African trypanosomiasis (sleeping sickness) occurs in 36 sub-Saharan countries, within the area of distribution of the tsetse fly. According to recent estimates, the disability adjusted life years (DALYs) lost due to sleeping sickness are 2.0 million (WHO Report 2000).\textsuperscript{1} Recent estimates indicate that over 60 million people living in some 250 foci are at risk of contracting the disease, and there are about 300,000 new cases each year (WHO, 1998).\textsuperscript{2} However, less than 4 million people are under surveillance and only about 40,000 are diagnosed and treated, due to difficulty of diagnosis and remoteness of some affected areas. These figures are relatively small compared to other tropical diseases, but African trypanosomiasis, without intervention, has the propensity to develop into epidemics, making it a major public health problem. Furthermore, the case fatality rate in untreated patients is 100%. This fact, combined with the focal nature of the disease, means that the disability adjusted life years (DALY’s) averted per infection cured or prevented are very high. As a result, control of this disease in endemic areas is highly cost-effective, falling well below the accepted threshold value for money of US$ 25 per DALY averted.\textsuperscript{3}

The disease occurs in two forms: a chronic one caused by \textit{Trypanosoma brucei gambiense}, which occurs in west and central Africa; and an acute form, caused by \textit{T. b. rhodesiense}, which occurs in eastern and southern Africa. The chronic infection lasts for years, whilst the acute disease may last for only weeks before death occurs, if treatment is not administered. The epidemiology of sleeping sickness is complex and transmission cycles are subject to interactions between humans, tsetse flies and trypanosomes, and significantly, in \textit{T. b. rhodesiense} sleeping sickness, domestic and wild animals. The role of an animal reservoir in the epidemiology of \textit{T. b. gambiense} has not been determined. In the 1960s, the prevalence of sleeping sickness had been successfully reduced in all endemic countries to less than 100 cases per 100,000 per year, through historic campaigns by the former colonial powers. Soon after independence however, national governments were either lacking in resources or diverted resources to other pressing health problems. Breakdown of specialized mobile teams and health facilities in several countries, as a consequence of war and civil strife, or changes in health policy, resulted in dramatic resurgence of African trypanosomiasis. Today, epidemics occur in the Democratic Republic of Congo (DRC), Angola, and Sudan. Other affected countries include Uganda, Central African Republic, Congo Republic, and Tanzania. The increasing trend of human African trypanosomiasis (HAT) incidence is shown in the figure below:

\textbf{INCIDENCE OF AFRICAN TRYPANOSOMIASIS (1977 – 1999)}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{incidence.png}
\caption{Incidence of African trypanosomiasis from 1977 to 1999.}
\end{figure}

\begin{itemize}
\item \textsuperscript{3} Shaw APM et al. \textit{Report of the Scientific Working Group meeting on African trypanosomiasis}, June 2001, Annex 4 III.
\end{itemize}
The social and economic impact of sleeping sickness is often underestimated. Epidemics have serious social and economic consequences and the disease has been a major cause of depopulation of large tracts of Africa. The fear it causes has led to abandonment of fertile lands, and is an impediment to development. The disease mainly strikes the active adult population.

Current control strategy

Regular active surveillance, involving case detection and treatment, and where applicable, tsetse fly control, is the backbone of the strategy for control of sleeping sickness. Systematic screening of communities in identified foci is the best approach as case-by-case screening is not practically possible in highly endemic regions. Systematic screening may be in the form of mobile clinics or fixed screening centres where teams travel daily to the foci. The nature of gambiense disease is such that patients don’t seek treatment early enough because the symptoms at that stage are not evident or serious enough to warrant seeking medical attention, considering the remoteness of some affected areas. Also, diagnosis of the disease is difficult and most health workers may not be able to detect it. Systematic screening allows early-stage disease to be detected and treated before the disease progresses, and removes the potential human reservoir. Therefore, the systematic screening of communities in identified foci is essential for the surveillance programme to be effective.

Also for surveillance to be effective, it is important to train the teams responsible for systematic screening. About 80% of endemic countries have national control programmes which are responsible for identifying the teams and through which appropriate training (in diagnosis, treatment) can be provided or requested.

The national control programmes are encouraged to form networks so that they can share ideas and experiences, and to closely collaborate with NGOs and other bodies involved in control activities. The WHO Communicable Disease Surveillance and Response (CDS/CSR) unit is actively helping endemic countries to establish national control programmes. It is also responsible for coordination of the Human African Trypanosomiasis Treatment and Drug Resistance Network that has as its objectives: to assess the effectiveness of current treatment regimens, collect and disseminate information on refractoriness to treatment, ensure availability and affordability of existing drugs, provide guidelines for treatment, and promote research on drugs and treatment and causes of treatment failures.

Another element of control is to strengthen the treatment capability of control programmes by looking at drug availability, increasing research capacities, monitoring drug resistance, and geographical information system (GIS) mapping of the foci. With the tools available today, continual control, rather than eradication, is possible.

Major problems and challenges for disease control

Significant resurgence of the disease has occurred, notably in Angola, DRC, Uganda and Sudan, in recent years, and new foci of the disease have emerged. The persistence and re-emergence of sleeping sickness is attributable to a number of factors, which constitute challenges for control.

Means for regular surveillance are often inadequate while, at the individual and family levels, there may be inadequate knowledge of disease symptoms, transmission dynamics and treatment. Population movements due to seasonal migration and refugees, may increase human-fly contact and hinder regular medical surveillance of the population at risk. In rhodesiense sleeping sickness, cattle movements also increase the risk of infection. Agro-ecological changes may alter tsetse habitat and increase human-fly contact.
The chemotherapy of African trypanosomiasis relies on a few drugs which have adverse side-effects and are unsatisfactory: pentamidine for early-stage *T. b. gambiense* sleeping sickness, suramin for early-stage *T. b. rhodesiense* sleeping sickness, and melarsoprol for late-stage disease of both forms of sleeping sickness. Increasing numbers of patients, 20-25% in certain foci, do not respond to melarsoprol treatment, probably due to resistance, but this needs to be proven. Eflornithine is the only alternative registered drug for the treatment of *T. b. gambiense* sleeping sickness patients who do not respond to melarsoprol. However, apart from other drawbacks, it costs US 300-500 per patient. Nifurtimox, although not registered for African trypanosomiasis, has been used experimentally and on compassionate grounds for *T. b. gambiense* sleeping sickness patients who did not respond to melarsoprol, with varying results. New drugs that are safe, effective and affordable are needed.

Ministries of health, research organizations and services often lack or do not have adequate economic resources for sleeping sickness control programmes due to competing health priorities. Recruitment of medium-level personnel is inhibited by lack of incentives and career prospects. Ministries may lack funds for the purchase of diagnostic tests and drugs, except as part of externally-funded programmes.

Other factors that increase the risk of infection are agricultural developments such as coffee and cocoa plantations, and the tourism industry, both of which increase human-fly contact.

Central governments often accord sleeping sickness a low priority, until it assumes epidemic proportions. In addition, political upheavals, civil strife and wars lead to breakdown of health services, and hence of control programmes.

**Research needed to address these constraints**

*Long-term commitment*, rather than support as crisis management, by governments of endemic countries and the international community to national sleeping sickness control programmes is essential for sustained control, as African trypanosomiasis afflicts the poorest of African countries.

Factors that militate against the effective use of existing tools, such as continued worsening economies and structural adjustment programmes in the affected countries should be addressed.

There is an urgent need for better tools. More effective, affordable and more tolerable drugs are needed. With the exception of eflornithine that was registered for human African trypanosomiasis in 1990, no new drug has been developed in over 50 years due to lack of interest by industry. Tests are needed to diagnose late-stage disease and to determine cure after treatment.

There is a need for implementation strategies that are better adapted to the health systems and socioeconomic constraints in the endemic countries. Simple surveillance systems are needed, that can be integrated into available capacities to improve case detection, permit earlier diagnosis of cases, and establish the prevalence of resistance to melarsoprol. Research is needed on how to effectively apply the available tools with the existing capacities, including in the health services, strong control programmes for other diseases, NGOs.

There is need for more basic knowledge in relation to drug resistance, risk factors for the resurgence and persistence of African trypanosomiasis, and the significance of animal reservoirs of *T. b. gambiense*.

There is need for capacity building for research and control of human African trypanosomiasis in the endemic countries through strengthening laboratories and research centres, training scientists, and encouraging networking.
Recommendations of the Scientific Working Group

The Scientific Working Group (SWG) on African Trypanosomiasis met in June 2001. It brought together a multidisciplinary group of scientists, partners and collaborators from academia, public and private sectors, sleeping sickness control programmes, and both endemic and non-endemic countries. The objectives of the meeting were to chart out a global research agenda on African trypanosomiasis, closely linked to control needs and open to opportunities arising from basic science, to guide TDR and others interested in research on African trypanosomiasis, and to provide data for use in advocacy to convince policy makers and donor agencies to place control of the disease higher on their agendas.

The meeting provided an opportunity to: identify the knowledge that could be exploited for developing new tools for disease and vector management, and improving existing tools; determine the needs for research capability strengthening in disease endemic countries for basic sciences. TDR’s comparative advantage in enhancing the existing and developing new partnerships for maximal application of the available knowledge was highlighted. The SWG recommendations fell within the following emphases:

Advocacy for long-term commitment
- The SWG noted with concern that sleeping sickness is a re-emerging disease which is not given due attention by governments of endemic countries and the international donor community until it attains epidemic proportions. The SWG recommended strong advocacy to persuade disease-endemic country governments to accord priority attention to research and control of African trypanosomiasis amidst their other health priorities. The disease burden and cost-effectiveness of control strategies should be calculated to show that the social and economic consequences of epidemics outweigh the costs of maintaining surveillance.

New and better tools
- Noting the lack of appropriate field applicable diagnostic tools for disease detection, and that staging critically affects the control of sleeping sickness, the SWG recommended development and validation of simple non-invasive, single-format, field-applicable tests for diagnosis and disease-stage determination.
- Considering the small number of anti-trypanosomal drugs available, the SWG recommended integration of synthetic and natural product libraries in the drug development pathways.
- Acknowledging that the development of drugs for late-stage disease is hindered by the blood-brain barrier that prevents delivery of drugs to the central nervous system (CNS), the SWG recommended incorporation of the use of CNS-penetration models in HAT drug development strategies, and the development of strategies that facilitate the delivery of drugs across the blood-brain barrier.
- The SWG acknowledged the difficulties associated with the treatment and lengthy post-treatment follow-up of sleeping sickness patients, and recommended investigation and application of new information on immune parameters that can be used to: (i) determine the disease stage, (ii) prevent and/or ameliorate the encephalitis and encephalopathy associated with the disease and its treatment respectively, and (iii) develop and validate a non-invasive protocol for determining cure and shortening the duration of after-treatment follow-up.
- Taking into account the limited evidence suggesting combination therapy with late-stage drugs has an additive effect, and in view of the urgent need to have alternative treatments for melarsoprol refractory patients, the SWG recommended that combination chemotherapy using late-stage drugs be optimized.
**Improved implementation strategies**

- The SWG noted that far-reaching changes in the institutional environment, such as decentralization, integration of surveillance into primary health care, and cost recovery, have had a major impact on the organization and implementation of sleeping sickness control. There is a need to evaluate the impact of these changes on the effectiveness of control, and to develop optimal strategies for systematic monitoring of disease incidence and prevalence, especially in relation to control measures.
- There is a need to clarify issues that influence individual and community participation in control measures in order to develop approaches for enhancing and sustaining community participation in the control and surveillance of sleeping sickness.
- The SWG recommended studies to assess the epidemiological and clinical significance of ‘unconfirmed suspects’ (sero-positive but parasitologically negative individuals) and the epidemiological significance of animal reservoirs of *T. b. gambiense*.

**Basic research**

- Noting the possible co-existence of *T. b. rhodesiense* and *T. b. gambiense* sleeping sickness patients in foci where refugees have been settled, the difficulties in differentiating the two trypanosome species, and their different treatment schedules, the SWG recommended application of genomics to a comparison of *T. brucei* sub-species, strains and life cycle stages for their differentiation and disease management.
- Appreciating the important role played by vector control in reducing the transmission of vector borne diseases, the SWG recommended investigation of tsetse-trypanosome interactions to determine the molecular basis of refractoriness to trypanosome transmission, and mechanisms for driving desirable genes into the vector populations.

**Capacity building**

- The SWG was concerned that the limited number of suitable centres in Africa created a situation where research was increasingly compartmentalized, and recommended capacity strengthening of laboratories/centres within Africa in basic sciences including bioinformatics, genomics and applied genomics, drug discovery and development.
- Recognizing the inadequacy of infrastructure for research in different endemic countries, the SWG recommended networking and cross-country comparison of research progress to assist in capacity building and stimulate cross-border interest and advocacy.

**Ongoing research in African trypanosomiasis**

The trypanosome, due to its many unique biological characteristics, is one of the most studied parasites and offers many opportunities for basic research. Though it is difficult to get funds for the control of sleeping sickness, important sums of money are invested annually, particularly in the North, on basic research on African trypanosomes. There is probably more information on the biochemistry and molecular biology of trypanosomes than any other non-mammalian cell type and a great deal is known about the differences between trypanosomes and mammalian cells, and yet no drug has yet been designed rationally.

TDR’s drug discovery programme comprises integrated screening of molecules from the chemical libraries of pharmaceutical companies and academia against African trypanosomes, *T. cruzi*, *Leishmania*, and malaria parasites. The TDR drug development portfolio comprises the development of an oral formulation of eflornithine, which has many advantages, apart from ease of administration, over the injectable formulation. TDR operational research activities include evaluation of the card indirect agglutination test for trypanosomiasis (CIATT), and of treatment with
pentamidine of serologically positive individuals who are not proven parasitologically positive with *T. b. gambiense*.

The Bill & Melinda Gates Foundation recently awarded US$ 15 million to a consortium of scientists for the development of drugs for African trypanosomiasis and leishmaniasis.

**TDR’s comparative advantages**

TDR has links with the outside world of product development. Over its lifetime, TDR has generated multiple partnerships for product development and has gained considerable experience. It has successfully taken some products up to registration in collaboration with the private sector, e.g. mefloquine, efloornithine, AmBisome.

TDR provides an essential link between research institutions in the North and endemic countries, through access to a network of national field projects and control programmes, where spin-offs from basic research can be evaluated as tools for the control and prevention of sleeping sickness. A successful example is the card agglutination test for trypanosomiasis (CATT), that evolved from studies on the variant surface glycoproteins (VSGs) in trypanosomes. TDR could preserve this unique role by introducing seed money where likely spin-offs from basic research will be of public health importance.

For institutions in the South, TDR has been a conspicuous source of funding for research on African trypanosomiasis and institutional strengthening activities. Consequently, drastic reduction in funding in TDR for African trypanosomiasis, which started in 1994, has had adverse effects on trypanosomiasis research in the endemic countries, in terms of human resources and institutional capabilities.

During 1993/94, TDR initiated global parasite genome networks for *T. b. brucei*, *T. cruzi*, *Leishmania major*, *Schistosoma mansoni*, and *Brugia malayi*. The networks are now orientated towards post genomics, and bioinformatics networks are being expanded for data mining, annotation and in-depth analysis.

**Strategic emphases for African trypanosomiasis research in TDR**

**New and basic knowledge**

- Development of basic knowledge in applied genomics – identification of drug targets and diagnostics, including use of bioinformatics.
- Elucidation of the pathogenesis of the disease, and parasite/host interactions.
- Evaluation of the socioeconomic impact of HAT and the cost-benefits of control.
- Evaluation of the effect of health systems and policy changes on HAT control, re-emergence and epidemics of the disease.
- Determination of factors which influence individual and community participation in control.
- Tsetse genomics: investigation of tsetse-trypanosome interactions to determine the molecular basis of refractoriness to trypanosome transmission and mechanisms for driving desirable genes into vector populations.

**New and better tools**

- Development of new drugs that are safe, effective, affordable, and which can treat both *T. b. gambiense* and *T. b. rodesiense* at all disease stages, including integration of synthetic and natural product libraries in the search for lead compounds.
- Development of new interventions using existing drugs - new treatment regimens, formulations and drug combinations.
• Development of a diagnostic test for stage determination and assessment of cure.
• Development and validation of simple, non-invasive, single-format, field-applicable diagnostic tests.

**Improved interventions and implementation (disease control) strategies**
• Assessment of the epidemiological and clinical significance of unconfirmed suspects, and the epidemiological significance of animal reservoirs of *T. b. gambiense*.
• Evaluation of short treatment duration with pentamidine, suramin and melarsoprol.
• Investigation of the existence of melarsoprol resistance.
• Development of sustainable community-based strategies for tsetse control.

**Capacity building**
Based on an inventory of existing facilities and human resources available in disease endemic countries (DECs):
• Strengthening of research capabilities for biomedical and social research on HAT in DECs.
• Development of research networks and partners in DECs.
• Encouragement of transfer of appropriate technology to DECs.

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