The burden of Human African Trypanosomiasis

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List of abbreviations

DALY: Disability Adjusted Life Year
DRC : Democratic Republic of Congo
HAT: Human African Trypanosomiasis
NGO: Non-Governmental Organisation
T.b.: Trypanosoma brucei
WHO: World Health Organisation
YLL: Years of Life Lost

Abstract

Human African Trypanosomiasis (HAT), a once largely forgotten disease, is back on the agenda. A public-private partnership between World Health Organisation (WHO), pharmaceutical companies and international donors succeeded in curbing the recent epidemic, but active transmission is still ongoing in several countries. The burden of the disease in affected individuals is high. Untreated the disease is always fatal and estimates of the Disability Adjusted Life Year's (DALY) lost per premature death range from 25 – 33 years. Even for successfully treated patients, the burden on households and livelihoods is high – between 1.5 and 10 months' income, even when diagnostics and HAT drugs are provided for free. Costs ranging from $10 - $17 per DALY averted for case-finding and treatment of chronic sleeping sickness places the control of HAT firmly in the category of highly cost-effective health interventions.

.Introduction

Human African Trypanosomiasis (HAT), also known as 'sleeping sickness' is one of the neglected diseases of this world. It is endemic in 36 countries of sub-Saharan Africa where it affects mainly the rural poor. The disease is caused by protozoa of the species *Trypanosoma brucei (T.b.)* and is transmitted by tsetse flies. Infection with such parasites eventually leads to death in the absence of appropriate treatment, but the disease presents differently by region. In East Africa, HAT is a zoonotic disease involving domestic animals and wildlife, caused by *T. b. rhodesiense,* and cattle are often the main reservoir. In West and Central Africa it is caused by *T. b. gambiense* and transmitted in a man-fly-man cycle. HAT caused by *T.b.gambiense* accounts for over 90% of all reported cases and has a much more protracted course than the *rhodesiense* (or East African) type. The disease evolves in two stages, i) an early stage when infection is limited to blood and lymph circulation and that is treated with pentamidine or suramin with over 90% cure rates, and ii) the late meningo-encephalitic stage when the parasites have invaded the central nervous system. An arsenicum-derivative, melarsoprol, was until recently the recommended drug for this late stage, but, because of its toxicity and as it was gradually loosing its efficacy, eflornithine is now promoted in this indication (Priotto et al, 2008). Because of the lack of specific symptoms in the early stage, patients usually consult a health professional when the disease is already well advanced and involves the central nervous system. At that point, the patient may have irreversible brain damage, requires the more expensive and toxic drugs and has posed a risk to other members of the community due to his infectiousness to tsetse flies. Therefore, population screening for HAT is the main control strategy for the *gambiense* form of HAT.

Magnitude of the problem

During the 1940s, 1950s and 1960s large-scale control programmes based on active case detection had succeeded in reducing the incidence of the *gambiense* form to some 4000 - 6000 reported cases a year during the 1960s (World Health Organization - WHO, 2000). There were still regular outbreaks of the acute, *rhodesiense,* form, with as many as 8000 cases being reported during a single year in the epidemic in Uganda which started in the late 1970s, but their severity was to some extent mitigated by vector control activities. However, during the 1980s the number of reported HAT cases increased gradually and towards the end of the 1990's disturbing evidence of a large scale resurgence of the *gambiense* form of the disease began to emerge, as the number of reported cases rose to 45,000 annually, a more than ten-fold increase since the sixties. Although this latter number might seem relatively low, when viewed against the other health problems faced by Africa's people, the clustering of this disease in localised foci where its burden is very heavy, and its potential for epidemic outbreaks meant that this resurgence of sleeping sickness needed to be treated with great seriousness. In addition the reported cases were mainly found by passive surveillance rather than through active surveillance and were thought to represent only the tip of a large iceberg. By the late 1990s there was a widespread general awareness that this largely forgotten disease had made a frightening comeback and that a hidden epidemic of sleeping sickness had been ravaging African countries.

Fortunately, this awareness was also translated into a major investment in the control of HAT in recent years. Bilateral donors stepped up their aid (Lutumba *et al.* 2005) and a partnership between the World Health Organization (WHO), private pharmaceutical companies, Non-governmental organizations (NGOs), bilateral donors and the health services of the countries affected lead to an important increase of HAT control activities and a curbing of the case load. The recent trend in the Democratic Republic of Congo (DRC) is shown in Figure 1. Nonetheless intensive transmission of the disease is still taking place in several areas of Central Africa. The most recent figures published by WHO (2006) for *gambiense* HAT were 17036 reported cases in 2004, which were extrapolated to an estimated worldwide annual caseload of 50 000 to 70 000. Sixty-one percent of the reported cases (10 369/17 036) were from a single country: DRC. Sudan and Angola each reported more than 1500 cases, while 50 to 1500 cases per year were reported in the Central African Republic, Chad, Côte d'Ivoire, Guinea and Uganda. Burkina Faso, Cameroon, Equatorial Guinea, Gabon and Nigeria each reported less than 50 cases (see figure 2).

Estimating the DALYs

Published global estimates of the annual burden of this disease have ranged between 1.5 and 2.0 million disability-adjusted life years (DALYs) per annum (WHO, 2004), based on the number of reported cases and using the same weightings for the burden associated with both the chronic and acute forms. A number of recent studies have provided the basic data needed for a more accurate global estimate. For the *gambiense* form, estimates of the DALY burden in affected individuals have been made by interviewing hospital patients diagnosed with the disease. In untreated individuals in Southern Sudan, the number of years of life lost (YLL) due to premature mortality from HAT were estimated at 33 per death (D McFarland, personal communication, based on work in Trowbridge *et al*., 2001), in Angola the figure estimated was 30 years per death (Schmid *et al.*, 2004) and in the Democratic Republic of Congo (DRC) a figure of 27 years per death was obtained (Lutumba, 2005). The long term sequelae, which can include neurological impairment, make the morbidity component significant as well, even for treated patients. For *rhodesiense*, an initial estimate (Politi *et al.*, 1995) based on data from Uganda, estimated the number of DALYs incurred per premature death to be 25, a more recent estimate (Odiit, 2003) puts them at 31. Additionally, the acute nature of *T.b. rhodesiense* results in a high burden per affected case, making the morbidity component of the *T.b. rhodesiense* DALY high. These estimates show the number of DALYs caused by both forms of the disease to be substantial, and well above those incurred by other tropical diseases such as dengue and filariasis which receive a great deal of international attention. This reflects, firstly, the fact that HAT is nearly always fatal in untreated individuals and secondly that the majority of the people affected are economically active adults. For example data on *rhodesiense* from Uganda showed 25% of cases occurring in those aged 20 to 29 years and 60% of those affected being in the 10 to 39 year age group (Fèvre

et al. 2008), for *gambiense* in DRC (Lutumba *et al*, 2007a) very similar percentages were found (21% and 58% ,respectively). These DALY estimates provide us with an overall view of the impact of the disease on affected individuals, but it should be noted that few DALY estimates have been made for HAT and that those reported are deterministic estimates, referring to the average impact per patient. Furthermore, the potential long term impacts of HAT on treated and cured patients have not been investigated for either form of the disease, so the DALY estimates do not include sequelae.

Having established what the losses in infected individuals are likely to be, extrapolating these to a national or continental scale is more problematical. So far, only one published study (Odiit *et al*., 2005) has addressed this directly. Using an epidemiological model, applied to data on the number of patients presenting in first and second stage of the *rhodesiense* form of disease in south-eastern Uganda, the study concluded that for every reported death from the disease, a further twelve remained unreported; this work has been validated in other parts of Uganda (Fèvre *et al.,* 2005), demonstrating that in a localised epidemic with 500 reported cases, approximately 300 *additional* cases died undiagnosed in the community. For *gambiense*, where the course of the disease is much more extended and more variable, and where a large proportion of the reported cases is usually found by exhaustive population screening, such approach would not be applicable. Work by Robays *et al*. (2004) gives insight in the proportion of HAT patients who are likely to missed out in active screening exercises for *gambiense* HAT. This study estimated that between 40% and 50% of patients in the community are missed by the campaign, because some individuals do not present themselves for the initial screening and because of the poor sensitivity of some of the tests used to confirm the presence of the parasite.

Developing an effective methodology for estimating the degree of under-reporting for *gambiense* disease remains a challenge. WHO estimated the total population at risk to be 60 million in 1998 (WHO, 1998). Further work is being undertaken, remapping the foci of the disease and refining this calculation.. At the start of the 1997-2005 epidemic, when most cases were passively detected, WHO estimated that only about one in ten HAT patients had been found and correctly diagnosed – however, after more than 5 years of active case-finding, it is hoped that a far higher proportion of patients have been found and treated.

Thus, while work on recalculating the global burden of HAT in terms of DALYs is ongoing, it looks as though, despite the falling number of reported cases, the figure is likely to range between 0.5 and 1.5 million DALYs, reflecting new research showing a higher burden per affected individual and depending on the results of evidence-based estimates of the proportion of unreported cases.

Recently, Lutumba *et al.* (2007a) have pointed to the risks when using DALYs for priority setting in HAT. At a global level, the absolute figures do not reflect the major impact the disease can have on local communities and regions, because the disease has such a clustered occurrence. Secondly, it is vital that declining trends in case numbers or DALYs should not lead to a reduction in resource allocation for HAT control because there are many documented examples of resurgence after abrupt cessation of active screening campaigns (Moore *et al.* 1999, Moore and Richer 2001, Lutumba *et al.* 2005, Van Nieuwenhove *et al.* 2001) and indeed the increase in cases leading to the current epidemic closely mirrored the decline in active surveillance

The economic burden on households and communities

The key to the high burden this disease places on affected households and communities lies not just in the difficulties individuals face in obtaining a correct diagnosis and thus the treatment required to prevent a fatal outcome, but also in its focal nature. Within these foci the prevalence can be high, often around 1% in the absence of active screening. If intense transmission goes unnoticed in a focus, the prevalence rates can rise relatively rapidly, sometimes over half the population of certain villages have been found affected. Thus the burden of this disease falls very heavily on a few locations, as argued in Lutumba *et al.* (2007a). As well as often being the active adults in a household, HAT patients also require very high levels of care, placing a further burden on the household. There have been few attempts to quantify the full costs borne by households with HAT patients which include their care at home and during hospital treatment, seeking a diagnosis, lost income, medical fees, transport, etc. In the Republic of Central Africa, the cost to households containing HAT patients who were correctly diagnosed and treated came to an amount equivalent to just under 1.5 months' household income from agriculture (Gouteux *et*

al., 1987). A recent study in DRC (Lutumba *et al.*, 2007a), where the direct costs of screening and treatment are fully subsidized by the HAT program, undertook a detailed calculation of household costs for diagnosed and treated patients; these came to 5 month's household income on average, but rose to over 10 months' income for patients with complications. Just seeking a diagnosis can be both time-consuming and costly: a study in a *rhodesiense* area of Uganda showed that over 70% of patients had to make 3 or more visits to a health unit before being correctly diagnosed and just over half had to sell agricultural produce to pay for health care costs (Odiit *et al.*, 2004). Lastly, HAT is overwhelmingly a disease of isolated rural populations and within these populations it is the poorer families who have the most difficulty in obtaining a correct diagnosis for their affected family members and on whom the burden of care and the expenditures needed to deal with the disease weigh most heavily.

The cost-effectiveness of controlling HAT

A number of approaches can be used alone or in various combinations to control HAT – finding and treating affected individuals, thus reducing the human reservoir of the disease, dealing with the animal reservoir and controlling the vector.

For *gambiense* disease, active case-finding and treatment is essential to reduce transmission and to find and treat affected individuals. The costs of this approach have been estimated in a number of studies (WHO, 1998; Shaw and Cattand, 2001; Trowbridge *et al.*, 2001; Lutumba *et al.*, 2005 – which provides templates showing how the costs could be calculated for various screening strategies). The costs of screening populations range around $1 - $1.50 per person. The costs of treatment are usually cited as around $100 for first stage patients and $300 for second stage patients treated with melarsoprol, increasing to over $600 if eflornithine is used (WHO, 1998). More recent estimates by Robays *et al.* (2008) in Angola put these figures at a cost of $ 604 for melarsoprol and $ 844 for eflornithine treatment. The cost is very sensitive to assumptions made about the cost of hospitalisation (WHO, 1998; Shaw and Cattand, 2001). Several attempts to calculate the cost of a patient-day in sleeping sickness treatment centres have been made and these show the costs to be highly variable – estimated at around $2 in Uganda (Odiit, 2003), while a more detailed analysis showed them to be $10 in DRC and $66 in a well-equipped treatment centre in Angola (Schmid *et al.*, 2004). Overall, looking at the breakdown of costs for case-finding and treatment (Shaw and Cattand, 2001, WHO, 1998), it is clear that once the prevalence exceeds 1%, hospitalisation costs become the main component of overall costs. Prolonged hospitalisation also places a very heavy burden on households. The newly developed 10-day melarsoprol schedule thus represents a very welcome improvement, making it possible to substantially reduce the cost of treatment, for example from $12 to $7 per DALY averted in DRC (Schmid, 2004).

The cost-effectiveness of case-finding and treatment approaches has been calculated in several studies (Politi *et al.*, 1995; WHO, 1998; Shaw and Cattand, 2001; Trowbridge *et al.*, 2001; Schmid *et al.*, 2004; Lutumba *et al*., 2007b). In southern Sudan, the cost per DALY averted was estimated at $10 for periodic screening and $17 for emergency intervention after a 9-year interval (Trowbridge, 2001). In DRC, a similar figure of $17 per DALY averted was calculated for active case-finding and treatment using mobile teams (Lutumba *et al.*, 2007a). A range of situations was modelled (Shaw and Cattand, 2001), showing that for most situations the cost fell below the $25 threshold of good value for money. This thus places HAT control firmly in the category of highly cost-effective interventions, comparing favourably with immunisation programmes and usually cheaper, for example, than malaria control using treated bed-nets (Goodwin *et al.,* 2000). However, the benefit of active screening for *gambiense* goes beyond simply finding and treating existing patients, to reducing the size of the human reservoir, thus preventing new infections. Accurately quantifying this component would require epidemiological modelling. There is ample historical evidence to show that active screening maintains a low prevalence, so that these costs per DALY averted would be even lower if the effect in lowering the incidence of the disease were taken into account.

A limited number of studies have looked at the economic aspects of vector control in HAT. Vector control is usually undertaken alongside the above measures to find and treat affected people, a summary of costs can be found in Shaw, (2004). The costs of vector control to reduce the transmission of HAT have been further discussed by Gouteux and Sinda, (1990), Lancien (1991)

and Laveissière *et al.* (1994). Simarro *et al*., (1991) compared different combinations of both active screening and vector control. Shaw (1989) found active case finding to be more cost-effective than vector control.

For *rhodesiense* disease, recent research (Welburn *et al.*, 2001) has demonstrated that cattle are the main reservoir of the disease to a far greater extent than was previously thought. This has opened up the possibility of treating cattle in order to control the disease in humans and this approach is being adopted in Uganda. From the economic point of view this involves a very interesting scenario. Since the trypanocides used to deal with the pathogens affecting people will also attack those which affect animals, the health of the livestock population will be improved, leading to monetary benefits which together with the costs saved by preventing the disease in people, are likely to outweigh the costs of the control strategy (Shaw, 2004). Thus a net financial benefit is realised, without even considering DALYs and through healthier livestock, people's livelihoods as well as their own health is improved. Controlling sleeping sickness, a disease of poor and marginalised populations, thus offers a highly cost-effective opportunity for poverty alleviation.

What lessons can be drawn for other diseases ?

The global burden of the disease is not so important in absolute terms, however, as HAT is a very focal disease, it has serious consequences at the local level, disrupting entire communities. When evaluating the cost effectiveness of interventions it is important to realise that most control efforts have an effect on transmission and thus the benefits of preventing epidemics or controlling them at an early stage are considerable.

Summary points

- By the year 2000 Human African Trypanosomiasis (HAT), a largely forgotten disease, had made a frightening comeback.
- The burden of the disease in affected individuals is high. Untreated it is always fatal and estimates of the DALYs lost per premature death range from 25 – 33 years. The morbidity component is also high.
- Due to the inherent difficulties of diagnosing sleeping sickness, under-reporting has always been problematic. At the start of the present epidemic, it was thought that for every reported case, ten remained undiagnosed and untreated. Recent research in endemic *rhodesiense* areas and in areas where active surveillance for the chronic *gambiense* form of the disease occurs indicates that even in active population screening campaigns 40% to 50% of patients are not found.
- In 1999 the annual global burden was estimated at 2 million DALYs, based on the number of reported cases. Now it looks as though, despite the falling number of reported cases, the figure is likely to range between 0.5 and 1.5 million DALYs, reflecting new research showing a higher burden per affected individual and depending on the results of evidence-based estimates of the proportion of unreported cases.
- HAT affects above all economically active adults, and patients require a lot of care from the other adults in the family. Seeking a diagnosis and obtaining treatment is costly and time-consuming. Thus the burden on households and livelihoods is high – between 1.5 and 10 months' income, even when diagnostics and HAT drugs are provided for free and patients have been successfully treated with no long term after-effects from the treatment or the disease.
- Costs ranging from $10 - $17 per DALY averted for case-finding and treatment of chronic sleeping sickness places the control of HAT firmly in the category of highly cost-effective health interventions, well below the $25 threshold of 'very good value for money'. This cost estimate would be even lower if the effect in reducing the human reservoir of the disease, and thus preventing future epidemics, were taken into account.

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Definitions, Acronyms and Synonyms of Keywords and Phrases (see guidelines: an essential component of each contribution)

Name of the author: Jo Robays

Title: Human African Trypanosomiasis (HAT):

Text: Human African Trypanosomiasis (HAT), also known as 'sleeping sickness', is a parasitic disease caused by *Trypanosoma brucei gambiense* and *Trypanosoma brucei Rhodesiense.* is the parasite is transmitted by the tsetse fly. The name of the disease stems from the rather typical sleep disturbances, with a disappearance of the circadian rhythm of sleep and wakefulness. Mental confusion and a wide range of psychiatric disorders including personality disorders, behavioural changes and mood alterations are often the symptoms that alert the patient and the people surrounding him. If it remains untreated the disease ends with coma and ultimately death.
Synonym: sleeping sickness

Name of the author: Jo Robays

Title: *Trypanosoma brucei*
Text : *Trypanosoma brucei* is a parasite belonging to the genus Trypanosoma and transmitted by a tsetse fly. The species *Trypanosoma brucei* is traditionally divided into three subspecies, *Trypanosoma brucei brucei*, *Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense*. The parasites are morphologically indistinguishable. *T. b. brucei* is not pathogenic for humans. *T. b. rhodesiense* causes East African sleeping sickness and *T. b. gambiense* causes West African sleeping sickness.

Name of the author: Jo Robays

Title: East African sleeping sickness.
Text: Form of Human African Trypanosomiasis caused by *Trypanosoma brucei rhodesiense.* It presents as an acute syndrome and is maintained by an animal reservoir. It is generally transmitted by tsetse flies (glossinna) species of the savanna (*morsitans*) and can also be transmitted by *G. fuscipes fuscipes*.

Name of the author: Jo Robays

Title: West African sleeping sickness.
Text: Form of Human African Trypanosomiasis caused by *Trypanosoma brucei gambiense.* It has a slow course with few symptoms in the initial phase. It is usually transmitted by tsetse fly (glossinna) species of the riverine (*palpalis*) group in a man-fly-man cycle; while animals can be infected with *T. b. gambiense,* the role of an animal reservoir still needs to be clarified.

Name of the author: Jo Robays

Title: Tsetse fly.
Text: Genus of biting flies feeding exclusively on blood. Different species are involved in the transmission, not only of East and West African sleeping sickness, but also of animal trypanosomiasis, causing substantial economic damage to the affected regions.
Synonymus: glossinna.

Name of the author: Jo Robays

Title: Disease reservoir.
Text: Pool of infected humans or animals that are a source of infection and therefore drive the transmission of HAT. Screening and treatment programs aiming at eliminating the HAT reservoir has always been the cornerstone of the control of West African sleeping sickness. Actions targeting the animal reservoir are common in East African sleeping sickness but the role of an animal reservoir in West African sleeping sickness is unclear.

Name of the author: Jo Robays

Title: hematolymphatic stage of Human African Trypanosomiasis
Synonyms: first stage, early stage.
Initial stage of the disease, where it is assumed that there is no central nervuous system involvement. Symptoms are not specific and include fever, severe headache, joint pains and muscle aches. It is treated with either Pentamidine or Suramine. The duration of the first stage varies from a few months to several years but there are no reliable estimations of its average duration.

Name of the author: Jo Robays

Title: meningo-encephalitic stage of Human African Trypanosomiasis
Synonyms: second stage, advanced stage.
Stage of the disease where neurological and psychiatric symptoms appear. At that stage more expensive and toxic drugs are needed, either melarsoprol or eflornithine.

Name of the author: Jo Robays

Title: active case finding
Synonyms: population screening
Text: activity that was the cornerstone of the control of West African HAT since colonial times and where mobile teams go from village to village in an endemic area with the objective of screening the whole population.

Name of the author: Jo Robays

Title Vector control.
Text: activity where transmission is reduced by killing the vector. Mechanical traps or targets with or without insecticide and/or odour baits have beenare the most commonly used method, but other options are the use of live baits (insecticide-treated cattle), aerial spraying and the realease of sterile male tsetse flies where tsetse populations have been suppressed using another technique.

Fig 1. Number of new cases reported by the national control program in Democratic Republic of Congo (1926-2004)

< please insert figure 1 here>

Legend: NC = New Case

This graph shows how the number of new cases of Human African Trypanosomiasis (HAT) gradually declined after a peak in 1930 to reach a historical low in 1960. Then, despite ongoing control activities, the number of cases slowly increased to reach a new peak in 1999, from that moment it was brought down again by an intensified control program.

Fig. 2. Annual number of Human African Trypanosomiasis (HAT) cases reported between 2000 and 2005. Source: Adapted from World Health Organization website: http://www.who.int/trypanosomiasis_african/disease/en/index.html

<please insert map>

Legend

This map shows how Democratic Republic of Congo, Sudan and Angola each reported more than 1500 cases, while 50 to 1500 cases per year were reported in the Central African Republic, Chad, Côte d'Ivoire, Guinea and Uganda. Burkina Faso, Cameroon, Equatorial Guinea, Gabon and Nigeria each reported less than 50 cases

Table 1: Key facts for Human African Trypanosomiasis (HAT).

HAT is transmitted by tsetse flies
There are two forms of the disease. In East Africa HAT presents as an acute syndrome caused by *T. b. rhodesiense*, and is maintained by an animal reservoir. West African HAT is caused by *T. b. gambiense*, has a much more protracted course than East African HAT and is transmitted in a man-fly-man cycle. The role of an animal reservoir still needs to be clarified.
There are two stages of the disease, an early stage (hemolymphatic stage), with few or aspecific symptoms in the beginning, and a late (meningo-encephalitic) stage.
Main symptoms of HAT are neuro-psychiatric, including behavioural problems, personality disorders, sleep disturbances and coma. It leads nearly invariable to death if untreated.
Treatment of patients in the meningo-encephalitic stage requires more expensive and toxic drugs. Melarsoprol, still the most commonly used drug for second stage, kills between 5 and 10 % of the patients. The only alternative, eflornithine, is expensive and difficult to administer.
Ninety percent of HAT cases in the world are caused by *T.b. gambiense*. *T. b. gambiense* often occurs in epidemics and active case finding conducted by mobile teams have been the cornerstone of the control of HAT since colonial times.
If treated at a late stage sequelae, mainly persistence of personality disorders and decreased mental capacities, are very frequent and pose a huge burden on the community long after the epidemics are brought under control.