An elimination investment case (EIC) for human African trypanosomiasis (HAT)
Trypanosoma brucei (T.b.) gambiense ("sleeping sickness")

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Dedication

This thesis is dedicated to

... the people in the field and villages that 'sleeping sickness' affects in Sub-Saharan Africa: May you one day read this thesis and think of it as a historical piece; a study of an eliminated disease that once affected your ancestors long ago and now no longer burdens your people.

Acknowledgments

I am thankful for my faith in Christ that gave me the courage to continue to pursue post-graduate studies, even though I was rejected from seven institutions over seven years after matriculating from my undergraduate degree. It will take my entire lifetime to understand how you work Lord, but I have already learned and acknowledged that you are good, loving and kind and have the best plan in the midst of any circumstance. Thank you for being with me through my life's journey, and teaching me enjoy the process.

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If 'it takes a village to raise a child', then it takes a world to help someone complete a PhD – you all mean so much to me and I hope this thesis makes you proud of the woman I have become.

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Abbreviations

AB	Arab bank
ADB	African development bank
AECID	Agency of International Cooperation for Development (Spain)
AU	African union
BDC	Business development bank of Canada
BIA	Budget Impact Analysis
BMBF	Bundesministerium für Bildung und Forschung (Germany)
BMF	Bundesministerium für finanzen (Austria)
BMGF	Bill and Melinda Gates Foundation
BOI	Burden of illness
C	Consumption
CAR	Central African Republic
CATT	Card agglutination test for trypanosomiasis
CBA	Cost-benefit analysis
CDT	Community direct treatment
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CHE	Catastrophic health expenditures
CHEERS	Consolidated health economic evaluation reporting standards
CHW	Community health worker
CI	Confidence interval
CPI	Consumer price index
CSF	Cerebrospinal fluid
CTC	Capillary tube centrifugation
CUA	Cost-utility analysis
DALY	Disability adjusted life year
DARE	Database of Abstracts of Reviews of Effects
DES	Discrete event simulation
DFID	Department for international development United Kingdom (UK)
DFMO	difluoromethylornithine (eflornithine)
DM	Decision maker
DNDi	Drugs for Neglected Diseases initiative
DRC	Democratic Republic of the Congo
DT	decision tree
EEACT	Economic evaluation along-side clinical trial
EIC	Eradication/Elimination investment case

EMBASE	Excerpta Medica Database
EPH	Epidemiology and public health
EQ-5D™	EuroQol 5 dimensions
EVPI	Expected value of perfect information
FAO	Food and agriculture organization of the United Nations
FBE	Fresh blood examination
FIND	Foundation of Innovative New Diagnostics
FN	False negative
FP	False positive
GDP	Gross domestic product
GE	General electric
GNI	Gross national income
GTZ	Gesellschaft für Technische Zusammenarbeit (Germany)
HAT	Human African trypanosomiasis
HC	Healthcentre
HIV	Human immunodeficiency virus
HRQoL	Health related quality of life
HSM	Health systems model
HTA	Health technology assessment
HTC	HAT treatment centre
IAEA	International atomic energy agency
ICER	Incremental cost-effectiveness ratio
ICIPE	International centre of insect physiology and ecology
IDM	Institute for disease modelling
IHMT	Instituto de higene e medicina tropical (Universidade nova de Lisboa), Portugal
INRB	Institut National de Recherche Biomédicale, DRC
IoTM/ITM	Institute of Tropical Medicine - University of Antwerp
IRD	Institut de recherche pour le développement
IRD-CIRAD	IRD Centre de coopération internationale en recherche agronomique pour le développement
ITC	Insecticide treated cattle
JSTOR	The Journal Storage
LAMP	Loop-mediated isothermal amplification
LED	Light emitting diode
LGH	Lancet global health
LHC	Local health centre
LLIN	Long lasting insecticide-treated nets
LNP	lymph node puncture
LSTM	University of Liverpool
LYS	Life-years saved
M	Medical expenses

mAECT	Mini-anion exchange centrifugation technique
MAEE	The Ministry of Foreign and European Affairs
MCDA	Multi-criteria decision analysis
MD	Medical doctor
MDA	Mass Drug Administration
MDG	Millennial development goals
Med profess	Medical professional
MEDLINE	Medical Literature Analysis and Retrieval System Online
MEDTAP	Medical Technology Assessment and Policy
MEEP	Methods for economic evaluation project
MeSH	Medical Subject Headings
MID	Modelling infectious diseases
MoH	Ministry of health
MSF	Médecins sans Frontières
NA	Not applicable
NCD	Non-communicable disease
NECT	Nifurtomix-eflornithine combination therapy
NGO	Non-governmental organization
NHSEED	National Health Service Economic Evaluation Database
NM	Non-medical expenses
NMB	Net Monetary Benefit
NORAD	Norwegian Agency for Development Cooperation Governmental
NSCCP	National sleeping sickness control program
NTD	Neglected tropical disease
OOP	Out-Of-Pocket
OWSA	One way sensitivity analysis
PAAT	Programme Against African trypanosomiasis
PATH	Programs
PATTEC	Pan African Tsetse Eradication Campaign
PG	Palpation ganlionnaire
PICOS	Population (P), Intervention (I), Comparators (C), Outcomes (O), Study (S)
PNTHLA	Programme National de Lutte contre la Trypanosomiase Humaine Africaine
PPP	Purchasing power parity
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic Sensitivity Analysis
QALY	Quality adjusted life year
R&D	Research and development
RDT	Rapid diagnostic test
SA	Sensitivity analysis
SAT	Sequential aerial techniques

SDC	Swiss development corporation
SDG	Sustainable development goals
SDI	Standard diagnostics inc.
SF-36	Short form health survey (36 questions)
SIGN	Scottish Intercollegiate Guidelines Network
SIT	Sterile insecticide technique
SJA	Social justice assessment
Swiss TPH	Swiss Tropical and Public Health Institute
T.b.	Trypanosoma brucei
TAG	Technical Advisory Group
TAG	Task advisory group
TBF	Thick blood film
TDR	Tropical Disease Research
TN	True negative
TP	True positive
UNK	Unknown
USAID	United States Agency for International Development
USD	United States dollar
VC	Vector Control
VEERU	Veterinary Epidemiology and Economics Research Unit
VOI	Value of Information
WEO	World Economic Outlook
WHO	World health organization
WHO AFRO	WHO Africa Regional Office
WHO GPS	WHO guidance on priority setting
WHO HQ	WHO headquarters
WHO-CHOICE	WHO-CHOosing Interventions that are Cost-Effective
WTP	Willingness-to-pay
YLD	Years life disability
YLL	Years life lost

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Summary

Discoveries related to the peculiar disease of African trypanosomiasis have occurred throughout the centuries. 'Sleeping Sickness', the short name for human African trypanosomiasis (HAT), is derived from changes in the sleep-wake pattern seen in HAT patients as the presence of the trypanosoma parasite in the brain causes a slow neurological breakdown. Although major epidemics have been recorded over the past centuries, the number of cases have declined rapidly over the last decade placing HAT in the position of reaching elimination. In 2011, the World Health Organization (WHO) set a range of targets for eradication, elimination, or control of 17 neglected tropical diseases, but it still remains unclear how achievable many of these goals are, and what are the best ways forward. The Swiss Tropical and Public Health Institute (Swiss TPH) was supported to develop EICs for onchocerciasis, lymphatic filariasis (LF), and human African trypanosomiasis (HAT). Unlike filarial parasites that respond well to preventative chemotherapy oral treatments, trypanosoma parasites involve a more complex diagnostic and treatment paradigm. For this reason, a unique approach was taken to developing an EIC for HAT *T.b. gambiense.*

Evidence was collected systematically to address the initial questions posed by the Ernst Strüggmann Forum "Eradication Investment Case" (EIC) framework. From this information, potential strategies using current available tools and potential technologies were hypothesized that could be simulated through prospective modelling exercises to evaluate various outcomes. A dynamical model was also developed to simulate HAT *T.b. gambiense* transmission, and to forecast the impact of current and emerging innovations on the key concerns of the EIC: elimination, costs, health impact, cost-effectiveness, and number of cases. Modelling was also done to simulate household surveys to evaluate the impact of elimination on poverty. In addition a discrete event simulation model evaluated the possibility of integration comparing old and new strategies, while a social justice assessment was undertaken to ascertain which strategies would lead to ethical compromises within potential elimination programs.

The EIC results provide various options for stakeholders moving towards HAT elimination, but substantial funds will be required. In addition, trade-offs between cost-effectiveness, social justice and elimination targets in the next few decades will need to be made. Integration is feasible with new technologies and will provide more flexibility to capacity in high risk foci areas, but further exploration of this methods use within an EIC still needs to be explored. The multiple components of the EIC appear suitable for MCDA and this is also a methodological option to consider for future decision making within EICs.

Overall, the EIC has proven to be a useful approach that is both technically feasible and informative for deliberations within a disease under review for elimination. It is now recommended that funders use the results to move forward with elimination campaigns.

1. Introduction

1.1   A historical overview of African trypanosomiasis

African trypanosomiasis is a disease caused by the transmission of the *Trypanosoma* parasite by the tsetse fly from host to host. The first written account of African trypanosomiasis began during Antiquity where the Egyptians noticed their cattle manifesting a disease with similar symptoms of what is described as African animal trypanosomiasis ('nagana') today.(Headrick 2014) Subsequently, an Arabian geographer and historian mentioned cases approximately during the 10th and 12th centuries.(Steverding 2008) The transatlantic slave trade during the 16th century presented an opportunity for the western world to witness the disease, as medical personnel responsible for the health of individuals purchased into slavery noticed they had peculiar symptoms. The first signs of neurological problems were seen at the end of the 18th century while the link to the disease to swollen lymph glands was discovered by Thomas Winterbottom(1766-1859) in the early 19th century.(Steverding 2008) In 1889-1896, post-industrial technologies in combination with colonial expansion into Africa displaced communities and allowed for movement into areas infested with flies that were previously uninhabitable making inhabitants susceptible to a new killer – 'sleeping sickness'. (Steverding 2008; de Raadt 2015) This incited a disease outbreak from 1896 thru 1906 with such significance that colonies decided to intentionally fund scientific investigation into the disease transmission and possible treatments.(Headrick 2014) The results were a series of key discoveries in the early 1900s from European Scientists regarding the parasite and role of the tsetse fly in transmission of the disease from host to host. At this time, the parasite was differentiated from those transmitted to animals (i.e. *Trypanosoma congolense, Trypanosoma vivax)* and those primarily affecting human reservoirs (*Trypanosoma brucei (T.b.) rhodesiense* and *T.b. gambiense*) A few drugs to treat the disease were identified at the beginning of the 20th century along with ideas for 'bush clearing' to prevent transmission in areas densely populated by the tsetse fly. Post-world war I (1914-1918)(Steverding 2008), a second major HAT epidemic began but since there was now a treatment available; surveillance teams were able to be deployed, under the direction of Eugene Jamot (1879-1937), to systematically identify and treat individuals for the disease.(Steverding 2008) In addition, insecticides and

DDT aerial spraying were discovered for fly eradication along with two additional drug treatments during the 1930s and 1940s. The plethora of activity near this era for sleeping sickness was so vast that it gained international attention and was often a topic of European media. (Refer to Figure 1)

Although the drug treatments and insecticides are now known to be highly toxic (Robays et al. 2007) and the military approach to forcing individuals to participate in village screening activities would now be seen as unethical – this combination of activities led to the rapid decline of disease by the 1960s. At this time in history, many African nations were able to develop independence from colonial rule and in turn abandoning to previous efforts to maintain disease suppression. Furthermore in the 1970s a global ban on DDT aerial spraying prevented vector control endeavours leading to the return of tsetse infestation and parasite transmission to resurge.(Steverding 2008) Although the card agglutination trypanosomiasis test (CATT) was developed during 1978 to assist with disease staging and drug treatments were identified as potentials in 1980 and 1990, HAT control fell to the background. It was not until 1997, as case numbers began to rise again, active surveillance teams of the colonial era were re-established through Medecin sans Frontieres (MSF). Successful eradication of tsetse flies in Zanzibar in 1997, also gave hope to the possibility that fly eradication was possible while groups dedicated to new diagnostics and treatments (Foundation for Innovative New Diagnostics n.d.; Drugs for Neglected Diseases initiative (DNDi) 2014b) were launched in 2006 demonstrating a new interest for the disease that had not been seen since the earlier 20th century.

Figure 2. Historical overview of African trypanosomiasis (historical points summarized from Steverding
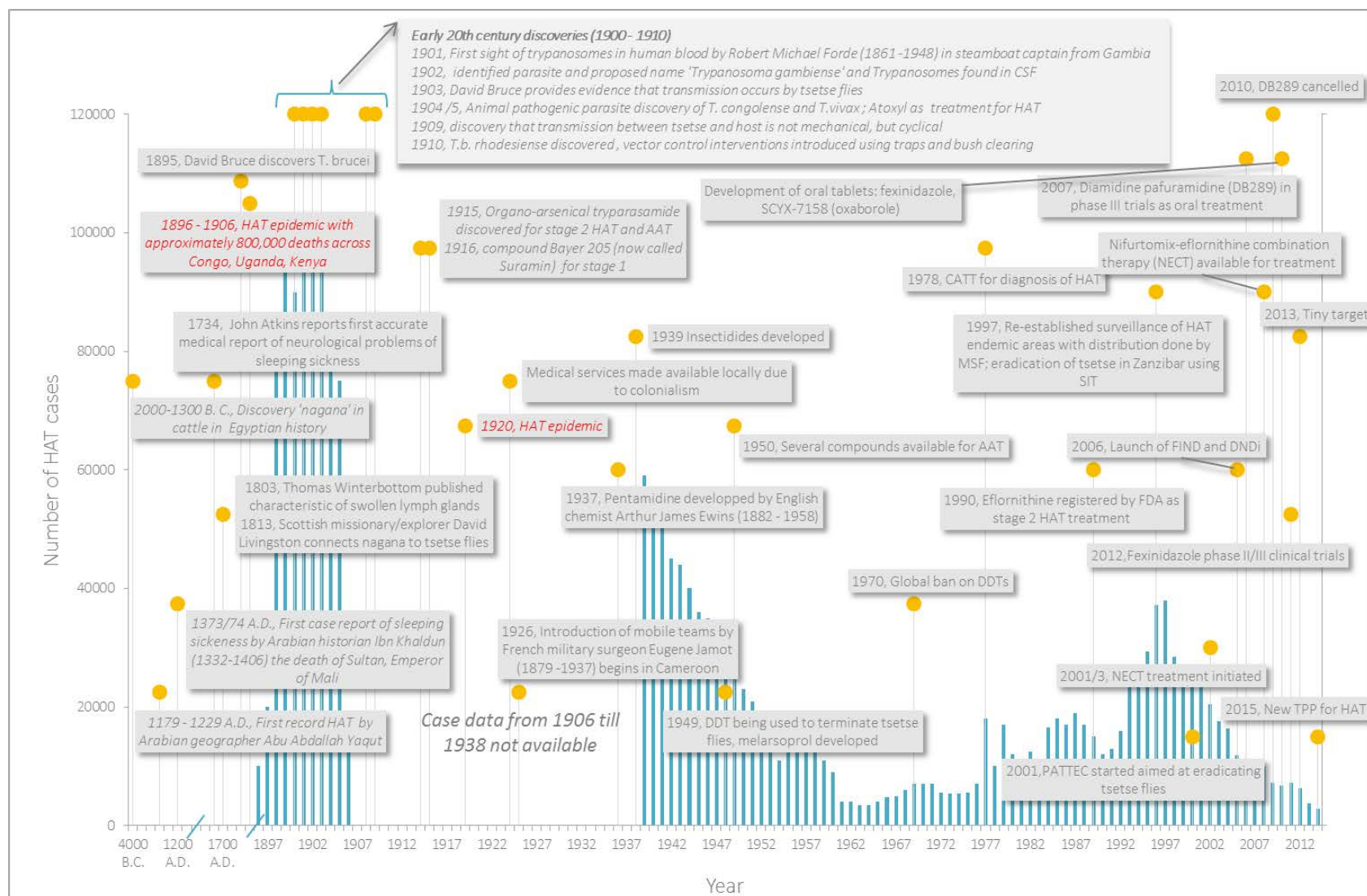
1.2   **A current synopsis of human African trypanosomiasis**

Trypanosoma brucei gambiense

Today African trypanosomiasis is colloquially referred to as 'sleeping sickness'. African animal trypanosomiasis (AAT) which is at times referred to as '*nagana*' is caused by the parasite *Trypanosoma brucei (T.b.) rhodesiense*, *T.b. vivax*, and *T.b. evansi.*(Molyneux & Ashford 1983) *Trypanosoma brucei rhodesiense* can also be transmitted to humans and is an acute illness lasting 6 months before inevitable death in the absence of treatment, while the main reservoir host for *T.b. gambiense* are humans. The main focus of the thesis presented here will be on *Trypanosoma brucei (T.b.) gambiense* hence onward since it is of primary health concern for human hosts.[1] *T.b. gambiense* is often referred to as Gambiense HAT or g-HAT.

Figure 3. Cases of human African trypanosomiasis across the Democratic Republic of the Congo - *T.b. gambiense*

(Simarro et al. 2010)
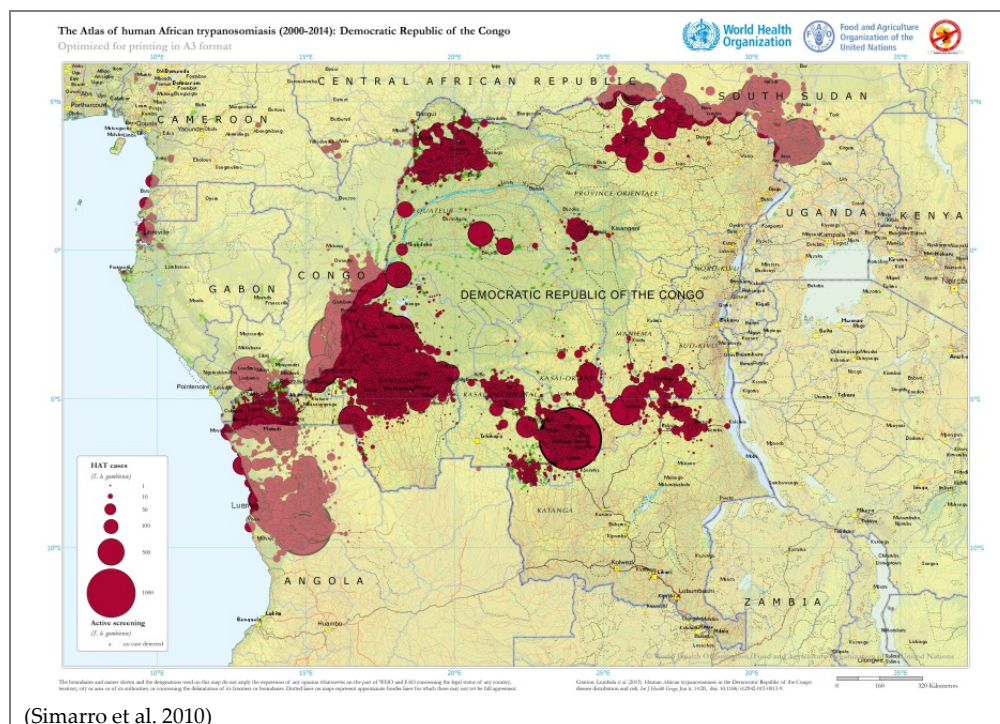
Geographically, *T.b. gambiense* has been restricted to Sub-Saharan African with no overlap of rhodesiense HAT except in Uganda where both parasitic strains are found. Geographic areas

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[1] The expert task advisory group (TAG) that was created for the EIC grant # OPP1037660 by the BMGF decided in September 2013 that the focus for HAT elimination should be on *T.b. gambiense* as it proportionately affects a greater amount of humans, than *T.b. rhodesiense* and the current interventions are targeted to *T.b. gambiense* specifically

with the potential for transmission are referred to as a 'focus', and have been categorized into areas of low, moderate and high transmission .(Jose R Franco et al. 2014; World Health Organization (WHO) 2013c) Currently there are over 57 million living in areas at risk of g-HAT with 63% of the at risk population coming from the Democratic Republic of the Congo as shown in Figure 3. (Jose R Franco et al. 2014)

Much of what is known about HAT still arises from the early discoveries at the beginning of the 20th century previously described. The family of *Trypanosoma* that affects homosapiens was found by the Scottish pathologist, David Brucei and hence the 'subgenus' name of brucei is attached to such *Trypanosoma*. The trypanosomes come from the family of unicellular parasites with single flagella. The parasite has one large mitochondria and is surrounded with an outer coat of variant surface glycoproteins (VSG) that can change repeatedly to evade attacks of human antibodies the human body.(Brun et al. 2010) Although the body responds with specific antigens to fight of *Trypanosoma* infection, researchers still struggle to understand which antigens are most important with the continually morphology of the VSG coat. This has led to delays in technologies for diagnostics as the sensitivity for detecting the correct antigen are difficult.(Sutherland 2016) Potential treatments that counteract the parasite usually act on 'paralyzing' the trypanosomes and arrest the proliferation of cells which is a similar property of cancer cells – hence chemotherapy approaches have proven to be successful treatments for Gambiense HAT.(Swiss TPH 2015)

It is known that the tsetse fly of the genus *Glossina* is the primary vector living near streams in foci of woodland savannah and riverine forests, with *G. palpalis palpalis, G.p. gambiensis* and *G. fuscipes* being the three main vectors for Gambiense HAT transmission. (Jose R Franco et al. 2014) Their life cycle unlike other insects is more similar to mammals as female flies only mate once and has one larva in her lifetime. For this reason, fly eradication is seen as feasible as vector control methods interrupt the life cycle with ease.(Swiss TPH 2015) Prevention for disease transmission can be taken against the vectors through targets, sterile insect technique (SIT), aerial spraying; insecticides poured over cattle however for the most part have been restricted to uses of AAT.(Keating et al. 2015)

As outlined in Figure 4, the tsetse fly is not simply a mechanical vector of transmission but plays a role in the cyclical transmission of the parasite. The fly ingests the parasite from an

infected individual from its salivary glands which undergo transformation in its midgut and are then return to the salivary glands to transmit to another host. Within host, the trypanosomes enter the blood stream and over time progress to the blood lymph and cerebral spinal fluid (CSF). Although traditionally the main routes of transmission are confirmed through the fly and host interactions, recent reviews postulate there may be alternative routes of transmission. These include congenital transmission from mother to child, infection via blood transfusions or organ transplants, and one historically documented incidence through sexual transmission. (Lindner & Priotto 2010; Jose R Franco et al. 2014) There are also cases throughout history of asymptomatic carriers with case reports of individuals presenting with disease more than 10 years after infection.(De Silva & Sumarto 2014; Sudarshi & Brown 2015; Bucheton et al. 2011) Human hosts for Gambiense HAT are indisputably the main reservoir, but evidence of trypanosomes in pigs and dogs show that there could be potential animal hosts that serve as reservoirs.(Bucheton et al. 2011)

Figure 4. Life cycle of human African trypanosomiasis

Lifecycle of the African trypanosome, (Kennedy 2013)
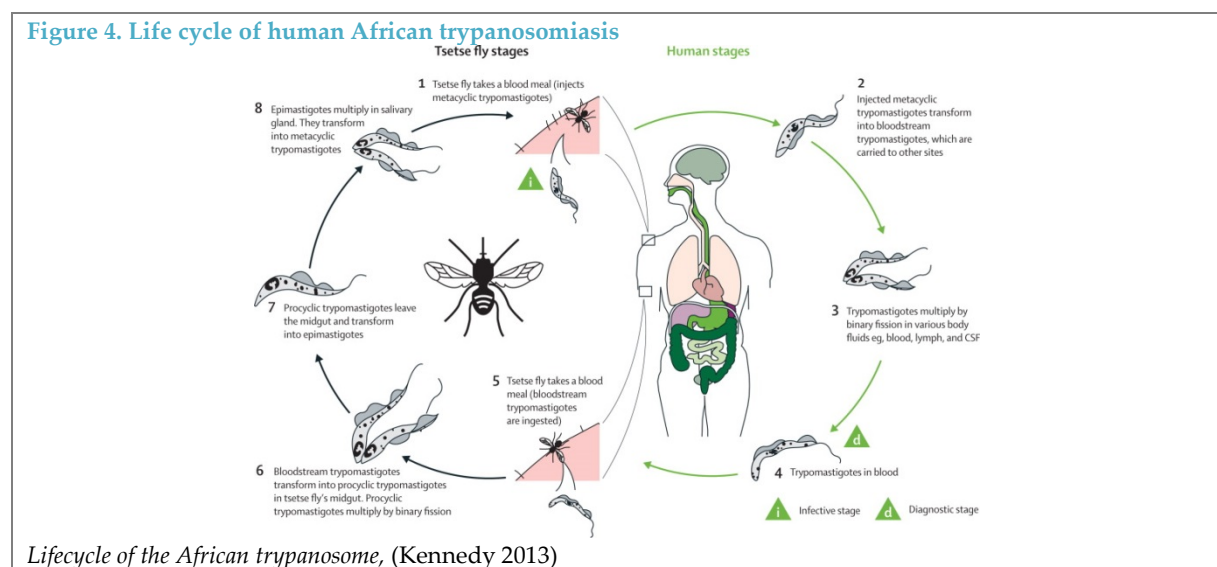
The presence of the trypanosome in the blood represents only the first stage of disease which presents itself with mild symptoms of fever, headache, pruritus, lymphadenopathy and at times hepatosplenomegaly (Brun et al. 2010). Stage 2 of the disease occurs once the parasite has passed the blood-brain barrier and occurs in approximately 18 months without intervention. The symptoms here are sleep disturbances (hence the colloquial name 'sleeping sickness') and psychiatric manifestations which may be misdiagnosed as mental illness. (Brun et al. 2010)

As previously described, active case detection by Eugen Jamot began in 1926 (Refer to Figure 5A) and the mechanism to identify patients in their villages then is still used today (Refer to Figure 5B) "Passive surveillance" refers to the healthcare system where patients self-report to local facilities (refer to Figure 5C) however this is usually once symptoms have progressed to stage 2 as the mildness of earlier symptoms from stage 1 are often misdiagnosed as other febrile related illness. Risk factors in rural areas generally are related to interactions by rivers, in combination with farming or work related activities in tsetse infested areas. (Jose R Franco et al. 2014) There are also risk factors in areas with water supply in peri-urban settings.(Bilonda Mpiana et al. 2015; Jose R Franco et al. 2014)

Figure 5. Surveillance mechanisms for human African trypanosomiasis

ɸ   ɸ

A. Active screening in colonial era HAT patient

B. Active screening in the 21st century *(courtesy of Dr. Christian Burri)*

ɸ

C. Health care centre (passive surveillance) in rural health care system *(courtesy of Dr. Christian Burri)*

ɸ*Images in Figure 5 may be available in the printed version upon request to the University of Basel (diss-ub@unibas.ch)*

1.3 The Elimination Investment Case (EIC) for human African trypanosomiasis *Trypanosoma brucei gambiense*

It is at this point in history where global funders interested in seeing the elimination of HAT across the planet find themselves. Based on the historical evidence, HAT has now repositioned itself near elimination that was once observed in the 1960s. Efforts to eradicate infectious diseases have occurred numerous times over the past century. The most commonly remembered eradication campaigns include the malaria spraying programs in Latin America from the 1930s to 1970 (Centers for Disease Control and Prevention (CDC) 2012) as well as the successful March of Dimes campaign for poliomyelitis in the United States of America.(Global Polio Eradication Initiative n.d.; March of Dimes n.d.) Although global eradication efforts for malaria and polio continue to take economic and disease burden assessments into account to allow for strategic planning (Duintjer Tebbens et al. 2010; Penny et al. 2016), clear analysis for many of the world's neglected diseases remain to be done. The number of cases for HAT reported in 2015 is expected to be less than 3000 which is the lowest number of HAT cases documented to date.[2] (Sutherland 2016) But in order to move towards successful elimination without coming face with disease resurgence needs to be strategic. While historically the response to HAT interventions has been reactive, we are provided with the unique position of evaluating how to move forward with the current and potential tools in the pipeline for elimination and beyond.

In 1998, Dowdle first proposed specific descriptions of what control, elimination, eradication and extinction were. (Refer to Table 1) Then WHO brought to light many abandoned diseases (NTDs) in 2011 and provided a roadmap to elimination (WHO 2012) as a guide to catalyse nations towards elimination measures. This initiated a global response to focus on the suggested 17 disease areas identified, that were later endorsed by the London Declaration.(London Declaration 2013) With global funders and national leaders interested in elimination, there was a need to provide comprehensive information regarding what such

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[2] *The reader should note that the cases surveyed annual are only a proportion of all potential areas. The true number of HAT cases is unknown and is estimated to be 3x the number of cases found* (Stone et al. 2016)

campaigns would entail and more importantly the monetary requirements that would be needed. As elimination campaigns ensue, it is thought the costs begin to rise which often leaves funders with angst regarding how to prepare, ensure or secure funds for eradication and elimination campaigns.(Sutherland 2016) Hence there is a need to formally assess and anticipate approaches to eradication/elimination in order to sustain successful campaigns of this sort.

Table 1. Definitions of control, elimination, eradication and extinction

	Definition
Control	The reduction of disease incidence. prevalence ,morbidity or mortality to a Locally acceptable level as a result of deliberate efforts; continued intervention measures are required to maintain the reduction. *Example: diarrhoeal diseases.*
Elimination	
Disease	Reduction to zero of the incidence of a specified disease in a defined geographical area as a result of deliberate efforts. Continued intervention measures are required. *Example: neonatal tetanus.*
Infection	Reduction to zero of the incidence of infection caused by a specific agent in a defined geographical area as a result of deliberate efforts: continued measures to prevent re-establishment of transmission are required. *Example: measles, Poliomyelitis.*
Eradication	Permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts: intervention measures are no longer needed. *Example: smallpox.*
Extinction	The specific infectious agent no longer exists in nature or in the laboratory *Example: none.*
(Dowdle 1998)	

In 2010 the Ernst Strüngmann Forum provided a guide to developing an elimination or eradication investment case (EIC) (Tediosi et al. 2013) with a comprehensive list of open questions (refer to appendix A) that should be addressed if such an endeavour was to be undertaken. However, the document provided a more generic approach and did not specify which methodologies would be necessary to assess such investments or how it could be amended depending on the disease being evaluated. In 2012 a grant from the Bill and Melinda Gates Foundation (BMGF)[3] was provided to the Swiss Tropical and Public Health Institute (Swiss TPH) under the direction of Dr. Fabrizio Tediosi to complete an EIC for three neglected tropical diseases (NTDs): onchocerciasis (river blindness), lymphatic filariasis (LF) (elephantiasis) and human African trypanosomiasis (sleeping sickness). Both *river blindness* and *elephantiasis* have well established mass drug administration (MDA) campaigns already

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[3]BMGF Grant # OPP1037660

underway to elimination that would have to scale up in order to reach disease eradication, but the case for HAT was not so clear. As the project progressed, the approach to assessing eradication goals was deemed unfeasible hence the term 'elimination' investment case is taken for HAT (Sutherland 2016).

Many nations that provide national health services (NHSs) (World Health Organization (WHO) 2015) use a health technology assessment approach to decide whether or not a new drug or intervention is worth investing in for their national budgets. Hence, at the onset of the project HTA techniques of using secondary evidence for clinical epidemiology and economic evaluation were readily adopted. It was proposed at that time that the main analyses would use modelling to conduct a cost-effectiveness analysis, and also explore health systems modelling. However, even with these two analyses, additional questions regarding socio-economic outcomes, health systems strengthening, equity and governance would need to be resolved.

1.3.1 Thesis objective

The main objective was to address questions proposed in Ernst Strüngmann Forum for an EIC taking in considerations elements of strategies for control and elimination in relation to: budget, cost-effectiveness, financial protection, equity, health systems and governance.

1.3.2 Thesis outline

The 1st chapter of the thesis by Steinmann et al.(Steinmann et al. 2015) describes an overview of HAT treatments, diagnostics, surveillance approaches and possible vector control tools. The 2nd chapter is a review of economic evaluations for HAT (Sutherland et al. 2015) that was undertaken to determine if there was a need to pursue a formal economic evaluation for HAT or if cost-effectiveness analysis of the current and future treatments had already been assessed. Once it was established that previous economic evaluations had not been done in regards to control and elimination using current and future interventions, a systematic review of costs was completed in the 3rd chapter (Keating et al. 2015) to gather the necessary financial parameters that would be needed to complete such an analysis. The 4th chapter then describes a full economic evaluation of the control and elimination strategies by foci area based on the

dynamical transmission model developed by at the Swiss TPH for the EIC project. (Chris M. Stone & Chitnis 2015) Financial costs and out-of-pocket payments will be forecasted at a global level within the 5th chapter while the 6th chapter focuses on the potential integration of the new technologies in the healthcare systems. The 7th chapter addresses ethical concerns using a normative approach developed in collaboration with Dr. Maria Merrit. The overall results of the assessments conducted as part of the EIC in regards to their benefits, limitations, applications and potential for further research in relation to investments for elimination are then reviewed in the final discussion.

2. Contemporary and emerging strategies for eliminating human African trypanosomiasis due to *Trypanosoma brucei gambiense*: review

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2.1   Abstract

Objectives

The World Health Organization (WHO) has identified Human African Trypanosomiasis (HAT) as a candidate disease for elimination by 2020. We review current and emerging tools for Gambiense HAT control and elimination, and propose strategies that integrate these tools with epidemiological evidence.

Methods

We reviewed the scientific literature to identify contemporary and emerging tools and strategies for controlling and eliminating Gambiense HAT. Through an iterative process involving key stakeholders, we then developed comprehensive scenarios leading to elimination, considering both established and new tools for diagnosis, case treatment and vector control.

Results

Core components of all scenarios include detecting and treating cases with established or emerging techniques. Relatively more intensive scenarios incorporate vector control. New tools considered include tiny targets for tsetse fly control, use of rapid diagnostic tests and oral treatment with fexinidazole or oxaboroles. Scenarios consider the time when critical new tools are expected to become ready for deployment by national control programmes. Based on a review of the latest epidemiological data, we estimate the various interventions to cover 1,380,600 km2 and 56,986,000 people.

Conclusions

A number of new tools will fill critical gaps in the current armamentarium for diagnosing and treating Gambiense HAT. Deploying these tools in endemic areas will facilitate the comprehensive and sustainable control of the disease considerably, and contribute to the ultimate goal of elimination.

2.2 Introduction

Human African trypanosomiasis (HAT) or sleeping sickness is a neglected tropical disease (NTDs) that has been earmarked by the World Health Organization (WHO) for elimination by 2020 (WHO 2012). In 2014, WHO approved a declaration on Gambiense HAT elimination (http://www.who.int/trypanosomiasis_african/meeting_declaration_2014/en/) (Holmes 2014) and one on Rhodesiense HAT (http://www.who.int/trypanosomiasis_african/meeting_declaration_rhodesiense_2014/en/). The two disease forms are caused by *Trypanosoma brucei gambiense* and *T. b. rhodesiense*, respectively. They occur in separate geographical regions, are transmitted in different ecological settings and by different Glossina (tsetse fly) species, and have different hosts and degrees of virulence(Brun et al. 2010; Malvy & Chappuis 2011). *T. b. gambiense* is endemic in west and central Africa where it occurs in riverine savannah, forests and mangroves. It is an anthroponotic parasite found in a range of animals, most notably pigs, but the role of the zoonotic reservoir in human epidemiology is still not fully understood for the different endemic settings. *T. b. rhodesiense* occurs mainly in savannah areas in eastern and southern Africa. It is a typical zoonotic parasite that infects mostly wild mammals and cattle, and only occasionally crosses over to humans (Welburn et al. 2009; Funk et al. 2013). Infections progress in two stages: haemo-lymphatic and meningo-encephalitic. *T. b. gambiense* is a chronic disease characterised by fever, chills, headache, pruritus, lymphadenopathy and, less commonly, hepatosplenomegaly during the first phase; and by sleep disturbances, neurologic and psychiatric disorders in the second stage. Rhodesiense HAT has a more acute course. Untreated, HAT is usually fatal. Considering the profound differences between the biology and epidemiology of Gambiense and Rhodesiense HAT, distinct strategies for their control and elimination are required (Simarro et al. 2013). Our focus here is on Gambiense HAT, as the animal reservoir of *T. b. rhodesiense* includes wild animals and would require their treatment or removal of tsetse flies from all endemic areas to permanently prevent human infections.

Gambiense HAT occurs in 24 countries (Anonymous 2006). However, cases are currently only reported from 13 countries. The total endemic area is estimated to be 1.3808 million km2, with a population of 56.983 million people (Pere P Simarro et al. 2012). A total of 7,106 cases were

reported in 2012 (http://apps.who.int/gho/data/node.main.A1635?lang=en). In 2001, 26,117 Gambiense HAT cases were reported(Simarro et al. 2013). The estimated number of cases per year is currently about three times higher than the diagnosed number, down from a factor of 12 in 1995 (Simarro et al. 2013; Anonymous 2006; Fevre, Wissmann, et al. 2008). In 2010, the estimated burden of HAT was 560,000 DALYs (Murray et al. 2012), including 9,100 deaths (Lozano et al. 2012). A comparison of total DALYs in 1990 and in 2010 suggests a reduction of 72.5% (Murray et al. 2012).

For historical, epidemiological and ecological reasons, elimination of Gambiense HAT has been deemed a feasible pursuit. Following epidemic outbreaks in the early 1900s, extensive and strictly enforced parasitological screening and treatment of populations came close to reducing the number of yearly reported cases to zero (Simarro et al. 2008), although many cases may have gone undiagnosed. Following a resurgence in the 1990's, cases are again on the decline and control is aided by a renewed focus on the disease and by a number of improvements in diagnostics and treatments (reviewed below) that have helped to reduce the rate of underreporting. Gambiense HAT appears to be an anthroponotic disease, so treating the human population alone should reduce R_c, the reproduction number of the disease in the presence of control, to less than one. However, epidemiological and ecological questions remain. Consequently, there is uncertainty about how best to maximise the effectiveness of available tools and about the best way forward as new diagnostics, treatments and vector control options become available. In resource-constrained settings, optimising approaches while accounting for the various sources of uncertainty is an important but challenging task.

Here, we synthesise our findings from a literature review and from consultations with experts on currently available and emerging tools. Based on these findings, we propose different scenarios for combining and deploying them, and discuss how these tools may change the landscape of HAT control. These scenarios will be used to develop models examining the financial, operational and technical feasibility of HAT elimination and eradication. Results will be communicated in a subsequent report.

2.3   Methods

This work is part of an Eradication Investment Case (EIC) for HAT. An integral part of developing EICs is developing scenarios that can then be compared. We followed the general principles for scenario development outlined by Tediosi et al (Tediosi et al. 2013). The process started with a survey of peer-reviewed scientific literature and relevant grey literature, including official WHO statistics about the epidemiology of Gambiense HAT over the last century, with a focus on the contemporary situation and fluctuations in response to targeted interventions. The same sources were consulted to review current activities for controlling the disease. The review was complemented by a survey of national HAT control programme managers to identify commonly used tools and strategies along with their coverage and effectiveness. In a next step, information was collected on Gambiense HAT control tools under development, their predicted effectiveness and the proposed strategies for their deployment. Lastly, data from the literature review was corroborated and complemented by key informant interviews with representatives from academia and from relevant institutions such as the WHO, the Drugs for Neglected Diseases initiative (DNDi), the Foundation for Innovative New Diagnostics (FIND), and the Pan African Tsetse and Trypanosomiasis Eradication Campaign (PATTEC). The information was used to develop preliminary scenarios describing possible control and elimination strategies. In an iterative process, these draft scenarios were circulated widely among the constituents mentioned above and improved based on their feedback.

Three periods were defined based on the time during which important tools currently under development are expected to be available for deployment by national Gambiense HAT control programmes: 2013 – 2015, 2016 – 2018 and 2019 onwards. A baseline scenario (2013 – 2015) was identified, considering the current standard tools for diagnosing and treating Gambiense HAT and contemporary strategies for deploying them in endemic countries. An elimination scenario I (2013 – 2015) was also developed to include vector control with standard methods. Alternative scenarios were prepared considering the key diagnostics, drugs and vector control tools currently being brought to market or in the later stages of development, and their respective target dates for mass deployment. The less ambitious scenarios (elimination III for 2016 – 2018 and elimination V and VII for 2019 onwards) served as counterfactual conditions

against which to compare one or more other scenarios for the respective period, in terms of cost and benefits.

To construct standardised scenarios that consider key differences between the epidemiology and ecology of endemic areas, foci were stratified by intensity of transmission as suggested by the WHO (Simarro et al. 2013). The following WHO goals and definitions were incorporated: elimination in 80% of all endemic foci by 2015 and global elimination by 2020 (WHO 2012), with the latter goal defined as (i) <1 case/10,000 people/year in at least 90% of all endemic foci; and (ii) <2000 new cases annually (Maurice 2013; World Health Organization (WHO) 2013b). After 2020, efforts should be made to ultimately reduce incidence to 0 by 2030 (World Health Organization (WHO) 2013b).

2.4   Results: Tools for HAT control

2.4.1 Evolution of HAT control principles

Historically, sleeping sickness went through several cycles of epidemic, intensive control in response to high numbers of fatalities, tapering off of the epidemic, and neglect (Courtin, Jamonneau, Duvallet, Garcia, et al. 2008; Hide 1999; Nimmo 2010; Steverding 2008). Early efforts focused on vector control through bush clearing (predominant in English colonies) (Solano et al. 2013), chemoprophylaxis (predominant in French colonies) and mobile teams for active case finding and treatment. The latter still constitutes the mainstay of efforts to control *T. b. gambiense* (Brun et al. 2010). History suggests that any new attempt to eliminate the disease will only succeed if commitment is sustained through appropriate investments, efficacious tools and approaches, effective deployment, and programme adaptations to local conditions (Welburn et al. 2009).

Theoretically, the incidence of Gambiense HAT can be reduced in two ways: (i) by reducing the parasite reservoir in humans through diagnosis and treatment of those infected, thereby minimising the chances of a feeding tsetse fly becoming infected, and (ii) by curbing transmission from the flies to humans via vector control efforts that reduce the tsetse population and/or reduced tsetse life expectancy (Simarro et al. 2013). The optimal balance between treating humans and vector control has only been explored theoretically and without

considering costs (Artzrouni & Gouteux 2007). At realistic rates of disease progression, the decision to add vector control to case detection and treatment should depend on the "intrinsic contamination rate" (a term proportional to vectorial capacity) in a focus. The intensity of transmission should inform the design of locally-adapted and effective interventions (Simarro et al. 2013). The focus should be on diagnosing and treating human cases to reduce the parasite reservoir, supplemented by vector control to reduce transmission. While active and passive case detection yield excellent public health benefits, the strategy usually does not result in the cessation of local HAT transmission as often the ones who are the most exposed (farmers, fishermen, hunters, plantation workers) (Laveissière et al. 2005) do not get screened. It has been estimated that when 75% of the population is screened for HAT, only 50% of the actual cases are detected. Furthermore, there is increasing evidence that traditional screening approaches miss some T. b. gambiense infections among people that are either asymptomatic carriers or sero-positives; these individuals are not confirmed as infected by parasitological techniques but will ultimately develop HAT (World Health Organization (WHO) 2013c)(Jamonneau et al. 2012; Bucheton et al. 2011). In the presence of the vector, these untreated carriers contribute to parasite dissemination. Under such conditions, transmission of *T. b. gambiense* will not be interrupted without vector control (Solano et al. 2013). Vector control is recommended by the WHO in areas where case findings do not result in satisfactory incidence reductions (Simarro et al. 2013). If vector control results in a reduction of animal trypanosomiasis, economic benefits often ensue, providing a powerful argument in favour of promoting — and adopting — tsetse control measures (Swallow et al. 1995). However, the number of cattle is low in many Gambiense HAT foci.

Low parasite concentrations in blood make HAT diagnosis complex (World Health Organization (WHO) 2013a). The card agglutination test for trypanosomiasis (CATT) was developed in the 1970s and remains the standard screening test to detect *T. b. gambiense* infections (Patrick Mitashi et al. 2012). Parasitological confirmation is mandatory for treating a patient, and stage differentiation is needed to determine the treatment strategy. CATT performance is generally good, with 87 – 98% sensitivity and 93 –95% specificity (Malvy & Chappuis 2011). However, the positive predictive value (PPV) is low as the disease prevalence is usually very low. The following drugs and regimens are commonly used to treat Gambiense HAT: pentamidine (intramuscular; first stage); nifurtimox-eflornithine combination therapy

(NECT; nifurtimox oral, eflornithine intravenous infusion; second stage) and melarsoprol (intravenous; second line drug for second stage disease). Prompt treatment offers good prospects for curing first stage cases and second stage cases (treated with NECT). Melarsoprol is highly toxic, causing an encephalopathic syndrome that can be fatal. In addition, high rates of treatment failure have been reported from some locations (Brun et al. 2010; Malvy & Chappuis 2011).

2.4.2 Case detection, diagnostics and treatment

There are two strategies for identifying Gambiense HAT cases, with the choice of strategy depending on endemicity levels (Simarro et al. 2013): (i) passive case detection through routine health care activities, and (ii) active case detection via screen and treat campaigns by specialised mobile teams. As Gambiense HAT is a chronic disease, passive case detection is an important strategy for identifying cases, accounting for half of all identified cases. However, health care facilities are either absent or insufficiently equipped and staffed throughout many HAT endemic areas (Simarro et al. 2014). In screen and treat campaigns, residents of *T. b. gambiense*-endemic areas are systematically tested with the CATT (Patrick Mitashi et al. 2012). Positive results are confirmed parasitologically, followed by disease staging and initiation of appropriate treatment in appropriately equipped health facilities. Screening campaigns are vertical interventions that can be deployed in the absence of local health care infrastructure. Campaigns typically focus on high-incidence areas for 1-2 years, until case numbers drop to a level that no longer justifies the massive effort. Thus, passive case detection needs to be maintained simultaneously in areas covered by screen and treat campaigns. The latter tend to identify mainly stage 1 cases while the majority of cases identified through passive case detection are stage 2. Patients suffering from stage 2 of the disease are more likely to seek health care and receive a correct diagnosis from the health care system than those in stage 1. Epidemiologically, stage 1 cases are more significant for transmission as they are more infectious and exposed to tsetse than stage 2 cases. While diagnostic capacity to identify suspect cases must be available down to the lowest and most peripheral level of the health care system, confirmation and treatment capacity can be concentrated at regional or, ideally, district level (Simarro et al. 2013; Palmer et al. 2013).

WHO suggests the following thresholds for the frequency of active case finding (Simarro et al. 2013): (i) high-intensity transmission (≥1 case/1000 population and year; corresponding to very high and high risk areas (Pere P Simarro et al. 2012)): screening once/year; (ii) moderate-intensity transmission (≥1 case/10,000 population and year but <1 case/1000 population and year; corresponding to moderate risk areas (Pere P Simarro et al. 2012)): screening once every two years; (iii) low-intensity transmission (<1 case/10,000 population and year; corresponding to low and very low risk areas (Pere P Simarro et al. 2012)): no active case finding.

It is impossible to repeatedly screen the entire human population due to avoidance (resulting from fear of stigma) and costs (Robays et al. 2007; Hasker et al. 2011). Other problems include indifference to repeated testing and waning interest in the face of declining local incidence, population mobility, poor access (logistics, social and political fragility) and the high costs of vertical screen and treat campaigns. There are also sero-positive individuals who are parasitologically negative and therefore not treated (Jamonneau et al. 2012; Kagbadouno et al. 2012), while some identified cases may refuse treatment. All of these factors pose challenges to eliminating the parasite from the human reservoir.

2.4.3 Vector control

The fragile biological cycle of *T. b. gambiense*, including the low reproductive capacity of the tsetse fly and the low proportion of infected tsetse (Brun et al. 2010; Malvy & Chappuis 2011), indicates that transmission breaks down with reduced tsetse population density. In west African savannahs, transmission no longer exists despite the continuous presence of tsetse; yet transmission had been intense in the 1930s – 40s (Courtin, Jamonneau, Duvallet, Camara, et al. 2008). Of note, the cessation of transmission in these areas cannot be linked to deliberate tsetse control activities. A variety of tools for tsetse control are available in Gambiense HAT endemic areas, most notably traps and insecticide-treated targets. Targets — essentially simplified traps — are assumed to be more efficient for vector control than traps. While large targets are optimal for savannah tsetse (Morsitans group), multiple smaller targets have been shown to be more effective than fewer, larger ones for riverine tsetse (Palpalis group) (Esterhuizen et al. 2011). The exact colour of the targets is also important (Lindh et al. 2012). Targets are well accepted by local people but questions regarding the sustainability of deployment remain. The

environmental impact of vector control using traps and targets is considered to be acceptable, even within national parks (Esterhuizen et al. 2011).

Pyrethroids (e.g. deltamethrin) are used to spray tsetse resting and breeding sites. Aerial spraying of tsetse habitats is less relevant for *T. b. gambiense*, which is primarily found in forested areas nowadays. To be successful, the scale of control operations focusing on T. b. gambiense depends on the size of the focus (generally <500 km2) and must aim to reduce tsetse populations by 70% – >95% (Ian Hastings, *personal communication*) for 5 – 6 years (e.g. by implementing fly control at a level that results in a daily death rate of 2 – 4% (Artzrouni & Gouteux 2007)), after which time local *T. b. gambiense* transmission is assumed to have ceased, particularly if initial screen and treat efforts have reduced the parasite reservoir in the human population.

The sterile insect technique (SIT; the release of sterile males) is not well suited to eliminate Gambiense HAT from its typically small-scale foci where tsetse constantly immigrate from surrounding, non-HAT-endemic areas. Technical, financial and operational issues also limit mass deployment of SIT (Torr et al. 2005).

2.4.4 Tools currently under development

A number of new tools are currently being developed to diagnose and treat HAT and to control tsetse. Novel diagnostic tools and drugs promise to make diagnosis easier and more sensitive and to make treatment safer. Tiny targets for tsetse promise monetary savings and easier deployment compared to current standard traps and targets (Box 1). Figure 6 summarises the current development status of a number of diagnostic tools and drugs that are potentially relevant for HAT control and elimination. The year in which new technologies become available is uncertain. In general, the development and release of diagnostic tests is faster than that of novel drugs. The delay between the availability of a new tool and its adoption and use in national Gambiense HAT control programmes is similarly uncertain but experience with NECT suggests that transition times can be fairly short(P P Simarro et al. 2012). However, it must be noted that the introduction of a new molecule might need more time than the switch to other known molecules, as was the case for NECT.

Box 1.

The first generation RDTs using native antigens, now produced by Standard Diagnostics (SD) and Coris, are an alternative to CATT. Owing to their product specifications, they can be used both for individual screening in health centres and for mass screening of the population. They require minimal infrastructure and medical training. As in the case of positive CATT results, parasitological confirmation of positive cases is required prior to the start of treatment due to their insufficient specificity (resulting in a low positive predictive value, given the low prevalence of infections) and due to the cost and complexity of current treatments. The second generation tests using recombinant antigens promise the following benefits: (i) easier and cheaper production compared to first generation tests; and (ii) detection of both *T. b. gambiense* and *T. b. rhodesiense* (CATT only works for *T. b. gambiense*).

The mAECT, LED fluorescence microscopy and LAMP improve the sensitivity of parasitological diagnosis (confirmation of T. b. gambiense infection) in CSF (mAECT) and blood (LED fluorescence microscope and LAMP). LAMP facilitates DNA detection in both fresh and dry blood, making it possible to centrally test samples collected in locations without suitable laboratory infrastructure. Current development efforts for these tools focus on technology transfer, reducing costs and demonstrating the suitability of the methods for HAT endemic settings.

The current approach for disease staging involves a lumbar puncture to obtain CSF, followed by its examination (with or without prior concentration) to determine the presence or absence of parasites and a white blood cell count. An RDT for HAT staging and monitoring treatment progress based on CSF biomarkers would improve the suitability of the test for resource-constrained settings and likely its sensitivity. If such an RDT were based on blood biomarkers instead of CSF biomarkers, it would remove the need for lumbar puncture, again greatly improving its appeal to patients (pain) and health care professionals (ease of handling, need for specialised training).

Two compounds are currently undergoing clinical tests: fexinidazole and an oxaborole. Fexinidazole is being developed as an alternative to NECT for the treatment of stage 2 *T. b. gambiense* HAT. The primary outcome of the current phase II/III trial is non-inferiority of fexinidazole to NECT. There are strong indications that fexinidazole could also be used to treat stage 1 *T. b. gambiense* and *T. b. rhodesiense* (both stages). Fexinidazole offers the following advantages: (i) superior safety profile compared to that of NECT and other drugs that it could potentially replace; (ii) easier administration than NECT (fexinidazole: one oral dose per day for 10 days; NECT: nifurtimox: three oral doses per day for 10 days plus eflornithine: 2x2 h intravenous infusions per day for seven days); (iii) long shelf life under tropical climate conditions; (iv) simplified logistics (NECT: four full treatments: 36 kg of 37.5 dm3); (v) reduced costs in terms of production (currently used drugs are donated rather than purchased by endemic countries), logistics, storage, administration, side effect management, etc.; (vi) better acceptance by patients. Together, these benefits would enable treatment provision at more peripheral levels of the health care system, facilitating access to treatment in rural settings. From the patient's perspective, treatment with fexinidazole is more attractive due to easier administration and a favourable side effect profile, potentially reducing no-show rates after diagnosis and drop-out rates during treatment.

Using similar fexinidazole regimens to treat stage 1 and 2 *T. b. gambiense* HAT would eliminate the need for staging. Combined with a sensitive test for confirmatory parasitological diagnosis in blood, it would remove the need for lumbar puncture. This could also reduce drop-out/no-show rates of HAT suspects identified with rapid screening tests.

The oxaborole SCYX-7158 has some advantages over fexinidazole, namely a single oral dose as opposed to 10 daily oral doses and protection against re-infection for a limited period due to the high level of active compound retained in the body over an extended period of time (at least two months). Some of the assumed advantages of both drugs still need to be confirmed in the on-going and upcoming clinical trials.

The combination of a highly sensitive screening tool (i.e. RDT) and a safe (i.e. few and only trivial – moderate side effects), relatively cheap and easily administered (i.e. oral) drug (ideally single dose) for both stage 1 and 2 of both T. b. gambiense and *T. b. rhodesiense* could justify the unintentional treatment of a certain number of false-positive cases (note: a screening test needs to maximise sensitivity at the cost of specificity), altogether removing the need for confirmation of infections, staging and treatment progress monitoring.

Figure 6. Current developmental status of selected new tools for the diagnosis, treatment and surveillance of HAT that are relevant for its control and elimination (Source: DNDi and FIND)
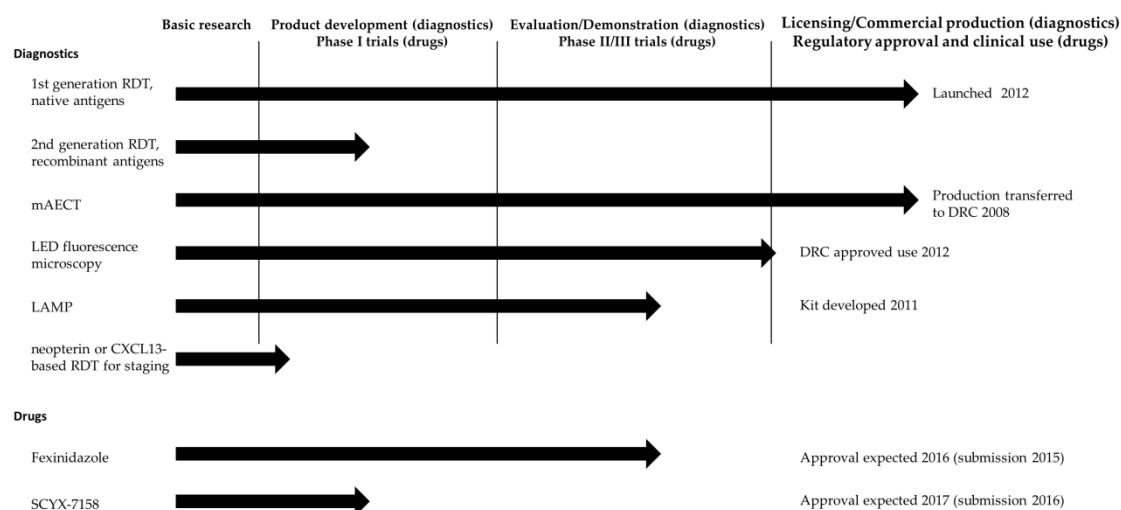
FIND has recently summarised advances in the development of rapid screening tests for T. b. gambiense, including tests to confirm the disease, to determine disease stage and to monitor treatment progress (FIND 2013). Other tests are also being developed (Büscher et al. 2014; Büscher et al. 2013), including syndromic algorithms (Palmer et al. 2013). The Institute of Tropical Medicine in Antwerp, Belgium has recently developed two rapid diagnostic test formats, a dipstick and a lateral flow device, the latter of which has been commercialised by Coris (Büscher et al. 2014; Büscher et al. 2013). A first generation lateral flow rapid diagnostic test (RDT) using native trypanosome antigens is commercially available (SD Bioline HAT) and used in Uganda and other countries. In our scenarios, we expect universal adoption of RDTs by 2016. The SD tests are individually packed and stable at 40°C for 25 months. The test substrate is whole blood from a finger prick and no additional infrastructure is required to run the test. The Coris test has comparable characteristics. A second generation RDT is under development and is based on recombinant antigens and designed to detect both *T. b. gambiense* and *T. b. rhodesiense* (for which currently no serological tests exist). We expect it to be available

in 2019. Considering the limited positive predictive value of serological tests in low-prevalence settings, parasitological tools remain important. The production of the mini-anion exchange centrifugation technique (mAECT), an established technique for parasitological confirmation of HAT infections in cerebrospinal fluid (CSF), has been successfully transferred to the Democratic Republic of Congo (DRC). Further parasitological confirmation tests to detect parasites in blood based on a light-emitting diode (LED) fluorescence microscope or loop-mediated isothermal amplification of DNA (LAMP) are being evaluated. These methods promise cost savings and higher diagnostic sensitivity than conventional methods. An RDT for disease staging and for monitoring treatment progress based on molecules (namely, neopterin or CXCL13) in the CSF is being developed, though its use may be limited if new drugs come to market that can safely and efficiently treat both disease stages. The possibility of exploiting blood biomarkers is also being explored.

With regard to drugs, the nitroimidazole compound fexinidazole (Torreele et al. 2010; Brun et al. 2011; Maser et al. 2012) is currently undergoing phase II/III trials for treating Gambiense HAT stage 2 disease and is scheduled to be submitted for registration in late 2015 (approval expected in 2016). Originally, fexinidazole was intended to first replace nifurtimox-eflornithine combination therapy (NECT) for treating stage 2 *T. b. gambiense* HAT and later, in a second step in 2019, stage 1 *T. b. gambiense* and *T. b. rhodesiense* HAT. Efforts are now underway to amend the protocol of the current trial to allow simultaneous registration for treating stage 1 and stage 2 Gambiense HAT. Administration of the drug is oral, with one daily dose for 10 days. The benzoxaborole SCYX-7158 is another drug candidate currently under development. It is well absorbed upon oral administration and is designed as a single dose application to cure both stage 1 and stage 2 forms of T. b. gambiense and *T. b. rhodesiense* (Maser et al. 2012; Jacobs et al. 2011). The drug is only slowly metabolized and eliminated from the body, and is expected to confer protection against re-infection for at least two months post-treatment. The drug is currently undergoing phase I clinical trials and we expect it to be commercially available by 2019.

Mini targets of reduced size (Esterhuizen et al. 2011) and higher attractiveness to tsetse flies (Lindh et al. 2012; Rayaisse et al. 2010) compared to standard ones promise considerable cost effectiveness gains as they are more effective, require less material per killed tsetse, and are

easier and thus cheaper to deploy (Solano et al. 2013). They are already available for deployment.

2.5 Results: Scenarios for HAT control

Proposed scenarios for controlling and eliminating Gambiense HAT

A total of nine scenarios were developed based on the overview of current and emerging tools for diagnosing and treating Gambiense HAT and for killing tsetse flies. Each scenario describes interventions for case identification, diagnostics, treatment and vector control to be implemented in the given period (Figure 7).

Figure 7. Summary of scenarios for control and elimination of Gambiense HAT
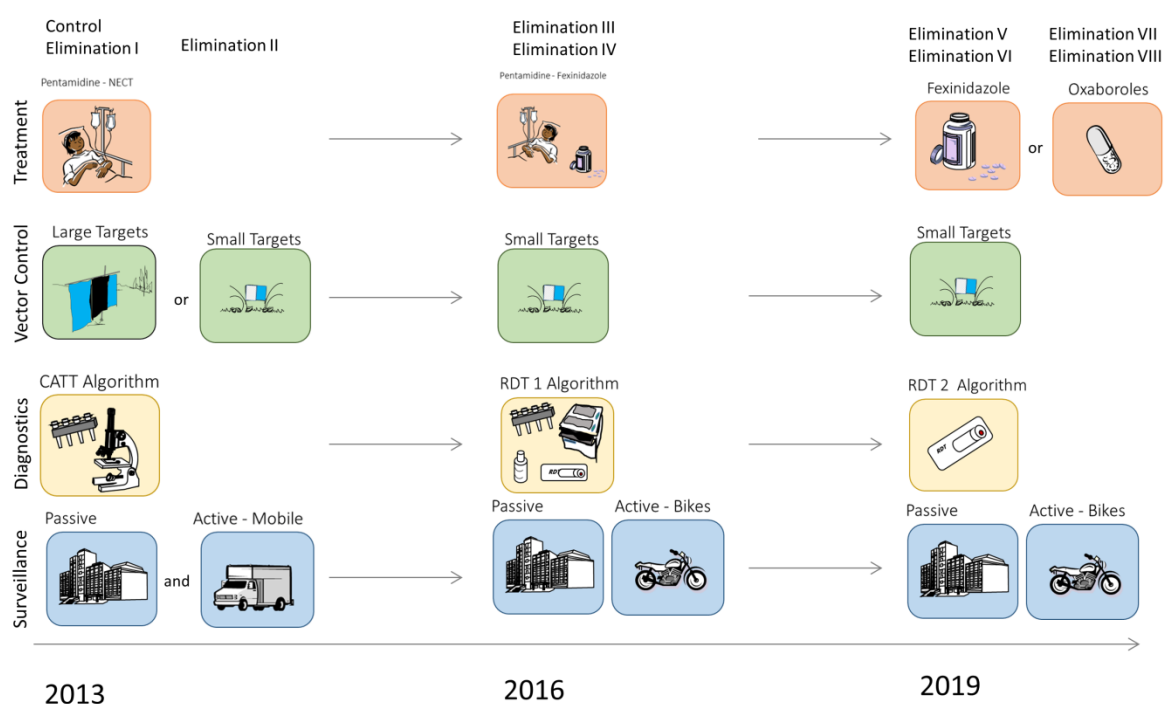
The baseline scenarios for each period rely on case detection for identifying infected individuals and for determining their treatment, i.e. a reduction of the parasite reservoir in humans. Diagnosis and treatment approaches evolve as new technologies become available.

Suggested intervals for active case finding (screening) campaigns depend on the current transmission intensity (once a year in high-intensity transmission areas, every two years in moderate-intensity transmission areas) while passive case detection must be available throughout the endemic area. Active screening is implemented until incidence reaches the low-transmission threshold (<1 case/10,000 population per year). In the period 2013 – 2015, diagnosis and treatment follow current standard approaches: truck-based mobile teams use CATT for screening, parasitological confirmation of infection is based on the visualization of parasites, lymph node aspirate or CSF is obtained by lumbar puncture, staging is based on CSF examination (criteria for stage 2: detection of parasites or >5 white blood cells/mm3), treatment is with pentamidine for stage 1 disease and NECT for stage 2, and treated patients are followed to detect relapses and to verify treatment success.

Changes for the period 2016 – 2018 include the introduction of RDTs (first generation) for screening by mobile teams relying on motorbikes instead of trucks, and the introduction of fexinidazole to treat stage 2 patients. Parasitological confirmation and staging remain important and are performed either by truck-based teams or in health facilities. From 2019 onwards, option 1 assumes that staging (and hence, obligatory lumbar puncture) is not required anymore as fexinidazole is used to treat both stage 1 and stage 2 of the disease. In option 2, a switch to second generation RDTs and the introduction of oxaboroles for treatment mean that neither confirmation nor staging of infections are required any longer, and that treated individuals are protected against re-infection for a certain period.

To accelerate Gambiense HAT elimination, vector control is proposed for high-transmission foci or even across all areas with active transmission, along with screen and treat and passive case detection, as appropriate. The cheapest and most effective vector control tools available are proposed, i.e. baited and insecticide-treated targets, deployed at a density of 20/linear km or ~10/km2 for palpalis group tsetse in riverine foci. Depending on local conditions, modifications may ultimately be required along these lines: (i) foci with high cattle/livestock density: insecticide treatment of livestock; (ii) forest foci: targets at higher density; (iii) mangrove foci: ground/boat-based spraying (in addition to targets if the latter can be deployed at all). Elimination scenario I for 2013 – 2015 can be summarised as follows: standard targets are used for vector control in addition to the diagnostic and treatment algorithms established

for the Gambiense HAT control scenario for the same period. In elimination scenario II for 2013 – 2015, tiny targets replace the standard targets for vector control. Elimination scenario IV for 2016 – 2018 and elimination scenarios VI and VIII for 2019 onwards resemble the control scenarios for the respective periods with the addition of tiny targets for vector control.

2.5.1 Target areas and target population for Gambiense HAT control and elimination

The basic Gambiense HAT control and elimination scenarios III, V and VII cover all areas and populations at very high to moderate risk according to Simarro et al. (Pere P Simarro et al. 2012), translating into a an area of 693,600 km2 inhabited by 19,596,000 people in 13 countries (Table 2). Among them, three countries (Cameroon, Côte d'Ivoire, Sierra Leone) had no functional national HAT programme at the time of the last comprehensive review (Anonymous 2006). Meanwhile, Cameroon and Côte d'Ivoire have been able to re-establish their respective programmes. The population at risk in Sierra Leone is 1,000 people on <100 km2.

A comprehensive Gambiense HAT elimination programme would need to cover all potential transmission areas. This translates into an area of 1,380,600 km2, inhabited by 56,986,000 people in 14 countries (Table 2). The population at risk in countries without a functional control programme (Anonymous 2006) is 171,000 people on 1,800 km2 in Sierra Leone and 2,182,000 people on 71,000 km2 in Nigeria.

Compared to the base scenarios, interventions with the aim of accelerated Gambiense HAT elimination would need to cover twice the area at risk (an expansion from 693,600 km2 to 1,380,600 km2) and 2.9 times more people (an expansion from 19,596,000 individuals to 56,986,000 individuals).

Table 2. Area and population at risk of Gambiense HAT, stratified by control and programme status and scenario (source: Simarro et al.)

National programme status	Number of countries	Area (km²)				Population			
		Very high and high risk	Moderate risk	Low and very low risk	Total	Very high and high risk	Moderate risk	Low and very low risk	Total
Current control and elimination scenarios III, V and VII									
Active national HAT control programme	10[4]	234,500	454,600	N.A.	689,100	5,162,000	14,175,000	N.A.	19,337,000
No active national HAT control programme	3[5]	0	4,500	N.A.	4,500	0	259,000	N.A.	259,000
Total	*13*	*234,500*	*459,100*	*N.A.*	*693,600*	*5,162,000*	*14,434,000*	*N.A.*	*19,596,000*
Elimination scenarios I, II, IV, VI and VIII									
Active national HAT control programme	10[6]	234,500	454,600	636,700	1,325,800	5,162,000	14,175,000	31,993,000	51,330,000
No active national HAT control programme	4[7]	0	4,500	50,300	54,800	0	259,000	5,397,000	5,656,000
Total	*14*	*234,500*	*459,100*	*687,000*	*1,380,600*	*5,162,000*	*14,434,000*	*37,390,000*	*56,986,000*

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[4] *Angola, CAR, Chad, Congo, DRC, Equatorial Guinea, Gabon, Guinea, South Sudan, Uganda.*

[5] *Cameroon, Côte d'Ivoire and Sierra Leone (with 1,800 km² at risk, inhabited by 171,000 people where transmission is believed to have ceased).*

[6] *Angola, CAR, Chad, Congo, DRC, Equatorial Guinea, Gabon, Guinea, South Sudan, Uganda.*

[7] *Cameroon, Côte d'Ivoire, Nigeria and Sierra Leone (the last with 1,800 km² at risk, inhabited by 171,000 people where transmission is believed to have ceased).*

2.6   Discussion

Eliminating Gambiense HAT is a declared goal of WHO (WHO 2012). However, the most effective strategy for reaching this outcome is not yet clear. Elimination, defined as the sustained cessation of transmission of a pathogen in a defined geographic area as a result of human activities, can be achieved by ensuring that R_c, is below 1 for a sufficient amount of time. This can be achieved either by reducing the force of infection on humans through vector control or by reducing the force of infection on vectors by treating infective humans. As has been pointed out for malaria elimination (Moonen et al. 2010), sustaining the status of elimination requires either: i) eliminating the vector in addition to the pathogen; ii) preventing re-introduction from neighbouring areas that may not (effectively) be pursuing elimination through border screening; or iii) coordinating and implementing an effective elimination campaign in all endemic areas. Although elimination of tsetse may be easier to achieve than that of mosquito species (e.g. (Vreysen et al. 2000)), many areas, particularly riverine ones, may be prone to reinvasion due to the dispersal behaviour of tsetse (Rogers & Randolph 2002). Likewise, border screening for HAT is complicated by test system specifications, movements related to armed conflict and the occurrence of the disease in remote, often inaccessible or poorly served locations. Thus, in the absence of eradication, most HAT endemic countries will need to maintain post-elimination surveillance and response systems to prevent reestablishment via migrant cases. What is unknown is whether post-elimination surveillance can rely on the currently established passive case detection or whether more intense, active surveillance will be required and should the approach differ between areas with varying basic reproduction numbers (receptivity).

Although Gambiense HAT elimination has been deemed achievable, several challenges and uncertainties remain, such as gaining access for sufficient periods of time to areas that are currently experiencing political upheaval or strife (Simarro et al. 2013) or are otherwise inaccessible, as well as uncertainty regarding the extent to which these areas serve as sources of reinfection to nearby foci. Similarly, although case underreporting has greatly decreased over the past two decades, the latest estimates still assume a factor of three (Simarro et al. 2011). The spatial distribution of these unrecognised cases could affect elimination campaigns

if they represent previously unknown pockets of transmission. Other sources of reinfection relate to uncertainty regarding the true case fatality rate (Jamonneau et al. 2012; Checchi et al. 2008), the frequency of non-fatal infections and the extent to which trypanotolerant individuals contribute to transmission, if at all.

Similar uncertainty exists regarding the existence and importance of non-human animal reservoirs for *T. b. gambiense*. Based on investigations using mathematical models of pathogen transmission, several authors have posited that since the contribution of humans to the basic reproduction number of HAT is below one, a contribution from a non-human reservoir is probable (Funk et al. 2013; Rogers 1988). Others have argued that the contribution of animal reservoirs is likely negligible (Simarro et al. 2013). Resolving this debate is currently a priority as the existence of non-human reservoirs would necessitate a change in strategy or even affect the prospects of elimination.

We present options for achieving Gambiense HAT elimination that include both established and novel tools and that are considered relevant by a large panel of experts. These scenarios are simplified representations of the true efforts needed to eliminate the disease and it is likely that a combination of strategies will be needed to account for local realities. The inclusion of tools currently under development increases the uncertainty that the scenarios can one day be applied as described but most agree that only the advent of critically needed drugs and diagnostic tools will allow for Gambiense HAT elimination (Brun et al. 2010). The location and extent of traditional Gambiense HAT foci has been mapped over recent years and is now well established in most countries (Pere P Simarro et al. 2012; Simarro et al. 2010). Thus, mapping requirements for planning Gambiense HAT elimination are minimal. Another critical issue for any elimination programme is the sustainability of efforts needed until the last case has been treated and recurrence of the infection can be ruled out with a high degree of confidence. Surveillance and active response systems will become increasingly important as case numbers decline and the focus shifts from standardised approaches to tailored solutions adapted to the realities of the remaining pockets of transmission. Gambiense HAT arguably is already close to such a situation, with transmission mostly restricted to remote and under-served communities.

Any effort to eliminate Gambiense HAT must ensure that capacity for passive case detection and appropriate treatment of identified cases can reach the required levels across the entire focus. Following the cessation of local Gambiense HAT transmission, robust and effective surveillance coupled with an active rapid response mechanism to any new cases is required until transmission also ceases in neighbouring foci. Surveillance thus needs to be established throughout the focus and maintained for several years after the last case has been detected (World Health Organization (WHO) 2013b). Projecting the effectiveness and costs of such an active surveillance-response system is challenging as little experience exists to guide such efforts, not only in the field of Gambiense HAT but also for other diseases (Kelly et al. 2013).

Other important research questions are: What is the likelihood that the stated goal will be achieved when a given scenario is implemented over a certain time and how long would it take to achieve the intended outcome? What is the overall cost of implementing the scenarios and what are the public health and health service implications? For established methods, experience with control programmes can provide insights into these questions for specific localities. For instance, an intense period of twice-yearly population screening using the indirect immunofluorescent antibody test (IFAT) and treatment of serological cases resulted in a remarkable decline of prevalence from 1.42% to 0.03% over the course of six years in the Luba focus of Bioko Island. Less frequent screening of the population was maintained for the following 14 years until the focus was considered inactive (Simarro et al. 2006). Such insights clearly have value for policy makers but it is debatable whether these experiences can be extrapolated to other foci with different characteristics. For example, Luba is located on an island and would therefore be less prone to immigration of either infected flies or humans; it also had an excellent level of participation and acceptance of screening and treatment. Such extrapolation is necessary, however, and will also have to include predictions about the duration of interventions and the likelihood of reaching elimination. By considering (multiple) technologies that are currently under development, we increased the uncertainty of the expected outcomes; some tools may not ultimately become available or only become available later than anticipated. Additionally, new tools may lead to more than increased efficacy or decreased costs; they could also potentially allow for strategic changes.

Here, we have given an overview of nine distinct strategies that reflect not only the currently available tools at our disposal but also highlight novel strategies according to their projected release dates and speculate on their relevance for Gambiense HAT elimination. The multitude of options available and the low number of cases precludes conducting controlled trials for all of these scenarios. Finding the optimal scenario for a given endemic setting should therefore be informed by theoretical work. A possible framework for guiding such decisions is given by benefit-cost and cost-effectiveness analyses, based on appropriate costing and dynamic transmission models and on an understanding of the wider societal implications of HAT elimination. Our scenarios can form the basis for modelling feasibility and the health and economic impacts of Gambiense HAT elimination (Tediosi et al. 2013), providing valuable information to a wide range of actors working on HAT control, research and development. The advent of powerful tools to detect and treat HAT cases and control tsetse flies at a time of unprecedented political commitment and financial investments in NTD control offers a unique opportunity to eliminate the disease. The rigorous implementation of trials to test the efficacy of novel tools will already go some way towards contributing to the local Gambiense HAT elimination, since they require an appropriate number of patients, the provision of quality care and the establishment of infrastructure, all of which will have a lasting impact on the local epidemiology in the few remaining foci where an appropriate number of new cases occur.

2.7   Acknowledgements

2.8   Funding

3. A Literature Review of Economic Evaluations for a Neglected Tropical Disease: Human African Trypanosomiasis ("Sleeping Sickness")

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3.1   Abstract

Human African trypanosomiasis (HAT) is a disease caused by infection with the parasite *Trypanosoma brucei gambiense* or *T. b. rhodesiense*. It is transmitted to humans via the tsetse fly. Approximately 70 million people worldwide were at risk of infection in 1995, and approximately 20,000 people across Africa are infected with HAT. The objective of this review was to identify existing economic evaluations in order to summarise cost-effective interventions to reduce, control, or eliminate the burden of HAT. The studies included in the review were compared and critically appraised in order to determine if there were existing standardised methods that could be used for economic evaluation of HAT interventions or if innovative methodological approaches are warranted. A search strategy was developed using keywords and was implemented in January 2014 in several databases. The search returned a total of 2,283 articles. After two levels of screening, a total of seven economic evaluations were included and underwent critical appraisal using the Scottish Intercollegiate Guidelines Network (SIGN) Methodology Checklist 6: Economic Evaluations. Results from the existing studies focused on the cost-effectiveness of interventions for the control and reduction of disease transmission. Modelling was a common method to forecast long-term results, and publications focused on interventions by category, such as case detection, diagnostics, drug treatments, and vector control. Most interventions were considered cost-effective based on the thresholds described; however, the current treatment, nifurtomix-eflornithine combination therapy (NECT), has not been evaluated for cost-effectiveness, and considerations for cost-effective strategies for elimination have yet to be completed. Overall, the current evidence highlights the main components that play a role in control; however, economic evaluations of HAT elimination strategies are needed to assist national decision makers, stakeholders, and key funders. These analyses would be of use, as HAT is currently being prioritized as a neglected tropical disease (NTD) to reach elimination by 2020.

3.2   Background

Human African trypanosomiasis (HAT) is a disease caused by infection with the parasite *Trypanosoma brucei gambiense* or *T. b. rhodesiense* and is transmitted to humans via the tsetse fly. Approximately 70 million people worldwide were at risk of infection in 1995 (WHO n.d.), and although 7,216 cases were reported in 2012 (World Health Organization (WHO) 2013c), it is estimated that approximately 20,000 people across Africa are infected with HAT (World Health Organization (WHO) 2013c). According to the Global Burden of Disease, recent estimates of years lived with disability (YLDs) for HAT annually range from 2,000 to 25,000 (Vos et al. 2012). There are approximately 30 African countries affected by this disease, and it has been identified by the World Health Organization (WHO) as a neglected tropical disease (NTD) (WHO 2013).

WHO describes the disease as a neurological breakdown that is caused by the trypanosome parasite in the brain, which eventually leads to a coma or death if a patient is not treated (World Health Organization (WHO) 2013a). Patients are identified by self-reporting to health care centres (referred to as "passive case detection"), while active screening by trained professionals in mobile teams continues in high- and moderate-transmission areas. Active screening campaigns are carried out in remote villages, and a series of tests are used for the diagnosis of the disease. The current diagnostic algorithms for HAT include the card agglutination test for trypanosomiasis (CATT) followed by full blood assays to identify the parasite microscopically. Lumbar puncture with parasitological confirmation is then used for staging of the disease. Patients that are diagnosed with HAT are then referred to HAT treatment centres. Limited active screening is done for *T. b. rhodesiense* because there is no serological test available to facilitate easy identification. Hence, most *T. b. rhodesiense* cases are detected by clinical signs and symptoms. The subsequent diagnostic steps are similar to *T. b. gambiense* in that parasite detection is done using chancre aspirate or blood, and staging of the disease again uses cerebrospinal fluid obtained from lumbar puncture. The treatments for *T. b. gambiense* and *T. b. rhodesiense* also differ. Treatment for *T. b. gambiense* includes a 7-day intramuscular injection treatment of pentamidine for patients in stage 1 of the disease that is generally well tolerated, with minor adverse events. Nifurtimox-eflornithine combination therapy (NECT) is a 14-day in-hospital chemotherapy treatment that is required for patients

suffering from stage 2 of HAT. The adverse events commonly seen in patients treated with NECT are considered to be mild to moderate in severity. For HAT *T. b. rhodesiense*, the treatment for stage 1 includes weekly intravenous injections of suramin over the course of 5 weeks (World Health Organization (WHO) 2013a). Negative reactions to suramin coincide with the patient's health status, but overall, it is a well-tolerated treatment. Stage 2 treatment for *T. b. rhodesiense* is a 10-day treatment of melarsoprol. Melarsoprol is the most toxic of the HAT treatments, leading to encephalopathic syndrome in 5% to 18% of patients treated and often resulting in death. Vector control methods for prevention of HAT *T. b. rhodesiense* are commonly used, as the disease is well-known to have an animal reservoir that contributes to transmission in both human and animal populations (World Health Organization (WHO) 2013a). In regards to HAT *T. b. gambiense*, historically, vector control has not been suggested. However, evidence of an animal reservoir for *T. b. gambiense* has been discussed (Simo et al. 2014; Funk et al. 2013), and vector control was recently encouraged by WHO as an integrated strategy for HAT (World Health Organization (WHO) 2013a).

The year scheduled for HAT elimination is 2020 (WHO 2012), and as this deadline approaches, research groups are currently developing new drug treatments and diagnostic tools (Büscher et al. 2014; Drugs for Neglected Diseases initiative (DNDi) 2014b; Foundation for Innovative New Diagnostics n.d.) for HAT. Additionally, experts in vector control methods are also seeking interventions that would be more cost-effective and feasible for communities at risk for the disease. Even traditional teams that have gone out via trucks are now being reconsidered in combination with newer drug treatments using motorbike teams. Although some screening programs include a component of community sensitization, community involvement within control and elimination campaigns and knowledge of how this "disease awareness" is translated into behavioural changes and attitudes within affected populations need to be considered. There is now a need to evaluate not only the possibility of control and elimination for HAT but also how these new interventions and approaches may contribute to the grand scheme of such endeavours.

WHO has provided recommendations to improve certain factors likely to achieve elimination (World Health Organization (WHO) 2013c), and decision makers have also committed to funding the elimination of the disease (London Declaration 2013); yet, a clear path to the

achievement of this goal is not available, nor is it clear what the most efficient pathway towards elimination would be. In addition, thus far there has been no synthesis of the current costs and effectiveness of all strategies that could intervene in the transmission of the disease. The objective of this review was to identify existing economic evaluations in order to summarise cost-effective interventions to reduce, control, or eliminate the burden of HAT. The studies included in the review were compared and critically appraised in order to determine if there were standardised methods that could be used for economic evaluations of HAT interventions or if innovative methodological approaches are warranted.

3.3   Methods

3.3.1 Literature Search Strategy

A literature search was conducted via the OvidSp interface on January 22, 2014 using keywords for HAT specific to the Medical Subject Headings (MeSH) terms required for Medical Literature Analysis and Retrieval System Online (MEDLINE) and Embase databases. An economic filter developed by Scottish Intercollegiate Guidelines Network (SIGN) was also applied. (Refer to Supporting Information S1.) The Journal Storage (JSTOR) database was also searched using the following key words: African trypanosomiasis OR trypanosom& OR "sleeping sickness" AND cost& AND economics. In addition, the following keywords were also searched in the Database of Abstracts of Reviews of Effects (DARE), National Health Service Economic Evaluation Database Health Technology Assessment (NHSEED HTA), and Cochrane databases: "African" AND "Trypanosomiasis" OR "sleeping sickness". All citations were downloaded into Mendeley, where duplicates were identified and removed.

3.3.2 Literature Screening & Inclusion/Exclusion Criteria

Screening of the articles was done in two stages. At the first level, all titles and abstracts were screened. Articles that were considered potentially relevant were then assessed at the second level, in which the full text was read. After reading the full text, articles that still met the inclusion criteria were considered. A full description of the inclusion and exclusion criteria is available in appendix B. Data were screened on both levels according to the outline of

population-intervention-comparators-outcomes-setting (PICOS) criteria, in which the population pertained to humans. Evaluations regarding strains of both HAT *T. b. gambiense* and *T. b. rhodesiense* were reviewed, although outcomes only pertaining to humans impacted by the disease were taken into consideration (no animal implications). Interventions (I) and comparators (C) included any intervention that could lead to prevention or reduction of disease in human populations (including vector control). The outcomes (O) that were considered for review were costs, consequences (life-years saved [LYS], disability-adjusted life years [DALYs], etc.), and the incremental cost-effectiveness ratio (ICER), while the setting (S) included any African country. For the purpose of this analysis, an economic evaluation was defined by the Drummond et al. definition of a "full economic evaluation," and therefore, both costs and consequences of two or more alternatives had to be present in the analyses evaluated (Drummond et al. 2005). In cases in which an incremental analysis was not performed, articles were not excluded. Instead, if there was sufficient information in the publication to calculate the ICER, it was calculated during the review process. If there was insufficient information to calculate the ICER, it was noted in the critical appraisal that an incremental analysis was not present. No time constraints were added to the search.

3.3.3 Quality Assessment and Critical Appraisal

The quality of the included studies was assessed using the SIGN Methodology Checklist 6: Economic Evaluations Version 3.0 (Scottish Intercollegiate Guidelines Network (SIGN) n.d.), which was composed of two parts. The first portion contained questions regarding the internal and external validity of the publication. Items in the sections were assessed using answers of "Yes," "No," or "Can't say." The second portion of the checklist addressed the reviewers overall assessment of the study and also provided the reviewer with an area to judge if the article was "unacceptable," "acceptable," or of "high quality." Studies that received a "Yes" on 65% or more of the questions in Section 1 were considered acceptable to the authors.

3.4   Results

3.4.1 Literature Search Results

The NHSEED, JSTOR, MEDLINE, and Embase searches yielded a total of seven articles, 1,000 articles, 595 articles, and 673 articles, respectively. An additional eight articles from the grey literature, reference lists, and referrals from subject matter experts were also included. There were a total of 2,283 studies found, and after the removal of duplicates, 2,095 were chosen for primary screening (title and abstracts). A total of 41 publications were then selected for full-text screening. Thirty-four studies were excluded after full-text review, and reasons for exclusion were recorded. (Refer to Table 3) Seven full texts (Shaw 1989; Politi et al. 1995; Shaw & Cattand 2001; Lutumba, Robays, Miaka, et al. 2005a; Lutumba, Meheus, et al. 2007; Lutumba, Makieya, et al. 2007b; Robays et al. 2008) were included for full critical appraisal and data abstraction for analysis. (Refer to Figure 8)

Table 3. Characteristics of excluded studies at second-level screening

Author	Year	Reason excluded
Abila (Abila et al. 2007)	2007	Cost-effectiveness but interventions and outcomes related to fly population only
Brandl (F E Brandl 1988)	1988	Costs only, no effectiveness
Brightwell (Brightwell et al. 1991)	1991	Cost per trap discussed, paper related to effectiveness of trap as opposed to cost-effectiveness of relative comparators
Checchi (Checchi et al. 2011)	2011	Screening algorithms (sensitivity/specificity outcomes only)
Esterhuizen (Esterhuizen et al. 2011)	2011	No actual costs discussed, just effectiveness of fly traps
Etchegorry (Etchegorry et al. 2001)	2001	Costs only, no effectiveness
Fèvre (Fevre, Wissmann, et al. 2008)	2008	DALYs and burden of illness
Fèvre (Fevre, Odiit, et al. 2008)	2008	DALYs and burden of illness
Gouteux (Gouteux et al. 1987)	1987	Costs only, no effectiveness
Jordan (JORDAN 1961)	1961	Discussion only of economic importance, not actual economic analysis
Kamuanga (Mulumba Kamuanga et al. 2001)	2001	CBA using CV but outcomes based on preference for animals and not HAT
Laveissière (Laveissiere & Grebaut 1990)	1990	Costs only, no effectiveness
Laveissière (Laveissiere et al. 1998)	1998	Costs only, no effectiveness
Leygues (Leygues & Gouteux 1989)	1989	Socioeconomic outcomes, not cost-effectiveness
Lutumba (Lutumba, Robays, Miaka mia Bilenge, et al. 2005)	2005	Costs only, no effectiveness
Lutumba (Lutumba et al. 2006)	2006	Costs only, no effectiveness
Matemba (Matemba et al. 2010)	2010	Costs and DALYs for one area, not comparative analysis
McDermott (McDermott & Coleman 2001)	2001	Modelling of vector control only, not actual economic analysis

Mitashi (P Mitashi et al. 2012)	2012	Screening algorithms (sensitivity/specificity outcomes only)
Mugasa (Mugasa et al. 2012)	2012	Screening algorithms (sensitivity/ specificity outcomes only)
Okoth (Okoth 1991)	1991	Costs only, no effectiveness
Putt (Putt et al. 1988)	1988	Costs only, no effectiveness
Ruiz-Postigo (Ruiz Postigo et al. 2001)	2001	Costs only, no effectiveness
Shaw (Shaw 2004)	2004	Chapter 20 about the economics of trypanosomiasis; summary of research but no formal incremental CEA
Shaw (Shaw et al. 2006)	2006	Prevention and outcomes focussed on livestock, not human outcomes
Shaw (Shaw et al. 2007)	2007	Costs only, no effectiveness
Shaw (Shaw 2009)	2009	Costs only, no effectiveness
Shaw (Shaw et al. 2013)	2013	Costs only, no effectiveness
Simarro (Simarro et al. 2011)	2011	Costs only, no effectiveness
Simarro (P P Simarro et al. 2012)	2012	Costs only, no effectiveness
Trowbridge (Trowbridge et al. 2000)	2000	Abstract only; did not mention any costs, just DALYs
Vale (Vale & Torr 2005)	2005	Cost and benefits but related to vector control interventions related to fly populations only
Vos (Vos et al. 2012)	2012	DALYs and burden of illness
WHO Report (World Health Organization (WHO) 1998)	1998	Costs only, no effectiveness

Abbreviations: CBA, cost-benefit analysis; CV, contingent valuation, CEA = cost-effectiveness analysis, DALYs=disability adjusted life years

Figure 8. PRISMA diagram
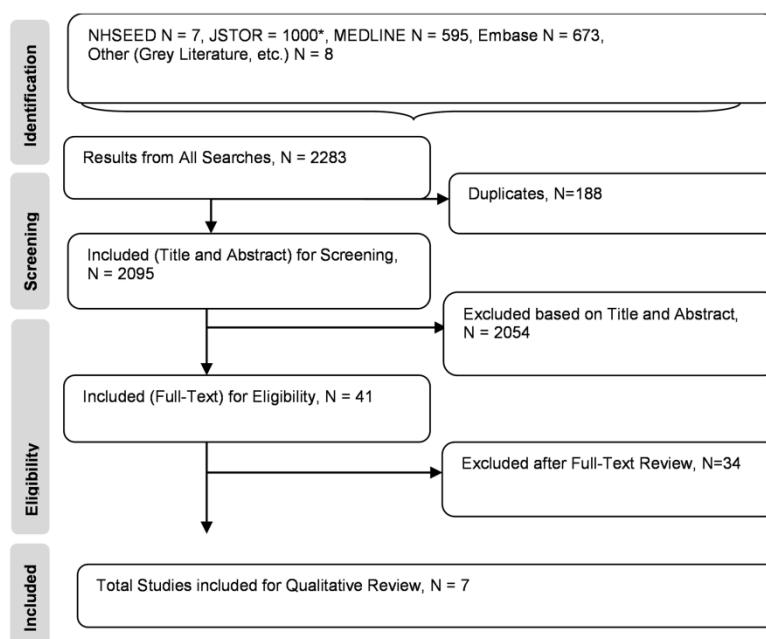
3.4.2 Quality Assessment and Critical Appraisal

The quality scores for the seven included studies (Shaw 1989; Politi et al. 1995; Shaw & Cattand 2001; Lutumba, Robays, Miaka, et al. 2005a; Lutumba, Meheus, et al. 2007; Lutumba, Makieya,

et al. 2007b; Robays et al. 2008) displayed in Table 4 (SIGN Methodology Checklist 6: Economic Evaluations) demonstrated that on average 81% (67%–89%) of the items stipulated by the SIGN checklist were addressed. Economic theory suggests that individuals have a time preference in regards to gains, and hence, costs and outcomes in the future are less valuable than those in the present (Morris et al. 2007). This concept is referred to as "discounting" and is standard methodology in economic evaluation; however, five out the seven studies in this review did not address it (Politi et al. 1995; Shaw & Cattand 2001; Lutumba, Robays, Miaka, et al. 2005a; Lutumba, Meheus, et al. 2007; Robays et al. 2008). Each publication considered the cost and consequence compared to more than one intervention for HAT; however, three of the publications (Shaw 1989; Shaw & Cattand 2001; Lutumba, Robays, Miaka, et al. 2005a) did not include an incremental analysis to examine the marginal benefit of adopting one intervention compared to the next best option. A single study (Lutumba, Meheus, et al. 2007) did not have a clear objective, and Shaw's study did not justify the study design or clearly describe the cost sources (Shaw 1989). All but one study (Lutumba, Makieya, et al. 2007b) completed a sensitivity analysis in addition to the base results. All studies discussed the economic importance of the question and had outcomes that could be relevant for decision makers. Overall, all studies were judged to be "acceptable" for this review.

Table 4. Critical appraisal (Scottish Intercollegiate Guidelines Network (SIGN) Methodology Checklist 6: Economic Evaluations)

Author	Question	Shaw (Shaw 1989)	Politi (Politi et al. 1995)	Shaw (Shaw & Cattand 2001)	Lutumba(Lutumba, Robays, Miaka, et al. 2005b)	Lutumba (Lutumba, Makieya, et al. 2007b)	Lutumba (Lutumba, Meheus, et al. 2007)	Robays (Robays et al. 2008)
Year		1989	1995	2001	2005	2007	2007	2008
SECTION 1.	**Internal Validity**							
1.1	The study addresses an appropriate and clearly focused question	Yes	Yes	Yes	Yes	No	Yes	Yes
1.2	The economic importance of the question is clear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
1.3	The choice of study design is justified	Can't say	Yes	Yes	Yes	Yes	Yes	Yes
1.4	All costs that are relevant from the viewpoint of the study are included and are measured and valued appropriately	No	Yes	Yes	Yes	Yes	Yes	Yes
1.5	The outcome measures used to answer the study question are relevant to that purpose and are measured and valued appropriately	Yes	Yes	Yes	Yes	Yes	Yes	Yes
1.6	If discounting of future costs and outcomes is necessary, it has been performed correctly	Yes	NA	No	NA	Yes	NA	Can't say

1.7	Assumptions are made explicit and a sensitivity analysis performed	Yes	Yes	Yes	Yes	No	Yes	Yes
1.8	The decision rule is made explicit, and comparisons are made on the basis of incremental analysis	No	Yes	No	No*	Yes	Yes	Yes
1.9	The results provide information of relevance to policy makers	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Total fulfilment		6	8	7	7	7	8	8
		67%	89%	78%	78%	78%	89%	89%

SECTION 2. Overall Assessment of the Study

| 2.1 | How well was the study conducted? | Acceptable | Acceptable | Acceptable | Acceptable | Acceptable | Acceptable | Acceptable |
| 2.2 | Are the results of this study directly applicable to the patient group targeted by this guideline? | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

*Base case analysis was not incremental, but sensitivity analysis had an incremental analysis

3.4.3 Characteristics of Included Economic Evaluations

Each of the seven included publications had varying characteristics, as summarised in Table 5. The first publication of a full economic evaluation for HAT identified was completed in 1989 by Alexandra Shaw (Shaw 1989), with the next publication coming in 1995 (Politi et al. 1995). The remaining five publications were published from 2005 to 2008 (Lutumba, Robays, Miaka, et al. 2005b; Lutumba, Makieya, et al. 2007b; Lutumba, Meheus, et al. 2007; Shaw & Cattand 2001; Robays et al. 2008). The evaluations covered four African countries: Democratic Republic of the Congo (DRC), Uganda, Côte d'Ivoire, and Angola. Most (3/7) evaluations (n=3) came from DRC (Lutumba, Robays, Miaka, et al. 2005b; Lutumba, Meheus, et al. 2007; Lutumba, Makieya, et al. 2007b), with one study from Côte d'Ivoire (Shaw 1989), one study from Uganda (Politi et al. 1995), one study from Angola (Robays et al. 2008), and finally one study that included an analysis from both Uganda and Côte d'Ivoire (Shaw & Cattand 2001). Economic evaluations concerning HAT in human populations looked almost exclusively at the disease *T. b. gambiense* (71%), although in two instances the disease strain was not specified explicitly (Shaw 1989; Robays et al. 2008). A total of four economic evaluations (Shaw 1989; Lutumba, Robays, Miaka, et al. 2005b; Lutumba, Meheus, et al. 2007; Robays et al. 2008) were considered cost-effectiveness analyses (CEA) in which the cost for a desired effect or consequence (e.g., lives saved, years of infection avoided, etc.) was measured. Two studies (Politi et al. 1995; Lutumba, Makieya, et al. 2007b) included both a CEA and cost utility analysis (CUA) in which the utility was measured in DALYs. One study exclusively completed a CUA in which cost per DALY averted was measured as the main outcome (Shaw & Cattand 2001). Overall, there was only one publication that was found in an "economic" journal, as the remaining articles were published in journals pertaining to tropical medicine and infectious diseases. Funding for the research was often not mentioned. However, WHO was referred to as a means of support in two publications (Politi et al. 1995; Lutumba, Robays, Miaka, et al. 2005b), and support from the Belgian Directorate General for Development Cooperation was also mentioned (Lutumba, Robays, Miaka, et al. 2005b).

Table 5. Characteristics of included economic evaluations

Author	Shaw (Shaw 1989)	Politi (Politi et al. 1995)	Shaw (Shaw & Cattand 2001)	Lutumba(Lutumba, Robays, Miaka, et al. 2005b)	Lutumba (Lutumba, Makieya, et al. 2007b)	Lutumba (Lutumba, Meheus, et al. 2007)	Robays (Robays et al. 2008)
Year	1989	1995	2001	2005	2007	2007	2008
Type of Intervention	Case Detection and Diagnosis + Treatment, Vector Control	Treatment	Case Detection and Diagnosis	Diagnosis	Case Detection and Diagnosis	Diagnosis	Treatment
Country	Côte D'Ivoire	Uganda	Uganda, Cote D'Ívoire	DRC	DRC	DRC	Angola
Disease Strain	Not mentioned	*T. b. gambiense*	*T. b. gambiense*	*T. b. gambiense*	*T. b. gambiense*	*T. b. gambiense*	*T. b. gambiense**
Type of Economic Evaluation	CEA	CEA/CUA	CUA	CEA	CEA/CUA	CEA	CEA
Journal	Annales de la Société belge de médecine tropicale	Health Economics	Médicine Tropicale	Tropical Medicine and International Health	Emerging Infectious Diseases	Emerging Infectious Diseases	Tropical Medicine and International Health
Funding	Not mentioned	Internship at WHO	Not mentioned	WHO (Organisation mondiale de la Santé) and bourse de doctorat Direction Générale de la Coopération au Développement du Royaume de Belgique avec l'Institut de Médecine Tropicale Prince Leopold	Financed partly by doctoral grant from the Belgian Directorate General for Development Cooperation by WHO	None mentioned	None

| Additional Institutional Collaborators | Members at WHO, member from Oxford University; VEERU | Departments in WHO: Division of Intensified Cooperation with countries, Division of Control of Tropical Diseases and Special Programme in Tropical Disease Research; Batelle MEDTAP, London; anonymous referees | TDR/WHO as Institutional collaborators | None | National Program in DRC | HAT experts | None |

*Abbreviations: MEDTAP, Medical Technology Assessment and Policy; TDR, Tropical Disease Research; VEERU, Veterinary Epidemiology and Economics Research Unit. *Inferred T. b. gambiense because of treatments being used.*

3.4.4 Interventions

The majority (5/7) of the publications evaluated interventions that included case detection and diagnosis, while two of the articles evaluated treatment interventions of melarsoprol and eflornithine (difluoromethlyornithine [DFMO]) for stage 2, as the treatment for stage 1 was always considered to be pentamidine (Politi et al. 1995; Robays et al. 2008). Two publications by Lutumba (Lutumba, Robays, Miaka, et al. 2005b; Lutumba, Meheus, et al. 2007) looked exclusively at sensitivity and specificity of diagnostic algorithms and staging algorithms, while one study also looked at the differences between treatment and vector control interventions in addition to case detection and diagnosis (Shaw 1989). The study by Shaw in 1989 was the only publication that included a comparative economic analysis for vector control as an intervention to control HAT in a human population.

3.4.5 Economic Evaluation Description

Key insights regarding the details of the included economic evaluations are described below and also summarised in Table 6.

Methods and Software

Six of the seven included studies used modelling to measure outcomes for the economic evaluation. Only one study completed an economic evaluation alongside a clinical trial. The most common form of modelling was decision tree modelling; the structure of the remaining models was not described in detail although they were all described as being implemented with spreadsheets. For decision tree models, TreeAge software (TreeAge Software, Williamstown, Massachusetts, United States) was used for three of four studies (Lutumba, Robays, Miaka, et al. 2005b; Lutumba, Meheus, et al. 2007; Robays et al. 2008), and one publication did not mention which software was used. The two spreadsheet models that were reviewed (Shaw 1989; Shaw & Cattand 2001) used Super-Calc 4 (Sorcim, Silicon Valley, California, US) and Microsoft Excel (Microsoft Corp., Redmond, Washington, US) software, while the economic evaluation alongside clinical trial (EEACT) (Lutumba, Makieya, et al. 2007b) relied on Microsoft Access (Microsoft Corp., Redmond, Washington, US), Microsoft

Excel (Microsoft Corp., Redmond, Washington, US), and Epi Info 2002 (Centers for Disease Control and Prevention, Atlanta, Georgia, US).

Model Structure, Assumptions & Validation

A visual diagram of the model was provided for five of the six studies that included models (Politi et al. 1995; Shaw & Cattand 2001; Lutumba, Robays, Miaka, et al. 2005b; Lutumba, Meheus, et al. 2007; Robays et al. 2008). Although descriptions of the six models were available, no details of the assumptions or justification for the inputs used in the modelling were addressed in any of the included literature. None of the articles reported completing an internal validation of the models, but the authors of one article (Lutumba, Meheus, et al. 2007) did compare their outcomes to other literature in similar areas for external validity.

Population, Setting, and Perspective

In one of the modelling studies, the number of patients modelled was not mentioned, while the remaining studies included 690 to 1,000,000 hypothetical patients. The clinical trial included a total of 57 patients from 47 households (Lutumba, Makieya, et al. 2007b). As mentioned previously, the populations were based on four countries (DRC, Côte D'Ivoire, Angola, and Uganda), with different settings including: rural communities, health centres, and a sleeping-sickness hospital ward.

In one case (Shaw 1989), the perspective of the analysis was not mentioned, but two articles approached the economic evaluation from a societal perspective (Politi et al. 1995; Lutumba, Makieya, et al. 2007b), and the remaining four articles used the provider perspective (e.g., a donor or national health service) (Shaw & Cattand 2001; Robays et al. 2008; Lutumba, Robays, Miaka, et al. 2005b; Lutumba, Meheus, et al. 2007).

Additional Inputs, Outcomes, and Features of Included Economic Evaluations

Data sources for the economic evaluations came from clinical trials, primary data collection from national programmes (e.g., Programme National de Lutte contre la Trypanosomiase Humaine Africaine [PNTHLA], Médecins Sans Frontières [MSF], and National Sleeping Sickness Programme Uganda), reports from WHO, available literature, and from speaking with experts in the arena of HAT. Prevalence values were not mentioned in two studies and ranged from 0.1% to 70% in the remaining literature.

All costs were evaluated in US dollars (USD} (Shaw 1989; Politi et al. 1995; Shaw & Cattand 2001; Lutumba, Robays, Miaka, et al. 2005b; Lutumba, Makieya, et al. 2007b; Robays et al. 2008) except for one study by Lutumba et al. (Lutumba, Meheus, et al. 2007) that estimated cost-effectiveness in euros. Three studies reported only one outcome, while the remaining studies reported two outcomes in terms of cost per outcome. Cost per DALY averted was reported in three studies, while cost per LYS was reported in four studies. Cost per years of life lost (YLL), cost per patient/control case detected or patient cured, and cost per infection prevented were also examples of cost-effectiveness reported in the literature reviewed. Shaw (1989) and Shaw and Catt and reported time horizons of 20 years and one year, respectively (Shaw 1989; Shaw & Cattand 2001). Studies that used decision tree modelling did not report time horizons as decision trees have no time-related component (Politi et al. 1995; Lutumba, Robays, Miaka, et al. 2005b; Lutumba, Meheus, et al. 2007). The two remaining studies did not report a discrete time horizon for the analysis (Lutumba, Makieya, et al. 2007b; Robays et al. 2008). Two publications reported using discount rates of 10% (Shaw 1989; Robays et al. 2008), while one publication reported using a discount rate of 3% (Lutumba, Makieya, et al. 2007b). The remaining publications did not mention any discounting (Politi et al. 1995; Shaw & Cattand 2001; Lutumba, Robays, Miaka, et al. 2005b; Lutumba, Meheus, et al. 2007), which was probably due to the fact that decision trees were used and therefore had no time horizon that or the time span modelled was one year or less. Two of the seven articles made explicit references to willingness-to-pay (WTP) thresholds for the cost-effectiveness of HAT as US$25/DALY (Politi et al. 1995; Shaw & Cattand 2001). One article mentioned that the WHO-CHOICE (CHOosing Interventions that are Cost-Effective) considered the gross domestic product (GDP) per capita of a country to be used as the WTP threshold for choosing between competing interventions (Robays et al. 2008; Evans et al. 2005). The remaining publications (Shaw 1989; Lutumba, Robays, Miaka, et al. 2005b; Lutumba, Makieya, et al. 2007b; Lutumba, Meheus, et al. 2007; Robays et al. 2008) made no reference to a WTP threshold for the economic analysis under evaluation.

Table 6. Description of included economic evaluation

Author	Shaw (Shaw 1989)	Politi (Politi et al. 1995)	Shaw (Shaw & Cattand 2001)	Lutumba(Lutumba, Robays, Miaka, et al. 2005b)	Lutumba (Lutumba, Makieya, et al. 2007b)	Lutumba (Lutumba, Meheus, et al. 2007)	Robays (Robays et al. 2008)
Year	1989	1995	2001	2005	2007	2007	2008
Method/Structure	Modelling	Modelling	Modelling	Modelling	Field Study (Economic Study)	Modelling	Modelling
Model Description (if applicable)	Spreadsheet model that simulates outcomes	Decision Tree with inclusion of relapses	Spreadsheet model that simulates outcomes based on the five strategies identified	Decision Tree	NA	Decision Tree. Complex decision tree model with separate arms for each stage of detection in the treatment algorithm specified. End diagnosis for positive tests is first or second stage of HAT. HAT-positive and HAT-negative populations examined to account Sens and Spe for	Decision Tree. Melarsoprol and DMFO treatment arm options. Patients treated with melarsoprol have no complications or arsenic encephalopathy. Patients with no complications may relapse or be cured, while patients with an adverse event AE have a probability of survival prior to being cured or relapsing. Patients treated with DMFO have a

						TN, TP, FP, and FN.	probability of surviving treatment or dying. Survivors are cured or relapse. All relapse patients (DMFO and melarsoprol) have the possibility of being cured or proceed to death.
Software	Super-Calc 4	Not mentioned	Microsoft Excel	TreeAge	Microsoft Access, Microsoft Excel, Epi Info 2002	Data Pro 2004 (TreeAge)	TreeAge Pro 2006
Population Description	HAT population	1,000 hypothetical patients with *T. b. gambiense* in stage 2	100,000 hypothetical people modelled, containing 10 rural health centres and 20 community health workers	1,000,000 hypothetical patients	Economic study of 57 patients, 47 households (21%); Median age was 26 years (4–72 years); 57% of patients were female; 63% of patients in stage 1	In model 50% of patients in stage 1 and 2 equally	690 stage 2 patients
Area Description	Cote D'Ívoire (Vavoua focus), forest zone with scattered hamlets	Uganda	Daloa, Côte D'Ivoire/Moyo District Uganda	DRC	Single outbreak of HAT in 2000–2002 Buma, a rural community of 1,300 people (Buma centre +	Probabilities, baseline data, costs and time developed from study in Kwamouth	Sleeping sickness ward in Caixto, Angola

					Kimpolo) 35 km south of Kinshasa in the DRC affected by outbreak of HAT	between February and March 2004	
Prevalence	5% year one (incidence 1%)	Not mentioned	Range 0.01%– 70%	1.00%	Buma: 5.92% (77 Cases/1,300 population). Based on local data: Buma centre—2% (20/1,000) Kimpolo—19% (57/300)	1.00%	Not mentioned
Data Sources/Inputs	CATT test & mAECT— Côte D'Ivoire	Available literature, clinical trials; reports of National Sleeping Sickness Programme-Uganda, personal communication from experts, WHO/CDT/TDR	Costs and estimates from WHO Technical Report Series 881, published in 1998	HAT Programme in the DRC, PNTHLA, literature and reports from Trypanosomiasis Bureau	Data from this study, information from PNTHLA in DRC; costs included cost consultation fees, cost of travel, lab, household expenses (except diagnostictest), and cost of hospitalization (including food for patient and caregiver); treatment costs (drug cost included but	Annual reports from PNTHLA; study in Kwamouth, previous literature regarding Sen and Spe; treatment efficacy rates included were for first generation treatment pentamidine (stage 1) and melarsoprol (stage 2). Costs include screening,	MSF Program in Angola

					specific treatments not mentioned, injections, small materials, syringes, and needles); value of each work day lost (estimated on a person basis). DALYs were calculated estimated based on HAT-related death based on family recall and possible HAT-related deaths. Calculated HAT disability before, during, and after treatment. DALYs calculated as per Murray et al.	confirmation and treatment and costs generated by each algorithm. screening costs included vehicle, depreciation, operation costs, and CATT reagents.	
Perspective	Not mentioned	Societal	Donors and National Healthcare System	Healthcare system	Societal	Healthcare system	Healthcare system
Costs Valuation	$ (USD UNK year)	$ (USD 1992)	$ (USD 1995)	$ (USD 2002)	$ (USD 2002)	€ (May 2003)	$ (USD 2005)

Consequence Units	1. Year of infection prevented per person.	1. DALY. 2. Life saved.	1. Patient detected. 2. DALY averted.	1. Life saved.	1. DALY. 2. Control case detected/patient cure.	1. Life saved.	1. Life saved. 2. YLL.
Cost/Consequence valuation	$/infection prevented	1. $/DALY averted***. 2. $/life saved.	1. $/patient detected. 2. $/DALY averted.	1. $/life saved.	1. $/DALY averted. 2. $/control case detected or patient cured.	€/life saved	1. $/life saved. 2. $/YLL averted.
Time Horizon	20 years (Vector Control and Screen & Treat)	NA—DT	One year (simulation repeated at different prevalence, but always same time horizon)	NA—DT	None	NA—DT	20 Years. (Although, this seems a bit unclear since a DT requires no discounting due to short time horizon)
Discount rate	10%	NA—DT	NA—one year only	NA—DT	DALYs—3%	NA—DT	10% on hospital building
Validation	No	No	No	No	Compared their results to other literature (e.g., Shaw and Cattand, etc.)	They discussed the limitations of the study	No
CE Threshold	Not mentioned	$25/DALY (World Bank)	$25/DALY (WHO)	Not mentioned	Not mentioned—just mentioned that within range of Shaw and Cattand (2001) results	Not mentioned, but competing strategies made a clear case for CE due to dominance and extended dominance	WHO-CHOICE (World Health Organization (WHO) 2003) threshold; products less than GDP per capita (very cost-effective); products less than three times the GDP per

							capita (cost-effective)
Alternative Scenarios/Interventions	1. Assumption A (constant incidence): find and treat vector control (traps/targets + ground spraying). 2. Assumption B (variable incidence): find and treat vector control (traps/targets + ground spraying).	1. None. 2. Melarsoprol → Melarsoprol. 3. Melarsoprol → Eflornithine (DFMO). 4. Eflornithine → Eflornithine (DFMO).	First Scenario: 1a. Systematic fixed postsurveillance at rural health centres (N=1, screens 300 ppl). 1b. Road blocks near centres, usually set up on market days. 2. Filter paper sample (rural health centres N=10, screens 3,000 ppl). 3. Filter paper sample (community health workers N=20, screens 24,000 ppl). 4. Polyvalent mobile teams (N = 1, screens 20,000). 5. Monovalent mobile teams (N=1, screens 36,000). Second	1. PG (LNP). 2. CATT. 3. PG (LNP) + CATT.	None versus active screening. 1. Treatment alone. 2. Active screening + treatment.	1. LNP-FBE-TBF. 2. LNP-CTC. 3. LNP-CATT titration-CTC-mAECT. 4. LNP-CTC-mAECT. 5. LNP-TBF-CTC-mAECT. 6. LNP-CTC-CATT titration. 7. LNP-TBF-CTC-mAECT-CATT titration.	1. Melarsoprol. 2. Eflornithine (DFMO).

			Scenario: same as above but using data from Moyo District of Uganda				
ICER Results	Refer to Table 7.						
Subgroup Analyses	No	No	No	No	No	No	No
SA	Yes	Yes	Yes	Yes	No	Yes	Yes
Description of SA and Results	1. Costs were double and halved. 2. Prevalence at the start of the model. 3. Incidence in the absence of control work. 4. Stability of prevalence in the absence of control activities. 5. Number of years control was	1. Consequences of modified assumptions regarding treatment effectiveness. 2. Modified assumptions regarding the costs of treatments and working days lost by patients and/or relatives. 3. Other variables (under table payments, shadow price of working day, rates of noncompliance). Results: If melarsoprol is less	SA looked at multiplying the number of DALYs averted per patient (which was assumed to be 15) by 1.5, 2, or 2.5 at varying prevalence. Results: Cost per DALY averted becomes more favourable as prevalence increases. None of these results	1. The Spe of PG test was varied comparing CATT to PG + CATT. 2. Additional SA of the ($/LYS) varying the prevalence of HAT, costs of tests, and Sen/Spe of PG, CATT, and Sen of parasitology. Results: When the Spe of PG was 52%, the ICER of CATT + PG compared to CATT was $5,000/LYS. When the Spe of PG was	NA	Looked at several parameters including prevalence of HAT, cost of mAECT, CATT whole blood Spe and Sens of CTC, mAECT, FBE, CATT whole blood, and LNP. Results: Tornado diagram demonstrated	Authors explored both situations with drug costs and excluding drug costs. Tornado diagram demonstrated that the following parameters were examined: death rate, relapse rates of treatments, death rates and death rates due to AEs, drug

undertaken was varied. 6. Importance of animal reservoir by varying assumptions in A and B (this was a bit unclear). Results: When costs were halved or doubled, the cost per benefit unit was also halved or doubled. It was more cost-effective to carry out interventions in areas with higher prevalence. Increasing incidence made vector control more profitable under A and B, but not for finding and treating patients.	effective than current evidence, then the relative cost-effectiveness of eflornithine would improve making scenario/interventions '2', '3' and '4' potentially cost-effective. If melarsoprol effectiveness improved, then scenario/intervention '3' would be dominated by scenario/intervention '2' making scenario/intervention '2' the most cost-effective option. If the effectiveness of eflornithine in late stage patients is as high in refractory patients who take melarsoprol, then scenario/intervention '3' dominates scenario/intervention '4' leaving both scenario/intervention '2' and '3' as potentially cost-effective options. Working days lost by	were incremental.	70%, the ICER of CATT + PG compared CATT was $3,175/LYS. When the Spe of PG was 90%, the ICER of CATT + PG compared to CATT was $1,225/LYS. Results from varying prevalence showed that $/LYS decreased as prevalence increased; however; none of these results were incremental.	that CATT whole blood Spe had the greatest impact on the ICER; also examined function as variation of prevalence and CE ratio (but this was not an incremental analysis) was more favourable as prevalence increased. They also varied the impact of discovering the FN (data was not shown) and stated that if FNs presented themselves for treatment the differences in CE were reduced.	costs, building costs. Results: DMFO treatment becomes CE when melarsoprol death rate is greater than 16% and when death rate due to melarsoprol is greater than 70%

	Prevalence had a positive correlation with profitability over time. Adding years to which control was undertaken reduced the cost per benefit for finding and treating patients, but not for vector control. Variance in the animal reservoir had a larger impact on the cost-effectiveness of finding and treating patients than on vector control. None of these results were incremental.	patients and/or relatives as well as other variables had little impact on cost-effectiveness when varied.					
PSA	No	No	No	No	No	No	No

VOI	No	No	No	No	No	No	No

** calculated ICERs based on information presented in the paper.

Abbreviations: CDT, community-directed treatment; CE, cost-effectiveness; DT, decision tree; FN, false negative; FP, false positive; FBE, fresh blood examination; NA, not applicable; PG, palpation ganglionnaire; PNLTHA, Programme National de Lutte contre la Trypanosomiase Humaine Africaine; Sen, Sensitivity; Spe, Specificity; SA, sensitivity analysis; TDR, Tropical Disease Research; TN, true negative; TP, true positive; USD, United States dollar; UNK, unknown; VOI, value of information analysis. .

Base Case and Sensitivity Analyses

A full description of the economic outcomes for each study is outline in Table 7. The results from the sensitivity analyses conducted for the included publications are provided in Table 6.

A total of 5 studies (Politi et al. 1995; Lutumba, Meheus, et al. 2007; Lutumba, Robays, Miaka, et al. 2005b; Lutumba, Makieya, et al. 2007b; Robays et al. 2008) discussed cost-effectiveness results by calculating incremental cost-effectiveness ratios (ICERs), which are summarised in Table 6. Lutumba and colleagues published cost-effectiveness analyses of varying diagnostic algorithms for HAT (Lutumba, Robays, Miaka, et al. 2005b; Lutumba, Meheus, et al. 2007). Their results in 2005 demonstrated that lymph node puncture (LNP) in addition to CATT was more cost-effective ($20/LYS) relative to CATT alone or LNP alone (Lutumba, Robays, Miaka, et al. 2005b). In 2007, LNP followed by capillary tube centrifugation (CTC) and mini-anion exchange centrifugation technique (mAECT) (€76/LYS); LNP followed by thick blood film (TBF), CTC, and mAECT (€200/LYS); and LNP followed by TBF, CTC, mAECT, and CATT titration (€2,618/LYS) were deemed cost-effective relative to four other diagnostic algorithms. Although the strengths of these cost-effective algorithms were noted, Lutumba and colleagues noted that some of these algorithms may not be feasible to carry out in the field (Lutumba, Meheus, et al. 2007). In regards to treatment regimens, Politi's analysis (Politi et al. 1995) in 1995 demonstrated that based on a WTP of US$25/DALY, melarsoprol alone (initial treatment and relapses) was cost-effective at US$8/DALY (US$209/LYS) compared to no treatment. Politi's analysis also demonstrated that a treatment pathway of melarsoprol with treatment relapses on Eflornithine (difluoro-methylornithine [DMFO]) (US$41/DALY and US$1,033/LYS) or DMFO for both treatment and relapses (US$167/DALY and US$4,444/LYS) would not have been considered cost-effective based on the aforementioned cost-effectiveness threshold of US$25/DALY (Politi et al. 1995). A more recent publication by Robays demonstrated that DFMO was more cost-effective than melarsoprol (US$1,596/LYS and US$58/control case detected) when donated drug costs were not included; the analysis of cost-effectiveness was based on WHO-CHOICE's suggestion that interventions at a cost of GDP per capita are very cost-effective and interventions at three times GDP per capita are cost-effective (WHO n.d.). When donated drug costs were included, Robays found that DFMO was more cost-effective than melarsoprol at US$8,169/LYS and US$299/control case detected. Lutumba et al. (Lutumba, Makieya, et al. 2007b) found that active screening (case detection) in

addition to treatment was more cost-effective than treatment alone at $17/DALY averted and $301/control case detected or patient cured.

Two studies (Shaw 1989; Shaw & Cattand 2001) did not report cost and effect results incrementally. Although Shaw et al. (Shaw & Cattand 2001; Shaw 1989) conducted several analyses exploring combinations of case detection, diagnostics, treatment, and vector control, outcomes were not compared incrementally; consequently, ICERs were not attained. They did calculate $/patient detected with varying prevalence for five strategies and found that lower prevalence rates were associated with higher $/DALY and higher prevalence rates with lower $/DALY; these were based on average cost-effectiveness ratios, not ICERs.

All but one study included some form of one-way sensitivity analysis (OWSA). No studies completed subgroup analyses or conducted probabilistic sensitivity analyses (PSA), and hence, results were not presented using cost-effectiveness acceptability curves (CEAC). Additional measures of uncertainty were not explored in the form of a value of information (VOI) analysis in any of the reviewed publications.

Table 7. ICER results from economic evaluations

Author, Year	Type of Intervention	Name of Intervention	ICER Results			
			Cost/DALY Averted	Cost/LYS	Cost/YLL Averted	Cost/Control Case Detected
Shaw, 2001 (Shaw & Cattand 2001)	Case detection and diagnosis	1. Systematic fixed post surveillance at rural health centres	NA	NA	NA	NA
		2. Filter paper sample (rural health centres)				
		3. Filter paper sample (community health workers)				
		4. Polyvalent mobile teams				
		5. Monovalent mobile teams				
Lutumba, 2005 (Lutumba, Robays, Miaka, et al. 2005b)	Diagnosis	1. CATT	-	1. -	-	-
		2. LNP		2. dominated by 1		
		3. LNP + CATT		3. $20*		
Lutumba, 2007 (Lutumba, Meheus, et al. 2007)	Diagnosis	1. LNP-FBE-TBF	-	1. -	-	-
		2. LNP-CTC		2. ED by 4		
		3. LNP-CATT titration-CTC-mAECT		3. ED by 4		
		4. LNP-CTC-mAECT		4. €76		
		5. LNP-TBF-CTC-mAECT		5. €200		
		6. LNP-CTC-CATT titration		6. dominated by 5		
		7. LNP-TBF-CTC-mAECT-CATT titration		7. €2,618		

Study	Intervention	Option	Col1	Col2	Col3	Col4
Politi, 1995 (Politi et al. 1995)	Treatment	1. None	1. -	1. -	-	-
		2. Melarsoprol → Melarsoprol	2. $8	2. $209		
		3. Melarsoprol → DFMO	3. $41	3. $1,033		
		4. DFMO → DFMO	4. $167	4. $4,444		
Robays, 2008 (Robays et al. 2008)	Treatment		-	*Donated drug costs not included:*	*Donated drug costs not included:*	-
		1. Melarsoprol		1. -	1. -	
		2. DFMO		2. $1596	2. $58	
				Donated drug costs included:	*Donated drug costs included:*	
				1. -	1. -	
				2.$8,169	2.$299	
Lutumba, 2007 (Lutumba, Makieya, et al. 2007b)	Case detection and diagnosis, treatment	1. Treatment alone	1. -	-	-	1. -
		2. Active screening + treatment	2.$17			2. $301
Shaw 1989 (Shaw 1989)	Case detection and diagnosis, treatment , vector control	1. Find and Treat	NA	NA	NA	NA
		2. Vector control (traps/targets + ground spraying)				

3.5   Discussion

A review of previous evidence has demonstrated that there have been only a few economic evaluations conducted to assess the cost-effectiveness of interventions to control HAT and reduce disease burden. From this evidence alone, it would prove difficult for decision makers to strategize on which interventions would be most cost-effective for elimination; however, the results do provide some insights into the key components of HAT disease control and how these components could be translated into HAT elimination strategies, which could then be assessed through economic evaluation.

Overall the strengths of this review are that it highlights the components that play a role in disease control and reduction of transmission and emphasizes that these are the components that should be incorporated into elimination strategies. Case detection, diagnosis, treatment, and vector control are the four categories of interventions that have been considered thus far in the literature. Strategies towards elimination should continue to consider the impact of these components but also aim to highlight their individual and collective use within a formal strategy for reaching elimination. This was highlighted in the study by Lutumba et al. (Lutumba, Makieya, et al. 2007b) in which case-detection with treatment was compared to treatment alone and also in the work by Shaw and colleagues in 1989 in which essentially all four categories were evaluated with varying incidence. Within diagnostics, algorithms for CATT showed that the addition of tests led to more efficient outcomes (Lutumba, Meheus, et al. 2007). However, there is still a gap in cost-effectiveness knowledge of the current treatment for HAT, NECT. Global investors, partners, and academic groups (World Health Organization (WHO) n.d.; Bill & Melinda Gates Foundation n.d.; Department for International Development n.d.; Swiss TPH 2014; Liverpool School of Tropical Medicine n.d.; Foundation for Innovative New Diagnostics n.d.; Drugs for Neglected Diseases initiative (DNDi) 2014b) are now working together not only to control and treat this disease but also to develop novel diagnostic tools (Foundation for Innovative New Diagnostics n.d.; Büscher et al. 2014) and drug treatments (Drugs for Neglected Diseases initiative (DNDi) 2014b). It would be useful to compare NECT to interventions that have recently come or are near entry to the market (e.g., fexinidazole

(Drugs for Neglected Diseases initiative (DNDi) 2014b) and rapid diagnostic tests (Foundation for Innovative New Diagnostics n.d.; Büscher et al. 2014)). Shaw et al (Shaw 1989; Shaw & Cattand 2001) and Lutumba (Lutumba, Makieya, et al. 2007b) both made reference to the benefits of combining interventions for treatment, and it would be wise for stakeholders to move beyond this and develop more complicated and time-sensitive strategies with interventions not only on their own but in combination to identify the most cost-effective pathways towards elimination.

There are still some additional considerations that have not been considered as components in HAT economic evaluations. Although *T. b. gambiense* HAT contributes to 95% of the HAT disease (World Health Organization (WHO) 2013a), separate strategies for *T. b. rhodesiense* could also be considered. Cultural beliefs and attitudes towards HAT will also play a role in the effectiveness of interventions (Leygues & Gouteux 1989), and although education and community sensitization programs for HAT have been evaluated in terms of their societal benefit and impact on changing knowledge and behaviour (Kovacic et al. 2013; Palmer et al. 2014; Waiswa & Kabasa 2010), no studies have shown their benefit in terms of cost-effectiveness. Methods of delivery and integration of health systems should also be further explored in terms of accessibility and availability, as resource constraints and lack of access in remote areas may delay elimination timelines if not considered beforehand (Laveissiere et al. 1998; Simarro et al. 2014).

3.5.1 Potential Use of Cost-Effective Modelling for HAT Control and Elimination

It was quite evident from the literature review that modelling will play a role in the economic evaluation of HAT. Most of the previous economic evaluations conducted were based on models, and modelling is known to assist with forecasting future economic consequences (Drummond et al. 2005). Decision makers would benefit from the use of whole disease modelling of alternative elimination scenarios because it would allow them to consider the implications and incremental benefits of each potential strategy. Previous economic evaluation studies reliant on modelling have addressed how individual interventions reduced transmission but not how these interventions, or combinations of them, could lead to eventual

elimination or interruption of disease transmission. Current modelling techniques for economic evaluation, including those used to evaluate the impact of uncertainty related to model parameters, would also be useful for decision makers in communicating the consequences of choosing non-cost-effective strategies (Claxton 1999). Additionally, modelling the feasibility of interventions through health service delivery is also necessary. For example, the results from an economic evaluation regarding diagnostic algorithms (Lutumba, Meheus, et al. 2007) showed that sometimes even the most cost-effective tools may not be affordable or feasible in some of the locations where HAT occurs (Lutumba, Meheus, et al. 2007).

3.5.2 Potential Use of Economic Evaluation Methodology in HAT Control and Elimination

A few considerations of cost-effective interventions could be gleaned from the few economic evaluations found. This was highlighted in the scenario described by Lutumba et al. (Lutumba, Makieya, et al. 2007b) in which case-detection with treatment was more cost-effective than treatment alone, and an economic evaluation of diagnostic algorithms showed that the addition of tests to CATT could increase cost-effectiveness (Lutumba, Meheus, et al. 2007). Treatment regimens including melarsoprol and eflornithine were considered cost-effective (Politi et al. 1995; Robays et al. 2008) for patients with HAT *T. b. gambiense,* and Politi's analysis in 1995 also demonstrated a good understanding of economic outcomes because dominance was assessed and the importance of the efficiency frontier was illustrated (Politi et al. 1995). Dominance refers to the economic concept that an intervention that costs less and has better outcomes relative to its comparator is considered dominant (Drummond et al. 2005). In regards to budgeting, sensitivity analyses (Shaw 1989; Shaw & Cattand 2001; Lutumba, Robays, Miaka, et al. 2005b) demonstrated that prevalence is related to costs. This will be important to consider because the cost per patient will increase towards the end goal of HAT elimination, but the overall cost per benefit still needs to be ascertained.

The economic evaluations reviewed presented some methodological inconsistencies. For example, there was a lack of clarity in reporting costs and consequences incrementally to a base-case scenario or relative to the next-best intervention. Historically calculations may have

been done this way because of the "generalized cost-effectiveness" method (Hutubessy et al. 2003), but if incremental and net benefits are always compared to "do nothing" instead of to the next-best option available, then the consequences of this methodology could lead to error (Weinstein 1990). Furthermore, when multiple strategies are being considered, dominance needs to be examined. Although four out of seven studies had more than two competing strategies, dominance was only addressed once. Evaluations that ignore dominance could lead to decision errors in which the health utility is not maximised at a societal level (Drummond et al. 2005; Torrance et al. 1972). Cost-effectiveness was also referred to by the authors without making reference to a cost-effectiveness threshold. WHO-CHOICE (WHO n.d.) has defined thresholds previously; however, it is not clear if these thresholds values are acceptable for all global stakeholders because the authors did not always refer to a threshold value to determine cost-effectiveness.

The methodology of CEA with different interventions permits one to compare varying strategies across a disease, but the outcomes need to be unified so that decision makers can assess these comparators with ease and clarity. It is evident from this review that although CEA research may be conducted, the results are hard to interpret without standardization or reporting in a common metric (e.g., cost per DALY). Following existing guidelines for economic evaluation such as the SIGN Guidelines (Scottish Intercollegiate Guidelines Network (SIGN) n.d.) and the more recent Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement (Husereau et al. 2013) or developing guidelines that stakeholders feel acceptable for an elimination strategy would allow for consistency of analyses for HAT and other neglected tropical diseases. Formal economic evaluation guidelines and even a standard reference case have been developed by various public health funders (Stevens & Longson 2013; Canadian Agency for Drugs and Technologies in Health (CADTH) 2006; National Institute for Health and Clinical Excellence (NICE) International 2014), and researchers should consider these standards to further the future of CEA within tropical disease and disease elimination decision-making. In addition, traditional CEA measures two outcomes (cost and effects), but programs for elimination also need to consider time. Health economists will need to consider how to make recommendations to stakeholders for strategy prioritization considering all three elements for elimination.

3.6   Conclusions

This review has demonstrated that previous research highlights the main components that play a role in elimination. Furthermore, cost-effective modelling and economic evaluation have been used and could address future economic concerns regarding elimination. Researchers interested in evaluating economic concerns regarding HAT elimination should think about modelling elimination strategies to assess cost-effectiveness using standardized methodology in order to assist stakeholder and key funders. These analyses would be of use since HAT is currently being prioritized as a NTD to reach elimination by 2020.

4. Human African trypanosomiasis prevention, treatment and control costs: A systematic review

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4.1 Abstract

The control and eventual elimination of human African trypanosomiasis (HAT) requires the expansion of current control and surveillance activities. A systematic review of the published literature on the costs of HAT prevention, treatment, and control, in addition to the economic burden, was conducted. All studies that contained primary or secondary data on costs of prevention, treatment and control were considered, resulting in the inclusion of 42 papers. The geographically focal nature of the disease and a lack of standardization in the cost data limit the usefulness of the available information for making generalizations across diverse settings. More recent information on the costs of treatment and control interventions for HAT is needed to provide accurate information for analyses and planning. The cost information contained herein can be used to inform rational decision making in control and elimination programs, and to assess potential synergies with existing vector-borne disease control programs, but programs would benefit significantly from new cost data collection.

4.2 Introduction

Human African trypanosomiasis (HAT), which is also known as sleeping sickness, is caused by an infection with either of two parasites*: Trypanosoma brucei rhodesiense* or *Trypanosoma brucei gambiense*. Both types are transmitted by different tsetse fly species. They are microscopically indistinguishable, but occur in separate areas of Sub-Saharan Africa (SSA). A total of 37 countries between 14◦N and 20◦S latitude and covering 1.55 million km^2 have reported cases (P P Simarro et al. 2012; Pere P Simarro et al. 2012). *T.b. gambiense* occurs in west and central Africa, while *T.b. rhodesiense* is endemic in eastern and southern Africa. There is no overlap between the endemic areas with Uganda being the only country endemic for both forms, albeit in different areas of the country (Burri 2008). An estimated 70million people (P P Simarro et al. 2012; Pere P Simarro et al. 2012) and about 50 million head of cattle are at risk of trypanosomiasis infection (Fevre, Wissmann, et al. 2008; Kristjanson et al. 1999). The main reservoir host for *T.b. gambiense* is humans, while cattle or wild bovids serve as the main reservoir host for *T.b. rhodesiense*. Animal to human, animal to animal, and human to human transmission all occur with *T.b. rhodesiense*. Transmission varies as a function of vector density and biting behaviour. A total of 7216 HAT cases for both *T.b gambiense* and *T.b rhodesiense* were

reported in 2012 (World Health Organization (WHO) 2013c) and the World Health Organization (WHO) estimates the number of actual infections to be around 20,000 (World Health Organization (WHO) 2013c). In 2014, WHO approved a declaration to target gambiense HAT elimination (Holmes 2014) and one to target rhodesiense HAT (WHO n.d.).A previous review of the available economic evaluations for HAT (Sutherland et al. 2015) demonstrates that although cost-effectiveness has been assessed previously for control of the disease little is known about the cost-effectiveness of strategies targeting elimination. Funding and support for HAT declined from the1970s through the 1990s, contributing to the resurgence of the disease in the late 1990s (Smith et al. 1998); however, since the WHO's roadmap to NTD control and elimination was published in 2012 (WHO 2012), there is a renewed commitment from global stakeholders to achieve HAT elimination by 2020 (Zhang et al. 2010; London Declaration 2013; WHO 2012; Bill & Melinda Gates Foundation n.d.). This requires that the total cost of potential strategies for elimination along with current and emerging technologies (Steinmann et al. 2015) are accurately estimated to ensure that funding is sustained throughout the elimination process. The purpose of this paper is to summarize the available information on costs for HAT prevention, treatment, and control to serve as a reference for future economic evaluations and national budgeting endeavours. The paper begins with a brief description of the treatment, prevention and control strategies for the disease to provide relevant contextual information and some potential interventions for elimination. It then presents a systematic review of the published literature that included primary and secondary data on costs, indirect costs and economic burden related to HAT programs. The paper concludes with a discussion on priority areas of economic data collection for elimination strategy development.

4.2.1 Prevention, treatment, control of HAT

In general, the prevention of HAT includes reducing bites from tsetse flies, early diagnosis and treatment of cases. While individual protection against bites may be useful in some instances, the fly can penetrate light weight clothing and repellants are not common in many endemic areas. Thus community level vector control and screen and treat programs, which involve the detection of human cases for subsequent treatment, are typically employed together. Several techniques are recommended for the control of tsetse fly populations: sequential aerial insecticide spraying to tar-get adult flies during the first spray and tsetse flies

as they emerge from pupal stages in the ground during subsequent sprays; ground spraying to target pupae and resting flies; the use of odor-baited or visual-baited (e.g. black or blue cloth) insecticide treated traps and targets; sterile insect release; and insecticide treatment of cattle(ICT) (Welburn et al. 2009). A total of 13 Sleeping Sickness National Control Programs are developing vector control activities (out of 24 countries reporting HAT cases) (J R Franco et al. 2014), although in some countries institutions other than national control programs are also engaged in vector control activities. Few drugs are available for the treatment of trypanosome infections. Pentamidine and suramin are the main treatments for 1st stage *T.b. gambiense* and *T.b. rhodesiense*, respectively (World Health Organization (WHO) 2013c).The 2nd stage of *T.b. rhodesiense* is treated with the organo- arsenical compound melarsoprol (World Health Organization (WHO) 2013c), which is associated with severe adverse reactions, mainly arsenical encephalopathy, occur-ring in 10% of the patients and frequently fatal (10–70% mortality)(Pépin & Milord 1994; Burri 2008). Nifurtomix–eflornithine combination therapy (NECT) is currently the treatment of choice for stage 2 *T.b. gambiense* and is listed on the WHOs Model List of Essential Medicines (http://apps.who.int/iris/bitstream/10665/93142/1/EML 18 eng.pdf?ua=1). It involves an in-hospital treatment combining intravenous infusions of eflornithine with oral treatments of nifurtimox (World Health Organization (WHO) 2013c). An alternative treatment for *T.b gambiense* is eflornithine monotherapy which must be given in a high dose for an extended duration and is recommended when NECT is unavailable, but is not as well tolerated as NECT (World Health Organization (WHO) 2013c). Melarsoprol is used when patients treated with NECT relapse (World Health Organization (WHO) 2013c). New treatments are currently being developed: fexinidazole is a 10-day oral medication (Tarral 2014) that could potentially be used even if health systems lack the infrastructure or resources to administer NECT. Another potential treatment option is a single-dose oxaborole compound (Tarral 2014), allowing patients to be potentially treated locally and thus avoiding travel to specialized treatment centres that are often far from home. Active and passive case finding are crucial to identify and treat cases to curb transmission.

4.3   Methods

A systematic electronic search of literature published in the English and French language was conducted using PubMed (MED-LINE), EMBASE, and JSTOR databases in 2013. The following search terms were used: trypanosomiasis, African sleeping sickness, and (econ, economics, cost, cost-effectiveness, cost-benefit, economic, internal rate of return, eradication, elimination, health systems, vertical, integration). All results were initially reviewed for relevance based on a review of the title and abstract; the selected publications were then further reviewed for relevance using the full text. The bibliographies of identified references were also searched, as well as the grey literature using Google and Open Content search engines. All papers with primary or secondary data on economic burden, costs of interventions, or health system implications of control and elimination programs were selected for more detailed review. All papers with primary data on costs of any topic related to treatment, prevention, control, indirect costs and economic burden were included. Figure 9 illustrates the incremental results of the search. A total of 960 papers were identified as potentially relevant; a total of 42 papers met the criteria. All cost data were adjusted to USD in the year of the initial study (if the researchers had not already done so) if this information was available using historical exchange rate data from the Oanda currency converter (http://www.oanda.com/currency/converter/). If information on the year of the study was not available, the year of the publication was used as a basis for adjustment. The availability of historical exchange rates varies across countries; as such, studies identified with foreign cost data prior to historical exchange rate availability were first converted to USD using the first year exchange rate data were available. All costs were then adjusted to 2012 USD using the U.S. Gross Domestic Product Deflator series from the U.S. Bureau of Economic Analysis(http://www.bea.gov).

Figure 9. Incremental search results and final studies included
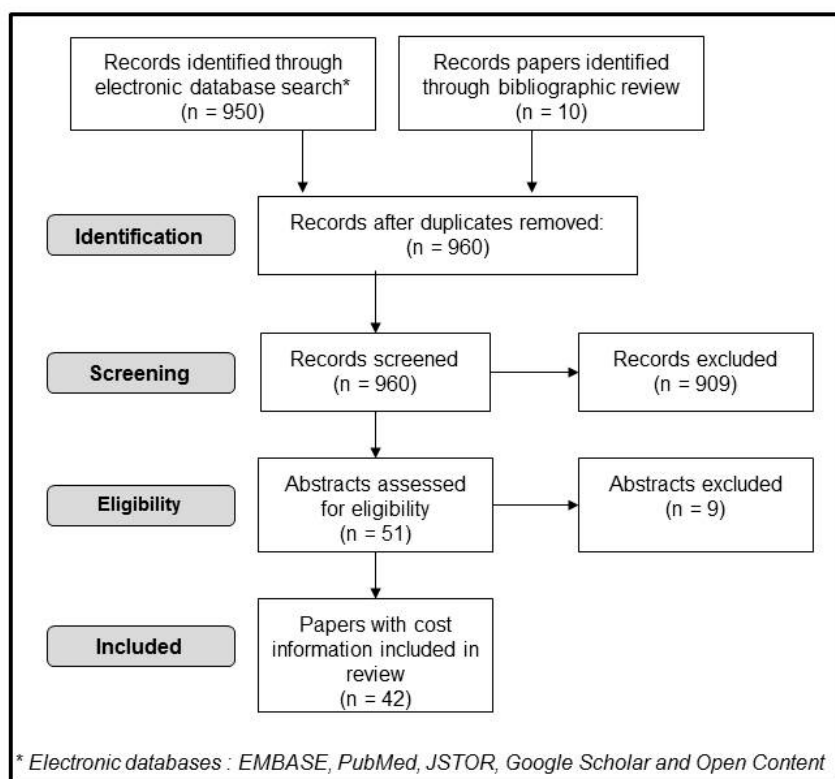
4.4 Results

4.4.1 Prevention: vector control costs

Sequential aerosol techniques

Sequential aerosol techniques (SAT) refer to the spraying of targeted areas with a non-residual insecticide from a fixed wing of an airplane at set intervals. The first spray is designed to kill adults, with subsequent sprays targeted at killing young adult tsetse as they emerge from puparia buried in the ground but before they deposit larvae. Few cost estimates of SAT were identified. Shaw and others used data collected from SAT activities in Botswana to develop a cost model and hypothetical budget for Uganda; SAT in both settings were estimated to cost USD 410.56 per km2, with the bulk of costs incurred due to flying time of the aircraft and type of insecticide used (Shaw et al. 2007; Shaw et al. 2013).While relatively few peer reviewed

published studies of SAT were identified through electronic searches, several secondary sources of historical cost data from African locations were noted in Allsopp and Hursey (Allsopp & Hursey 2004). Botswana and Zambia (1973, 1980) reported USD 231.95 per km² of Endosulfan and pyrethroids; Nigeria (1977) reported USD 890.62 per km²of Endosulfan (Lee 1983); Cote d'Ivoire (1979) reported USD 617.00 per application of Endosulfan (Lee 1983); and Zambia (1968–1978) reported a range of USD 827.38–1,103.19 per km², although the insecticide used was not mentioned (Allsopp & Hursey 2004; Evinson & Kathuria 1984). One study in West Africa also reported the cost of non-SAT from a helicopter to be between USD 1.55–2.75per hectare, assuming 2000–3,500 hectares covered per application, respectively (F. E. Brandl 1988). The historical literature also suggests that the cost per area covered is inversely proportional to the total area sprayed, because fixed and capital costs for SAT do not increase proportionally with the total area covered. Additionally it is noted that elimination of tsetse from targeted areas requires high dosages of insecticide sprayed five times at narrow spray band widths, while SAT or other aerial insecticide application targeted only at control of tsetse could relax all these parameters and perhaps reduce cost per km² by 30–50% (Allsopp & Hursey 2004). Across several ecologically distinct settings, SAT in general is thought to cost between USD 285.81 628.79 per km² (Cattand et al. 2001).

Sterile insect techniques

Sterile insect technique (SIT) refers to mass release of sterile male tsetse flies, which then compete with non-sterile males to mate with females, resulting in adult female flies unable to produce offspring. This method of vector control is generally used in areas where the number of flies is relatively low; as such, it is typically employed following SAT or other vector control strategies that first reduce vector density. Using a 10% discount rate, SIT was estimated to cost USD 840.76 per km² over a ten year period (Shaw et al. 2007). In West Africa, the estimated the cost of adding SIT to an existing intervention was USD 970.00/km², although in areas where substantially fewer sterile males would be required, the cost of SIT could fall to USD 303.12-363.75/km² (Feldman 2004) depending on how many sterile males are released per kilometre and the cost of the flight plan employed (Vale & Torr 2005).

Ground spraying

Ground based spraying of insecticides can be conducted using either pressurized spray pumps or thermal fogging equipment and may be targeted to wide swaths or to specific areas or habitat believed to be tsetse resting areas. Relatively little literature on the costs of ground spraying was identified, including three studies cited which could not be obtained in hard copy for review, but whose results are summarized from secondary sources. A study during the late 1950's in Kenya reported ground spraying costs at USD 367.26 per km^2. In Nigeria, from 1955 to 1969, costs were reported to range between USD 29.74–592.84 per km^2; and, in Zimbabwe during the early 1980's cost ranged between USD260.68–274.05 per km^2 (Allsopp & Hursey 2004). One study reported cost between USD 315.00–1,574.98 per km^2 in 1989, although no additional information was provided (Shaw 1989).

Traps and targets

Traps and targets refer to direct suppression methods that function by trapping flies or by using visual attractants such as large dark coloured cloth (targets), which can be treated with insecticide. These tools can be baited with odour based attractants to attract flies from a distance, or modified in various manners and produced in alternate sizes and shapes. Such vector control tools have been deployed for direct tsetse suppression and as a barrier method to prevent invasion/re-invasion of tsetse into specific geographic areas. Costs first estimated in 1997 have recently been updated, suggesting that targets cost between USD 266.75 and USD 466.81 per km^2 (Shaw 2004; Barrett 1997). The cost of using targets to produce a linear barrier has been estimated to be USD 2425.00 per km to establish and USD 1940 per km per year to maintain (Shaw 2004). The cost of using monopyramidal traps are estimated at USD 31.52 per km^2, assuming 17 cattle per km^2 (Shaw 2004). The cost of targets has also been estimated at USD 305.76 per km^2 in Botswana (McCord et al. 2013; Mullins et al. 1999), and USD 128.03when used for control (Allsopp & Hursey 2004; McCord et al. 2012). Traps used for reclamation purposes have been estimated to cost between USD 1.05 and USD 2.05 per hectare per year over a period of 5–20 years, when fully discounted (F E Brandl 1988). The cost perkm2when traps and targets are deployed for elimination purposes ranges from USD 343.14 and USD 880.27 per km2, depending on the discount rate and the number of traps deployed per km^2 (Shaw et al. 2007). Other factors influencing trap or target cost include the size and type of trap

used, insecticide or odour based attractant used and dosage, as well as the deployment method and density and lifetime of the trap in the field (Shaw et al. 2007; Esterhuizen et al. 2011).

Insecticide treated cattle (ITC)

In West Africa ITC is mainly limited to control of animal trypanosomiasis (nagana), but in East Africa it has also been shown to help control HAT because cattle serve as an important reservoir for *T.b. rhodesiense*. The costs for ITC vary depending on the scope of application (i.e., whole cattle pour-on vs. leg and belly application only), the density of cattle in the area, and the insecticide chosen. The cost of ITC has been estimated to be USD 164.54 per km^2 for the full pour-on treatment when there are 15 cattle per km^2 (Barrett, 1997; Budd, 1999; Shaw, 2004). Updated cost estimates from Uganda suggest that the least expensive application is treatment of cattle legs and belly with α-cypermethrin spray (USD14.55 per km^2 assuming 8 cattle per km^2) followed by full body α -cypermethrin spray (USD 67.90 per km^2) and pour on treatment(USD 218.25 per km^2) (Shaw et al. 2007). Models restricting the application of insecticide to only the legs and bellies of cattle, where most tsetse bites occur, produced similar cost estimates (Torr et al. 2007; Vale & Torr 2005). Table 8 presents additional vector control cost information.

Table 8. Other vector control costs

Authors	Year	Description of cost	Cost
Sequential Aerial Techniques (SAT)			
Shaw	2007	Administration, supervision, and other indirect "non-field" costs	USD 36.37/km² (14% of non-field costs)
		Entomological surveys, monitoring, feasibility studies	USD 223.10/km²
		Aerial spraying- five cycles	USD 3,734.99/km²
		Cost for creating a tsetse-free zone for isolated tsetse populations	USD 720.22/km² & USD 608.67/km²
Sterile Insect Technique (SIT)			
Vale & Torr	2005	Cost of rearing and sterilizing a male	USD 0.11
		Cost of release including accompaniment	USD 1.01/km²/week
		Eradication Estimate	USD 42,033.91/insect population
Shaw	2007	Administration, supervision, and other indirect "non-field" costs	USD 56.99 km² (19% of non-field costs)
		Entomological surveys, monitoring, feasibility studies	USD 235.22/km²
		Capital items, fly rearing, fly release	USD 801.46/km²
		Creating a tsetse-free zone for isolated tsetse populations: + SIT alone	USD 919.07/km²
		Creating a tsetse-free zone for isolated tsetse populations: SIT + 90 day ITC	USD 1,228.26/km²
		Creating a tsetse-free zone for isolated tsetse populations: SIT + 80% SAT	USD 1,228.26/km²
Traps and Targets			
Shaw	1989	Total cost per trap (per person protected in 1st year)	USD 24.50-27.76/ trap (USD 0.82/person)
		Total cost per screen (per person protected in 1st year)	USD 6.53-13.07 per screen (USD 3-6.53/person)
Gouteux	1987	Cost per kit	USD 14.70
Brightwell	1991	Trap/odor bait system per unit	USD 12.96
Okoth	1991	Monoscreen - local	USD 1.86
		Monoscreen - imported materials	USD 1.92
		Biconical - local	USD 7.23
		Biconical - imported	USD 7.47
		Pyramidal Traps - local	USD 3.68

		Pyramidal Traps - imported	USD 3.87
Abila	2007	Pyramidal Traps cost per m	USD 4.50
		Modified pyramidal cost per m	USD 3.86
		Biconical & modified cost per m	USD 4.50
		Monoscreen cost per m	USD 2.89
Shaw	2007	Administration, supervision, and other indirect "non-field" costs	USD 36.37/km² (14% of non-field costs)
		4 Traps/km² (10 teams)	USD 213.40
		4 Traps/km² (15 teams)	USD 277.66
		4 low cost Traps/km² (10 teams)	USD 191.57
		4 low cost traps/km² (15 teams)	USD 244.92
		8 Traps/km² (20 teams)	USD 426.80
		8 Traps/km² (30 teams)	USD 444.32
		10 Traps/km² (25 teams)	USD 534.71
		10 Traps/km² (38 teams)	USD 693.55
		20 Traps/km² (50 teams)	USD 1,068.21
		20 Traps/km² (75 teams)	USD 1,388.31
		Creating a tsetse-free zone for isolated tsetse populations: *G. fuscipes*	USD 1,115.50/km²
		Creating a tsetse-free zone for isolated tsetse populations: Savannah tsetse	USD 602.61/km²
		Creating a tsetse-free zone for isolated tsetse populations: Savannah tsetse	USD 491.06/km²
		Creating a tsetse-free zone for isolated tsetse populations: Savannah tsetse species + local labor	USD 563.81/km²
Shaw	2013	Average field cost per km²	USD 561.25
		Average cost of field studies per km²	USD 188.56
		Average cost of field deployment teams based on 10 teams	USD 15.53
		Cost of trap maintenance per annum per km²	USD 61.67
Insecticide Treated Cattle (ITC)			
Vale & Torr	2005	Insecticide containing 20% α-cypermethrin purchased and shipped	USD 30.46 per liter
		Cost per animal	USD 0.002/animal/day
Torr et al 2007	2007	Savings in insecticide: only treating the belly & legs of cattle	80 %
		Cost per animal whole-body regime	USD 2.22/animal/year

		Estimated cost per animal for restricted regime	USD 0.22/animal/year
Shaw	2007	Administration, supervision, and other indirect "non-field" costs	USD 36.67/km² (14% of non-field costs)
		Entomological surveys, monitoring, feasibility studies	USD 223.10/km²
		α-cypermethrin spray	USD 8.49 per animal per year
		α-cypermethrin spray, restricted application	USD 1.82 per animal per year
		Traditional pour-on (spot-on)	USD 27.28 per animal per year
		Creating a tsetse-free zone for isolated tsetse populations: pour (4/km²)	USD 368.60/km²
		Creating a tsetse-free zone for isolated tsetse populations: spray (4/km²)	USD 293.42/km²
		Creating a tsetse-free zone for isolated tsetse populations: pour-on (8/km²)	USD 477.72/km²
		Creating a tsetse-free zone for isolated tsetse populations: spray (8/km²)	USD 327.37/km²
		Creating a tsetse-free zone for isolated tsetse populations: restricted (8/km² and fewer studies)	USD 162.47/km²
		Creating a tsetse-free zone for isolated tsetse populations: spray	USD 215.82/km²

4.4.2 Costs of treatment and hospitalization for HAT

Treatment costs

For treatment of first stage *T.b. gambiense* infection, pentamidine is the WHO recommended drug (WHO n.d.). In Africa, approximately 1% of patients die due to pentamidine, though why pentamidine mortality occurs is not well explored (Burri 2008). No costing studies on the treatment of first stage HAT due to *T.b. gambiense* with pentamidine were identified in the literature search. Costs of pentamidine treatment were estimated by Lutumba et al.(Lutumba, Meheus, et al. 2007) and Shaw and Cattand (Shaw & Cattand 2001) to be USD 2.05 per vial and USD 25.61 total drug costs, respectively. Suramin, although effective as a treatment for first stage illness is largely avoided for *T.b.gambiense* infection because of the potential for allergic reactions associated with onchocerciasis co-infection (Burri 2008). The recommended treatment for first stage *T.b. rhodesiense* infection is suramin administered parenterally over a period lasting up to 30 days (Burri 2008). Record reviews of hospital data combined with past literature were used to estimate the cost of treatment for early and late stage *T.b. rhodesiense* in Urambo district Tanzania; although this study failed to differentiate costs of late stage versus early stage patients, they reported an estimated cost of USD 130.95 per patient, including admission, hospitalization, diagnostic and patient costs. Of this, the patient paid USD 30.31 out-of-pocket, while the net cost to the health system was estimated to be USD 100.64 (Matemba et al. 2010).The first line second-stage treatment of *T.b gambiense* is NECT and has been estimated to cost USD 1550.74 for a kit containing 4treatments resulting in the cost of USD 387.68 for one treatment.(Pere P Simarro et al. 2012) Alternative treatments such as melarsoprol or eflornithine may be used as well (World Health Organization (WHO) 2013c). Using clinical data from *T.b. gambiense* patients in Caitxo, Angola, a decision tree model was developed to estimate the total cost per patient treated, including costs of supportive care in addition to adverse events such as arsenical encephalopathy; treatment with melarsoprol was USD 708.03, while treatment per patient with elflornithine was approximately USD 997.14 (Robays et al. 2008). Eflornithine was more efficacious in terms of mortality prevention; this translated into improved cost-effectiveness for eflornithine vs. melarsoprol despite the higher cost. Melarsoprol is currently the only drug available for treatment of stage II *T.b rhodesiense* infection. No studies on the costs of treatment for stage II *T.b. rhodesiense* infection were

identified; however, as the treatment regimen is expected to be similar to that used for stage II *T.b. gambiense* infection, the costs from the two studies discussed above may be relevant (Robays et al. 2008; Politi et al. 1995). No specific studies on the costs of encephalopathy as a severe adverse event associated with the administration of melarsoprol were identified; however, the direct costs of management of these complications were estimated in the context of the decision model discussed above to be between USD 23.60–59.00 (Robays et al. 2008).The cost of the new treatment options, fexinidazole has been estimated to be less than USD 50 per patient (Tarral 2014) while no estimates have been confirmed for oxaborole. Table 9 lists additional treatment costs identified.

Table 9. Costs for diagnostics and treatment for HAT

Authors	Year	Description	Cost (USD)
Diagnostics			
Lutumba	2006	Lymph node puncture (LNP)	USD 0.28/per test
		FBE	USD 0.30/per test
		TBF	USD 0.78/per test
		CTC	USD 1.10/per test
		mAECT	USD 4.08/per test
Lutumba	2005	Cost per person screened	USD 2.23
WHO	1998	CATT test screen per person (one time) -	USD 0.73
		CATT test screen per person (one time) -	USD 0.44
		CATT test screen per person (one time) -	USD 0.26
Wastling	2010	LAMP with Quant-IT Pico Green (per 100	USD 371.30
		LAMP with Turbidity (per 100 reactions)	USD 0.001
		LAMP with hydroxynapthol blue (per 100	USD 0.001
		LAMP with Calcein and $MnCl_2$ (per 100	USD 0.001
Treatment			
Lutumba	2003	Pentamidine per vial	USD 2.05
Shaw & Cattand	2001	Pentamidine drug costs per treatment	USD 25.61
Shaw & Cattand	2001	Suramin drug costs per treatment	USD 41.79
Politi	1995	1 treatment of Elfornithine	USD 285.06
Robays	2008	2 treatments of Elfornithine	USD 334.31
Simarro	2012	Average total cost of Elfornithine administration	USD 745.08
Simarro	2012	NECT 4 treatments	USD 1,550.74
Simarro	2012	NECT 1 treatment	USD 387.68
Lutumba	2003	Melarsoprol per vial	USD 7.06
Lutumba	2007	Melarsoprol treatment	USD 144.10
Politi	1995	Melarsoprol treatment per patient	USD 66.99
Robays	2008	Melarsoprol-Prednisolone treatment per	USD 75.52

Hospitalization costs

Treatment of HAT generally requires close supervision due to the risks associated with treatment; treatment of late stage disease invariably requires hospitalization. There is little in the literature about specific costs of hospitalization for treatment due to HAT. When including both early and late stage infections, the mean length of a hospital stay has been estimated at 25 days (Matemba et al. 2010). In this study the total costs to the health service were estimated to be USD 2.42 per patient per night in the hospital and USD 1.21 per initial diagnosis. A second study in Angola estimated the auxiliary staff cost to be USD 7.43 and USD 17.70 per patient per day for treatment with melarsoprol and eflornithine, respectively; the cost of expatriate staff regardless of which drug was used was estimated to be USD 6.73 (Robays et al. 2008). In addition, the cost of nurse time per diem for the administration of melarsoprol and eflornithine is USD 5.90–17.70 and USD 5.90 - 23.60, respectively; the cost of an adverse event associated with the administration of melarsoprol is estimated to be USD 44.61 (Robays et al. 2008).

4.4.3 Control costs for HAT

Case detection and surveillance costs

Of the 60 million people estimated to be at risk for HAT, only 3-4 million are under any form of surveillance (Cattand et al. 2001). A 2001 paper by Shaw and Cattand builds on a series of previous WHO reports and analytical work on control and surveillance of trypanosomiasis to outline five potential surveillance methods and to estimate their costs and cost-effectiveness using as spreadsheet model (Shaw & Cattand 2001). These include active case detection, which is divided into (1) monovalent surveillance teams looking only for sleeping sickness, (2) polyvalent teams looking for other diseases in addition to HAT, and (3) sampling of community workers to collect blood on filter paper. Passive case detection, which is divided into (4) fixed-post surveillance or traditional surveillance in which patients who cannot be diagnosed with another disease are eventually referred to a HAT treatment center for further testing, or (5) sampling of patients at rural health centres to collect blood on filter paper regardless of the reason for the patients original presentation. Road blocks near health centers have also been used as a form of active case detection. Table 10 summarizes costs associated with case detection and surveillance.

Table 10. Cost for case detection/surveillance strategies for *T.b. gambiense* HAT

Authors	Year	Description of cost	Cost (USD)
Shaw	1989	Surveillance at health center	USD 2.20 per person tested (USD 0.62 per population)
		Road blocks near health centers	USD 1.34 per person tested (USD 0.13 per population)
		Multipurpose mobile team	USD 1.25 per person tested (USD 0.16 per population)
		Single-purpose mobile team	USD 1.71 per person tested (USD 0.85per population)
		Cost per serological test	USD 1.58
		Cost per parasitological exam	USD 2.53
Shaw & Cattand	2001	Rural health centers and mobile teams (0.05%)	USD 2,696.15 per patient found
		Rural health centers and mobile teams (1%)	USD 161.77-188.73per patient found
		Rural health centers and mobile teams (1%-5%)	Approximately USD 40.44 per patient found
		Rural health centers and mobile teams (20%)	Approximately USD 13.48
		Rural health centers and mobile teams (50%)	Approximately USD 6.74
		Community health workers (0.05%)	Just under USD 2,700 per patient found
		Community health workers (1%)	Less than USD 134.81 per patient found
		Community health workers (1% -5%)	USD 29.66 per patient found
		Community health workers (20%)	Approximately USD 13.48 per patient found
		Community health workers (50%)	Approximately USD 6.74 per patient found
		Passive or fixed detection posts (0.05%)	USD 67.40 per patient found
		Passive or fixed detection posts (1%)	USD 26.96 per patient found
		Passive or fixed detection posts (1%-5%)	USD 18.87 per patient found
		Passive or fixed detection posts (20%)	Approx. USD 13.48 per patient found
		Passive or fixed detection posts (50%)	Approx. USD 13.48 per patient found
		Initial screening and parasitological exams	USD 3.37-4.72 per person
Lutumba et al	2007	Annual costs for operations of mobile teams	
		Vehicles	USD 7,212.62
		Medical and lab supply (includes CATT reagents)	USD 3,884.26
		Training	USD 945.25
		Personnel	USD 16,212.57
		Medical and lab supply	USD 20,826.57
		Essential drugs (not for HAT)	USD 2,955.42
		Vehicle operation & maintenance	USD 7,318.18

Diagnostic costs

The most frequently used method for diagnosis of *T.b. gambiense* is the card agglutination test for trypanosomiasis (CATT); lumbar puncture is also necessary for determination of cerebrospinal fluid involvement. Controlled lumbar punctures are recommended for late stage

West African trypanosomiasis every 6 months for up to 3years after diagnosis and therapy. In East African trypanosomiasis they should be carried out more frequently (i.e. every 3 months during the first year). The cost of CATT is estimated at USD 2.51 per test (Molyneux et al. 2010). Costs associated with diagnostic tests, in addition to new loop-mediated isothermal amplification (LAMP) methodologies are presented in Table 9. Some of the treatment and surveillance studies noted above also include the costs of diagnosis of the disease in their total cost estimates (Shaw & Cattand 2001).

4.4.4 Economic burden

Human and animal trypanosomiasis has been estimated to cause a large economic burden to families and livestock producers in endemic areas. The diseases are thought to be important contributors to rural underdevelopment (Kristjanson et al. 1999; Budd 1990; Swallow 2000). While this review focuses on the human health and economic effects of HAT, *T.b. rhodiesiense*, which infects both humans and animals, may also be responsible for a significant economic impact through limitations on land use and livestock rearing due to increased mortality and limited weight gain among infected livestock (Jemal et al. 1995; Jemal & Hugh-Jones 1995; Agyemang et al. 2010; Agyemang et al. 1991; Wilson et al. 1986; M Kamuanga et al. 2001).Although the economic impact of trypanosomiasis has been addressed in recent years, much of this research has been focused on animal trypanosomiasis (nagana or other variants). While HAT is related and overlapping geographically with transmission of animal trypanosomiasis, interactions between the two diseases and the associated economic impacts are fairly complex. For instance in areas where similar vectors transmit both human and animal trypanosomes, vector control interventions against tsetse are likely to reduce the burden of both human and animal disease. Similarly in East Africa where the parasite affects both humans and animals, many preventative and treatment interventions could bring benefits through reduced transmission to both humans and animals. However, in West Africa where *T.b. gambiense* infects only humans, trypanosome targeted interventions, such as case detection and treatment, are likely to bring benefits only to humans; interventions targeting the trypanosomiasis burden in livestock may provide benefits to humans only through improved agricultural productivity, and are unrelated to the burden of HAT, except where these interventions might have an effect on vectors that transmit the human parasite. More

complicated to estimate or measure are the indirect costs which could be the result of long-term changes in production systems or land use due to the presence or risk of trypanosomiasis in both animal and human populations (Shaw, 2004). Several studies were identified that attempted to quantify the economic burden of African trypanosomiasis, or estimate returns to investment in the control of animal or human trypanosomiasis (Wilson et al. 1986; Woudyalew Mulatu, Swallow, B.M. et al. 1997; Rowlands et al. 1999; BLANC et al. n.d.; Shaw & Munstermann 1994; F. Brandl 1988; Putt et al. 1980). It is also estimated that across sub-Saharan Africa farmers spends upwards of USD 30 to 40 million a year on trypanocides to protect their livestock (Holmes & Geerts 2004). Approximately 45-50 Million cattle are thought to live in zones of trypanosomiasis risk (Kristjanson et al. 1999; Budd 1990) ; significant increases in numbers of adult cattle and in cattle ownership were observed after the rollout of tsetse control measures in Burkina Faso (M Kamuanga et al. 2001). In the late 1990s it was estimated that improved trypanosomiasis control could return benefits of USD 700 million per year in Africa in terms of meat and milk productivity alone, and USD 1.3 billion if producer and consumer surpluses were considered (Kristjanson et al. 1999); other studies estimated considerably higher increases in annual agricultural out-put of approximately USD 4.5 billion (Budd 1990; Swallow 2000).Using interviews, one study estimated the direct and indirect costs to patients and their families to be a net loss of approximately 25% of the families' annual income per case (Gouteux et al. 1987). Additional results from a study in the DRC reported that the median loss per HAT patient household on average was USD249.94, which is approximately 43% of annual household revenue based on agricultural (Lutumba, Makieya, et al. 2007b), while in Tanzania USD 30.54–61.08 was the estimated total household loss (Reid et al. 2012). Out-of-pocket expenses for patients and their families also contribute to economic burden for HAT. Matemba and colleagues (Matemba et al. 2010) found that on average USD 0.59 per night was required for relatives accompanying the patient to the hospital for treatment. Matemba and colleagues (Matemba et al. 2010) also found a return trip for treatment had a mean cost of USD 7.91, while meals were USD 17.70 per patient treated. Family members that had to pay for accommodation, on average spent USD 29.50 over the course of treatment. Out-of-pocket payments were also required for direct medical expenses including a screening treatment card (USD 0.46 - 0.57) (Robays et al. 2008) or lab tests (USD 0.59) (Matemba et al. 2010). Lastly, non-medical costs for hospital patients have been estimated to

be USD 80.72 in rural Tanzania, including the costs associated with an accompanying person to the hospital/clinic (Matemba et al. 2010).

4.5   Discussion

This paper reviews the literature on the costs associated with the prevention, treatment and control of HAT. This information is important, as donors and control programs increase funding and attention to strategies for eventual elimination. Importantly, this review lends insight into the scarcity of literature on costs that if updated, could improve the efficiency of prevention and control activities. In addition, this information is useful for collating cost information in a common valuation system is also important for stakeholders interested in developing economic evaluations to aid the decision making process. There were few studies focused specifically on the costs related to health systems research principles to the prevention, control, or treatment of HAT. This is likely due to the limited focal nature of the disease, which complicates our general understanding of how HAT control and treatment interaction complement one another. Though large swaths of the African continent are theoretically at risk, in reality there are relatively few cases, which tend to be concentrated in known foci. For this reason, potential health system interactions likely have limited application at a national or regional scale. It is likely that HAT deaths are greatly underreported (Odiit et al. 2004). Underreporting suggests that there is a gap in terms of how HAT control and treatment impact health information systems. Improving disease surveillance and case detection is seen as one of the great challenges to reducing morbidity and mortality due to HAT. While polyvalent screening teams might be more efficient than the use of single purpose HAT active case detection (Shaw & Cattand 2001), the disease remains highly focal and thus investment in the use of integrated surveillance is unlikely to impact health information system quality or coverage outside of the foci of HAT transmission. In addition, since HAT is invariably fatal if left untreated, all medicines required for HAT care must be considered essential for HAT endemic countries, and are listed as essential drugs by the WHO. As a neglected tropical disease, relatively little funding for new drug development is available globally, and the drugs for treatment of the disease are not marketed. These drugs (elfornithine, pentamidine and melarsoprol manufactured by Sanofi-Aventis, and suramin and nitrofurimox manufactured

by BayerSchering Pharma) are made available freely to the WHO by the manufacturers. We were unable to identify any studies examining the impacts of HAT programs on the availability and quality of human resources. Much of the control of HAT is based on vector control programs, which are typically vertically organized and run either in parallel or entirely outside of existing health system infrastructure. They thus pose a risk for diversion of human resources outside of the public health sector in some cases. Alternatively, surveillance strategies could be built on existing health management information systems (HMIS) or community based surveillance platforms potentially improving both, albeit in the limited areas of HAT foci. Another gap relates to a paucity of cost information on how HAT control and treatment impacts service delivery. While the global impact of HAT treatment on service delivery is likely limited, the need for invasive and painful diagnostic measures (i.e. lumbar puncture) and dangerous treatments that require expensive monitoring over long periods of time suggests the potential for a serious burden on the health systems delivery of other services in areas with significant case-loads. Furthermore, there is documented evidence of increases in HAT transmission and risk in areas of conflict, both increasing the burden of disease in areas with major challenges for service delivery but also disproportionately increasing the need for improved service delivery (Berrang-Ford et al. 2011). Lastly, many of the studies identified lack standardization in terms of cost estimates, methods for presenting results, criteria for which costs are presented, and an overall accounting of all inputs as part of a treatment or control program. In addition, many of the vector control costs are quite old. This complicates the differentiation between financial and economic costs, which in turn creates challenges when making comparisons. In the context of increased attention to neglected topical diseases in general, and HAT specifically, recent and standardized information on the costs for prevention, treatment and control interventions is needed.

4.6   Conclusion

The disease and disability resulting from HAT infection is enormous, which could negatively affect overall productivity of an individual and household. The results of this review show that recent and standardized information on the costs for prevention, treatment and control interventions is very scarce. While the literature available on costs provides useful

information, most of the literature is outdated, focused on specific ecological contexts within countries, and is limited in terms of usefulness for developing estimates of the economic burden across Africa. The information presented herein should be updated to improve cost estimation. The collection of relevant and current cost data could play a meaningful role in funding and advocacy for resource mobilization for the control and elimination of HAT.

4.7   Acknowledgments

5. Seeing beyond 2020: An economic evaluation of contemporary and emerging strategies for elimination of *Trypanosoma brucei gambiense*

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5.1   Summary

Background

Trypanosoma brucei (T b) gambiense is targeted to reach elimination as a public health problem by 2020 and full elimination by 2030. To achieve these goals, stakeholders need to consider strategies to accelerate elimination. Hence, we aimed to model several options related to current and emerging methods for case detection, treatment, and vector control across settings to assess cost-effectiveness and the probability of elimination.

Methods

Five intervention strategies were modelled over 30 years for low, moderate, and high transmission settings. Model parameters related to costs, efficacy, and transmission were based on available evidence and parameter estimation. Outcomes included disability-adjusted life-years (DALYs), costs, and long-term prevalence. Sensitivity analyses were done to calculate the uncertainty of the results.

Findings

To reach elimination targets for 2020 across all settings, approaches combining case detection, treatment, and vector control would be most effective. Elimination in high and moderate transmission areas was probable and cost- effective when strategies included vector control and novel methods, with incremental cost-effectiveness ratios (ICERs) ranging from US$400 to $1500 per DALY averted. In low transmission areas, approaches including the newest interventions alone or in combination with tiny targets (vector control) were cost-effective, with ICERs of $200 or $1800 per DALY averted, respectively, but only strategies including vector control were likely to lead to elimination. Results of sensitivity analyses showed that allowing for biennial surveillance, reducing vector control maintenance costs, or variations of active surveillance coverage could also be cost-effective options for elimination, depending on the setting.

Interpretation

Although various strategies might lead to elimination of *T b gambiense*, cost-effective approaches will include adoption of emerging technologies and, in some settings, increased surveillance or implementation of vector control.

Funding

Bill and Melinda Gates Foundation.

5.2   Introduction

Human African trypanosomiasis, or sleeping sickness, is caused by *Trypanosoma brucei (T b)* *gambiense* and *T b rhodesiense*. Approximately 70 million people live in at-risk areas in sub-Saharan Africa.(Jose R Franco et al. 2014)   According to Global Burden of Disease (GBD) data from the Institute for Health Metrics and Evaluation (IHME), human African trypanosomiasis contributes an estimated 560 262 disability-adjusted life-years (DALYs) to the global burden of disease and ranks sixth in reference to the number of deaths among neglected tropical diseases.(GBD 2013 Mortality and Causes of Death Collaborators 2014) *T b gambiense* is primarily maintained in a human–tsetse cycle, whereas *T b rhodesiense* transmission entails a large spectrum of reservoir animals, mainly game. Thus, elimination efforts have primarily targeted *T b gambiense*. In 2011, WHO published a roadmap towards overcoming the impact of ten neglected tropical diseases (NTDs),(WHO 2012) and this commitment was renewed in January, 2012, as the London Declaration on Neglected Tropical Diseases, supported by the collaboration Uniting to Combat NTDs, became a new benchmark for elimination goals. It was then that the goal of control, described as reduction of disease to acceptable levels, was shifted to elimination, which pursues zero incidence in a defined geographical area.(Dowdle 1998)   Human African trypanosomiasis caused by *T b gambiense* was one of the diseases targeted for elimination as a public health problem by 2020, which is defined as less than one case per 10 000 people per year,(WHO 2012; World Health Organization (WHO) 2013a) and complete elimination by 2030. As the year 2020 approaches, stakeholders committed to *T b gambiense* elimination have recognised that current interventions are resource-intensive, costly, and infeasible in remote or sociopolitically unstable areas, hindering foreseen elimination goals.(World Health Organization (WHO) 2013a; Holmes 2014; Yamey et al. n.d.) Moreover, with several emerging novel technologies and approaches for surveillance, diagnosis, treatment, and prevention (vector control) of *T b gambiense*, now is the time to investigate whether new technologies can accelerate elimination and, if so, how to allocate current resources to the right combination of interventions.(Tediosi et al. 2013)

We aimed to analyse the cost-effectiveness of strategies for control and elimination of human African trypanosomiasis caused by *T b gambiense* and to forecast the effect of these approaches

on disease transmission. The outcomes presented here aim to assist decision makers in determining which strategies are most likely to lead to elimination and will show good value for money.

5.3   Methods

5.3.1 Potential strategies for control and elimination

Various scenarios of current interventions and emerging methods have been proposed for control and elimination of human African trypanosomiasis caused by *T b gambiense*.(Steinmann et al. 2015)   We developed a series of strategies using these scenarios over time to ascertain which combination of interventions would be most likely to sustain control or accelerate towards elimination. After preliminary modelling (appendix C.7), we identified five strategies as relevant options for control or elimination of human African trypanosomiasis caused by *T b gambiense*, which are depicted in Figure 10. Strategy A, "control", is one of two strategies recommended by WHO(World Health Organization (WHO) 2013a)   and aims to bring the number of annual cases to an acceptable level. It focuses on screening and treating patients and reflects the current approach practised by most national sleeping sickness control programmes across   sub-Saharan Africa. In strategy A, patients self-report to local health centres (referred to as passive surveillance) and active case- finding is done by teams of health workers who seek out patients living in affected areas (active surveillance). Diagnosis is done in public during in-village screening campaigns and requires blood testing for serological confirmation of antigens in response to the parasite. Blood tests are confirmed using the card-agglutination trypanosomiasis test (CATT). Patients who have a positive CATT undergo parasitological confirmation of the disease. If confirmation is received they are referred for lumbar puncture to check the cerebrospinal fluid, to differentiate if the disease is in the early stages of development (stage 1 disease) or if the parasite has entered the CNS (stage 2 disease). In October, 2016, the approved treatment for human African trypanosomiasis on WHO's essential drug list for stage 1 disease was pentamidine, whereas nifurtimox-eflornithine combination therapy was the first-line, parenteral treatment for patients who have progressed to stage 2.

Strategy B, "control plus tiny targets", is the second strategy recommended by WHO and incorporates vector control to supplement the screen-confirm-stage-treat approach. Tiny targets are small insecticide-impregnated screens measuring 0·5 × 0·25 m that are more cost-effective and easier to deploy than are their larger predecessors (1 × 1 m² target; Box 1).(Shaw et al. 2015; Solano et al. 2013)

The remaining three strategies incorporate innovative approaches in relation to surveillance, diagnosis, and treatment for control of *T b gambiense*, which are expected to arrive between 2016 and 2019. Strategy C, "new technologies 2016", maintains strategy A until 2016, after which time case-detection will be switched to more flexible teams on motorbikes and diagnosis of disease will be done using a first-generation rapid diagnostic test algorithm (panel). Confirmation and staging will be done using the loop-mediated isothermal amplification (LAMP) technique, and treatment for the second stage of disease will switch to ten oral doses of fexinidazole. This process is continued until 2019, when fexinidazole will be considered for treatment of both stage 1 and 2 disease and a second-generation rapid diagnostic test will be available (panel). Strategy D, "new technologies 2016 and 2019", mirrors strategy C until 2019, when a new oxaborole compound, SCYX-7158, will be available for treatment of both stages of disease with one oral dose (Box 1).

Figure 10. Summary of potential strategies for control and elimination of human African trypanosomiasis caused by *T b gambiense*

Feasible scenarios are shown that could lead to elimination of human African trypanosomiasis caused by *Trypanosoma brucei (T b) gambiense*, based on current interventions and those in the pipeline.(Steinmann et al. 2015) Every scenario contains a component of surveillance, diagnostics, and treatment interventions to interrupt transmission of *T b gambiense* for a population at risk. Passive surveillance is combined with annual active surveillance in high-risk areas and with biennial surveillance in moderate-risk areas. In low-risk settings, active surveillance is not done and reliance is solely on passive surveillance. These approaches are based on recommendations for *T b gambiense* control outlined by WHO.(World Health Organization (WHO) 2013a) For all scenarios when the model reaches elimination, it switches to passive surveillance only (the model assumes no reinvasion of cases or flies after elimination is reached). CATT=card-agglutination trypanosomiasis test. NECT=nifurtimox-eflornithine combination therapy. RDT=rapid diagnostic test.

Finally, strategy E, "new technologies 2016 and 2019 plus tiny targets", assesses the effect of combining strategy D with tiny targets. In strategies C, D, and E, we assumed that, by 2019, oral treatment will be appropriate for either stage of disease and, hence, parasitological confirmation for staging will no longer be necessary.

Based on recommendations by WHO, (World Health Organization (WHO) 2013a) we assumed that active screening was done annually in settings with high transmission and

biennially in areas with moderate transmission, and that no active screening component was included in low transmission settings, where detection relies solely on passive surveillance. We also assumed that only passive surveillance would be implemented after elimination, until 2042. We did not model scenarios in which reinvasion of cases (tsetse fly or human) happened after elimination. We based our estimated timelines on every producer's estimate of products in the pipeline for human African trypanosomiasis caused by *T b gambiense* during 2013; hence, the timelines we present here are to be taken as examples because, in reality, technologies could arrive sooner or later on the market than planned. For example, a first-generation rapid diagnostic test arrived on the market in 2013 and has been used in endemic countries across sub-Saharan Africa since 2016. Moreover, evaluation of a second-generation rapid diagnostic test has been completed by the Foundation for Innovative New Diagnostics (FIND) and commercialisation is now expected in December, 2016, rather than 2019 as forecasted.

5.3.2 Health effect and economic modelling

To assess the long-term costs, health effects, and likelihood of the given strategies maintaining control or leading to elimination, we used an ordinary differential equation model of human African trypanosomiasis caused by *T b gambiense* (Figure 11; appendix C.4).(Chris M. Stone & Chitnis 2015) We divided the human population into several compartments: susceptible (ie, uninfected); infected (but not yet infective); asymptomatic (ie, stage 1 disease); removed (ie, stage 2 disease); or being treated. The asymptomatic state is not synonymous with the absence of symptoms in the clinical sense but is stated as such to differentiate the primary stage of the disease from the second, more severe, stage. We also tracked the number of people who died from human African trypanosomiasis over time and assumed that, although human beings have stage 2 disease or are being treated, they are generally recumbent and not present in tsetse habitat. We divided tsetse flies into susceptible, exposed, and infected compartments. We accounted for heterogeneity in exposure to tsetse bites by modelling two human populations, one in which individuals lived and worked in a low transmission setting and the other in which people travelled between a low transmission area and one with greater exposure to tsetse bites. A possible animal reservoir was assumed to not contribute significantly to transmission of human African trypanosomiasis caused by *T b gambiense*.(Jose R Franco et al. 2014) The model structure, transmission parameters for areas with high,

moderate, and low transmission, and investigations of the use of current technologies to reach elimination have been described in detail elsewhere.(Chris M. Stone & Chitnis 2015) We fitted the model using a Bayesian importance resampling procedure to three stable prevalence levels that coincide with slightly above low (0·02%), moderate (0·112%), and high (1·61%) transmission areas, defined previously by WHO. Parameters that varied between the strategies related to specific interventions are provided in appendix C.2.

For every model run, we allowed populations to reach a stable level of transmission over a 300-year period, in the absence of interventions. We then introduced interventions as specified by the different control and elimination strategies. If elimination was achieved in any run, we switched the interventions to post-elimination activities (passive surveillance). We tracked the disease burden attributable to human African trypanosomiasis by assigning a DALY value whenever an individual entered a relevant compartment (stage 1 disease, stage 2 disease, or death from disease). We calculated costs associated with interventions through incorporated cost functions.

Figure 11. Ordinary differential equation model
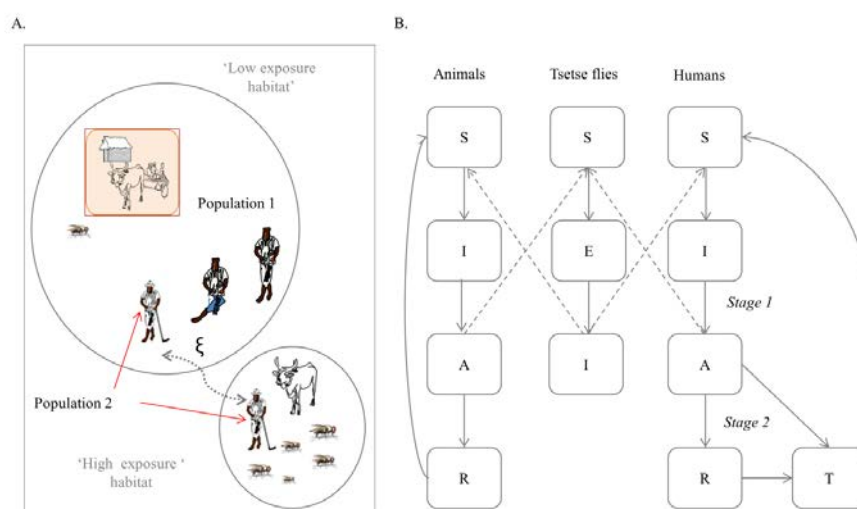
(A)Heterogeneity captured by differing exposure levels of two populations living in the same area. Population 1 lives and works in a low-exposure habitat (eg, village). Population 2 commutes between habitats with low and high exposure, each harbouring tsetse and animal populations (eg, cattle) of varying sizes. (B) Transmission for populations in each habitat includes susceptible, infected, asymptomatic, and removed compartments (health states) for human beings, and susceptible, exposed, and infected compartments for tsetse flies (vectors).

5.3.3 Costing inputs, sources, perspective, and outcomes

Our analysis is from the perspective of a funder of a national sleeping sickness control programme; we modelled the annual prevalence, costs, and health outcomes (defined as DALYs)(World Health Organization (WHO) n.d.) over 30 years, starting in 2013 (appendix C.1). We discounted costs and DALYs at 3% annually(National Institute for Health and Clinical Excellence (NICE) International 2014; World Health Organization (WHO) 2003) and assessed cost-effectiveness by calculating the incremental cost-effectiveness ratio (ICER) of each strategy relative to its next best comparator.

We developed a common unit for every intervention within a specific category then calculated a per diem cost based on cost functions for case detection, diagnostics, drug treatment, and vector control interventions. We took data inputs for direct costs from previous work,(Keating et al. 2015) country reports, expert opinions, and manufacturers, when estimates were not published or available publicly. Cost parameters and formulas for cost functions are available

in appendix C.2. We converted unit prices from countries other than the USA to US$ using purchasing power parity listed in the World Economic Outlook database, (International Monetary Fund (IMF) 2014) and changed costs reported in € to US$ with the average exchange rate lists published on the European Central Bank Statistical Data Warehouse. We then inflated these values to 2013 prices with average consumer price indices.(International Monetary Fund (IMF) 2014)

5.3.4 Uncertainty analysis

We did a probabilistic sensitivity analysis to establish the effect of parameter uncertainty on the cost-effectiveness and probability of elimination. We imputed parameters related to surveillance coverage, cost of interventions, cost of drug treatments, case-detection sensitivity, and cost and efficacy of vector control probabilistically based on latin hypercube sampling, and we ran 500 simulations. A full description of input parameters is provided in the appendix C.2. We plotted probabilistic results as cost-effectiveness acceptability curves for low, moderate, and high trans- mission areas and reported the probability of elimination over the investigated period. We presented results in probabilistic terms and assessed them at two thresholds: elimination as a public health problem (less than one case in 10 000 people) by the year 2020; and full elimination (zero cases) by 2030. We did a one- way sensitivity analysis of discount rates, vector mortality, and coverage levels across all settings. Because we modelled no active surveillance in low transmission settings (based on WHO recommendations) in the base case analysis, we varied surveillance intensity in this setting to ascertain the potential effect on elimination and cost-effectiveness. Previously, another molecule in development for human African trypanosomiasis failed to reach the market in late phase trials.(Wenzler et al. 2009; Harrill et al. 2012) Therefore, we modified and modelled the strategies to assess the potential effect of the oxaborole compound SCYX-7158 experiencing market failure. Furthermore, clinical trials for fexinidazole are underway (NCT02169557); hence, we decided to investigate the potential effect on elimination if fexinidazole arrives on the market earlier than expected (to capture putative positive effects of ongoing trials).

5.3.5 Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

5.4 Results

Table 12 shows results from the base case analysis. In high transmission settings, strategy E—comprising new technologies in 2016 and 2019 plus tiny targets—resulted in an ICER of $386 per DALY averted. In a moderate transmission setting, strategy E was also cost-effective, at an ICER of $1509 per DALY averted. In low transmission areas, strategy D, consisting solely of new technologies in 2016 and 2019, resulted in an ICER of $160 per DALY averted; the next best approach after this one was strategy E, leading to an ICER of $1812 per DALY averted. Strategy A, the current control, was dominated consistently across settings, meaning that this approach costs more money and averted fewer DALYs.

Table 11. Cost-effectiveness analysis of different strategies, by risk transmission area

Strategy	Total Mean Costs (USD) per person	Total Mean DALYs per person	Incremental Cost-effectiveness Ratio (ICER)
High risk transmission area			
D. New technologies in 2016 and 2019	$45	0.22	-
C. New technologies in 2016	$47	0.25	Dominated by Strategy D
E. New technologies in 2016 and 2019 with tiny targets	$61	0.18	$386 per DALY averted*
B. Control with tiny targets	$82	0.20	Dominated by Strategy E
A. Control	$115	0.34	Dominated by Strategy E
Moderate risk transmission area			
D. New technologies in 2016 and 2019	$20	0.03	-
C. New technologies in 2016	$20	0.03	-
E. New technologies in 2016 and 2019 with tiny targets	$38	0.02	$1509 per DALY averted* and ¥
B. Control with tiny targets	$48	0.02	Dominated by Strategy E
A. Control	$55	0.04	Dominated by Strategy E
Low risk transmission area			

C. New technologies in 2016	$2	0.04	-
A. Control	$3	0.04	Dominated by Strategy C
D. New technologies in 2016 and 2019	$3	0.03	$160 per DALY averted¥
E. New technologies in 2016 and 2019 with tiny targets	$42	0.01	$1'812 per DALY averted*
B. Control with tiny targets	$45	0.01	Dominated by Strategy E
DALY = disability adjusted life year.*Relative to strategy D. ¥Relative to strategy C.			

Figure 12 shows the variability surrounding mean costs and DALYs of every strategy and cost-effectiveness acceptability curves. In high transmission areas, at the cost-effectiveness threshold of $400 per DALY averted, strategy E had the highest probability of being cost-effective. In settings of moderate transmission, strategies D and E both had the highest probability of being cost-effective, at a threshold of $1500 per DALY averted. In low transmission settings, strategy D had the highest probability of being cost- effective, at a threshold of $200 per DALY averted, but at a threshold of $1800 per DALY averted, strategy B (in which tiny targets are added to current control efforts) had the highest probability of being cost-effective, competing with strategy E.

The results of the one-way sensitivity analysis are summarised in appendix C.5.2. In high transmission areas, strategy E remained cost-effective over a range of parameter variations; however, the ICER for this approach decreased relative to base case estimates when mortality with tiny targets increased ($244 per DALY averted), when annual costs of vector control maintenance were reduced ($309 per DALY averted), when patients received oral treatments at home exclusively ($318 per DALY averted), or when active surveillance coverage was less than 80% ($49–205 per DALY averted). In areas of moderate transmission, strategy E also remained the most cost-effective option, with reductions in ICER from the base case analysis ranging from $317 to $1447 per DALY averted using the same parameter variations as for high transmission settings. In low transmission settings, strategy D typically remained the most cost-effective option across a range of parameter variations and was near to or lower than $100 per DALY averted either when maximum increases to passive surveillance were attributed to the arrival of fexinidazole on the market ($33 per DALY averted) or when biennial active surveillance campaigns were initiated ($123 per DALY averted).

Figure 13 shows that, in high transmission areas, achieving the London Declaration targets for elimination of *T b gambiense* by 2020 and full elimination in 2030 is probable (appendix C.8). Particularly, strategies with vector control alone or vector control combined with new technologies (strategies B and E, respectively) have a more than 90% chance of reaching elimination in 2020 and 2030, whereas strategies including new technologies alone (strategies C and D) have an 80% chance. If regimens currently in place are maintained (strategy A), reaching elimination by 2020 or 2030 is less likely (roughly 50%). In areas of moderate transmission, all strategies have a more than 80% chance of reaching the London targets by 2020. Full elimination by 2030 would be feasible with strategies that include vector control (96%; strategies B and E), whereas adopting new interventions in the absence of tiny targets (68%; strategies C and D), or current control activities (roughly 50%; strategy A), are less likely to reach full elimination in the next few decades. Similar to moderate transmission settings, in areas of low transmission, achieving elimination as a public health problem is almost certain with strategies that include tiny targets (97–99%; strategies B and E). Adopting new technologies alone without vector control (strategies C and D) are unlikely to reach 2020 targets (24–45%) but are superior to the current control approach (0·05%; strategy A). Full elimination in low transmission areas will require strategies that include vector control (83–86%; strategies B and E), but will lead to delays in achieving elimination goals.

In high and moderate transmission areas, where active surveillance is maintained, a decrease in the effectiveness of vector control (from 5·49% to 1% mortality) would have no effect on elimination targets, however; in low transmission areas, ineffective vector control would render elimination elusive. Further improving the efficacy of targets (increase from 5·49% to 10%) would have relatively little effect compared with the base case analysis for high transmission areas but would guarantee elimination in moderate and low transmission settings with strategies that include vector control. Including active surveillance in addition to passive surveillance in low transmission areas, whether biennial or annual, would ensure that 2020 elimination targets will be achieved, but full elimination by 2030 is still most likely to occur with strategies that include vector control (appendix C.8). By contrast, the strategy currently in place (strategy A) is least likely to achieve full elimination. Varying the coverage of new technologies in low transmission zones had little effect relative to the base case results; however, an increase in treatment coverage with the oxaborole compound SCYX-7158 to

approximately 45% led to a slight increase in the probability of elimination for strategies that included the oxaborole molecule (ie, strategies D and E) in these same areas. As provided in appendix C.8, coverage levels were varied in high and moderate transmission areas and showed overall that strategies with vector control (strategies B and E) would probably lead to elimination even when coverage was as low as 20%. Elimination as a public health problem (less than one in 10 000) was also achievable by 2030 when active screening coverage was equivalent to 60% and if oral tablet interventions become available (strategies C and D).

Figure 12. Probabilistic sensitivity analysis

Cost-and-effect planes (left) and cost-effectiveness acceptability curves (right) for areas of high, moderate, and low transmission. Dots in the cost-and-effect planes represents the outcome of costs per person versus disability-adjusted life years (DALYs) per person for every simulation. Mean results for every strategy are depicted as squares. The cost-effectiveness acceptability curves show the probability that a given strategy is cost-effective based on the net monetary benefit of every strategy at varying cost-effectiveness thresholds.

Figure 13. Probability of reaching targets

Probability of achieving London declaration targets (left) and full elimination (right) in areas of high, moderate, and low transmission. The London Declaration defines elimination, in concordance with the WHO roadmap, as either elimination as a public health problem or less than one case in 10 000 people.(World Health Organization (WHO) 2013a)
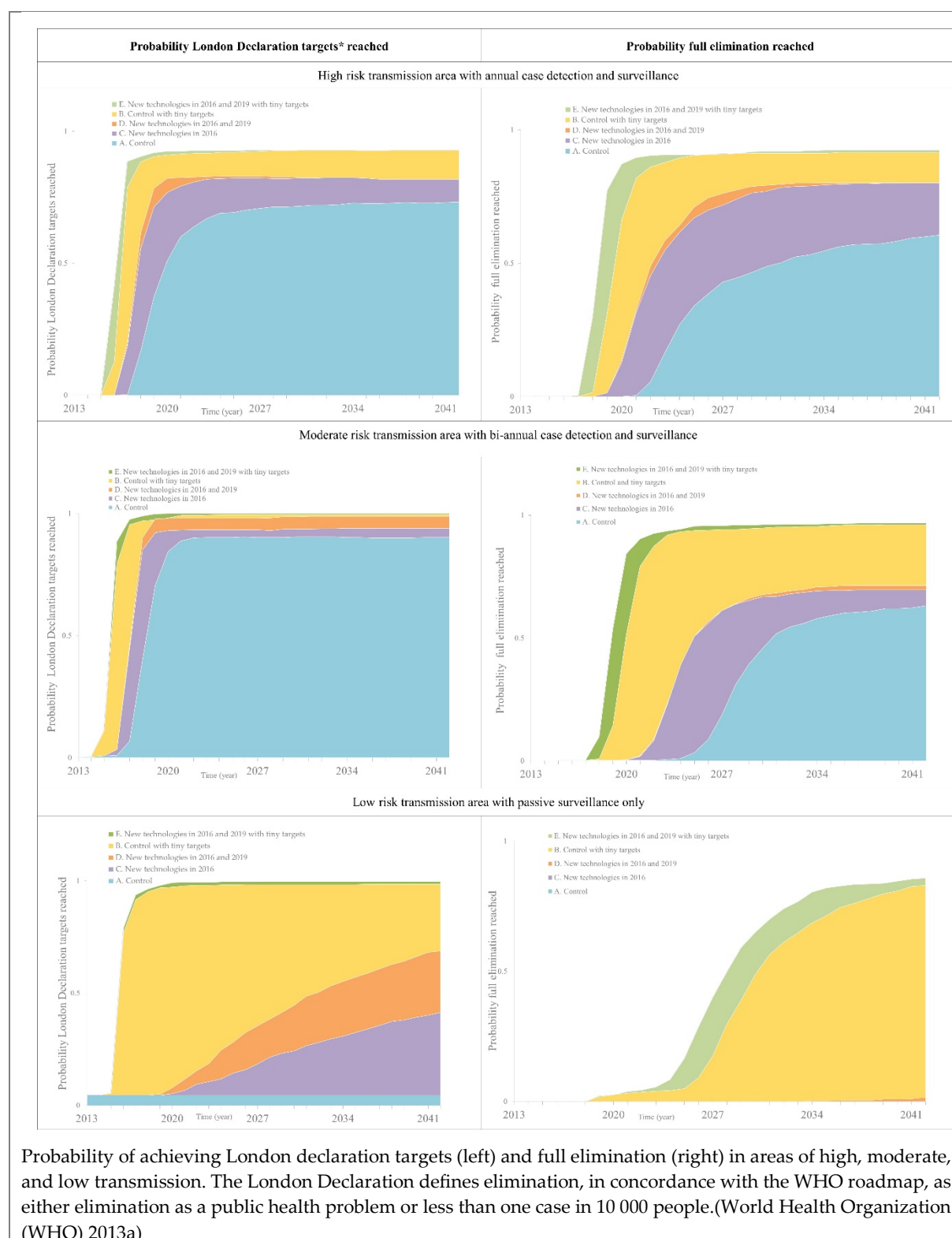
5.5   Discussion

Overall, our simulations show that continuing to screen and treat individuals for human African trypanosomiasis caused by *T b gambiense*, using currently available drugs and diagnostic methods (strategy A), is not cost-effective compared with alternative strategies that are becoming available. Although this approach might lead to control over the next four decades, it is less likely to reach full elimination across transmission settings by 2030. Adopting new interventions as they arrive on the market in combination with use of tiny targets (strategy E) is the most cost-effective approach for control and elimination of   human   African trypanosomiasis   caused   by *T b gambiense*, at a threshold appropriate for low-income and middle-income countries,(The World Bank 2016) while leading to elimination goals in high transmission areas. In moderate transmission zones, continually adopting new technologies as they arrive on the market alone (strategy D) or combined with tiny targets (strategy E) has a probability of being cost-effective near thresholds suitable for middle-income nations, (The World Bank 2016) with both these strategies likely to achieve London Declaration targets; however, only strategy E is likely to reach full elimination. In low transmission areas, a conundrum for decision makers between cost-effectiveness and elimination persists. Adopting new interventions in the absence of vector control measures (strategy D) has the highest probability of being cost-effective at a threshold of $200 per DALY averted(National Institute for Health and Clinical Excellence (NICE) International 2014) but is unlikely to achieve short-term or longterm elimination targets. Adding tiny targets to current control measures (strategy B) or in combination with new technologies (strategy E) is more likely to lead to elimination but is only likely to be cost-effective at thresholds above $1500 per DALY averted.(The World Bank 2016) These results highlight the economic constraints for global investments for elimination in areas with moderate and low transmission across sub-Saharan Africa. More than 98% of current cases of human African trypanosomiasis caused by *T b gambiense* are in low-income countries with a reported gross national income of roughly $400 per person annually, (The World Bank 2016) whereas cost- effectiveness thresholds for global investors are closer to $300 per DALY averted.(National Institute for Health and Clinical Excellence (NICE) International 2014)

It is important to note that these insights are based on a limited number of strategies, for which results reflect the synergies of the input parameters available: in specific situations, current methods could well be adequate. For instance, elimination of human African trypanosomiasis caused by *T b gambiense* in Equatorial Guinea (Luba, Bioko Island) focused on a screen-and-treat campaign mechanism.(Simarro et al. 2006) Furthermore, our results show that addition of active biennial surveillance in low transmission areas would be a cost-effective option, leading to elimination at less than $150 per DALY averted. Findings of field studies and modelling exercises(Tirados et al. 2015; Courtin et al. 2015; Pandey et al. 2015; Rock et al. 2015; de Vries et al. 2016) have confirmed our work, also showing that surveillance and treatment in combination with vector control can interrupt transmission in a shorter time span than can screen-and-treat campaigns alone. However, our analysis also examines the economic outcomes of these strategies, showing that although the cost-effectiveness of adding tiny targets will vary by setting, reducing vector control maintenance costs or varying surveillance coverage rates in combination with tiny targets could improve cost-effectiveness in high transmission areas while still possibly reaching elimination targets.

Many aspects of *T b gambiense* epidemiology remain elusive. For example, in recent years, the implications of asymptomatic carriers,(Bucheton et al. 2011; Welburn et al. 2016) potential animal reservoirs for human African trypanosomiasis caused by *T b gambiense*,(Bucheton et al. 2011) case reports of congenital transmission,(Lindner & Priotto 2010) systematic non-compliance of at-risk subgroups,(Welburn et al. 2016; Bilonda Mpiana et al. 2015) and the part played by vectors(Welburn et al. 2016) have been considered or reconsidered. Changes to available evidence could potentially affect optimum elimination strategies, because our model assumes that animal reservoirs do not contribute significantly to transmission of *T b gambiense*,(Chris M. Stone & Chitnis 2015) that asymptomatic carriers are sufficiently rare in their occurrence,(Checchi et al. 2008) that vectors do transmit *T b gambiense*, and that sexual transmission is infrequent. If additional evidence to the contrary becomes available, new modelling studies should be developed to assess the effect that these novel insights into the epidemiology of human African trypanosomiasis might have on elimination goals.

Our assessments of new technologies have been made in the hope that the foreseen molecules would reach the market. Fexinidazole is now in phase 3 trials, (Drugs for Neglected Diseases initiative (DNDi) 2014a) with new studies for stage 2 human African trypanosomiasis in adults

and children. Findings of interim analyses show that fexinidazole is on track to come to the market, with a high possibility that it might be available for both stages of the disease in 2019.(Jones & Avery 2015) Furthermore, results from the one-way sensitivity analysis also showed that if oxaborole compounds fail to reach the market, fexinidazole in combination with new diagnostic methods would still be a cost-effective alternative likely to lead to elimination. Assuming that the oxaborole compound SCYX-7158 becomes available in the near future as a safe, single-dose oral compound, elimination becomes highly feasible and could possibly be considered as a tool for mass drug administration to prevent resurgence in areas that have high exposure rates to infected vectors. There is also uncertainty surrounding the sensitivity and specificity of current and emerging diagnostic tests, because diagnostic accuracy is related directly to prevalence and to identification by the diagnostic test of antibodies that the hosts produce. These difficulties within diagnostic methods have also hindered research and development of a rapid diagnostic test that can differentiate stages of disease, meaning that lumbar puncture might be necessary for a longer time than once hoped.

Economic concerns still remain because emerging technologies might also need a change in the health-care structure of affected countries. Although our analysis assesses the cost-effectiveness of strategies, financing for a chosen strategy and assessing the budget effect that an elimination campaign would have on the current allotted fiscal space of decision makers are both necessary for global commitments towards elimination to be sustained.(Lee et al. 2015) The indirect costs to society also need to be assessed because new treatments and reduced transmission will decrease potential out-of-pocket expenditures for affected families(Matemba et al. 2010) and reduce productivity losses for affected individuals. Moreover, reduction of tsetse flies could potentially afford communities access to land currently not inhabited, cultivated, or used for alternative economic gains.(Radio New Zealand 2015)

Progress reports for elimination show that cases of human African trypanosomiasis caused by *T b gambiense* are on the decline,(Simarro et al. 2015) which is a tribute to the concerted efforts of the global community working towards elimination of this disease. However, there are still populations living in at-risk areas not under surveillance. This situation calls for continued and swift diffusion of upcoming interventions in the pipeline across sub-Saharan Africa to

further accelerate the decline of human African trypanosomiasis transmission and to ensure that 2020 targets and beyond become a reality.

5.6 Research in context

5.6.1 Evidence before this study

Efforts to estimate the financial resources needed for elimination of neglected tropical diseases have been done by WHO and collaborations including Uniting to Combat NTDs and The Lancet Commission on Investing in Health. Furthermore, in 2015 and 2016, several researchers used modelling exercises to investigate the probability of elimination with available interventions in west and central Africa. However, a full economic assessment of multiple interventions for human African trypanosomiasis caused by *Trypanosoma brucei (T b) gambiense* has not been attempted. Building on our previous work, in which we identified and considered new technologies as potential strategies to achieve elimination, we used a modelling approach to assess the cost-effectiveness and the probability of elimination of five intervention strategies.

5.6.2 Added value of this analysis

Our analysis shows that potential additional gains can be made with emerging technologies, particularly short or single-dose oral treatments (fexinidazole and the oxaborole compound SCX-7158), rapid diagnostic tests, and tiny targets. We also addressed trade-offs between costs, health effects and elimination timelines that need to be considered by decision makers. Additionally, our results indicate that strategic planning for elimination campaigns should be tailored to suit the transmission situation of a given focus.

5.6.3 Implications of all the available evidence

The results presented in this report harmonise the contributions of current and emerging technologies that will be available to eliminate sleeping sickness and show good value for money, hence providing national sleeping sickness control programmes and global funders

with evidence-based solutions for the elimination of human African trypanosomiasis caused by *T b gambiense*.

5.7 Contributors

CSS, CMS, and FT designed the study. PS and MT contributed to development of the strategies modelled. CSS did the analysis and wrote the first draft of the report. All authors contributed to data interpretation and writing of the final report.

5.8 Declaration of interest

MT is chair of the board of the Drugs for Neglected Diseases initiative, which is leading development of fexinidazole and the oxaborole compound SCYX-7158 considered in our analysis. CSS, CMS, PS,and FT declare no competing interests.

5.9 Acknowledgements

6. The elimination of "sleeping sickness" – who will pay the price?: Assessing the financial burden for the elimination of human African trypanosomiasis *Trypanosoma brucei gambiense* in sub-Saharan Africa

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6.1   Abstract

Introduction

Global health expenditures continue to increase albeit the fact that countries are being encouraged to achieve universal health coverage and alleviate poverty. It is hoped that elimination of HAT Tbg would assist in this goal, but the financial estimates to do this are still unknown. The objectives of this analysis are: 1) forecast the financial cost of control and elimination programs; and 2) estimate the risk to poverty by assessing financial protection.

Methods

In order to estimate the total costs to health services and individuals: 1) potential elimination programs were defined; 2) the direct costs of programs was calculated; and 3) the per case out-of-pocket payments (OOPs) by program and financial risk protection indicators were estimated. Unit prices were converted in International Dollars (USD) using purchasing power parity (PPP) listed in the World Economic Outlook (WEO) database and discounted at 3%. The mean results for both direct program costs and OOPs were calculated from a number of simulations and reported along with 95% confidence intervals. Total costs per program were reported for the financial program costs. Proportions of catastrophic health expenditures at 10% and 25% were reported for OOPs related to HAT Tbg.

Results

Across sub-Saharan Africa, HAT Tbg maintaining "Control" would lead to a decline in cases and cost $630M. In comparison, the cost of "Elimination" programs ranged from $410.9M to $1.2 billion. Maintaining "Control" would continue to cause impoverishment and CHEs to households; while all Elimination programs would lead to significant reductions.

Conclusion

Overall, the total costs of either control or elimination programs would be near 1 billion USD in the next decade. However, only elimination programs will reduce the number of cases and improve financial risk protection for households who are impacted by HAT Tbg.

6.2   Introduction

Over the last two decades, global health expenditures per capita have more than doubled, and continue to increase annually.(World Health Organization n.d.) In several countries a large proportion of the health expenditure is funded by patients out-of-pocket with severe consequences to the financial protection of the household. Yet policy makers at all levels rarely take into account the potential consequences on a household's economic conditions of health policies and interventions. In the last decade, Neglected Tropical Diseases (NTDs) increasingly attracted the interested of global health investors and there is currently a global mandate to achieve disease elimination of several NTDs.(Uniting to Combat Neglected Tropical Diseases 2016) In order to comprehensively define the economic implications for NTDs in particular for key stakeholders, an "Eradication" or "Elimination Investment Case" (EIC) framework was developed.(Tediosi et al. 2013) At present, this approach has been applied to *onchocerciasis* ("river blindness") and *lymphatic filariasis* (LF, "elephantiasis"), highlighting that investments in elimination or eradication of such diseases leads to economic, health and ethical benefits.(Kastner et al. 2015; Stone et al. 2016; Kastner et al. 2017; Kastner et al. 2016; Kim, Remme, et al. 2015; Kim, Sicuri, et al. 2015; Kim et al. 2017; Bailey et al. 2015) Thus far, cost-effective elimination strategies for human African trypanosomiasis (HAT) *Trypanosoma brucei gambiense (T.b.g)*. have been identified,(Sutherland et al. 2017) and the ethical considerations of each strategy have been formally assessed (*Merritt et al, under review*); however, a summary of the direct costs required for national control and elimination programs have yet to be ascertained.

HAT *T.b.g*, also known as "sleeping sickness" is caused by the presence of the *T.b.g* parasite that is transmitted by the bite of a tsetse fly from human reservoirs.(World Health Organization (WHO) 2013c) Symptoms of the disease in the early stages include fever, headaches, joint pain and itching(Uniting to Combat NTDs n.d.); however, second stage symptoms resemble more severe neurological elements as the parasite eventually crosses the blood brain barrier. Affected individuals in the second stage may display behaviours similar to that of a patient with mental illness leading to societal rejection, disdain and isolation even after the disease has been treated and the patient recovers.(Mpanya et al. 2012) Although several Sub-Saharan nations have tsetse inhabited areas with the potential of transmitting *T.b. gambiense*, currently there are 14 endemic countries that still reported having HAT cases in

2013(Jose R Franco et al. 2014) with Ghana having one case in 2014 after several years of being case free(Jose R Franco et al. 2014). Patients infected with the disease are traditionally required to undergo a chemotherapy regimen at treatment centres that are accessible but often far from the villages of those most affected(Simarro et al. 2014). This requires that patients be away from their families and absent from occupational obligations post-treatment resulting in financial consequences.(Mpanya et al. 2012)

Recent technological developments in treatments, surveillance approaches and diagnostics, along with feasible vector control interventions(Steinmann et al. 2015) have shown that there are new alternatives to treat, identify and prevent g-HAT that are cost-effective; decision makers now need to calculate the annual and future budget implications to sustain elimination strategies, as well as consider the economic implications for the communities involved. This manuscript aims to estimate the potential costs associated with these two perspectives. First, to forecast the financial impact that elimination programs may need to sustain elimination targets; and secondly, to alert decision makers of the implications for financial risk protection to households affected by HAT *T.b.g.*

6.3   Methods

In order to estimate the direct costs and societal impacts, the current control and potential elimination programs at a national level needed to be defined. Then for each program it is necessary to estimate the associated direct costs, households out of pocket payments and financial risk protection indicators. Our approach considers both the perspective of the national and global funders who are interested in the direct costs associated with HAT *T.b.g.* elimination (including health services and vector control), and a societal perspective (i.e. out-of-pocket payments).

Unit prices were converted in International Dollars (USD) using purchasing power parity (PPP) listed in the World Economic Outlook (WEO) database.(International Monetary Fund (IMF) 2014) Prices that were reported in Euros were converted to International Dollars (USD) using the average exchange rates lists on the European Central Bank Statistical Data Warehouse. Once all costs were converted to USD, they were then inflated to 2013 dollars using average consumer price indices (CPI).(European Central Bank (Eurosystem) 2014) The mean results for both direct program costs and societal costs are calculated along with 95% CI are to express the uncertainty surrounding the mean simulations. Costs are discounted at 3% and reported from 2013 and 2020 for a time horizon of 7 years.

6.3.1 Defining control and potential elimination programs

A priority setting exercise was undertaken in order to define optimal programs according to cost-effectiveness and probability of elimination based on a previously published economic evaluation for strategies including new technologies in the elimination of *T.b. gambiense*(Sutherland et al. 2017). The micro-strategies originated from potential approaches to elimination foreseen with technologies that became available in 2013 and onwards described in Steinmann et al(Steinmann et al. 2015). The strategies ranged from adding new tiny targets for vector control in addition to the current 'screen and treat' programs readily available, to including a new oral tablet (i.e. oxaboroles) treatment that may eliminate the need for prolonged in-hospital treatment. These were further combined in Sutherland et al in 2017(Sutherland et al. 2017) and modelled as five mutually exclusive macro-strategies for elimination to determine cost-effective options per foci. These macro-strategies for elimination were further categorized into national elimination programs, based on several cost-effectiveness thresholds. Each program is briefly described hereafter and within Table 12, with additional details for the approach provided in appendix D.1.

Table 12. Description of programs for control and elimination

Program	Cost-effectiveness threshold	Scenario description
Control	Reference	In alignment with the EIC methodology (Tediosi et al) we use the "control" as the counterfactual scenario which equates to recommendations by the WHO during 2013: total reliance on passive reporting in low transmission areas, biennial screening in moderate areas and annual screening in high transmission with the screening and treatment of CATT and pentamidine (stage1)/NECT(stage 2) respectively.
Elimination I	~$200 per DALY averted	Involves the recommended surveillance levels for HAT by "Control", but switching to new technologies for treatment (fexinidazole and oxaboroles) and diagnostics (rapid diagnostics with motorbike screening campaigns) in all areas but *not* implementing vector control strategies including tiny targets
Elimination II	~$700 per DALY averted	Involves biennial surveillance in low risk transmission areas, currently recommended surveillance levels for HAT by WHO in moderate and high risk areas, switching to new technologies for treatment and diagnostics in all areas, *and* implementing vector control strategies including tiny targets but **only** in high risk transmission areas
Elimination III	~$1500 per DALY averted	Involves biennial surveillance in low risk transmission areas, currently recommended surveillance levels for HAT by WHO in moderate and high risk areas, switching to

		new technologies for treatment and diagnostics in all areas, **_and_** implementing vector control strategies including tiny targets but **only** in moderate **and** high risk transmission areas

WHO surveillance recommendations: Low risk (no active surveillance, passive surveillance only), Moderate – biennial surveillance, High – annual surveillance

Control

In alignment with the EIC methodology (Tediosi et al) we use "Control" as the counterfactual scenario which equates to recommendations by the WHO: total reliance on passive reporting in low transmission areas, biennial screening in moderate areas and annual screening in high transmission foci. The screening and treatment include the card agglutination trypanosomiasis test (CATT) and nifurtomix-eflornithine combination therapy (NECT) respectively.

Elimination I (~$200 per DALY averted)

Involves currently recommended surveillance levels as defined by the WHO, switching to new technologies for treatment (fexinidazole and oxaboroles) and diagnostics (rapid diagnostics with motorbike screening campaigns) in all foci.

Elimination II (~$700 per DALY averted)

Involves scaling up to biennial surveillance in low risk transmission areas, currently recommended surveillance levels for HAT by WHO in moderate and high risk areas, switching to new technologies for treatment and diagnostics in all area. The deployment of tiny targets is included, but only in high risk foci.

Elimination III(~$1500 per DALY averted)

Involves scaling up to biennial surveillance in low risk transmission areas, maintaining the current recommendations of surveillance by WHO in moderate (biennial) and high risk areas (annual), switching to new technologies for treatment and diagnostics in all areas, and implementing vector control strategies including tiny targets for both moderate and high risk transmission areas.

6.3.2 Forecasting the financial impact of national programs

A "bottom-up approach" was used to estimate the total sub-Saharan costs. A dynamical transmission model developed by Stone & Chitnis(Christopher M. Stone & Chitnis 2015) has been used previously to estimate long-term costs and effects for control and elimination

programs for HTA *T.b.g.*(Sutherland et al. 2017). In our analysis, we exported the mean annual cost per person per foci (from 500 simulations) for each program related to: surveillance (including diagnostics), treatment and vector control. These per person estimates were then projected to estimate country related costs based at risk populations areas(World Health Organization (WHO) 2013c) and finally aggregated for a cumulative cost across the 14 endemic sub-Saharan countries.

The calculated estimations and methods for the programs and interventions are provided in appendix D.2.

6.3.3 Forecasting financial protection (financial protection analysis (FPA))

The estimated number of cases in 2013 was 6228 by Franco et al (Franco et al. 2017) and, based on the four aforementioned programs for control and elimination, the number of expected cases was projected across sub-Saharan Africa, again using the model published by Stone and Chitnis (Chris M. Stone & Chitnis 2015). It was assumed that each estimated *Tbg* case would represent a single household. A financial risk protection analysis (FPA) model was built in MS Excel 2010, and used Bayesian sampling techniques to estimate the household related data required for the FPA including: income, non-medical (NM) expenses (i.e. food) and medical expenses (i.e. out-of-pocket payments (OOP)). The median income of $1360 per annum was derived from the average gross national income (GNI) of the 13 endemic nations impacted by *Tbg*, with costs of non-medical expenses (i.e. food) derived from the literature(Depetris Chauvin et al. 2012; Lutumba, Makieya, et al. 2007b). The total medical expenses paid by households was estimated from HAT studies found in the literature as well.(Matemba et al. 2010) For the purpose of this analysis, we assumed that 100% of affected households would actually incur medical expenses. The catastrophic health expenditures (CHE) was calculated using the proportion of medical expenses related to g-HAT from a household's total income less a basic need (i.e. food). The proportions of CHE at 10% and 25% were reported as defined by the SDG 3.8.2.(Bank 2017). A normal distribution was applied to case estimates, while gamma distributions were applied to all cost inputs. A poverty line (PL) of $1.9 per diem (Bank 2017) was used to account for the economic status of sub-Saharan Africa. It was assumed that the PL would be the same in 2013 and 2020. For each program, 10,000 simulations were run to generate the mean reported outcomes and 95% Confidence Intervals. To understand the potential impact of poverty with current and future technologies, the program "Control 2013" was used as a comparative baseline measure to the alternative options. The outcomes of the FPA are reported across Sub-Saharan African and by country income levels. A full summary of the input parameters and calculations for the financial protection analysis are provided in appendix D.3.

6.4 Results

6.4.1 Financial impact

From 2013 until 2020, the cumulative costs of control and elimination programs of the strategies modelled are listed in Table 13. The results demonstrate that maintaining the current control programs, without taking new technologies into consideration, will incur a total cost of $630.6 million (95% CI: $630.3 to $631.0 million) across sub-Saharan Africa. Introducing the first option of elimination programs ("Elimination I") leads to a total financial impact of $410.9 million (95% CI: $410.7 to $411.1 million); while scaling up to "Elimination II" would yield a total of $988.0 million (95% CI: $987.6 to $988.5 million). Implementing "Elimination III" across all sub-Saharan nations would lead to a total cost of $1248.1 million (95% CI: $1247.2 to $1249.1 million). The net impact of each program in comparison to "Control" demonstrates that "Elimination I" would actually lead to cost-savings ($-219.8, 95%CI: $-219.6 to $-219.9), while net increases of $357.4 million (95% CI: $357.3 to $357.5 million) and $617.5 million (95% CI: $616.9 to $618.1 million) for "Elimination II" and "Elimination III" respectively. When evaluating the proportion of health expenses further, 80-87% of financial burden for g-HAT will allotted to low-income countries. In particular, the Democratic Republic of the Congo (DRC), which has the second lowest income of all the endemic Sub-Saharan countries, but the highest number of cases, would be responsible for 65-72% depending on the program selected. Furthermore, if affordability was being assessed using GNI levels, CAR, DRC, Guinea and Uganda would only be able to afford "Elimination II".

For each program, as depicted in Figure 14, the majority of costs for control and elimination programs are driven by screening and diagnostic costs that come passive, and/or active screening campaigns (68-90% of total costs). The ongoing costs for control also begin to plateau after several years; while, although the costs of elimination programs are high in the earlier years, they decline to 3-5% of the overall costs in later years. The additional cost of vector control to "Elimination II" and "Elimination III" programs contribute to 9% and 29% of the total program costs respectively.

Figure 14. Financial impact: categorical costs across time horizon
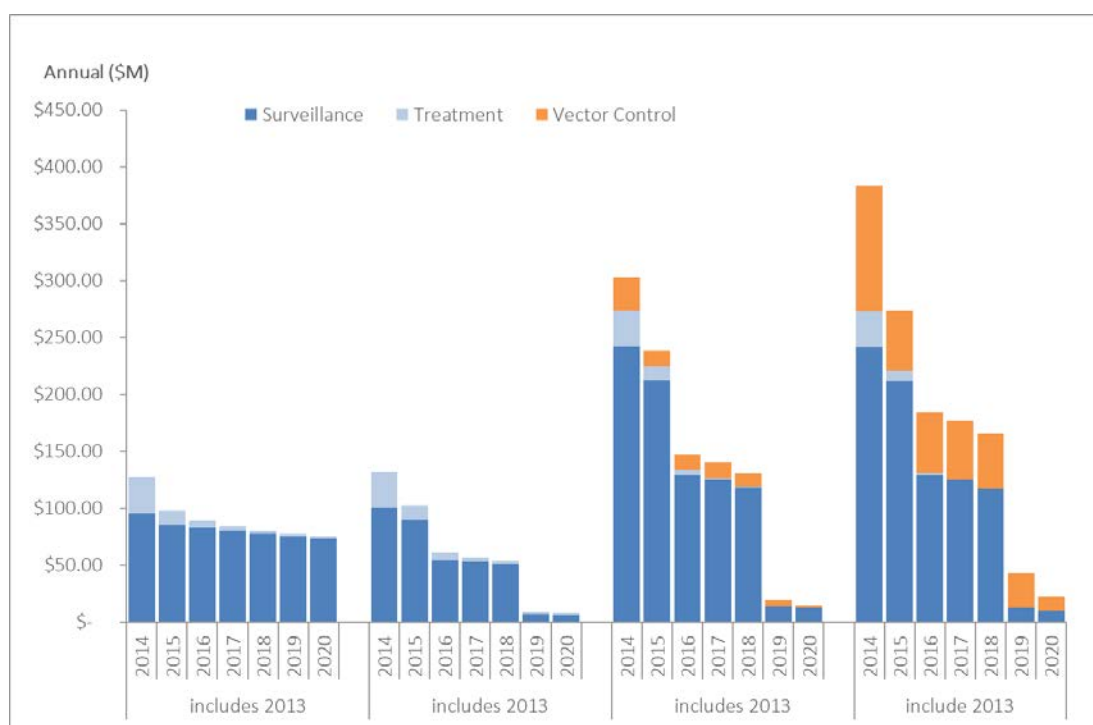
NOTE: 2014 includes costs from 2013 and 2014 combined

Table 13. Financial impact: *T.b. gambiense* programs across across sub-Saharan Africa

	GNI	Cases in 2013¥	Population at risk* (x10³)	Control 2020 (Counterfactual) Total (USD million)	Control 2020 (Counterfactual) 95%CI (USD million)	Elimination I 2020 ~$200 per DALY averted Total (USD million)	Elimination I 2020 ~$200 per DALY averted 95%CI (USD million)	Elimination II 2020 ~$700 per DALY averted Total (USD million)	Elimination II 2020 ~$700 per DALY averted 95%CI (USD million)	Elimination III 2020 ~$1500 per DALY averted Total (USD million)	Elimination III 2020 ~$1500 per DALY averted 95%CI (USD million)
Total, gross-financial impact*		6228	54958	630.6	630.3- 631.0	410.9	410.7-411.1	988.0	987.6-988.5	1248.1	1247.2-1249.1
Total, net-financial impact**		NA	NA	NA	NA	-219.8	-219.6 to -219.9	357.4	357.3-357.5	617.5	616.9-618.1
Country, income-level, gross-financial impact											
LIC	1006 or less	6105	45,325	546.97	546.65 to 547.28	353.05	352.77 to 333.14	765.29	764.92 to 765.34	998.19	997.45 to 999.04
LMIC	1006-3995	33	4369	23.15	23.13 to 23.15	17.82	17.80 to 17.82	116.90	116.84 to 116.96	129.68	129.61 to 129.76
UMIC¶	3996-12235	89	5209	60.51	60.47 to 60.55	40.08	40.06 to 40.11	105.85	105.79 to 105.91	120.21	120.12 to 120.28
Country, gross-financial impact											
CAR	330	59	555	6.94	6.93-6.94	4.5	4.45-4.46	8.66	8.66-8.66	11.00	10.99-11.01
DRC	380	5647	38032	454.66	454.40-454.93	293.6	293.4-293.7	641.1	640.8-641.4	835.1	834.5-835.8
Guinea	470	78	1279	4.44	4.44-4.44	3.89	3.88-3.89	36.50	36.48-36.52	39.87	39.85-39.89
Uganda	680	9	2116	38.13	38.11-38.15	23.81	23.80-23.82	35.42	35.40-35.43	58.39	58.33-58.46
South Sudan	940	117	2397	34.00	33.98-34.02	21.59	21.58-21.61	33.08	33.06-33.11	41.25	41.21-41.29
Chad	980	195	946	8.80	8.79-8.80	5.66	5.66-5.66	10.53	10.52-10.53	12.58	12.57-12.59
Cameroon	1360	6	221	0.67	0.67-0.67	0.7	0.70-0.70	8.83	8.82-8.83	9.33	9.33-9.34
Cote d'Ivoire	1460	7	1300	5.46	5.46-5.46	4.52	4.51-4.52	37.43	37.41-37.45	41.58	41.55-41.60
Congo, Rep.	2710	20	2380	17.01	17.00-17.02	11.53	11.52-11.53	40.16	40.14-40.18	48.29	48.26-48.32
Nigeria	2970	0	468	0.01	0.01-0.01	1.07	1.07-1.07	30.48	30.47-30.50	30.48	30.47-30.50
Angola	4850	69	4300	59.15	59.11-59.19	38.85	38.83-38.88	93.86	93.81-93.91	107.36	107.28-107.43
Gabon	9450	17	878	0.61	0.61-0.61	0.76	0.76-0.76	11.30	11.29-11-31	11.68	11.67-11.68
Equatorial Guinea	12640	3	31	0.75	0.75-0.75	0.47	0.47-0.47	0.69	0.69-0.69	1.17	1.17-1.17

95% CI = 95% confidence interval

CAR = Central African Republic; DRC = Democratic Republic of Congo

*Includes countries with endemic cases from 2000-2014 reported in Franco et al 2017; **net budget impact compared to "Control" ¥Includes 13 endemic countries in 2013, excluding Ghana ¶Includes UMIC and one HIC (Equatorial Guinea GNI greater than $12236)

Blue indicates countries that can afford the Elimination program using GNI as cost-effectiveness threshold

6.4.2 Financial risk protection

The impacts related to poverty from the Financial Protection Analysis (FPA) are summarized in Table 14. Overall, in comparison to the baseline year 2013, maintaining a similar "Control" program till 2020 will not have an impact on poverty indices. Although the number of cases may decline, the OOP health expenditures related to attending treatment centres for HAT treatment will still lead to impoverishment (22%), immiserization (31%) and catastrophic health expenditures at both 10% and 25% of HAT *Tbg* households. Scaling up to "Elimination" programs, that result in medications that can be taken at home or within local villages, will reduce the risk of impoverishment in the future by at least 5% for all elimination programs in comparison to control and reduce the number of households facing CHEs to less than 1%. In addition, "Elimination" programs lead to the fewest number of forecasted cases in the future. This dual impact is on households with *Tbg* is shown in the series of Pen's Parade diagrams illustrated in Figure 15. Unfortunately, the reduction of OOP will not end poverty completely.

Additional FPAs were evaluated by country income levels (Refer to Table 3). The results again demonstrate that the LICs would be the most vulnerable to OOPs with 99.4% and 98.8% of the households experiencing CHEs at 10% and 25% respectively if "Control" is maintained. Pursuing "Elimination" programs would reduce the number of households facing CHEs to less than 1%. In addition, although at first glance it appears that there are fewer being impoverished, this is only due to the fact that the majority of the households in LICs will risk immiserization (approximately 85%) for healthcare payments related to HAT, even with "Elimination" programs. LMICs have smaller populations of households at risk of impoverishment (0.49%) and CHEs when "Control" is in place, however; introducing "Elimination" programs could also eliminate CHEs and reduce the proportion of those impoverished to less than 0.5%. There is not foreseen risk to poverty related to HAT *Tbg* expenditures in UMICs.

Table 14. Financial protection: poverty impact of out-of-pocket payments related to *T.b. gambiense* households in sub-Saharan Africa for control and elimination programs

	Control 2013 (95% CI)	Control 2020 (95% CI)	Elimination I 2020 (95% CI)	Elimination II 2020 (95% CI)	Elimination III 2020 (95% CI)
Total cases (N)	6228*	2319	1768	76	56
Sub-Saharan Africa					
Impoverishing	22.00% (21.96 to 22.03)	21.99% (21.94 to 22.04)	15.64% (15.59 to 15.70)	15.48% (15.23 to 15.73)	15.41% (15.11 to 15.71)
Immiserizing	30.95% (30.92 to 30.99)	30.95% (30.90 to 31.01)	30.95% (30.88 to 31.01)	30.94% (30.61 to 31.27)	30.91% (30.53 to 31.30)
Catastrophic (CHE) at 10%	62.89% (62.85 to 62.93)	62.93% (62.87 to 62.99)	1.25% (1.23 to 1.27)	1.27% (1.20 to 1.35)	1.23% (1.14 to 1.32)
Difference in % from Control 2013	NA	0.04% (0.02 to 0.06)	-61.64% (-61.61 to -61.66)	-61.61% (-61.65 to -61.,57)	-61.66% (-61.71 to -61.61)
Catastrophic (CHE) at 25%	30.95%	30.96% (30.90 to 31.02)	0.49% (0.48 to 0.50)	0.51% (0.46 to 0.56)	0.48% (0.43 to 0.54)
Difference in % from Control 2013	NA	0.01% (-0.01 to 0.04)	-30.46% (-30.44 to -30.49)	-30.44% (-30-45 to -30.42)	-30.46% (-30.49 to -30.44)
LIC					
Impoverishing	15.04% (15.02 to 15.07)	15.09% (15.04 to 15.13)	14.98% (14.92 to 15.03)	15.23% (14.98 to 15.48)	15.02% (14.71 to 15.32)
Immiserizing	84.95% (84.93 to 84.98)	84.91% (84.87 to 84.96)	84.95% (84.89 to 85.00)	84.72% (84.47 to 84.97)	84.89% (84.59 to 85.19)
Catastrophic (CHE) at 10%	99.44% (99.43 to 99.45)	99.43% (99.42 to 99.44)	0.86% (0.84 to 0.87)	0.82% (0.76 to 0.88)	0.91% (0.83 to 0.99)
Difference in % from Control 2013	NA	-0.01% (-0.02 to -0.01)	-98.58% (-98.59 to -98.57)	-98.62% (-98.68 to -98.56)	-98.53% (-98.61 to -98.46)
Catastrophic (CHE) at 25%	98.80% (98.80 to 98.81)	98.78% (98.77 to 98.80)	0.24% (0.24 to 0.25)	0.25% (0.21 to 0.28)	0.26% (0.22 to 0.30)
Difference in % from Control 2013	NA	-0.02% (-0.03 to -0.01)	-98.56% (-98.56 to -98.56)	-98.56% (-98.58 to -98.53)	-98.54% (-98.58 to -98.51)
LMIC					
Impoverishing	0.49% (0.49 to 0.50)	0.49% (0.48 to 0.50)	0.08% (0.08 zo 0.09)	0.09% (0.07 to 0.11)	0.10% (0.07 to 0.13)
Immiserizing	0.00% (NA)	0.00% (NA)	0.00% (NA)	0.00% (NA)	0.00% (NA)
Catastrophic (CHE) at 10%	29.07% (29.04 to 29.11)	29.07% (29.01 to 29.13)	0.00% (NA)	0.00% (NA)	0.00% (NA)
Difference in % from Control 2013	NA	0.00% (-0.03 to 0.02)	-29.07% (-29.04 to -29.11)	-29.07% (-29.04 to -29.11)	-29.07% (-29.04 to -29.11)
Catastrophic (CHE) at 25%	0.03% (0.03 to 0.03)	0.03% (0.03 to 0.03)	0.00% (NA)	0.00% (NA)	0.00% (NA)
Difference in % from Control 2013	NA	0.00% (NA)	-0.03% (-0.03% to -0.03%)	-0.03% (-0.03% to -0.03%)	-0.03% (-0.03% to -0.03%)
UMIC*					
Impoverishing	0.00% (NA)	0.00% (NA)	0.00% (NA)	0.00% (NA)	0.00% (NA)
Immiserizing	0.00% (NA)	0.00% (NA)	0.00% (NA)	0.00% (NA)	0.00% (NA)
Catastrophic (CHE) at 10%	0.00% (NA)	0.00% (NA)	0.00% (NA)	0.00% (NA)	0.00% (NA)
Difference in % from Control 2013	NA	0.00% (NA)	0.00% (NA)	0.00% (NA)	0.00% (NA)
Catastrophic (CHE) at 25%	0.00% (NA)	0.00% (NA)	0.00% (NA)	0.00% (NA)	0.00% (NA)
Difference in % from Control 2013	NA	0.00% (NA)	0.00% (NA)	0.00% (NA)	0.00% (NA)

95% CI = Confidence interval; *Estimated cases from WHO (Franco 2017),***Includes UMIC and one HIC (Equatorial Guinea GNI greater than $12236)

Figure 15. Pen's Parade: Estimated out-of-pocket payments impact on poverty related to *T.b. gambiense* **households in sub-Saharan Africa for control 2013 vs. elimination II**

A. Control 2013
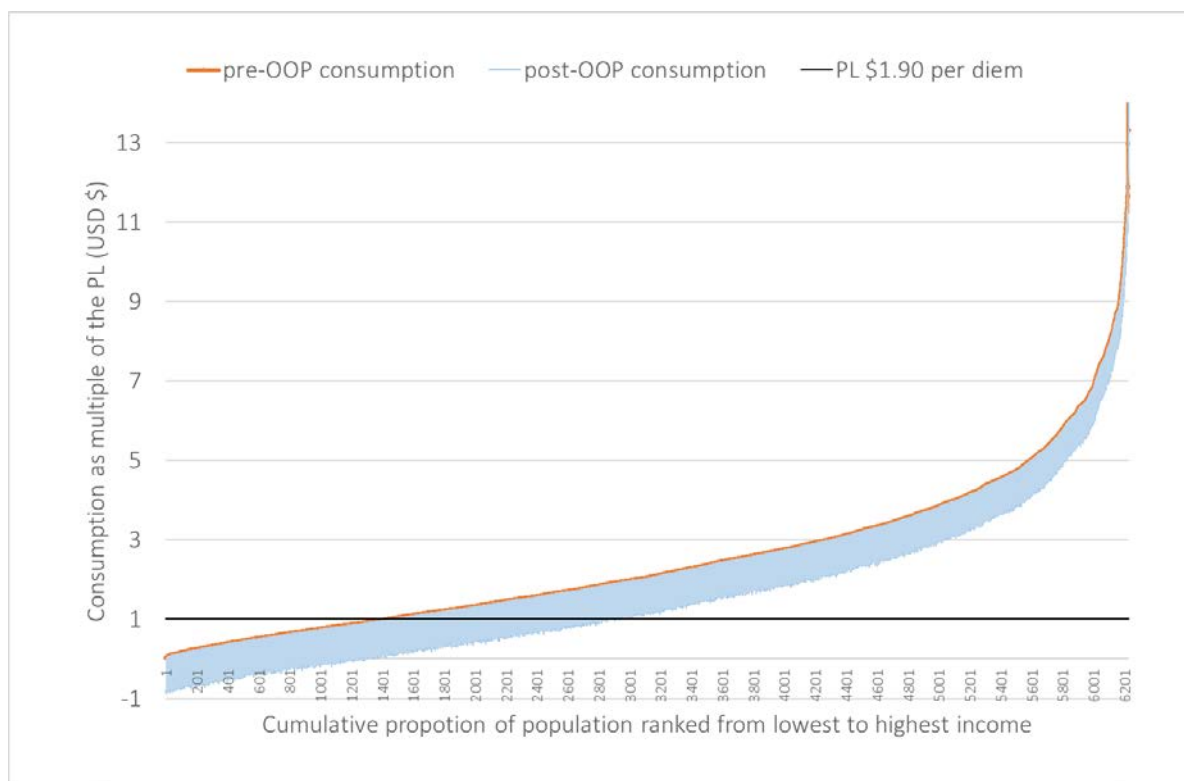
B. Elimination II 2020
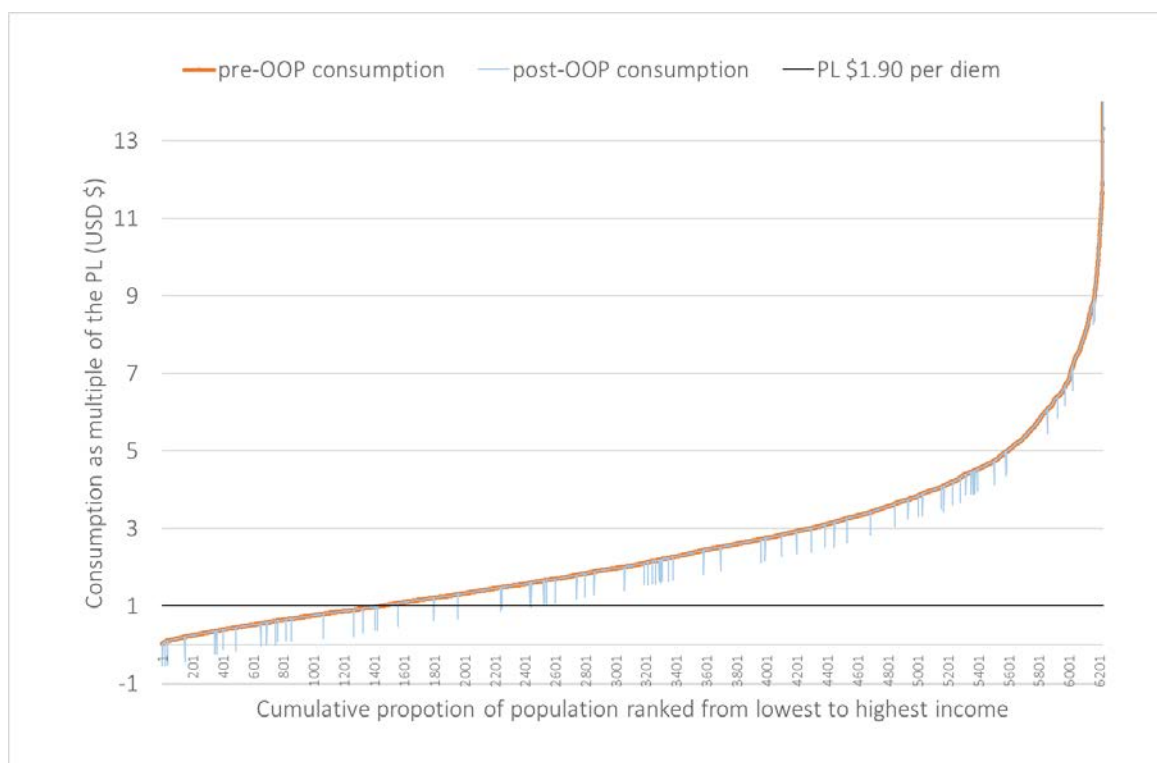
6.5   Discussion

Across sub-Saharan Africa, HAT *T.b.g* control and elimination programs will require substantial funding and fiscal commitments over the coming years. A "Control" program will lead to fewer cases in the coming years, but will still cost millions of dollars to funders and have no impact on reducing poverty indices encouraged by the SDGs. Moving to "Elimination" is an attractive option, but the "Elimination" programs that are most likely to reduce cases and alleviate OOPs related to g-HAT (Elimination II and III), may not be affordable for LICs that share the greatest burden of at risk communities. In addition, the majority of the funding required will need to be allocated to in-country surveillance and diagnostics annually, while traditionally for HAT only the treatments have been donated with the majority of the healthcare costs reliant on NGOs and national fragile health systems. The results of this two-part analysis demonstrate that there is a need to prepare substantial funds for elimination, not only for treatments and preventative measures (i.e. vector control) but also to the health system itself. In addition, it has demonstrated that the strive to elimination programs may alleviate the risk of impoverishment and thus contributing to reach the millennial SDGs.

The results of the analysis on financial burden highlight that "Elimination" programs are the most favourable in achieving global goals. However decision makers will have to assess the fiscal space needed especially since availability of new HAT treatments has historically had delays in Pan-African uptake in the market. There may be a risk that LICs will opt for the less aggressive "Elimination I" program, but this will not lead to a slower decline in cases compared to other elimination options. In addition, to offset the costs of surveillance that are the main driver of these programs, community health workers or volunteers may be enlisted. Again, as in other NTD efforts, this may alleviate direct costs, but increase productivity losses.

In addition, HAT is not the only NTD ear-marked for elimination/eradication, and so it must be kept in mind that there is still competition for funds even though the costs of elimination are known. For instance, the pan-African costs for HAT elimination programs range from $0.42 to $1.24 billion, while world-wide onchocerciasis elimination and eradication programs are estimated to be $2.7 and $2.9 billion respectively.(Kim, Sicuri, et al. 2015) This may pose a challenge for HAT during prioritization of funding for NTDs. For example, the onchocerciasis, eradication and elimination programs are cost-saving relative to control and the per person at risk cost for HAT remains a relatively costly disease with programs ranging from $3 to $10 per person annually compared to ranges of $1.5 to $3.9 per treatment in the onchocerciasis programs.(Kim, Sicuri, et al. 2015)

HAT *T.b. gambiense* is already known to be a disease that affects the poor, but the current results demonstrate that households who are already near the poverty line, may fall: closer to the poverty line, under the poverty line (impoverished), or further into poverty (immiserized). However, the results of this analysis are still conservative as, recent evidence shows that there are often additional expenses prior to the diagnosis of HAT as households seek alternative care and guidance when family members are ill.(Bukachi et al. 2017)

Although the methodology for poverty assessments using household surveys has been established(Wagstaff & van Doorslaer 2003; Bank 2017), the approach of modelling prospectively to understand its impact on future technologies within an EIC is novel. The financial protection analysis presented here is also not based on household surveys and instead relies on secondary data and modelling to generate conclusions. However, it demonstrates the potential to provide useful information in a decision making context for new technologies. In addition, the FPA does not address other societal costs, such as the loss of wages (productivity), which has been done within an eradication investment case for other neglected diseases.(Stone et al. 2016; Kim, Sicuri, et al. 2015) These costs have recently been estimated along with other NTDs for elimination by Lenk et al., and demonstrate that the contribution of productivity loss to HAT is substantial.(Lenk et al. 2018)

There are also economic gains from elimination that could also be considered in future EIC assessments. For instance, tsetse free areas may increase access to water areas without menace and even land use opportunities. The concept of addressing both positive and negative impacts to households related to disease expenditures has been recently explored in observance of non-communicable diseases in Bangladesh.(Mirelman et al. 2016) Future research in prospective FPA could also consider if and how additional income to at risk communities (i.e. households) that may result from elimination and assist to offset OOPs related to CHEs.

Although this analysis highlights the financial benefits of elimination programs, at the time of its inception, it was assumed that novel interventions would arrive on the market as scheduled. The efficacy of fexinidazole has been proven(Mesu et al. 2018) however it still awaits European Medicines Agency (EMA) approval as of January 2018.(Drugs for Neglected Diseases initiative (DNDi) 2018) In addition, previous modelling (Sutherland et al. 2017) estimated the arrival of a novel one time treatment in 2018, while it is currently estimated to be submitted to the EMA in 2021.(Drugs for Neglected Diseases initiative (DNDi) 2017) In the interim, subsidies for travel, accommodation and food could be considered, with the current national sleeping sickness control programs (NSCCPs) to encourage patients to attend without

the risk of poverty. Nonetheless, the scale up of elimination activities has begun in at least nine endemic nations,(FIND n.d.) and there is a continual decline in cases supporting the model's estimations.

Our results also assume 80% coverage is maintained for surveillance programs. This coverage rate shows promise in leading to elimination but may be hard to achieve. Although 30% of the high transmission areas are covered, on average, only 2% of the continent is experiencing some level of screening. Furthermore, there are several countries that have not established formal NSCCPs (i.e. Gambia, Guinea-Bissau, Liberia), although foci risk areas exist.(Franco et al. 2017) Hence, the scale up to elimination will be substantial not only in funds, but for logistics on the ground. Scaling up coverage may reveal also that there are more cases than once thought, and adjustments to the elimination forecast and budgets will have to be made. Long-term commitments to funding post-elimination will be needed as the possibility of asymptomatic cases and unknown reservoirs comes to the forefront. An example of this was seen recently in Ghana where one case was found in 2013 after 12 years of no cases being reported.

6.5.1 Conclusion

Overall, the results demonstrate that an "Elimination II" foci–specific program that deploys: targets in high risk areas with annual surveillance, adopts new technologies in all areas and implements biannual surveillance in moderate and low transmission zones, remains within cost-effectiveness thresholds for some low and lower-middle income countries. It could also achieve elimination goals for 2020 in the long-run and leads to financial protection for families impacted by HAT *T.b.g.* Global stakeholders and funders should ensure that low income countries whose national sleeping sickness control programs (NSCCPs) are unable to secure funds nationally for elimination should be supported as they share a disproportionate load of the disease burden. The elimination of HAT *T.b.g.* does have a high cost, but with continued efforts and support from global stakeholders, it is hoped that those already at risk of poverty will not be the ones to pay it.

6.6 Summary Box

Key questions

- **What is already known about this topic?**
  - Financing sustainable health systems will increase Universal Health Coverage, but there are unknown costs related to elimination of neglected tropical diseases; in particular, human African trypanosomiasis (HAT) *Trypanosoma brucei gambiense (T.b.g).*
  - The cost-effectiveness of strategies to eliminate HAT *T.b.g.* have proven to differ by foci, but how this translates into financial burden for funders and the communities at risk is still unknown
- **What are the new findings?**
  - National programs that combine varying cost-effective strategies and lead to elimination of HAT *T.b.g.* will generate millions of dollars in the coming decade, and improve financial protection (alleviate poverty) by reducing the occurrence of catastrophic health expenditures (CHE) to households impacted by HAT *T.b.g.*
  - Several countries burdened with sleeping sickness may not be able to afford optimal elimination programs based on GNI levels
- **How might this influence practice**
  - Decision makers interested in elimination should not only consider the costs associated with the national programs but also the societal perspective when prioritizing programs for the elimination of neglected tropical diseases (NTDs)
  - Health financing and funding support will need to be addressed if elimination goals and sustainable development goals (SDGs) to eliminate

6.7 Keywords

economics, sleeping sickness, NTDs, elimination, finance, budget, out-of-pocket, catastrophic health expenditures, financial protection, *Trypanosoma brucei gambiense, priority setting, health policy decision making*

6.8   Funding

6.9   Authors contributions

CSS completed the analyses, write-up and intellectual development of this manuscript. FT contributed to the conceptual, intellectual development, writing and supervision of the manuscript.

6.10   Acknowledgements

7. Its' time to lose control: Systems thinking and an analytic approach in the context of health systems integration for the elimination of *'sleeping sickness'*

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Working paper

7.1 Abstract

Human African trypanosomiasis (HAT), commonly known as 'sleeping sickness', is a neglected tropical disease (NTD) targeted for elimination as a public health problem by 2020. Knowing the restrictions that the diagnostic and treatment paradigm for HAT incurs, researchers for HAT *Trypanosoma brucei (T.b.) gambiense* encourage the adoption of new technologies that will improve chances of health systems integration. Taking on a health systems thinking approach, this paper aims to describe the systemic implications of moving from a non-integrated to integrated system, and to use health systems modelling to determine if future integrated approaches could be of use if analysed prior to implementation.

In the context of sleeping sickness integration will change the health systems approach that active surveillance programs have relied on for the last century. The main changes in the system scaling up to elimination will be seen at the local and national level as the burden of care will shift to countries. Using modelling to simulate potential impacts could provide useful information to decision makers at the national level in order for them to anticipate which changes need to be addressed to maximize capacity and ensure that HAT patients do not go untreated.

Integration is an inevitable change that will be needed for sustainable healthcare systems and autonomy for nations that have had healthcare services managed by external collaborators for decades. Careful planning and consideration using systems thinking and modelling analyses can help decision makers to contain the processes as they occur and it is hoped that these approaches can be used as an option for decision makers to evaluate anticipated changes more critically.

7.2   Backgrounds

Human African trypanosomiasis (HAT) is a neglected tropical disease (NTD) targeted for elimination as a public health problem by 2020. Detection of HAT currently relies on vertical surveillance programs where patients are identified in their villages or self-report to specialized health centres, and endure delays in waiting for confirmation of laboratory tests and further results in large out-of-pocket payments (*Sutherland 2016, under development*). Knowing the restrictions that the diagnostic and treatment paradigm for HAT incurs, researchers for gambiense HAT encourage the adoption of new technologies that will improve chances of health systems integration.(Palmer 2012; Burri 2014; Lejon et al. 2013) Hence as new technologies become available, understanding the benefits and/or consequences of integration need to be fully evaluated. An EIC investment case for HAT (Tediosi et al. 2013) has used dynamical modelling to evaluate the long-term cost-effectiveness of new technologies,(Sutherland et al. 2017) forecast elimination, assess financial and socio-economic implications;[8] and assess ethical impacts; however, the operational feasibility of such interventions has not yet been ascertained. Health system modelling has proven to be useful in several examples in literature in evaluating the operational constraints that changes in health service delivery may have on the systems components (Pilgrim et al. 2008; Pilgrim & Chilcott 2007; Lim et al. 2013). In addition, modellers working on NTDs also recognize the need to not only address the transmission components of infectious disease, but how campaigns and strategies towards elimination will operate on the field.(Hollingsworth et al. 2015) It is proposed that the integration of programs into the local health centres could be modelled to forecast outcomes related to capacity, service delivery and even perhaps estimate the level of diagnostic proficiency that would be necessary from the health care workforce to sustain elimination efforts.

Taking on a holistic thinking method commonly practised in health systems thinking, the first part of this paper aims to discuss the components of the current system, along with potential integration that is predicted to be feasible with new interventions arriving on the market. Secondly, using a simple health systems model, scenarios will be simulated at the local setting

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to determine if future integrated approaches can be tested for benefits or losses prior to implementation.

7.3   Overview of health systems in the context of Gambiense HAT

7.3.1 'Control' of Gambiense HAT in relation to the health system

To understand the current context of HAT within the health system, and overview of the present day events were compartmentalized into the six building blocks of the health system.(de Savigny & Adam 2009) This evidence was gathered from the most recent global stakeholders meeting for Gambiense HAT elimination(Sutherland 2016) and are summarized in Figure 24 with further details listed in Appendix H.

In regards to the delivery of medical services for HAT, the approach is quite vertical and with the main governance coming from MSF and the NSSCP with little involvement from the local health care system although this is expanding(Sutherland 2016; Simarro et al. 2014). As outlined in the supply chain delivery diagram in Figure 25A., the current approach to providing treatment relies on the countries requesting medication through the WHO and then in turn the treatment supplies being provided to the countries after WHO has procured the items from the pharmaceutical companies. Although WHO recommends NECT as the appropriate stage two treatments for HAT, the nifurotomix tablets are used off – label and hence the countries take the sole responsibility for this. This requires some regulatory clearance from the WHO and countries prior to the drug being available. It should be noted that melarsoprol is still used in some areas when there are treatment failures. The supplies are then delivered to MSF who distributes them to the appropriate programs. Aside from the NSCCP that operate under the MoH in affected nations, the operations of HAT control are quite peripheral to the system. MSF operates their own sleeping sickness supply chain, surveillance and treatment centres – and although they work in collaboration with the national programs, they are essentially an independent entity.

A large number of actors in regards to financing come from the western hemisphere and the same trend are true for those involved research and development activities (R&D). However, countries with national programs within their Ministry of Health (MoH) receive country funding; and vector control initiatives are also often funding at the country level within

agriculture departments.(Sutherland 2016) Those participating in the countries are the people and community themselves along with the local health care workforce, national sleeping sickness control programs (NSCCP) and treatment centres in the at risk nations. The current paradigm does not incorporate community health workers to treat disease as the medical expertise to diagnose and treat HAT is quite specialized.

Figure 16. Health systems building blocks for Gambiense HAT services

MSF= Médecins sans Frontières, NSSCP = National sleeping sickness control program, LHC = local health centre, CHW = community health worker, CATT = card agglutination trypanosomiasis test, IoTM = Institute of Tropical Medicine - University of Antwerp , RDT = rapid diagnostic test, WHO = world health organization, NTD = neglected tropical disease, PATTEC = Pan African Tsetse Eradication Campaign , FAO=Food and Agriculture organization of the United Nations , PAAT = Programme Against African trypanosomiasis, NGO = non-governmental organization, R&D = research and development, TAG = task advisory group

Orange indicates potential changes in health system due to integration

7.3.2 Systems thinking for emerging technologies related to Gambiense HAT services

Refer to Figure 16, the script highlighted in orange identifies the potential additions to the health system resulting from integration. Governance, finance and information appears to

remain the same current funders are still committed to support HAT programs(Sutherland 2016), but realizing the substantial efforts and financial resources that elimination will bring, there may be a need for new funders to come aboard. Also with the integration of new personnel and the national systems, the ministries of health of the nations involved will be required to play a stronger role in the governance. Changes for service delivery are also highlighted in Figure 17B. The diagnostics and medical treatments although simpler to disseminate will continue to come from abroad, which may still impose challenges in health service delivery that are seen in countries with war zones and in adequate transport routes to isolated areas, especially during rainy seasons(USAID 2009). The hope for integration is that with rapid diagnostic test and oral tablets, HAT will be a 'normal disease'(Burri 2014; Sutherland 2016) and tasks for diagnosis and treatment can be shifted to community health workers and/or the local workforce through training initiatives.(Bukachi et al. 2005; Palmer 2012) Tiny targets are also easier to deploy that their larger predecessors and several studies have shown that community involvement in vector control interventions is feasible.(Kovacic et al. 2013; Sutherland 2016). Taking into consideration that new diagnostics, treatments and vector prevention tools are hoped to be deployed in a non-vertical manner; the greatest changes from the systems perspective for integration will be within countries in relation to service delivery and health workforce.

Figure 17. Overview of service delivery for HAT diagnostics and treatment
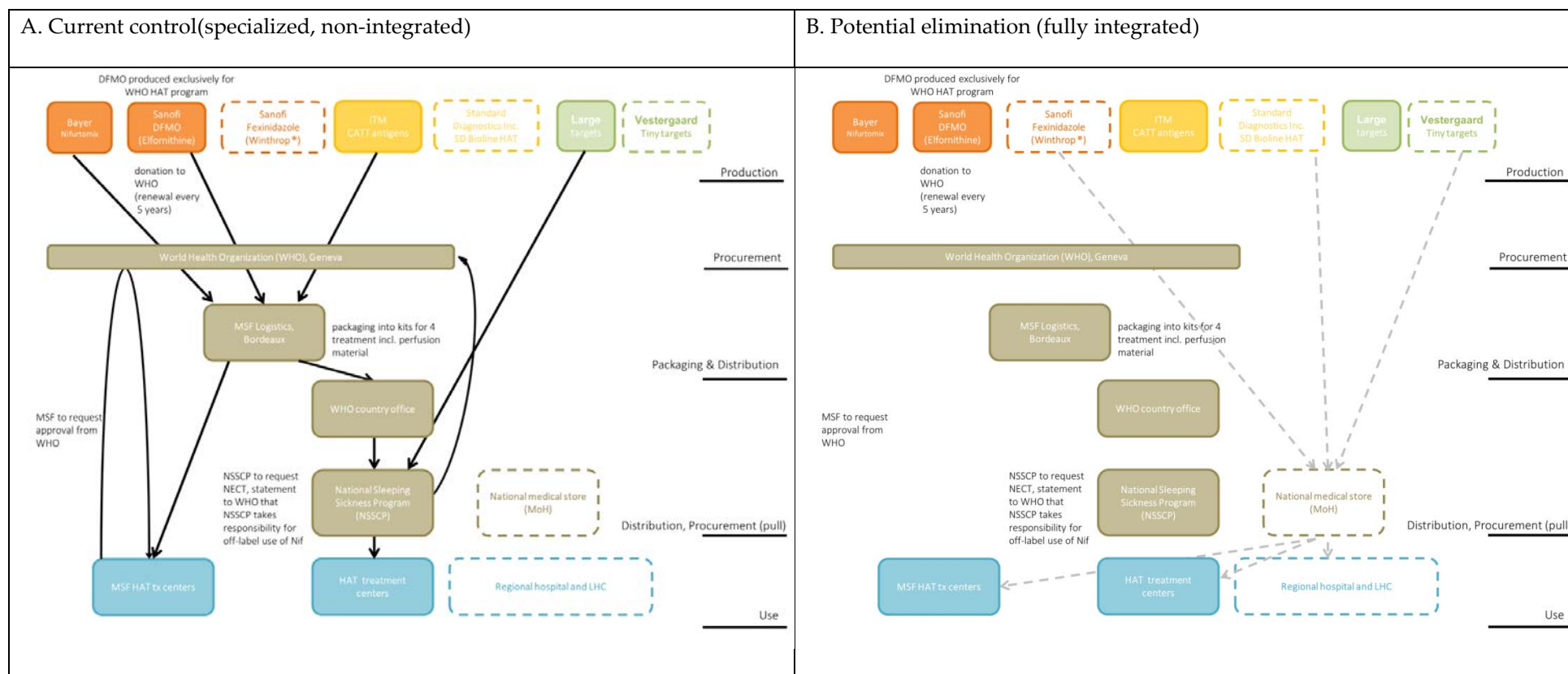
7.4 Potential analytical approach for systems integration

From systems perspective, adoption of new interventions will impact the health care workforce and health service delivery the most of integration is to move forward. Knowing this, one can develop a simple system to reflect the current scenario, and then model alternative scenarios to evaluate the impact on the system. Models to demonstrate operation concerns have been used form health systems to replicate systems dynamics (Windisch et al. 2011), supply chain management (Assi et al. 2011; Alfonso et al. 2012; Spiliotopoulou et al. 2013) and patient interactions with services while in the system. (Pilgrim et al. 2008; Pilgrim & Chilcott 2007; Lim et al. 2013)

7.4.1 Control versus elimination scenarios
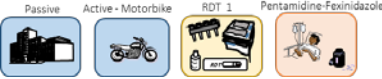
Potential scenarios of current and new technologies coming available(Steinmann et al. 2015) were presented 2014, and were further evaluated for cost-effectiveness,[9] financial expenditures and OOPs[10] driven by a dynamical transmission model(Christopher M. Stone & Chitnis 2015). As an example, only three situations were considered as depicted outlined in Table 15 focusing control as a non-integrated system and elimination scenarios as integrated treatment options.

Table 15. Scenarios modelled for integrated and non-integrated health systems

Scenario	Health system structure	Description
Control	Non-integrated	Self-reporting patients may go to a local health centre first or may decide to go directly to specialise HAT treatment centre for diagnosis. Regardless of where patient presents with symptoms, treatment is done with pentamidine for stage 1 or NECT for stage 2 at the specialized treatment centre.

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[9] Chapter 5. Sutherland et al., Seeing beyond 2020: An economic evaluation of contemporary and emerging strategies for Trypanosoma brucei gambiense elimination *(under review LGH)*

[10] Chapter 6. Sutherland et al., Counting the costs: Financial costs and out-of-pocket expenditures related to control and elimination plans for Trypanosoma brucei gambiense across sub-Saharan Africa *(under development)*

Elimination 2016 Passive Active - Motorbike RDT 1 Pentamidine-Fexinidazole	Fully integrated	Patient self-reports to any centre and rapid diagnostics are used at local centres local health centres to determine if patient has HAT and treatment with pentamidine for stage 1 while fexinidazole (Winthrop ®) is being used for stage 2 treatment.
Elimination 2019 Passive Active - Motorbike RDT 2 Oxaborole	Fully integrated	Patient self-reports to any centre and can receive diagnosis and treatment immediately regardless of stage with oxaborole.

7.4.2 Modelling the health system

In order to envision the potential implications of health system integration for HAT, a discrete-event simulation (DES) health systems model has been developed using SIMUL8®. (Sutherland et al. 2014) The model inter-arrival time was parameterized to simulate 100,000 patients (refer to appendix E.2) over a one year time horizon (passive reporting only) with a prevalence of 1.61%, 0.112%, 0.020% to represent foci of high, moderate and low transmission according to the thresholds indicated by the World Health Organization(World Health Organization (WHO) 2013c). The hypothetical village had access to three health centres containing different resources and capacity as presented in Figure 18. This structure was based on evidence from mapping efforts in the DRC that show that there are often several local centres closer to villages prior to reaching a specialized HAT treatment centre (refer to appendix E.3). Data inputs for the model were estimated based on the literature, grey literature, national program reports and clinical trial site characteristics[11] with the majority of evidence originating from the Democratic Republic of the Congo (DRC). Two types of health systems were modelled: A "Non-Integrated HS" where patients could report to local centres but would be referred to HAT Centres for treatment versus an "Integrated HS" where patients could be screened and treated at any centre. The model considers components related to time (e.g. treatment time, etc.) and probability of events occurring (e.g. patient's reporting to a health centre, etc.). Details regarding the input parameters are available in Table 16.

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[11] Information regarding staff resources at clinical trial sites in DRC were provided by MedRes, SwissTPH

Figure 18. Discrete event simulation (DES) model in Simul8® for health systems servicing Gambiense HAT
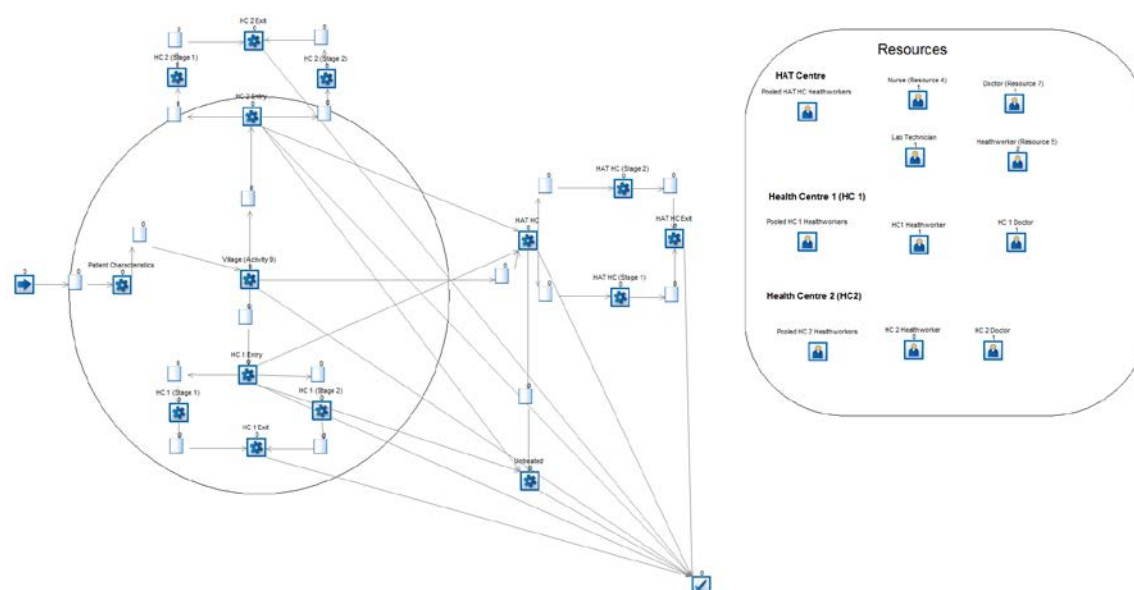
It was assumed in the model that patients that report to health centres with HAT and were not diagnosed (false negatives) went untreated. The main outcome evaluated was the number of patients treated and time that the patients spent in the 'health systems'. This model only looks at self-reporting to the health system and not those who may have been detected by an active surveillance campaign and are now arriving at a centre for treatment. It assumes that patients will receive treatment soon after diagnosis. Model assumes that patients will be able to access a health facility once they have made the decision to 'self-report' travel. Hence road delays or turning back from war torn zones is not taken into account in the current version of the model.

Model structure permits one to evaluate patient's accessibility (includes desire to seek treatment, geographic nearness of health facility and way to reach health facility (time, method of transportation, etc.) and the availability of being able to get the health services that they seek once they have accessed the health centre.(Levesque et al. 2013) In this case outcomes of number of patients treated, time spent in the system and wait times were measured. A sensitivity analysis (SA) was conducted by examining low and high values for the mean distribution of the probability of self-reporting, the diagnostic accuracy of the healthcare centre 1 (HC 1) and healthcentre 2 (HC 2), and prevalence to examine the impact on the number of patients treated.

Table 16. Key input parameters

Parameter Name	Mean Estimate	Data Source
Health service resources		
HAT centre		
Nurse, MD, Lab technician, Health worker	1, 1, 1, 2	Treatment centres, DRC
HC 1		
MD, Health worker (CHW)	1, 1	Assumption
HC 2		
MD, Health worker (CHW)	1, 1	Assumption
Epidemiological characteristics		
HAT prevalence (high, moderate, low)	1.61%, 0.112%, 0.020%	Sutherland, under review
Stage 1 prevalence	32.5%	PNTHLA report
Probability patient self-reports to HC	0.6 – 0.65*	
Treatment time (pentamidine (stage 1), NECT (stage 2))	12 days, 14 days	
Treatment time fexinidazole (both stages)	10 days	
Treatment time oxaborole (both stages)	1 day	
Health centre characteristics		
Distance HC 1	1 hour	(Simarro et al. 2014)
Distance HC 2	3 hours	(Simarro et al. 2014)
Distance HAT HC	5 hours	(Simarro et al. 2014)
Probability HC 1 correct diagnosis	0.5	
Probability HC 2 correct diagnosis	0.5	
Probability HAT HC correct diagnosis	1.0	

HC = Health Centre, HAT = human African trypanosomiasis, HS = Health System, NECT = Nifurtimox-Eflornithine Combination Therapy, SA = Sensitivity Analysis, *Patient reporting probability varies from HC to HAT treatment centre

7.4.3 Potential impacts

In low and moderate risk settings the impact on the number of patients treated was similar. However, in areas with transmission over 1%, integration increases by 87% (fexinidazole); and improves a further 90% when oxaborole is introduced in 2019.(Refer to Figure 19)

Figure 19. Number of patients treated in the system by risk transmission area
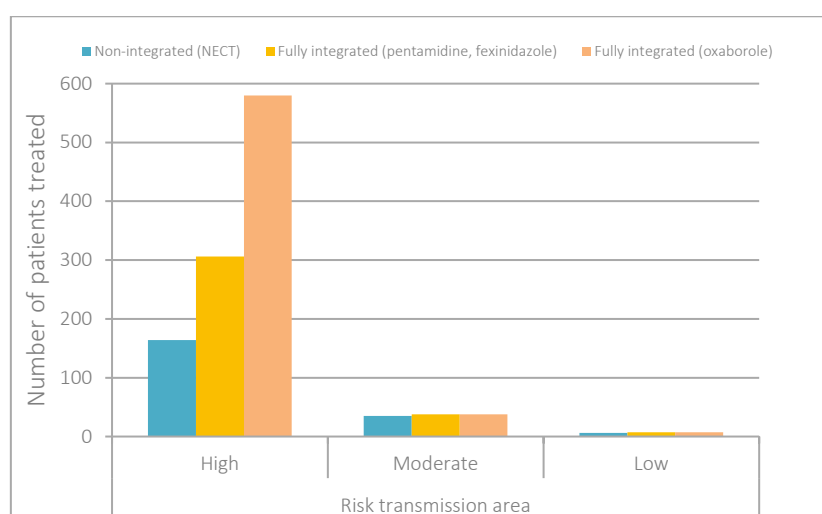
Seeing that the variation of patients treated was highest when transmission risk is high, a sensitivity analysis was done for this focus specifically. The results listed in Table 17 demonstrate that in a non-integrated system, the prevalence rates have little impact as it appears that the current system is likely acting at capacity in a high transmission area. Improving diagnostic accuracy and encouraging patients in combination with integrated treatments reaches more patients. Although decreases in prevalence will open up space in the health system, foci with high transmission or areas experiencing outbreaks would be better handled with an integrated system.

Table 17. Sensitivity analysis results (high risk foci only)

	Number patients treated		
Parameter	*Non-integrated*	*Fully integrated*	*Fully integrated*
Treatment	*pentamidine, NECT*	*pentamidine, fexinidazole*	*oxaborole*
Base case value	164	306	580
HC diagnostic accuracy (0.3, 1.0)	163,164	296,320	384,763
Probability patient self-reports to HC1 (0.3, 0.9) or HC2 (0.35, 0.95)	163,162	302,311	552,623
Prevalence (0.5%, 5%)	46,165	47, 321	55, 1646

7.5   Discussion

Health systems thinking is important process to conceptualize the impacts that moving from control to elimination will have on the health system. In the context of sleeping sickness, this is especially true as new interventions providing room for integration will change the health systems approach that active surveillance programs have relied on for the last century.(Steverding 2008) The main changes in the system scaling up to elimination will be seen at the local and national level as the burden of care will shift to countries. Using modelling to simulate potential impacts could provide useful information to decision makers at the national level in order for them to anticipate which changes need to be addressed to maximize capacity and ensure that HAT patients do not go untreated. For instance the current modelling results show that in high risk foci, adopting new technologies in an integrated system while improving patient self-reporting and health care workers to correctly identify patients leads to highest number of patients treated. Although this approach has provided a framework for thinking about health system changes in moving towards elimination there are still several issues to be addressed.

7.5.1 Are we ready to lose 'control'?

The goal of integration seems desirable however; there are still concerns, that the current infrastructure of the nations burdened with HAT, may not be ready. Examples from the past including supply chain integration efforts in Mozambique (USAID DELIVER PROJECT 2012) show that the transfer of responsibilities can lead to inefficiency if not addressed prior to implementation. Also, risk associated with shifting the responsibility of distribution of treatments to national medical stores needs to also ensure that the donated interventions reach the patients and are not lost to corrupt processes. As fexinadzole in tablet form is already available in online as Winthrop®, countries will need to maintain regulatory processes so that sub-standard or counterfeit tablets lacking the active ingredient do not proliferate the market. The consequences of ignoring this will only lead to delays in elimination and increase financial and societal costs associated with the disease burden. Delivery approaches to tools also needs to be taken into consideration with a bit of creativity at hand. It has already been proposed that motorbike carriers are sufficient to deliver rapid diagnostic tests and oral tablets(Sutherland 2016), but considering alternative transportation mechanism such as

helicopters (*Burri, personal communication)* or drones (*Awoonor-Williams, personal communication*) to isolated areas could prove to be useful in remotes areas across sub-Saharan Africa. There is also a need to think over maintaining a consistent supply of tools in areas experiencing civil conflict or war where routine deliveries may not be feasible. Looking for local storage with the new technologies, as is done with long lasting insectide net (LLINs) for malaria,(Roll Back Malaria n.d.; Roll Back Malaria n.d.) could be adopted for integration as there will be no need for a cold chain.

As demonstrated in this overview, the people involved in HAT treatment and the at risk populations themselves will play a larger role if integration is to come to pass. This may prove to be difficult since as cases dwindle motivation and opportunities to train and treat staff are difficult.(Sutherland 2016) People with experience in HAT near to larger hospitals may be able to transfer expertise in chemotherapy over to oncology if possible, or move into areas of animal trypanosomiasis where understanding of the parasite is transferable. This paper has focused on gambiense HAT integration in the health system, however gambiense HAT is small component of the health system in sub-Saharan Africa that are burdened also with malaria, HIV, NCDs and other NTDs to name a few. NTD programs often operate in specialized silos, but with the context of moving towards MDGs of sustainability in health systems, a systems thinking approach would be valuable in also assessing combined NTD programs and the ability of the health care workforce to appropriate differentiate between the plethoras of symptoms that patients present themselves with. Integrating HAT programs with other NTD programs may encourage interest, and training with the new diagnostics as well as disease differentiation could help motivate interest and will improve accuracy of syndromic algorithms.(Palmer 2012) Community health workers (CHW) will be encouraged to take on a larger role, but as various vertical NTD programs are happening simultaneously, this may be too much pressure or workload on communities. Integrating NTD programs without losing the quality and community relationships that successful programs have instilled needs to be addressed. Communication between the NSSCP and communities will also be crucial. Encouraging patient self-reporting at health care facility may happen inadvertently when communities become aware that the new interventions are less invasive to diagnose and have simpler routes for treatment. Passive health care approaches should be sensitive to

community preferences(Palmer 2012; Mpanya et al. 2015; Mpanya et al. 2012) and ethical consideration will be further evaluated elsewhere.

In regards to information for the health care system, thus far the WHO has the most information as it collects data from all the NSSCPs and has also combined efforts with FAO to identify at risk transmission areas and locations of health facilities using spatial information (Pere P Simarro et al. 2012; Simarro et al. 2014) However, this information is not always publically available and is limited as not all areas are under surveillance, hence the global stakeholders should consider who to harmonise data in order to accurately track elimination progress as integration rolls-out.

There are several institutions and financiers involved in HAT, but as integration will bring on new entities for service delivery and the health care workforce, there do not seem to be new donors or funding avenues on the horizon. As elimination for HAT ensues and steps towards integration are made additional funds will be required. For instance, in addition to elimination costs that are already estimated to be millions annually for HAT(Seddoh et al. 2013)[12] increasing the community health workforce will also come at a cost (McCord et al. 2013; Singh & Sachs 2013). In order to avoid 'donor fatigue', again combining HAT with other NTD programs or beginning to seeking alternative funding mechanisms will also be inevitable. Although from economic and business level perspective program integration and alternative funding sources this seems logical, the changes that may be thrust upon the current governing bodies if not done appropriately may hinder elimination efforts on the ground. This is yet another caveat to consider when thinking of integrative efforts for elimination.

7.5.2 Being one step ahead of integration concerns

Despite the anticipated concerns regarding moving to an integrated system in order to scale up control to elimination, modelling health systems provides an opportunity for decision makers to assess initiatives. This simple analysis focuses on three of the nine scenarios developed by Steinmann et al(Steinmann et al. 2015), but there are also still alternative scenarios that could be run through the model. An example of this would be to vary parameters to evaluate how preventing access to one of the centres in the system (i.e. due to

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war or route unavailable in the rainy season) would impact treatment and to plan buffer stocks for such circumstances. As previously stated, building a model that evaluates 'combined' NTD programs or various diseases would also be of use. Planning for integration could also be done by varying the number of health centres available to treat HAT in the system to determine the minimum number of centres needed in an area to alleviate travel burden. Future health systems modelling efforts could also include cost parameters so that the relative costs and even cost-effectiveness of programs for integration can be determined.

While the results thus far have focused primarily on accessibility with time and location being the main adaptation of moving from a non-integrated to integrated system, issues associated with availability related to supply chain constraints and health care worker availability could be further manipulated in the model. Adding in medical supplies to the model could allow national programs to estimate supplies and minimum stock levels required; and varying the number of health professionals available to treat could also be varied in the model to estimate the number of trained workers needed.

There are also technical aspects to consider within discrete-event simulation (DES) models. For instance, with limited data available, further research will be needed to validate the outcomes using real-world evidence. There are also several assumptions made during this first iteration of model development that may impact outcomes if the model is to be used further. For instance, the model assumes that people treated immediately while in real life people may have to go home and wait for parasitological confirmation, and it does not track misdiagnosed individuals (i.e. false negatives, false positives) or repeated screeners. The model could be adapted to include this. There is also no consideration of uncertainty or consideration of how patients diagnosed with active surveillance interact with the system. The benefits of using the Simul8® software allow decision makers to evaluate resource constraints related to staff and medical supplies but it remains difficult to incorporate disease transmission hence a dynamical model is still needed for this component of assessing elimination. Further modelling efforts could work towards combining these components so that health resources and transmission can be analysed in unison.

7.6   Concluding remarks' - Getting a grip'

Integration is an inevitable change that will be needed for sustainable healthcare systems and autonomy for nations that have had healthcare services managed by external collaborators for decades. These changes may lead to a feeling of uncertainty, or 'losing control'. Careful planning and consideration using systems thinking and modelling analyses can help decision makers to contain the processes as they occur. In the context of an elimination investment case, it is important to see the operational challenges to be assessed not as an additional analysis to the EIC but maybe the most crucial. The funding will come, the drugs and diagnostics made – but if system is not properly prepared to treat patients, what good is it? The investments for elimination for neglected tropical diseases will require millions of dollars annually(Seddoh et al. 2013)and billions over the next few decades(Kim, Sicuri, et al. 2015)[13] and often fail to formally address the implementation process, it is hoped that this approach can be used as an option for decision makers to evaluate anticipated changes more critically.

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8. Ethical considerations for global health care decision making: Justice-enhance cost-effectiveness analysis of new technologies for *Trypanosoma brucei gambiense*

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8.1   Summary

We sought to assess formally the extent to which different control and elimination strategies for human African trypanosomiasis *Trypanosoma brucei gambiense* (Gambiense HAT) would exacerbate or alleviate experiences of societal disadvantage that traditional economic evaluation doesn't take into account. Justice-Enhanced Cost-Effectiveness Analysis (JE-CEA) is a normative approach under development to address social justice considerations in public health decision making alongside other types of analyses. It aims to assess how public health interventions under analysis in comparative evaluation would be expected to influence the clustering of disadvantage across 3 core dimensions of well-being: agency, association and respect. As a case study to test the approach, we applied it to 5 strategies for Gambiense HAT control and elimination, in combination with 2 different other evaluations: a cost-effectiveness analysis, and a probability of elimination analysis. We have demonstrated how JE-CEA highlights the ethical importance of adverse social justice impacts of otherwise attractive options and how it indicates specific modifications to policy options to mitigate such impacts. JE-CEA holds promise as an approach to help decision makers and other stakeholders consider social justice more fully, explicitly, and systematically in evaluating public health programs.

8.2   Introduction

In 2010, the World Health Organization (WHO) published a Roadmap to Elimination for several neglected tropical diseases ((Cochi & Dowdle 2011; Thompson, K. M., Rabinovich & Contch 2011; Walker & Rabinovich 2011; Walker & Lupp n.d.)NTDs)(WHO 2012). It was endorsed by global donors who signed the London Declaration targets for 2020 NTDs elimination (London Declaration 2013). Since then, committed decision makers have struggled to assess formally the feasibility, costs, and consequences of eliminating or eradicating a target disease. In 2012, an investment case was proposed for 3 NTDs – onchocerciasis, lymphatic filariasis, and human African trypanosomiasis – to serve as a comprehensive analysis of clinically efficacious, feasible pathways to disease elimination or eradication, including required resources and operational investments (Tediosi et al. 2013). This initiative deployed the eradication investment case (EIC) framework, developed expressly to support the use of traditional techniques of health and economic assessment in deliberations about whether to undertake elimination or eradication of candidate infectious diseases (Cochi & Dowdle 2011; Thompson, K. M., Rabinovich & Contch 2011; Walker & Rabinovich 2011; Walker & Lupp n.d.). EIC components related to probability of elimination and cost-effectiveness have been assessed for onchocerciasis, lymphatic filariasis, and human African trypanosomiasis, but methods have been lacking to guide comparative assessment of broader social impacts across candidate elimination and eradication scenarios as called for by the EIC designers (Thompson, K. M., Rabinovich & Contch 2011; Walker & Rabinovich 2011; Tediosi et al. 2013; Sutherland et al. 2017).

The EIC designers' conception of broader social impacts encompasses not only effects on intergenerational justice and global health equity (Emerson 2011; Tediosi et al. 2013), but also forms of psychological, psychosocial, and social impact that primarily affect people as subjects of personal life experience (Muela & Hausmann-Muela 2013; Tediosi et al. 2013). We focus here on the need for a method to assess the latter, experiential forms of impact in the EICs for NTDs. In an effort to fill this gap in the context of EICs for lymphatic filariasis and onchocerciasis, Bailey and colleagues (Bailey et al. 2015) first presented a method of ethical analysis informed by theories of social justice. As a pilot case, however, their discussion considered mainly the impacts attributable to the diseases, not to interventions, and did not

attempt a finer-grained comparison among different pathways toward the goal of disease elimination or eradication.

Zwerling and colleagues (Zwerling et al. 2017) have built upon Bailey and colleagues' approach in developing an innovative methodology called justice-enhanced cost-effectiveness analysis (JE-CEA). They have presented an initial proof-of-concept illustration, using a hypothetical example (and moving outside of the NTD EICs discussion) specifically to suggest how JE-CEA might be used to compare novel *vs.* standard treatment regimens for multi-drug resistant tuberculosis (Zwerling et al. 2017). The justice enhancement (JE) component of JE-CEA is intended to assess, alongside the results of cost-effectiveness analysis (CEA), the compared options' expected impacts upon patients' experiences of societal disadvantage, such as "stigma, shame, social isolation, loss of agency and family strain" (Zwerling et al. 2017). In the present article, operating for the first time with a completed CEA and probability of elimination analysis (Sutherland et al. 2017), we explore the adaptation of Zwerling and colleagues' JE-CEA methodology for use in the economic assessment of pathways to the elimination or eradication of NTDs, taking human African trypanosomiasis *Trypanosoma brucei gambiense* as a salient NTD example.

8.2.1 Human African trypanosomiasis *T.b. gambiense*

Human African trypanosomiasis *Trypanosoma brucei gambiense*, or 'Gambiense HAT' for short, is one of 10 NTDs targeted for elimination by 2030 (WHO 2012; Uniting to Combat NTDs n.d.; World Health Organization (WHO) 2013a). Gambiense HAT, often called 'sleeping sickness', is an insect-borne parasitic infectious disease with at-risk areas spanning 24 African countries. Cases are currently being reported from 13 countries (Jose R Franco et al. 2014). Gambiense HAT is most prevalent in low-income countries with the areas at risk encompassing mainly the poor rural population (Pere P Simarro et al. 2012). It has 2 clinical manifestations as it progresses from a less acute to more severe stage. Stage 1 is a febrile illness; Stage 2 brings more severe symptoms, including disruption of the sleep-wake cycle, seizures, paralysis, weakness, confusion, psychosis, and eventual progression to coma and death if untreated (World Health Organization (WHO) 2013a). Historically, disease control measures have focused on treatment of human cases to reduce the parasite reservoir, and, in some areas, vector control programs to reduce transmission (Bennett et al. 2016).

A recent modelling study has compared the most promising Gambiense HAT elimination strategies in terms of cost-effectiveness and probability of reaching elimination (Sutherland et al. 2017). Although the disability-adjusted life-year (DALY) measure used in the cost-effectiveness analysis captures some disease-associated disability and mortality, the potential impacts of elimination strategies on the distribution of intervention-induced disadvantages like stigma and social exclusion have yet to be assessed (Sutherland et al. 2017).

8.3　Normative approach

Cost-effectiveness analysis (the CEA component of JE-CEA) is a prominent form of economic evaluation, a set of methods for comparative analysis often used to help prioritize budget-constrained resource allocation for public health program options (Drummond et al. 2005; Walker et al. 2011). Norms of distributive justice are pervasively implicated in health-related uses of economic evaluation, starting with the concern to consider opportunity costs in allocating limited public resources (Brock et al. 2017). To deliberate on what would constitute an optimal use of resources in public health decision contexts, however, it's necessary also to consider (*inter alia*) other applicable norms of distributive justice.

One of these other norms is social justice. The concept of social justice invokes a "moral imperative to avoid and remediate unfair distributions of societal disadvantage" (Dukhanin et al. 2018; Faden & Shebaya 2016; Powers & Faden 2006; Wolff et al. 2007). Social justice as a moral consideration is of major importance to public health and, in the economic evaluation of public health program options, it can either converge with or present trade-offs with comparably important moral considerations like the maximization of aggregate health benefit (Kass 2001; Childress et al. 2002; Faden & Shebaya 2016; Brock et al. 2017). Different conceptions of social justice vary in their accounts of what societal disadvantage is and what makes for inequitable distributions of it. JE-CEA is an analytic technique designed for use by economic evaluators who seek to apply to the decision context at hand a certain conception of social justice, which is centered on *protecting and relieving people from severe societal disadvantage in multiple dimensions of well-being*. Like other normative approaches to justice in public health, this conception of social justice can be explicated in terms of its position along each of two normative axes featuring, respectively, objects of distribution and distributive principles (Persad 2018; Dukhanin et al. 2018).

8.3.1 Objects of Distribution: Multidimensional Metrics of Well-Being

Whereas the object of distribution for traditional CEA is aggregate health benefit, typically assessed by summary measures like DALYs averted, alternative techniques enable users to consider other objects as well. JE-CEA is meant to help users apply to health-related economic evaluation the normative proposition *that health is one among other core dimensions of well-being holding fundamental ethical importance* as "basic determinants of the character and quality of human life" (Bailey et al. 2015). This proposition is common to a family of theories of justice grounded in multidimensional metrics of well-being, whose defining members are capabilities theories and well-being theories. Each theory in its own way focuses the requirements of justice on societal obligations to enable people to exercise core capabilities or to function in core dimensions of well-being(Nussbaum 2011; Wolff et al. 2007; Powers & Faden 2006).

We don't aim here to add new substantive argumentation to the cumulative case that proponents of these theories have already made for regarding other dimensions of well-being as comparable to health in fundamental ethical importance. Because of the importance of social justice as a moral consideration in public health, it is ethically preferable for the methodological repertoire of health-related economic evaluation to encompass the full range of leading conceptions of social justice, and so, with respect to objects of distribution, to include techniques for assessing the impacts of compared options on people's experiences of disadvantage in multiple dimensions of well-being (Dukhanin et al. 2018). Expanding the methodological repertoire in this way still leaves it up to users and their stakeholders to determine whether, under what conditions, and for what reasons the use of such techniques is warranted.

8.3.2 Distributive Principles: Prioritization Norm

JE-CEA belongs to a family of techniques designed for use by people who seek to temper the maximizing distributive principle familiar to users of traditional CEA (Cookson et al. 2017; Johri & Norheim 2012; Norheim et al. 2014). The purpose of the JE component is to enable users to apply a prioritization norm that is broadly consistent with prioritarian, egalitarian, and sufficientarian distributive principles, and which we articulate here as '*to protect and relieve people from severe societal disadvantage*'. This norm is of comparable concern to

prioritarians aiming to uplift the worst off in society (Wolff et al. 2007), egalitarians aiming to avoid and redress undue inequalities, and sufficientarians aiming to avoid and remediate each person's experience of shortfalls from sufficient levels of, for instance, capability (Nussbaum 2011) or functioning (Powers & Faden 2006). Again, we don't aim here to make additional arguments in support of these non-maximizing distributive principles. Rather, our point is that so far as it's ethically preferable for the methodological repertoire of economic evaluation to be able to accommodate the full range of leading conceptions of social justice, it should include techniques for applying this prioritization norm to relevant forms of program impact.

JE-CEA is meant to help users apply this prioritization norm in the first instance to certain dimensions of well-being besides health. The JE component is designed to assess the impacts of compared public health program options in multiple *non-health* dimensions of well-being, and to do so alongside the CEA component, which retains its traditional maximizing distributive principle with respect to its traditional target object, aggregate *health* benefit. One might ask, why not also modify the CEA component internally? That is, if health is comparable to other dimensions of well-being in ethical importance, and is thus one among other sites of societal disadvantage potentially subject to the prioritization norm, why continue to assess program options' health impacts only in terms of traditional CEA? While we acknowledge that this question must be addressed in due course, we have chosen to bracket it at the present early stage in JE-CEA's development. Our starting point is the fact that traditional CEA is in wide use, and indeed has been used in preparing the EIC for Gambiense HAT, presenting a timely real-world occasion to explore the use of JE-CEA. Too, whereas there is already a robust scholarly literature on internal modifications to CEA, a recent systematic review finds relatively little work on how to complement economic evaluation with assessment of the comparably important moral concern about the impacts of health interventions on people's experience in multiple non-health dimensions of well-being (Dukhanin et al. 2018). What we explore here is a decidedly incremental approach, attempting to make methodological progress one step at a time, holding CEA's traditional normative bearings constant and supplementing it with JE.

8.4   Structure of JE-CEA

Even holding CEA internally constant, there might be many ways to design an analytic technique that would fill the identified methodological gap. By demonstrating the use of JE-CEA as overlaid onto a completed CEA in a specific decision context, we hope also to advance the discussion of kindred techniques for which JE-CEA might serve initially as a foil. The longer-term goal is to strengthen methodological capacity in the field of health-related economic evaluation to represent the relevant conception of social justice. As we outline the structure of JE-CEA, then, we describe key methodological choices in the awareness that other designers might reasonably choose differently.   Zwerling and colleagues construct the JE component of JE-CEA as a more formal expression of the method of ethical analysis that Bailey and colleagues first developed to extend the EIC framework. The structure of that precursor method responds to a set of desiderata, derived from the EIC literature, on meeting the need for a method to assess psychological, psychosocial, and social impacts in the NTD EICs (Bailey *et al.*, 2015: 630-631):

> "Ideally, this method should strengthen EIC-supported deliberations by (1) delineating ethically important categories of benefits and burdens not otherwise captured in the EIC framework, (2) assessing aspects of distributive equity and fairness not otherwise captured, (3) recognizing widely varying life circumstances among people affected by the diseases and interventions, and (4) ethically interpreting the evidence base concerning disease-specific psychological, psychosocial, and social impacts."

> Desideratum (3) provides the rationale for Bailey and colleagues' choice to draw on theories of justice derived from multidimensional metrics of well-being (Powers & Faden 2006; Wolff et al. 2007; Venkatapuram 2011; Sen 2009; Alkire 2002; Crocker 2008; Ruger 2009; Nussbaum 2011). In attributing fundamental ethical value to each of the basic dimensions of well-being that affect the quality of human lives across widely varied conceptions of the good life, this approach…has fair claim to support a maximally broad consensus among people with different national, cultural, and personal backgrounds. Breadth of consensus is a matter of great importance in the EICs and for related global policy choices about eradicable infectious diseases considering the wide range of individuals and groups who stand to be involved or affected."

While some of these theories in themselves identify as many as ten or fourteen core dimensions, Bailey and colleagues focus on four points of convergence or overlap identified in virtue of their robust endorsement across multiple theories: three core dimensions of well-being that ought to be protected and promoted by socially just health policies; and one core prioritization norm.

The supposition behind the choice to focus on points of convergence or overlap across the theories is not the implausible expectation that each theory, taken in its entirety, would deliver the same result in the EIC decision context, but rather that the few elements on which the theories converge or overlap, in virtue of their plural theoretical grounding, have "more robust stability and salience for ethical assessments" than would the other, "relatively more controversial elements…that lack plural grounding in multiple theories"(Bailey et al. 2015; Sen 2009). These four elements form a core framework of social justice, embodying a distinct specification of the more generic conception of social justice (*protecting and relieving people from severe societal disadvantage in multiple dimensions of well-being*) discussed farther above.

8.4.1 Specification of Normative Proposition about Objects of Distribution

In response to EIC desideratum (1), *agency*, *association*, and *respect* are the core categories of benefits and burdens (besides life and health, which are otherwise captured in the EIC framework by traditional assessment techniques like CEA) that Bailey and colleagues identify as points of convergence or overlap among the contributing theories of justice. They characterize *agency* as "the ability to lead one's own life and engage in activities one finds meaningful"; *association* as "the ability to engage in a full range of intimate, familial, friendly, community, economic, and civic relationships with other people"; and *respect* as "the recognition, by others and oneself, of one's equal moral value, worth, and dignity as a person" (Bailey *et al.*, 2015: 631-632; see 631-632 for detailed derivations from contributing theories).

We explicate here a corresponding specification of the more generic normative proposition – *that health is one among other core dimensions of well-being holding fundamental ethical importance* – entertained farther above about objects of distribution: namely, *that, whatever non-health dimensions of well-being hold fundamental ethical importance,* **agency**, **association**, *and* **respect** *are the least controversial candidates for representation among potential objects of distribution that users of health-related economic evaluation ought to have the methodological capacity to assess.*

This specification does not deny that other dimensions of well-being might also be worthy candidates; rather, it selects agency, association, and respect as dimensions that it makes the most sense to start with in building the methodological capacity to assess non-health dimensions. Bailey and colleagues (2015: 631-632) justify the selection of agency, association, and respect by appeal to distinctively robust inter-theoretical agreement on their 'core' status. This selection might be challenged by disputing the choices to include or exclude certain theories of justice in the set of contributing theories, and by reexamining the contributing theories to confirm or disconfirm the identified loci of convergence/overlap. Either or both forms of challenge could generate variant sets of 'least controversial candidate' dimensions of well-being, with corresponding variations in the structure of JE-CEA. Even so, the overall approach of identifying such focal points remains viable as a means of seeking the least controversial normative grounding for JE-CEA. For the sake of simplicity in the initial stages of JE-CEA's methodological development, Zwerling and colleagues follow Bailey and colleagues' selection by focusing the JE component of JE-CEA on agency, association, and respect. We do the same in our exploration of JE-CEA in the Gambiense HAT EIC decision context.

8.4.2 Specification of Prioritization Norm

In response to EIC desideratum (2), Bailey and colleagues (2015: 631, italics added) find that theories of justice using multidimensional metrics of well-being converge on the following core prioritization norm, which picks out aspects of distributive equity and fairness not otherwise captured in the EIC framework: *that "it is a priority and duty of justice to avert and alleviate clusters of disadvantage in multiple dimensions of well-being."* For purposes of the present discussion, we read this as a specification of the more generic prioritization norm discussed farther above (*to protect and relieve people from severe societal disadvantage*). The key normative commitment defended in the contributing theories' explicit supporting arguments for the specified prioritization norm is to protect and relieve already-disadvantaged people from vicious cycles whereby personal setbacks caused by adverse impacts in some dimensions of well-being expose them to adverse impacts in other dimensions, making them even worse off (Wolff et al. 2007; Powers & Faden 2006; Venkatapuram 2011). This commitment has heightened salience for public health programs addressing health problems to which people are disproportionately exposed through pre-existing disadvantages such as severe poverty

and social marginalization (Faden & Shebaya 2016). The intent of JE-CEA is to focus on just such decision contexts, NTDs being a prime example (Azoh Barry 2014).

In response to EIC desideratum, Bailey and colleagues (Bailey et al. 2015) propose to interpret the evidence base on disease-specific psychological, psychosocial, and social impacts by first examining the empirically known impacts on each of the three selected core dimensions of well-being, then asking "how those impacts might create or exacerbate" cross-dimensional clustering of disadvantage, and finally comparing the scenarios under analysis in terms of the revealed patterns of impacts on disadvantage by the lights of the prioritization norm. They use this method chiefly to analyze the evidence about disease-attributable impacts of lymphatic filariasis (LF) and onchocerciasis (oncho), with the aim of informing the ethical rationale for investing global health resources in programs to control, eliminate, or eradicate LF and oncho. For each of these NTDs, neither of which is fatal in short order if untreated, the evidence indicates many distinctly disadvantageous impacts of the disease itself upon agency, association, and respect, impacts that stand in need of distinct assessment by means over and above the traditional measures that can already assess impacts on life (survival) and health.

By contrast, because of Gambiense HAT's catastrophic morbidity and rapid progression to fatality if untreated, the disease's adverse impacts on life and health as assessed by traditional measures are largely coextensive with its disadvantageous impacts on agency, association, and respect. For this reason, our background assumption is that effective interventions used in the Gambiense HAT disease control and elimination strategies will themselves avert and alleviate *disease*-attributable adverse impacts on pre-existing clustered disadvantage as experienced by individual members of the at-risk population. The distinct purpose of JE-CEA, as we are exploring its use in the Gambiense HAT EIC decision context, is to compare the candidate disease control and elimination strategies with respect to how far they might worsen (or not) any pre-existing clustered disadvantage through adverse impacts attributable to people's undergoing the public health *interventions* that the strategies deploy. That is, relative to a population baseline of pre-existing clustered disadvantage, some interventions in themselves may have the effect of worsening that clustered disadvantage whereas others under comparison do not -- for example, diagnostic testing for Gambiense HAT by means of lumbar puncture conducted in public *vs.* a rapid diagnostic test that can be done in private.

The scope of application for the prioritization norm in JE-CEA is given by the prior scope of the policy question addressed by the CEA component (Zwerling et al. 2017). In the context of deciding on optimal strategies for control and elimination of Gambiense HAT, the scope of the relevant CEA component is restricted to populations whose members are, largely because of the pre-existing clustered disadvantage that they are likely to have in common, at risk of Gambiense HAT in endemic areas. With reference to the population inside the scope of the policy comparison, the ideal social justice outcome is for *no one* to experience worsened clustering of disadvantage through their experience of undergoing the interventions; short of the ideal, it is better for *as few people as possible* to experience worsened clustering of disadvantage, and for those who do to experience *as little of it as possible*. For this reason, the principal attribute on which the JE component of JE-CEA is meant to help users to evaluate the options under comparison is the extent to which each option might worsen pre-existing clustered disadvantage by imposing adverse intervention-attributable impacts.

This emphasis is in keeping with the analytic orientation of traditional CEA, which is designed to compare options partly in terms of incremental differences in units of effectiveness (such as DALYs); similarly, JE-CEA is designed to present alongside CEA an additional comparison of the same options, in terms of incremental differences in their impacts on people's experiences of disadvantage. JE-CEA takes empirical findings as input "to track the occurrence, magnitude, and breadth of cross-cutting impacts on the three core dimensions of well-being" where, "[u]sing three impact levels, the social justice assessment for a given scenario under analysis could be either 'expected not to worsen. . .', 'may worsen. . .', or 'expected to worsen...'," the pre-existing clustering of disadvantage (Zwerling et al. 2017). These assessments can then be examined alongside the results of CEA, and any other applicable forms of evaluation of interest to decision makers, as performed for the same set of options.

The contributing theories of justice that converge on JE-CEA's specified prioritization norm use the idea of clustered disadvantage for various purposes. One of these theories, that of Wolff and de-Shalit (2007) uses it to solve "the indexing problem" of identifying who is among the least advantaged in society at large: with the answer being "groups of people who appear towards the bottom in several important categories of disadvantage, whose functionings in these categories are at a low level or very insecure". Within JE-CEA's scope of application in the types of decision contexts for which it is designed, we take the indexing

problem to have been pre-solved by the restriction of programmatic scope to a disease, like Gambiense HAT, to which people are typically exposed by conditions likely to impose multidimensional disadvantage (*e.g.,* being both impoverished to the point of curtailed agency and marginalized to the point of curtailed association). The guiding ethical concern for users of JE-CEA, given that the compared program options' intended beneficiaries are likely already among the worst off in those terms, is to give some priority to not exacerbating the prior clustering of disadvantage in non-health dimensions of well-being as an unintended consequence of health-promoting interventions. An intervention-attributable adverse impact in any one of JE-CEA's core dimensions – agency, association, or respect – might exacerbate prior clustering of disadvantage even by compounding a person's prior disadvantage only in that one dimension, so far as they were already disadvantaged in one or two of the other core dimensions too, making the post-intervention cross-dimensional pattern even more disadvantageous than the pre-intervention pattern. Intervention-attributable impacts that cross two or three core dimensions add further clustering in themselves. Nonetheless, variants on JE-CEA, or kindred techniques, might specify differently the generic prioritization norm, for instance by somehow weighting impacts on the selected core non-health dimensions, without using the idea of clustering either to describe the prior baseline of disadvantage or to make the social justice assessment in evaluating the compared program options. Again, for the sake of simplicity in the initial stages of JE-CEA's methodological development, Zwerling and colleagues retain Bailey and colleagues' specified version of the generic prioritization norm, and we do the same here.

Whereas Zwerling and colleagues illustrate the use of JE-CEA in conjunction with a decision tree technique for CEA comparisons (Zwerling et al. 2017), our adaptation will instead illustrate it in conjunction with a dynamical transmission modelling approach for CEA comparisons, as is more appropriate for the Gambiense HAT decision context (Steinmann et al. 2015; Sutherland et al. 2017). In addition, whereas Zwerling and colleagues confine their discussion of justice enhancement to its conjunction with the main CEA analysis in their example of novel *vs.* standard multi-drug resistant tuberculosis regimens, we consider in the Gambiense HAT decision context the conjunction of justice enhancement not only with CEA but also with a probability of elimination analysis.

8.5 Justice-enhance cost-effectiveness analysis for Gambiense HAT control and elimination strategies

8.5.1 Overview of Methods

In our proposed adaptation for the Gambiense HAT disease control and elimination decision context, JE-CEA proceeds in 3 phases (Box 1). Phase 0 is to identify the options to be evaluated. Phase 1 is to construct social justice assessments, drawing on the best available evidence, corresponding to people's experiences of disadvantage under each option. Phase 2 is to represent these assessments along with the CEA to demonstrate JE-CEA. We will also extend the justice enhancement technique of social justice assessment to the probability of elimination predictions for Gambiense HAT.

Box 1. Overview of methods for Justice-Enhanced Cost-effectiveness Analysis (JE-CEA) as applied to Gambiense HAT test case

	Description
Phase 0	Identify options of interest and articulate them in a form suitable for evaluation
Phase 1	Construct social justice assessments corresponding to people's experiences of disadvantage under each option
	Step 1. Assess quality of people's experiences in core dimensions of well-being
	Step 2. Assess impact on clustering of disadvantage across core dimensions of well-being
Phase 2	Combine social justice assessments with cost-effectiveness analysis (CEA)

8.5.2 Phase 0: Identify options of interest

CEA compares health interventions in terms of their incremental cost-effectiveness ratio (ICER). The ICER is defined as the incremental cost of implementing a given intervention relative to the next best intervention (the difference in cost between the two) divided by the incremental effectiveness of implementing it relative to the next best intervention (the difference in effectiveness between the two). Traditionally, effectiveness has been measured in

terms of health, using health measures such as DALYs averted. The ICER can be expressed as the incremental cost per DALY averted. An intervention is 'dominated' when another intervention costs less and has better outcomes relative to it.

Our application of JE-CEA builds on a prior CEA study that modelled cost-effectiveness and probability of reaching elimination of Gambiense HAT for several strategies featuring different combinations of standard approaches and emerging technologies for HAT diagnosis and treatment over 30 years (2013-2042), using a dynamical transmission model (Sutherland et al. 2017). These strategies are composed of varying scenarios previously described, where each scenario is characterized by its availability between 2013 and 2042, its approaches to case identification, diagnosis, and treatment, and whether vector control is included as an additional method to prevent transmission (Steinmann et al. 2015). A major aim of the prior modelling study was to assess the value of investing in novel Gambiense HAT technologies vis-à-vis the goal of reaching elimination.

The objects of analysis in the prior CEA study by Sutherland and colleagues (2017), and correspondingly in our illustration of JE-CEA, are the strategies considered as each would be implemented over the full 30-year time horizon. It is important to distinguish between the cost of investing in a strategy over that full 30-year time horizon and the annual cost per case found, which may fluctuate from year to year, and which for elimination strategies will increase over time as disease prevalence declines. Whereas the CEA highlights the value for money of investing in each strategy relative to its comparators over the 30-year time horizon, the annual cost per case relates instead to the annual budget for carrying out the selected program (which would be assessed differently in the decision-making dossier).

For purposes of illustrating JE-CEA, we focus on the 5 strategies most important to consider for areas where transmission risk is low (Figure 20) (Sutherland et al. 2017). The first strategy continues the current paradigm. The other 4 strategies, which deploy varying combinations of novel technologies, were shown to dominate all other alternatives to the current paradigm on grounds of *either* probability of elimination *or* cost-effectiveness, *or* both (Sutherland et al. 2017).

The *Control* strategy (Strategy A in Sutherland *et al.*, (2017)) depicts the current Gambiense HAT treatment paradigm. The term *Control* in this analysis refers to a form of *disease control* program in the sense of a public health intervention strategy intended to 'control' the disease, that is, to reduce its "incidence, prevalence, morbidity or mortality to a locally

acceptable level as a result of deliberate efforts" with the understanding that "continued intervention measures are required to maintain the reduction" (Dowdle 1998). (This is by contrast with 'control' in the experimental sense of a neutral, non-intervention, no-impact baseline, and by contrast too with 'control' in what is perhaps a colloquial sense of merely observing the status quo while taking no deliberate action to influence future disease parameters.) Thus, the Gambiense HAT *Control* strategy, like all the other strategies under comparison in our analysis, is an active public health intervention that must be assessed for its potential adverse impacts on pre-existing clustered disadvantage. During *Control*, in low-transmission settings, WHO advises that patients seek out treatment (passive surveillance) (World Health Organization (WHO) 2013a). Suspected cases undergo blood serum tests (card agglutination test for trypanosomiasis, or CATT) to find antigens in response to parasite presence. To determine the stage of the disease, lumbar puncture at a health facility is required to draw cerebrospinal fluid for parasitological confirmation. Confirmed cases are referred to specialized treatment centres. People in stage 1 of the disease require 12-day intravenous treatment in hospital with pentamidine. People in stage 2 require 14 days of nifurtomix-eflornithine (chemotherapy) in hospital.

Control with tiny targets (Strategy B in Sutherland *et al.*, 2017), a potential strategy for elimination, combines the current treatment paradigm (*Control*) with novel vector control interventions called 'tiny targets': small flag-like traps colored to attract tsetse flies and covered with insecticide to kill them (Steinmann et al. 2015).
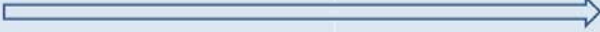
Accelerated technologies (Strategy D in Sutherland *et al.*, 2017) maintains *Control* until 2016, when new diagnostics become available. Local health centers could then use a rapid diagnostic test (HAT Sero K) instead of CATT, and use loop-mediated isothermal amplification of DNA (LAMP) for parasitological confirmation. Lumbar puncture would still be required at a health facility for staging. Stage 1 treatment remains the same but patients in stage 2 can take a 10-day oral regimen of fexinidazole. Then in 2019, a novel one-day oral tablet, oxaborole SCYX-7158, is expected to become available to treat both stages of the disease, rendering differential diagnosis unnecessary, so that a rapid diagnostic test alone would suffice with no lumber puncture for staging. The all-oral treatment for both stages could also mean that patients no longer need to leave their village for treatment.

Accelerated technologies with biannual surveillance is the same as *Accelerated technologies* except that screening is conducted every two years ('Strategy D+ in Sutherland *et al.*, 2017).

Because surveillance teams conduct open screening campaigns in villages, the diagnostic procedures, including lumbar puncture for staging, would all be done publicly, until the oral Oxaborole treatment arrives for both stages in 2019.

Accelerated technologies with tiny targets (Strategy E in Sutherland *et al.*, 2017) is the same as *Accelerated technologies* except that it simultaneously deploys vector control with tiny targets.

Figure 20. Strategies for control and elimination in low risk transmission areas*

8.5.3 Phase 1: Construct social justice assessments

Phase 1 is to construct social justice assessments corresponding to people's experiences of disadvantage for each option under evaluation (Bailey *et al.*, 2015: 632; *cf.* Zwerling *et al.*, 2017: S71-S72). Step 1 is to assess people's experience *in* core dimensions of well-being under each option. Step 2 is to assess the impact of each option on the clustering of disadvantage *across* core dimensions of well-being.

Step 1. Assessment of people's experience in core dimensions of well-being

Because all untreated cases of HAT are debilitating and fatal, any safe and effective preventive or therapeutic intervention that people willingly accept is clearly better than none in terms of agency, respect, and association. But the standard and novel interventions deployed under different Gambiense HAT control and elimination strategies may themselves vary in the nature, intensity, and distribution of their impacts on core dimensions of well-being. The point of constructing social justice assessments is to estimate the 'price' in mal-

distributed disadvantage imposed by the current paradigm (*i.e.*, *Control* as an ongoing public health intervention strategy) as compared with alternative strategies.

Step 1 is to ask whether and, if so, how, people experience adverse impacts on agency, respect, or association because of their exposure to the specific health interventions deployed under each strategy. To find out, primary qualitative data collection would be ideal (Zwerling *et al.*, 2017: S72). Future qualitative studies are required for the development and refinement of JE-CEA methodology for use in any specific decision context, including the Gambiense HAT context. For purposes of the present analysis, however, we drew on a systematic review of empirical literature about people's experiences of standard HAT diagnosis and treatment interventions (Muela and Hausmann-Muela, 2013).(Muela & Hausmann-Muela 2013) Table 1 relates the most striking findings from this literature to the strategies under analysis.

Our application of JE-CEA in this paper deals only with low-transmission areas, where case identification is limited to passive surveillance undertaken in more private clinic settings under 4 of the 5 strategies considered: *Control*, *Control with tiny targets*, *Accelerated technologies*, and *Accelerated technologies and tiny targets*; thus, for each of those 4 strategies, the literature indicates that social justice impacts would occur mainly through treatment experiences. Under 1 of the 5 strategies considered, namely *Accelerated technologies with biannual surveillance,* the literature indicates that standard approaches to active surveillance for HAT, because they occur in public, bring embarrassment and shame (especially for those who need lumbar puncture to determine their stage of a stigmatized disease), and thereby infringe significantly on **respect** (Mpanya *et al.*, 2012). In the Discussion section, we will return to this point and consider the need for more private and dignified approaches to active screening.

Regarding treatment technologies, the most marked impacts on disadvantage under both strategies deploying standard treatment (*Control* and *Control with tiny targets*) are experienced by patients at disease Stage 2, and they arise from the 6+ months' post-treatment prohibitions on patients' activities. For example, qualitative studies conducted in the Democratic Republic of Congo report that communities commonly uphold prohibitions on heavy labor and sexual intercourse during the 6+ month post-treatment period (Robays et al. 2007; Mpanya et al. 2012; Mpanya et al. 2015). The prohibition on heavy labor amounts to "forced inactivity" (Robays et al. 2007) that severely restricts the patient's **agency**. The prohibition on sexual intercourse stirs up "marital problems and conflicts" ,(Robays et al. 2007)

a critical setback in *association*. Moreover, "a strong element of social control" and victim-blaming in the event of "[t]reatment failure and other complications" arise from the widely held perception that patients' adherence to post-treatment prohibitions – which also preclude smoking, drinking alcohol, eating hot food, and walking in the sun – is key to recovery (Mpanya *et al.*, 2012: 7). As one focus group participant said, "A person must be near at all times to keep an eye on him, to make sure he avoids all these things" (Mpanya *et al.*, 2012: 7, Table 3). Such intense social monitoring and potential victim-blaming are setbacks in the domain of *respect*. JE-CEA is precisely intended to represent these sorts of adverse impacts on agency, association, and respect, over and above the costs already measurable by existing evaluation techniques.

We hypothesize that the substitution of novel diagnostic and treatment technologies would remove the specific adverse impacts of standard approaches without introducing comparable new ones. By contrast, the addition of 'tiny targets' as a vector control intervention would not in itself change the quality of people's diagnostic and treatment experiences, but would rather serve to reduce HAT incidence over time so that fewer people are exposed to HAT diagnosis and treatment.

Wherever novel diagnostic and treatment technologies are implemented in the future, their successful implementation will require ongoing community consultation, and empirical research would be needed to test our substitution hypothesis. As noted by Mpanya and colleagues, the intensive post-treatment prohibitions that presently take the form of taboos originated in communities' uptake of past communications with healthcare providers trying to manage HAT treatment with a relatively toxic drug (melarsoprol) (Mpanya et al. 2015; Kovacic et al. 2016). Even where the use of less toxic drugs makes such prohibitions no longer medically necessary, they might still be believed necessary by the community. Under those circumstances, on one hand, the possibility arises for public health interventions to facilitate the evolution of community norms through respectful dialogue and education in collaboration with community opinion leaders; on the other hand, if community norms do not evolve for whatever reason, the social justice impacts resulting from enforcement of the prior norms might carry over to new treatment modalities.

Step 2. Assessment of impact on clustering of disadvantage across core dimensions of well-being

The next step is to assess the impact of each strategy on the clustering of disadvantage. At least 3 assessment levels are possible. For ease of visualization when considering social justice impacts alongside results from other forms of evaluation, Zwerling and colleagues proposed a color-coding scheme representing 3 levels of expected impact (Zwerling et al. 2017). We propose a similar color-coding scheme (adjusted for readers with color-blindness) as follows:

- Orange: "Expected to worsen the clustering of disadvantage",
- Yellow: "*May* worsen the clustering of disadvantage" and
- Turquoise: "Expected *not* to worsen the clustering of disadvantage."

While finer, intermediate gradations are possible in principle, their definition requires further development of JE-CEA methodology. Meanwhile, JE-CEA can still reveal striking contrasts among the social justice impacts of different strategies under analysis (Figure 2)[14].

Because standard treatment for Stage 2 of HAT tends to impose post-treatment burdens in all 3 core dimensions of well-being (Figure 21), the *Control* and *Control with tiny target* strategies warrant an assessment of "Expected to worsen the clustering of disadvantage", relative to the pre-existing clustered disadvantage shared by the population at risk of Gambiense HAT. By contrast, the *Accelerated technologies* and *Accelerated technologies with tiny target* strategies, under their component scenarios that roll out post-2016, promise to avoid imposing comparable post-treatment burdens(Sutherland et al. 2017), and so they warrant an assessment of "Expected not to worsen the clustering of disadvantage". *Accelerated technologies with biannual surveillance* continues to impinge on respect through the screening campaigns that will require public lumbar puncture for staging until a treatment for both stages arrives in 2019. Because social justice impacts are attributable to this strategy in only 1 core dimension of well-being, it is assigned an assessment of 'May worsen the clustering of disadvantage"

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[14] Our analysis departs here from the originally proposed JE-CEA approach (Zwerling *et al.*, 2017) in that we don't use length of colored bars to highlight the number of people impacted, because our extension of the Phase 2 social justice assessment to the probability of elimination analysis will indirectly highlight the number of people potentially impacted over time.

(depending on the extent to which this impact might compound pre-existing disadvantages in the experiences of people affected).

Figure 21. Summary of 'clustering of disadvantage' across well-being by colour

	2013 - 2015	2016 - 2018	2019 - 2042
Control (Strategy A)			
Control with tiny targets (Strategy B)			
Accelerated technologies (Strategy D)			
Accelerated technologies with biannual surveillance (Strategy D+)			
Accelerated technologies and tiny targets (Strategy E)			

8.5.4 Phase 2: Consider social justice impacts with CEA

Figure 22A shows the results of the prior CEA study for the 5 strategies we considered here. The *Control* strategy would cost $3 ($2.52) and incur 0.04 DALYs per person at risk in a low-transmission area and is dominated by *Accelerated technologies*, which costs approximately the same ($2.97) but incurs 0.01 DALYs less than the control (ICER = $160/DALY averted). Scaling up surveillance in low transmission areas to once every two years (*Accelerated technologies with biannual surveillance*) would cost a total $20 per person at risk, but would incur only 0.004 DALYs resulting in an ICER of $654 per DALY averted. *Control with tiny targets* and *Accelerated technologies and tiny targets* are both dominated.

Accelerated technologies with biannual surveillance and *Accelerated technologies* would be considered cost-effective. However, some influential global health funders consider $300 per DALY averted as a threshold of cost-effectiveness for investments in low income countries (National Institute for Health and Clinical Excellence (NICE) International 2014). With that constraint, *Accelerated technologies* would be the only option.

When we overlay our social justice assessments onto the prior CEA results (Figure 22B), the social justice assessments and CEA results are concordant. *Accelerated technologies* is cost-effective, and in the long run is not expected to worsen clustering of disadvantage.

Figure 22. Economic evaluation in low risk transmission areas of Gambiense HAT

A.

Strategies	Cost	DALYs	ICER
Control (Strategy A)	$3	0.04	Dominated by Strategy D
Accelerated technologies (Strategy D)	$3	0.03	$160 per DALY averted
Accelerated technologies with biannual surveillance (Strategy D+)	$20	0.004	$654 per DALY averted
Accelerated technologies and tiny targets (Strategy E)	$42	0.01	Dominated by Strategy D+
Control with tiny targets (Strategy B)	$45	0.01	Dominated by Strategy D+

B.

Strategies	Cost	DALYs	ICER
Control (Strategy A)	$3	0.04	Dominated by Strategy D
Accelerated technologies (Strategy D)	$3	0.03	$160 per DALY averted
Accelerated technologies with biannual surveillance (Strategy D+)	$20	0.004	$654 per DALY averted
Accelerated technologies and tiny targets (Strategy E)	$42	0.01	Dominated by Strategy D+
Control with tiny targets (Strategy B)	$45	0.01	Dominated by Strategy D+

An applied extension of Phase 2: Social justice impacts alone considered alongside probability of disease elimination (separate from CEA)

In a previous analysis of elimination targets, the probability of elimination (Figure 23A) appeared to be highest under *Accelerated technologies with biannual surveillance, Accelerated technologies with tiny targets,* and *Control with tiny targets* (Sutherland et al. 2017). Therefore, in

the absence of social justice assessment, we would conclude that these 3 options would be the best for elimination in a low-transmission area. But when we overlay our social justice assessments onto these same outcomes (Figure 23B), *Control with tiny targets*, in addition to performing worse than the other 2 strategies with respect to probability of elimination, has the major drawback of being expected throughout its course to worsen the clustering of disadvantage for people exposed to stage 2 treatment. As for *Accelerated technologies with biannual surveillance*, although it has the highest probability of leading to elimination at the quickest rate, it also has an interim time when it may worsen the clustering of disadvantage for people exposed to active surveillance. Thus, *Accelerated technologies* and *Accelerated technologies with tiny targets*, under which the Gambiense HAT interventions that people would experience are not expected to worsen clustering of disadvantage for them, are preferable in terms of social justice impacts attributable to interventions.

Figure 23. Probability of elimination in low risk transmission areas of Gambiense HAT

A.

B.

Legend:
- □ D+. Accelerated technologies with biannual surveillance
- ▨ E. Accelertated technologies with tiny targets
- □ B. Control with tiny targets
- ▨ D. Accelerated technologies
- ≡ A. Control

Y-axis: Probability London Declaration targets reached (0, 0.5, 1)

X-axis: Time (year) (2013, 2020, 2027)
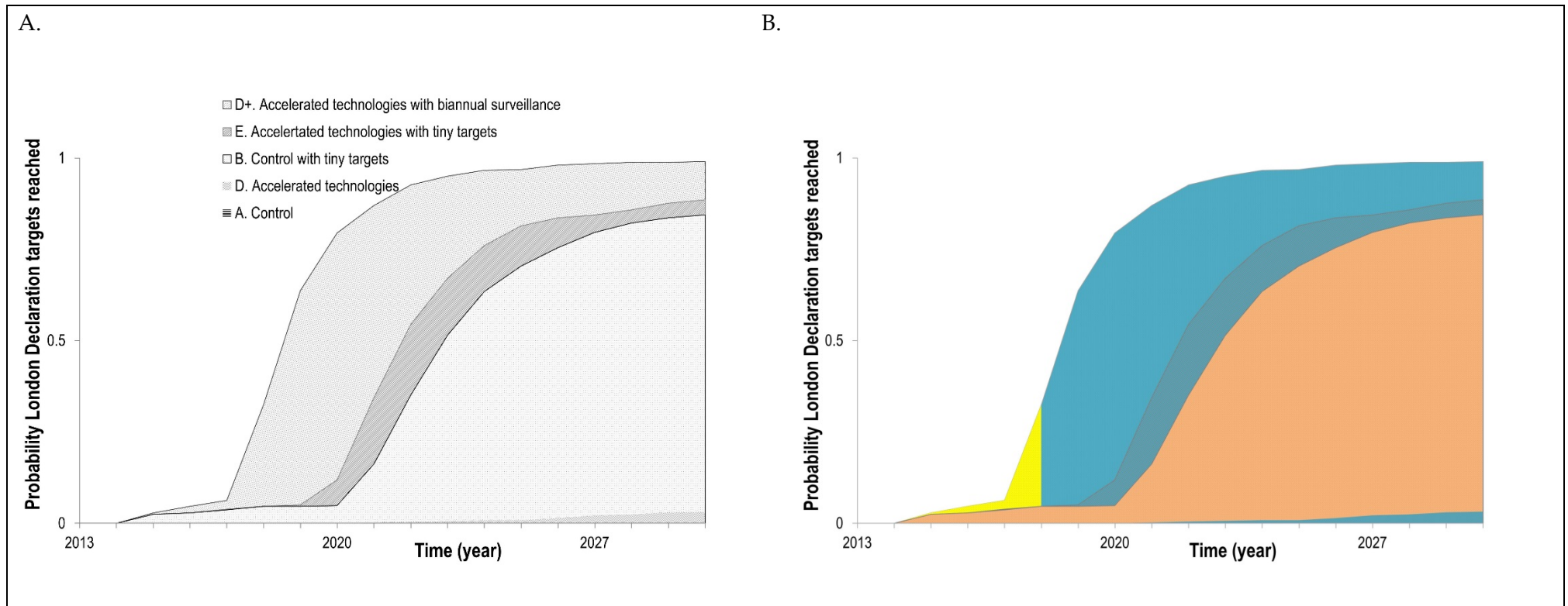
8.6   Discussion

Although *Accelerated technologies* is cost-effective and not expected to worsen the clustering of disadvantage, it is unlikely to lead to elimination. The low probability of elimination under *Accelerated technologies* thus presents a trade-off *within* social justice so far as ongoing residual disease incidence would impose future social justice impacts attributable to the disease (Bailey et al. 2015) – impacts that could be averted with eventual elimination under *Accelerated technologies with biannual surveillance*, but at the risk of exposing people to other social justice impacts attributable to active screening, at least until 2019 when the oral Oxaborole treatment suitable for both disease stages would remove the need for public lumbar puncture to determine disease stage. Under *Accelerated technologies*, with the permanent prospect of residual disease incidence, all three core dimensions of well-being could remain precarious for anyone at risk of Gambiense HAT (because all untreated cases are debilitating and fatal), except so far as they could count on timely diagnosis and treatment. From this standpoint, however, the saving grace of *Accelerated technologies* is the roll-out of increasingly simplified diagnosis and treatment that would be expected to avert disease-attributable social justice impacts while refraining from imposing intervention-attributable social justice impacts. This prospect suggests that *Accelerated technologies* might be favored on social justice grounds over *Accelerated technologies with biannual surveillance*, even taking into account the residual disease incidence under *Accelerated technologies*. The social justice assessments and CEA results (setting aside for a moment the probability of elimination analysis) converge on recommending *Accelerated technologies*, given the prevailing cost-effectiveness threshold among global heath funders. If that threshold were to increase, however, to the point of admitting *Accelerated technologies with biannual surveillance*, it could present a trade-off between cost-effectiveness of *Accelerated technologies with biannual surveillance* and the superior protections against treatment-attributable social justice impacts afforded under *Accelerated technologies*. This may truly be an option, as low middle-income countries may consider cost-effectiveness thresholds near $1000 per DALY based on their GDP (Santatiwongchai et al. 2015). Indeed, the global health commitment to Gambiense HAT elimination may require a cost-effectiveness threshold of around $700 per DALY averted, to accommodate increased active surveillance in low transmission areas (Sutherland et al. 2017). Another reason why

increased active surveillance may be necessary to reach elimination is that the current prevalence of HAT is truly unknown. Less than 10% of the at-risk population has been screened.

Putting all these considerations together, the value that JE-CEA ultimately adds to deliberation in the Gambiense HAT decision context is to underscore the ethical importance of flagging adverse social justice impacts of otherwise attractive options, so that opportunities to mitigate those impacts can then be explored. In this case, JE-CEA renders highly salient the need to devise approaches to active screening that protect people's privacy, confidentiality, and dignity better than the current standard procedure. Of course, the ethical importance of such protections is a reason, independent of the public health decision context surrounding Gambiense HAT elimination, to develop a more respectful active screening approach. So far as the global health commitment to NTD elimination is motivated by considerations of social justice, consistency and coherence require stakeholders to pursue pathways toward the goal that best avert or alleviate adverse social justice impacts for members of at-risk communities along the way. If the most attractive option in terms of probability of elimination and cost-effectiveness turns out to be *Accelerated technologies with biannual surveillance*, JE-CEA reveals that it's ethically preferable to avoid active screening procedures that require public diagnostic procedures. A more progressive solution to the trade-off identified above, between bringing future disease incidence to zero and protecting people actively screened along the way, could be to develop a modified strategy incorporating more private and dignified active screening, *Accelerated technologies with biannual surveillance**. On the other hand, the time it would take to develop, pilot, and scale up this improved screening procedure might run through 2019, at which point the projected availability of oral Oxaborole treatment would permit active screening to be done without the need for public diagnostic procedures. This raises the possibility of a differently modified strategy, *Accelerated technologies with biannual surveillance*** that would involve delaying the start of biannual surveillance pending the availability of oral Oxaborole. Both modified strategies would need to be re-assessed under the other forms of evaluation (probability of disease elimination and CEA).

8.7   Limitations and directions for future work

There are still many refinements to be considered as JE-CEA develops. Primarily, JE-CEA is not meant to be a decision algorithm. It does not itself resolve ethical tensions or trade-offs but rather articulates them explicitly: Is it better to delay elimination until more equitable tools are available? Or should we pursue elimination and try to improve the mitigation of social justice impacts along the way? Can we increase our cost-effectiveness threshold for this decision? While we have indicated in the Discussion section the beginning of a possible deliberative pathway informed by JE-CEA, it is truly up to the stakeholders involved to work through these ethical trade-offs. The main normative contribution of JE-CEA is to identify and make salient the social justice impacts of options under analysis. The experiential nature of the impacts highlighted by JE-CEA suggests that the involvement of patient and community representatives and local NTD activists is of utmost importance. For instance, NTD activists belonging to at-risk communities could decide to lead a de-stigmatization campaign alleviating the current social justice impacts of *Accelerated technologies with biannual surveillance*, so that it could be implemented as is. To facilitate the emergence of community-led solutions, JE-CEA could help to organize systematic stakeholder deliberation using multiple criteria decision analysis (MCDA) frameworks (Thokala & Duenas 2012) or Delphi panel approaches (Assasi et al. 2014).

Concerns remain regarding our hypothesis that the substitution of novel Gambiense HAT diagnostic and treatment technologies would remove the specific adverse impacts of standard approaches without introducing comparable new ones. Local perceptions of novel technologies are currently unknown and will need to be assessed by medical anthropologists and other social scientists. Outdated post-treatment taboos might evolve in synch with the appearance of safer treatments on the market (Mpanya et al. 2015). There is evidence that rapid diagnostic tests (RDTs) for a disease with a symptomatic profile like that of Gambiense HAT (Bisser et al. 2016) are considered acceptable if the communities feel confident in the healthcare workers providing the services (Mukanga et al. 2010; Mushi et al. 2016), the supply of RDTs is maintained (Diggle et al. 2014) and the cost to the community is minimal (Cohen et al. 2015).

The initial version of the JE-CEA framework proposed by Zwerling and colleagues (2017) focuses on capturing the "worsening of disadvantage" for interventions under assessment. The thought here is that it's of paramount moral importance to expose and avoid

unintended consequences whereby health interventions might worsen further the position of people "who were already relatively badly off before enactment of the policy, and who may have come into the line of fire of adverse policy impacts through the very pre-existing circumstances by which they were already disadvantaged" (Zwerling et al. 2017). There is also a potential, however, to consider the positive impacts of new technologies so far as they might protect and relieve intended beneficiaries from severe societal disadvantage by promoting "'fertile functionings' (*i.e.* those functionings the securing of which is likely to secure further functionings)" (Wolff et al. 2007). For instance, there is emerging evidence that including women in vector control campaigns (tiny targets) and elimination programs for Gambiense HAT may lead to female empowerment and increase community engagement (Kovacic et al. 2013; Kovacic 2015). Further research toward the more complete development of JE-CEA and kindred techniques should explicitly account for how positive and negative components interact when assessing the clustering of disadvantage in Phase 1 of the social justice assessment.

There is also the need to evaluate these results in the context of uncertainty. For instance, even in well-funded screening campaigns, systematic bias and social exclusion preference may occur, as local campaigns may prioritize urban areas that are more feasible to reach, leading to unintentional geographical isolation of rural communities in hard-to-reach areas. To take into consideration such situations or other scenarios that deviate from the assumptions in the main analysis, the JE-CEA assessment could be conducted for each area separately so that decision makers can infer how distributions of social justice impacts vary by region. This form of sensitivity or scenario analysis is common practice in CEA modelling, and hence the uncertainty analyses for JE-CEA are highly recommended in further applications.

The approach to conjoining justice-enhancement with traditional techniques of economic evaluation may also require refinement. In this study we used the DALY as the main outcome, but other health-related quality-of-life (HRQoL) values use indices that ask patients about their ability to conduct everyday activities. Hence impacts on agency may already partly be captured by such measures. Further applications of JE-CEA may need to ensure that 'double-counting' for components of well-being is ruled out.

8.8   Conclusion

Zwerling and colleagues (2017) have presented JE-CEA as a novel methodology based on the method of ethical analysis that Bailey and colleagues (2015) had earlier proposed as suitable to inform public health decision making in EIC decision contexts for NTDs. In this paper, we have tested the use of JE-CEA in the context of the Gambiense HAT EIC, demonstrating how JE-CEA can help global health decision makers and stakeholders to evaluate not only the economic consequences but also the social justice impacts of different pathways towards disease control and elimination.

In the Gambiense HAT decision context, the structure of JE-CEA as an 'alongside' method allows its justice enhancement (JE) component to be applied not only to CEA but also to probability elimination analysis. In principle, given its structural flexibility, JE-CEA is transferable to similar decision contexts for other kinds of public health programs, where decision makers commonly evaluate clinical effectiveness, safety, value for money (i.e. cost-effectiveness), budget impact, and ethical considerations. JE-CEA could help to articulate as part of the overall evaluation the sorts of ethical considerations that might otherwise end up in a dossier paragraph summarizing available literature on social disparities. Motivated by social justice as a moral imperative to avoid and remediate inequitable distributions of societal disadvantage, and resting on a normative basis derived from the family of capabilities and well-being theories of justice, JE-CEA can be further developed to assess explicitly the expected social justice impacts of the options compared. In addition to broadening the evidence base available to stakeholders and decision makers, JE-CEA also offers a promising approach to including the voices and experiences of people whom public health programs are intended to benefit.

8.9   Key words

economic evaluation; elimination investment cases; neglected tropical diseases; social justice; Trypanosoma brucei gambiense

8.10   Funding

8.11   Acknowledgments

8.12   Conflict of Interests Declaration

We have no conflicts of interest to declare.

9. Discussion

An EIC has been shown to be a labour intensive analysis, but bears the fruit of useful and applicable results for decision makers considering investments in NTD elimination. Although thus far various components of the EIC have been discussed as individual elements in chapters, they are now summarized in Table 18. At a national program level, it was consistently throughout all the analyses that the current control program is inferior to other elimination alternatives. Surveillance programs operating at 80% coverage in moderate and risk transmissions areas may reduce the cases, but reaching elimination in low risk transmission areas by relying on patients to self-report and bear the burden of out-of-pocket (OOP) expenditures to seek treatment will not lead to full elimination across sub-Saharan Africa. This in turn renders that current approach to HAT control programs to be dominated in all cost-effectiveness analyses and incur the highest societal burden over time, and impinge of patient's core dimensions of well-being. An elimination program that focused on adopting new technologies for surveillance delivery, diagnostics and treatment (Elimination I) will save costs in the long run while reducing more cases than the current control program, and can be fully integrated into the system eventually. It will also reduce CHE related to OOP and improve social justice across all domains of respect, association, and agency, however, it may not lead to complete elimination in low foci areas. Scaling-up surveillance in low risk foci all the while adopting new innovations and deploying tiny targets in high foci (Elimination II and III) seemed to be the optimal approach. Although they require a higher cost-effectiveness threshold than $300 per DALY averted used by the BMGF (National Institute for Health and Clinical Excellence (NICE) International 2014) they both lead to elimination and have the possibility to be fully integrated into the health system. The main concern with these programs is that the interim intensive surveillance campaigns low transmission areas may worsen disadvantage, and this will need to be addressed. In addition, Elimination III deploys tiny targets in moderate risk foci which in turn increases the overall costs and cost-effectiveness, but ensures the probability of elimination this area.

These results hence provide a series of information for stakeholders to decide which option is the most attractive for their concerns. For instance, global non-governmental (NGOs)

organizations may be most concerned with global elimination and prefer elimination programs (II and III) that excel in reaching elimination goals. On the other hand, national decision makers and investors may be more concerned with cost-effectiveness and may choose a more affordable program (Elimination I) forgoing elimination goals within this generation, but ensuring case declines in high and moderate risk foci. There are also other combinations of programs for elimination that could be further explored.

Table 18. Summary of outcomes for EIC of HAT *T.b. gambiense*

For comparison across		Control	Elimination I	Elimination II	Elimination III
Strategies (by foci)					
	Low		Strategy D	Strategy D+	Strategy D+
	Moderate	Strategy A	Strategy D	Strategy D	Strategy E
	High		Strategy D	Strategy E	Strategy E
Elimination *Number of cases expected in 2020*		less than 3000 cases	less than 2000 cases	less than 100 cases	less than 100 cases
Probability full elimination (% chance)					
	Low	No chance in low	No chance in low	70%	70%
	Moderate	60%	70 - 80%	90%	98%
	High				90%
Cost-effectiveness		Dominated	Approx. $300 per DALY averted	Approx. $700 per DALY averted	Approx. $1500 per DALY averted
Financial (until 2020)		$0.63 billion	$0.42 billion	$0.98 billion	$1.25 billion
Out-of-pocket (OOP) in 2020 **CHE 10%** **CHE 25%**		62.93% 30.96%	1.25% 0.49%	1.27% 0.51%	1.23% 0.48%
Health systems (passive surveillance) treatment integration potential		Pentamidine-NECT No integration	Full integration FEXI 2016 → Full integration OXA 2019	Full integration FEXI 2016 → Full integration OXA 2019	Full integration FEXI 2016 → Full integration OXA 2019
Ethical considerations*		▮▮▮	▮▮▮	▮▮▮	▮▮▮

*SJA based on low risk transmission areas only where orange = expected to worsen, yellow = may worsen disadvantage, turquoise = not expected to worsen; FEXI = fexinidazole, OXA = Oxaborole SCYX-7158; TBD = to be determined, NOTE; (London declaration targets less than 2000 cases in 2020)

9.1 EIC results for investment decisions (direct applications)

9.1.1 EIC for the BMGF

As the Eradication Investment Case (EIC) project came to a close in 2014, the three reports were delivered to the Bill and Melinda Gates Foundation (BMGF) in the summer of 2015 in order to make decisions for control, elimination and eradication campaigns relative to the diseases over the next coming years. At the initiation of the project the design of the EICs for lymphatic filariasis (LF) and onchocherciasis (oncho) were more similar and hence it was thought that human African trypanosomiasis *Trypanosoma brucei gambiense* (hereunto referred to as 'HAT') could not be compared; but in the end, there are core components of the EIC that resonate throughout the three dossiers. Components related to economic and elimination outcomes for the three are summarized in Table 19. Across the three diseases, the results demonstrate unanimously that the current strategies are insufficient to reach global goals of eradication or elimination. The overall incremental cost-effectiveness rations (ICERS) for elimination and or eradication demonstrate that HAT has higher cost-effectiveness ratios than the other two. This is due to the fact that extensive financial resources (i.e. surveillance, vector control prevention) are necessary investments to detect and treat HAT cases. In regards to societal costs, LF and oncho both calculated economic loss as volunteers are used to administer mass drug administration (MDA) campaigns for disease eradication. Since there is no safe and preventative oral treatment available as yet for HAT, MDA campaigns are not feasible and hence the burden of direct costs related to seeking treatment rely on households of HAT patients. For this reason OOP expenditures were a more appropriate societal related cost for HAT. Overall, the results show that disease specific costs and benefits of eradication and elimination, and also demonstrate that EIC can be compared across diseases for possible discussions of investment prioritisation. Recent feedback from the BMGF also (*personal communication*, BMGF) reinforced that the dossiers were helpful in NTD funding prioritisation.

Table 19. Summary of several components of EICs for onchocerciasis (oncho), lympahtic filariasis (LF) and human African Trypanosomiasis (HAT) *Trypanosoma brucei (T.b.) gambiense*

	oncho 'river blindness'	LF 'elephantiasis'	HAT 'sleeping sickness'
Current strategy	Control	Elimination	Control
Alternative strategies	Elimination Eradication	Eradication I Eradication II Eradication III	Elimination program I Elimination program II Elimination program III
Elimination/Eradication outcomes	Current (*Control*) unlikely to reach eradication in next 3 decades, while scaling up to *Eradication* probable of reaching global goals in 2040(Beer et al. 2015)	Current (*Elimination*) likely to reach eradication in next 4 decades, while scaling up to *Eradication* programs probable of reaching global goals near 2030(Wellcome Trust 2015)	Current (*Control*) unlikely to reach elimination targets in next 3 decades, while scaling up to *Elimination* programs with new technologies, vector control and surveillance likely to reach global goals
Cost-effectiveness	Eradication dominant(Sutherland 2016)	$73 to $220 per DALY averted*(Barton et al. 2008)	Less than $200 to greater than $1500 per DALY averted
Financial costs	Costs ranging from $640 million(*Control*) to $650 (*Elimination, Eradication*)[18]	Costs ranging from $930 million (*Elimination*) to $1.3 billion (*Eradication I*)[19]	Costs ranging from $410 million (*Elimination I*) to $1.2 billion (*Control Elimination II, III*)) till 2020
Societal costs**	Current (*Control*) program costs $3.7 billion but *Elimination & Eradication* reduce costs to $2 billion[18]	Current (*Elimination*) program costs $5 billion while *Eradication* programs increase costs near $8 billion[19]	Current program (*Control*) leads in incurrence of CHEs, while *Elimination* programs would reduce CHE to less than 2%

NA = not available
*CE compared to Elimination, although results suggest that if examined for dominance, Eradication III would be the dominant strategy
** economic costs for onchocerciasis and LF calculated as donated volunteer time from CHWs, HAT used OOP
CHE=catastrophic health expenditure

9.1.2 Drug discovery funding case for Novartis Institute for Tropical Disease (NITD), Singapore

Another direct application of how these results could be used for funding decisions, was in regards to an application for development of a new target product profile (TPP) drug for HAT in case oxaborole experiences market failure. The model was used to forecast several strategies for treatment in a low transmission area in the absence of vector control to evaluate the potential impact that a new TPP would have if fexinidazole arrived in 2016 to treat both disease

stages with or without oxaborole arriving on the market a couple years later.(M Kawonga et al. 2015; Mary Kawonga et al. 2015) The results presented in Figure 24 demonstrated that the approval of a new TPP in 2022 that could improve coverage due to its ease of use (*'fexinidazole, oxaborole and TPP approved'*) would further reduce transmission, even in the absence of active surveillance. Furthermore, if oxaborole failed to reach market in 2019, but a new TPP was available in 2022, reduction of cases could still be attained (*'fexinidazole and oxaborole approved'*). These outcomes were presented to the Wellcome Trust and resulted in an 8 million GBF grant for the development of a new TPP awarded to NITD in collaboration with several academic laboratories.(Hoaglin et al. 2011; Jansen et al. 2011) According to the VOI analysis, this also seems a reasonable investment given the uncertainty of elimination over the next 30 years for an at risk population of nearly 60 million people.

Figure 24. Control and elimination strategies of new oral treatments
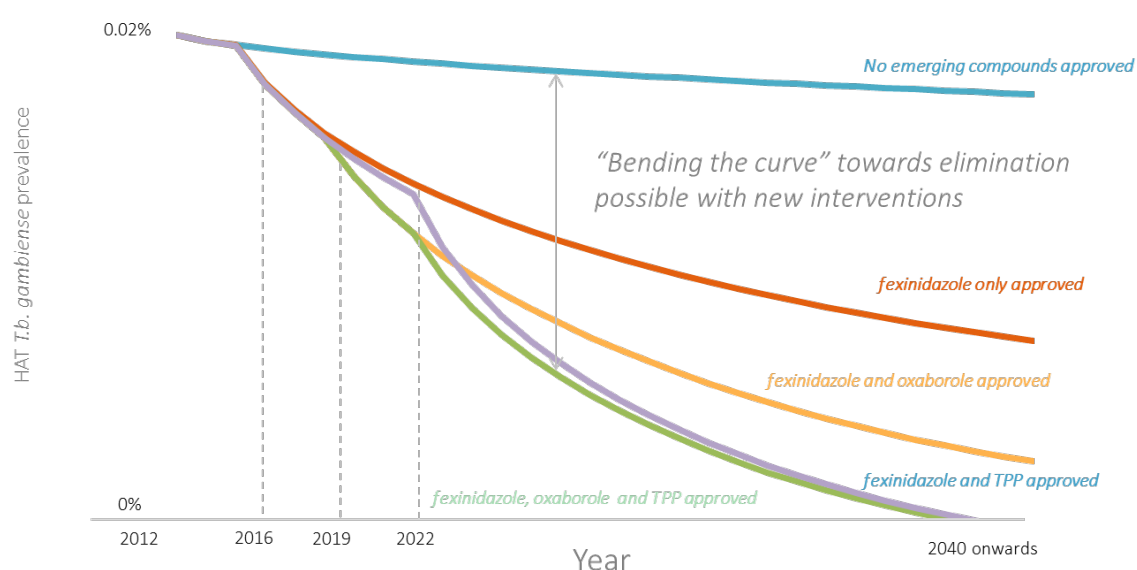
*Projections based on HAT dynamical transmission model estimates of low risk transmission areas for Eradication Investment Case (EIC) project, Swiss TPH, Health Systems Research Dynamical Modelling Unit; elimination defined by London Declaration targets as less than 1 in 10,000

9.2   Lessons learned from the EIC

As mentioned within the introduction of this thesis, at the onset of the project no formal methodology or protocol had been described for the EIC besides the itemized questions proposed by the Ernst Strüngmann and hence already established approaches were completed along with a few innovative approaches. In the end, the core analytical methodologies were completed and this process is outlined in Figure 25.

The evidence base collected relied largely on the available literature and hence several reviews were undertaken. Accessing national reports, case data available from the WHO repository and also speaking to experts in the field were key to understanding this neglected disease as often information goes unpublished due to lack of funding or interest from journals. Gathering a broad evidence base also highlighted the use of vector control use mainly for prevention in animal African trypanosomiasis (AAT), which in turn resulted in a more holistic approach to elimination thinking for HAT. This also highlighted that aggregate secondary evidence is quite informative in decision making and also time efficient, and makes use of work done by previous researchers. The irony is that, resource rich countries are beginning to spend less on primary research and use secondary evidence for investments in health care decision making (HTA) while health research in resource poor countries rely more on evidence from high cost epidemiological studies to lobby for funding. Unfortunately this is not a sustainable approach. There is also a tendency to 'over-innovate' and seek out funding for new research before clearly evaluating the existing evidence and seeing if we can use already well-established methodologies or liase with a group that may be more advanced than we are. This can be a humbling exercise for academics, but is essential for those working in situations with limited resources as was the case for HAT. Conceptualising current and alternative strategies was also a key process needed at the beginning of the EIC that in the end drove all the subsequent analyses. In the case of HAT, this was also a progressive process as potential scenarios involved into foci related strategies which in turn became potential control and elimination programs. Although further scenarios, strategies and programs could be hypothesized, this processed generated a series of relative options for the various investment profiles of the decision makers that will use this information. However, further work on HAT scenarios could involve strategies with more variation of the diagnostics tests as these parameters are not thought to be a bit more variant that once perceived (M Kawonga et al. 2015; Mary Kawonga et al. 2015) and also to explore the possibility of targeted campaigns to high risk sub-populations that may be contributing to the overall community disease transmission.

Figure 25. EIC project processes
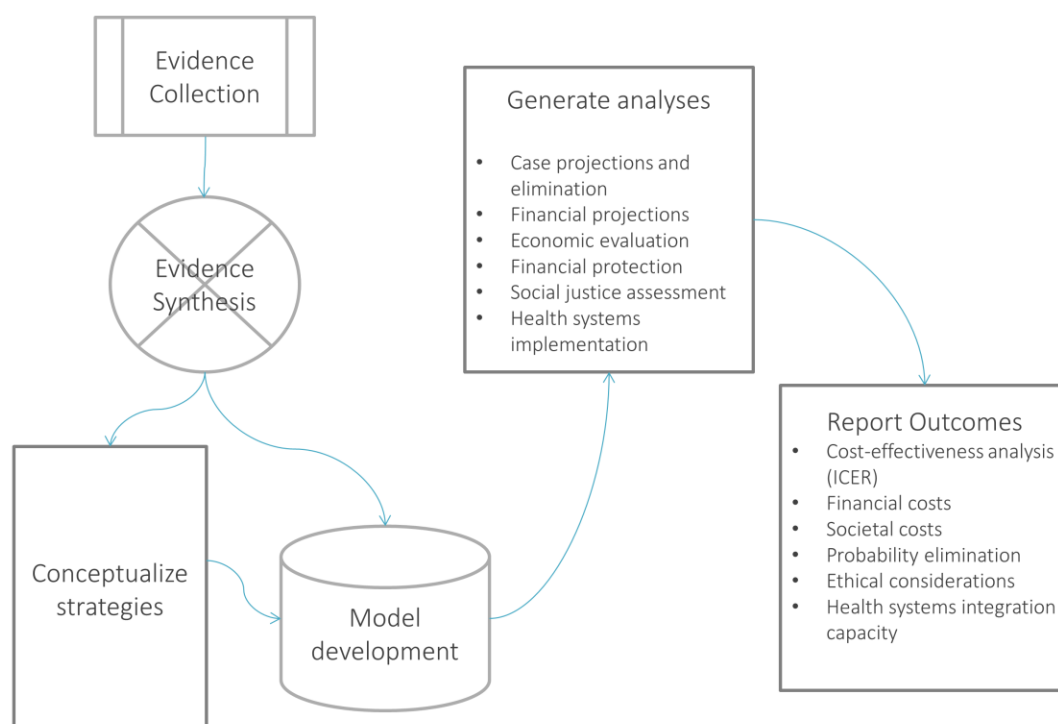
Modelling proved to be one of the key components of the project as it forecasted elimination probability for strategies, percentage reduction used to estimate the number of cases, health impacts calculated in the modelling using DALYs and cost projections. Subsequently as models are data driven, such analyses required a large number of input parameters. The model also contains stochastic inputs that led to the calculation of uncertainty in economic evaluation. One issue that came to light during the economic evaluation was when the time for choosing optimal strategies came. To evaluate the optimal strategy related to the foci specific areas, a cost-effectiveness acceptability frontier (CEAF) was generated. The results shown in (Figure 26) confirm that Strategy D or E are the most CE strategies in high and moderate areas based on different CE thresholds; however, in low transmission areas, strategy B no longer serves as an option as it was dominated in the base case analysis. From recommended techniques (Sutherland 2016) strategy B should not be included as it was dominated in the base case analysis, but even when other strategies are removed, it does not compete as an artefact but as a cost-effective option with some probability for low risk foci. This is something that decision makers need to consider under uncertainty and hence was why it was still considered a possible option in HAT elimination program development.

Figure 26. CEAC versus CEAF in low transmission foci

A. CEAC

B.CEAF
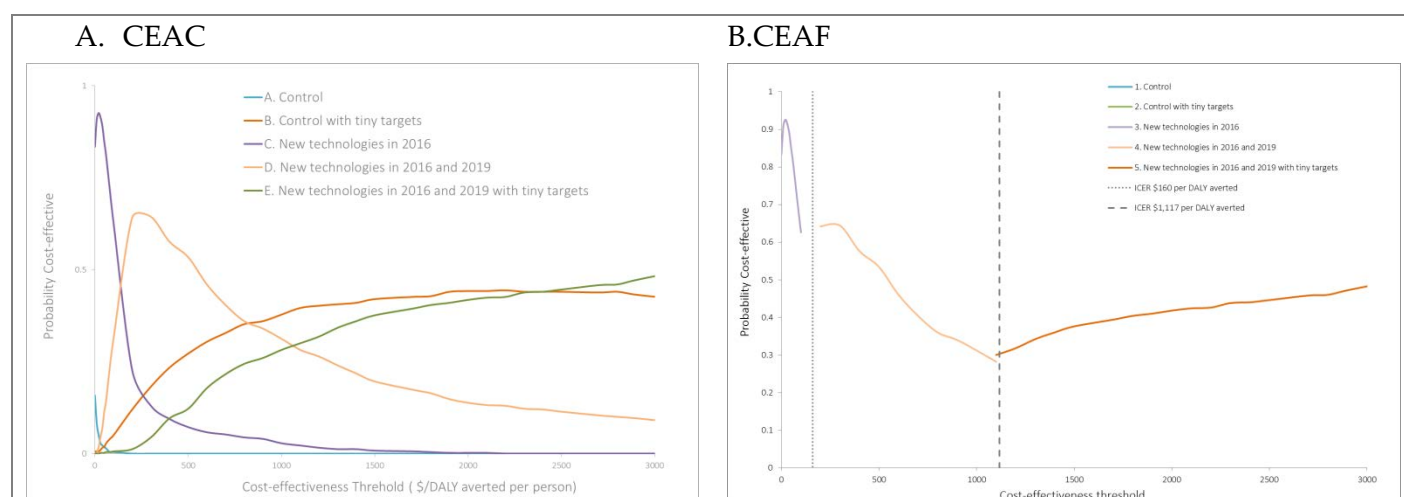
Through the process of the EIC, it also became evident that it is a work that re of analyses and expertise required and experts from various fields (i.e. Modeller, economist, information specialist (literature reviewer), ethical philosopher, epidemiologist, principal investigator (project manager)) committed over an extended amount of time. This in turn means that future EICs, will not come at a small price; however, it has already been shown that these investments are worthwhile.

9.3   Further and continued research within the EIC

9.3.1 Governance and funding

In *Chapter 7*, health systems thinking was used to amalgamate key actors in the Gambiense HAT elimination, and also highlighted that integration would influence most actors at the National level with few changes in governance, finance and information. However, there is still a need to evaluate the current power structure of governance for HAT to ensure that integration goes smoothly and also to ensure that the key players collaborate towards global elimination. Network analyses using social network analysis (Barrett 2013) or Bayesian network analysis commonly used in indirect-treatment comparison(Policy Cures 2008), could be a potential avenue to further evaluate the implications that relationships in governance have in relation to what is achieved on the ground in the affected nations. Without any formal analysis, the known connections of the actors in the health building blocks (*Chapter 7*) already

reveal (refer to Figure 27) that the BMGF are a high frequency donor with several connections to financial ties to MSF, R&D, and WHO. MSF and the NSSCP have the greatest links to the patients, families and communities. There are quite a few peripheral institutions whose complete roles would require future research. This could be done to discern each players' involvement as the role of new individuals as integration occurs. Network analysis can also be done to show the strengths of the relationships that have the most impact on making changes (Sutherland 2016).

Figure 27. Network of actors included in Gambiense HAT elimination

Legend: **grey** = internal connection (same institution); **green** = funding, **blue** = delivery of services/flow of communications; perforated lines indicate new players included in integration of health system

Health systems building blocks: H = Healthworkforce, S = Service and delivery, G = governance, I = Information, F = Finance;

MSF=Médecins sans Frontières, NSSCP=National sleeping sickness control programs, CHW=community health worker, Med profess=Medical professional, HC=health centre, ITM = Insitute of Tropical Medicine, SDI=Standard Diagnostics Inc., R & D=Research and development, FAO = Food and Agriculture organization of the United Nations, PAAT = Programme Against African trypanosomiasis, WHO = WHO headquarters (HQ) and WHO (African Regional Office (AFRO), IAEA= International atomic energy agency, AU=African Union, PATTEC= Pan African Tsetse Eradication Campaign, ADB = African Development Bank, NORAD = Norwegian Agency for Development Cooperation Governmental, BMF = Bundesministerium für finanzen, SDC= Swiss Development Corporation, BDC=Business Development Bank of Canada, GE = General Electric, DFID= Department for international development United Kingdom , AB = Arab Bank, GTZ = Gesellschaft für Technische Zusammenarbeit, AECID= Agency of International Cooperation for Development, MAEE= Ministry of Foreign and European Affairs, BMBF= Bundesministerium für Bildung und Forschung,Note: R& D includes academic and research and development partners including: WHO collaborating centres, DNDi, FIND, ICIPE, IRD, INRB, ITM, IHMT, Makere University, Swiss TPH (University of Basel) , University of Glasgow, University of Liverpool (LSTM), University of Oxford,. University of Warwick, Yale University, Oregon University, IDM = Institute for disease modelling

In order to be fully incorporated into the EIC, examining governance changes by program would also be necessary. Although maybe integration seems optimal, there could be synergistic impacts or relational repercussions from well-established programs that could

inadvertently hinder progress even though well intended. This is an application that could be further developed in future EIC methodological research.

There are 24 countries at risk, with 13 endemic, but only 18 representatives listed with NSSCP as of 2016.(Winkler et al. 2013) Although some countries may be near declaring status for elimination, there is still a concern that there may be foci that are still endemic and six nations with no NSSCP, it will be difficult to achieve global elimination. Additionally, with the large investments required for elimination discussed previously, some nations make opt for cost-effective programs at a lower threshold in turn leading to elimination delays. Applications of cooperation stemming from 'game theory' (Goeree & Levin 2006) could be of potential use in understanding impact of collaboration versus no collaboration globally or also how bordering countries and weak control over migrating populations could impact elimination efforts.

Funding is also closely connected to governance issues. As depicted in Figure 27, financing is key part of the health system and it is important to know who the key funders are and also which components of elimination are being covered. This is often disease and treatment specific for global health donations. As is with the case of HAT, the pharmaceutical companies donate their treatments, the vector control programs can provide targets at reduced costs, but the coverage of the surveillance and health care system then falls on the ministry of health or local NGOs. In order to achieve elimination it will be necessary to make sure that funds for all components of elimination programs are covered.   A funding gap analysis is also part of the EIC that has gone unanswered. To date there is still a need to ascertain is how much money is specifically be invested for HAT to understand the additional funds required. G-FINDER (Dixit & Pindyck 1994) estimates that in 2014 alone nearly 50 million was spent on R & D alone for sleeping sickness. As there seem to be enough tools necessary for elimination, perhaps R&D investments can be diverted to elimination campaigns. This is not to say that R&D is to be stopped, but as funders are already overwhelmed by demands, should not prioritisation of funds go towards on the ground research that can contribute to elimination? R & D efforts can make more direct links to work on the field so that R&D contributes to elimination. For instance, drug trials recruit from the population at risk, contributing to reducing global number of cases and field studies with RDTs and tiny targets also simultaneously train health workers and with communities respectively. Modelling geographical at risk areas may be needed, but maybe this can be done in collaboration with collecting field surveillance

databases that can simultaneously improve information systems, surveillance coverage and be used for future epidemiological modelling forecasts. These sort of R&D endeavours should be encouraged. Overall HAT is a costly disease, so countries and programs may need to be innovative in securing funds. Exploring options for fundraising (E.g. March of Dimes Franklin D Roosevelt) can generate global awareness and impresses funders. For example, a campaign called 'trips for tryps' could be initiated where airline companies and have passengers donate spare change, or even have a 'pop-up' advertisement when purchasing travels online that asks for a small donation. This is simply an idea, but if the campaign then approached a donor and asked them to match dollar for dollar, twice as many funds could be generated. Other funding options could also include collaborating elimination projects that use tiny targets with AAT programs that often receive national funding from agricultural and/or economic departments.

9.3.2 Additional EIC questions unanswered

There are still issues related to risk and contingency planning for failure to reach targets due to unforeseen circumstances (i.e. war, natural disaster) but also to consider formal post-elimination planning. For instance, once cases have been reduced to zero, surveillance still needs to remain intact in the event of resurgence in a given foci. Integration with the healthcare system and improving information systems with 'triggers' would be useful so the medical professionals are able to catch 'alerts' when an outbreak begins. The operational planning and implementation still needs to be discussed. The EIC for HAT has provided several programs that could be used for elimination, but how countries will implement the scaling up of these programs on a daily basis still relies on the NSCCP. Motivation and incentives have also not yet been discussed but could be useful if addressed in an EIC. As has been shown with the forecasting, the timeline to elimination is long and in the final years uneventful. Already it has been seen that health workers in the field for HAT are demotivated and losing interest.(Thokala & Duenas 2012; Diaby et al. 2015; Diaby & Goeree 2013) Creative discussion may be needed to prevent fatigue during elimination and increase intrinsic motivation and interest. For example, countries looking to eliminate HAT could consider giving a national holiday once disease elimination is achieved. Now that the HAT EIC is complete, there will probably be a tendency to disregard the results after programs for elimination have been chosen. However, global planners should continue to monitor the forecasted outcomes, to

ensure that elimination is on track and to update the modelling to readjust the forecast as additional information becomes available. This then becomes an iterative process as is seen other health decision making processes in health impact assessment (HIA) (Uniting to Combat NTDs n.d.) or the PRUFE[15] framework within the ministry of health in Ontario, Canada.(Goeree & Levin 2006)

9.3.3 Methodology and use

As this was one of the first projects to formally develop an EIC, the methodology still needs to be formalized; but given the lessons that have been learned from this project, there is a possibility now to develop formal guidelines or protocols for EIC development that are non-disease specific and also transferable. Instruction should also be given for appropriate timelines for the stages involved and perhaps even split the project into phases with interim deadlines. Referring again to Figure 33, the first phase could involve the evidence collection, synthesis and model development within the first 6-18 months, with the analyses and outcomes generated in the next 6-18 months. Outcomes should be harmonized so that decision makers are able to prioritize across diseases as was illustrated in Table 23. Still, there remain additional analyses that could have been undertaken for the EIC. For instance, it has been mentioned that pursue further research would be worthwhile (*Chapter 5, Value of information*), but the expected value of parameter perfect information (EVPPI) could also be to tell decision makers *which* parameters should be the focus on further research. Additionally, the EIC has a close connection to time and delays in investments for decision in elimination have not yet properly been discussed. Exploring the techniques available on calculating the pros and cons of delayed decisions for investors as discussed by economists (SCORE n.d.) could be of interest for further research in EICs. Financial and societal costs outcomes for the HAT EIC were limited to a financial protection analysis and cost forecasting but productivity losses could also be considered as a formal component of the methodology. In addition, no formal budget impact analysis was done, but perhaps this is a method better left to national decision makers. As previously stated, if further research on EIC methodology is to continue, developing the health systems thinking and modelling component would be of use, but also broader

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[15] Program for Assessment of Technology in Health (PATH) reduction of Uncertainty through Field Evaluation (PRUFE)

implications of local settings could be considered. For instance, depending on the tropical disease, water and sanitation (WaSH) programs can have quite an impact. Ethical considerations also have been shown to highlight discordance between components of cost-effectiveness and elimination targets, but these discrepancies still need to be resolved.

The EIC also has various components that allow for the possibility of a multi-criteria decision analysis (MCDA) framework. (Molyneux et al. 2010; Zhang et al. 2010) Using this approach, decision makers could decide on which components of that full analysis have greater weight (i.e. cost-effectiveness, social justice, etc.) and then after completing each assessment would receive a score for each disease based on the a priori weighting scheme.

9.3.4 EICs for other NTDs investment decisions

Elimination and eradication campaigns are still underway for several other diseases,(World Health Organization (WHO) n.d.) and investors committed to other disease areas are beginning to see a need to develop elimination programs that demonstrate good value for money. The Novartis Foundation has already initiated an EIC for Buruli ulcer (Leprosy (Hansen disease))(Hackett et al. 2014) and now Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) also plans to formally assess elimination with an EIC dossier.(Chris M. Stone & Chitnis 2015) Yet there are still many other neglected diseases that will benefit from EIC reporting (e.g. American trypanosomiasis (Chagas), Trachoma, Soil-transmitted Helminthiasis), and new epidemics continually on the rise in tropical environments (i.e. Ebola, Zika Virus) and these areas should be explored.

9.4   Conclusion

The EIC has proven to be a useful approach that is both technically feasible and informative. However a continued development of methodology may be needed if it is to be applied to other NTDs to assist global DMs in eradicating diseases that affect the poor and improving sustainable development goals (SDGs). The EIC for HAT has provided various options for stakeholders to move towards elimination, but funding gaps may abound so countries may need to be innovative in securing additional funds for HAT specifically as donors may favour alternative diseases that appear more cost-effective according to their willingness-to-pay thresholds. Integration is inevitable and necessary for the advent of sustainable health systems

in the developing world, but more strategic planning in this area is needed. Health systems modelling and operational research methods show promise but may need to be explored further to see their use within an EIC.

Now is the time to move forward. Although impact of delayed investment not formally assessed, delays in actions inevitably lead to delays in reaching elimination timelines. Declines in cases will be seen, but additional, continuous and sustained pressure will be required for elimination. This is not the time for lethargy or complacency in moving ahead, and global investors should not relax as cases decline. To full stop transmission getting less than one case will be the most difficult as the tail end of elimination is logarithmic and tends to plateau at low numbers. There are still unanswered concerns about elimination, but decision makers should be cautious to not 'over-analyse' when things just need to get done. The truth is we know what to do and we have the tools to do it,(National Institute for Health and Clinical Excellence (NICE) International 2014), hence the current need is to put research into practise and prioritize moving forward instead of contemplating additional research questions.

Researchers and medical professionals also need to make an effort to translate knowledge to next generation as if the hope of elimination is achieved; this will be the last generation to observe various cases, parasite and treatment, to allow for a combination of trained professionals but also younger health workers who will be around for the next half century to offer expertise.

9.5   Recommendations towards HAT elimination

9.5.1 Immediate goals

- National Sleeping Sickness Control Programs (NSSCP) should *select appropriate programs* towards elimination with the given tools so that they can begin to secure appropriate funding and establish networks for smooth delivery of products. The WHO stakeholders for Gambiense HAT elimination could be used as an opportunity to commit to or make a declaration of chosen elimination strategies

- Secure *long-term funding commitments* and consider additional funding innovations

- *Surveillance* needs to be improved and will probably require a combination of active and passive surveillance until the passive healthcare system is prepared to integrate

the newer technologies. Increases in surveillance coverage need to be initiated while simultaneously collecting surveillance from the field into an accurate case reporting information systems. Starts identifying local health centres and local NTD initiatives to partner with to be ready to integrate fexinidazole in 2018.

- Maximise efforts work with clinical trial people to refer cases for clinical trials and researchers work directly with new technologies in field studies so that progress in R&D contributes to overall elimination goals.

- *Local initiatives* Scale up health workforce to have working knowledge of 'sleeping sickness' as well as differentiation between it and other febrile illness also common in other tropical diseases. Deploy targets and teaching communities to maintain traps for sustainability.

9.5.2 Long-term goals

- Monitoring EIC projections on annual basis
- Integration with other elimination/eradication campaigns for NTDs

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APPENDICES

Appendix A: Chapter 1

A.1 *Guiding Questions (from Guide to Preparing EIC version 07.11.11)*

		Overarching question research question(s)	Methodology	Result (Outcome measure)
Section I: The proposed investment				
I.1	The disease and its global health significance	*What options are available?*	• Literature review of available and emerging interventions	Scenarios, strategies, programs options
I.2	The current state of control efforts	•	•	
I.3	How eradication can be achieved	•	•	
I.4	Post-eradication scenarios	•	•	
Section II: Rationale for investing		•	•	
II.1	Biological and technical feasibility	•	•	
II.2	Health and economic burden of disease	•	•	
II.3	Assessment of total costs	•	•	
What is the total cost of the post-eradication plan?				
II.4	Cost-effectiveness and cost-benefit analyses	•	•	
II.5	Public goods obtainable through eradication	•	•	
II.6	Strengthening health systems	• *What options demonstrate good value for money?* • *What options can we afford?* • *What options are logistically and operationally feasible?*	• Dynamical disease transmission modelling • Economic evaluation • Health system modelling	Probability Elimination ICERs Capacity
Section III: Challenges, risks and constraints			•	
III.1	Stakeholder involvement		• Survey of stakeholder commitments	?

	• *Who will do it?(Whose involved?)*		
III.2 Challenges, risks and constraints Ethical, Social, and Political	• *What is the ethical option?*	• Justice-enhanced CEA	Impact on well-being and population affected
III.3 Epidemiologic Technical and Geopolitical Market Dynamics	•	•	
III.4 Critical risks and risk management plan	• *What is our contingency plan? ? (E.g. if new technologies don't make it…then what? Should consider increases in surveillance and vector control more seriously – what about wars? Strategies for containment?)*		?
Section IV: Management and governance			
IV.1 Partnerships and governance			
IV.2 Critical milestones and monitoring confirm that appropriate standards are being met?			
IV.3 Operational Research Plan	•		
IV.4 Evaluating impacts on health systems	• *Who will do it? ?* • *How will it get done?*		?

Appendix B: Chapter 3

B.1 *Search strategy*

Type	Keywords for MEDLINE	Keywords for EMBASE
Population – Human African trypanosomiasis	1. Trypanosomiasis, African/ 2. exp Trypanosoma brucei gambiense/ or 3. Trypanosom$.mp. 4. Tsetse fl$.mp. 5. HAT.mp. 6. sleeping sickness.mp. 7. human african trypanosomiasis.mp. 8. Glossin$.mp. 9. Tb gambiense.mp. 10. Tb rhodesiense.mp. 11. T brucei gambiense.mp. [mp=title, 12. T brucei rhodesiense.mp. 13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	1. Trypanosomiasis, African/ 2. exp Trypanosoma brucei 3. Trypanosom$.mp. 4. Tsetse fl$.mp. 5. HAT.mp. 6. sleeping sickness.mp. 7. human african 8. Glossin$.mp. 9. Tb gambiense.mp. 10. Tb rhodesiense.mp. 11. T brucei gambiense.mp. 12. T brucei rhodesiense.mp. 13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
SIGN Filter – Economic Models and Evaluations	1. Economics/ 2. "costs and cost analysis"/ 3. Cost allocation/ 4. Cost-benefit analysis/ 5. Cost control/ 6. Cost savings/ 7. Cost of illness/ 8. Cost sharing/ 9. "deductibles and coinsurance"/ 10. Medical savings accounts/ 11. Health care costs/ 12. Direct service costs/ 13. Drug costs/ 14. Employer health costs/ 15. Hospital costs/ 16. Health expenditures/ 17. Capital expenditures/ 18. Value of life/ 19. exp economics, hospital/ 20. exp economics, medical/ 21. Economics, nursing/ 22. Economics, pharmaceutical/ 23. exp "fees and charges"/ 24. exp budgets/ 25. (low adj cost).mp. 26. (high adj cost).mp. 27. (health?care adj cost$).mp. 28. (fiscal or funding or financial or 29. (cost adj estimate$).mp. 30. (cost adj variable).mp. 31. (unit adj cost$).mp. 32. (economic$ or pharmacoeconomic$ or 33. or/1-32	1. Socioeconomics/ 2. Cost benefit analysis/ 3. Cost effectiveness analysis/ 4. Cost of illness/ 5. Cost control/ 6. Economic aspect/ 7. Financial management/ 8. Health care cost/ 9. Health care financing/ 10. Health economics/ 11. Hospital cost/ 12. (fiscal or financial or finance or 13. Cost minimization analysis/ 14. (cost adj estimate$).mp. 15. (cost adj variable$).mp. 16. (unit adj cost$).mp. 17. or/1-16

B.2   *Information, inclusion-exclusion criteria legend*

PICOS Criteria	Include	Exclude
Population (P)	- African trypanosomiasis in humans - Children, adults, men, women	- Chagas - American Trypanosomiasis - Other neglected diseases - Cattle and/or livestock populations - Tsetse fly populations
Intervention(I) & Comparators (C)	Interventions that contribute to reduction in transmission of disease in humans: - Passive + Active Surveillance Programs - Detection and Diagnosis - Treatment - Vector Control - Other (E.g. Health systems, community sensitization, etc.)	Interventions that DO NOT contribute to reduction in transmission of disease in humans
Outcomes (O)	- Costs - Consequences (E.g. $/DALYs, $/LYG, $/LYS, etc.)	- Costs only - Consequences only
Study (S)	- Economic evaluations as defined by Drummond et al. - CEA, CBA, CUA - Health Technology Assessment (HTA) reports with economic evaluations - Modelling studies with economic outcomes - EEACTs	- Editorials - Mathematical modeling studies with no economic outcomes - HRQoL studies - Cost analyses - BIA - BOI studies - Costing papers/studies

CEA=Cost-effective Analysis; CUA= Cost-Utility Analysis; CBA = Cost-Benefit Analysis; DALYs =Disability adjusted Life Years, LYG =Life years gained, LYS =Life years saved , HRQoL =Health Related Quality of Life, BIA=Budget Impact Analysis, BOI=Burden of illness; EEACTs= Economic evaluations alongside clinical trials

Appendix C: Chapter 5

C.1 *Methods (additional information)*

C.1.1 *Description of potential 'strategies' for control or elimination*

Potential Strategy	Description
Strategy A Control	Involves the current recommendations for control requiring screening and diagnosis. This begins by patients reporting themselves to local health centres (*passive surveillance*) or being detected through an *active screening surveillance** in his/her community. Blood serology tests using the card-agglutination trypanosomiasis test (CATT) identify suspected cases. Lumbar puncture is then performed to determine the disease stage. Patients confirmed with stage one are treated with pentamidine and stage 2 patients with nifurtomix-eflornithine combination therapy (NECT).
Strategy B Control with tiny targets	The same as *'Strategy A - Control'* in combination with insecticide treated screens deployed across foci areas to interrupt transmission.
Strategy C New technologies in 2016	The same as *'Strategy A - Control'* until 2016. At this time some cases to be treated with fexinidazole for second stage HAT as most facilities would still be implementing pentamidine for Stage 1 treatment. Diagnosis is hoped to be done with a rapid diagnostic test (RDT) and using loop-mediated isothermal amplification (LAMP) for parasitological confirmation.
Strategy D New technologies in 2016 and 2019	The same as *'Strategy C – New technologies in 2016'* until 2019, where it is hoped that at this time a novel oral tablet (oxaborole) that can treat both stages of diseases will be available and diagnosis done with a simple RDT.
Strategy E New technologies in 2016 and 2019 with tiny targets	The same as *'Strategy D – New technologies in 2016 and 2019'* in combination with insecticide treated screens deployed across foci areas to interrupt transmission.

*This includes passive surveillance combined with annual active surveillance in high risk areas and passive surveillance combined with biennial surveillance in moderate risk areas. In low risk settings, active surveillance not done and reliance solely on passive surveillance. These are based on the recommendations for T.b. gambiense control outlined by WHO(World Health Organization (WHO) 2013c)

C.1.2 Choice of health outcomes and measurement of effectiveness

The DALY was chosen as the outcome measure and cost USD per DALY averted was the item used to measure CE. Cost-effectiveness was assessed by evaluating the incremental cost-effectiveness ratio (ICER). Strategies were first aligned from lowest to highest cost, with the incremental costs and DALYs averted calculated for each strategy relative to its next best option and assessed for dominance. The annual prevalence, costs, time to elimination and DALYs over 30 years were calculated for each strategy by transmission area.

C.1.3 Disability adjusted life years (DALY)

Disability adjusted life years were calculated per diem based on traditional methods(World Health Organization (WHO) n.d.) and included the years life lost in combination with the years lost to disability (YLD). YLD for stage one and two of the disease were considered to be different and estimated values were taken from a recent publication by Hackett et al..(Hackett et al. 2014) In order to derive a value for YLLs, life expectancy was assumed to be 66years and the average patient age upon infection was assumed to be 25 years of age. The formula for DALY calculations is shown below.

$$DALYs\ per\ diem = ((mu\_s*Rh) + mu\_t*Th))*(41.3-((1/s+1/mu\_s)/365)) + q*Ih*yldI + s*Ah*yldII)$$

$$+ (((mu\_s*RhB + mu\_t*ThB))*(41.3-((1/s+1/mu\_s)/365)) + q*IhB*yldI + s*AhB*yldII)$$

Where,

mu_h = normal human mortality, mu_s = death related to HAT disease, mu_t = death rate, s= rate of progression to stage 2 and q= the duration of incubation

And where compartments described are,

Sh = susceptible humans, Ih incubating humans , Ah= infective humans (stage I of disease), Rh= removed humans (due to stage II of disease) and Th = treated humans

And *yldI* and *yldII* = refer to years lost to disability for stage 1 and stage 2 respectively when,

$$yldI = dw1*(1/((r1+s+mu\_h)*365))$$

$$yldII = dw2*(1/((r2+mu\_s+mu\_h)*365))$$

The disability weights for Stage 1 (*dw1)* and Stage 2 *(dw2)* of the disease were 0.191 and 0.81, respectively.

C.1.4 Coverage rate assumptions related to surveillance

The baseline values for coverage in the passive healthcare system and active screening campaigns were taken from the PNTHLA report(Programme National de Lutte Contre La Trypanosomiase Humaine Africane (PNLTHA) 2013) Active surveillance of 80.25% refers to the participation rate of a given foci. Hence, this should be interpreted as an active screening campaign covering 80% of the population in a given foci, not as a the coverage rate of foci across sub-Saharan Africa. In addition, the screening rate of for the passive health care system of 2.46% was also taken from the PNTHLA report.(Programme National de Lutte Contre La Trypanosomiase Humaine Africane (PNLTHA) 2013) An assumption was made that new technologies would improve passive coverage due to their ease of use by factors of 3, 6.5 and 10 resulting in coverage improvements of approximately 7.4%, 16% and 25% as listed in the table below.

Improvements of 5% coverage were assumed for active surveillance campaigns using motorbikes when new oral tablets (fexinidazole or Oxaborole) and rapid diagnostics become available in 2016 and/or 2019. This assumption was based on intuition from experts (*DNDi, personal communication*) that foresaw the ease of distribution and feasibility that came with the new technologies. Recent evidence from the field also suggests that this may be even higher since the motorbike campaigns may increase coverage to nearly 100%.(Sutherland 2016)

Parameter Description	Distribution	Point Estimate	alpha*	beta*	Source
Passive surveillance					
Coverage rate for passive healthcare system	Beta	2.46%	2.46	97.54	PNLTHA(Programme National de Lutte Contre La Trypanosomiase Humaine Africane (PNLTHA) 2013)

Coverage rate for new technology for passive screening					
NECT with CATT algorithm (2013)	Fixed	1*2.46%			
Pentamidine, Fexinidazole with RDT 1 algorithm (2016)	Fixed	3*2.46%			DNDi 2014 Annual Report(Drugs for Neglected Diseases initiative (DNDi) 2014a)
Fexinidazole (both stages) with RDT 1 algorithm (2019)	Fixed	6.5*2.46%			DNDi 2014 Annual Report(Drugs for Neglected Diseases initiative (DNDi) 2014a)
Oxaboroles with RDT algorithm 2 (2019)	Fixed	10*2.46%			DNDi 2014 Annual Report(Drugs for Neglected Diseases initiative (DNDi) 2014a)
Coverage rate for active screening program	Beta	80.25%	80.25	19.75	PNLTHA(Programme National de Lutte Contre La Trypanosomiase Humaine Africane (PNLTHA) 2013)
NECT with CATT algorithm 2013 (Mobile trucks)	Fixed	0			
Pentamidine, Fexinidazole with RDT 1 algorithm (2016)	Fixed	80.25%+5%			DNDi 2014 Annual Report(Drugs for Neglected Diseases initiative (DNDi) 2014a)
Fexinidazole (both stages) with RDT 1 algorithm (2019)	Fixed	80.25%+5%			DNDi 2014 Annual Report(Drugs for Neglected Diseases initiative (DNDi) 2014a)
Oxaboroles with RDT algorithm 2 (2019)	Fixed	80.25%+5%			DNDi 2014 Annual Report(Drugs for Neglected Diseases initiative (DNDi) 2014a)
*alpha and beta are the parameter properties required for a beta distribution					

C.1.5   Discounting

Costs and DALYs were discounted at an annual rate of 3% based on the Bill and Melinda Gates (BMGF) Foundation Methods for Economic Evaluation Project (MEEP) guidelines(National Institute for Health and Clinical Excellence (NICE) International 2014) and the WHO-CHOICE guidelines.(World Health Organization (WHO) 2003) Discounting was translated to a per diem instantaneous discount rate based on the formula:

$$T_{2013-2042} = \sum_{t=2013}^{2042} \frac{T_t}{(1+r)^{(t-2012/365)}}$$

Where r = discount rate, t = time, T = total costs or total DALYs accumulated per diem

C.2 Input parameters

Parameter Description	Distribution	Point Estimate	SD	alpha$^{\top}$	beta$^{\top}$	Source
Case detection (surveillance and diagnostic)						
Population						
Total at risk population (*pop_ar*)		100000				Assumption
Percentage of patients in stage 1	Normal	32.50%	0.0325			PNLTHA(Programme National de Lutte Contre La Trypanosomiase Humaine Africane (PNLTHA) 2013)
Percentage of patients in stage 2	Normal	66.94%	0.0669			PNLTHA(Programme National de Lutte Contre La Trypanosomiase Humaine Africane (PNLTHA) 2013)
Passive surveillance						
Coverage rate **for passive healthcare system**						
NECT with CATT algorithm (2013)	Beta	2.46%		2.46	97.54	PNLTHA(Programme National de Lutte Contre La Trypanosomiase Humaine Africane (PNLTHA) 2013)
Pentamidine, Fexinidazole with RDT 1 algorithm (2016)	Fixed, Beta**	7.38%				DNDi 2014 Annual Report(Drugs for Neglected Diseases initiative (DNDi) 2014a)
Fexinidazole (both stages) with RDT 1 algorithm (2019)	Fixed, Beta**	15.99%				DNDi 2014 Annual Report(Drugs for Neglected Diseases initiative (DNDi) 2014a)
Oxaboroles with RDT algorithm 2 (2019)	Fixed, Beta**	24.60%				DNDi 2014 Annual Report(Drugs for Neglected Diseases initiative (DNDi) 2014a)
Cost annual surveillance passive	Normal	$1.35	0.1350			
Active surveillance						
<u>**Truck teams**</u> **Cost annual surveillance start up active pp**	Normal	$0.42	0.0420			Lutumba 2007(Lutumba, Makieya, et al. 2007a)
<u>**Truck teams**</u> **Cost annual surveillance maintenance active pp**	Normal	$1.55	0.1549			Lutumba 2007(Lutumba,

						Makieya, et al. 2007a)
Motorbike teams Cost annual surveillance start up active pp	Normal	$0.21	0.0205			WHO(World Health Organization (WHO) n.d.)
Motorbike teams Cost annual surveillance maintenance active pp	Normal	$0.89	0.0886			WHO(World Health Organization (WHO) n.d.)
Coverage rate **for active screening programs**						
NECT with CATT algorithm (2013)	Beta	80.25%		80.25	19.75	PNLTHA(Programme National de Lutte Contre La Trypanosomiase Humaine Africane (PNLTHA) 2013)
Pentamidine, Fexinidazole with RDT 1 algorithm (2016)	Fixed, Beta**	85.25%				DNDi 2014 Annual Report(Drugs for Neglected Diseases initiative (DNDi) 2014a)
Fexinidazole (both stages) with RDT 1 algorithm (2019)	Fixed, Beta**	85.25%				DNDi 2014 Annual Report(Drugs for Neglected Diseases initiative (DNDi) 2014a)
Oxaboroles with RDT algorithm 2 (2019)	Fixed, Beta**	85.25%				DNDi 2014 Annual Report(Drugs for Neglected Diseases initiative (DNDi) 2014a)
Diagnostics						
CATT algorithm sensitivity	Beta	84	NA	84	16	Mitashi, 2012(Patrick Mitashi et al. 2012)
RDT 1 algorithm sensitivity	Beta	96.13	NA	96.13	3.87	Buscher 2014,(Büscher et al. 2014)
RDT 2 algorithm sensitivity	Beta	96.13	NA	96.13	3.87	Buscher 2013(Büscher et al. 2013) Jamonneau 2015(Jamonneau et al. 2015)
CATT algorithm cost	Normal	6.17				Lutumba 2005(Lutumba, Robays, Miaka, et al. 2005b) WHO Technical report

						1998,(World Health Organization (WHO) 1998) Lutumba 2006(Lutumba et al. 2006)
RDT 1 algorithm cost	Normal	3.86				Lutumba 2006,(Lutumba et al. 2006) Ndung'u 2015(Ndung'u 2015) FIND(FIND n.d.)
RDT 2 algorithm cost	Normal	0.5	0.05			FIND(FIND n.d.)

Cost treatment - *pentamidine (stage 1),* per diem	Gamma	4.50		1	4.50	Shaw & Cattand 2001,(Shaw & Cattand 2001) Politi 1995(Politi et al. 1995)
Cost treatment - NECT(stage 2), per diem	Gamma	30.89		1	30.89	Simarro 2011 and 2012(P P Simarro et al. 2012; Simarro et al. 2011)
Cost treatment - *fexinidazole) per diem*	Gamma	5.00		1	5	DNDi (Drugs for Neglected Diseases initiative (DNDi) 2014b)
Cost treatment - *oxaborole per diem*	Gamma	2.00		1	2	DNDi *(DNDi 2013, oral communicatio n, 01 October 2013)*
Days Treatment						
Days treatment - pentamidine	Normal	12	0.12			Shaw & Cattand 2001, (Shaw & Cattand 2001) Politi, 1995(Politi et al. 1995)
Days treatment – NECT	Normal	14	0.1			Priotto, 2009(Priotto et al. 2009)
Days treatment – fexinidazole	Normal	10	0.100			Tarral, 2014(Tarral et al. 2011)
Days treatment – oxaborole	Normal	1.00	0.100			DNDi(Drug s for Neglected Diseases initiative (DNDi) 2014b)
Death rates (Stage 2 only)						
Death rate – NECT	Beta	0.0019	0.9982			Priotto 2009(Priotto et al. 2009)
Death rate – fexinidazole	Fixed	0.00				Tarral, 2014(Tarral et al. 2011)
Death rate – oxaborole	Fixed	0.00				DNDi 2014 Annual Report(Drug s for Neglected Diseases initiative (DNDi) 2014a)***
Recovery rates (Stage 2 only)						
Recovery rate – NECT	Beta	0.03836		0.0384	0.9616	Priotto 2009(Priotto et al. 2009)
Recovery rate – fexinidazole	Beta	0.02740		0.0274	0.9726	Tarral, 2014(Tarral et al. 2011)

Recovery rate – oxaborole	Beta	0.002740		0.0027	0.9973	DNDi(Drugs for Neglected Diseases initiative (DNDi) 2014b)
Hospitalisation						
Cost hospitalisation treatment	Gamma	$ 24.89		1	24.89	WHO(World Health Organization (WHO) n.d.)
Adverse Events						
Days AE treatment stage 1, stage 2	Normal	1.50	0.150			*Assumption*
AE st1 (%)	Beta	0.0001	0.0000	0.01	99.99	WHO(World Health Organization (WHO) n.d.)
AE st 2 (%)	Beta	0.14	0.0140	14	86.00	WHO(World Health Organization (WHO) n.d.)
Vector control input parameters						
Km²		*pop_ar*/29.3				
Tiny Targets						
VC unit per km2- *Tiny Targets*		6.2	0.62			Shaw 2015(Shaw et al. 2015)
VC annual startup per unit per km2 – *Tiny Targets*	Gamma	$13.8	NA	1	13.8	Shaw 2015(Shaw et al. 2015)
VC annual maintenance cost per unit per km2– *Tiny Targets*	Gamma	$13.8	NA	1	13.8	Shaw 2015(Shaw et al. 2015)
Vector mortality related to VC- *All Targets*	Beta	5.49	NA	5.49	94.51	Stone & Chitnis, 2015(Chris M. Stone & Chitnis 2015)
Stage 1	Fixed	0.191				Hackett, 2014(Hackett et al. 2014)
Stage 2	Fixed	0.81				Hackett, 2014(Hackett et al. 2014)

*detailed descriptions of costs and costing functions available in Appendix
**Increases in coverage for new technologies based on baseline coverage (beta distribution)multiplied by a 'fixed' number assumed to improve coverage based on assumption that oral treatments combined with new RDTs will be able to reach patients at the village level – refer to Appendix for further description
***Target product profile expected to be safe and non-toxic for SCYX-7158
****Includes nurse time and hospital bed, hospitalization costs estimated from Shaw & Cattand 2001, Politi 1995, Simarro 2012, and Robays 2008
ᶠalpha and beta are the parameter properties required for a beta distribution

C.2.1   Cost Functions and Parameterization

Cost Functions

Costs were pooled when more than one data point was found and a distribution was assigned to take the cost variability into account. When only one point estimate was found for a cost, 10% of the point estimate was assumed to be the standard deviation. In regards to equipment and vehicles, capital costs were taken from published estimates and therefore no annuititization was performed as it was assumed that this was taken into consideration by the authors who published the estimates. It is also important to note that each strategy involves different technologies during different times in the time horizon and the input parameters that were associated with each intervention were programmed in the model to switch accordingly.

Case Detection (Surveillance and Diagnostics)

Cost functions were developed to calculate case detection per diem based on the surveillance strategy and diagnostic algorithm for each time horizon. Active surveillance in high transmission areas was calculated at a per diem rate annually in High transmission areas, whereas it was calculated bi-annually in moderate transmission areas. In low transmission areas, the costs of active surveillance were excluded.

The calculations for surveillance were built on assumptions of coverage, where the coverage rates for passive and active surveillance for stages 1 and 2 are defined below:

$$total\_cov\_p1 = tech\_cov\_p*(per\_p1*cov\_p)*sens$$
$$total\_cov\_p2 = tech\_cov\_p*(per\_p2*cov\_p)*sens$$
$$total\_cov\_a = (1 + tech\_cov\_a)*(cov\_a)*sens$$

$$rate1\_p1 = -log\ (1-(total\_cov\_p1))/365$$
$$rate2\_p1 = -log\ (1-(total\_cov\_p2))/365$$
$$rate\_a1 = -log\ (1-(total\_cov\_a))/365$$

Data referring to active and passive surveillance programs were calculated into per person per year, and per person for ½ year for bi-annual programs and then developed into various cost functions and inputted into the model. Passive costs included the total cost of creating a health Centre including: building construction, medical and lab supply, and CATT reagents, training, and other equipment.(Lutumba, Makieya, et al. 2007a)

Start-up costs were calculated at the beginning of the model on a per person basis, and then a maintenance cost function was calculated annual (high risk transmission_, bi-annually (moderate risk transmission) or not at all (low risk transmission) depending on the risk

transmission area being modelled. Case detection and surveillance costs estimated include (Building overhead costs, Personnel, Medical and lab supply (includes CATT reagents), Essential Drugs, Stationary, Vehicle, operation and maintenance and other operating input) It was assumed that active surveillance campaigns have some component of community sensitization included and that passive infrastructure already exists to some extent, so no initial start-up cost for building passive health care infrastructure was included.

$$Annual\ surveillance\ start\text{-}up = surv\_cost\_startup*pop\_ar$$

$$Annual\ active\ surveillance\ maintenance = (surv\_cost\_pp\_mob*pop\_ar*rate\_a1) + (cost\_dtest*pop\_ar*rate\_a1) +$$

$$Annual\ passive\ surveillance\ maintenance = (surv\_cost\_passive*pop\_ar*(rate1\_p1 + rate2\_p1))$$

There have been several studies conducted regarding the diagnostic accuracy of HAT diagnostic tests. For this model, only the sensitivity estimates are included, and the results are also listed in Table 1. . The CATT algorithm accuracy includes the CATT, dilution, parasitology, mini Anion Exchange Centrifugation Technique (mAECT) and LNP(Patrick Mitashi et al. 2012) while the RDT algorithms 1 was based on recent estimates from HAT Sero-K Set test(Büscher et al. 2013; Büscher et al. 2014; Jamonneau et al. 2015) and parasitology confirmation for RDT 1 using LAMP. The sensitivity of the RDT algorithms was based on the HAT Sero-K Set test alone.(Büscher et al. 2013; Büscher et al. 2014; Jamonneau et al. 2015)

Parameter Description	Short name	Distribution	Point Estimate	SD	alpha	beta
Population						
Total at risk population	*pop_ar**		100000			
Percentage of patients detected in stage 1	*per_p1*	Normal	32.50%	0.0325		
Percentage of patients detected in stage 2	*per_p2*	Normal	66.94%	0.0669		
Passive surveillance						
Coverage rate **for passive healthcare system**	*cov_p*	Beta	2.46%		2.46	97.54
Coverage rate for new technology for passive screening		Fixed				
NECT with CATT algorithm	*tech_cov_p*	Fixed	1*2.46%			
Pentamidine, Fexinidazole with RDT 1 algorithm	*tech_cov_p*	Fixed	3*2.46%			
Fexinidazole (both stages) with RDT 1 algorithm	*tech_cov_p*	Fixed	6.5*2.46%			
Oxaboroles with RDT algorithm 2	*tech_cov_p*	Fixed	10*2.46%			
Cost annual surveillance passive	*surv_cost_passive*	Normal	$1.35	0.1350		

Active surveillance						
Truck teams Cost annual surveillance start up active pp	*surv_cost_startup*	Normal	$0.42	0.0420		
Truck teams Cost annual surveillance maintenance active pp	*surv_cost_pp_mob*	Normal	$1.55	0.1549		
Motorbike teams Cost annual surveillance start up active pp	*surv_cost_startup*	Normal	$0.21	0.0205		
Motorbike teams Cost annual surveillance maintenance active pp	*surv_cost_pp_mob*	Normal	$0.89	0.0886		
Coverage rate for active screening program with Mobile teams	*cov_a*	Beta	80.25%	13.9000	80.25	19.75
Coverage rate for new technology for active screening (%) (0, 5)						
NECT with CATT algorithm	*tech_cov_a*	Fixed	0			
Pentamidine, Fexinidazole with RDT 1 algorithm; Fexinidazole (both stages) with RDT 1 algorithm; Oxaboroles with RDT algorithm 2	*tech_cov_a*	Fixed	80.25%+5%			
Diagnostics						
CATT algorithm sensitivity	*sens*	Beta	84	NA	84	16
RDT 1 algorithm sensitivity	*sens*	Beta	96.13	NA	96.13	3.87
RDT 2 algorithm sensitivity	*sens*	Beta	96.13	NA	96.13	3.87
CATT algorithm cost	*cost_dtest*	Normal	6.17			
RDT 1 algorithm cost	*cost_dtest*	Normal	3.86			
RDT 2 algorithm cost	*cost_dtest*	Normal	0.5	0.05		

There are three main diagnostic algorithms that are used in the model and listed in the manuscript. The cost of the CATT algorithm included the average cost of CATT testing including fees for reagents ($0.60),(Lutumba, Robays, Miaka, et al. 2005a; World Health Organization (WHO) 1998) cost of fresh blood examination (FBE) ($0.36),(Lutumba et al. 2006) mAECT ($4.87),(Lutumba et al. 2006) and lumbar puncture ($0.33).(Lutumba et al. 2006) Costs associated with the current rapid diagnostic test was based on the reported cost of RDT SD Bioline HAT($0.50),(FIND n.d.) with the additional cost of FBE and parasitological screening and staging confirmation with LAMP ($3.00).(Ndung'u 2015) It was assumed that the future RDT would be able to diagnose and stage HAT all in one test, so the only expected expense would be the cost of the diagnostic test (0.50) similar to something like RDT SD Bioline

HAT.(FIND n.d.) In regards to the diagnostic test accuracy, sensitivity estimates for diagnostic tests for the CATT algorithm were taken from the published literature.(P Mitashi et al. 2012) In addition, estimates regarding the diagnostic accuracy of the rapid diagnostic were taken from a recent publication by Buscher et al,(Büscher et al. 2014) It was assumed that the current RDT algorithm and future RDT algorithm would be equally accurate.

*The at risk population (*ar_pop*) in the model was approximately 100,000. This was based on the fact that 82,500 people were in the larger population with a smaller group of people migrating in from the high risk area yielding a total population of 100,000 on average.

Treatment

Treatment cost functions included the cost of treatment and transportation costs (when available), also the health resource utilization (E.g. nurse time, hospital bed, etc.) by treatment regimen. All related inputs are provided in Table 2. . Costs were calculated into per patient per diem costs.

Total treatment costs = (r1*Ahb*s1c) +(r2*Rhb*s2c) +(r1*Ah*s1c) +(r2*Rh*s2c)

Where,

s1c =(s1_days*s1_tx_cost)+(s1_days*s1_hosp_cost) +
(s1_probAE*s1_days_AE*s1_hosp_cost)

s2c =(s2_days*s2_tx_cost) +(s2_days*s2_hosp_cost)+
(s2_probAE*s2_days_AE*s2_hosp_cost)

Note: refer to 'Model' section for further details regarding *Ahb, Rhb, Ah,* and *Rh.* When active surveillance is on in the model active, it is assumed to include passive coverage and *r1* and *r2 = rate_a1;* while when passive detection is on only in the model, *r1 =rate1_p* and *r2= rate2_p.* Refer to the 'Case Detection and surveillance' section for further details regarding *rate_a1.*

Treatment	Short Name	Distribution	Point Estimate	SD	Alpha	Beta
Cost treatment - *pentamidine (stage 1)*	s1_tx_cost	Gamma	4.50		1	4.50
Cost treatment – *NECT (stage 2)*	s2_tx_cost	Gamma	30.89		1	30.89
Cost treatment - *fexinidazole (stage 1 and/or 2)*	s1_tx_cost,s2_tx_cost	Gamma	5.00		1	5
Cost treatment - *oxaborole (stage 1 and/or 2)*	s1_tx_cost, s2_tx_cost	Gamma	2.00		1	2
Days Treatment						
Days treatment - pentamidine	s1_days	Normal	12	0.12		
Days treatment – NECT	s2_days	Normal	14	0.1		
Days treatment – fexinidazole	s1_days, s2_days	Normal	10	0.100		
Days treatment – Oxaborole	s1_days, s2_days	Normal	1.00	0.100		
Death rates (Stage 2 only)						
Death rate – NECT	mu_t	Beta	0.0019	0.9982		
Death rate – fexinidazole	mu_t	Fixed	0.00			
Death rate – Oxaborole	mu_t	Fixed	0.00			
Recovery rates (Stage 2 only)						
Recovery rate – NECT	r3	Beta	0.03836		0.03836	0.96164
Recovery rate – fexinidazole	r3	Beta	0.02740		0.02740	0.97260
Recovery rate – Oxaborole	r3	Beta	0.002740		0.00274	0.99726
Hospitalisation						
Cost hospitalisation treatment	s1_hosp_cost, s2_hosp_cost,	Gamma	$ 24.89		1	24.89
Adverse Events						
Days AE treatment stage 1, stage 2	s1_days_AE,s2_days_AE	Normal	1.50	0.150		
AE st1 (%)	s1_probAE	Beta	0.0001	0.0000	0.01	99.99
AE st 2 (%)	s2_probAE	Beta	0.14	0.0140	14	86.00

Vector Control

Start-up costs for vector control were calculated upfront while maintenance costs were calculated on a per diem basis in the model and totaled in the end. It was assumed that vector control maintenance occurred annually.

The sources for costs related to vector control were taken primarily from 2 recent publications by Shaw and colleagues.(Shaw et al. 2015; Shaw et al. 2013) Annual Start-up costs per km²′ for

vector control were calculated upfront as capital investments, while maintenance costs were calculated on a per diem basis in the model and totaled in the end.

The annual unit costs for both large and tiny targets are provided in Table 3. The cost function for vector control in the model was calculated as follows:

$$\textit{Vector Control Total Startup cost} = (km^2 * vc\_startup\_cost * vc\_units)$$
$$\textit{Vector Control Maintenance} = (km^2 * vc\_maint\_cost * vc\_units)$$

The total start-up cost for the large targets was based on the assumption that targets were used per km² at a cost of $10.00 each and additional services related to starting a large target program would be $118.88 for a total of $128.88 per unit per km² per target. Assuming that on average 10 large targets are deployed per km², this would be a total of $1288.80 in USD 2013. Maintenance fees for large targets were also based on estimates from Shaw et al,(Shaw et al. 2013) where annual cost for 4 and 10 traps per km were reported as $222 and $556 respectively, resulting in an annual maintenance cost of approximately $55.60 per km² per unit. In regards to tiny targets, start-up fees including expenditures related to preliminary surveys, sensitization, trap monitoring, target maintenance and office support resulting in a cost of $85.40 per km² (including cost of targets, 1.1 USD each), or $13.8 per km² per tiny target where there are approximately 6.2 targets per km² (1551/250km²).(Shaw et al. 2015) Costs for annual maintenance of the vector control program for tiny targets were assumed to remain the same as setting up the program as indicated by experts in the field.(Shaw et al. 2015) (*personal communication, Dr. Alexandra Shaw*) It should be noted that that different target densities and deployment rates will be used in real-world settings,(Courtin et al. 2015) resulting in variations in targets used per km² and prices per target as negotiated by national programs. However, the current field work suggests that $85.4 is likely to remain a representative average cost per km² across sub-Saharan Africa. (*personal communication, Dr. Alexandra Shaw*) In the model the annual costs are divided by 365 to yield a per diem cost.

Vector control (VC)	Short Name	Distribution	Point Estimate	SD	Alpha	Beta
Km²	Km2		pop_ar/29.3			
Large targets						
VC unit - *Large Targets*	vc_units	Normal	10.000	1.0000		
VC start-up per km2 - *Large Targets*	vc_startup_cost	Gamma	$128.88	NA	1	128.88
VC maintenance cost - *Large Targets*	vc_maint_cost	Gamma	$55.6	NA	1	55.60
Tiny Targets						
VC unit per km²- *Tiny Targets*	vc_units		6.2	0.62		
VC startup per unit per km² – *Tiny Targets*	vc_startup_cost	Gamma	$13.8	NA	1	13.8
VC maintenance cost per unit per km²– *Tiny Targets*	vc_maint_cost	Gamma	$13.8	NA	1	13.8
Vector mortality related to VC- *All Targets*	mu_vec	Beta	5.49	NA	5.49	94.51

C.3 Rationale for one-way sensitivity analysis

Two additional situations were modelled to observe the long-term outcomes if fexinidazole were to reach the market for treatment of both stages of HAT in 2016, and also what the implications would be if oxaborole failed to reach the market in 2019. These additional analyses were run for all three transmission areas. Two specific situations were run through the model to specifically evaluate implications in low risk transmission settings. For instance, currently WHO does make consideration for surveillance in low transmission areas(World Health Organization (WHO) 2013c) yet the authors wanted to consider the impact that adding active surveillance in such settings would have on elimination targets and cost-effectiveness. Additionally, the base case analysis included improvements in the coverage of the passive healthcare systems that were based on the assumption that the ease of deployment would increase the availability and self-seeking patterns of symptomatic individuals suffering from Gambiense HAT.

C.4 Modelling

C.4.1 Description

The model used is based on the version without an animal reservoir as described in Stone & Chitnis 2015. Briefly, the equations describing the changes of numbers in human compartments (see main text) are given by:

$$\frac{dS_{h1}}{dt} = \beta_{h1} + r_3 T_{h1} - \mu_h S_{h1} - \frac{b\,f\,\theta_{h1,1}\,I_{v1}(t)}{N_{h1}}\,S_{h1}(t),$$

$$\frac{dI_{h1}}{dt} = \frac{b\,f\,\theta_{h1,1}\,I_{v1}(t)}{N_{h1}}\,S_{h1}(t) - (\mu_h + \eta)\,I_{h1},$$

$$\frac{dA_{h1}}{dt} = \eta\,I_{h1} - (\mu_h + s_1 + r)A_{h1},$$

$$\frac{dR_{h1}}{dt} = s_1 A_{h1} - (\mu_h + \mu_{s1} + r)R_{h1},$$

$$\frac{dT_{h1}}{dt} = rA_{h1} + rR_{h1} - (\mu_h + \mu_t + r_3)\,T_{h1},$$

$$\frac{dS_{h2}}{dt} = \beta_{h2} + r_3 T_{h2} - \mu_h S_{h1} - b\,f\left(\frac{\theta_{h2,1} I_{v1}(t)}{N_{h2}} + \frac{\theta_{h,2}\,I_{v2}(t)}{N_{h2}}\right)S_{h2}(t),$$

$$\frac{dI_{h2}}{dt} = b\,f\left(\frac{\theta_{h2,1} I_{v1}(t)}{N_{h2}} + \frac{\theta_{h,2}\,I_{v2}(t)}{N_{h2}}\right)S_{h2}(t) - (\mu_h + \eta)\,I_{h2},$$

$$\frac{dA_{h2}}{dt} = \eta\,I_{h2} - (\mu_h + s_1 + r)A_{h2},$$

$$\frac{dR_{h2}}{dt} = s_1 A_{h2} - (\mu_h + \mu_{s1} + r)R_{h2},$$

$$\frac{dT_{h2}}{dt} = rA_{h2} + rR_{h2} - (\mu_h + \mu_t + r_3)\,T_{h2}.$$

The probability of biting a human for N_{v1} is:

$$\theta_{h,1} = \frac{\sigma_h(N_{h1} + (1-\xi)N_{h2})}{\sigma_h(N_{h1} + (1-\xi)N_{h2}) + \sigma_{a1}N_{a1}}$$

where σi represents the relative preference for human and non-human host types. The probability of biting a human for N_{v2} is:

$$\theta_{h,2} = \frac{\sigma_h \xi N_{h2}}{\sigma_h \xi N_{h2} + \sigma_{a2} N_{a2}}$$

The forces of infection on vectors are:

$$\Lambda_{v1} = cf\theta_{h1,1}\frac{A_{h1}}{N_{h1}}S_{v1} + cf\theta_{h2,1}\frac{A_{h2}}{N_{h2}}S_{v1} + c_{a1}f\theta_{a,1}\frac{A_{a1}}{N_{a1}}S_{v1} = f\frac{c_{a1}\sigma_{a1}A_{a1} + c\,\sigma_h(A_{h1} + (1-\xi)A_{h2})}{N_{a1}\sigma_{a1} + \sigma_h(N_{h1} + (1-\xi)N_{h2})}S_{v1}$$

$$\Lambda_{v2} = cf\theta_{h,2}\frac{A_{h2}}{N_{h2}}S_{v2} + c_{a2}f\theta_{a,2}\frac{A_{a2}}{N_{a2}}S_{v2} = f\frac{c_{a2}\sigma_{a2}A_{a2} + c\,\sigma_h\xi\,A_{h2}}{N_{a2}\sigma_{a2} + \sigma_h\xi\,N_{h2}}S_{v2}.$$
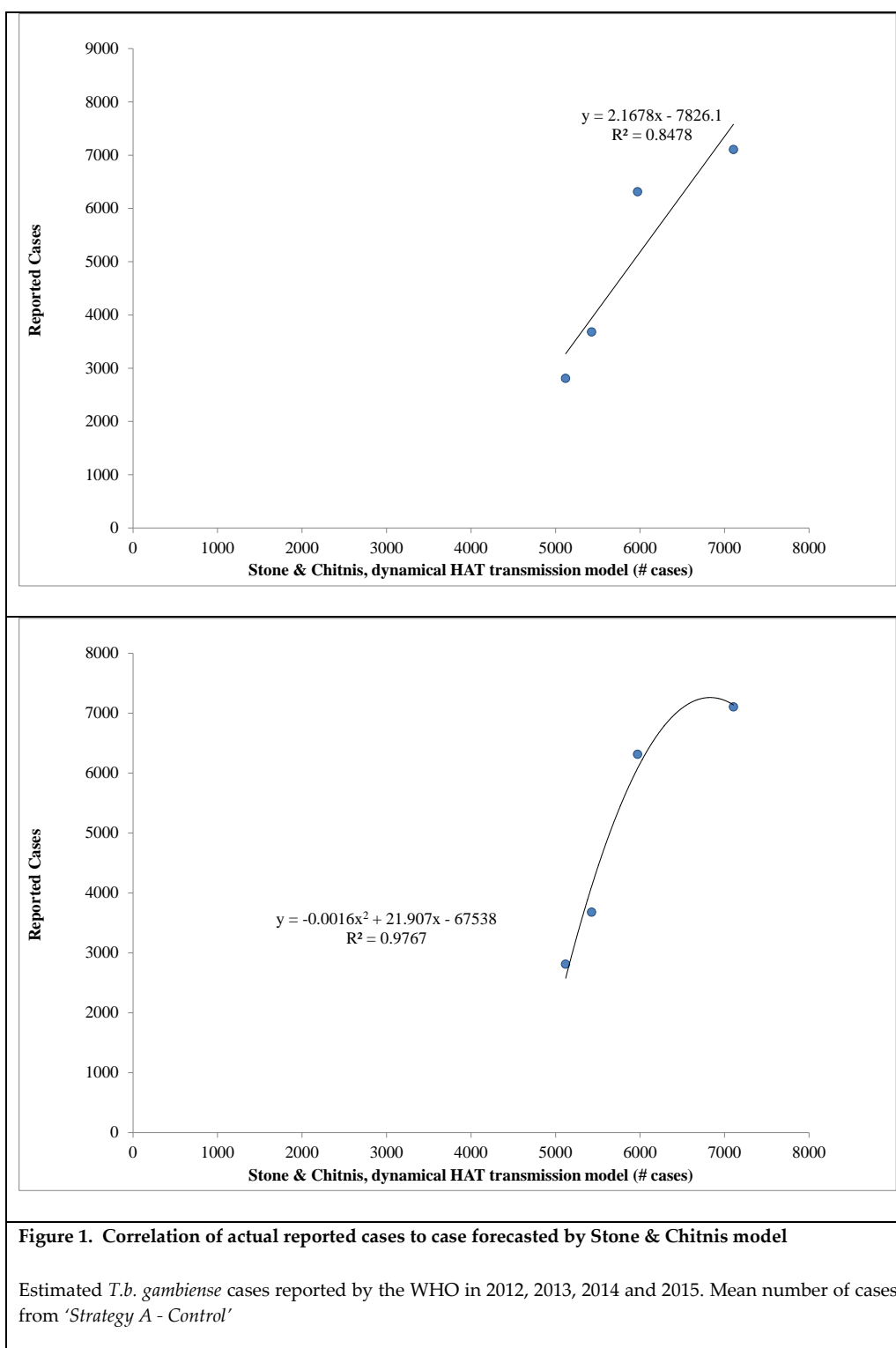
The ordinary differential equations describing changes in the vector compartments (with i indicating population 1 or 2) are:

$$\frac{dSvi}{dt} = \beta_{vi}(t) - \mu_v S_{vi}(t) - \Lambda_{vi}(t)$$

$$\frac{dEvi}{dt} = \Lambda_{vi}(t) - (\mu_v + v_e)E_{vi}$$

$$\frac{dIvi}{dt} = v_e E_{vi} - \mu_v I_{vi}$$

See Stone & Chitnis 2015(Christopher M. Stone & Chitnis 2015) for a complete description of the model, how the model was fit to low, moderate, and high transmission foci, and a table of transmission parameter values and ranges used in the model.

C.4.2   *Predictive accuracy*

We also have compared our model with the annual case numbers reported since 2012. The estimated sample is based on a combination of low, moderate and high transmission risk settings where it was assumed that 63% of cases were stage 1 and 37% of cases were stage 2. It was assumed that the percentage of cases reported from high, moderate and low foci were 9%, 25% and 66% respectively. This distribution is equivalent to the at risk transmission areas.(Jose R Franco et al. 2014) The mean results of *'Strategy A. Control'* forecast real-world data with a $R^2 = 0.85$ when fitted to a linear function, and $R^2 = 0.98$ when fitted to a polynomial function as seen in Figure 1 below.
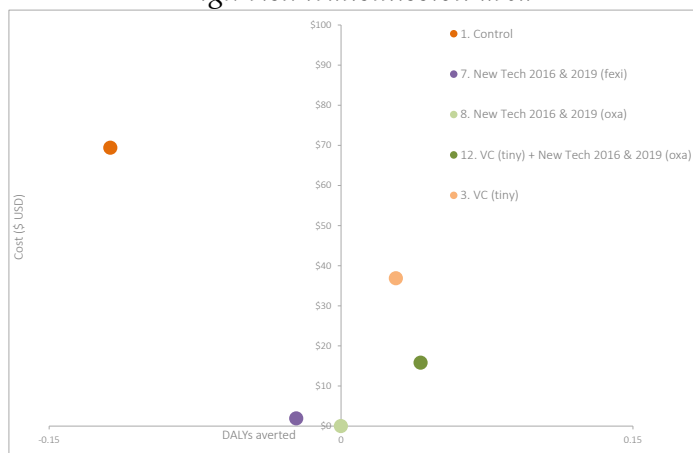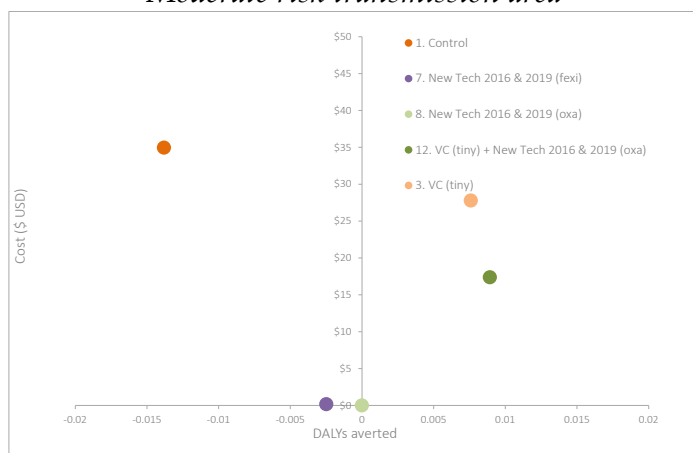
Figure 1. Correlation of actual reported cases to case forecasted by Stone & Chitnis model

Estimated *T.b. gambiense* cases reported by the WHO in 2012, 2013, 2014 and 2015. Mean number of cases from *'Strategy A - Control'*

C.5 Results (Strategies A thru E)

C.5.1 Cost-effectiveness results, base case

A. Mean incremental CE plane and efficiency frontier

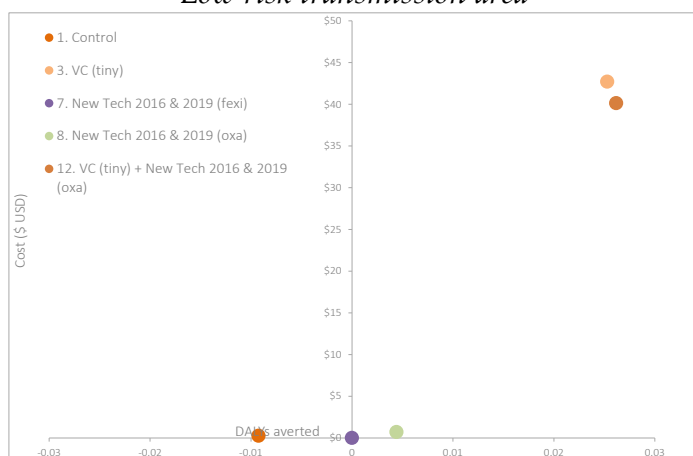**B. Incremental CE planes (PSA)**

High risk transmission area

High risk transmission area

Moderate risk transmission area

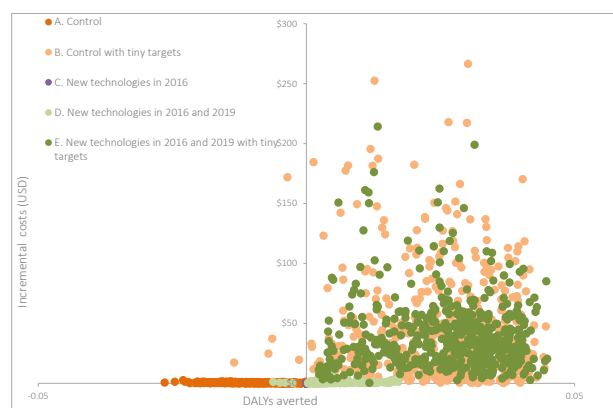*Moderate risk transmission area*
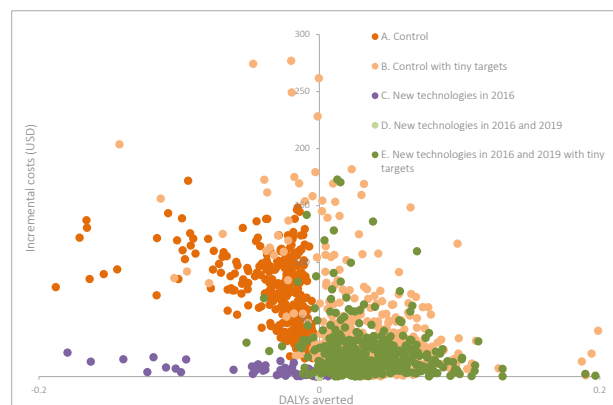
Low risk transmission area
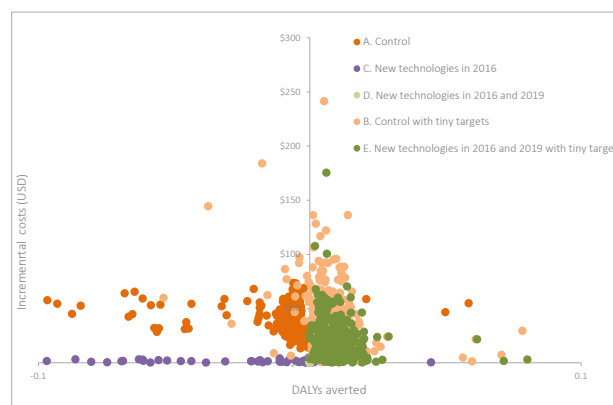
Low risk transmission area

C.5.2 One-way Sensitivity Analysis (OWSA)

C.5.2.1. Sensitivity Analysis Results

| Parameter variation from Base case analysis	Summary of changes relative to base case analysis (ICERs at cost /DALY averted*)					
One-way sensitivity analysis						
Lower range , Upper range	**Low**		**Moderate**		**High**	
	Lower range	Upper range	Lower range	Upper range	Lower range	Upper range
1. Discount rate (0%, 5%)	Strategy D - $150 Strategy E - $1,550	Strategy D - $167 Strategy R - $1991	Strategy E - $1,764	Strategy E - $2044	Strategy E - $390	Strategy E - $385
2. Vector control mortality rate (1%, 10%)	Strategy D - $160 Strategy E - $6,477	Strategy D - $160 Strategy E - $1290	Strategy E - $7,310	Strategy E - $1447	Strategy E - $1,971	Strategy E - $244
3. Vector control costs (annual maintenance) per unit/ km² ($11.30 , $16.13)	Strategy E - $1,509	Strategy E - $2,117	Strategy E - $1,248	Strategy E - $1,791	Strategy E - $309	Strategy E - $469
4. Low transmission – coverage rates of new technologies in passive surveillance						
a. Pentamidine (stage 1), fexinidazole (stage 2) (~3%, 30%)	Strategy D - $158 Strategy E - $1,630	Strategy C - $148 Strategy E - $1,508	NA	NA	NA	NA
b. Fexinidazole (both stages) (~3%, 30%)	Strategy D - $144 Strategy E - $1,812	Strategy C - $33 Strategy D - $33 Strategy E - $1,735	NA	NA	NA	NA
c. Oxaborole (both stages) (~3%, 45%)	Strategy B - $976	Strategy C - $216 Strategy D - $1,544	NA	NA	NA	NA
5. Low transmission – active surveillance (biennial 80%, annual 80%)	Strategy D - $123 Strategy E - $15,930	Strategy E - $9,899	NA	NA	NA	NA
Variation of strategies analysis						
6. Oral treatments taken at home in 2019	Strategy D - $165 Strategy E - $1,365		Strategy E - $1,348		Strategy E - $318	
7. Oxaborole not available in 2019**	Strategy B - $1,689		Strategy B - $2,739		Strategy B - $683	

8.	Accelerating timeline for fexinidazole arriving on the market for both stages in 2016	Strategy D - $163 Strategy E - $1878	Strategy E - $1,949	Strategy E - $400
9.	Active surveillance coverage – moderate and high			
	i. 20%	NA	Strategy E - $317	Strategy E - $49
	ii. 40%	NA	Strategy E - $617	Strategy E - $108
	iii. 60%	NA	Strategy E - $1080	Strategy E - $205
	iv. 95%	NA	Strategy E - $2354	Strategy E - $98

*Only incremental cost-effectiveness ratios (ICERs) of cost-effective strategies listed, dominated strategies not shown but are available in the Appendix, NA = not applicable, **Means that only strategies A, B and C are available.*

C.5.3   Sensitivity analysis - Probability full elimination reached in low risk transmission areas with additional surveillance

Full elimination threshold set at less than 1 in a million.
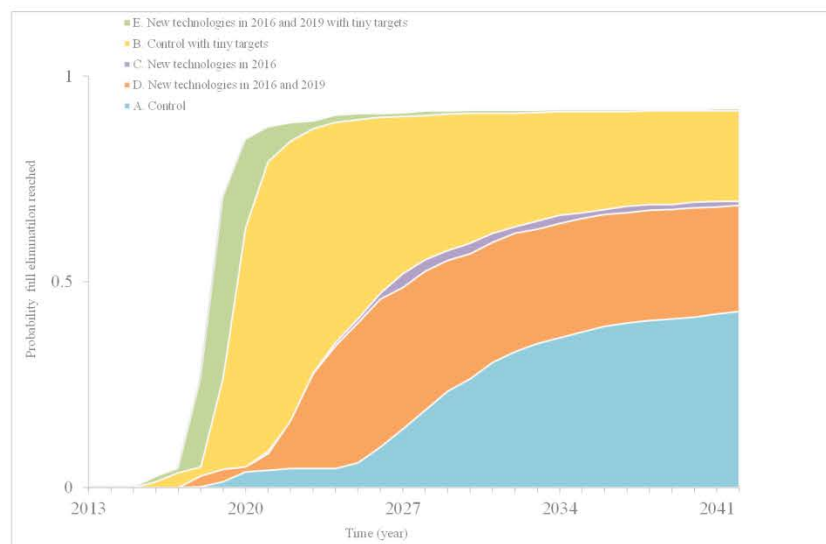
Biannual surveillance in low risk transmission areas   Annual surveillance in low risk transmission areas
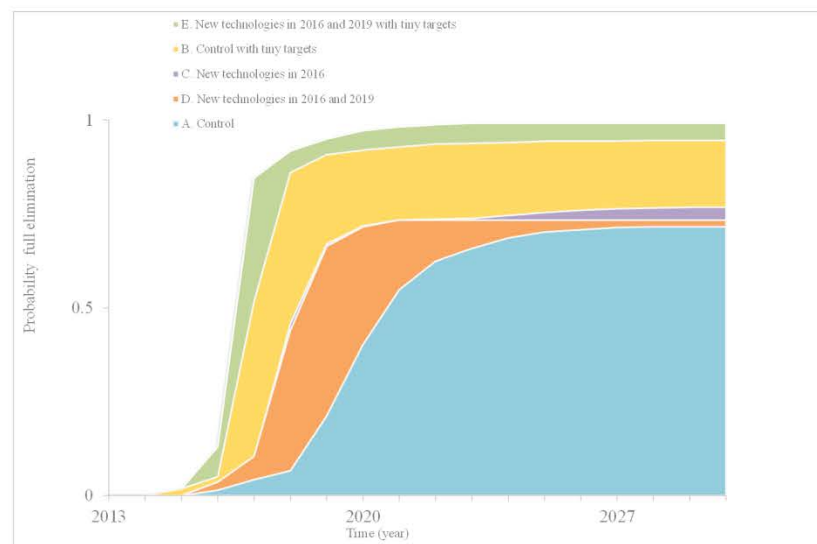
C.5.4 Sensitivity analysis - Probability 'London Declaration'* targets reached in high and moderate transmission areas with varying coverage levels for active surveillance
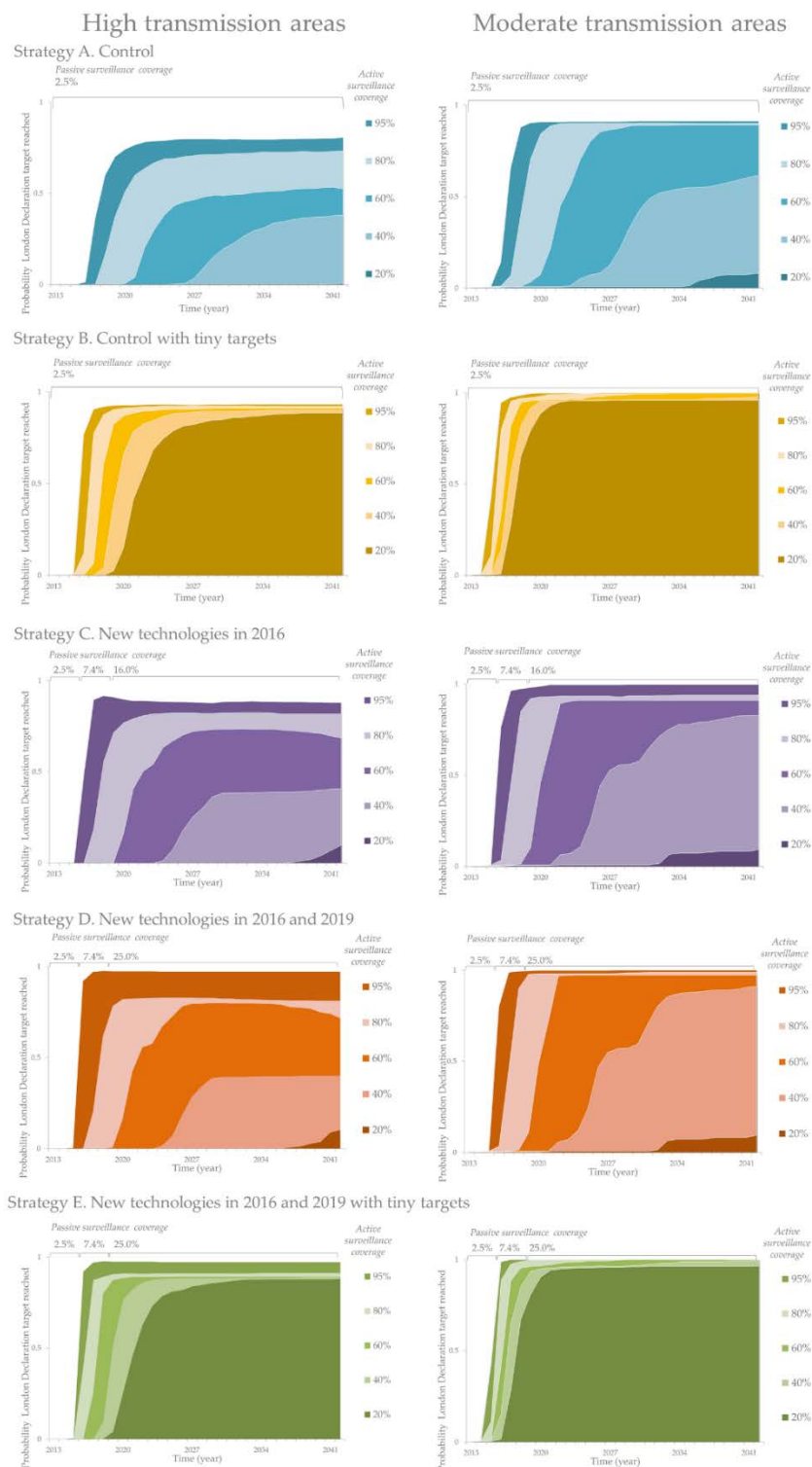
*The London Declaration targets elimination, defined in concordance with the WHO Roadmap, as 'elimination as a public health problem' or less than 1 case in 10,000 population

C.5.5   Detailed Sensitivity analysis results

1.   Discount rate variation

Strategy	Total Mean Costs (USD) per person	Total Mean DALYs per person	Incremental Cost-effectiveness Ratio (ICER)	Strategy	Total Mean Costs (USD) per person	Total Mean DALYs per person	Incremental Cost-effectiveness Ratio (ICER)
DISCOUNTING 0%				DISCOUNTING 5%			
High risk transmission area				*High risk transmission area*			
Strategy D	$50	0.23	-	Strategy D	$43	0.219	
Strategy C	$53	0.27	Dominated by D	Strategy C	$44	0.238	Dominated by D
Strategy E	$68	0.19	$390	Strategy E	$58	0.181	$385
Strategy B	$97	0.20	Dominated by E	Strategy B	$75	0.192	Dominated by E
Strategy A	$155	0.40	Dominated by E	Strategy A	$97	0.316	Dominated by E
Moderate risk transmission area				*Moderate risk transmission area*			
Strategy D	$23	0.03	-	Strategy D	$19	0.03	-
Strategy C	$23	0.03	-	Strategy C	$19	0.03	Dominated by D
Strategy E	$41	0.02	$1,764	Strategy E	$36	0.02	$2,044
Strategy A	$75	0.05	Dominated by E	Strategy B	$44	0.02	Dominated by E
Strategy B	$144	0.02	Dominated by E	Strategy A	$46	0.04	Dominated by E
Low risk transmission area				*Low risk transmission area*			
Strategy C	$3	0.05		Strategy C	$2	0.03	
Strategy A	$4	0.07	Dominated by C	Strategy A	$2	0.04	Dominated by C
Strategy D	$4	0.04	$150	Strategy D	$2	0.03	$167
Strategy E	$54	0.01	$1,550	Strategy E	$37	0.01	$1'991
Strategy B	$59	0.01	Dominated by E	Strategy B	$39	0.01	Dominated by E

2.   Vector control mortality

Strategy	Total Mean Costs (USD) per person	Total Mean DALYs per person	Incremental Cost-effectiveness Ratio (ICER)	Strategy	Total Mean Costs (USD) per person	Total Mean DALYs per person	Incremental Cost-effectiveness Ratio (ICER)
Vector control mortality 1%				Vector control mortality 10%			
High risk transmission area				*High risk transmission area*			
Strategy D	$45	0.22		Strategy D	$45	0.22	
Strategy C	$47	0.25	Dominated by D	Strategy C	$47	0.25	Dominated by D
Strategy E	$73	0.21	$1'971	Strategy E	$57	0.18	$244
Strategy B	$127	0.27	Dominated by E	Strategy B	$73	0.18	Dominated by E
Strategy A	$115	0.34	Dominated by E	Strategy A	$115	0.34	Dominated by E
Moderate risk transmission area				*Moderate risk transmission area*			
Strategy D	$20	0.03	-	Strategy D	$20	0.03	-
Strategy C	$20	0.03	Dominated by D	Strategy C	$20	0.03	-

Strategy	Total Mean Costs (USD) per	Total Mean DALYs per	Incremental Cost-effectiveness Ratio (ICER)	Strategy	Total Mean Costs (USD)	Total Mean DALYs per person	Incremental Cost-effectiveness Ratio (ICER)
Strategy E	$49	0.02	$7,310	Strategy E	$35	0.02	$1477
Strategy A	$55	0.04	Dominated by E	Strategy B	$42	0.02	Dominated by E
Strategy B	$78	0.03	Dominated by E	Strategy A	$55	0.04	Dominated by E
Low risk transmission area				*Low risk transmission area*			
Strategy C	$2	0.035	-	Strategy C	$2	0.04	
Strategy A	$3	0.045	Dominated by D	Strategy A	$3	0.04	Dominated by C
Strategy D	$3	0.031	$160	Strategy D	$3	0.03	$160
Strategy E	$60	0.022	$6447	Strategy E	$33	0.01	$1290
Strategy B	$60	0.030	Dominated by E	Strategy B	$36	0.01	Dominated by E

3. Vector control costs

Strategy	Total Mean Costs (USD) per	Total Mean DALYs per	Incremental Cost-effectiveness Ratio (ICER)	Strategy	Total Mean Costs (USD)	Total Mean DALYs per person	Incremental Cost-effectiveness Ratio (ICER)
Vector control maintenance costs $11.30 per unit/km² (~$70 per km²)				*Vector control maintenance costs $16.13 per unit/km2 (~$100 per km²)*			
High risk transmission area				*High risk transmission area*			
Strategy D	$45	0.22	-	Strategy D	$45	0.22	-
Strategy C	$47	0.25	Dominated by D	Strategy C	$47	0.25	Dominated by D
Strategy E	$58	0.18	$309	Strategy E	$65	0.18	$469
Strategy B	$79	0.20	Dominated by E	Strategy B	$86	0.20	Dominated by E
Strategy A	$115	0.34	Dominated by E	Strategy A	$115	0.34	Dominated by E
Moderate risk transmission area				*Moderate risk transmission area*			
Strategy D	$20	0.03	-	Strategy D	$20	0.03	-
Strategy C	$20	0.03	Dominated by Strategy D	Strategy C	$20	0.03	Dominated by Strategy D
Strategy E	$35	0.02	$1'248	Strategy E	$41	0.02	$1'791
Strategy B	$45	0.02	Dominated by Strategy E	Strategy B	$52	0.02	Dominated by Strategy E
Strategy A	$55	0.04	Dominated by Strategy E	Strategy A	$55	0.04	Dominated by Strategy E
Low risk transmission area				*Low risk transmission area*			
Strategy C	$2	$0.0353	-	Strategy C	$2	$0.0353	-
Strategy A	$3	$0.0445	Dominated by Strategy C	Strategy A	$3	$0.0445	Dominated by Strategy C
Strategy D	$3	$0.0309	$160	Strategy D	$3	$0.0309	$160
Strategy E	$36	$0.0091	$1'509	Strategy E	$49	$0.0091	$2'117
Strategy B	$38	$0.0100	Dominated by Strategy E	Strategy B	$53	$0.0100	Dominated by Strategy E

4. Coverage rate improvement related to new technologies in low transmission areas

Strategy	Total Mean Costs (USD) per person	Total Mean DALYs per person	Incremental Cost-effectiveness Ratio (ICER)	Strategy	Total Mean Costs (USD) per person	Total Mean DALYs per	Incremental Cost-effective
pentamidine-fexinidazole with RDT 1 in 2016, 1x				*pentamidine-fexinidazole with RDT 1 in 2016, 10x*			
Strategy C	$2	0.04		Strategy A	$3	0.04	

Strategy	Total Mean Costs (USD) per person	Total Mean DALYs per person	Incremental Cost-effectiveness Ratio (ICER)	Strategy	Total Mean Costs (USD) per person	Total Mean DALYs per person	Incremental Cost-effectiveness Ratio (ICER)
Strategy D	$2	0.03	$158	Strategy C	$4	0.03	$148
Strategy A	$3	0.04	Dominated by D	Strategy D	$5	0.03	Dominat
Strategy E	$39	0.01	$1630	Strategy E	$41	0.01	$1508
Strategy B	$45	0.01	Dominated by E	Strategy B	$45	0.01	

fexinidazole-fexinidazole with RDT 2 in 2019, 1x				*fexinidazole-fexinidazole with RDT 2 in 2019, 10x*			
Strategy C	$1	0.04	-	Strategy A	$3	0.04	-
Strategy A	$3	0.04	Dominated by C	Strategy D	$3	0.03	$33
Strategy D	$3	0.03	$144	Strategy C	$3	0.03	$33
Strategy E	$42	0.01	$1'812	Strategy E	$42	0.01	$1735
Strategy B	$45	0.01	Dominated by E	Strategy B	$45	0.01	

oxaborole with RDT 2 in 2019, 1x				*oxaborole with RDT 2 in 2019, 15x*			
Strategy D	$1	0.04	-	Strategy C	$2	0.04	-
Strategy C	$2	0.04	Dominated by D	Strategy A	$3	0.04	
Strategy A	$3	0.04	Dominated by D	Strategy D	$4	0.03	$216
Strategy B	$34	0.01	$976	Strategy E	$32	0.01	$1'544
Strategy E	$45	0.01	Dominated by B	Strategy B	$45	0.01	
							Dominat

5. Surveillance in low transmission

Strategy	Total Mean Costs (USD) per	Total Mean DALYs per person	Incremental Cost-effectiveness Ratio (ICER)	Strategy	Total Mean Costs (USD) per	Total Mean DALYs per	Incremental Cost-effecti
Biannual				*Annual*			
Strategy C	$20	0.005	-	Strategy C	$34	0.002	-
Strategy D	$20	0.004	$123	Strategy D	$34	0.002	-
Strategy E	$38	0.003	$15930	Strategy E	$37	0.002	$9899
Strategy B	$49	0.003	Dominated by E	Strategy B	$49	0.002	
Strategy A	$59	0.006	Dominated by E	Strategy A	$71	0.003	

6. Oral treatments taken at home in 2019

Strategy	Total Mean Costs (USD) per person	Total Mean DALYs per person	Incremental Cost-effectiveness Ratio (ICER)
High risk transmission areas			
Strategy D	$45	$0.224	-
Strategy C	$46	$0.247	Dominated by D
Strategy E	$58	$0.184	$318
Strategy B	$82	$0.196	Dominated by E
Strategy A	$115	$0.343	Dominated by E
Moderate risk transmission areas			
Strategy D	$20	0.03	

Strategy	$20	0.03	Dominated by Strategy D
Strategy E	$36	0.02	$1'348
Strategy B	$48	0.02	Dominated by Strategy E
Strategy A	$55	0.04	Dominated by Strategy E

Low risk transmission areas			
Strategy C	$2	0.0353	-
Strategy A	$3	0.0445	Dominated by C
Strategy D	$3	0.0309	$165
Strategy E	$33	0.0091	$1'365
Strategy B	$45	0.0100	Dominated by Strategy 12

7. Oxaborole fails to reach market (strategies D and E removed)

Strategy	Total Mean Costs (USD) per person	Total Mean DALYs per person	Incremental Cost-effectiveness Ratio (ICER)
High risk transmission areas			
Strategy C	$47	0.25	
Strategy B	$82	0.20	$683
Strategy A	$115	0.34	
Moderate risk transmission areas			
Strategy C	$20	0.03	-
Strategy B	$48	0.02	$2739
Strategy A	$55	0.04	Dominated by B
Low risk transmission areas			
Strategy C	$2	0.04	-
Strategy A	$3	0.04	Dominated by C
Strategy B	$45	0.01	$1689

8. Accelerating timeline for fexinidazole arriving on the market for both stages in 2016

Strategy	Total Mean Costs (USD) per person	Total Mean DALYs per person	Incremental Cost-effectiveness Ratio (ICER)
High risk transmission areas			
Strategy D	$30	0.22	-
Strategy C	$31	0.25	Dominated by D
Strategy E	$46	0.18	$400
Strategy B	$82	0.20	Dominated by E
Strategy A	$115	0.34	Dominated by E

Moderate risk transmission areas			
Strategy D	$12	0.03	
Strategy C	$13	0.03	Dominated by D
Strategy E	$30	0.02	$1949
Strategy B	$48	0.02	Dominated by E
Strategy A	$55	0.04	Dominated by E
Low risk transmission areas			
Strategy C	$1.7	$0.034	
Strategy D	$2 .4	$0.030	163
Strategy A	$3	$0.04	Dominated by D
Strategy E	$42	$0.01	$1878
Strategy B	$45	$0.01	Dominated by E

9. Active surveillance coverage

	Moderate risk transmission areas				*High risk transmission areas*		
Strategy	Total Mean Costs (USD) per	Total Mean DALYs per person	Incremental Cost-effectiveness Ratio (ICER)	Strategy	Total Mean Costs (USD) per person	Total Mean DALYs per person	Incremental Cost-effective
20%							
Strategy D	$4	0.15		Strategy D	$11	1.37	
Strategy C	$4	0.16	Dominated by D	Strategy C	$14	1.59	
Strategy A	$12	0.18	Dominated by D	Strategy A	$34	1.92	
Strategy E	$37	0.04	$317	Strategy E	$50	0.57	$49
Strategy B	$41	0.04	Dominated by E	Strategy B	$62	0.61	
40%							
Strategy D	$8	0.08		Strategy D	$21	0.65	
Strategy C	$8	0.09	Dominated by D	Strategy C	$24	0.80	
Strategy A	$26	0.10	Dominated by D	Strategy E	$50	0.38	$108
Strategy E	$36	0.03	$617	Strategy B	$64	1.05	
Strategy B	$43	0.04	Dominated by E	Strategy A	$70	0.41	
60%							
Strategy D	$13	0.05		Strategy D	$32	0.37	
Strategy C	$13	0.05	Dominated by D	Strategy C	$34	0.45	
Strategy E	$36	0.03	$1'080	Strategy E	$53	0.27	$205
Strategy A	$42	0.07	Dominated by E	Strategy B	$76	0.29	
Strategy B	$45	0.03	Dominated by E	Strategy A	$91	0.62	
95%							
Strategy D	$31	0.02		Strategy D	$65	0.16	
Strategy C	$31	0.02	Dominated by D	Strategy C	$66	0.16	
Strategy E	$40	0.02	$2'354	Strategy E	$66	0.14	$98

| Strategy B | $50 | 0.02 | Dominated by E | Strategy B | $87 | 0.15 |
| Strategy A | $65 | 0.03 | Dominated by E | Strategy A | $122 | 0.22 |

C.6 Elimination results (Full results refer to Appendix C.6)

C.6.1 Coverage results

20%	London Declaration						Full Elimination					
	Moderate			High			Moderate			High		
Intervention	2020	2030	2042	2020	2030	2042	2020	2030	2042	2020	2030	2042
Strategy A	0	0.01	0.08	0.00	0.00	0.01	0	0	0	0	0	0
Strategy B	0.89	0.96	0.96	0.15	0.85	0.89	0	0.84	0.95	0	0.58	0.8
Strategy C	0	0.01	0.09	0	0	0.10	0	0	0	0	0	0
Strategy D	0	0.01	0.09	0	0	0.10	0	0	0	0	0	0
Strategy E	0.90	0.96	0.96	0.25	0.86	0.88	0	0.85	0.95	0	0.64	0.84

40%	London Declaration						Full Elimination					
	Moderate			High			Moderate			High		
Intervention	2020	2030	2042	2020	2030	2042	2020	2030	2042	2020	2030	2042
Strategy A	0.01	0.43	0.62	0.00	0.20	0.38	0	0	0.01	0	0	0.08
Strategy B	0.95	0.96	0.98	0.66	0.89	0.90	0	0.92	0.95	0	0.81	0.89
Strategy C	0.01	0.58	0.83	0	0.38	0.41	0	0	0.04	0	0	0.26
Strategy D	0.01	0.59	0.91	0	0.39	0.40	0	0	0.04	0	0	0.29
Strategy E	0.95	0.97	1.00	0.76	0.88	0.89	0	0.92	0.95	0	0.84	0.88

60%	London Declaration						Full Elimination					
	Moderate			High			Moderate			High		
Intervention	2020	2030	2042	2020	2030	2042	2020	2030	2042	2020	2030	2042
Strategy A	0.07	0.89	0.89	0.01	0.49	0.53	0	0.01	0.48	0	0.15	0.38
Strategy B	0.46	0.91	0.91	0.87	0.91	0.91	0.09	0.94	0.96	0.02	0.89	0.91
Strategy C	0.46	0.91	0.91	0.16	0.73	0.69	0	0.06	0.55	0	0.39	0.47
Strategy D	0.49	0.97	0.97	0.16	0.80	0.72	0	0.06	0.56	0	0.40	0.49
Strategy E	0.95	1.00	1.00	0.88	0.89	0.89	0.21	0.94	0.95	0.18	0.89	0.89

80%	London Declaration						Full Elimination					
	Moderate			High			Moderate			High		
Intervention	2020	2030	2042	2020	2030	2042	2020	2030	2042	2020	2030	2042
Strategy A	0.84	0.90	0.90	0.51	0.72	0.73	0	0.46	0.63	0	0.49	0.61
Strategy B	0.98	1.00	1.00	0.91	0.92	0.92	0.52	0.95	0.96	0.67	0.91	0.92
Strategy C	0.93	0.94	0.94	0.77	0.82	0.82	0	0.67	0.70	0.13	0.77	0.80
Strategy D	0.98	0.99	0.99	0.82	0.82	0.81	0	0.68	0.71	0.14	0.79	0.80
Strategy E	1.00	1.00	1.00	0.91	0.91	0.91	0.84	0.96	0.97	0.86	0.90	0.91

95%	London Declaration						Full Elimination					
	Moderate			**High**			**Moderate**			**High**		
Intervention	**2020**	**2030**	**2042**	**2020**	**2030**	**2042**	**2020**	**2030**	**2042**	**2020**	**2030**	**2042**
Strategy A	0.91	0.91	0.91	0.74	0.80	0.81	0	0.65	0.69	0.17	0.72	0.77
Strategy B	1.00	1.00	1.00	0.93	0.93	0.93	0.85	0.96	0.97	0.88	0.93	0.93
Strategy C	0.99	1.00	1.00	0.90	0.88	0.88	0.61	0.83	0.86	0.80	0.84	0.84
Strategy D	1.00	1.00	1.00	0.97	0.97	0.97	0.60	0.83	0.83	0.91	0.92	0.93
Strategy E	1.00	1.00	1.00	0.97	0.97	0.97	0.96	0.98	0.98	0.91	0.92	0.93

C.7 *Preliminary results for 12 strategies for control and elimination of Gambiense HAT*

C.7.1 Description of all 12 strategies for control and elimination

We have previously developed and reported on (Steinmann et al. 2015) 12 strategies for elimination by combining existing and emerging technologies for Gambiense HAT (refer to Figure 1). The current approach for HAT case detection (Control - Strategy 1) relies on patients to self-report to local health centers (referred to as passive surveillance) and on active case finding done by teams that actively seek out patients living in remote areas (active surveillance). Diagnosis is done in public during in-village screening campaigns, and requires blood testing as well as a lumbar puncture to confirm the stage of disease. The current approved treatment for HAT on the WHO essential drug list for stage 1 of the disease is pentamidine while nifurtomix-eflornithine combination therapy (NECT) is the first-line, parenteral treatment for patients who have progressed to stage 2.(World Health Organization (WHO) 2013c) Strategies 2 and 3 are essentially identical to control (Strategy 1) with regard to case detection and treatment; however, vector control is added with large targets (Strategy 2) or small targets (Strategy 3). Strategy 4 begins with control (Strategy 1) until 2016 when case detection is switched to more flexible teams on motorbikes and detection of the disease is done using a rapid diagnostic test (RDT) algorithm with confirmation and staging done using the loop-mediated isothermal amplification (LAMP) technique(Steinmann et al. 2015) and the treatment for the second stage of disease switches to 10 oral doses of fexinidazole (Refer to Box 1). The impact of adding on vector control is evaluated by the addition of large targets then switching to small targets (Strategy 5) or using small targets for the entire time period (Strategy 6). Strategy 7 initially is the exact same strategy as Strategy 4, up until 2019 when fexinidazole is considered for treatment of both stage 1 and 2 of the disease. Likewise, Strategy 8 is the same as Strategy 4 up until 2019, when a new compound, oxaborole, will be available for the single oral dose treatment of both stages. Strategies 9 through 12 replicate either strategy 7 or 8 by adding on vector control with large targets or switching to small targets. Based on recommendations from the WHO,(World Health Organization (WHO) 2013c) it was assumed that active screening was done annually in high transmission settings, bi-annually in

moderate transmission settings and no active screening component was included in the low risk transmission settings, where detection therefore relied solely on passive surveillance. Considerations were made for post-elimination activities in that it was assumed that after elimination, only passive surveillance would be implemented until 2042. Reinvasion of cases was not permitted after elimination was achieved in the model.

C.7.2   Rationale for five main strategies in final manuscript

The results from the CEA of the 12 strategies, listed in Table 4 below, demonstrated that all strategies including large targets were dominated (Strategies 2, 5, 9 and 10). In addition, strategies that on only included new technologies in 2016 (Strategy 4, 5 and 6) were always dominated by strategies that continually switched to a oral tablet for both stages. Furthermore, tiny targets with a one-time oral dose in 2019 (Strategy 12) always dominated or was equivalent to fexinidazole in combination with tiny targets. (Strategy 11) This highlighted that Strategies 7, 8 and 12 were the main comparators for strategies relating to cost-effectiveness. Results for the probability of elimination analysis also showed that they each exhibited characteristics highlight gains for or against elimination that were representative of the original 12. For this reason these four strategies were highlighted as the main options for the modelling in the manuscript, and strategy 1 and 3 were included to represent the current status quo of what is used in the field for national sleeping sickness control programs. Strategies 1, 3, 7, 8 and 12 are referred to as '*Strategy A'*, '*Strategy B'*, '*Strategy C'*, '*Strategy D'* and '*Strategy E'* respectively in the manuscript.

Total mean costs, DALYs and incremental cost-effectiveness ratios (ICERs)

Strategy in manuscript	Strategy in preliminary analysis	Incremental (ICER)	Cost-effectiveness Ratio
	High risk transmission area		
D	8. New Tech 2016 & 2019 (oxa)	-	
C	7. New Tech 2016 & 2019 (fexi)	Dominated by Strategy 8 (D)	
E	12. VC (tiny) + New Tech 2016 & 2019 (oxa)	$386 per DALY averted*	
B	3. VC (tiny)	Dominated by Strategy 12 (E)	
A	1. Control	Dominated by Strategy 12 (E)	
	11. VC (tiny) + New Tech 2016 & 2019 (fexi)	Extendedly dominated by Strategy 12 (E)	
	6. VC (tiny) + New Tech 2016	Dominated by Strategy 12 (E)	
	4. New Tech 2016	Dominated by Strategy 12 (E)	
	9. VC (large) + New Tech 2016 & 2019	Dominated by Strategy 12 (E)	

	10. VC (large) + New Tech 2016 & 2019	Dominated by Strategy 12 (E)
	5. VC (large) + New Tech 2016	Dominated by Strategy 12 (E)
	2. VC (large)	Dominated by Strategy 12 (E)
	Moderate risk transmission area	
D	8. New Tech 2016 & 2019 (oxa)	-
C	7. New Tech 2016 & 2019 (fexi)	-
E	12. VC (tiny) + New Tech 2016 & 2019 (oxa)	$1509 per DALY averted* and **
B	3. VC (tiny)	Dominated by Strategy 12 (E)
A	1. Control	Dominated by Strategy 12 (E)
	11. VC (tiny) + New Tech 2016 & 2019 (fexi)	$1509 per DALY averted* and **
	6. VC (tiny) + New Tech 2016	Dominated by Strategy 12 (E)
	4. New Tech 2016	Dominated by Strategy 12 (E)
	9. VC (large) + New Tech 2016 & 2019 (fexi)	Dominated by Strategy 12 (E)
	10. VC (large) + New Tech 2016 & 2019	Dominated by Strategy 12 (E)
	5. VC (large) + New Tech 2016	Dominated by Strategy 12 (E)
	2. VC (large)	Dominated by Strategy 12 (E)
	Low risk transmission area	
C	7. New Tech 2016 & 2019 (fexi)	-
A	1. Control	Dominated by Strategy 7 (C)
D	8. New Tech 2016 & 2019 (oxa)	$160 per DALY averted**
E	12. VC (tiny) + New Tech 2016 & 2019 (oxa)	$1'812 per DALY averted*
B	3. VC (tiny)	Dominated by Strategy 12 (E)
	4. New Tech 2016	Dominated by Strategy 8 (D)
	11. VC (tiny) + New Tech 2016 & 2019 (fexi)	Dominated by Strategy 12 (E)
	6. VC (tiny) + New Tech 2016	Dominated by Strategy 12 (E)
	10. VC (large) + New Tech 2016 & 2019	Dominated by Strategy 12 (E)
	9. VC (large) + New Tech 2016 & 2019 (fexi)	Dominated by Strategy 12 (E)
	5. VC (large) + New Tech 2016	Dominated by Strategy 12 (E)
	2. VC (large)	Dominated by Strategy 12 (E)
*relative to Strategy 7 (C), **relative to Strategy 8 (D)		

C.8 *Probability of Elimination results (detailed)*

C.8.1 *Base case analysis results*

London Declaration Targets (less than 1 in 10,000)

	Low			Moderate			High		
Intervention	2020	2030	2042	2020	2030	2042	2020	2030	2042
Strategy 1 (A)	0.05	0.05	0.05	0.84	0.90	0.90	0.51	0.72	0.73
Strategy 2	0.97	0.98	0.99	0.98	1.00	1.00	0.91	0.93	0.93
Strategy 3 (B)	0.97	0.98	0.99	0.98	1.00	1.00	0.91	0.92	0.92
Strategy 4	0.05	0.10	0.16	0.94	0.95	0.95	0.76	0.81	0.81
Strategy 5	0.98	0.99	0.99	1.00	1.00	1.00	0.92	0.92	0.92
Strategy 6	0.98	0.99	0.99	1.00	1.00	1.00	0.92	0.92	0.92
Strategy 7(C)	0.05	0.24	0.41	0.93	0.94	0.94	0.77	0.82	0.82
Strategy 8 (D)	0.08	0.45	0.69	0.98	0.99	0.99	0.82	0.82	0.81
Strategy 9	0.98	0.99	1.00	1.00	1.00	1.00	0.92	0.93	0.93
Strategy 10	0.99	1.00	1.00	1.00	1.00	1.00	0.91	0.91	0.91
Strategy 11	0.98	0.99	1.00	1.00	1.00	1.00	0.92	0.93	0.93
Strategy 12 (E)	0.99	1.00	1.00	1.00	1.00	1.00	0.91	0.91	0.91

Full elimination (less than 1 in 1,000,000)

	Low			Moderate			High		
Intervention	2020	2030	2042	2020	2030	2042	2020	2030	2042
Strategy 1 (A)	0.00	0.00	0.00	0.00	0.46	0.63	0.00	0.49	0.61
Strategy 2	0.03	0.49	0.83	0.52	0.96	0.97	0.66	0.91	0.92

Strategy 3 (B)	0.03	0.49	0.83	0.52	0.95	0.96	0.67	0.91	0.92
Strategy 4	0.00	0.00	0.00	0.00	0.66	0.70	0.13	0.75	0.79
Strategy 5	0.03	0.54	0.84	0.84	0.97	0.97	0.87	0.92	0.92
Strategy 6	0.03	0.54	0.84	0.84	0.97	0.97	0.87	0.92	0.92
Strategy 7(C)	0.00	0.00	0.00	0.00	0.67	0.70	0.13	0.77	0.80
Strategy 8 (D)	0.00	0.00	0.02	0.00	0.68	0.71	0.14	0.79	0.80
Strategy 9	0.03	0.61	0.85	0.85	0.97	0.97	0.87	0.92	0.92
Strategy 10	0.03	0.65	0.86	0.84	0.96	0.97	0.86	0.91	0.91
Strategy 11	0.03	0.61	0.85	0.85	0.97	0.97	0.87	0.92	0.92
Strategy 12 (E)	0.03	0.65	0.86	0.84	0.96	0.97	0.86	0.90	0.91

C.8.2   One-way Sensitivity Analysis Results

For the SA results, 2020 based on London declaration targets, full elimination considered for long-term goals at 2030 and 2042.

Vector control

Vector control mortality 1%

	Low			Moderate			High		
Intervention	2020*	2030	2042	2020*	2030	2042	2020*	2030	2042
Strategy 1 (A)	0.05	0.00	0.00	0.84	0.46	0.63	0.51	0.49	0.61
Strategy 2	0.29	0.02	0.09	0.92	0.74	0.79	0.70	0.71	0.78
Strategy 3 (B)	0.29	0.02	0.09	0.91	0.74	0.79	0.70	0.71	0.78
Strategy 4	0.05	0.00	0.00	0.94	0.66	0.70	0.76	0.75	0.79
Strategy 5	0.32	0.03	0.11	0.97	0.81	0.83	0.84	0.82	0.83
Strategy 6	0.32	0.03	0.11	0.97	0.82	0.83	0.84	0.82	0.83
Strategy 7(C)	0.05	0.00	0.00	0.93	0.67	0.70	0.77	0.77	0.80

Intervention	2020*	2030	2042	2020*	2030	2042	2020*	2030	2042
Strategy 8 (D)	0.08	0.00	0.02	0.98	0.68	0.71	0.82	0.79	0.80
Strategy 9	0.35	0.03	0.12	0.97	0.81	0.84	0.84	0.83	0.84
Strategy 10	0.40	0.04	0.15	1.00	0.82	0.83	0.86	0.82	0.83
Strategy 11	0.35	0.03	0.12	0.97	0.82	0.84	0.84	0.83	0.84
Strategy 12 (E)	0.40	0.04	0.15	1.00	0.82	0.83	0.86	0.82	0.83

Vector control mortality 10%

	Low			Moderate			High		
Intervention	2020*	2030	2042	2020*	2030	2042	2020*	2030	2042
Strategy 1 (A)	0.05	0.00	0.00	0.84	0.46	0.63	0.51	0.49	0.61
Strategy 2	1.00	0.95	1.00	1.00	1.00	1.00	0.95	0.95	0.95
Strategy 3 (B)	1.00	0.95	1.00	1.00	1.00	1.00	0.94	0.94	0.95
Strategy 4	0.05	0.00	0.00	0.94	0.66	0.70	0.76	0.75	0.79
Strategy 5	1.00	0.96	1.00	1.00	1.00	1.00	0.96	0.95	0.95
Strategy 6	1.00	0.96	1.00	1.00	1.00	1.00	0.96	0.95	0.95
Strategy 7(C)	0.05	0.00	0.00	0.93	0.67	0.70	0.77	0.77	0.80
Strategy 8 (D)	0.08	0.00	0.02	0.98	0.68	0.71	0.82	0.79	0.80
Strategy 9	1.00	0.98	1.00	1.00	1.00	1.00	0.96	0.96	0.96
Strategy 10	1.00	0.99	1.00	1.00	1.00	1.00	0.95	0.94	0.95
Strategy 11	1.00	0.98	1.00	1.00	1.00	1.00	0.96	0.96	0.96
Strategy 12 (E)	1.00	0.99	1.00	1.00	1.00	1.00	0.95	0.95	0.95

In 2020, threshold is London Declaration target which I defined as less than 1 in 10,000

Surveillance in low transmission

	Biannual surveillance			Annual surveillance		
Intervention	2020*	2030	2042	2020*	2030	2042
Strategy 1 (A)	0.95	0.26	0.43	1.00	0.72	0.72
Strategy 2	1.00	0.92	0.92	1.00	0.95	0.96
Strategy 3 (B)	1.00	0.91	0.92	1.00	0.95	0.96
Strategy 4	1.00	0.58	0.69	1.00	0.76	0.77
Strategy 5	1.00	0.94	0.94	1.00	0.99	1.00
Strategy 6	1.00	0.94	0.94	1.00	0.99	1.00
Strategy 7(C)	1.00	0.59	0.70	1.00	0.77	0.77
Strategy 8 (D)	1.00	0.57	0.69	1.00	0.73	0.73
Strategy 9	1.00	0.92	0.93	1.00	0.99	0.99
Strategy 10	1.00	0.92	0.92	1.00	0.99	0.99
Strategy 11	1.00	0.93	0.93	1.00	0.99	0.99
Strategy 12 (E)	1.00	0.92	0.92	1.00	0.99	0.99

In 2020, threshold is London Declaration target which I defined as less than 1 in 10,000

Coverage rate improvement related to new technologies in low transmission areas

Pentamidine-fexinidazole with RDT 1 in 2016

	Low 1x			High 10x		
Intervention	2020	2030	2042	2020	2030	2042
Strategy 1 (A)	0.05	0.00	0.00	0.05	0.00	0.00
Strategy 2	0.97	0.49	0.83	0.97	0.49	0.83
Strategy 3 (B)	0.97	0.49	0.83	0.97	0.49	0.83
Strategy 4	0.05	0.00	0.00	0.14	0.00	0.02
Strategy 5	0.97	0.49	0.83	0.99	0.66	0.86
Strategy 6	0.97	0.49	0.83	0.99	0.66	0.86
Strategy 7(C)	0.05	0.00	0.00	0.11	0.00	0.00
Strategy 8 (D)	0.06	0.00	0.01	0.16	0.00	0.02
Strategy 9	0.98	0.60	0.86	0.99	0.62	0.86
Strategy 10	0.99	0.65	0.86	0.99	0.66	0.85
Strategy 11	0.98	0.60	0.86	0.99	0.62	0.86
Strategy 12 (E)	0.99	0.65	0.86	0.99	0.66	0.85

Fexinidazole-fexinidazole with RDT 2 in 2019

	Low 1x			High 10x		
Intervention	**2020**	**2030**	**2042**	**2020**	**2030**	**2042**
Strategy 1 (A)	0.05	0.00	0.00	0.05	0.00	0.00
Strategy 2	0.97	0.49	0.83	0.97	0.49	0.83
Strategy 3 (B)	0.97	0.49	0.83	0.97	0.49	0.83
Strategy 4	0.05	0.00	0.00	0.05	0.00	0.00
Strategy 5	0.98	0.54	0.84	0.98	0.54	0.84
Strategy 6	0.98	0.54	0.84	0.98	0.54	0.84
Strategy 7(C)	0.05	0.00	0.00	0.07	0.00	0.02
Strategy 8 (D)	0.08	0.00	0.02	0.08	0.00	0.02
Strategy 9	0.98	0.50	0.83	0.99	0.65	0.87
Strategy 10	0.99	0.65	0.86	0.99	0.65	0.86
Strategy 11	0.98	0.50	0.83	0.99	0.65	0.87
Strategy 12 (E)	0.99	0.65	0.86	0.99	0.65	0.86

Oxaborole with RDT 2 in 2019

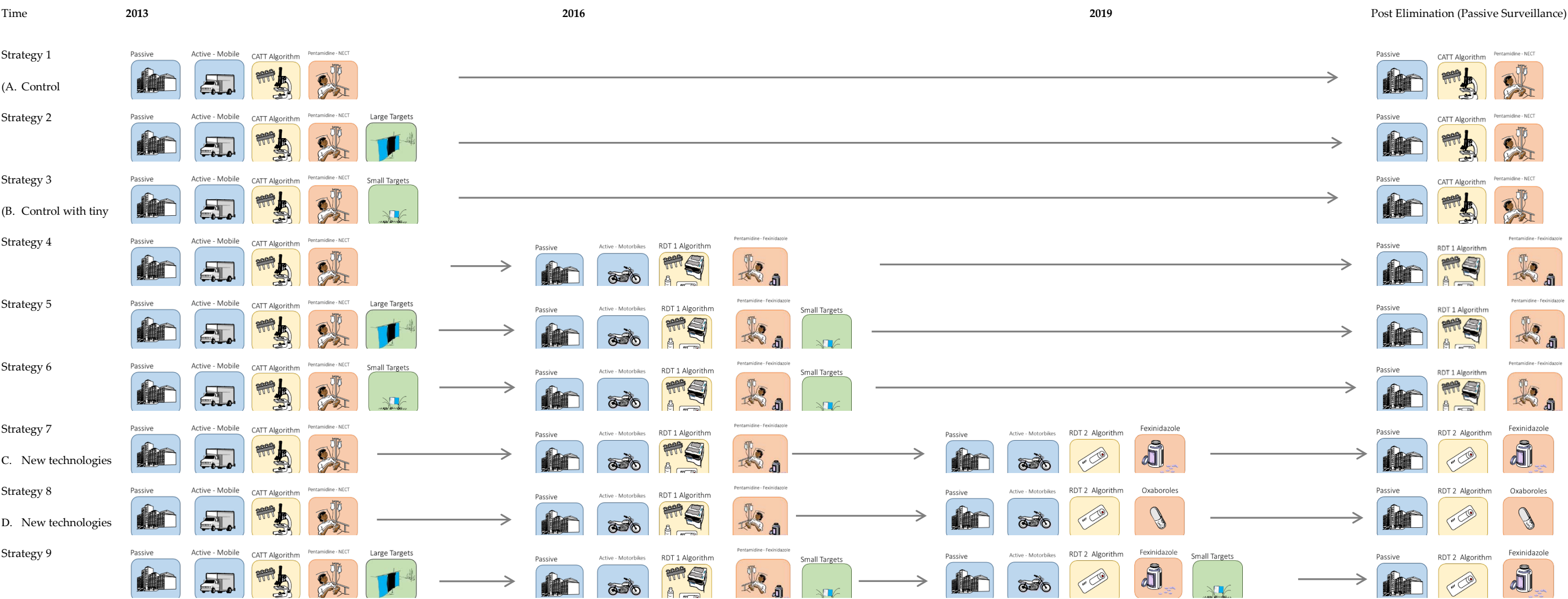|	Low 1x			High 15x		
Intervention	**2020**	**2030**	**2042**	**2020**	**2030**	**2042**
Strategy 1 (A)	0.05	0.00	0.00	0.05	0.00	0.00
Strategy 2	0.97	0.49	0.83	0.97	0.49	0.83
Strategy 3 (B)	0.97	0.49	0.83	0.97	0.49	0.83
Strategy 4	0.05	0.00	0.00	0.05	0.00	0.00
Strategy 5	0.98	0.54	0.84	0.98	0.54	0.84
Strategy 6	0.98	0.54	0.84	0.98	0.54	0.84
Strategy 7(C)	0.05	0.00	0.00	0.05	0.00	0.00
Strategy 8 (D)	0.05	0.00	0.00	0.12	0.01	0.03
Strategy 9	0.98	0.61	0.85	0.98	0.61	0.85
Strategy 10	0.98	0.50	0.83	0.99	0.72	0.88
Strategy 11	0.98	0.61	0.85	0.98	0.61	0.85
Strategy 12 (E)	0.98	0.50	0.83	0.99	0.72	0.88

Accelerating timeline for fexinidazole arriving on the market for both stages in 2016
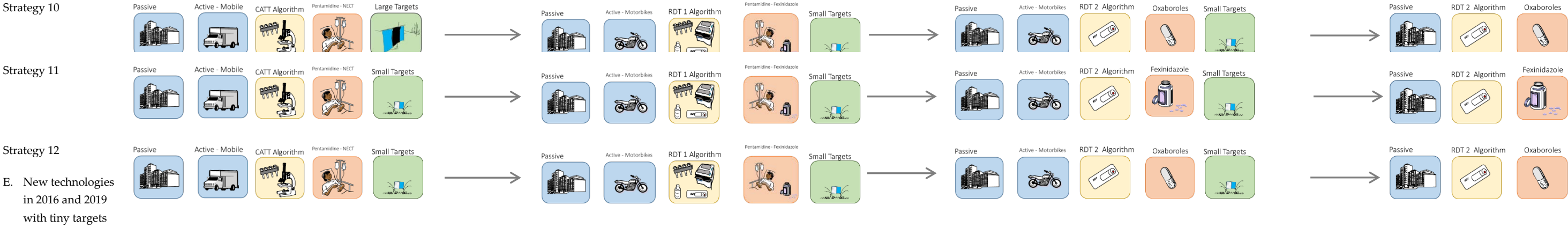
Intervention	Low			Moderate			High		
	2020*	2030	2042	2020*	2030	2042	2020*	2030	2042
Strategy 1 (A)	0.05	0.00	0.00	0.84	0.46	0.63	0.51	0.49	0.61
Strategy 2	0.97	0.49	0.83	0.98	0.96	0.97	0.91	0.91	0.92
Strategy 3 (B)	0.97	0.49	0.83	0.98	0.95	0.96	0.91	0.91	0.92
Strategy 4	0.09	0.00	0.00	0.93	0.67	0.70	0.76	0.75	0.79
Strategy 5	NA	NA	NA	NA	NA	NA	NA	NA	NA
Strategy 6	NA	NA	NA	NA	NA	NA	NA	NA	NA
Strategy 7(C)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Strategy 8 (D)	0.12	0.00	0.02	0.98	0.68	0.71	0.82	0.79	0.80
Strategy 9	0.99	0.62	0.86	1.00	0.97	0.97	0.92	0.92	0.92
Strategy 10	0.99	0.65	0.85	0.91	0.90	0.91	0.91	0.91	0.91
Strategy 11	0.99	0.62	0.86	1.00	0.97	0.97	0.92	0.92	0.92
Strategy 12 (E)	0.99	0.65	0.85	1.00	0.97	0.97	0.91	0.90	0.91

In 2020, threshold is London Declaration target which I defined as less than 1 in 10,000

NOTE: in the published manuscript, Strategy 1 = Strategy 1; Strategy 3 = Strategy B; Strategy 7 = Strategy C; Strategy 8 = Strategy D and Strategy 12 = Strategy E.

Pictorial description of 12 strategies for control and elimination

Time	2013	2016	2019	Post Elimination (Passive Surveillance)

Strategy 1

(A. Control

Strategy 2

Strategy 3

(B. Control with tiny

Strategy 4

Strategy 5

Strategy 6

Strategy 7

C. New technologies

Strategy 8

D. New technologies

Strategy 9

Strategy 10

Strategy 11

Strategy 12

E. New technologies
    in 2016 and 2019
    with tiny targets

Appendix D: Chapter 6

D.1 *Priority setting exercise*

Strategies selected using a rationale choice approach. The ICERs included represent strategies that were cost-effective as per Sutherland et al 2017.

Strategies (High risk transmission)	Cost	DALYs	ICER ($ per DALY averted)
Strategy D, new technologies 2016 and 2019	$45	0.22	
Strategy C, new technologies 2016	$47	0.25	Dominated by Strategy D
Strategy E, new technologies 2016 and 2019 plus tiny targets	$61	0.18	$386
Strategy B, control with tiny targets	$82	0.20	Dominated by Strategy E
Strategy A, control	$115	0.34	Dominated by Strategy E
Strategies (Moderate risk transmission)	**Cost**	**DALYs**	**ICER**
Strategy D, new technologies 2016 and 2019	$20	0.03	-
Strategy C, new technologies 2016	$20	0.03	Dominated by Strategy D
Strategy E, new technologies 2016 and 2019 plus tiny targets	$38	0.02	$1509
Strategy B, control with tiny targets	$48	0.02	Dominated by Strategy E
Strategy A, control	$55	0.04	Dominated by Strategy E
Strategies (Low risk transmission)	**Cost**	**DALYs**	**ICER**
Strategy C, new technologies 2016	$3	0.04	
Strategy A, control	$3	0.04	Dominated by Strategy C
Strategy D, new technologies 2016 and 2019	$3	0.03	$160
Strategy E, new technologies 2016 and 2019 plus tiny targets	$42	0.01	1812
Strategy B, control with tiny targets	$45	0.01	Dominated by Strategy E

However, SA demonstrated that increased surveillance could be CE, and when compared to the current interventions it dominated Strategy E and B. Hence, strategy D plus bi-annual surveillance could be considered a CE strategy in areas where the cost-effectiveness threshold is near $650 per DALY averted or greater.

Strategies (Low risk transmission)	Cost	DALYs	ICER
Strategy C, new technologies 2016	$3	0.04	
Strategy A, control	$3	0.04	Dominated by Strategy C
Strategy D, new technologies 2016 and 2019	$3	0.03	$160
Strategy D, new technologies 2016 and 2019 +bi-annual surveillance	$20	0.004	$654
Strategy E, new technologies 2016 and 2019 plus tiny targets	$42	0.01	Dominated by Strategy D+
Strategy B, control with tiny targets	$45	0.01	Dominated by Strategy D+

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Therefore it was decided that 3 options could potentially be available in low transmission areas depending on cost-effectiveness thresholds and feasibility of running additional surveillance programs. In cases where there was no ICER since the strategy was the comparator, the strategy with the lowest cost was considered.

Range of GNIs from impacted nations ranged from $300 to $13,000 with median near 1410. CE thresholds were selected using the GNIs of impact countries as a proxy.

Program plan	Cost-effectiveness threshold	Low (ICER)	Moderate	High
Control	Reference	A	A	A
Elimination I	~$300 per DALY averted	D ($160)	D (lowest cost)	D (lowest cost)
Elimination II	~$700 per DALY averted	D+ ($654)	D (lowest cost)	E ($386)
Elimination III	~$1500 per DALY averted	D+ ($654)	E ($1509)	E ($386)

D.2   *Financial forecast*

The modelling simulates three foci areas reflecting the WHO definition of low, moderate and high risk transmission. It also maintains the WHO recommendations for surveillance in such areas meaning that no active surveillance is occurring in low transmission areas, whilst moderate and high transmission areas experience active screening campaigns with an average coverage rate of 80% of the 57 million people reported to be at risk(Franco et al. 2017). Again, according to recommendations from the WHO, surveillance in moderate risk areas was simulated bi-annually and high transmission areas done annually.

As the model represents three hypothetical risk transmission areas based on low, moderate and high prevalence, the annual percentage reduction of cases per year was extracted from the model respective to the three risks areas under evaluation. The estimated number of cases was then forecasted into the future using the 6228 *T.b. gambiense* cases reported in 2013 across 13 endemic nations as a baseline. Estimations from the model and WHO reported cases up to 2014 were compared for validation of the model's predictive capacity. Forecasting estimates and current estimates for reported cases is depicted in the figure displayed in section D.3.1 of this appendix. When the mean of control strategies (with and without vector control) from 2012 to 2014 was compared to the data currently available, the model predicted cases well (R^2= 0.8301), however the available data is limited and the model's predictive ability will need to be assessed continually. Although control will reduce the number of cases over time, these reductions are expected to plateau over the next decade leading to delays in meeting elimination targets. However, if elimination strategies that include increased surveillance in low transmission areas, innovative technologies to improve coverage or targets to interrupt vector transmission (Elimination programs I, II and III) are implemented; the outcome would result in achieving near 2000 cases or less across Africa by 2020. Optimal declines were

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observed in Elimination II and III, where less than 500 cases could be feasible by 2020, and also contain strategies that have the highest probability of elimination (Sutherland et al, 2017).

Stone & Chitnis (Chris M. Stone & Chitnis 2015) and used to calculate cost-effectiveness over time (Sutherland et al. 2017) was again used to estimate annual cases, as well as costs for treatment, vector control and surveillance.

D.2.1   Health care expenditures

National 'screen & treat' programs and vector control program costs

Cost functions related to the expenses incurred for surveillance, treatment, diagnostics and vector control programs of *T.b. gambiense* were developed and incorporated into the model to generate an annual cost per person in an at risk transmission area (Sutherland et al. 2017). These per person estimates were taken directly from the model outputs annually and then multiplied to the at foci defined by WHO(World Health Organization (WHO) 2013c) and calculated for current at risk populations of the 14 endemic countries. The formula to represent these calculations can be described as follows:

$$\sum_{t=1}^{30} \overline{C_f} = (c_{sur} + c_{tx} + c_{vc})_f \times n_f$$

Where t represents the years and $\overline{C}$ are the mean costs over the 30 year time horizon. The costs for surveillance $= C_{sur}$, treatment $= C_{tx}$ and vector control $= C_{vc}$. All are represented as units per person in an at risk focus, hence n = number of people at risk in a focus. A specific focus is represented by f for which there are three: low, moderate and high. And hence the total cost of a program is the sum of the three foci areas can be described as:

$$\overline{TC} = \overline{C}_{low} + \overline{C}_{moderate} + \overline{C}_{high}$$

	Mean estimate Cost $US, (SD)	Sources
Financial costs		
Surveillance	Cost per person in at risk transmission area	
Annual surveillance	0.42	Lutumba 2007
Mobile team start-up	1.55	Lutumba 2007
Mobile teams annual maintenance	0.21	Lutumba 2007
Motorbike team start-up	0.89	Lutumba 2007
Motorbike team annual maintenance	0.42	Lutumba 2007
Passive surveillance	1.35	Lutumba 2007
Diagnostics		
CATT algorithm	8.19	Lutumba 2005,WHO Technical report 1998, Lutumba 2006
RDT 1 algorithm	6.17	Lutumba 2006,Ndung'u 2015,FIND
RDT 2 algorithm	3.86	FIND

.

Treatment*	Cost per person in at risk transmission area	
Pentamidine	367.56	Shaw 2001, Politi 1995
NECT	816.46	Simarro 2011 and 2012
fexinidazole	55.23	DNDi
oxaborole	2.00	DNDi
Vector control program	Cost per km in at risk transmission area	
Tiny targets start-up	13.8	Shaw 2015
Tiny target maintenance	13.8	Shaw 2015
SD = standard deviation *(per diem, Including hospitalization)		

D.3   *Financial protection analysis*

D.3.1   *Number of cases (household) estimations*
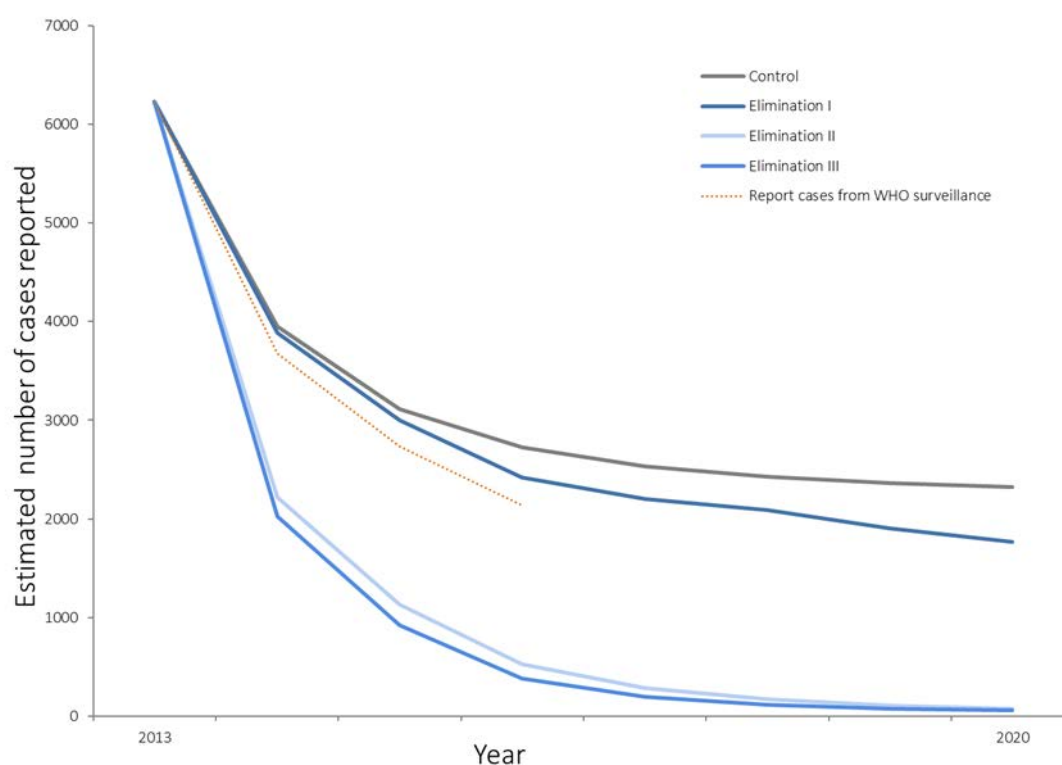
Year	Control 2020						
(based on 500 simulations)	Mean	SD	SE	95% CI low	95% CI high	Min	Max
2013	6228	0	0			6228	6228
2014	3951	261	12	3950	4297	3343	5252
2015	3109	365	16	3108	3381	2593	5086
2016	2725	404	18	2724	2964	2245	5030
2017	2532	420	19	2530	2753	2079	5002

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2018		2425	428	19	2423	2637	1983	4987
2019		2361	432	19	2359	2568	1916	4978
2020		2319	435	19	2318	2523	1863	4973

Year (based on 500 simulations)	Elimination I						
	Mean	SD	SE	95% CI low	95% CI high	Min	Max
2013	6228	0	0			6228	6228
2014	3889	193	9	3888	4230	3343	4526
2015	3000	202	9	2999	3263	2593	4228
2016	2421	144	6	2420	2633	1997	3709
2017	2201	137	6	2200	2394	1745	3633
2018	2092	148	7	2092	2276	1582	3602
2019	1902	224	10	1901	2068	979	3495
2020	1768	283	13	1766	1922	701	3465

Year (based on 500 simulations)	Elimination II						
	Mean	SD	SE	95% CI low	95% CI high	Min	Max
2013	6228	0	0			6228	6228
2014	2217	633	28	2215	2412	943	3395
2015	1133	421	19	1131	1232	326	2114
2016	523	239	11	522	569	108	1333
2017	281	156	7	280	306	42	1158
2018	167	114	5	166	182	17	1066
2019	108	89	4	108	117	6	961
2020	76	74	3	76	82	2	892

Year (based on 500 simulations)	Elimination III						
	Mean	SD	SE	95% CI low	95% CI high	Min	Max
2013	6228	0	0			6228	6228
2014	2023	639	29	2020	2200	724	3177
2015	917	420	19	915	997	133	1834
2016	383	229	10	383	417	20	1015
2017	197	142	6	197	215	3	881
2018	117	99	4	117	128	1	817
2019	77	75	3	77	84	0	743
2020	56	61	3	55	61	0	695

D.3.2 Out-of-pocket (OOP) Household health expenditures related to T.b. gambiense

A cost function for per household OOP expenditure was then developed taking into consideration that a family member or friend would attend the treatment clinic with the diagnosed individual, and was calculated as follows:

$$\sum_{t=1}^{30} \overline{OOP_{s_i}} = p_i \times [c_{fee} + (c_{accomodation} \times (tx_{days_{s_i}} + r_{days_{s_i}})) + 2(c_{transportation}) + 2(c_{meals} \times (tx_{days_{s_i}} + r_{days_{s_i}}))]$$

Where p_i are the number of cases per stage, and c costs refer to meals ($c_{meals,}$), a return trip for transportation to the treatment facility ($c_{transportation}$) and the per diem accommodation rates ($c_{accomodation}$). The per diem treatment days defined as $tx_{days_{s_i}}$ are relative the treatment in the foreseen program (i.e. Control 2020, Elimination 2020, etc.) The average cost of treatment for stage 1 and 2 is used as a the final mean OOP costs per program(refer to the Table in D.3.3).

Short name	OOP Description	Cost	Source
One time OOP			
c_{fee}	Hospital entry fees (one time)	$2.52	Matemba, 2010
$c_{transportation}$	Transportation (roundtrip)	$9.65	Matemba, 2010
Per diem OOP			
$c_{accomodation}$	Accommodation per diem	$1.90	Matemba, 2010
c_{meals}	Meals per diem	$2.28	Matemba, 2010
tx_{days}	Days of treatment		
	Pentamidine	12	Steinmann et al
	NECT	14	Steinmann et al
	fexinidazole	10	Steinmann et al
	oxaborole	1	Steinmann et al
r_{days}	Days of recovery (related to treatment)		
	pentamidine	7	Assumption
	NECT	7	Assumption
	fexinidazole	4	Assumption
	oxaborole	2	Assumption

HAT *T.b. gambiense* affects rural populations across Sub-Saharan Africa, hence mean consumption (C) was based on the gross national income (GNI) of the endemic nations. Non-medical expenses (NM) were estimated using food expenditures as a proxy and it was assumed on average that 66.3% of a rural household income (~ $320 annual) was spent on food expenditures (Depetris Chauvin et al. 2012). In order to estimate the relative CHE related to OOP (shown as 'M'), the recommended methodology was used(Bank 2017) where:

$$\frac{M}{(C - NM)}$$

To visualize the impact that OOP had on a household relative to the poverty line, a Pen Parades' diagram, was generated. This image is often used to assist policy makers in reviewing the impact that OOP may have on subjecting households to poverty (impoverishing) or pushing families with an income below the poverty line, further into poverty ('immiserizing').

D.3.3   Summary of inputs for the Financial Protection Analysis (FPA)

Description									95% Confidence (CI)		Source
Households (cases)	Mean	Distribution	alpha	beta	SD	SE	MIN	MAX	low	high	
Control **2013**	6228										Franco et al, 2017
Control 2020	2333	Normal			435	19	1863	4973	2318	2523	Stone & Chitnis, France et al 2017
Elimination I 2020	1774	Normal			283	13	701	3465	1766	1922	HAT model (Stone & Chitnis), projections
Elimination II 2020	77	Normal			74	3	2	892	76	82	HAT model (Stone & Chitnis), projections
Elimination III 2020	57	Normal			61	3	0	695	55	61	HAT model (Stone & Chitnis), projections
Income (C), annual	**Median**										
Income - GNI	$1,360	Gamma	2	835	3843	1066	330	12640	2438	3596	World Bank 2013
Income - lower income GNI	$575	Gamma	25	23	283	115	330	980	538	722	World Bank 2013
Income - lower-middle income GNI	$2,085	Gamma	25	83	833	417	1360	2970	1717	2533	World Bank 2013
Income - middle-upper income GNI	$9,450	Gamma	17	541	3916	2261	4850	12640	6421	11539	World Bank 2013
Non-medical expenses (NM), annual											
Non-medical expenses (i.e food)	$320	Gamma	319.566	1							Lutumba 2007, Chauvin 2012
OOPs, Medical expenses related to HAT *Tbg* (M)											
	Mean										
Control 2013	$151	Gamma	151.02	1	9.136						Matemba 2010
Control 2020	$151	Gamma	151.02	1	9.136						Matemba 2010
Elimination I 2020	$3	Gamma	2.52	1							Matemba 2010
Elimination II 2020	$3	Gamma	2.52	1							Matemba 2010,
Elimination III 2020	$3	Gamma	2.52	1							Matemba 2010
Other inputs											
CHE threshold	10% and 25%										World Bank 2017
Poverty line	1.9										World Bank 2017
Discount rate	3%										WHO-CHOICE

C=consumption, income; GNI=gross national income, NM=non-medical expense, M=medical expense, OOP=out-of-pocket payments, CHE = catastrophic health expenditure

Appendix E: Chapter 7

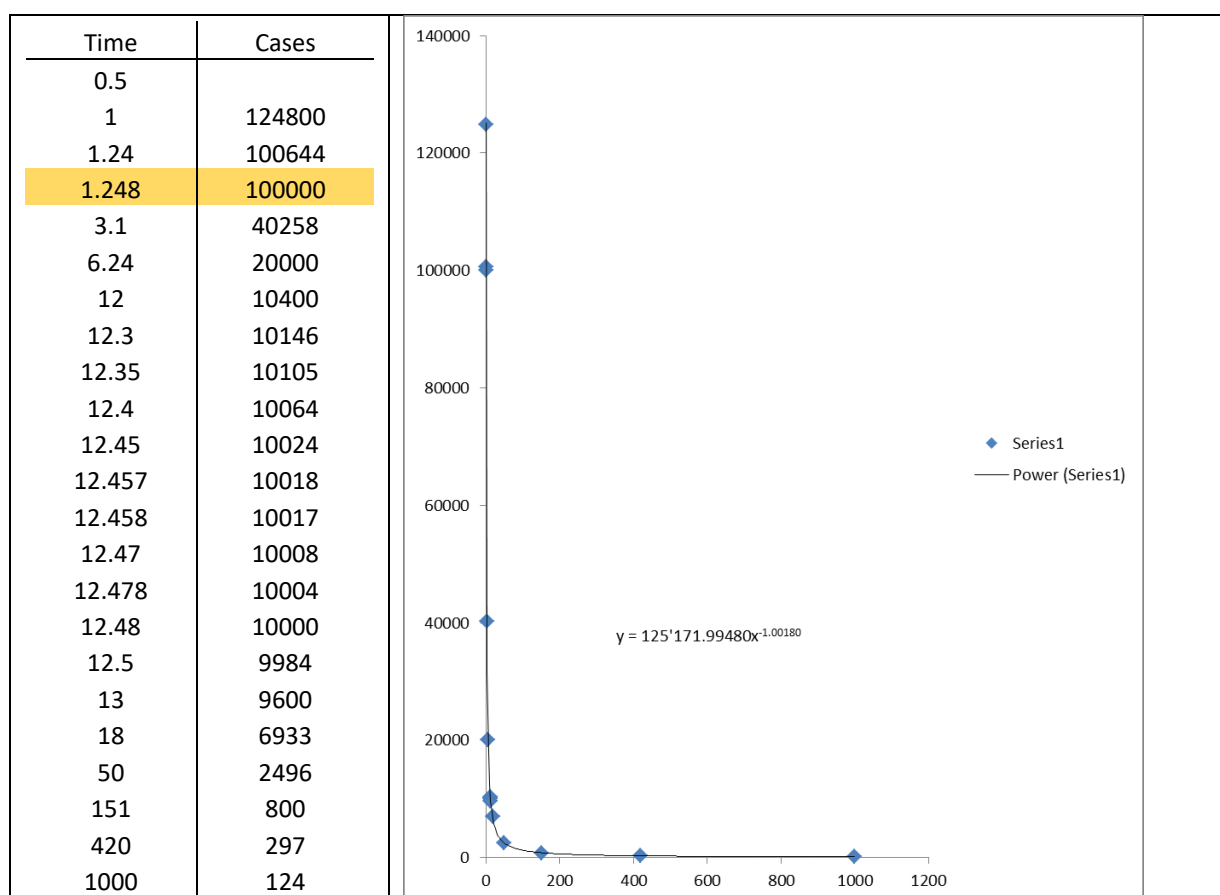### E.1   *Summary of health systems actors and responsibilities*

Health system component	Current	Future	Responsibility	Source/link
Finance				
	African Development Bank (ADB)		Funding, donations	
	Arab Bank			
	BMGF		Funding (modelling, R&D, NSSCPs)	
	Department for International Development (DFID) of the United Kingdom			
	Deutsche Gesellschaft für Technische Zusammenarbeit (GTZ) on behalf of the Government of the Federal Republic of Germany			
	National budget		Funding	
	Spanish Agency of International Cooperation for Development (AECID).			
	The Ministry of Foreign and European Affairs (MAEE) of France			
	Wellcome Trust		Financing R & D	
Governance				
	WHO Gambiense HAT stakeholders for elimination		Support	
	PATTEC (vector control)		Coordination and support	
	WHO TAG NTD			
	WHO (country offices)		Procurement	
	NSSCP or NTD programs(MoH) (E.g. National HAT Control Programme of the DRC (PNLTHA, Democratic Republic of the Congo)		In country coordination	
	Community			
Service Delivery				

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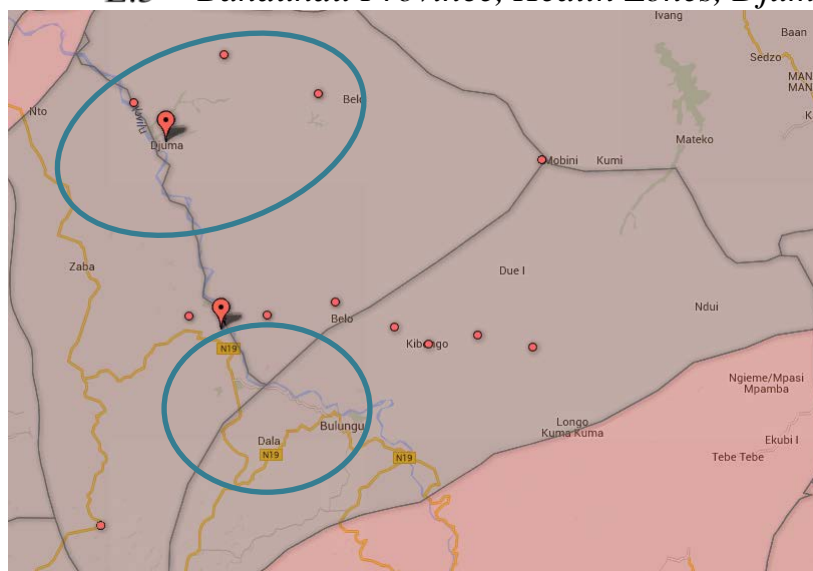|			
	Médecins sans Frontières (MSF) /Doctors without Borders		Logistics (Bordeaux)
	MSF treatment centres		In country
	NSSCP (MoH)		In country
	NSSCP treatment centres		In country
		National medical stores	
		CHW	
Medicine and technology (research)			
Treatment	pentamidine, melarsoprol and eflornithine (DMFO), Sanofi	fexinidazole (Winthrop ®)	
	Nifurtomix (Bayer HealthCare)		
Diagnostics	Anitgens for CATT (ITM, Belgium)		
		HATSeroK-SeT Coris BioConcept, Belgium	http://www.dndi.org/wp-content/uploads/2015/09/Bscher_DNDi_ECTMIH_2015.pdf
		SD Bioline HAT - Standard Diagnostics, Inc. (Republic of Korea).	http://www.finddiagnostics.org/resource-centre/press/121206.html
		Antigens for RDTs MicroCoat Biotechnologie GmbH (Germany)	(https://www.google.com/patents/WO2001032896A1?cl=en)
			(http://www.itg.be/itg/Uploads/TTP/CATT%20gambiense%20engels%20PDT_BR_0001_E_6.1.pdf)
	UNK	LAMP and parasitological confirmation laboratory testing	

Vector control		Tiny targets Vestergaard		http://www.vestergaard.com/zerofly-screen
Surveillance	Mobile truck, MSF	motorbike teams		
	Mobile truck , NSSCP	motorbike teams		
	UNK	PDA and solar panels for motorbike teams		
Human Resources				
	MSF			
	Doctors			
	Nurses			
	Lab technicians (Parasitology)			
	VC maintenance & deployment teams			
	Active surveillance teams, drivers, diagnosticians			
	NSSCP employees (Management and Support)			
		CHW		
People				
	Patients		Self-report, seek treatment	
	Families		Support and attend ill family member seeking treatment	
	Communities		Support community member seeking treatment	
Information				
	FAO (PAAT)	Mapping		
	WHO			
	SSNCP			
Research & Development	The International Livestock Research Institute (Kenya)			
	the Institute of Tropical Neurology (France), the			
	the Centrafrican Institute of Agronomical Research (Central African Republic),			

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FIND	Diagnostics
Antwerp(Belgium)	Diagnostics
Institute of Tropical Medicine (ITM)(Belgium)	Diagnostics
Glasgow	Diagnostics
Liverpool	Vector control
Warwick & Yale	Disease modelling
FAO	Mapping
IDM	Disease prevalence modelling and mapping
Swiss TPH	Clinical trials, public policy briefs (economics and modelling)
DNDi	Drug discovery and development
NITD	Drug discovery and development
Liverpool, Centre of African Studies at the University of Edinburgh, LSHTM, Institute of Tropical Medicine (ITM)(Belgium)	Medical anthropology

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E.2 *Inter-arrival time estimations*

Time	Cases
0.5	
1	124800
1.24	100644
1.248	100000
3.1	40258
6.24	20000
12	10400
12.3	10146
12.35	10105
12.4	10064
12.45	10024
12.457	10018
12.458	10017
12.47	10008
12.478	10004
12.48	10000
12.5	9984
13	9600
18	6933
50	2496
151	800
420	297
1000	124

$$y = 125'171.99480x^{-1.00180}$$

E.3 *Bandundu Province, Health Zones, Djuma, Vanga, Bulungu*

Map of DRC health facilities: https://dl.dropboxusercontent.com/u/16026677/DRC_Map_v1_9.html

Note: Shows 3 health zones in Bandundu Province service by 2 HAT treatment hospitals, surrounded by 13 local facilities with the capacity to diagnose, but not treat. The example of 1 HAT treatment hospital with 2 alternative local centres was based on this representation.