Acta Tropica 150 (2015) 4–13

Contents lists available at ScienceDirect

Acta Tropica

journal homepage: www.elsevier.com/locate/actatropica

Review

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

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ARTICLE INFO

Article history:
Received 31 March 2015
Received in revised form 2 June 2015
Accepted 3 June 2015
Available online 6 June 2015

Keywords:
Trypanosomiasis
Sleeping sickness
Cost
Prevention
Treatment
Control

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.

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http://dx.doi.org/10.1016/j.actatropica.2015.06.003
0001-706X/

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1. 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 (Simarro et al., 2012a,b). *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 70 million people (Simarro et al., 2012a,b) and about 50 million head of cattle are at risk of trypanosomiasis infection (Fevre 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 behavior. A total of 7216 HAT cases for both *T.b gambiense* and *T.b rhodesiense* were reported in 2012 (WHO, 2013) and the World Health Organization (WHO) estimates the number of actual infections to be around 20,000 (WHO, 2013). In 2014, WHO approved a declaration to target *gambiense* HAT elimination (Holmes, 2014) and one to target *rhodesiense* HAT (WHO, 2014a).

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 the 1970s 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 to Combat NTDs, 2013; WHO, 2012; BMGF, 2015). 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 endeavors. 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.

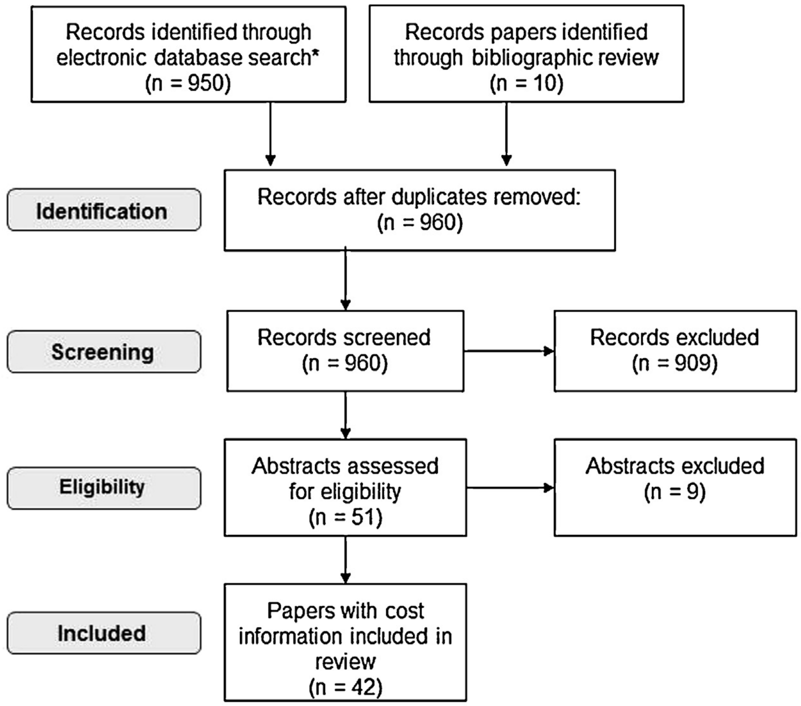
1.1. Prevention, treatment, control of HAT

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 target 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) (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 (WHO, 2013). The 2nd stage of *T.b. rhodesiense* is treated with the organoarsenical compound melarsoprol (WHO, 2013), which is associated with severe adverse reactions, mainly arsenical encephalopathy, occurring in 10% of the patients and frequently fatal (10–70% mortality) (Pepin and 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 (WHO, 2013). 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 (WHO, 2013). Melarsoprol is used when patients treated with NECT relapse (WHO, 2013). New treatments are currently being developed: fexinidazole is a 10-day oral medication (DNDi, 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 (DNDi, 2014), allowing patients to be potentially treated locally and thus avoiding travel to specialized treatment centers that are often far from home. Active and passive case finding are crucial to identify and treat cases to curb transmission.

2. Methods

A systematic electronic search of literature published in the English and French language was conducted using Pubmed (MEDLINE), 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,



** Electronic databases : EMBASE, PubMed, JSTOR, Google Scholar and Open Content*

Fig. 1. Incremental search results and final studies included.

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. Fig. 1 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).

3. Results

3.1. Prevention: vector control costs

3.1.1. 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 km^2, 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 (2004). Botswana and Zambia (1973, 1980) reported USD 231.95 per Km^2 of Endosulfan and pyrethroids; Nigeria (1977) reported USD 890.62 per Km^2 of Endosulfan (Lee et al., 1982); Cote d'Ivoire (1979) reported USD 617.00 per application of Endosulfan (Lee et al., 1982); and Zambia (1968–1978) reported a range of USD 827.38–1,103.19 per Km^2, although the insecticide used was not mentioned (Evinson and Kathuria, 1984; Allsopp and Hursey, 2004). One study in West Africa also reported the cost of non-SAT from a helicopter to be between USD 1.55–2.75 per hectare, assuming 2000–3,500 hectares covered per application, respectively (Brandl, 1988a). 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 km^2 by 30–50% (Allsopp and Hursey, 2004). Across several ecologically distinct settings, SAT in general is thought to cost between USD 285.81 628.79 per Km^2 (Cattand et al., 2006).

3.1.2. *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 km^2 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/km^2, although in areas where substantially fewer sterile males would be required, the cost of SIT could fall to USD 303.12-363.75/km^2 (Feldman, 2004) depending on how many sterile males are released per kilometer and the cost of the flight plan employed (Vale and Torr, 2005).

3.1.3. *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 USD 260.68–274.05 per km^2 (Allsopp and 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).

3.1.4. *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 colored cloth (targets), which can be treated with insecticide. These tools can be baited with odor 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., 2012; Mullins et al., 1999), and USD 128.03 when used for control (Allsopp and Hursey, 2004; McCord, 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 (Brandl, 1988a). The cost per km^2 when traps and targets are deployed for elimination purposes ranges from USD 343.14 and USD 880.27 per km^2, 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 odor 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).

3.1.5. *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 an α-cypermethrin spray (USD 14.55 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 and Vale, 2007, Vale and Torr, 2005). Table 1 presents additional vector control cost information.

3.2. *Costs of treatment and hospitalization for HAT*

3.2.1. *Treatment costs*

For treatment of first stage *T.b. gambiense* infection, pentamidine is the WHO recommended drug (WHO, 2014b). 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. (2007) and Shaw and 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 4 treatments resulting in the cost of USD 387.68 for one treatment. (Simarro et al., 2012a,b) Alternative treatments such as melarsoprol or eflornithine may be used as well (WHO, 2013). Using clinical data from 690 s stage *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 melarsoporol were identified; however, the direct costs of management of these complications were esti-

Table 1
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/km^2 (14% of non-field costs)
		Entomological surveys, monitoring, feasibility studies	USD 223.10/km^2
		Aerial spraying- five cycles	USD 3734.99/km^2
		Cost for creating a tsetse-free zone for isolated tsetse populations	USD 720.22/km^2 & USD 608.67/km^2
Sterile Insect Technique (SIT)			
Vale and Torr	2005	Cost of rearing and sterilizing a male	USD 0.11
		Cost of release including accompaniment	USD 1.01/km^2/week
		Eradication Estimate	USD 42,033.91/insect population
Shaw	2007	Administration, supervision, and other indirect “non-field” costs	USD 56.99 km^2 (19% of non-field costs)
		Entomological surveys, monitoring, feasibility studies	USD 235.22/km^2
		Capital items, fly rearing, fly release	USD 801.46/km^2
		Creating a tsetse-free zone for isolated tsetse populations: +SIT alone	USD 919.07/km^2
		Creating a tsetse-free zone for isolated tsetse populations: SIT + 90 day ITC	USD 1228.26/km^2
		Creating a tsetse-free zone for isolated tsetse populations: SIT + 80% SAT	USD 1228.26/km^2
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/km^2 (14% of non-field costs)
		4 Traps/km^2 (10 teams)	USD 213.40
		4 Traps/km^2 (15 teams)	USD 277.66
		4 low cost Traps/km^2 (10 teams)	USD 191.57
		4 low cost traps/km^2 (15 teams)	USD 244.92
		8 Traps/km^2 (20 teams)	USD 426.80
		8 Traps/km^2 (30 teams)	USD 444.32
		10 Traps/km^2 (25 teams)	USD 534.71
		10 Traps/km^2 (38 teams)	USD 693.55
		20 Traps/km^2 (50 teams)	USD 1068.21
		20 Traps/km^2 (75 teams)	USD 1388.31
		Creating a tsetse-free zone for isolated tsetse populations: *G. fuscipes*	USD 1115.50/km^2
		Creating a tsetse-free zone for isolated tsetse populations: Savannah tsetse	USD 602.61/km^2
		Creating a tsetse-free zone for isolated tsetse populations: Savannah tsetse	USD 491.06/km^2
		Creating a tsetse-free zone for isolated tsetse populations: Savannah tsetse species + local labor	USD 563.81/km^2
Shaw	2013	Average field cost per km^2	USD 561.25
		Average cost of field studies per km^2	USD 188.56
		Average cost of field deployment teams based on 10 teams	USD 15.53
		Cost of trap maintenance per annum per km^2	USD 61.67
Insecticide Treated Cattle (ITC)			
Vale and Torr	2005	Insecticide containing 20% α-cypermethrin purchased and shipped	USD 30.46 per liter
		Cost per animal	USD 0.002/animal/day
Torr	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

Table 1 (*Continued*)

Authors	Year	Description of cost	Cost
Shaw	2007	Administration, supervision, and other indirect “non-field” costs	USD 36.67/km^2 (14% of non-field costs)
		Entomological surveys, monitoring, feasibility studies	USD 223.10/km^2
		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/km^2)	USD 368.60/km^2
		Creating a tsetse-free zone for isolated tsetse populations: spray (4/km^2)	USD 293.42/km^2
		Creating a tsetse-free zone for isolated tsetse populations: pour-on (8/km^2)	USD 477.72/km^2
		Creating a tsetse-free zone for isolated tsetse populations: spray (8/km^2)	USD 327.37/km^2
		Creating a tsetse-free zone for isolated tsetse populations: restricted (8/km^2 and fewer studies)	USD 162.47/km^2
		Creating a tsetse-free zone for isolated tsetse populations: spray	USD 215.82/km^2

mated 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 (DNDi, 2014) while no estimates have been confirmed for oxaborole. Table 2 lists additional treatment costs identified.

3.2.2. 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).

3.3. Control costs for HAT

3.3.1. 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). em>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 meth-

Table 2
Cost 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) – whole blood	USD 0.73
		CATT test screen per person (one time) – filter paper	USD 0.44
		CATT test screen per person (one time) – micro method	USD 0.26
Wastling	2010	LAMP with Quant-IT Pico Green (per 100 reactions)	USD 371.30
		LAMP with Turbidity (per 100 reactions)	USD 0.001
		LAMP with hydroxynapthol blue (per 100 reactions)	USD 0.001
		LAMP with Calcein and $MnCl_2$ (per 100 reactions)	USD 0.001
Treatment			
Lutumba	2003	Pentamidine per vial	USD 2.05
Shaw and Cattand	2001	Pentamidine drug costs per treatment	USD 25.61
Shaw and 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 1550.74
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 patient	USD 75.52

Table 3
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 and Cattand	2001	Rural health centers and mobile teams (0.05%)	USD 2696.15 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 2700 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	2007	Annual costs for operations of mobile teams	
		Vehicles	USD 7212.62
		Medical and lab supply (includes CATT reagents)	USD 3884.26
		Training	USD 945.25
		Personnel	USD 16,212.57
		Medical and lab supply	USD 20,826.57
		Essential drugs (not for HAT)	USD 2955.42
		Vehicle operation & maintenance	USD 7318.18

ods and to estimate their costs and cost-effectiveness using a spreadsheet model (Shaw and 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 centers 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 3 summarizes costs associated with case detection and surveillance.

3.3.2. *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 3 years 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 2. Some of the treatment and surveillance studies noted above also include the costs of diagnosis of the disease in their total cost estimates (Shaw and Cattland, 2001, Robays et al., 2008).

3.4. *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, 1999; 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 and Hughjones, 1995; Jemal et al., 1995; Agyemang et al., 1991, 1990; Wilson et al., 1986; 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 et al., 1999; Rowlands et al., 1999; Blanc et al., 1995; Shaw and Munstermann, 1994; Brandl 1988b; 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 and Geerts, 2004). Approximately 45-50 Million cattle are thought to live in zones of trypanosomiasis risk (Kristjanson et al., 1999; Budd, 1999); significant increases in numbers of adult cattle and in cattle ownership were observed after the rollout of tsetse control measures in Burkina Faso (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 output of approximately USD 4.5 billion (Budd, 1999; 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 USD 249.94, which is approximately 43% of annual household revenue based on agricultural (Lutumba et al., 2007), 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 (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 (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, 2008) or lab tests (USD 0.59) (Matemba, 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. 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 and 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 Bayer Schering Pharma) are made available freely to the WHO by the manufactures.

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.

5. 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.

Acknowledgments

This research was supported by the Bill and Melinda Gates Foundation – through a Grant awarded to the Swiss Tropical and Public Health Institute (grant number OPP1037660). The opinions and assertions expressed herein are those of the authors and do not necessarily reflect the official position or policy of Tulane University or the Swiss Tropical and Public Health (Swiss TPH) Institute. The authors would like to express our gratitude to Dr. Peter Steinmann, who provided a thorough review of the manuscript and suggested edits to improve the final text.

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