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# Controlling sleeping sickness – a review

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## SUMMARY

Following a period characterized by severe epidemics of sleeping sickness, restoration of effective control and surveillance systems has raised the question of eliminating the disease from sub-Saharan Africa. Given sufficient political and financial support, elimination is now considered a reasonable aim in countries reporting zero or less than 100 cases per year. This success may lead health authorities across the affected region to downgrade the disease from ‘neglected’ to simply being ignored. In view of the significant levels of under-reporting of sleeping sickness mortality in rural communities, this could be a short-sighted policy. Loss of capacity to deal with new epidemics, which can arise as a consequence of loss of commitment or civil upheaval, would have serious consequences. The present period should be seen as a clear opportunity for public-private partnerships to develop simpler and more cost-effective tools and strategies for sustainable sleeping sickness control and surveillance, including diagnostics, treatment and vector control.

Key words: Sleeping sickness, neglected diseases, surveillance, tsetse control.

## IMPACT OF SLEEPING SICKNESS

### *A colonial disease or the colonial disease?*

The starting point for sleeping sickness control is inextricably linked to the incursion of the European powers into sub-Saharan Africa in the 19th century. Colonists hoping to profit from Africa’s abundance of raw materials and cheap or even ‘free’ (i.e. slave) labour were disturbed to discover towards the end of that century that the workforce was succumbing in unprecedented numbers to a mysterious illness. The disease was also perceived to be spreading across the continent from the French, Portuguese and Belgian territorial interests in West and Central Africa towards the British and German colonies in East Africa. A flurry of scientific activity quickly identified trypanosomes as the causative organisms and that they were being transmitted exclusively by tsetse flies (for a detailed account of this brilliant, yet often acrimonious, period in parasitological research see the Reports of the Sleeping Sickness Commission of the Royal Society, for example, Bruce *et al.* 1903).

There is no doubt that ‘the colonial disease’ (Lyons, 1992) was responsible, in the absence of host immunity and effective drugs, for hundreds of thousands of deaths in the colonial period. We are now aware that, even with the advantage of more effective

diagnostics, data concerning sleeping sickness deaths are subject to gross errors due to under-reporting (Odiit *et al.* 2005). With hindsight it is reasonable to infer that millions died from sleeping sickness during the colonial period; to get some idea of the seriousness of the situation facing the colonial authorities, this pandemic could be compared to the current HIV/AIDS situation in Africa (Maudlin, 2006).

To further complicate control initiatives, it soon became apparent that sleeping sickness was not a single entity. The human disease in West and Central Africa, referred to as Gambian sleeping sickness and caused by *Trypanosoma brucei gambiense*, is chronic in form. Because of the chronic nature of this disease and the inaccessibility of the endemic regions it has been difficult to determine how long a patient may have been infected with *T. brucei gambiense*; recent studies have estimated that, on average, it is usually fatal within three years in the absence of treatment (Checchi *et al.* 2008a). Rhodesian sleeping sickness, the human disease in East and southern Africa caused by *Trypanosoma brucei rhodesiense* is usually fatal within 6–8 months of infection in the absence of treatment (Odiit *et al.* 1997; Fèvre *et al.* 2004). Rhodesian sleeping sickness, if left untreated, is always fatal in humans but there have always been suggestions that self-resolving and asymptomatic chronic infections of Gambian sleeping sickness may occur but it is accepted that even if they do exist they will be few in number (Checchi *et al.* 2008b) or misdiagnosed due to transient infections with other trypanosome subspecies (Deborggraeve *et al.* 2008). Critically, diagnosis and treatment of the two forms

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of sleeping sickness require differing approaches (Chappuis *et al.* 2005; Barrett *et al.* 2007).

### *The burden of sleeping sickness*

As a result of intensive efforts to control the disease by colonial regimes using a variety of methods, there was a steady decline in the number of reported cases of sleeping sickness across Africa from the 1930s onwards. However, the post-independence period of the 1960s saw interest in, and funding for, control programmes within the endemic countries falter, resulting in a steep rise in incidence for the following thirty years. As surveillance and health care programmes in the affected regions were slowly restored following this period of neglect there has been, from 1997 onwards, a decline in reporting of new cases (Simarro *et al.* 2008). WHO (World Health Organization) has listed 36 countries endemic for sleeping sickness, of which 24 are affected by *T. b. gambiense*; seven countries (Angola, Democratic Republic of the Congo, Sudan, Chad, Central African Republic, Congo and Uganda) represent 98% of all reported Gambian sleeping sickness cases. Thirteen countries are endemic for Rhodesian sleeping sickness with Uganda and Tanzania accounting for most new cases.

1.35 million DALYs are lost due to sleeping sickness; mortality related to sleeping sickness is ranked ninth out of 25 among the human infectious and parasitic diseases in Africa (Fèvre *et al.* 2008a). However, in considering these data, it must be borne in mind that under-reporting is a major problem in estimating the burden of sleeping sickness. This is illustrated by the study of an outbreak of Rhodesian sleeping sickness in Uganda, which alarmingly found that 92% of sleeping sickness deaths are never reported (Odiit *et al.* 2005). This, despite the fact that drugs to treat sleeping sickness are provided free of charge by WHO thanks to a public-private partnership with Sanofi-Aventis. Treatment costs are high because of the supplementary drugs involved and the need for long hospitalization. It costs around US\$150 per patient (including drugs and hospitalization) to treat a Rhodesian sleeping sickness case in Uganda (Fèvre *et al.* 2008b) – this may be compared with the US\$18 available per capita for healthcare in Uganda (World Bank, 2006). The costs for treating Gambian sleeping sickness are similarly relatively high; for example a study of an outbreak in Democratic Republic of Congo (DRC) found sleeping sickness-related costs were equivalent to 5 months' income for affected households (Lutumba *et al.* 2007). We may conclude that the burden sleeping sickness imposes on rural settings is much greater than might be expected from its relative incidence.

### *From primacy to neglect*

From being 'the Colonial disease' (Lyons, 1992) at the beginning of the 20th century, sleeping sickness

is now relegated to membership of a group defined as the 'neglected tropical diseases' (NTDs), which includes leprosy, schistosomiasis, onchocerciasis, soil-transmitted helminths, lymphatic filariasis, dracunculiasis, dengue, cholera, trachoma, leishmaniasis, Chagas disease and Buruli ulcer. NTDs affect several hundred million people but because they attract little attention from donors, policymakers or public health officials they are designated 'neglected' (Molyneux *et al.* 2005). It has been suggested that this neglect results largely from over-reliance on DALY estimates in policy planning. For most sub-Saharan African countries, accurate measurements of morbidity and mortality from neglected tropical diseases are difficult to obtain and disease burden is inevitably underestimated (King and Bertino, 2008). This insight is pertinent when considering resources for sleeping sickness which, as we have seen, is subject to gross under-reporting (Fèvre *et al.* 2008b) so that its true burden may not be reflected in current estimates (WHO Weekly Epidemiological Record at <http://www.who.int/wer/2006/wer8108/en/index.html>).

## CONTROLLING SLEEPING SICKNESS

### *Reservoirs of disease*

Existence of a reservoir of a disease is confirmed when an infection within the target population cannot be sustained after all transmission between target and non-target populations has been eliminated (Haydon *et al.* 2002). The persistence of infection in a reservoir can be determined by longitudinal studies and, in the case of Rhodesian sleeping sickness, such studies were carried out exhaustively. In the Tinde experiment in Tanzania (Ashcroft, 1959), *T. b. rhodesiense* isolated from humans were serially transmitted by tsetse through sheep for over 20 years and remained human-infective. That wild animals could be the reservoir of Rhodesian sleeping sickness was established by injecting blood from an infected bushbuck into a human volunteer (Heisch *et al.* 1958). Human volunteers were later used to demonstrate that domestic animals, in this case cattle, could also act as reservoirs of Rhodesian sleeping sickness (Onyango and de Raadt, 1966). The relative epidemiological significance of wild/domestic animal reservoirs for persistence of Rhodesian sleeping sickness was not resolved until recently, when a molecular marker (SRA gene) was used to distinguish non-human infective *T. b. brucei* from human infective *T. b. rhodesiense* in livestock (Welburn *et al.* 2001a). Studies using this marker have demonstrated the overwhelming importance of the domestic animal reservoir for transmission of Rhodesian sleeping sickness in present day Uganda, with up to 40% of cattle carrying human infective trypanosomes in some endemic areas (Fèvre *et al.* 2001).

There have been no longitudinal studies reported for *T. b. gambiense* but, given the long-term nature of

this form of disease, such experiments were probably simply considered impractical. There is evidence from studies in West Africa using PCR diagnostics that *T. b. gambiense* is present in both domestic and wild animals (Njiokou *et al.* 2006; Simo *et al.* 2006). However, in the absence of experiments that show *T. b. gambiense* is persistent in animals and animal-to-human transmission, an animal reservoir for Gambian sleeping sickness cannot and perhaps need not be factored into the epidemiology of this form of the disease (Welburn *et al.* 2001*b*). This difference in primary reservoir of disease has always, consciously or unconsciously, dictated differences in approach to controlling the two forms of sleeping sickness.

#### *Controlling Rhodesian sleeping sickness*

In controlling Rhodesian sleeping sickness, the importance of the animal reservoir was recognised by Bruce from the start of his studies in Uganda (Bruce *et al.* 1903). Armed with this knowledge it was but a short step for colonial regimes to advocate the destruction of wildlife and habitat that supported wildlife to control outbreaks of disease in East Africa. While this approach may have seemed logical, the ecological consequences of these methods were not thought through. The ecology of much of this region has changed considerably since colonial times and wildlife populations are much reduced in comparison with cattle forming the major reservoir of Rhodesian sleeping sickness in present-day Uganda. This change in the perception of the epidemiology of the disease has had considerable impact on control strategies. Modelling control options (whether to target the animal reservoir, humans or vector) has shown that, given the significance of the animal reservoir, vector control is by far the most efficient method for bringing outbreaks of Rhodesian sleeping sickness under control (Welburn *et al.* 2001*b*).

If we assume that vector control is the desired control option, this inevitably leads to a highly contentious issue – how best to control the fly? The technical choices are simply laid out: (1) if insecticides are the chosen route, synthetic pyrethroids are now accepted as the insecticide of choice (Allsopp and Hursey, 2004) (2) if a non-insecticide approach is chosen then the alternatives are (a) baits (traps, targets etc. with or without attractants and live baits,) or (b) the sterile insect technique (SIT). There the simplicity of tsetse control ends and more complex economic and socio-economic factors must be weighed. If the situation has already reached epidemic proportions then choices are stark and all options are open to use; in the most recent epidemic of Rhodesian sleeping sickness in Uganda in the 1980s–1990s, the whole gamut of vector control methods were deployed including aerial and ground spraying of insecticides, trapping involving local communities and insecticide treated cattle (Lancien,

1991; Okoth *et al.* 1991; Okoth, 1999). Alongside these tsetse measures, the human reservoir was dealt with by treating those infected and attempts were made to reduce the reservoir in cattle by chemotherapy. Taken together, these methods brought the epidemic under control though the relative efficacy of these disparate approaches is not open to analysis given the security situation in the country at that time (Welburn *et al.* 2006). In such a serious situation, where thousands of people are infected and millions are at risk, it is understandable that every measure available is thrown at the problem. In a sense, the epidemic situation is the easier to deal with, as economics must take a back seat in such circumstances. This is in stark contrast to the endemic situation when, with low levels of mortality, health economists must weigh sleeping sickness control costs against the many other demands on their budgets and particularly the pressure to devote available resources to the ‘big three’ (HIV, TB and malaria), the temptation being to ignore NTDs (Molyneux, 2008). We have seen in the 20th century that the results of this neglect can be disastrous, sowing the seeds for further epidemics sooner or later. One solution would be to remove the vector altogether which could eliminate Rhodesian sleeping sickness. The Pan African Tsetse and Trypanosomiasis Eradication Campaign (PATTEC) ([http://www.who.int/trypanosomiasis\\_african/partners/pattec/en/index.html](http://www.who.int/trypanosomiasis_african/partners/pattec/en/index.html)) aims to eliminate tsetse and trypanosomiasis from Africa altogether. Isolated tsetse populations have been eliminated on Unguja Island, Zanzibar using SIT (Vreysen *et al.* 2000) and the Okavango Delta in Botswana by aerial spraying (Kgori *et al.* 2006). These approaches were not aimed at sleeping sickness but rather to remove tsetse as a threat to livestock with the economic advantages that could accrue. However, if the target tsetse population is not isolated then re-invasion makes elimination unlikely which in turn raises awkward economic and social questions (Hargrove, 2003; Enserink, 2007).

#### *Controlling Gambian sleeping sickness*

While removing the vector that transmits Rhodesian sleeping sickness is seen as a practical proposition on the back of programmes to control animal reservoir, the ancient foci of Gambian sleeping sickness are largely concentrated in the humid zones of west and central Africa, not suitable for the rearing of cattle and not targeted by trypanosomiasis control programmes. Modelling different control strategies showed that early case detection and treatment is most effective against Gambian infections when the involvement of an animal reservoir in the epidemiology of this form of the disease remains unresolved (Welburn *et al.* 2001*b*). The fact that in practice active case finding has proven effective over many decades in controlling this form of the disease

indicates that humans are the primary reservoir of *T. b. gambiense* (Jannin and Cattand, 2004).

There are logistical problems with active case finding in remote rural areas where health systems are weak and attendance rates at screening are often low. This approach to control relies on early diagnosis and appropriate chemotherapy, which both pose problems due to the poor sensitivity and specificity of available parasitological and serological tools but also due to the dangerous and cumbersome drugs available for treatment.

Diagnosis is reliant firstly on serological screening of the population at risk, usually by means of a Card Agglutination Test for Trypanosomiasis (CATT). Before treatment can commence clinicians would normally require parasitological confirmation of the CATT-positive test as recommended by WHO (1998); this usually involves simple microscopy or, where available, more sophisticated techniques such as the mini-anion exchange centrifugation method (Lutumba *et al.* 2006). Treatment of serologically positive individuals without parasitological confirmation remains controversial yet failure to respond to a CATT-positive test may have serious epidemiological consequences (Simarro *et al.* 1999). Staging sleeping sickness is mandatory to determine the choice of drug therapy and at present staging requires lumbar puncture to examine cerebrospinal fluid for parasites or, if parasites are not detected, CSF white blood cell count (WHO, 1998).

Chemotherapy for first (haemo-lymphatic) stage of Gambian sleeping sickness is straightforward involving a single drug, pentamidine. Treatment of the second stage, when parasites invade the central nervous system, is a much more fraught process and still largely relies on the use of melarsoprol, which is followed by a severe post-treatment reactive encephalopathy in 10% of cases, of which half die (Kennedy, 2006). Eflornithine (DFMO), a novel alternative to melarsoprol treatment (only for Gambian sleeping sickness), is safer to use (Burri and Brun, 2003; Chappuis *et al.* 2005) but has the major disadvantage that administration is labour intensive, requiring intravenous infusion every six hours for 14 days (56 infusions in total), a real problem for rural clinics (Priotto *et al.* 2008).

#### ENDEMICITY AND CONTROL

In countries reporting zero or less than 100 cases of sleeping sickness per year, elimination<sup>1</sup> is now

<sup>1</sup> Elimination is the reduction to zero of the incidence of a disease in a defined geographical area as a result of deliberate efforts. Eradication is the permanent reduction to zero of the worldwide incidence of infection as a result of deliberate efforts. Elimination demands continued efforts to prevent re-establishment while intervention is no longer needed if eradication is achieved (Molyneux *et al.* 2004).

thought to be feasible given sufficient political and financial support (Simarro *et al.* 2008). While acknowledging the success that active surveillance measures have had from 1997 to 2006 in reducing the number of new cases of Gambian sleeping sickness in some settings, it is important to recognise that this may lead health authorities to downgrade the disease in their list of priorities. Such complacency has in the past led to a loss of capacity to deal with the disease when new epidemics arise. There must be continuing concerns about the effects which civil upheaval can have on apparently stable endemic foci (Kaba *et al.* 2006; Berrang Ford, 2007; Courtin *et al.* 2008). The important issue, as we enter a period of endemicity for sleeping sickness is: how can the 'punishment of success' (Simarro *et al.* loc.cit.) be best avoided?

In endemic areas, sleeping sickness cases occupy more patient admission time than all other infectious diseases excepting malaria yet their treatment has been shown to be highly cost-effective. Far from being subject to neglect, increasing coverage of therapy and reducing under-reporting of both forms of sleeping sickness should instead be a priority for health authorities (Fèvre *et al.* 2008a). Lutumba *et al.* (2007) suggest that because sleeping sickness has such a serious economic impact on households while controlling the disease is highly cost-effective, health officials should take into account the impact of sleeping sickness on families in rural Africa, rather than deferring to global statistics for disease burden (published in WHO Weekly Epidemiological Record at <http://www.who.int/>).

#### Diagnosics and chemotherapy

In the case of Gambian sleeping sickness the priority is to develop new diagnostic and chemotherapeutic tools to ease the fiscal burden of surveillance on the affected countries and hence promote and facilitate its sustainability by integrating sleeping sickness control into the normal activities of the available health systems in transmission areas. Progress is being made in detecting trypanosomes in blood and cerebro-spinal fluid based on a variety of techniques including oligochromatography (Deborggraeve *et al.* 2006) and isothermal tests (Njiru *et al.* 2008) – the first steps towards a simplified molecular test. There are also several promising developments in disease biomarkers (Papadopoulos *et al.* 2004; Agranoff *et al.* 2005). Blood or CSF markers for staging are in the early stages of development (Lejon *et al.* 2002; Courtioux *et al.* 2005) as are non-invasive diagnostic tools (Lejon *et al.* 2006).

A major concern for the active case finding approach to controlling Gambian sleeping sickness is the increasing number of treatment failures with melarsoprol, reportedly as high as 30% in some foci (Burri and Keiser, 2001; Stanghellini and Josenando, 2001; Robays *et al.* 2008). Unfortunately there are



no new drugs forthcoming for the treatment of late-stage sleeping sickness (Croft, 2008) and focus has been on trying to improve treatment regimes and combination therapies using existing drugs. Combinations of eflornithine, melarsoprol with nifurtimox (used for treatment of Chagas' disease) have been trialled in Uganda (Priotto *et al.* 2006) and the Congo (Priotto *et al.* 2007) with encouraging results.

#### Vector control

If elimination of tsetse is unlikely to succeed on ecological grounds or is considered too costly for the endemic situation then alternative approaches for controlling Rhodesian sleeping sickness must be considered. We now have innovative tools to kill tsetse flies, which rely less on top-down interventions but rather on the efforts of the people at risk and avoiding impositions on constrained local health budgets. Long-lasting formulations of synthetic pyrethroids that may be poured on or sprayed on cattle (Thompson *et al.* 1991), while effective at killing tsetse proved too expensive for poor farmers in Africa. However, it has recently been shown that it is not necessary to treat the whole animal but only the parts of cattle on which tsetse prefer to feed i.e. legs and belly (Torr *et al.* 2007). This restricted application technology (RAP) has reduced the cost of treatment to around US 2 cents/animal/treatment which has been shown to be affordable and well within the reach of poor farmers. Following this breakthrough in the cost of treating livestock, a public-private partnership has been formed – the Stamp Out Sleeping Sickness campaign (<http://www.sleepingsickness.org/>) (Kabasa, 2007) – to promote the use of RAP (for vector control and to protect livestock from continued re-infection) combined with trypanocidal drugs to improve herd health and eliminate the animal reservoir of Rhodesian sleeping sickness. This campaign is aimed primarily at halting the northward spread of Rhodesian sleeping sickness to prevent it coalescing with the focus of Gambian sleeping sickness in the north west of Uganda (Picozzi *et al.* 2005). This approach benefits from farmers' natural desire to keep their herds healthy by reducing the burden of trypanosomiasis and also tick-borne diseases and the consequent control of the reservoir of human disease may be viewed as a very welcome public health bonus from a veterinary intervention. That farmers are willing to pay for this treatment promotes sustainability and avoids the public goods issues (Milinski *et al.* 2002) associated with community based trapping programmes (Brightwell *et al.* 2001).

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