Patients with VL		VL	Amount of money needed for diagnosis and treatment.	85-500 $

table continues

Sarnoff et al.	2010	India (Bihar)	Observation (household survey)	Sample of households from 80 villages. Households were included if any of the household members was currently suffering from VL	194 households, 227 individuals	VL	a. Direct and indirect costs prior to VL diagnosis (incl. treatments, transport, lodging) b. Direct and indirect costs of VL treatment per VL episode (incl. VL test, treatment, transport lodging) c. Additional expenses d. median total treatment expenses	a. 18 US$ (median) b. 85 US$ (median) c. 101 US$ (median) d. 131 per patient and 148 per household
Meheus et al.	2010	Indian subcontinent (India, Nepal, Bangladesh)	CEA	N/A	N/A	VL	Drug costs', 'other direct medical' (incl contraceptives, administration, laboratory, inpatient bad-days) & 'nonmedical & indirect costs' of alternative strategies for VL per patient: a. L-AmB+MF b. L-AmB+PM c. MF+PM	a. 95.7; 14.8; 12.8 US$

table continues

	d. SSG+PM	b. 87.1; 20.5; 25.3 US$
	e. MF	c. 29.5; 19.5; 23.8 US$
	f. PM	d. 45.1; 29.9; 43.6 US$
	g. AmB	e. 62.8; 22.0; 45.4 US$
	h. L-AmB10	f. 14.9; 30.6; 51.1 US$
	i. L-AmB20	g. 20.9; 131.6; 45.4 US$
	J. SSG	h. 140; 11; 2.5 US$
		i. 280; 24.7; 6.9 US$
		j. 57.8; 40.7; 73.4 US$

table continues

Meheus et al.	2006	India (Bihar)	Observational (Structured questionnaires and data from medical records)		77 patients (27 follow up, 50 inpatients)	VL	Out of pocket expenditures over the length of hospitalisation a. Total b. Medical costs (consultation, accommodation, investigations, medicines, medical supplies) c. Non-medical (transport, food) Prior to admission a. Total b. Medical cost c. Non-medical	a. 3920 rupees (median) b. 2510 rupees (median) c. 1410 rupees (median) a. 1220 b. 1090 c. 120
Sundar et al.	2010	India (Bihar)	Observational, semi-strucutered questionaire	patients who received VL treatment between september 2005 and september 2006	183 patients, 171 households	KA	a.Direct cost (inl. Provider, medicines, diagnostic, hospitalization) b.Indirect (inl. Travel/food) c.Total costs per patient (direct + indirect)	a. 83 US$ (median) b. 33 US$ (median) c. 127 US$ (median)

table continues

Olliaro et al.	2009	India (Bihar)	CEA			VL	Costs of care and drug costs available for different treatment strategies (table 2 and 3) but health care perspective.	
Adhikari et al.	2010	Nepal	CBA (discounted net benefits and internal rate of return)	N/A	N/A	VL	a. Average total direct costs (but based on other Adhikari et al. 2009) b. HH savings of KA interventions.	a. 7076 Nepalese Rupees b. 14927 Nepalese Rupees (23% of total benefits)
Shrestah et al.	2005	Nepal (Kathmandu)	Observational	VL patients	60	VL	Working days lost due to the disease.	100 (average, min 14 max 210)
Adhikari et al.	2009	Nepal (Siraha and Saptari)	Observational (questionaires)	KA patients	61	VL	Total direct costs of an episode of KA treatment (including medical costs 66,5%, food (22,6%), travel (8,9%) and other costs (1,9%).	7076 Napelese Rupees (average) 4805 (median)

table continues

Sharma et al.	2004	Nepal (Saptari and Siraha)	Observational (structured questionaires and focus group discussions)	KA patients	61 HHs	VL	Direct costs of treatment for one episode of KA, from the inception of the symptom to recovery (incl. medical, transportation, food and other costs).	7076,23 Napalese Rupees (average)
Adhikari et al.	2005	Nepal (Danusha and Mahottari districts)	Observational (structured questionaires)	VL patients	18 patients	VL	Direct costs of a KA episode (incl. medical costs (57%), food expenses (28%), transportation costs (5,4%), other costs (9,5%).	6853 Napalese Rupees (average)

CBA - cost-benefit analysis; CEA - cost-effectiveness analysis; HH – household; N/A - not applicable; NR – Not reported

VL – Visceral Leishmaniasis

PKDL - Post–kala-azar dermal leishmaniasis, a complication of visceral Leishmaniasis characterized by a macular, papular, or nodular rash, PKDL develops months months to years after apparently successful treatment of kala-azar or in rare cases, in the absence of clinical visceral leishmaniasis.

KA – Kala Azar (Visceral Leishmaniasis)

S3 File. Excel example of calculations of the counterfactual scenario for Onchocerciasis Skin Disease

S4 File. Excel example of calculations of the remaining case scenario for Onchocerciasis Skin Disease

S5 File. R scripts for the calculations of the counterfactual and remaining case scenarios for Onchocerciasis

Chapter 5

A test-and-not-treat strategy for onchocerciasis elimination in Loa loa co-endemic areas: cost analysis of a pilot in the Soa health district, Cameroon

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2019

Clinical Infectious Diseases, ciz461.

https://doi.org/10.1093/cid/ciz461

Abstract

Background

Severe adverse events (SAEs) after treatment with ivermectin in individuals with high levels of *Loa loa* microfilariae in the blood preclude onchocerciasis elimination through Community-Directed Treatment with Ivermectin (CDTI) in Central Africa. We measured the cost of a community-based pilot using a test-and-not-treat (TaNT) strategy in the Soa health district in Cameroon.

Methods

Based on actual expenditures, we empirically estimated the economic cost of the Soa TaNT campaign, including financial costs and opportunity costs that will likely be borne by control programmes and stakeholders in the future. In addition to the empirical analyses, we estimated base-case, less and more intensive resource use scenarios to explore how costs might differ if TaNT were implemented programmatically.

Results

The total costs of US$ 283,938 divided by total population, people tested and people treated with 42% coverage were US$4.0, US$9.2, and US$9.5, respectively. In programmatic implementation, these costs (base-case estimates with less and more intensive scenarios) could be US$ 2.2 ($1.9 – $3.6), US$ 5.2 ($4.5 – $8.3), and US$ 5.4 ($4.6 – $8.6), respectively.

Conclusions

TaNT clearly provides a safe strategy for large-scale ivermectin treatment and overcomes a major obstacle to the elimination of onchocerciasis in areas co-endemic for *Loa loa*. Although it is more expensive than standard CDTI, costs vary depending on the setting, the implementation choices made by the institutions involved, and the community participation rate. Research on the required duration of TaNT is needed to improve the affordability assessment, and more experience is needed to understand how to implement TaNT optimally.

Introduction

Community-Directed Treatment with Ivermectin (CDTI) has been used since 1999 as the main strategy to combat onchocerciasis in Africa.[1,2] While generally considered safe, ivermectin has been associated with severe adverse events (SAEs) in individuals with high levels of circulating microfilariae (mf) of *Loa loa* (another filarial parasite endemic in Central Africa).[3,4] CDTI has been implemented in coendemic areas where the proportion of individuals with *O. volvulus* nodules exceeds 20% (hyperendemic and mesoendemic areas), albeit with enhanced adverse events (AEs) surveillance. However, fear of SAEs has caused individuals in such areas to refuse treatment, leading to suboptimal drug coverage and continued *O. volvulus* transmission. Moreover, CDTI is not recommended in *Loa*-coendemic areas where *O. volvulus* is hypoendemic (nodule prevalence <20%), as the risk of SAEs is thought to outweigh the benefits of CDTI. This jeopardizes onchocerciasis elimination in Africa.[5,6]

A test-and-not-treat (TaNT) strategy using a smartphone-based videomicroscope (LoaScope) enabled the safe implementation of ivermectin treatment in a pilot study in the Okola health district (HD) in Cameroon where all individuals ≥5 years of age [7,8] were included. Of 16,259 tested individuals, only 340 (2.1%) were excluded from ivermectin treatment because of microfilarial counts >20,000 mf/mL; whereas 15,522 (95.5%) were treated without the occurrence of SAEs.[7] A second TaNT study in Soa HD also had no postivermectin SAEs and further demonstrated that TaNT could be performed by local health workers and community members under the supervision of the research team.[9] Additional information about this TaNT round in the Soa HD can be found in Supplementary Appendix 1.

Although TaNT is a promising strategy for onchocerciasis elimination in loiasis-coendemic areas, its implementation is expected to be costlier than that of CDTI. Consequently, there are affordability concerns at a wider scale. Thus, we measured the cost of community-based TaNT in the above-mentioned Soa pilot study [9]. In addition, we estimated the cost for three programmatic implementation scenarios (base-case, less and more intensive), to obtain a range of plausible estimates under different assumptions of resource use.

Methods

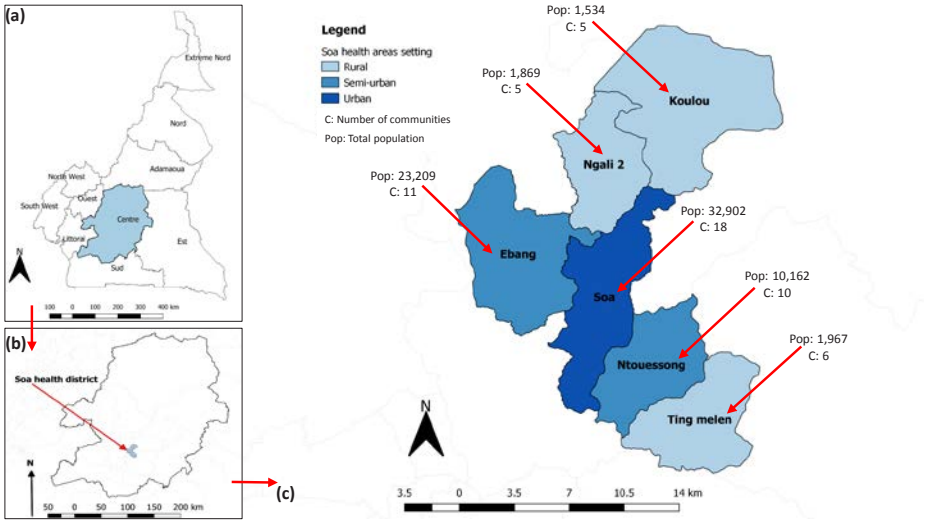
General approach

A micro-costing approach [10] was used to empirically assess the cost of a community-based TaNT in the Soa HD.[9] The empirical costing study reflects the costs borne by the organizations involved in implementing and executing the program in this specific pilot. A future program would likely be run by the Cameroonian Ministry of Health (MoH) in partnership with nongovernmental development organizations (NGDOs). We aimed to reflect this future situation in our cost calculations and therefore calculated the economic costs of the pilot, including financial costs (explicit cash expenditures on project activities) and added relevant opportunity costs (resources that could be used in other projects, if not used in this one).[11] We designed the protocol, data collection instruments and cost calculation sheets following standard guidelines and reported input quantities and costs to maximize comparability with other studies and recently published mass drug administration (MDA) benchmarks. [11,12]

Study area and population

The Soa HD in Cameroon (Figure 1) is an ivermectin-naive district that is hypo-endemic for onchocerciasis and co-endemic for loiasis.[13] It is located 17 km from Yaoundé (Cameroon's capital) and is easily accessible. Soa HD consists of 6 health areas (3 rural, 2 semiurban, 1 urban) and its population was estimated at 71,643 inhabitants, according to the census performed as part of the TaNT pilot.

Figure 1. Map of Soa health district in Cameroon, showing the rural/urban characterization, number of communities and population size by health area



Time window

The census, testing/treating and monitoring of SAEs in the TaNT round took place from September 2017 to February 2018. Costs were collected beginning with the preparation of the round in August 2017 until the last payments in March 2018.

Cost calculation components

The 'supplies' category includes (but is not restricted to) fuel, car maintenance, food, transportation, office materials, field materials, and drugs to treat AEs. The 'personnel' category includes per diems of community drug distributors (CDDs) and other staff, project staff salaries, and fringe costs for study personnel, when applicable. Overhead costs were not explicitly measured, but were assumed to be 15% of direct costs, as reported in the project budget. Supplementary Appendices 1 and 2 (Tables 1,2 and 4) provide additional information. We excluded the following costs: ivermectin costs (as the drug was donated); bank tariffs; management/administrative costs incurred outside the country; costs incurred by households to be treated; opportunity cost of time spent

by school staff; opportunity costs of buildings used by MoH staff and of capital items purchased for previous projects.

Costs of LoaScopes and capillaries were provided in US dollars (US$); all other costs were reported in Central African francs (XAF) and converted to US$ using the US Treasury Reporting Rates of Exchange of December 31st, 2017 (1 US$ = $ 568 XAF).[14]

Data collection

Costs were based on actual payments or booked transfers collected from all invoices and bank transactions provided by project managers. External MoH staff working in the project and CDDs were interviewed using structured questionnaires to obtain information about their time spent on the project and opportunity cost of their salaries. A summary of the design, structure and dissemination protocol for each questionnaire and English versions of these can be found in Supplementary Appendix 3 (Table 6 and Questionnaires 1 - 3).

Data entry, cleaning and analysis

The invoices were analysed and compared to the data provided by monthly financial reports and bank transactions for consistency and quality checks. The value of each invoice or bank transaction was labeled according to the input category, the health area in which the cost was incurred (using the label "district costs" if costs were not specific to any health area, but relative to the project as a whole), and the activity to which the cost could be attributed (advocacy, census, planning and budgeting, procurement, training, health education in the community and mobilization [HECM], delivery and distribution of interventions to target populations, AE surveillance and management, monitoring and evaluation, and general management). Data from invoices and questionnaires were entered into a Microsoft Excel spreadsheet for further analysis. Overhead costs were added to the subtotal and the final result was divided by the project outputs.

Scenario analysis

To assess the effect of different implementation strategies on the overall cost of TaNT, costs were calculated using three hypothetical alternative TaNT implementation scenarios: "base-case", "less intensive resource use" and "more intensive resource use". The scenarios were designed based on the literature and our own expertise in conducting CDTI in Cameroon, using the same HD for context (eg, applying the same rural/urban distribution, same distances to the capital, same mode of delivery). [2,15] Table 1 describes the main differences between the scenarios and the pilot. See Supplementary Appendix 4 (Tables 7 - 9) for a more detailed description.

Table 1. Summarized description of alternative scenarios

Cost Category	Cost scenario		
	Base-case	**Less intensive resource use**	**More intensive resource use**
Personnel			
Supervision and M&E	<< pilot Smaller teams and fewer days than pilot	<<< pilot Same team and fewer days than base-case	< pilot Bigger team and more days than base-case
HECM	< pilot (no sound car[a])	< pilot (no sound car[a])	< pilot (no sound car[a])
AE surveillance and management	= pilot	<< pilot (50% less than pilot)	= pilot

table continues

CDDs	< pilot (CDDs only paid for training days)	< pilot (CDDs only paid for training days)	>> pilot (CDDs were paid per diems for treatment days corresponding to the average income of an eight-hour work day (to account for income loss)
Blood drawers and loascopists	> pilot (were paid a higher transport fee per field day, to account for more distant communities - based on responses of questionnaires)	> pilot (= base-case)	>> pilot (higher transport fees than base-case)
School workers	None	None	100 workers
Supplies			
Fuel	> pilot (extra fuel allowance for MoH and NGDO cars)	> pilot (= base-case)	>> pilot (higher allowances than base-case)
LoaScopes and capillaries	< pilot (assumed large-scale prices)	< pilot (= base-case)	= pilot

table continues

Other consumables	< pilot (30% less than pilot)	< pilot (50% less than pilot)	= pilot

Abbreviations: <, less than; <<, lesser than; <<<, much lesser than; >, more than; >>, much more than; AE, adverse events; CDD, community drug distributors; HECM, health education in the community and mobilization; M&E, monitoring and evaluation; MoH, Ministry of Health; NGDO, nongovernmental development organization.

[a] Megaphone-equipped car.

Results

The population size and numbers of individuals tested, treated or excluded, as well as the occurrence of AEs, per health area are given in Table 2. Only 0.8% of the tested population was excluded from treatment. The overall coverage was relatively low (42%).

The costs of the pilot, disaggregated by programmatic activity, are presented in Table 3. The costliest activities were related to the actual delivery of the intervention (31%) and HECM (11%), although general management costs (not related to a specific activity) also formed a large part of the total costs (19%). The supplies input categories that were responsible for the highest shares of the total costs (from highest to lowest), are capillaries and information, education and communication materials leading with 12% and 10% of the total pilot costs, respectively (Supplementary Appendix 2: Table 3). Supplementary Appendix 5: Table 10 shows volumes and prices of supplies per input category.

Table 2. Programme outputs (number of individuals)

Health area	Censused	Censused Aged >5	Tested with LoaScope	Treated	Excluded for *Loa* > 20,000 mf/mL	Excluded for other reasons [a]	AEs[b]	Coverage (treated/ censused) (%)
Ting Melen (r)	1,967	1,697	1,644	1,585	16	43	7	81
Koulou (r)	1,534	1,342	1,035	975	38	22	18	64
Ngali 2 (r)	1,869	1,594	1,017	963	36	18	19	52
Ebang (su)	23,209	19,906	11,412	10,987	53	372	47	47
Ntouessong (su)	10,162	8,618	3,602	3,473	44	85	25	34
Soa (u)	32,902	29,524	12,098	11,765	58	275	68	36
TOTAL	71,643	62,681	30,808	29,748	245	815	184	42

Abbreviations: AE, adverse event; mf, microfilariae; r, rural; su, semiurban; u, urban.

[a]Pregnant and breastfeeding women, individuals suffering from chronic disease.

[b]Number of AEs (multiple AEs may occur in 1 person).

Table 3. Total costs of pilot per activity (US$)

Programme Activity	Supplies	Personnel	Total	Percentage of total pilot costs
1) Advocacy	6,020	843	6,864	2%
2) Census	741	18,975	19,715	7%
3) Planning and budgeting	100	8,071	8,170	3%
4) Procurement	30	9	39	0.01%
5) Training	2,537	13,542	16,078	6%
6) HECM	21,442	8,979	30,421	11%
7) Delivery intervention	46,527	42,137	90,115	31%
8) AE surveillance and management	2,048	10,253	12,300	4%
9) M&E	107	11,606	11,712	4%
10) General management [a]	18,280	34,613	52,892	19%
Subtotal Activities	97,830	149,027	248,308	87%
Overhead Costs	[b]	[b]	37,253[b]	13%
Total	112,504	171,381	283,885	100%

Abbreviations: AE, adverse event; HECM, health education in the community and mobilization; M&E, monitoring and evaluation.

[a] Includes all inputs related to the project as a whole and that could not be attributed to a specific activity (eg, electricity, some office supplies, communication, some of the fuel and car maintenance costs).

[b] Calculated as 15% of the activities subtotal.

The majority of the personnel costs were not related to a specific activity but to actions related to the implementation of the round as a whole. The same holds true for district and health area level MoH personnel. The main costs of all other categories were related to the delivery of the intervention (Supplementary Appendix 2: Table 5).

The total cost for the entire pilot was US$ 283,938 (Table 4), with a cost per person treated of US$ 9.5. The cost per person treated was reduced to US$ 5.4 for the base-case and to US$ 4.6 and US$ 8.6 for the less and more intensive scenarios, respectively.

The absolute costs of the Soa pilot and each of the implementation scenarios disaggregated by programmatic activity, as well as the percentages of each activity are given in Figure 2. The empirical study was more expensive than the scenarios, mainly due to the census, HECM, general management costs (for instance car maintenance and field materials) and the costs of LoaScopes and capillaries. Costs of delivering the intervention formed the largest share of the total costs, mainly due to the costs of capillaries, field material and per diems, which showed a reduction in the base-case and less intensive scenarios mostly due to less supervision and less expensive materials. Costs increased considerably in the more intensive scenario, due to the payment of higher per diems to CDDs to account for income loss. Even though general management costs were also reduced by less expensive materials in the scenarios, the percentage of the total costs did not change much. Costs of HECM were lower in the scenarios because of the exclusion of the costs of the megaphone-equipped car and the reduction of prices of materials.

Table 4. Total costs per round and per programme output (US$) – pilot and alternative scenarios

	Total costs of the pilot per health area	Total number censused	Cost per person censused	Cost per person tested	Cost per person treated	Coverage (treated/ censused) (%)
Empirical cost estimates by health area						
Ting Melen (r)	17,770	1,967	9.0	10.8	11.2[a]	81[b]
Koulou (r)	14,994	1,534	9.8	14.5	15.4[a]	64[b]
Ngali 2 (r)	16,161	1,869	8.6	15.9	16.8[a]	52[b]
Ebang (su)	90,425	23,209	3.9	7.9	8.2	47[c]
Ntouessong (su)	41,163	10,162	4.1	11.4	11.9	34[c]
Soa (u)	103,425	32,902	3.1	8.5	8.8	36[c]
Total costs of the TaNT pilot	283,938	71,643	4.0	9.2	9.5	42
Alternative implementation scenarios						
Base-case	159,349	71,643	2.2	5.2	5.4	42
Less intensive	137,289	71,643	1.9	4.5	4.6	42
More intensive	255,850	71,643	3.6	8.3	8.6	42

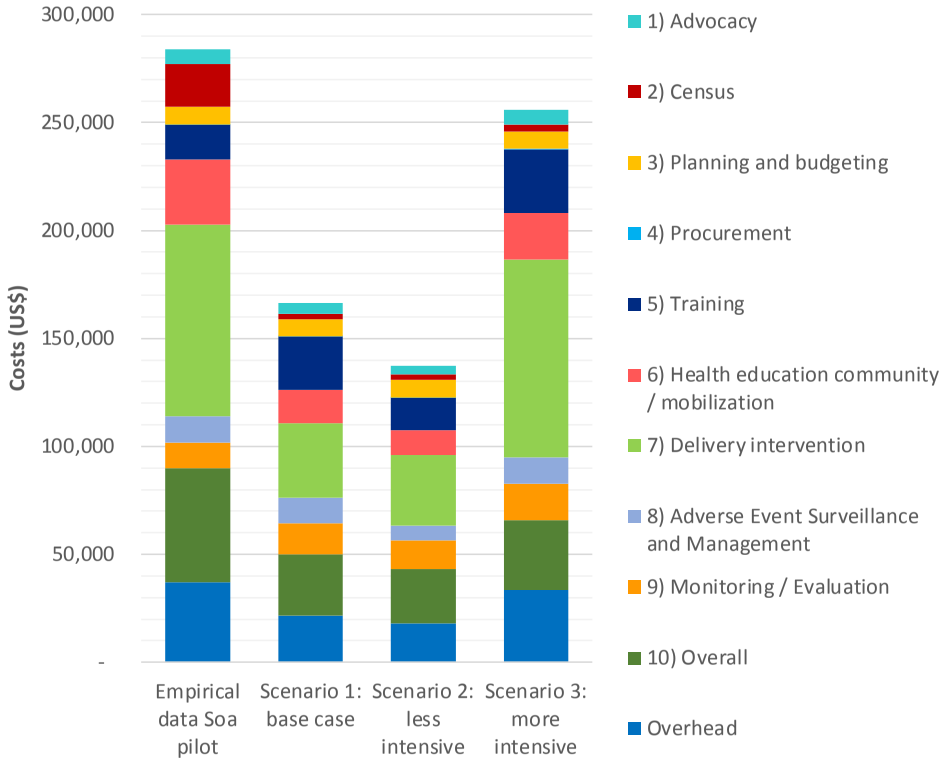
Abbreviations: r = rural, su = semi-urban, u = urban

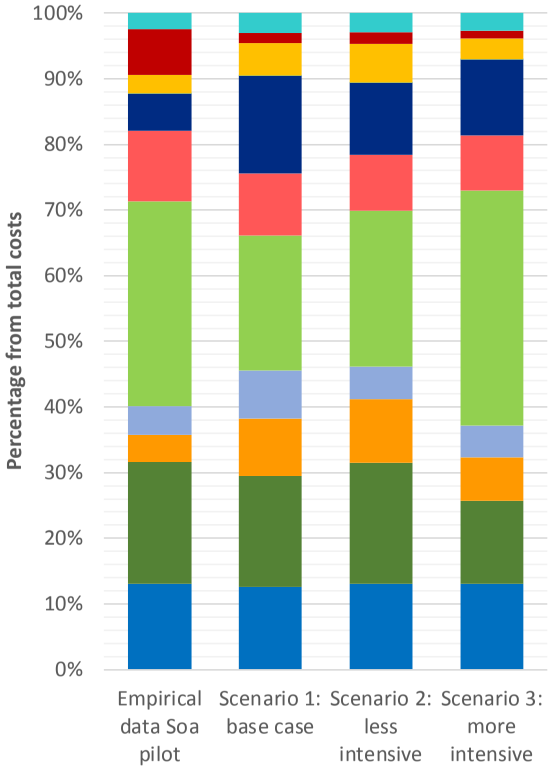
a. Rural areas had a higher cost per person treated due to more supervisory personnel (they were the first areas to participate in the pilot), more fuel costs (increased distance from the capital) and additional testing/treating at schools.

b. Rural areas had higher coverage because people are at home or work close to home and can be reached more easily by CDDs during the sensitization phase and because people are available during sampling hours (sampling needs to be done during regular school/work hours (between 10:00 am and 4:00 pm) due to the diurnal periodicity of *L. loa* microfilaremia).

c. Semi-urban and urban areas had lower coverage because of more treatment refusals and the absence of people at work/school during sampling hours.

Figure 2. Total costs: empirical vs. scenarios





Discussion

This study provides both empirical cost estimates of a pilot and projected costs based on scenario analyses using the new TaNT strategy in regions co-endemic for *O. volvulus and L. loa*. Based on actual expenditure during the pilot, this strategy cost US$ 4.0 per person in the population, US$ 9.2 for each person tested, and US$ 9.5 for each person treated. In the alternative implementation scenarios, these costs (shown as base-case estimates with less and more intensive scenarios) were estimated to be US$ 2.2 ($1.9 – $3.6), US$ 5.2 ($4.5 – $8.3), and US$ 5.4 ($4.6 – $8.6), assuming that population participation remained unchanged.

Several limitations apply to the internal validity of our study. Despite the careful collection of available data from invoices, bank transfers and questionnaires, we had to adapt to the system usually used by financial managers of the implementing institution, without explicit reporting of the cost of previously acquired capital items or building rental. Using a retrospective questionnaire investigating opportunity costs of MoH staff was also not ideal, since it allows recall bias. Opportunity costs of time spent by school staff when helping during the treatment phase and of vehicles and furniture acquired for other projects were not included in this study, leading to a slight underestimation of the costs of the pilot. These limitations should be addressed in future studies to increase the accuracy of cost estimates and enable policymakers to anticipate their costs more reliably. This would also allow economic costs to be presented separated from financial costs.

Because we measured costs in a study setting, alongside a pilot implementation of community-based TaNT, our results may not be fully representative of a programmatic setting, limiting the external validity. Some costs may have been higher than expected under programmatic implementation (eg, all personnel received intensive training and supervision and CDDs received payment). Further, best implementation practice still remains to be determined, and future programs may be implemented somewhat differently. The programmatic operationalization scenarios were designed to address the external validity limitations. They still do not cover all possible variations in implementation choices. We built the base-case scenario aiming to reflect Cameroonian reality as much as possible. As shown in the scenario analyses, costs heavily depend on implementation choices, and cost-savings compared to the pilot can be achieved through

reductions in supervisory personnel, health education and sensitization, surveillance and management of AEs and purchase prices of the LoaScopes and capillaries. The last two categories can be further reduced by implementing NGDOs/MoH if external funding agencies opt to donate these supplies to countries choosing to implement the TaNT strategy, as already done with the donation of ivermectin.

Overall study coverage was relatively low, particularly in the semi-urban and urban areas. Higher coverage is essential to onchocerciasis elimination. Achieving high coverage in urban areas is a known problem, even in standard CDTI, due to lack of trust in public programs, migrant populations, and disorganized poor urban settlements.[16,17] Yet, it may be even more difficult to achieve in TaNT programs, as blood sampling needs to be done during regular school/work hours; requires the involvement of additional people (blood drawers and "loascopists"), and is best done with a mobile station rather than house-to-house. Additional measures are needed to increase coverage, including continuous and improved health education/mobilization and alternative ways to offer testing and treatment, such as mobile stations at schools and in commercial/industrial areas. However, since it is difficult to predict the cost and impact of these measures on coverage, we have not considered increases in coverage in our implementation scenarios. Although there will be some economies of scale (fixed costs divided over a larger population), other costs are likely to increase with the number of people covered (eg personnel costs for delivering the intervention), resulting in a higher cost per person.

Our estimates, derived from a community-based single study, are not directly transferable to other settings due to many factors, such as variations in local prices, organization and availability of healthcare, and geographic characteristics such as remoteness, accessibility and level of "urbanness".[18,19]

To eliminate onchocerciasis, treatment would have to be repeated yearly (or more frequently) for many years with sufficient treatment coverage (ie, 80% of the eligible population per WHO guidance).[20] The costs of future rounds are likely to be significantly lower than the initial round for a number of reasons, including the absence of start-up costs, shared fixed costs (over multiple rounds within a given year), more efficient implementation (from the experience and structure provided by the first round), lower intensity of HECM (communities would already be aware of the strategy), and less

MoH advocacy and AE surveillance (since fewer cases would need to be followed). Further, as *L. loa* microfilarial densities remain low after treatment for at least 18 months, people proven to be treated in the previous round (using re-identification methods) would not need to be re-tested [21]. Capillary and LoaScope costs would only remain for the individuals not previously tested and treated, making costs much more comparable to those of standard CDTI.

To date, there are no studies of the costs of alternative strategies of measuring *L. loa* microfilarial densities before treating for onchocerciasis to which we could compare our results. We cannot directly estimate the difference in costs between TaNT and CDTI without empirical comparisons, as it is impossible to disentangle costs of treatment from those of testing in the TaNT strategy. A unit cost benchmarking study by Fitzpatrick et al. [11] showed that the unit cost of mass drug administration is highly variable, depending very much on the use of volunteers and economies of scale. This variation complicates a direct comparison of our results with any previously published figures. A web-based tool [11] that provides unit cost benchmarks for different settings allowed us to estimate the expected cost of a first round of standard CDTI in Soa, using the corresponding population and characteristics of the area (which the tool allows), and the resulting cost estimates were US$ 18.3 (95% confidence interval [CI], $6.9 – $35.6) per person treated using paid community health workers. The observed cost of TaNT for the pilot and more intensive scenario are closer to the lower end of the range despite the cost of testing. The benchmark unit cost of standard CDTI is considerably lower when implemented by unpaid community volunteers, US$ 3.9 [95% CI, $2.2 – $5.7], and the cost of our base-case and low-intensity implementation scenario comes quite close to this. Details on the use of the benchmark tool are provided in Supplementary Appendix 6.

Through TaNT, community treatment with ivermectin can be expanded into the many areas in central Africa that are hypoendemic for onchocerciasis and co-endemic for loiasis, where standard CDTI cannot be applied for safety reasons. Implementing treatment in these regions is crucial for the continent-wide elimination of onchocerciasis, with associated health and socio-economic benefits estimated at more than US$ 6 billion.[22] The populations concerned will not only benefit from the control and potential elimination of onchocerciasis but – as ivermectin is a broad-spectrum

anthelmintic drug - also from the effects of treatment of other parasitic diseases including scabies and soil-transmitted helminthiases.

Conclusion

Costs of TaNT are higher than costs of standard CDTI. How much higher will depend on how subsequent treatment rounds will be implemented and the required program duration. The duration will not be much longer than in *Loa*-free areas if the coverage is sufficiently high and the proportion of the population excluded from treatment (because of high-density loiasis) is as low as observed in Soa and Okola (1% on average). The effect of excluding people from treatment may be more important where the proportion of people excluded due to loiasis is higher, but this can be mitigated by offering alternative treatment for onchocerciasis, such as a course of doxycycline. Although we did not assess the costs associated with such treatment, these should be weighed against the impact on program duration and success.

Even though TaNT is undoubtedly more expensive than MDA, onchocerciasis elimination will not be reached without a strategy that can be safely used in areas co-endemic for *L. loa*. Our empirical study shows that TaNT using LoaScopes remains affordable, given the enormous potential economic benefits of reaching elimination of onchocerciasis in Cameroon and in other countries where *L. loa* is co-endemic with *O. volvulus*. Various implementation scenarios show that costs could be further reduced. Future studies in this field are needed to investigate the costs of a programmatic implementation.

Funding

This work was supported by the Bill and Melinda Gates Foundation [Grant Number: OPP1033740 to M.B., J.K., H.C.N., A.D.K., T.B.N., D.A.F., S.D.P., Y.N. and W.A.S.] and the Division of Intramural Research, NIAID, NIH [to A.D.K. and T.B.N.].

Acknowledgements

We would like to express our true appreciation to the following individuals whose important comments and insights contributed to this work: Ann Goldman, Paul Cantey, Sim Azebaze, Raoul Ghomsi, and Katia Urena.

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The authors alone are responsible for the views expressed in this article, which do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

Potential conflicts of interest

All authors declare no conflicts of interest and have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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Supplementary data

Appendix 1. Summarized description of the TaNT pilot in Soa HD

Cameroon participated in the African Programme for Onchocerciasis Control (APOC) between 1995 and 2015, adopting CDTI as its main strategy to control onchocerciasis morbidity in meso- and hyperendemic areas.[227,228] During this period, Cameroon reported 471 SAEs following ivermectin treatment (~34% of all reported cases in the Mectizan Donation Program). Encephalopathy was reported in 221 cases, mostly (90%) in individuals taking ivermectin for the first time.[229]

This pilot was implemented in the Soa Health District (HD) by the Centre de Recherche sur les Filarioses et autres Maladies Tropicales (CRFilMT), Cameroon in partnership with Institut Bouisson-Bertrand, France and was funded by the Bill and Melinda Gates Foundation (BMGF).

The round started with advocacy meetings, followed by health education and community mobilization about the importance and the dates of the upcoming TaNT-related activities. Community-directed distributors (CDDs) were selected within their own villages (approximately 1/100 inhabitants), whereas blood drawers and loascopists (those responsible for handling the LoaScope) were selected at the level of the health area. All three categories were trained by professionals from the implementing institution and the Ministry of Public Health (MoH). After the training, CDDs conducted village censuses and reported the population numbers to the implementing institution.

After completion of the training, the community teams spent several days in each village to test and treat the population. Inhabitants were invited to come to a central location in the village between 10am and 4pm (because of the diurnal periodicity of *Loa loa* mf in peripheral blood), where the team assessed whether they met the participation criteria (age ≥ 5 years, non-pregnant and without severe chronic diseases) and tested those eligible for participation. The entire eligible population was offered blood screening using a smartphone-based microscope called LoaScope, which provides an accurate estimate of *L. loa* mf counts within 2 minutes.[212] Tested individuals with a count lower than 20,000 *Loa* mf/mL were treated with ivermectin. Those with ≥20,000 *Loa* mf/mL - considered at risk of SAEs - received albendazole for deworming (a widely used, broad-

spectrum anthelmintic drug that has no direct effect on *L. loa* mf). The threshold used was lower than the 30,000 mf/mL suggested by the WHO to ensure the prevention of marked adverse events that could raise concern and reduce participation rates.[208,211] Additional testing and treating was performed in schools as a means to increase the coverage among children who were unable to attend the centralized treatment conducted in their communities. A team from the implementing institution (1 physician, 1 pharmacist, 1 nurse, 1 driver) supervised AE surveillance. The surveillance period comprised the first three consecutive days, and day 7 after treatment of each individual. A more detailed description of all activities undertaken for the pilot of community-based TaNT in Soa HD is provided in Table S1, with comparison to standard CDTI and the implementation of a TaNT base case scenario. The scenarios are described in more detail in Appendix 4.

Table S1. Comparison between the activities usually carried out in a standard CDTI round in Cameroon, the pilot of community-based TaNT in Soa HD, and the TaNT base case implementation scenario.[206,219]

Supplementary Table 1. Activities in standard CDTI in Cameroon, pilot of community-based TaNT in Soa HD, and TaNT base case implementation scenario

Activities	Standard local CDTI	Community-based TaNT pilot in Soa health district	Operational TaNT base case scenario
1. Advocacy	Advocacy meetings (one day each) with key stakeholders and opinion leaders at national, regional and district levels, also at communities, aiming to raise awareness on the campaign and solicit their engagement to support the intervention.	Same as in CDTI. In addition, big launching ceremony presided by the Minister of Health with the participation of various political, administrative and traditional authorities, to introduce a new strategy to the population in general.	Same as in CDTI.
2. Census	Enumeration of the population and acquisition of demographic information by CDDs through a house-to-house approach at their own pace within 1 or 2 weeks, with no per diems paid.	Same as in CDTI, but completed within 3 days, with a financial incentive paid to CDDs.	Same as in CDTI.
3. Planning & budgeting	Planning and budgeting for all activities per CDTI round, through preparatory meetings at central and regional levels and through visits to chiefs of villages (for drawing a list of CDDs).	Same as in CDTI.	Same as in CDTI.
4. Procurement	Order and purchase of drugs, equipment and supplies. Joint drug application package meeting	Same as in CDTI, with additional procurement of materials for TaNT. LoaScopes and capillaries. Other materials for field work (cotton, alcohol, tablecloth,	Same as in TaNT pilot in Soa, with cheaper LoaScopes and capillaries

table continues

	held at central level to define necessary amount of ivermectin (Mectizan®), provided via WHO.	bin bags, etc.) purchased locally by the implementing institution.	(due to large-scale production) and cheaper field material (purchased at reduced prices by the MoH).
5. Training	Training for any aspect of CDTI for health system employees and community volunteers through cascade training at regional (1 day), district (1 day), health area levels (2 days), CDDs (2 days).	Same as in CDTI, but also including training for blood drawers and loascopists (2 days) and spending 1 day for national level and 2 days for district level training.	Same as in TaNT pilot in Soa.
6. Health education/ community mobilization	Formal and informal education, information and communications about the intervention through different methods. Mass media campaign: radio/TV broadcasting of sensitization messages about the campaign. CDDs deliver health education messages during census and treatment to population, using flyers, posters, t-shirts, banners, and/or calendars. If specific issues hinder mass drug administration (MDA) coverage in an area, community meetings might be organized, facilitated by health area personnel and supervised by district and regional level staff and staff from NGDO involved in the program.	Same as in CDTI, with the additional use of a sound car (4x4 pick up car specially tuned and equipped with megaphone) manned by one sensitization team composed of one driver, one former NOCP coordinator (team lead) and one team member from CRFilMT. In each health area, this team worked at least 2 days before the census started and then all the period till the treatment ended in the health area.	Same as in CDTI.

table continues

7. Delivery of intervention (Treatment)	House-to-house case identification and treatment by CDDs at their pace within 1 or 2 weeks, with no per diems paid.	Testing and subsequent treatment offered at mobile stations in villages by teams consisting of a CDD, a LoaScopist and a blood drawer, within 3 days. CDDs are paid per diems.	Same as in TaNT pilot in Soa, but with per diems paid to CDDs only for training days.
8. Adverse event surveillance and management	Field and clinical monitoring and management of Adverse Events (AEs) and Severe Adverse Events (SAEs); field supervision of this activity. AEs are managed by health facilities at health area or district level, with patients paying for hospitalization, drugs and consultation fees. In case of a SAE, a technical team might go to see the patient and will cover the fees for healthcare.	A team from the implementing institution (1 physician, 1 pharmacist, 1 nurse, 1 driver) was in charge of AE surveillance. They started field surveillance in each health area 3 days after treatment had started and continued until 3 days after the treatment had ended in that health area. They took turns when going to the field. Drugs for AEs management (paracetamol, chlorpheniramine) and medical equipment (tensiometer, stethoscope, etc.) were purchased by implementing institution.	Same as in TaNT pilot in Soa, but with drugs and equipment purchased at reduced prices by the MoH.
9. Monitoring & evaluation (M&E)	Coverage surveys or epidemiological surveys, data quality assessment surveys, specific training on M&E tools (database) not necessarily involving CDDs. Data collection, data analysis and reporting: after census/treatment, CDDs bring back registers with data. Chief of each health area works about 5 days synthesizing data from the registers; district team (2 persons) then compiles it in Excel for 3-5 days;	The implementing institution took care of the entire data entry and management of Soa data.	Same as in CDTI, but with treatment data provided by both written registers and electronic tools.

table continues

		same happens at regional level. Besides, usually each level spends 3-5 days supervising data collection in the field (including national level and participating NGDO). The NGDO also helps with a data manager.		
10.	General Management		Inputs that were related to the project as a whole and that could not be attributed to a specific activity, for instance electricity, some of the office supplies, communication, fuel, car maintenance costs.	Same as in TaNT, except for consumables that could eventually be purchased for a lower price by the MoH (such as field material).

table continues

Appendix 2. Input categories

Tables S2 and S4 present the lists of input items used in the data collection and cost calculation, adapted from the DOLF (Death to Onchocerciasis and Lymphatic Filariasis) project: Protocol for Cost Data Collection in Community Trials.[216] Tables S3 and S5 present the costs of the input items responsible for the highest shares of the total costs, per input category and activity.

Supplementary Table 2. Inputs of supplies categories

Supplies categories	Comment
Electricity	Electricity bill of the building where the implementing institution is based, during the months of field work.
Office Supplies	Supplies used during the entire round.
Food Supplies	Coffee breaks during training.
Communication	Development of Information, Education and Communication (IEC) materials, media campaign and coverage, launching ceremony, IEC materials.
Fuel	Fuel used by the cars transporting personnel and/or material.
Car maintenance	Maintenance of the cars used in the round.
LoaScope kits (15)	The costs of each LoaScope (including cell phone, lens, charger) was US$ 700, and 15 LoaScopes were used in this project. The estimated average useful lifetime of a LoaScope was assumed to be 5 years, as suggested by the manufacturer. Since we are calculating the costs of the first year of a TaNT strategy using LoaScopes, the costs were divided by 5 and not discounted or annuitized.

table continues

Adverse reaction drugs	Drugs purchased by the implementing institution especially for the treatment of possible AEs during the round (more details in table S8).
Medical care/Hospitalization	When AEs eventually needed more than only drugs to be managed.
Field material	All material used in the field (more details in table S8).
Capillaries	Costs of the capillaries used were US$ 1.10 (unit price), and it was assumed that one capillary was used for each person tested.
Teaching material	Material used during training (paper, pens, chalk).
Other direct costs	Other direct costs include the following costs that could not be attributed to specific inputs: cleaning materials and toilet paper for field team, binding of registries, towel, cleaning of training room, per diem for driver to bring field waste to incineration site.
Sound car	Includes the preparation of 4x4 pick up car with megaphone, the fuel used only by the sound car and its maintenance.

Supplementary Table 3. Costs of supplies responsible for the highest shares of the total costs disaggregated by input category and activity (US$)

Supply Category	Quantity	Unit price (US$)	Total	1. Advocacy	2. Census	3. Planning and budgeting	4. Procurement	5. Training	6. HE community / mobilisation	7. Delivery intervention	8. AE surveillance & management	9. ME	10. General Management	% of total pilot costs
Capillaries	30,808	1.1	33,889	-	-	-	[a]	-	-	33,889	-	-	-	12%
IEC materials	[b]	[b]	27,398	5,844	44	18	[a]	9	20,060	49	9	-	1,365	10%
Field material	[b]	[b]	10,286	-	55	-	[a]	-	-	7,732	-	-	2,499	4%
Car maintenance (car/month) [c]	47	146	8,160	-	24	2	[a]	10	162	22	7	-	7,934	3%
Fuel (liters) [c]	7,614	129.6	7,260	176	618	53	[a]	863	106	2,691	1,220	-	1,533	3%
LoaScopes purchase	15	700	2,100 [d]	-	-	-	[a]	-	-	2,100	-	-	-	1%
Other categories	N.A.	N.A.	8,735			27	30	1,655	1,114	44	812	107	4,948	3%
Total Supplies	N.A.	N.A.	97,830	6,020	741	100	30	2,537	21,442	46,527	2,048	107	18,280	34%

[a] Procurement by administrative personnel (included under overhead costs)

[b] Appendix 5 includes a table with the quantities of the main elements of IEC and field material.

[c] Car maintenance and fuel costs given in average cost /car / month (7 vehicles during 8 months).

[d] Total of LoaScopes purchase divided by 5 (assuming 5 years of useful lifetime).

HE – Health Education

AE – Adverse Event

ME – Monitoring / Evaluation

IEC – Information, Education and Communication

N.A. – Not applicable

Supplementary Table 4. Inputs of personnel categories

Inputs - Personnel categories	Comment
Implementing institution	Salaries, fringe costs and/or per diems of manager, supervisors of training and field activities, general administration staff, team for information/sensitization at district level, and data management consultant, when applicable.
Ministry of Health (MoH) external staff[a]	Salaries and/or per diems of national, district and health facility level staff. Per diems of community leaders/mobilizers.
Drivers	Per diems.
Sound Car	Per diems of the sensitization team (one driver, one former National Onchocerciasis Control Program coordinator (team lead) and one team member from CRFilMT).
School staff	Per diems of school staff helping during testing and treating of children in schools.
Administrative authorities	Per diems of administrative authorities during advocacy phase.
CDDs	Per diems.
Loascopists and blood drawers	Per diems.

[a] The salaries of the Minister of Health and the director of MoH's Disease Control Division were not included, but apart from advocacy activities, they are not usually in the budget, so the impact on the total cost is assumed to be very small.

Supplementary Table 5. Costs of personnel disaggregated by category and activity (US$)

Personnel Category	#	Per diem days	Per diem (US$/day)	Total per diems	Salaries and fringe costs	Total payments	1. Advocacy	2. Census	3. Planning and budgeting	4. Procurement	5. Training	6. HE community / mobilisation	7. Delivery intervention	8. AE surveillance & management	9. ME	10. General Management	% of total pilot costs
Implementing institution																	
Manager	1	53	70	3,699	-	3,699	-	-	-	*	-	-	-	-	-	3,699	1%
Supervision of field activities	14	983	70	69,277	6,336	75,614	-	9,948		*	6,644	-	20,183	9,026	-	29,813	26%
General Administration	2	63	70	4,438	-	4,438	-	-	4,438	*	-	-	-	-	-	-	2%
IEC team	3	26	44	1,154	-	1,154	-	-	1,154	*	-	-	-	-	-	-	0·4%
Data management consultant	1	570	18	10,039	-	10,039	-	-	-	*	-	-	-	-	10,039	-	4%
MoH																	
MoH national level	5	114	53	6,030	623	6,653	402	1,177	1,559	9	1,514	-	1,975	-	18	-	2%
MoH district and health area levels	8	44	26	2,575	1,413	3,988	63	385	26	*	132	173	486	117	92	1,101	1%
Other																	
CDDs	600	4,153	4	18,287		18,287	35	6,006		*	3,538		7,343		1,365		6%
Drivers	7	349	26	9,211	-	9,211	-	1,459	-	*	796	1,198	4,649	1,110	-	-	3%
Loascopists & blood drawers	100	1,434	5	7,579	-	7,579	26	-	48	*	918	-	6,494	-	92	-	3%
Various personnel	N.A.	N.A.	N.A.	9,779		9,779	317	-	845	*	-	7,608	1,008	-	-	-	3%

table continues

Total	N.A.	N.A.	N.A.	140,655	8,372	149,027	843	18,975	8,071	9	13,542	8,979	42,137	10,253	11,606	34,613	52%

Number of professionals

* Procurement by administrative personnel (included under overhead costs)

HE – Health Education

AE – Adverse Event

ME – Monitoring / Evaluation

IEC team - Information, Education and Communication

MoH – Ministry of Health

CDDs – Community Drug Distributors

N.A. - Not applicable

Personnel were paid per diems for days of work outside their working place (receiving/giving training or any days of field work). To the costs of the per diems were added the costs of the daily salaries of each professional, to account for the opportunity cost of their time not spent in other projects. The structure needed for the use of the LoaScope still does not allow a house-to-house strategy, so we kept the costs of using mobile stations.

Overhead costs were included to capture the shares of the salaries of the administrative and financial managers (general administration), and the coordinator, building rental, cleaning and security services attributable to this project. Capital items are here defined as having a life expectancy of more than 5 years. Capital items such as vehicles, computers, software, office furniture, communication or audiovisual equipment used in the Soa campaign had already been paid by previous projects (except for the LoaScopes, no capital items were purchased specifically for this project) and were not included in the cost calculations. The variable running costs related to such capital items were explicitly included in the micro-costing study. Overhead costs were billed to the funding source (Bill and Melinda Gates Foundation via Institut Bouisson-Bertrand) as 15% of all actual expenditures of the entire round (of all costs of supplies and personnel). This seems to be a reasonable estimate of the overhead costs, considering that the TaNT campaign is not the only project to fund these expenses. These resources are jointly used by more programmes run by CRFilMT. A higher percentage bears the risk of double counting.

Costs exclusively related to research (research protocol driven costs) were not included in this study. They include costs related to travelling to and attending research meetings, congresses, research visits from international researchers for the development of data collection instruments, costs of all researchers working on the cost collection and calculations.

Appendix 3. Questionnaires

Questionnaires were adapted from those used in the DOLF project.[216]

A prospective questionnaire with a user-friendly design with tables, tick boxes and expected short answers was chosen based on feedback from the CDDs. This was used to investigate the number of hours CDDs spent on transportation, training, census-taking, treatment and reporting. It was also used to collect information about their occupation and income, capture their opportunity costs and enable the use of real information instead of arbitrary valuation systems such as Gross National Income (GNI) or rural wage as a proxy for an 8-hour day of volunteer labor.[230]

The English versions of the French questionnaires are included below.

Supplementary Table 6. Design, structure and dissemination of the questionnaires for CDDs and external staff from the Ministry of Health.

Questionnaire number and target	Content	Type	Number of pilot tests, pilot test dates and area	Dissemination method and time	Completion period
1. CDDs	Commuting time and costs to training, time spent in training, professional activity and income	Prospective	3 rounds of about 20 CDDs, October 2017, in Ting Melen, Koulou and Ngali health areas	Printed and distributed at the end of the training session	At the end of each CDD training session
2. CDDs	Education level, time spent for sensitisation, census and treatment, satisfaction regarding financial incentives	Prospective	3 rounds of about 20 CDDs, October 2017, in Ting Melen, Koulou and Ngali health areas	Printed and distributed at the end of the training session	At the end of each CDD treatment campaign
3. External staff from Ministry of Health (different levels)	Time spent on the TaNT project in Soa with break down by activity type, monthly salary, number and amount of received per diem	Retrospective	No pilot tests were carried out.	Applied individually during personal interviews	At the end of the TaNT round

Questionnaire 1

Questionnaire for community drug distributor ***(to fill in at end of training session)***

Name :				
Health area :				**Sex : male** ☐ **female** ☐
Village :				**Age :** ____ **years**
Days spent	**Date**	**Starting time**	**Ending time**	
Day 1				
Day 2				

1) Transportation

How long was the way for you to reach the health center for the training session ?_____minutes

How much have you spent as transportation fees to join the health center for training session ?_____ CFA F

2) Occupation (s)

What is your **main** activity in life *(to make money)* ?	☑	What is your **secondary** activity in life *(if any)* ?	☑
1 Unemployed	☐	1 Unemployed	☐
2 Housewife	☐	2 Housewife	☐
3 Agricultor	■	3 Agricultor	■
Cacao	☐	Cacao	☐
Coffee	☐	Coffee	☐
Banana	☐	Banana	☐
Other : _____	☐	Other : _____	☐
4 Farmer	☐	4 Farmer	☐
5 Shepherd /fish farmer	☐	5 Shepherd /fish farmer	☐
6 White palm wine collector	☐	6 White palm wine collector	☐
7 Hairdresser	☐	7 Hairdresser	☐
8 Teacher	☐	8 Teacher	☐
9 Big merchant	☐	9 Big merchant	☐
10 Small merchant	☐	10 Small merchant	☐
11 Cleaning	☐	11 Janitor	☐
12 Community health worker	☐	12 Community health worker	☐
13 Bricklayer/carpenter	☐	13 Bricklayer/carpenter	☐
14 Driver (car, bike)	☐	14 Driver (car, bike)	☐
15 Nurse	☐	15 Nurse	☐
16 Student	☐	16 Student	☐
17 Other : _____	☐	17 Other : _____	☐

How much of your time do you devote to this **main** activity?			How much of your time do you devote to this **secondary** activity?		
In 1 day		Hours	In 1 day		Hours
In 1 week		Days	In 1 week		Days
In 1 month		Weeks	In 1 month		Weeks
In 1 year		Months	In 1 year		Months
How much do you earn for this activity		Hours	How much do you earn for this activity		Hours
		Days			Days
		Weeks			Weeks
		Months			Months

Questionnaire 2

Questionnaire for community drug distributor

(to fill in at the end of treatment campaign)

Name : **Health area :** **Village :**	**Sex : male** ☐ **female** ☐ **Age : ____ years**

1) Sensitization/Census at community level

Days spent	Dates	Starting time	Ending time
Day 1			
Day 2			
Day 3			
Day 4			
Day 5 Day 6			
Day for verification of census at the health center at end of the treatment			
Day 7			

Education level	
Primary school	
Secondary school	
University level	

2) Treatment of tested people

Days spent	Dates	Starting time	Ending time
Day 1 Day 2			
Day 3 Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day to verify and retrieve registers at health center			
Day			

Adverse events management

How much time have you spent in managing adverse events?

_____hours

Financial incentive and satisfaction	Census	Treatment
How much did you receive for the work you did ?		
Are you satisfied of the amount you received for the work you did ?		
If no, how much were you willing to receive (per day)?		

Questionnaire 3

Retrospective questionnaire for people involved in TNT

To be completed by a CRFilMT interviewer for each staff of the Ministry of Health and NGOs involved in the TNT strategy. This does not include permanent CRFilMT staff. Please note that all questions refer to time spent during one year.

In 2017, did you spend time on TNT Loa loa project in **Soa** ?.

☐ **Yes** ☐ **No**

If yes, continue with questions below ; if else, stop interview.

1. Please allocate an estimate of your time spent on the TNT project for Loa loa in Soa across the following activities: (Note: total must equal 100%)

Activity codes	Nr days	Percentage of time allocated
(1) Advocacy		
(2) Supervision of census		
(3) Planning and budgeting		
(4) Procurement		
(5) Training		
(6) Supervision of health education/community mobilization		
(7) Delivery of interventions (treatment) to target populations		
(8) Adverse event surveillance and management		
(9) Monitoring and evaluation		
(10) Other:		

2. What is your monthly salary? _____

3. Did you receive per diems for the days you spent on TNT Soa? Yes ____ No ____

   If yes, for how many days? _____

   How much did you receive per day? _____ CFA francs /per day

Appendix 4. Scenarios

The scenarios were designed according to the literature and our own expertise in conducting CDTI rounds in Cameroon, using the same health district as context.[206,219]

Supplementary Table 7. Assumptions regarding differences in personnel costs between the base case, less intensive and more intensive resource use implementation scenarios. Costs are specified in Communauté Financière Africaine (CFA, African Financial Community) francs (XAF).

Input	Base case scenario		Less intensive resource use scenario		More intensive resource use scenario	
Supervision of census, training and treatment[a]						
Personnel type	**Number of persons**	**Number of days per person**	**Number of persons**	**Number of days per person**	**Number of persons**	**Number of days per person**
National level	1	6 days: 1 – receiving training, 2 – giving training, 1 – census, 2 – treatment	Same as base case.		**2**	Same as base case.
Regional level	1	7 days: 2 – receiving training, 2 – giving training, 1 – census,	Same as base case.		**2**	Same as base case.

table continues

		2 – treatment			
District level	2	7 days: 2 – receiving training, 2 – giving training, 1 – census, 2 – treatment	Same as base case.	**3**	Same as base case.
Health area level	6 chiefs of centers per District (on average)	11 days: 2 – receiving training, 1 – giving training, 3 – census, 5 – treatment	Same as base case.	Same as base case.	Same as base case.
NGDO (manager)	1	5 days: 2 – giving training, 1 – census, 2 – treatment	Same as base case.	Same as base case.	Same as base case.
NGDO (supervisors)	2	6 days: 1 – receiving training, 2 – giving training, 1 – census, 2 – treatment	Same as base case.	Same as base case.	Same as base case.

table continues

Drivers	5[b]	24 days:[c] 4 – receiving training 8 – giving training 4 – census 8 – treatment	Same as base case.	7[b]	Same as base case.
CDDs	716 (1/100 people)	2 days 2 – receiving training Census and treatment days not included in the calculations (not paid).	Same as base case.	Same as base case.	5 days 2 – receiving training 3 – treatment Census days not included in the calculations (not paid).
Loascopists and blood drawers.	478 (1/300 people)	5 days 2 – receiving training 3 – treatment	Same as base case.	Same as base case.	Same as base case.
Monitoring & evaluation (M&E)					

table continues

National level	1	4 days supervision of data collection	Same as base case.	3 days supervision of data collection	Same as base case.	6 days supervision of data collection
Regional level	2	4 days compiling it in Excel + 4 days supervision of data collection	Same as base case.	3 days compiling it in Excel + 3 days supervision of data collection	Same as base case.	6 days compiling it in Excel + 6 days supervision of data collection
District level	2	4 days compiling it in Excel + 4 days supervision of data collection	Same as base case.	3 days compiling it in Excel + 3 days supervision of data collection	Same as base case.	6 days compiling it in Excel + 6 days supervision of data collection
Chief of each health area	6	4 days synthesizing data from the registers brought by CDDs + 4 days supervision of data collection	Same as base case.	3 days synthesizing data from the registers brought by CDDs + 3 days supervision of data collection	Same as base case.	6 days synthesizing data from the registers brought by CDDs + 6 days supervision of data collection
NGDO	2	4 days supervision of data collection + data manager	Same as base case.	3 days supervision of data collection + data manager	Same as base case.	6 days supervision of data collection + data manager

table continues

Drivers (NGDO, Central level and Regional level)	5[b]	20 days [c]	Same as base case.	15 days [c]	7[b]	42 days [c]
Advocacy	Same as pilot.		Same as pilot.		Same as pilot.	
Planning and budgeting	Same as pilot.		Same as pilot.		Same as pilot.	
Procurement	Same as pilot.		Same as pilot.		Same as pilot.	
Health education / community mobilization	Same as pilot excluding all costs related to the sound car (same as CDTI).		Same as base case.		Same as base case.	
Adverse event surveillance and management	Same as pilot.		Assumed half of pilot costs.		Same as pilot.	

[a] Extra supervision costs by the implementing institution during the pilot were excluded from all scenarios.

[b] Total number of drivers for MoH personnel.

[c] Total number of days transporting MoH personnel.

Supplementary Table 8. Assumptions regarding differences in personnel per diems between the base case, less intensive and more intensive resource use implementation scenarios. Costs are specified in Communauté Financière Africaine (CFA, African Financial Community) francs (XAF).

Personnel type	Base case scenario	Less intensive resource use scenario	More intensive resource use scenario
National level	•5,000 transportation fee to receive training/day; •40,000 per diem to give training; •40,000 per diem / field day.	Same as base case.	Same amount paid per person as in base case, but for 2 professionals instead of 1.
Regional level	•5,000 transportation fee to receive training/day; •25,000 per diem to give training; •25,000 per diem / field day.	Same as base case.	Same amount paid per person as base case, but for 2 professionals instead of 1.
District level	•20,000 per diem to receive training + 10,000 transportation fee to receive training; •15,000 per diem + 5,000 transportation fee/day to give training; •15,000 per diem + 5,000 transportation fee / field day.	Same as base case.	Same amount paid per person as base case, but for 3 professionals instead of 2.
Health area level	•10,000 per diem to receive training + 3,000 transportation fee/day to receive training;	Same as base case.	Same as base case. 3,000 transportation fee to give/receive training/day;

table continues

	•5,000 per diem + 3,000 transportation fee/day to give training; •10,000 per diem + 2,000 transportation fee / field day.		3,000 transportation fee / field day.
NGDO manager	• 40,000 per diem to give training; • 40,000 per diem / field supervision day.	Same as base case.	Same as base case.
NGDO supervision	• 40,000 per diem to give training; • 40,000 per diem / field supervision day.	Same as base case.	Same as base case.
CDDs (1 CDD / 100 inhabitants)	• 2,000 per diem + 500 transportation fee/day for 2 training days; • not paid any per diems for census or treatment days.	Same as base case.	•3,000 per diem + 500 transport fee for each of 2 training days; • 5,700 per diem / field day (average income for an eight-hour day (to account for income loss), according the CDDs' responses in the questionnaires).
Blood drawers and Loascopists (1 of each / 300 inhabitants)	• 2,500 per diem + 600 transportation fee for each of 2 training days; • 3,000 per diem + 600 transportation fee for each of the 3 treatment days	Same as base case.	•2,500 per diem + 4,200 transport fee for each of 2 training days; •3,000 per diem + 4,200 transport fee for each of the 3 treatment days.

table continues

			(transportation fee = two-way maximum transportation costs to training sites, based on CDDs' responses)
Drivers (for national and regional levels and NGDO)	• 20,000 per diem	Same as base case.	Same per diem paid as base case, but more personnel (as shown above).
School staff	School staff not paid.	Same as base case.	1 school staff per community, assume 100 community in need of school treatment per district; 5,000 per diem for 1 day per staff.

Supplementary Table 9. Assumptions regarding differences in supplies costs between the base case, less intensive and more intensive resource use implementation scenarios. Costs are specified in Communauté Financière Africaine (CFA, African Financial Community) francs (XAF).

Input	Base case scenario	Less intensive resource use scenario	More intensive resource use scenario
Fuel	•30,000 XAF fuel allowance/day for central level and NGDO cars; 20,000 XAF fuel allowance /day for cars driven by regional level personnel; 10,000 XAF fuel allowance for district staff per field day	Same as base case.	40,000 XAF fuel allowance per day for Central level cars, paid to more personnel (as shown above).
Consumables likely to have different prices when purchased by MoH (office supplies, communication tools, car maintenance, adverse reaction drugs, field material, teaching material, other direct costs).	Assumed 30% less compared to the costs of consumables of actual TaNT pilot.	Assumed 50% less compared to the costs of consumables of actual TaNT pilot.	Same as TaNT pilot.
LoaScopes purchase price	US$ 400 unit price (large-scale manufacturer's prediction price).	Same as base case.	US$ 700 each (same as actual TaNT pilot).
Capillaries used for testing	US$ 0.40 unit price (large-scale manufacturer's prediction price).	Same as base case.	US$ 1.10 each (same as actual TaNT pilot).

Fuel and drivers. CRFilMT transported blood drawers and loascopists from their villages to the villages they were going to work at. In a CDTI round organized by the health district this would not be possible and it also decreases the efficiency of the work, since it delays the starting time in the field. To account for this, we added a transportation fee of 600 XAF to the per diems paid to blood drawers and loascopists in the base case scenario, using the average transportation cost paid by CDDs in our project to get to the trainings. They would still have to bring back LoaScopes to health centers at the end of each treatment day in order to recharge their batteries and check for any malfunction. Since personnel from the different levels would still need drivers to take them to training sites and to the field for supervision, we assigned one driver per person of the above-mentioned supervision team, for each day of work, with a per diem of 20,000 XAF. Since it is more difficult to have available drivers for district level staff, a fuel fee of 10,000 XAF was assigned to each of their days of work. Fuel allowance was also added to national and regional level personnel: 30,000 and 20,000 XAF, respectively. The sum of the per diem costs of drivers just mentioned replaced the costs of drivers' per diems of the original TaNT pilot for census, training and delivery of intervention. Fuel costs were kept as the original round costs, added the costs of the fuel for the national, regional and district personnel.

Since we are considering a first implementation round in the scenarios, health education and community mobilization costs would be similarly high. Unlike during the pilot, a sound car is not typical. Thus, we excluded all costs relative to its use in all scenarios.

Personnel costs related to administrative authorities (180,000 XAF) were kept the same.

Appendix 5. Volumes of supplies input categories

Supplementary Table 10. Volumes of supplies per input category. Prices specified in Communauté Financière Africaine (CFA, African Financial Community) francs (XAF).

Item	Quantity	Unit price	Total price
Personnel material (variable)			
Capillaries (receipt in Dec 2017)	66,274	1.1	72,901
LoaScopes purchase	15	212,000	3,180,000
Badges	566	263	149,000
Bags for blood drawers	15	5,000	75,000
T-shirts	700	1,800	1,260,000
Drugs for AE management (variable)			
Aerius 5mg coated tablet/7	1	2,600	2,600
Amoxicilline 500mg gel B/1000	1	29,000	29,000
Artemether	9	650	5,850
Arthemether+lumefantrin 20/120mg tablet disp B/6	10	1,121	11,210
Arthemether+lumefantrin 80mg/480mg B/6 tablet	10	910	9,100
Arthemether+lumefantrine 20/120mg tablet B/24	9	855	7,695
B complex vitamin tablet B/1000	1	13,146	13,146
Yellow Betadine dermatologic solution flacon /125ML	1	1,550	1,550
Chlorpheniramine B/10	60	500	30,000
Cloxacilin	6	500	3,000
Compress 40*40	1	1,450	1,450
Dexametazone	6	100	600

table continues

Diclofenac DENK 50 TABLET B/2x10	50	794	39,700
DIFENASOL flacon /5ML	10	680	6,800
Dynapar 100mg	1	950	950
Pregnancy test	1	500	500
Gentamycin eyedrops 10mL	5	525	2,625
GENTASOL CY flacon 5mL B/1	10	713	7,130
Glove	3	100	300
Glycaemia	1	1,000	1,000
Health care visit ticket	1	300	300
Ibuprofen 400 tablet B/10x10	5	1,050	5,250
Ibuprofen 400mg B/100 tablet	5	1,350	6,750
Iron sulfate 200mg+Folic acid 0.25mg tablet B/1000	2	22,000	44,000
Laritem 80mg/480mg tablet/6	1	2,650	2,650
Loratadine 10mg B/10 tablet	20	1,407	28,140
Metronizadole 250mg tablet B/1000 (Flagyl)	3	6,890	20,670
Crepe band 4*7C	1	600	600
Paracetamol 500mg tablet B/100	100	425	42,500
Patient card	1	300	300
Quinine sulfate 300mg tablet B/1000	1	32,400	32,400
Plaster 5x5cm	1	2,550	2,550
Syringe	6	100	600
Vitamin B complex tablet B/1000	2	13,146	26,292
Voltaren emulgel 1% T 50G	1	1,875	1,875
Hemoglobin test	1	500	500

table continues

Fuel and car maintenance (variable)			
Car maintenance (episodes)	47	98,584	4,633,429
Fuel (Liters)	7,144	577	4,121,900
IEC materials and registers (variable)			
IEC Leaflets	10,000	170	1,700,000
IEC Posters	1,000	2,500	2,500,000
Registers	900	2,777	2,499,000
Field materials (variable)			
Alcohol 95% (liters)	200	1,500	300,000
Bin bag 50Lx20	11	1,425	15,675
Bleach water (1 liter)	1	950	950
Bleach water 250ml	10	300	3,000
Hydrophilic cotton (pack of 500g)	130	1,900	247,000
Disposable cup	127	1,400	177,800
Chalk (pack of 100)	23	1,614	37,129
Gloves (pack of 20)	86	25,000	2,150,000
Grapefruit anti-bac	10	1,000	10,000
Hand washing gel 500ml	9	975	8,775
Lancets (pack of 200)	120	3,000	360,000
Paper towels	21	3,000	63,000
Paper towels large size*2	5	1,500	7,500
Paper towels large size*6	5	2,400	12,000
Mineral water (10L)	5	1,250	6,250
Recycle bin bags	20	1,750	35,000
Trash bucket	1	1,500	1,500
Tablecloth (pack)	1	14,000	14,000

table continues

Wraps (pack of 72)	21	2,350	49,350
Office supplies (fixed)			
Staple remover	1	500	500
Paper (reams of 500 sheets)	117	2,250	263,250
Pen (pack of 144)	4	40,750	163,000
Pencil	60	50	3,000
Pencil sharpener	20	150	3,000
File with 40 plastic bags	1	1,600	1,600
File with 40 plastic bags	1	1,850	1,850
Printer cartridge	14	47,000	653,000
Paper clips (1000)	1	2,000	2,000
Air time (global)	70	5,000	348,000

Appendix 6. Benchmark tool use

Fitzpatrick et al. (2016) developed a web-based software application that allows each user to calculate MDA round costs per person treated, varying different aspects according to each context.[215] We used the tool for the calculation of economic costs with a population of 71,643 (our censused total population), coverage rate of 42% (our final coverage rate), subnational, with no school-based delivery, no volunteers, 1 disease (stand-alone program), 1 round per year, first year of implementation, GDP per capita (2017) of US$ 1446.70 [231], and population density of 51.91/sq km [232] for the setting. We chose McFarland and Menzies (2005) for study-specific fixed effect, whose methodology was comparable to ours.[230]

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Chapter 7

Discussion

The main aim of the research presented in this thesis was to study the socioeconomic effect of neglected tropical diseases (NTDs) on individuals and society. Different aspects were investigated, from the description of productivity loss due to NTDs, to the economic benefit of reaching the London Declaration targets, to the cost of a new strategy to reach the targets for onchocerciasis, and the assessment of illness-related impoverishment. In general, lack of available data imposed extra challenges in the fulfillment of these objectives. Nevertheless, the results contributed to filling the existing gap in scientific knowledge related to this topic. In this chapter, by answering the research questions, the results will be put in a larger context of the literature and recommendations for further research. Furthermore, some additional perspectives on NTD research, policy making and a personal view on research in Brazil are provided before summarizing the main conclusions of this work.

7.1 Answering and discussing each research question

a. How (far) has productivity loss related to NTDs / disease been described in the literature?

It was logical to assume that the physical and psychological effects of NTDs affect productivity loss, and the results of the literature review described in Chapters 2 and 4 confirmed it, but more importantly, they also showed a vast gap in in the literature regarding this topic.

The focus of the literature on NTDs has been mostly epidemiological and clinical, so the impact of NTDs on productivity of affected men and women has been less frequently studied. The systematic literature review (Chapter 2) revealed a scarcity in studies on the productivity loss related NTDs, both those controlled by preventive chemotherapy (PCT) and intensified disease management (IDM), as summarized in the table below:

	NTD	Number of studies with any quantitative information on productivity loss
Preventive Chemotherapy (PCT)	Lymphatic filariasis	13
	Onchocerciasis	10
	Schistosomiasis	11
	Soil-transmitted helminths	6
	Trachoma	-
Intensified Disease Management (IDM)	Human African trypanosomiasis	3
	Chagas disease	12
	Visceral leishmaniasis	10
	Leprosy	4

There was a large variation in the definition of productivity loss used by the studies, and in the applied methodologies to quantify absolute and relative productivity loss. Furthermore, type and severity of the disease directly interfere on the actual impact, as well as the context where it occurs. Quality differed between studies for each disease, with 60% of the papers with an overall high risk of bias, mostly detection bias, selection bias, and attrition bias. No particular trend was observed, regarding over- or underestimation of results due to bias.

As with most reviews regarding costs and cost-effectiveness evidence, this systematic literature review conducted in 2013 focused on peer reviewed publications in the English language. We found only few studies published after our review that specifically reported productivity loss due to NTDs. One study measured 10% productivity loss for onchocerciasis patients via a household (HH) survey in Nigeria [1], less than the results for onchocerciasis found in this review and less than the values used in the calculations of the economic benefit in Chapter 3. Another study described a productivity loss of 3.8% from hospitalization of severe schistosomiasis cases in Brazil [2], also smaller than

the results for onchocerciasis found in this review, but similar to the values used in Chapter 3.

The general impression, also presented in Chapter 5, is that illness-related productivity loss related to low-income settings has not yet raised much academic interest. This might be explained from two angles. First, measuring productivity loss in low-income contexts might be more difficult than in high-income settings. Second, poor populations usually have little political voice and therefore might not be among the highest priorities of policy makers and research funds. Furthermore, the relation to poverty does not seem to be appealing to many scientists that aim to show societal impact of their research. Therefore, given the striking scarcity of peer reviewed evidence, we strongly recommend stimulation of research on productivity loss related to NTDs, but also to other diseases that have a high burden in low- and middle-income countries (LMICs).

b. How much economic benefit can be expected from reaching the targets for the 10 London Declaration NTDs?

There is an important economic benefit of reaching the 2020 NTD targets set by the WHO for PCT and IDM diseases, both in averted productivity loss and out-of-pocket payments (OPPs), as described by Chapters 3 and 4.

The economic benefit of reaching these targets was calculated by subtracting the costs calculated for a target achievement scenario from the costs of the counterfactual scenario of having done nothing for each disease, for the period between 2011 and 2030 (ten years before and after target-achievement). For the calculation of the costs, the estimated disease frequency was combined with productivity loss resulting from the disease, from the perspective of a person affected by each of the NTDs. The same was done for the healthcare costs paid by the affected individuals. The results based on conservative assumptions and subsequent uncertainty analyses are jointly summarized in the table below:

	Productivity loss averted (I$)		Out-of-pocket payments averted (I$)	
NTDs	2011 - 2020	2021 - 2030	2011 - 2020	2021 - 2030
Preventive Chemotherapy (PCT)	251 billion	313 billion	0.72 billion	0.96 billion
Intensified Disease Management (IDM)	23.1 billion	35.9 billion	14 billion*	18 billion*

(I$) – International dollars (2005 purchasing power parity)

* Already considering the latest WHO targets for 2030 (a minimum of 80% essential health services coverage and 100% of the population at risk protected against out-of-pocket health payments due to NTDs by 2030).

The economic impact varies between NTDs and regions, since it is determined by the prevalence, the OPPs and the degree of productivity loss caused by the sequelae of each NTD.

For both Chapters 3 and 4, the same limitations apply, such as the many assumptions that had to be formulated due to lack of available data, the exclusion of coping strategies and the productivity loss from subtle morbidity, or the use of the human capital approach. As a consequence, we were not able to calculate specific economic impact of NTDs for individual countries.

Since the publication of our estimates, there have not been other published results that could be compared to them. The lack of research on socioeconomic effects of NTDs is likely due to a higher priority in basic research towards building strategies to combat NTDs, which is understandable. For instance, the ability and feasibility of current diagnostics to provide an accurate view of disease epidemiology to inform decision

making still faces challenges for all London Declaration diseases (as also mentioned in point 7.1c) - except for LF, which faces minor delays/challenges. [3]

Since the country-specific estimates that were provided were based on OPPs and productivity loss from only a few countries (sometimes only one), future research regarding these topics could be conducted or commissioned by each government, in order to provide a convincing case for the realism of the results. Furthermore, a more realistic country-specific estimate of the economic benefit of reaching the London Declaration targets for local endemic diseases might complete the advocacy package of a country. Despite the fact that the timeframe for the London Declarations 2020- targets is short, such insights might be relevant for future health care decision making.

c. What are the costs and cost drivers related to new diagnostic strategies aimed at reaching the 2020 NTDs targets? The example of *Loa loa*

Costs of a new and safe diagnostic point-of-care strategy developed to avoid severe adverse events due to MDA in areas where onchocerciasis and loiasis are coendemic were higher than costs for usual treatment, but nevertheless affordable, as shown in Chapter 5. The main costs drivers were field material (capillaries especially developed for the diagnostic device) and salary costs of supervision personnel.

A micro-costing approach was used to empirically assess the cost of a community-based test-and-not-treat strategy in the Soa health district in Cameroon. The empirical costing study reflected the costs borne by the organizations involved in implementing and executing the program in this specific pilot. The total costs of US$ 283,938 divided by total population, people tested and people treated with 42% coverage were US$4.0, US$9.2, and US$9.5, respectively. In programmatic implementation, these costs (base-case estimates with less and more intensive scenarios) could be US$ 2.2 ($1.9 – $3.6), US$ 5.2 ($4.5 – $8.3), and US$ 5.4 ($4.6 – $8.6), respectively. Even though higher than standard mass treatment, affordability might increase with further reductions, for instance, once the purchase price of the tool and capillaries is reduced by large-scale production and once supervision personnel can be reduced.

Despite the use of a time-consuming micro-costing approach, for several items we were still not able to estimate costs, such as the cost of previously acquired capital items, building rental and opportunity costs of school staff when helping during the treatment phase. Furthermore, retrospective data collection might have introduced some recall bias.

The recent literature shows other examples of cost and feasibility of new strategies. One studied the integration of a field deployable, rapid diagnostic tool (based on detection of anti-Ov16 antibodies) into ongoing onchocerciasis surveillance programs in endemic countries. In Senegal, the total cost per participant in the surveillance activity showed a difference of $0.23 per method ($16.57 for the rapid test and $16.34 for skin snip microscopy), with a far bigger willingness to take the rapid test compared to the skin snip test. In this case, transportation costs accounted for the higher costs of the new strategy. [4]

Another example showed that swab tests for Chlamydia trachomatis infection can be applied in trachoma control to prevent further redundant MDA rounds and that in circumstances where an initial MDA round reduces infection below the decision threshold, this will save resources. When the swab test was included in the round, a $0.88 increase per tested child was calculated. Main cost drivers were personnel costs, followed by supervision. [5]

Regarding costing studies of new diagnostic strategies for targets in NTDs we have three recommendations. Firstly, a clear diagnostic strategy and the specific context of the health care system where it will be introduced need to be defined in order to collect the relevant surveillance data, including costing data. A clear diagnostic strategy and the implementation context might point out on forehand the main cost drivers and these should be measured prospectively in order to get unbiased cost estimates. In the case of point of care testing, for instance, cost might be mainly driven by field supervision of previously trained health care personnel when using the tests and effective supply chain, however, the cost-estimates will be specific to the local circumstances, giving effectiveness and fragility of health care systems due to shortage of human and other resources. [6] Secondly, since cost drivers might vary due to the local setting, for instance transportation and personal costs in areas with sparse population and difficult terrain, cost collection instruments should be adapted to collect such context-specific

information. [7] Thirdly, despite the undeniable importance of new diagnostic strategies, the third WHO global NTD report does not include extra costs for research and development of new diagnostic tests or strategies, let alone evaluation of their implementation. [8] Consequently, no specific funds are allocated for research and development of these strategies, so governments with the same challenges regarding NTDs endemic in their countries could join in the commissioning of studies on specific strategies according to their local demands.

d. What are the effects of combining OPPs and productivity loss in the assessment of illness-related impoverishment?

Combining the joint impact of OPPs and productivity loss to individuals affected by specific diseases might increase the likelihood of illness-related impoverishment, as shown in Chapter 6.

The impact of combining both productivity loss and OPPs on the likelihood of illness-related impoverishment was examined by looking at which moment the residual income of an individual affected by disease would cross the US$1.9 and US$3.2 poverty line (PL) thresholds: after deducting illness-related OPPs alone or after deducting OPPs combined with productivity loss. Analysing the joint impact, the percentage of countries where affected individuals were pushed below the poverty line clearly increased (from 0% to 46% using the US$1.9 PL; from 5% to 80% using the US$3.2 PL).

Again, despite the fact that we focused on one disease only, a limitation of our work is scarcity of available data: very little is known about OPPs, productivity loss and the characteristics and behavior of affected individuals. Furthermore, the individual perspective was used and we therefore did not consider other factors that could influence illness-related economic losses, including household coping, productivity loss of informal caregivers and intergenerational inequality.

Contrasting to the little data is the great importance of disease and its economic consequences (large expenditures and productivity loss) as causes of poverty. Literature on economic hardship due to illness and its effect on poverty has hardly ever addressed

out-of-pocket payments (OPPs) and productivity loss jointly. Joint assessment provides a more complete picture of an important and well-known cause of poverty. Besides, improvements in the quantity and quality of data would greatly enhance the ability to assess illness-related impoverishment, regardless of the disease. Therefore, research on the corresponding adjustments of household surveys on the quantification of OPPs, productivity loss, on the measurements of health-status, on the intangible costs related to illness but also on the feasibility and efficiency challenges of these measurements would be needed. Combining OPPs and productivity loss would show a more complete picture of poverty in all its forms, supporting priority setting and improving decision-making about policy instruments to reduce illness-related impoverishment and achieve the main aim of the Sustainable Development Goals (SDGs): to end poverty by 2030.

7.2 The larger perspective of this thesis

So far, NTDs have been regarded as important diseases to be addressed from the perspective of the physical and psychological suffering they cause to affected individuals, but also the consequences to the household, such as harming children's education and thus their future, and keeping families trapped into poverty. The work in this thesis shows that NTDs also deserve more attention because they might not only cause important economic consequences to affected individuals, but also to societies/nations. This section will discuss another aspect of the economic benefits of reaching the targets: return on investments. It will also approach the topic of transferability of research and data collection methods.

Return on investment

An important argument to reach NTDs' targets is that it would also have a direct and sustainable effect on the economic growth and financial welfare of the affected populations, and consequently lead to greater national and global prosperity.[9-11] This thesis provided the concrete economic estimates that were missing to be used in advocacy pro NTD control (see also 7.1b above). Moreover, these economic estimates were used to provide a very crude first calculation of the return on investment of reaching the 2020 targets for NTDs.[12]

	Return on investment*	
NTDs	**2015-2020**	**2021-2030**
Preventive Chemotherapy	27.4	42.8
Intensified Disease Management	0.9	2.8

* Net benefit per US dollar invested

There is a considerable difference between the estimated return on investments from avoided PCT versus IDM diseases, which can be explained by the difference in the investments that need to be made to achieve the targets for each of them. On the one hand, MDA treatment is relatively cheap: MDA drugs are safe and effective; the treatment can be delivered by health agents or trained community drug distributors, saving the costs of pre-treatment diagnosis for PCT diseases; and treatment of PCT chronic disease symptoms does not involve costly procedures in a high proportion of cases. On the other hand, IDM diseases are relatively expensive: cases need to be diagnosed and treated in health services by specialized health care personnel, using specific tests; treatment might need hospitalizations due to the severity of disease symptoms and high toxicity of drugs; and treatment of chronic disease symptoms frequently involves high costs due to high drug costs and severity of disease consequences.[12,13]

It was expected that showing the actual values of the economic benefit of productivity loss and OPPs averted would render a bigger interest from local governments to invest in reducing the NTD burden in each country, since the return on investment was shown to be big. But what was seen since the publication of these results in January 2017, is that investment is still one of the main priorities in the current NTD agenda. Healthcare financing is still rated as a high priority for Chagas disease, HAT, leprosy, LF, onchocerciasis, trachoma and VL, and as a critical priority for schistosomiasis and STH. The degree to which available funding is sufficient for program requirements is regarded as a critical priority for LF, onchocerciasis, schistosomiasis, STH and trachoma and as a high priority for Chagas disease, HAT, leprosy and VL. [3] A resource mobilization plan for meeting identified funding gaps is still a critical priority for HAT, leprosy, onchocerciasis, STH, trachoma and VL, and a high priority for Chagas disease, LF and schistosomiasis. The status ranking on the degree to which available funding is sufficient

for program requirements is referred to as presenting "moderate challenges/delays" for most of the London Declaration NTDs, except for schistosomiasis and trachoma, for which even substantial challenges/delays apply. [3] Apparently, high return on investments is still not reason enough to stimulate a higher commitment in combating NTDs.

Our crude calculations of return on investment of reaching the targets for NTDs did not include big investments in local long-term improvements such as clean water, sanitation, health/hygiene education and in equipping and strengthening local health systems with trained health care workers and adequate infrastructure. These actions are as necessary to address NTDs as the drug treatments donated by the pharmaceutical industry. Furthermore, enabling access to health care is not only critical to reach the targets, but also to sustain them in the long run. Addressing the human fundamental right to the highest attainable standard of health is a logical justification to address NTDs. Still, adding the significant economic benefit of reaching NTDs' targets to this argument did not exclude investment of the higher priorities' list on the current NTD agenda.

Globalize the framework, individualize the methods, localize the evidence

The economic benefit of reaching the targets for NTDs (and consequently the return on investment) is absolutely dependent on local circumstances. As such, the work of this thesis is a reminder of the transferability limitations of using the same methods in all countries and, more importantly, generalize data across jurisdictions. [14] Of course, global organizations such as the WHO and Uniting to Combat NTDs need standard indicators of the situation in each country, so they can act in the organization of general advocacy, strategies, and funding. As seen in the OPP literature and even more in that on productivity loss, as well as in our costing study of the test-and-not-treat (TaNT) strategy, the way information is collected should be individualized by each country and perhaps each region within a country, depending on the specific challenges they face. In short, the framing and choice of indicators ('what') should be 'globalized', defined by global organizations (to allow data comparison and data compilation), but the data collection per se should be 'individualized' to the local setting, in order to allow proper

prospective collection of the context-specific evidence. Between both steps is the adaptation of the 'how': the data collection instruments that will be used, by changing existing ones or creating and validating new ones. This adaptation process would follow the global guidelines, to ensure that information on the globally defined indicators will be collected. The adjustments would not only consider literally translating the instruments to the local language, but figuratively to the local culture and socioeconomic reality, and to the local available structure that will be used in the data collection. Evidently, each instrument should comply with the current knowledge on data collection instruments.

One example of the 'localization' of data collection was experienced in the development of the questionnaire to collect personal information from the community drug distributors (CDDs) working in the TaNT round. Three rounds of pilot tests took place, during which CDDs were individually assisted in reading, understanding and filling in the questionnaires. A user-friendly design with tables, tick boxes and expected short answers was adopted based on feedback from the CDDs, still providing all inputs requested by the data collection protocol.

Another example is the output approach, described in more detail in the prospects on future research below. In short, to measure household productivity loss secondary to malaria, not only the questions were adapted to the local setting, but also the way they were asked, for instance alternating the questions on income, in order to avoid distrust by the interviewed.[15]

7.3 Future prospects

This thesis contributed to the scientific evidence base on productivity loss related to NTDs, as well as the economic benefit of reaching the London Declaration targets, cost of one alternative strategy to enable reaching the target for onchocerciasis, and the likelihood of being impoverished from illness-related productivity loss. There are, however, important challenges for future research, many of which have already been cited while answering to the research questions. This section will discuss some additional general prospects of research regarding OPPs and productivity loss, more specifically

survey design, presenteeism, and the WHO recommended output approach. A more detailed data collection on the characteristics of the populations affected by NTDs and their intangible effects is also covered by this section. Furthermore, some considerations about how more detailed data collection relates to the results calculated in this thesis using data from the Global Burden of Disease study (GBD) are presented. This section concludes with an overview of prospects on policy making.

Prospects on research

First and foremost, more research is needed on how to better collect actual OPPs and productivity loss data from affected individuals and households and on how to measure the counterfactual (healthy individuals).

The development of instruments to capture illness-related OPPs and productivity loss should consider that there is evidence that estimates captured by surveys are extremely sensitive to survey design, preventing comparisons between them. The development of questionnaires/surveys considering wording, framing, recall periods, and number of questions, culturally and contextually adaptable to the population to be applied to would be a first step to address this issue. [16,17] As mentioned above, indicators should be defined globally, but the operationalization of the data collection should be defined locally. Ideally, questionnaires should ask for any health issue affecting an individual or the household, eventually adding extra questions, depending on the most prevalent or the diseases causing the highest burdens in each country.

Regarding productivity loss specifically, most NTD studies report lost working days, describing only absenteeism. Presenteeism (decreased on-the-job performance due to the presence of health problems) is also very relevant, especially due to chronic diseases that do not prevent the person from going to work and in countries with little or no social security.[18] In developing countries, employment opportunities tend to depend more on physical endurance and strength, so questions on the ability to perform job tasks involving bodily strength, movement, endurance, coordination, and flexibility are needed, as well as on the ability to produce work output in a high-quality or timely manner.[19] As seen in some of the studies describing productivity loss of individuals affected by NTDs, the magnitude of the productivity loss depends of course on the disease symptoms, but also on the profession of the affected person. Therefore, questions about

occupation and decreased work performance due to disease symptoms should also be included in future surveys/instruments.

The output approach is the method of measuring productivity loss recommended by the WHO. It is especially aimed at low-income settings, or settings where work is not paid by a salary. Attanayake et al [15] applied it to measure the productivity loss of households related to malaria in Sri Lanka, using a definition of productive work as 'involvement in any economic activity with the potential to add to the disposable income (in kind or cash) to the household'. Whenever illness had adversely affected the productive work of any household member, it was measured either in terms of output units or person days. Both completely and partially disabled days of the patients were considered and the valuation of indirect cost was based on actual loss of income attributable to illness. Loss of income could happen as the result of direct monetary loss, e.g. loss of daily wage of a casual labourer, or as a reduction in farm income or production 'such as due to being unable to harvest tobacco leaves at the proper time (and hence receiving a lower price) or the destruction of crops by wild animals as fields were left unattended'. Referred changes in agricultural production (for commercial or subsistence purposes), were translated into the market prices of those products in the respective subdistrict to calculate their money value. The opportunity cost of the time of other household members to cover the loss of productive work of patients or the household members caring for the patient was calculated using the average wage rates (of males and females separately) of the respective subdistrict. 'Complete disability period was defined as the number of days in which the patient had to avoid the engagement in his/her main and subsidiary occupations due to physical and/or mental disability. Partial disability was the inability to engage in some of those activities.' [15] The concepts used in the output approach could serve as basis for more encompassing and detailed surveys on productivity loss. With the standardization of the indicators and a clear definition of what each of them should be measuring, the comparison between them is possible, despite of the different methodology used to collect the data to generate them.

A more detailed and elaborate design like the output approach was also missing in the studies describing the population affected by NTDs. There is no doubt that most of them affect poor individuals, but it was not clear how poor these populations were, to allow a proper calculation of individual and societal economic benefit, since for instance

information on their occupation, their income, or other sociodemographic variables was not collected. Furthermore, social consequences were also hardly included in economic assessments related to NTDs. People's feelings, thoughts, wellbeing changed by the disease symptoms are mostly described as intangible, and therefore no monetary value is attached to them, as is was not in the work presented here. The same holds for potentially long-term consequences to a child being out of school, or a household member taking care of a sick person not having leisure activities: the impact on human/social capital formation is also not monetarily quantified. For these aspects to be included in future economic evaluations, they also have to be captured by data collection instruments.

In summary, establishing new methods to assess OPPs, productivity loss, and characteristics of affected populations validly and reliable is an important topic for future research.

Prospects on Global Burden of Disease

The economic benefit of reaching the NTD targets was calculated based on the 2010 Global Burden of Diseases, Injuries, and Risk Factors (GBD) study, which is a comprehensive study of health loss designed to capture complex patterns of disease and injury burden. The burden is reported in disability-adjusted life years (DALYs), calculated for each disease, considering both the years of life lost due to premature death caused by the disease and the years of life lost due to disability of living with the disease and enduring its consequences.[20,21]

Some of the 2010 criticisms as discussed in the literature will be elaborated upon below, to allow for a more critical view of the work in this thesis.

The GBD study uses disability weights to represent the severity of a disease/condition. These are standardized values that are assigned to non-fatal health outcomes to capture their severity on a scale between 0 (full health) and 1 (death), calculated by either a panel of experts or surveys not globally representative. The universal usage of these weights and their failure to account for both qualitative and cultural differences and differential access to resources around the world is still a cause for debate, since the same disease consequence can have more or less weight depending on the context of the affected individual. For instance, vision impairment has much less impact on daily lives in

developed nations compared to LMIC. Also, diseases that affect the use of a person's limbs will have a bigger negative impact in developing nations, where labor is frequently dependent on physical strength and mobility.[20,22] Disease weights have been used as a proxy for productivity loss when such an estimate was not available, which was the case for visual impairment caused by trachoma, for instance.[23-25] Better estimates on the productivity loss due to visual impairment from trachoma would lead to better estimates of the economic benefit of reaching the targets for trachoma.

Still on the parameters used by GBD, data sources range from scientific literature to survey data to epidemiological surveillance data. Nations might provide less-than-accurate surveillance data to inflate their progress, yielding results that are not always transparent and therefore questionable.[20,21] This would influence the prevalence and death estimates used to calculate the counterfactual scenarios for the comparison with the target reach scenario for each disease. If GBD used prevalence estimates with 'inflated progress', there is a possibility that even more prevalent cases existed in the years prior to reaching the targets, which would mean that the difference between the counterfactual scenario and the target reach scenario is in reality bigger, leading to an underestimate of the economic benefit of reaching the targets.

The use of single statistic metrics for evaluating health and for prioritizing resources has also been under ethical debate, since DALYs do not show who is being more affected.[22,26] This information would also have to be complemented with studies investigating the characteristics of people affected by each disease, as mentioned above. Ultimately, studies collecting better data on OPPs, productivity loss, income, occupation, intangible effects – only to name a few, as well as more reliable prevalence estimates, would also contribute to more accurate future GBD estimates.

Since 2010, the GBD study has undergone many updates and changes in methodology and reporting, to account for several issues, including the above-listed ones. Still, the debate on whether the use of ostensibly universal disability weights is possible, desirable or even useful for policy purposes continues. In this sense, future contextualized surveys could supplement indicators like the DALYs with local qualitative knowledge and support responsible health priority-setting.

Prospects on policy making

Our studies suggest that the economic benefit of reaching the 2020 targets for NTDs is considerable, which might ultimately influence health policy agenda in favor of addressing NTDs. Independently from the economic argument, there are more reasons that justify an increase in attention by policy makers and ultimately investments related to NTDs and their control.

First, countries are being called to invest more in combating NTDs and reaching the targets and to gradually depend less on foreign investments. The calculated economic benefit in this thesis could encourage countries to do so, as the investments would largely pay off. As mentioned previously, reaching the targets also depends on investments on instances linked not only to NTDs such as potable water supply, sanitation, education and health systems (including access to them). This should be done independently of reaching targets for NTDs and of the anticipated economic benefits. These are basic necessities that should be guaranteed to each individual by each government. Foreign investors could then still contribute with drug donations (which would gradually decrease with the decrease in the number of people needed to be treated) and with the research and development of the new strategies, specifically new diagnostic tools. The alignment of the local and global actions would be essential for the provision of real needs and to avoid waste of investments (double investments).

Second, new diagnostic strategies are essential for monitoring progress and impact of interventions and guiding treatment strategies of control, interruptions of transmission, elimination and post-elimination surveillance (reaching the targets and sustaining them). The absence of clear diagnostic strategies has resulted in limited and unreliable surveillance data. Point-of-care technologies are needed, that can be used in remote settings, designed in a "sample-in answer-out format", requiring minimal training and providing results in a relatively short time period. [6] As mentioned in the answer of question c above, financing of research and development of point-of care diagnostic tests is not included in the third WHO Global NTD report or in the London Declaration. [6,8] Ability and feasibility of current diagnostics to provide accurate view of disease epidemiology to inform decision making was ranked as a critical priority for HAT, leprosy and trachoma, and as a high priority for onchocerciasis, schistosomiasis and VL. [3] The

absence of the development of these new strategies in the London Declaration and in the investment costs makes it difficult to organize who should fund them. As suggested while answering question b, governments could jointly commission research on specific strategies that help them address common challenges to reach the targets for the same diseases. On the other hand, with the increase of investment of developing nations in many general instances, from basic potable water supply to sanitation and health care systems, international donors could commit to investing in the research and development of the new strategies needed to reach the London Declaration targets.

Third, NTDs are now directly or indirectly linked to almost all SDGs. So in fact, each government would not only be looking at investing in reaching London Declaration targets, but also at reaching many SDGs (including eradication of poverty) with the actions required to address NTDs. [27-30] In this sense, the economic and social intertwined benefits would certainly outweigh the ones calculated for reaching only the targets for NTDs. Perhaps this argument outweighs the argument of the economic benefit and might now interfere positively in the many gaps delaying NTDs to be properly addressed.[30,31]

7.4 Personal opinion - data collection in Brazil

As discussed above, the need for better data should be addressed by data collection of standardized indicators via instruments that will capture the information more accurately by adapting them to the local culture and to the local available infrastructure.

In Brazil, the possibility of integrating community health agents (CHAs) into the investigation/survey routines would be an interesting study of local adaptation of data collection methods. The first step in the implementation of the family health strategy in Brazil was the creation of the CHA profession. CHAs work as the bridge between the health teams in the primary health centers and the communities they are responsible for. Most of the times CHAs are part of those communities, since they live in the same area. CHAs develop activities to promote health, disease prevention surveillance, also through individual and collective educational actions in the community. They follow all families and individuals under their responsibility through home visits. The visits are scheduled

together with the health team, considering risk and vulnerability criteria, so that families with greater need are visited more often. The average frequency of visits is in theory one visit/family/month. [32,33]

This close contact with families/households and the scheduled frequent visits could be a good opportunity to apply questionnaires and have reliable responses – at least in theory, since the CHAs would know much about the dynamics of the communities, economic activities, epidemiological risks and the recall periods would be no longer than one month. This would be in line with the literature, which states that data collection methods also interfere with the results: diaries and/or face-to-face interviewing, telephone, postal survey, or computer assisted personal interviewing, with more reliability when performed face-to-face. Furthermore, the probability of misreporting (possibly due to forgetting) increases when the time between interview and event increases.[17] Also, collecting data on income is often difficult, since respondents tend to worry about intentions to collect income data, so indirect questions sometimes have to be used, asked randomly and informally. [15] CHAs would have the advantage of being known and trusted by the communities.

7.5 Main conclusion and recommendations

This thesis sheds some light on so far lacking information about the socioeconomic effects of NTDs on individuals and society. The main conclusions are as follows:

- There is a striking paucity of evidence on many aspects of illness-related consequences of NTDs, from OPPs and productivity loss, to intangible effects, characteristics and behavior of affected populations.
- The economic benefit of reaching the 2020 targets for nine NTDs mentioned in the London Declaration is considerable, totaling several hundred billions of dollars world-wide over a 20 year period.
- It is feasible to conduct studies to investigate costs of new diagnostic strategies to reach the London Declaration targets for NTDs.

- Combining OPPs and productivity loss offers a more comprehensive view on the likelihood of illness-related impoverishment. This information might support the development of policies to better address illness-related impoverishment and reach SDG 1.

Paucity of evidence from the literature was the main challenge throughout the thesis. More research is needed, also aiming at improving research methods, in order to obtain more accurate estimates of illness-related socioeconomic consequences, especially OPPs and productivity loss. The economic impact of NTDs related to patients, their families and societies is substantial. Although this important information did (so far) not seem to interfere positively in the increase of investments from local governments in addressing NTDs, improved understanding of the economic effect of NTDs on individuals, households and countries, should at least increase health policy and research dialogue. New diagnostic strategies also deserve attention and dedicated research, especially on their costs, to allow for advocacy on their affordability and ultimately to provide missing epidemiological information needed to reach and sustain NTDs' targets. Hopefully, these results can help advocating in favor of addressing the social and environmental determinants of health, especially for the poor and vulnerable, aiming at more equity, inclusion, productivity and health in societies.

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Summary

Physical and mental suffering caused by disease is known to anyone, even when experiencing a mild cold. But disease also has economic consequences to individuals, households and societies that not everybody might be aware of. Depending on the disease and on the context of the affected individuals, these consequences might lead to economic hardship (forcing the reduction of basic expenditures such as food and shelter or children's education) and even to impoverishment. Out-of-pocket payments (OPPs) can be described as the expenses attributable to a specific illness, directly related to medical costs or to non-medical costs, borne by an individual. Productivity loss refers to the short-term or long-term inability to work resulting from morbidity, disability and mortality related to a disease.

Economic hardship and poverty (from disease and from other causes) are unfortunately still so relevant that two of the Sustainable Development Goals are devoted to these causes. The first SDG is 'To end poverty in all its forms everywhere by 2030' and SDG 3 'Good health and well-being - Ensure healthy lives and promote well-being for all' has a specific goal to 'Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all'.

Neglected Tropical Diseases (NTDs)

NTDs are a group of communicable diseases associated with chronic, disabling and disfiguring morbidity, but also death. Most of them affect extremely poor populations with little political capital, living in slums or in rural areas, frequently also affected by conflict, predominantly in low–and middle-income countries. Almost everyone in the poorest bottom billion in the world has at least one NTD, which also contributes to keep them trapped in poverty.

In 2012, the World Health Organization (WHO) set targets for the year 2020 for 10 NTDs. In the same year, these targets were endorsed by partners in the London Declaration: eradication of Guinea worm; elimination of lymphatic filariasis (LF), leprosy, sleeping sickness (human African trypanosomiasis) and blinding trachoma; and

control of schistosomiasis, soil-transmitted helminthiasis (STH), Chagas disease, visceral leishmaniasis (VL) and onchocerciasis (river blindness). The WHO recommends five interventions to reach the NTDs targets: preventive chemotherapy (PCT) by mass drug administration (MDA); innovative and intensified disease management (IDM); vector ecology and management; veterinary public health services; and the provision of safe water, sanitation, and hygiene.

In addition to the disease burden, the economic burden that NTDs inflict on patients and their families is also heavy, but only a few studies have investigated the impact of NTDs on OPPs and productivity loss for individuals, households, and societies.

This thesis

By studying the socioeconomic effect of NTDs on individuals and society, this thesis aimed at providing an improved understanding on this poorly investigated topic. First, a systematic literature review describes how NTDs impact productivity loss in affected adults. The subsequent two chapters report the estimation of economic benefit (to individuals) of meeting the 2020 WHO targets for PCT and IDM NTDs respectively. The next chapter presents cost assessments of a pilot round for a new tested diagnostic strategy to enable the treatment of onchocerciasis in areas co-endemic for *Loa loa* worm infections. Thereafter, the joint impact of OPPs and productivity loss on the likelihood of illness-related impoverishment is examined, using Chagas disease as an example. The final chapter contains a general discussion of the research findings, leading to the main conclusions and recommendations derived from this thesis.

Productivity loss related to NTDs in the literature

The focus of the literature on NTDs has been mostly epidemiological and clinical. The impact of NTDs on productivity of affected men and women has been less frequently studied. A comprehensive systematic literature review was performed in November 2013, relating all 10 London Declaration NTDs to economic impact. Eleven databases were searched and out of 5,316 articles found regarding all NTDs only a few quantitatively

described productivity loss: 13 related to LF, 10 on onchocerciasis, 11 on schistosomiasis, 6 on STH, none for trachoma, 3 for human African trypanosomiasis (HAT), 12 for Chagas disease, 10 for VL and 4 for leprosy.

There was much variation in the definition of productivity loss and, consequently, in the methodology to measure it. For instance, the annual productivity loss range for LF was 10 – 23% for chronic and 0.9 – 9% for acute symptoms, looking mostly at lost working hours or days. Onchocerciasis studies looked at more specific effects, such as the difference in daily wages between individuals with and without the disease, or the difference in size of the farm that healthy men can keep satisfactorily weeded compared to affected ones, with onchocerciasis-related skin diseases causing productivity loss ranging from 10 – 34% and blindness assumed to be 100%. Studies looking at schistosomiasis measured absolute productivity loss in lost working days, but also comparing infected individuals with healthy ones, with a range of 8.7% – 23%, depending on the symptom. STH-related studies also investigated absolute and compared productivity loss, ranging from 0.1 – 35%. Quality also differed between studies for each disease, with 60% of the papers with an overall high risk of bias.

This study showed that, despite the scarcity in publications and the variation caused by different research methods it is clear that NTDs do affect productivity loss. Type and severity of the disease directly interfere on the actual impact, as well as the context where it occurs.

The economic benefit from reaching the targets for 9 London Declaration NTDs

The WHO defined targets for NTD control/elimination by 2020, reinforced by the 2012 London Declaration, which, if achieved, would result in benefits not limited to health gains. The economic benefit of reaching these targets was calculated by subtracting the costs calculated for a target achievement scenario from the costs of the counterfactual scenario of having done nothing for each disease, for the period between 2011 and 2030 (ten years before and after target-achievement). For the calculation of the costs, the estimated disease frequency was combined with productivity loss resulting from the disease, from the perspective of a person affected by each of the NTDs. The same was done for the healthcare costs paid by the affected individuals. In order to estimate the

economic impact of meeting the London declaration targets, data from various sources, heterogeneous background, and variable quality had to be combined. The results based on conservative assumptions were:

	Productivity loss averted (I$)		Out-of-pocket payments averted (I$)	
NTDs	**2011 - 2020**	**2021 - 2030**	**2011 - 2020**	**2021 - 2030**
Preventive chemotherapy (PCT)	251 billion	313 billion	0.72 billion	0.96 billion
Intensified disease management (IDM)	23.1 billion	35.9 billion	14 billion	18 billion

(I$) – International dollars (2005 purchasing power parity)

The economic impact varied between NTDs and regions, since it was determined by disease prevalence, the OPPs and the degree of productivity loss caused by the sequelae of each NTD.

Apart from addressing the human fundamental right to aim for the highest attainable standard of health, controlling and eliminating NTDs would also have a direct and sustainable effect on the economic growth and financial welfare of the affected populations, and consequently lead to greater national and global prosperity. Combining these arguments to the cost and return on investment estimates and the already existing estimates of disease burden might increase health policy dialogue and further encourage prevention and control actions, assuring funders and policymakers that resources committed to these efforts are a good investment.

Costs and cost drivers related to a new diagnostic strategy aimed at reaching the target for onchocerciasis: the example of *Loa loa*

Improved diagnostics are essential for monitoring progress and impact of interventions and guiding treatment strategies of control, interruption of transmission, elimination and post-elimination surveillance. Point-of-care technologies are needed, that can be used in remote settings, designed in a "sample-in answer-out format", requiring minimal training and providing results in a relatively short time period.

One example is a point-of-care strategy to test-and-not-treat individuals with high levels of *Loa loa* microfilariae in their blood, in areas hypoendemic for onchocerciasis and coendemic for loiasis, since they have a high risk of severe adverse events. This study calculated the costs of a pilot implementation round based on actual expenditures, including financial costs and opportunity costs that will likely be borne by control programmes and stakeholders in the future. In addition to the empirical analyses, three scenarios (base-case, less and more intensive resource use) were estimated to explore how costs might differ if TaNT were implemented programmatically. This strategy cost US$ 4.0 per person in the population, US$ 9.2 for each person tested, and US$ 9.5 for each person treated. In the alternative implementation scenarios, these costs were estimated to be US$ 2.2 [1.9–3.6], US$ 5.2 [4.5–8.3], and US$ 5.4 [4.6–8.6] (base-case estimates with less and more intensive scenarios in square brackets), assuming 42% programme coverage. These costs were higher than usual mass drug treatment, but still affordable and with room for further reduction, depending on the implementation choices made. For instance, the purchase price of the diagnostic tool and capillaries might be reduced by large-scale production and supervision personnel can be cut down.

Effect of combining out-of-pocket payments and productivity loss in the assessment of illness-related impoverishment

One important cause of poverty is disease and its economic consequences (large expenditures and productivity loss). Literature on economic hardship due to illness and its effect on poverty has hardly ever addressed out-of-pocket payments (OPPs) and productivity loss jointly.

The impact of combining both productivity loss and OPPs on the likelihood of illness-related impoverishment was examined by looking at which moment the residual income of an individual affected by disease would cross the US$ 1.9 and US$ 3.2 poverty line (PL) thresholds: after deducting illness-related OPPs alone or after deducting OPPs combined with productivity loss. The example used was heart failure due to Chagas disease in all countries endemic for Chagas disease. Analysing the joint impact, the percentage of countries where affected individuals were pushed below the poverty line clearly increased (from 0% to 46% using the US$ 1.9 PL; from 5% to 80% using the US$ 3.2 PL).

Including productivity loss in the assessment of illness-related impoverishment might provide a more complete picture of one of the causes of poverty, supporting the achievement of the main aim of the Sustainable Development Goals (SDGs): to end poverty by 2030.

Future prospects

Even though the fight against NTDs has seen huge progress, there are many challenges still to be faced before the targets can be met at a universal scale. Some of these challenges concern lack of available evidence on many aspects that might influence policy making. As shown in this thesis, there is a striking paucity of evidence on many aspects of illness-related consequences of NTDs, from OPPs and productivity loss to intangible effects, characteristics and behavior of affected populations.

This work also shows that the economic benefit of reaching the 2020 targets for nine NTDs mentioned in the London Declaration is estimated to be considerable, totaling several hundred billions of dollars world-wide over a 20 year period. Also, it is feasible to conduct studies to investigate costs of new diagnostic strategies to reach the London Declaration targets for NTDs, which is supported by the study on onchocerciasis and by the other studies cited from the literature.

Furthermore, as seen in the OPP literature and even more in that on productivity loss, as well as in our costing study of the test-and-not-treat (TaNT) strategy, the way information is collected should be individualized by each country and perhaps each region within a country, depending on the specific challenges they face. In order to gather needed and reliable data for global socioeconomic indicators and concomitantly address transferability issues, our work suggests to globalize the scientific framework, individualize the methods, and localize the evidence.

And finally, combining OPPs and productivity loss in the assessment of illness-related impoverishment offers a more comprehensive view on the likelihood of illness-related impoverishment. This information might support the development of policies to better address illness-related impoverishment and reach SDG 1. There is an undeniable link between addressing NTDs and reaching the SDGs. The core commitment of SDGs to

'leave no one behind' calls for global focus on reaching the most impoverished, excluded disadvantaged, who still face painful inequalities when accessing resources, services and rights. To focus on these populations means also focusing on NTDs.

Samenvatting

Het fysieke en mentale lijden wat ziekte met zich mee brengt is bij iedereen bekend, al gaat het maar om een milde verkoudheid. Wat wellicht niet iedereen zich realiseert is dat ziekte ook economische gevolgen kan hebben voor individuen, huishoudens en samenlevingen. Deze gevolgen kunnen, afhankelijk van de ziekte en de context waarin het individu zich bevindt, op hun beurt weer leiden tot verdere economisch tegenspoed (gedwongen vermindering van uitgaven ten behoeve van basale levensbehoeften zoals eten, onderdak en onderwijs van de kinderen) en zelfs tot armoede. Eigen bijdragen (ofwel *out-of-pocket payments*, OPPs) zijn medische of niet-medische kosten die direct zijn toe te schrijven aan een specifieke aandoening en die gedragen worden door een individu. Productiviteitsverliezen betreffen zowel de korte- als lange termijn beperkingen om te kunnen werken veroorzaakt door morbiditeit, chronische beperkingen en overlijden als gevolg van ziekten.

Economische tegenspoed en armoede (als gevolg van ziekten en andere oorzaken) komt helaas nog steeds zo vaak voor dat twee duurzame ontwikkelingsdoelen, de zogeheten Sustainable Development Goals (SDGs), hieraan zijn gewijd. Het eerste SDG is 'Beëindigen vanarmoede, overal en in al zijn vormen tegen 2030' en SDG 3 'Goede gezondheid en welzijn –Waarborgen van gezonde levens en bevorderen van welzijn voor iedereen' met als specifiek doel 'Bewerkstelligen van een zorgstelsel met universele dekking, inclusief bescherming tegen financiële risico's, toegang tot essentiële gezondheidszorgdiensten van goede kwaliteit, en toegang tot veilige, effectieve, betaalbare essentiële medicijnen van goede kwaliteit en vaccinaties voor iedereen'.

Vergeten tropische ziekten

Vergeten tropische ziekten (ofwel *neglected tropical diseases*, NTDs) zijn een groep overdraagbare ziekten die vaak samengaan met chronische beperkingen, invaliderende en verminkende klachten, en ook sterfte. NTDs komen het meest voor bij zeer arme populaties met weinig politieke zeggenschap, vooral wonend in de sloppenwijken of op het platteland van lage- en middeninkomens landen die regelmatig worden gekenmerkt

door langdurige conflicten. Bijna iedereen die behoort tot de armste miljard mensen van de wereld heeft een NTD, wat hen weer gevangen houdt in de armoedeval.

In 2012 heeft de wereldgezondheidsorganisatie (WHO) voor 10 NTDs doelen opgesteld voor het jaar 2020. Deze doelen zijn in datzelfde jaar door partners onderschreven in het Verdrag van London: uitroeiing van de guineawormziekte; eliminatie van lymfatische filariasis (LF), lepra, slaapziekte (Afrikaanse trypanosomiasis) en het blind makend trachoom; en controle van schistosomiasis, via de grond overgedragen parasitaire worminfecties (*soil-transmitted helminthiasis*, STH), ziekte van Chagas, viscerale leishmaniasis (VL) en onchocerciasis (rivierblindheid). De WHO beveelt vijf interventies aan om deze NTD-doelen te bereiken: preventieve chemotherapie (PCT) door massabehandeling (MDA); innovatief en geïntensiveerd ziektemanagement (IDM); vectorecologie en -beheer; veterinaire volksgezondheidsdiensten; en de voorziening van veilig water, sanitaire voorzieningen en hygiëne.

Naast de ziektelast is de economische last die NTDs toebrengen aan patiënten en hun families ook aanzienlijk. Opvallend is dat nog zo weinig onderzoek is gedaan naar de impact van NTDs op eigen bijdragen (OPPs) en productiviteitsverliezen voor individuen, huishoudens en samenlevingen.

Dit proefschrift

Het doel van dit proefschrift is een beter inzicht te verschaffen in het sociaal-economische effect van vergeten tropische ziekten (NTDs) op individuen en de samenleving. Het proefschrift begint met een systematisch literatuuronderzoek over hoe NTDs van invloed zijn op productiviteitsverliezen bij volwassenen. In de daaropvolgende twee hoofdstukken wordt een schatting gemaakt van het economische nut (voor particulieren) van het behalen van de WHO-doelstellingen van 2020 voor respectievelijk PCT- en IDM NTDs. In het hoofdstuk daarna worden de kosten bepaald van een nieuw geteste diagnostische strategie voor de behandeling van onchocerciasis in gebieden die co-endemisch zijn voor *Loa loa* worminfecties. In het volgende hoofdstuk wordt gepresenteerd in welke mate OPPs en productiviteitsverliezen tezamen zouden kunnen leiden tot ziekte-gerelateerde verarming. Hierbij is de ziekte van Chagas als

voorbeeld genomen. Het laatste hoofdstuk bevat een algemene bespreking van de onderzoeksresultaten, afgesloten met de belangrijkste conclusies en aanbevelingen uit dit proefschrift.

Productiviteitsverliezen gerelateerd aan NTDs in de literatuur

De bestaande literatuur over NTDs bleek voornamelijk epidemiologisch en klinisch van aard. De impact van NTDs op productiviteitsverliezen voor mannen en vrouwen met een dergelijk ziekte was minder vaak bestudeerd. In november 2013 werd een uitgebreid systematisch literatuuronderzoek gedaan naar de economische impact van alle 10 NTDs van het Verdrag van Londen. Elf databases werden doorzocht, en van de 5.316 gevonden artikelen over NTDs waren er maar weinig die productiviteitskosten op en kwantitatieve manier beschreven: 13 waren gerelateerd aan LF, 10 aan onchocerciasis, 11 aan schistosomiasis, 6 aan STH, er was geen enkele over trachoma, 3 waren er over slaapziekte, 12 over Chagas ziekte, 10 over VL en 4 over lepra.

Er bleek veel variatie in de definitie van productiviteitsverliezen. Als gevolg hiervan verschilden ook de gebruikte meetmethoden. Bijvoorbeeld, wanneer gekeken werd naar het aantal verloren werkuren of dagen, dan varieerden de jaarlijkse productiviteitsverliezen van LF van 10 tot 23% voor chronische symptomen en van 0,9 – 9% voor de acute symptomen. In studies over onchocerciasis werd met name gekeken naar specifieke effecten, zoals het verschil in het dagelijkse salaris van individuen met en zonder de ziekte of het verschil in oppervlakte gewasgrond dat mannen met en zonder onchocerciasis konden wieden. Op basis van deze studies varieerden de productiviteitsverliezen voor onchocerciasis-gerelateerde huidziekten van 10 - 34% met daarnaast de aanname dat blindheid tot 100% productiviteitsverlies leidde. In artikelen waarin gekeken werd naar schistosomiasis werd productiviteitsverlies gemeten in het aantal absolute verloren werkdagen, waar gezonde individuen met schistosomiasis patiënten vergeleken werden. De gevonden productiviteitsverliezen varieerden afhankelijk van de symptomen tussen 8,7 – 23%. STH-gerelateerde onderzoeken onderzochten ook absoluut en relatief productiviteitsverlies, met een variatie van 0,1 – 35%. De kwaliteit verschilde ook tussen studies voor elke ziekte, met bij 60% van de artikelen een algemeen hoog risico op bias.

Dit literatuuronderzoek toonde aan dat, ondanks het feit dat studies over productiviteitsverliezen schaars waren en dat verschillende manieren werden gehanteerd om productiviteitsverliezen te meten, NTDs duidelijk gerelateerd zijn aan productiviteitsverliezen. Er blijkt een relatie tussen het type en de ernst van de ziekte en de daadwerkelijke impact, waarbij ook de context waarin het gebeurt een rol speelt.

Het economische voordeel van het bereiken van de doelen voor 9 NTDs van het Verdrag van Londen

De WHO heeft doelen gesteld om voor 2020 ofwel controle te hebben over de NTDs ofwel ze te hebben geëlimineerd. Deze doelen zijn versterkt in het Verdrag van Londen van 2012, en het nut van het bereiken ervan beperkt zich niet tot alleen de gezondheidswinst. Het economische nut van het bereiken van de doelen werd geanalyseerd door allereerst de kosten te berekenen van een scenario waarin de doelen bereikt werden. Deze kosten werden vervolgens afgetrokken van de kosten van een 'counterfactual', ofwel een nulscenario waarbij per ziekte niets werd gedaan om de doelen te bereiken. Deze berekeningen werden gedaan voor de periode 2011 tot 2030 (tien jaar voor en na het bereiken van de doelen). Om de kosten te berekenen, werd de geschatte frequentie van de ziekte gecombineerd met de productiviteitsverliezen gerelateerd aan de verschillende ziekten, vanuit het perspectief van een persoon met de desbetreffende NTD. Hetzelfde werd gedaan voor de gezondheidszorgkosten betaald door de individuen zelf. Om de economische impact van het bereiken van de doelen uit het Verdrag van Londen te schatten moest informatie uit verschillende bronnen met elkaar worden gecombineerd. De resultaten gebaseerd op conservatieve aannames waren als volgt:

	Voorkomen productiviteitverlies (I$)		**Voorkomen eigen bijdragen (I$)**	
NTDs	**2011 - 2020**	**2021 - 2030**	**2011 - 2020**	**2021 - 2030**
Preventieve chemotherapie (PCT)	251 miljard	313 miljard	0,72 miljard	0,96 miljard

Innovatief en geïntensifieerd ziektemanagement (IDM)	23,1 miljard	35,9 miljard	14 miljard	18 miljard

(I$) – Internationale dollars (2005 koopkrachtpariteit)

De economische impact varieerde tussen NTDs en regio's doordat deze impact bepaald werd door de prevalentie van de ziekte, de OPPs en de mate van productiviteitsverlies per ziekteverschijnsel van de NTDs.

Naast het bevorderen van het fundamentele recht van de mens om te streven naar de hoogst haalbare standaard voor gezondheid, zal het bedwingen of elimineren van NTDs ook een direct en blijvend effect hebben op de economische groei en het financiële welzijn van getroffen populaties. Dit leidt dan vervolgens weer tot een groter nationaal en wereldwijd welzijn. Deze argumenten, gecombineerd met de schattingen van de kosten en het rendement op investeringen en de al bestaande schattingen van de ziektelast, zouden het debat over gezondheidszorgbeleid en verdere preventieve maatregelen kunnen aanmoedigen. Hierdoor kunnen investeerders en beleidsmakers overtuigd worden dat de inzet van middelen voor zulke inspanningen een goede investering is.

Kosten en kostenfactoren gerelateerd aan een nieuwe diagnostische strategie gericht op het bereiken van de doelstelling voor onchocerciasis: het voorbeeld van *Loa loa*

Betere diagnostiek is essentieel voor het monitoren van vooruitgang en de impact van interventies en voor het bepalen van behandelingsstrategieën bij controle, onderbreking van transmissie, eliminatie en post-eliminatie surveillance. Point-of-care technologieën die gebruikt kunnen worden in afgelegen gebieden zijn nodig. Deze zouden ontworpen moeten zijn volgens een "sample-in answer-out format", waarbij weinig opleiding nodig is en testresultaten in korte tijd beschikbaar zijn.

Een voorbeeld van een point-of-care strategie is de *test-and-not-treat* (TaNT) (wel testen en niet behandelen) strategie bij individuen met hoge aantallen *Loa loa* microfilariae in

het bloed, in gebieden die hoog-endemisch zijn voor onchocerciasis en co-endemisch voor loiasis, aangezien zulke mensen een hoog risico hebben op ernstige bijwerkingen. In deze studie werden de kosten van een pilot implementatieronde berekend op basis van daadwerkelijke uitgaven, inclusief financiële kosten en opportuniteitskosten die waarschijnlijk in de toekomst door bestrijdingsprogramma's en belanghebbenden gedragen moeten worden. Naast de empirisch analyses, werden er drie scenario's (basis, minder en meer intensief zorggebruik) geanalyseerd om uit te zoeken hoe kosten kunnen verschillen als TaNT programmatisch geïmplementeerd zou worden. Deze strategie kostte 4,0 US$ (Amerikaanse dollar) per persoon in de populatie, 9,2 US$ voor elk getest individu en 9,5 US$ voor elk individu dat behandeld werd. Bij de alternatieve implementatiescenario's waren de geschatte kosten 2,2 US$ [1,9–3,6], 5,2 US$ [4,5–8,3] en 5,4 US$ [4,6–8,6] (basisscenario en schattingen met minder of meer intensieve scenario's tussen vierkante haken). Hierbij werd uitgegaan van 42% dekking van het programma. Deze kosten waren hoger dan gangbaar bij massale medicinale behandeling maar nog steeds acceptabel en met ruimte voor eventuele vermindering van kosten, afhankelijk van verdere implementatiekeuzes. Bijvoorbeeld, de aankoopkosten van het nieuwe diagnostisch hulpmiddel en capillairen zouden kunnen worden verminderd door grootschalige productie. Daarnaast kan toezichthoudend personeel op termijn worden verminderd.

Het effect van het combineren van eigen bijdragen en productiviteitsverlies bij de beoordeling van ziekte-gerelateerde verarming

Een belangrijke oorzaak van armoede is ziekte en de economische consequenties hiervan (grote uitgaven en productiviteitsverliezen). Studies over ziekte-gerelateerde economisch tegenspoed en het effect daarvan op armoede nemen zelden het effect van eigen bijdragen (*out-of-pocket payments*, OPPs) en productiviteitsverliezen tezamen mee.

Het effect van het combineren van zowel productiviteitsverliezen als eigen bijdragen op de kans dat iemand door ziekte in armoede geraakt werd onderzocht door te kijken naar het moment dat iemands resterende inkomen minder wordt dan de armoedegrens (AG) bij een drempelwaarde van 1,9 US$ en 3,2 US$: na aftrek van alleen de ziekte-gerelateerde

OPPs of na aftrek van OPPs gecombineerd met productiviteitsverliezen. Hiervoor werd hartfalen door de ziekte van Chagas in alle landen endemisch voor deze ziekte als voorbeeld genomen. Bij analyse van het gecombineerde effect nam het percentage landen waar getroffen individuen onder de armoedegrens terecht zouden komen duidelijk toe (van 0% tot 46% bij gebruik van de 1,9 US$ AG; van 5% tot 80% bij de grens van 3,2 US$ AG).

Het meenemen van productiviteitsverliezen in de beoordeling van ziekte-gerelateerde verarming geeft mogelijkerwijs een completer beeld van een van de oorzaken van armoede. Dit ondersteunt daarmee het hoofddoel van de duurzame ontwikkelingsdoelen (SDGs): een einde maken aan armoede tegen 2030.

Toekomst

Ondanks de grote vooruitgang in de strijd tegen de vergeten tropische ziekten (NTDs), moeten nog vele obstakels overwonnen worden voordat de doelen op mondiale schaal bereikt kunnen worden. Een aantal van deze uitdagingen hebben te maken gebrek aan kennis over verscheidende aspecten die van invloed kunnen zijn op beleid. Zoals in dit proefschrift beschreven, is er een opvallend gebrek aan kennis over ziekte-gerelateerde gevolgen van NTDs, van eigen bijdragen en productiviteitsverliezen tot immateriële effecten, kenmerken en gedrag van getroffen populaties.

Dit werk laat ook zien dat het bereiken van de 2020 doelen betreffende negen NTDs een aanzienlijke economische impact kan hebben, oplopend tot honderden miljarden dollars wereldwijd over een periode van 20 jaar. Daarnaast laat de studie over onchocerciasis, evenals andere geciteerde studies, zien dat het goed mogelijk is om onderzoek te doen naar de kosten van nieuwe diagnostische strategieën die worden ingezet om de in het verdrag van London gestelde doelen voor NTDs te bereiken.

Daarnaast is het belangrijk dat, wanneer informatie verzameld wordt, deze geïndividualiseerd wordt naar land en misschien zelfsnaar regio's binnen een land, afhankelijk van de specifieke uitdagingen waarmee landen worden geconfronteerd. Deze relevantie van individualisering van informatie bleek uit de literatuur over OPPs en productiviteitsverliezen, evenals uit ons kostenonderzoek van de 'wel-testen-niet-

behandelen' (TaNT) strategie. Om de benodigde en betrouwbare gegevens voor mondiale sociaaleconomische indicatoren te verzamelen en tegelijkertijd problemen met de 'transferability' aan te pakken, suggereert ons werk het wetenschappelijk kader te globaliseren, de methoden te individualiseren en het bewijsmateriaal te lokaliseren.

Tot slot biedt de combinatie van eigen bijdragen en productiviteitsverlies bij de beoordeling van ziekte-gerelateerde armoede een uitgebreider beeld van de waarschijnlijkheid van het optreden van ziekte-gerelateerde armoede. Deze informatie kan de ontwikkeling van beleid ondersteunen om ziekte-gerelateerde armoede beter aan te pakken en SDG 1 te bereiken. Er is een onmiskenbaar verband tussen het aanpakken van NTDs en het bereiken van de SDGs. De kernverplichting van 'de SDGs om 'niemand achter te laten' vereist een wereldwijde focus op het bereiken van de allerarmste, uitgesloten kansarmen, die nog steeds met pijnlijke ongelijkheid worden geconfronteerd bij de toegang tot middelen, diensten en rechten. Focus op deze populaties betekent ook focus op vergeten tropische ziekten.

Resumo

É de conhecimento geral que doenças causam sofrimento físico e mental, até mesmo um simples resfriado. Mas doenças também têm consequências econômicas para indivíduos, famílias e sociedades, consequências essas das quais nem todos podem estar cientes. Dependendo da doença e do contexto dos indivíduos afetados, essas consequências podem levar a dificuldades econômicas (forçando a redução de gastos básicos, como alimentação e moradia ou educação das crianças) e até ao empobrecimento. Pagamentos diretos (OPP, sigla em inglês para out-of-pocket payment) podem ser descritos como as despesas atribuíveis a uma doença específica, diretamente relacionadas a custos médicos ou não médicos, pagos pelo indivíduo acometido. A perda de produtividade aqui se refere à incapacidade laboral a curto ou longo prazo, resultante de morbidade, incapacidade e mortalidade relacionadas a uma doença.

Infelizmente, dificuldades econômicas e pobreza (por doenças e outras causas) ainda são tão relevantes que dois dos Objetivos de Desenvolvimento Sustentável (ODS) são dedicados a essas causas. O primeiro ODS é 'Acabar com a pobreza em todas as suas formas em todos os lugares até 2030' e ODS 3 'Boa saúde e bem-estar - Garantir vidas saudáveis e promover o bem-estar para todos' tem um objetivo específico de 'Alcançar a cobertura universal de saúde, incluindo proteção contra riscos financeiros, acesso a serviços essenciais de saúde de qualidade e acesso a medicamentos essenciais seguros, eficazes, de qualidade e vacinas para todos '.

Doenças Tropicais Negligenciadas

Doeças Tropicais Negligenciadas (DTN) são um grupo de doenças transmissíveis associadas a morbidade crônica, incapacitante e desfigurante, mas também à morte. A maioria afeta populações extremamente pobres com pouco capital político, vivendo em favelas ou em áreas rurais, freqüentemente também afetadas por conflitos, predominantemente em países de baixa e média renda. Quase todas as pessoas pertencentes ao bilhão de pessoas mais pobres do mundo têm pelo menos uma DTN, o que também contribui para mantê-las presas na pobreza.

Em 2012, a Organização Mundial da Saúde (OMS) estabeleceu metas para o ano 2020 para 10 DTN. No mesmo ano, essas metas foram endossadas pelos parceiros da

Declaração de Londres: erradicação da doença do verme-da-Guiné; eliminação da filariose linfática (FL), hanseníase, doença do sono (tripanossomíase humana africana – HAT, sigla em inglês) e tracoma (conjuntivite granulomatosa); e controle da esquistossomose, geo-helmintíases, doença de Chagas, leishmaniose visceral (LV) e oncocercose (cegueira do rio). A OMS recomenda cinco intervenções para alcançar os objetivos das DTN: quimioterapia preventiva (PCT, sigla em inglês) por administração de medicamentos em massa (MDA, sigla em inglês); gestão inovadora e intensificada de doenças (IDM, sigla em inglês); ecologia e gerenciamento de vetores; serviços de saúde pública veterinária; e o fornecimento de água potável, saneamento e higiene.

Além da carga da doença, a carga econômica que as DTN infligem aos pacientes e suas famílias também é pesada, mas apenas alguns estudos investigaram o impacto das DTN nos pagamentos diretos e na perda de produtividade de indivíduos, famílias e sociedades.

Esta tese

Ao estudar o efeito socioeconômico das DTN nos indivíduos e na sociedade, esta tese teve como objetivo proporcionar uma melhor compreensão sobre esse assunto pouco investigado. Primeiro, uma revisão sistemática da literatura descreve como as DTN afetam a perda de produtividade em adultos afetados. Os dois capítulos subsequentes relatam a estimativa do benefício econômico (para indivíduos) do cumprimento das metas da OMS para 2020 para DTN tratadas por PCT e IDM, respectivamente. O próximo capítulo apresenta avaliações de custos de um projeto piloto de uma nova e testada estratégia de diagnóstico para permitir o tratamento da oncocercose em áreas onde esta coexiste com infecções pelo verme *Loa loa*. Posteriormente, examina-se o impacto conjunto dos OPPs e da perda de produtividade na probabilidade de empobrecimento relacionado à doença, usando a doença de Chagas como exemplo. O capítulo final contém uma discussão geral dos resultados da pesquisa, levando às principais conclusões e recomendações derivadas desta tese.

Perda de produtividade relacionada a DTN na literatura

O foco da literatura sobre as DTN tem sido principalmente epidemiológico e clínico. O impacto das DTN na produtividade de homens e mulheres afetados tem sido menos

estudado. Uma revisão sistemática abrangente da literatura foi realizada em novembro de 2013, relacionando todas as 10 NTD constantes da Declaração de Londres a impacto econômico. Foram pesquisadas onze bases de dados e, de 5.316 artigos encontrados sobre todas as DTN, apenas alguns descreveram perda de produtividade quantitativamente: 13 relacionadas a FL, 10 a oncocercose, 11 a esquistossomose, 6 a geo-helmintíases, nenhum a tracoma, 3 a HAT, 12 a doença de Chagas, 10 a LV e 4 a hanseníase.

Houve muita variação na definição de perda de produtividade e, consequentemente, na metodologia para mensurá-la. Por exemplo, a faixa anual de perda de produtividade para FL foi de 10 a 23% para sintomas crônicos e de 0,9 a 9% para sintomas agudos, medindo principalmente horas ou dias de trabalho perdidos. Os estudos sobre oncocercose analisaram efeitos mais específicos, como a diferença no salário diário entre indivíduos com e sem a doença, ou a diferença no tamanho da área que homens saudáveis conseguem manter livres de ervas daninhas em comparação com homens afetados. Doenças de pele relacionadas à oncocercose causaram perda de produtividade variando de 10 a 34% e a perda de produtividade por cegueira por oncocercose foi assumida como sendo de 100%. Estudos analisando a esquistossomose mediram a perda absoluta de produtividade em dias perdidos, mas também compararam indivíduos infectados com saudáveis, com uma variação de 8,7% a 23%, dependendo do sintoma. Os estudos relacionados às geo-helmintíases também investigaram a perda de produtividade absoluta e comparada, variando de 0,1 a 35%. A qualidade também diferiu entre os estudos para cada doença, com 60% dos artigos com um alto risco geral de viés.

Este artigo mostrou que, apesar da escassez de publicações e da variação causada por diferentes métodos de pesquisa, fica claro que as DTN afetam a perda de produtividade. O tipo e a gravidade da doença interferem diretamente no impacto sobre a produtividade, assim como o contexto em que a DTN ocorre.

O benefício econômico de serem alcançadas as metas para 9 NTD da Declaração de Londres

A OMS definiu metas para o controle/eliminação das DTN até 2020, reforçadas pela Declaração de Londres de 2012, que, se alcançadas, resultariam em benefícios não

limitados a ganhos em saúde. O benefício econômico de essas metas serem atingidas foi primeiramente calculado para um cenário de alcance das metas. Esses custos foram ent~ao subtraídos dos custos do cenário contrafactual de nada ter sido feito em relação a essas doenças para as metas serem atingidas. O cálculo foi feito para o período entre 2011 e 2030 (dez anos antes e após o alcance da meta). Para o cálculo dos custos, a frequência estimada da doença foi combinada com a perda de produtividade resultante da doença, na perspectiva de uma pessoa afetada por cada uma das DTN. O mesmo foi feito com os custos de saúde pagos pelos indivíduos afetados. Para estimar o impacto econômico do cumprimento das metas da Declaração de Londres, dados de várias fontes, contextos heterogêneos e qualidade variável tiveram que ser combinados. Os resultados baseados em premissas conservadoras foram:

	Perda de produtividade evitada (I$)		**OPPs evitados (I$)**	
DTN	**2011 - 2020**	**2021 - 2030**	**2011 - 2020**	**2021 - 2030**
Quimioterapia Preventiva (PCT)	251 bilhões	313 bilhões	0.72 bilhão	0.96 bilhão
Gerenciamento Intensivo de Doenças (IDM)	23.1 bilhões	35.9 bilhões	14 bilhões	18 bilhões

(I$) - Dólares internacionais (paridade do poder de compra de 2005)

O impacto econômico variou entre DTN e regiões, uma vez que foi determinado pela prevalência da doença, pelos OPPs e pelo grau de perda de produtividade causada pelas sequelas de cada DTN.

Além de garantir o direito humano fundamental de almejar o mais alto padrão de saúde possível, o controle e a eliminação das DTN também teriam um efeito direto e sustentável no crescimento econômico e no bem-estar financeiro das populações afetadas e, consequentemente, levariam a uma maior prosperidade nacional e global. A combinação desses argumentos com as estimativas de custo e retorno do investimento e as estimativas já existentes da carga de doenças pode aumentar o diálogo sobre políticas

de saúde e incentivar ações de prevenção e controle, garantindo aos financiadores e formuladores de políticas que os recursos comprometidos com esses esforços são um bom investimento.

Custos e direcionadores de custos relacionados a uma nova estratégia de diagnóstico visando atingir a meta de oncocercose: o exemplo de *Loa loa*

Técnicas de diagnóstico aprimoradas são essenciais para monitorar o progresso e o impacto de intervenções e orientar estratégias de tratamento, controle, interrupção de transmissão, eliminação e vigilância pós-eliminação. São necessárias tecnologias de ponto de atendimento (point-of-care, em inglês), que podem ser usadas em lugares remotos, projetadas em um formato "entrada de amostra e saída de resposta" ("sample-in-answer-out" em inglês), exigindo treinamento mínimo e fornecendo resultados em um período de tempo relativamente curto.

Um exemplo é uma estratégia de ponto de atendimento para testar e não tratar (TaNT, sigla para test-and-not-treat em inglês) indivíduos com altos níveis de microfilárias de *Loa loa* em seu sangue, em áreas hipoendêmicas para oncocercose e coendêmicas para loíase, pois apresentam alto risco de eventos adversos graves. Este estudo calculou os custos de uma rodada piloto de implementação com base em despesas reais, incluindo custos financeiros e custos de oportunidade que provavelmente serão arcados, no futuro, pelos programas de controle e pelas partes interessadas. Além das análises empíricas, foram calculados três cenários (caso base, uso de recursos menos intensivo e uso de recursos mais intensivo) para explorar como os custos podem diferir se o TaNT for implementado programaticamente. Essa estratégia custou US$ 4,0 por pessoa na população, US$ 9,2 para cada pessoa testada e US$ 9,5 para cada pessoa tratada. Nos cenários alternativos de implementação, esses custos foram estimados em US$ 2,2 [1,9–3,6], US$ 5,2 [4,5–8,3] e US$ 5,4 [4,6–8,6] (estimativas do caso base, cenários de uso de recursos menos e mais intensivo entre colchetes), assumindo 42% de cobertura programática. Esses custos foram mais altos que a administração de medicamentos em massa usual, mas ainda são acessíveis e com espaço para reduções adicionais, dependendo das escolhas de implementação feitas. Por exemplo, o preço de compra da nova ferramenta de

diagnóstico e dos capilares pode ser reduzido pela produção em larga escala e o pessoal de supervisão pode ser reduzido.

Efeito da combinação de pagamentos diretos e perda de produtividade na avaliação do empobrecimento relacionado à doença

Uma causa importante de pobreza é adoecimento e suas conseqüências econômicas (grandes gastos e perda de produtividade). A literatura sobre dificuldades econômicas devido a doenças e seus efeitos sobre a pobreza quase nunca abordou os pagamentos diretos (OPPs) e a perda de produtividade conjuntamente.

O impacto da combinação de perda de produtividade e OPPs na probabilidade de empobrecimento relacionado à doença foi examinado observando em que momento a renda residual de um indivíduo afetado pela doença ultrapassaria os limites de US$ 1,9 e US$ 3,2 da linha da pobreza (LP): após dedução isolada dos OPPs relacionados a doenças ou após dedução de OPPs somados à perda de produtividade. O exemplo utilizado foi insuficiência cardíaca secundária à doença de Chagas em todos os países endêmicos da mesma doença. Analisando o impacto conjunto, a porcentagem de países onde os indivíduos afetados foram empurrados abaixo da linha da pobreza aumentou claramente (de 0% para 46% usando a LP de US$ 1,9; de 5% para 80% usando a LP de US$ 3,2).

A inclusão da perda de produtividade na avaliação do empobrecimento relacionado a doenças pode fornecer uma imagem mais completa de uma das causas da pobreza, apoiando a conquista do objetivo principal dos Objetivos de Desenvolvimento Sustentável (ODS): acabar com a pobreza até 2030.

Perspectivas futuras

Embora a luta contra as DTN tenha visto um grande progresso, ainda há muitos desafios a serem enfrentados antes que as metas possam ser alcançadas em escala universal. Alguns desses desafios dizem respeito à falta de evidências disponíveis sobre muitos aspectos que podem influenciar a formulação de políticas. Como mostrado nesta tese, existe uma notável escassez de evidências sobre muitos aspectos das conseqüências

relacionadas às DTN, desde pagamentos diretos e perda de produtividade até efeitos intangíveis, características e comportamento das populações afetadas.

Este trabalho também mostra que o benefício econômico estimado de se alcançar as metas para 2020 para nove DTN mencionadas na Declaração de Londres é considerável, totalizando várias centenas de bilhões de dólares em todo o mundo durante um período de 20 anos. Além disso, é possível realizar estudos para investigar os custos de novas estratégias de diagnóstico para atingir as metas da Declaração de Londres para DTN, o que é apoiado pelo estudo sobre oncocercose e por outros estudos citados na literatura.

Além disso, como visto na literatura sobre OPP e ainda mais literatura sobre perda de produtividade, bem como em nosso estudo de custos da estratégia de teste e não tratamento (TaNT), a maneira como as informações são coletadas deve ser individualizada por cada país e talvez cada região de um país, dependendo dos desafios específicos que enfrentam. A fim de reunir dados necessários e confiáveis para indicadores socioeconômicos globais e, concomitantemente, abordar questões de transferibilidade, nosso trabalho sugere globalizar a estrutura científica, individualizar os métodos e localizar as evidências.

E, finalmente, combinar OPPs e perda de produtividade na avaliação do empobrecimento relacionado à doença oferece uma visão mais abrangente sobre a probabilidade de empobrecimento relacionado à doença. Essas informações podem apoiar o desenvolvimento de políticas para lidar melhor com o empobrecimento relacionado à doença e alcançar o ODS 1. Há um vínculo inegável entre alcançar as metas para DTN e alcançar os ODS. O compromisso central dos ODS de "não deixar ninguém para trás" exige um foco global em alcançar os mais pobres, excluídos e desfavorecidos, que ainda enfrentam desigualdades dolorosas ao acessar recursos, serviços e direitos. Focar nessas populações significa também focar em DTN.

List of publications and submissions

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2015 Thesis supervision course, Erasmus University, Rotterdam, the Netherlands.

Participation at conferences and other meetings

2013 Annual meeting of the Coalition for Operational Research on NTDs (COR-NTDs), Washington DC, USA.

2015 5th Annual Leverhulme Centre for Integrative Research on Agriculture and Health (LCIRAH) Conference, London, UK.

2015 Consultation and planning meeting around the envisaged CGIAR CRP pre-proposal on Agriculture for Nutrition and Health, Food & Business Knowledge Platform, The Hague, the Netherlands.

2015 11th World Congress in Health Economics, Milan, Italy.

Presentations at conferences and other meetings

2013 Poster presentation "Investigating the quality of the evidence provided by empirical studies on women with breast cancer treated with mistletoe using GRADE", International annual conference of the Medical Section at the Goetheanum, Dornach, Switzerland.

2014 Oral presentation at the expert and technical advisory group meeting for the project "The Socioeconomic Impact of NTDs", Public Health Department – EMC and ESHPM - Erasmus University Rotterdam, Rotterdam, the Netherlands.

2014 Oral presentation "The socioeconomic impact of control or elimination of five neglected tropical diseases", 63rd Annual Meeting of the American Society of Tropical Medicine and Hygiene, New Orleans, USA.

2014 Oral presentation at ESHPM Lunch Seminar, Erasmus University, Rotterdam, the Netherlands.

2015 Oral presentation: 'Calculating short and long term health and economic benefits of an early nutritional intervention: organic school meals' - Feasibility analysis at the 1st Erasmus Nutrition Economics Workshop – "Calculating the health and economic benefits of nutritional interventions for small children", ESHPM, Erasmus University, Rotterdam, the Netherlands.

2016 Oral presentation "The socioeconomic impact of control or elimination of the London Declaration neglected tropical diseases" at the monthly meeting of the Chagas group from the Medical Faculty - State University of Campinas, Campinas, Brazil.

Organization of scientific meeting

2015 1st Erasmus Nutrition Economics Workshop – "Calculating the health and economic benefits of nutritional interventions for small children", with participation of the Dutch National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu – RIVM), Nutricia, Nestlé, Unilever, Unicef, Save the Children, Health Sciences and Biology and Biostatics Department at the Vrije Universiteit Amsterdam (VU), Genetics and Cell Biology Department at Maastricht University, the Netherlands Organisation for applied scientific research (Nederlandse Organisatie voor toegepast-natuurwetenschappelijk onderzoek – TNO), Human Nutrition Division at Wageningen University.

Projects

2012 – 2014 Coordinator of the International Research Newsletter on Anthroposophic Medicine, University of Applied Sciences Leiden, Leiden, the Netherlands.

2015 Organization of a consortium between ESHPM - Erasmus University, Department of Epidemiology - Maastricht University and the Louis Bolk Institute for the CEBENI project (Calculating Economic Benefits of long term health outcomes based on short term health outcomes of Early Nutritional Interventions). Application for a grant from ZonMW - The Netherlands Organisation for Health Research and Development and from Ekhagastiftelsen, Sweden.

2015 Organization of a consortium between Dutch institutions and Brazilian institutions for the project: Pesticide and veterinary antibiotic food exposure via school meals in small children in Campinas - exploratory feasibility study on health impact and trajectories of participatory food safety in the provision of school meals. From the Netherlands: ESHPM - Erasmus University; Social Sciences Department and RIKILT laboratory from Wageningen UR (University & Research Centre); TNO (Bioinformatics, Microbiology, Molecular Biology, and Personalized Nutrition and Health). From Brazil: Center for Nuclear Energy in Agriculture (CENA), University of São Paulo (USP); Toxicogenomics and Nutrigenomics Laboratory at São Paulo State University- UNESP, São Paulo; Laboratory of Health Education and Promotion – LAPES, Nutrition department and Pediatric Investigation Center, Faculty of Medical Sciences, both from University of Campinas – Unicamp; Health Secretary of the Municipality of Campinas, São Paulo, Organic Farming Association of Campinas and School Meal Programme Supply Central from CEASA, Campinas. Application for an Agriculture-Nutrition Impact Studies grant from the Bill and Melinda Gates Foundation.

2018-2019 Leader of the cost analysis of a pilot in the Soa health district, Cameroon, together with Public Health Department – EMC, Rotterdam, the Netherlands; Centre for Research on Filariasis and other Tropical Diseases (CRFilMT), Yaounde, Cameroon; Institut de Recherche pour le Développement (IRD), University of Montpellier, Montpellier, France; Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland; National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, United States and the Department of Bioengineering, University of California – Berkeley, Berkeley, CA, United States.

Teaching

2014 - 2015 Lectures on Health Technology Assessment - Burden of illness (Neglected Tropical Diseases) - Global Health Economics course, HEPL Master programme, ESHPM, Erasmus University, Rotterdam, the Netherlands.

Student guidance and training

2014 Guidance of HEPL master thesis students: Danique Roodnat and Anna Righetti, ESHPM, Erasmus University, Rotterdam, the Netherlands.

2014 – 2015 Guidance of HEPL master thesis student: Ankie Kerstens, ESHPM in collaboration with Philips, Erasmus University, Rotterdam, the Netherlands.

2018 Training of master student from Master of Public Health programme - Quantitative and Econometric Methods for Health Research (MQERS) at Aix-Marseille University, France: Henri Claude Moungui and PhD student from ESHPM, Erasmus University, Rotterdam, the Netherlands, for field data collection of the cost of a pilot round of Test-and-Not-Treat strategy to treat onchocerciasis in Cameroon.

2018 – 2019 Guidance of student from Master of Public Health programme - Quantitative and Econometric Methods for Health Research (MQERS) at Aix-Marseille University, France: Henri Claude Moungui, ESHPM, Erasmus University, Rotterdam, the Netherlands.

About the author

Edeltraud Johanna Lenk (1976) is currently a researcher at the Erasmus School of Health Policy and Management (ESHPM), Erasmus University, Rotterdam. Her main research interests are in the field of public health and its economic aspects in developing countries. The focus so far has been neglected tropical diseases and the starting field of nutrition economics.

She graduated in Medicine at the State University of Campinas (Unicamp) in Brazil in 2000 and specialized in Family and Community Medicine from the same institution in 2003. She also specialized in Anthroposophic Medicine from the Brazilian Association of Anthroposophic Medicine in 2004. From 2003 until 2010 she was the general practitioner and medical coordinator of a multidisciplinary team responsible for attending approximately 7000 patients living in the area covered by a Primary Health Care Unit from the Brazilian National Health System – Municipality of Campinas (São Paulo State).

In 2010 she and her husband moved to the Netherlands. In 2013 she obtained a masters degree in Health Economics, Policy and Law from the Erasmus University in Rotterdam. Right thereafter, she was invited to join ESHPM as a scientific researcher in the project funded by Bill and Melinda Gates Foundation: Assessing the economic benefit of reaching the goals of the 2012 London Declaration for Neglected Tropical Diseases, in collaboration with the Public Health Department from Erasmus MC. She also participated in discussions in nutrition economics within ESHPM and organized 1st Erasmus Nutrition Economics Workshop – "Calculating the health and economic benefits of nutritional interventions for small children", with participation of academia, industry, and government. From 2011 until 2014 she also worked as policy advisor and editor of the International Research Newsletter on Anthroposophic Medicine at the Hogeschool Leiden – Lectoraat Antroposopfische Gezondheidszorg.

In 2015 the family moved back to Brazil, where she continued as an external PhD candidate at ESHPM, Their son Joaquim was born in 2016. From 2017 until 2019 she worked in further project funded by Bill and Melinda Gates Foundation, in a collaboration between ESHPM and the Public Health Department from Erasmus MC:

Cost analysis of a test-and-not-treat strategy for onchocerciasis elimination in a Loa loa co-endemic area in Cameroon.

Physical and mental suffering caused by disease are known to anyone, even when experiencing a mild cold. But disease also has economic consequences to individuals, households and societies that not everybody might be aware of. Depending on the disease and on the context of the affected individuals, these consequences might lead to economic hardship and even to impoverishment. Neglected tropical diseases (NTDs) are a group of communicable diseases associated with chronic, disabling and disfiguring morbidity, but also death, most of them affecting extremely poor populations. This thesis aimed at providing an improved understanding on the socioeconomic e□ect of NTDs on individuals and society, on the costs of a new diagnostic strategy to combat one of the NTDs, and on the impact of disease-related direct costs and productivity loss on the likelihood of impoverishment. This evidence can increase health policy dialogue and further encourage NTD prevention and control actions, assuring funders and policymakers that resources committed to these efforts will not only address poverty and the fundamental right to health, but are also a good investment.