

Aiming to eliminate tsetse from Africa

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The problem of tsetse-transmitted trypanosomiasis occurs only in sub-Saharan Africa, where it represents a major constraint to socio-economic development. The East African form of sleeping sickness, caused by *Trypanosoma brucei rhodensiense*, is an acute and fatal disease, whereas the West African form, caused by *Trypanosoma brucei gambiense*, is generally more chronic and debilitating. The African governments have developed a new initiative, known as the Pan African Tsetse and Trypanosomiasis Eradication Campaign, which seeks to employ an area-wide approach and appropriate fly suppression methods to eradicate tsetse from areas of tsetse infestation, at a time, to ultimately create tsetse-free zones.

WHO estimates that over half a million people are infected by trypanosomiasis, especially in war-torn zones such as Angola, Sudan and the Democratic Republic of Congo. The World Bank ranks trypanosomiasis (also known as sleeping sickness) third for its socio-economic impact (after malaria and schistosomiasis) out of all the parasitic diseases affecting Africa. The Food and Agriculture Organization of the United Nations (FAO) estimates that trypanosomiasis of livestock, nagana, is a major factor in rural poverty, severely limiting meat and dairy production, and preventing the use of draught oxen for ploughing. The Pan African Tsetse and Trypanosomiasis Eradication Campaign (PATTEC) initiative, set up by the African governments, is backed by a parallel programme of the WHO intended to detect and treat cases of human sleeping sickness.

PATTEC was derived from a decision made by the African Heads of State and Government at the 36th summit of the Organisation of African Unity (OAU)*, to 'act collectively and rise to the challenge of eradicating tsetse flies from the African

continent in the shortest time possible'. In response to this decision, the Secretary General of the OAU commissioned a task force of experts to develop the PATTEC plan of action, which was subsequently endorsed by the African Heads of State at the 37th OAU summit†, and referred to relevant offices for implementation. The Governments of Ethiopia, Mali and Burkina Faso, Botswana, Kenya, Uganda, and Tanzania have begun to implement the plan in selected areas of their countries. The Governments of Rwanda and Sudan have well developed plans to initiate similar action in their countries.

The magnitude of the problem

There is little doubt that elimination of the burden of tsetse and tsetse-borne trypanosomiasis would be of major benefit for the socio-economic development of sub-Saharan Africa. Sleeping sickness kills >50 000 people every year, with frequent reports of epidemics that decimate entire communities. Even tourists to certain parts of Africa can be affected, as illustrated by recent cases of trypanosomiasis in UK travellers returning from East Africa [1]. However, the impact of the animal disease – nagana – can be much greater, depriving much of Africa of milk, meat, and draught oxen for ploughing and transport. FAO has estimated that the cost to Africa of these problems is >US\$4.5 billion per year, including losses in agricultural production, and perennial expenditure on trypanocidal drugs and other local intervention schemes in attempts to cope with trypanosomiasis. The social and environmental costs are also high. Fear of the disease often limits community development, with families moving away from the more fertile, but tsetse-infested, areas to congregate in the few tsetse-free regions, leading to over-exploitation of marginal lands and environmental degradation, without significant economic return. Lack of

draught oxen leads to inefficient sub-subsistence agriculture over wide areas, contributing to limited productivity, poverty, marginalization, civil strife and land degradation. This does not need to be so. In Zanzibar, where tsetse (*Glossina austeni*) were eradicated in 1997 [2], local farmers gained confidence to acquire more productive breeds of cattle, such as Friesian, which previously could not be kept in the area because they are highly susceptible to nagana. In three years following tsetse eradication, Zanzibar has recorded substantial increases in milk and beef production, and expanded use of animal traction and manure for farming. By eradicating tsetse, the communities in Zanzibar have become less poor and more able to play a significant role in national socio-economic development. The hope behind the PATTEC initiative is that the example and experience of tsetse-free Zanzibar can be extended to the rest of Africa.

African unity with common purpose

PATTEC seeks to emulate the example of Latin American countries in organizing their successful regional initiatives against American trypanosomiasis – Chagas disease. These initiatives, particularly in Central America and the Southern Cone countries, were developed and implemented by the endemic countries themselves through a process of political decision, regional co-ordination, and scientific follow-up [3]. The approach of the PATTEC initiative is similar. It is a concerted effort mounted by Africans themselves to address a uniquely African problem of disease and agricultural development. However, this is not to say that external support would not be welcome. Whereas PATTEC will be financed largely from the national budgets of affected countries, external contributions in financial, material and technical assistance will be sought from all possible sources.

Of crucial strategic importance will be the need to emphasize the ownership and direct involvement of African governments in implementing the objectives of the PATTEC initiative. Trypanosomiasis

*Organisation of African Unity and African Heads of State: Government Decision no. 156 (XXXVI), passed at the 36th summit of the Organisation of African Unity, held 10–12 July 2000, in Lomé, Togo.

† Organisation of African Unity and African Heads of State: Government Decision no. 169 (XXXVII), passed at the 37th summit of the Organisation of African Unity, held 9–11 July 2001, in Lusaka, Zambia.

control has had a long history of external involvement, whether for technical or financial reasons. The efforts of the various colonial governments in Africa, up to the late 1960s, almost eliminated sleeping sickness and rendered large expanses of land tsetse-free, only to be followed by a steady resurgence of disease incidence and increased tsetse infestation during the post-independence years. The individual trypanosome treatment programmes and tsetse control interventions, which had been mounted by the colonial governments, were invariably successful – until they stopped. But wars, civil unrest, changed national priorities and poor institutional organization, which characterized the history of post-independence Africa, paid their toll on the successes achieved in earlier campaigns against the tsetse and trypanosomiasis problem. The decision by the African Heads of State and Government to embark on the PATTEC initiative not only underscores the seriousness and significance which African governments attach to the tsetse and trypanosomiasis problem, but it also defines their direct involvement in the implementation of the initiative.

The technology is available

The technical strategy for tsetse eradication is based on a wealth of proven techniques for eliminating tsetse, and is favoured by the tsetse's unusual behaviour and larviparous reproductive habits. Tsetse are slowly reproducing *K*-strategists, adapted for efficient exploitation of stable habitats, with a vulnerability to most insecticides. For example, with the correct formulations, exposure to even minute amounts of pyrethroids will kill them – at dose rates that would generally be ineffective against other insects such as mosquitoes. Furthermore, only a small increase in average mortality is required to drive tsetse populations to extinction. The required pyrethroids can be delivered in three ways: (1) sequential aerial spraying of ultra-low doses is used for open regions such as savannah areas; (2) tsetse-affected communities use odour-baited traps and pyrethroid-impregnated targets to suppress tsetse populations in densely vegetated areas, where aerial spraying would be less likely to reach the flies; and (3) pour-on formulations of insecticides, sprays and livestock dips are used for flies that feed primarily on cattle, especially the East African species [4]. Under certain

circumstances, selective spraying of known tsetse resting sites, such as the lower trunks of trees, could also be applied. This technique was used effectively against several tsetse species in East, West, and Southern Africa until ~20 years ago, but is now less frequently used because of environmental concerns.

The same methods, including traps and targets, can also be used to maintain temporary barriers around treated areas [5,6] until adjacent areas have also been treated. They can be highly effective in reducing tsetse populations and suppressing re-infestations, but are difficult to maintain because of possible damage by the weather and wild animals. Traps are also used to monitor progress of the control interventions and to confirm whether or not flies are still active in the controlled area. A crucial phase of each intervention will be to achieve final eradication of the local tsetse population, through the use of the sterile insect technique (SIT), a control method that has greatest efficiency at very low tsetse densities. This involves the release, into the intervention area, of factory-reared male tsetse, sterilized by radiation, which then compete with any remaining wild male tsetse to mate with female tsetse. Female tsetse usually mate once, and each female that mates with a sterile male becomes inseminated with sterile sperm and develops a non-viable zygote, thus causing a drastic reduction in the tsetse birth rate.

PATTEC plan of action

Although tsetse infest a vast area of sub-Saharan Africa (~10 million km²), the distribution of tsetse in this area is far from continuous; the flies generally inhabit the affected area in dynamic pockets, many of which are relatively discrete in space and time. The PATTEC plan of action seeks to apply area-wide principles to eliminate each pocket of tsetse infestation at a time; thus, creating a series of tsetse-free zones that can eventually be linked over a much larger area. The proposed interventions assume a minimum level of political and civil stability, and require the corresponding government commitment to allow the interventions to proceed.

Emphasis will be placed on the need to address the factors that were responsible for the lack of sustainability of previous intervention programmes, by developing

intervention strategies that lead not just to control but also to local elimination of the tsetse population. Once the tsetse population in a given area is eliminated, the question of sustainability of the control intervention will no longer arise, provided that the controlled area can be protected from re-invasion until when the neighbouring areas can also be treated. The techniques available for use in reducing the tsetse population, including odour-baited traps and insecticide-treated targets, pour-ons and ultra-low volume aerial spraying of insecticide, will be used singly or in combination, and supplemented with SIT to ensure total elimination of the target tsetse population. The isolation of intervention areas or their prevention from re-invasion from neighbouring untreated areas could be reinforced by the use of artificial barriers, in which any of the tsetse suppression techniques is applied singly or in combination.

The essential intervention strategy against tsetse makes use of all techniques that have proved successful in previous campaigns. The difference, as advocated by PATTEC, is the application of the area-wide principle that is planned, and the goal to continue the interventions in each identified area until confirmation of local elimination of the tsetse populations.

In parallel, a programme of case detection and treatment will be implemented under the co-ordination of the WHO. This involves strengthening and extending the rural medical services of endemic countries, to enhance their ability to carry out rapid diagnosis of human trypanosome infections, with prompt treatment using existing therapies. In support of this, public-private partnerships have been developed between WHO, private foundations and the pharmaceutical industries, so that the required drugs can be administered free of charge, and disease management and research on new therapeutic components can be reinforced.

One step at a time

PATTEC is currently based at OAU headquarters in Addis Ababa, Ethiopia, with regional co-ordination groups being set up for West, Central, East, and Southern Africa. The main role of PATTEC is to ensure political commitment to trypanosomiasis control and tsetse eradication programmes in each of the

endemic countries, to co-ordinate these efforts, provide technical guidance and enlist support wherever needed. The PATTEC initiative might seem ambitious, but it is based on the principle of one step at a time, dealing progressively with what is technically feasible within the constraints of available resources and political commitment, against a background of Africa's declared unwillingness to accept the consequences of continued tsetse infestation.

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Antimicrobial peptides versus parasitic infections?

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Reports of antimicrobial peptides generally have evaluations of their antibacterial and antifungal activities. By contrast, little is known of their activities against protozoan and metazoan parasites. *In vitro* antiparasitic assays suggest that antimicrobial peptides could represent a powerful tool for the development of novel drugs to fight the parasite in the vertebrate host, or to complement current therapeutic strategies.

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Multicellular organisms have developed an immediate immune response against infectious microorganisms [1,2]. During the past few years, studies on the components of this innate immune system have established the contribution of antimicrobial peptides (generally, small, cationic molecules of 2–8 kDa) to the defense response of the invertebrate host [3].

Peptides from the same families of antimicrobial peptides have been isolated from vertebrates, invertebrates and plants [4]. Similarities among natural antibiotics of distant evolutionary species have provided the basis for simple models to understand the innate immune system of more complex animals such as mammals. Many of these antimicrobial peptides present a strong activity *in vitro* against microorganisms that are resistant to conventional antibiotics, and they could provide design templates for anti-infectious agents in humans [3,5].

Development of antiparasitic drugs

Human parasite infections cause millions of deaths around the world every year. New antiparasitic drugs are needed that

can be used alone or to complement existing products, and to overcome problems such as chloroquine resistance of *Plasmodium*.

Antimicrobial activity of cationic peptides mainly is exerted against bacteria and fungi, but some antiviral and anticancer effects have been described [6]. In contrast to the huge amount of literature on antibacterial and antifungal activities, few reports describe activities against protozoan and metazoan parasites. Invertebrate antimicrobial compounds are generally ineffective against eukaryotic cells as a result of their mode of action, and due to the different compositions of the cell membranes between eukaryotic and prokaryotic cells [6].

Reports of antiparasitic activities of natural antimicrobial compounds are mainly related to *Plasmodium* and *Leishmania*, two of the most widely distributed parasites, worldwide (see <http://www.who.int>).

Antimalarials

Antimalarial activities have been described for two classes of cationic natural antibiotics: (1) the linear amphipatic peptides; and (2) the cysteine-rich open-ended peptides. Cecropin and magainin, two linear α -helical molecules isolated from the hemolymph of the giant silk moth *Hyalophora cecropia* and the skin of the African frog *Xenopus laevis*, respectively, significantly reduced oocyst development in various *Plasmodium* spp., when injected into different anopheline mosquito species [7]. A stronger effect against *Plasmodium* was observed when using synthetic hybrids of cecropin and melittin (a linear peptide isolated from bee venom) [8].

Another cecropin-like synthetic peptide, Shiva-3, blocked *Plasmodium berghei* ookinetes development *in vitro*, and was effective against the early sporogonic stages in the mosquito midgut [9]. Recent work demonstrated that a series of derivatives of dermaseptin, a peptide isolated from the skin of a frog, selectively lysed *Plasmodium*-infected erythrocytes [10].

The first cysteine-rich cationic peptides reported as active against *Plasmodium* were the defensins, a family of 4-kDa molecules widely distributed in plants and animals. Two insect defensins interfered with the development of *Plasmodium gallinaceum* oocysts, when injected into mosquitoes, and were highly toxic to isolated sporozoites *in vitro* [11]. Activities against *P. berghei* developmental stages were recently described for two novel cysteine-rich antimicrobial peptides: (1) gambicin (8 kDa) from *Anopheles gambiae*, which showed a slight *in vitro* effect against ookinetes [12]; and (2) scorpine (isolated from venom of the scorpion *Pandinus imperator*), which has an amino acid sequence similar to a cecropin–defensin hybrid, and inhibits gametes and ookinetes development more efficiently than Shiva-3 [13].

Antileishmanials

Leishmania represent one of the most used models for *in vitro* antiparasitic assays. Several linear amphipatic antibiotics, effective against different *Leishmania* stages, represent potential candidates to help design novel drugs for topical treatment of this disease [6]. Cecropins isolated from different insects showed a lytic effect on promastigotes [14],