health threat in sub-Saharan Africa, spreads among people bitten by the tsetse fly and is fatal unless treated. Because early-stage infection produces few symptoms, it is thought that only 10 percent of patients with the disease are accurately diagnosed. FIND and the World Health Organization will collaborate in seeking to identify, test and implement diagnostics that will increase the likelihood of early detection of HAT and the opportunity for treatment.

“The spread of human African trypanosomiasis has reached epidemic proportions in regions of Africa. There is clearly a great need for a simple, accurate and cost-effective way to diagnose this disease so that it can be better treated and controlled,” said Dr Giorgio Roscigno, CEO of FIND. “FIND is committed to identifying and implementing diagnostics for infectious diseases, and we look forward to securing partnerships and initiating field testing.”

“Existing diagnostics for sleeping sickness are difficult to implement in remote, impoverished settings,” said Dr Jean Jannin and Dr Pere Simarro, from the Neglected Tropical Diseases Control Department of the World Health Organization. “We look forward to working with FIND to advance new diagnostic tests that could revolutionize human African trypanosomiasis control.”

“Developing point-of-care tests to direct sleeping sickness treatment will greatly simplify patient care, allowing for early case detection, simpler and safer treatment, and higher rates of cure that will improve disease management and could lead to the elimination of the disease as a public health problem,” said Thomas Brewer, M.D., senior program officer, Infectious Diseases division, Global Health Program, at the Gates Foundation.

Currently, diagnosis of sleeping sickness is made by serologic examinations followed by microscopy, which is laborious, insensitive and costly. FIND’s and WHO’s efforts will be focused on developing tools that will be simple to use and effective in the remote field conditions that exist where it is most prevalent. In addition to developing appropriate diagnostic technologies, the objectives of the programme include establishing field research sites for clinical studies and evaluating prototype products.

2. Revised Fact Sheet on African trypanosomiasis (sleeping sickness)

Definition of the Disease
Human African Trypanosomiasis, also known as sleeping sickness, is a vector-borne parasitic disease. The parasites concerned are protozoa belonging to the *Trypanosoma* Genus. They are transmitted to humans by tsetse fly (*Glossina* Genus) bites which have acquired their infection from human beings or from animals harbouring the human pathogenic parasites.

Tsetse flies are found in sub-Saharan Africa. Only certain species transmit the disease. Different species have different habitats. They are mainly found in vegetation by rivers and lakes, in gallery-forests and in vast stretches of wooded savannah.

- Sleeping sickness occurs only in sub-Saharan Africa in regions where there are tsetse flies that can transmit the disease. For reasons that are so far unexplained, there are many regions where tsetse flies are found, but sleeping sickness is not.
- The rural populations living in regions where transmission occurs and which depend on agriculture, fishing, animal husbandry or hunting are the most exposed to the bite of the tsetse fly and therefore to the disease.
Sleeping sickness generally occurs in remote rural areas where health systems are weak or non-existent. The disease spreads in poor settings. Displacement of populations, war and poverty are important factors leading to increased transmission. The disease develops in areas whose size can range from a village to an entire region. Within a given area, the intensity of the disease can vary from one village to the next.

Human African Trypanosomiasis takes two forms, depending on the parasite involved:

- Trypanosoma brucei gambiense (T. b. g.) is found in west and central Africa. This form represents more than 90 percent of reported cases of sleeping sickness and causes a chronic infection. A person can be infected for months or even years without major signs or symptoms of the disease. When symptoms do emerge, the patient is often already in an advanced disease stage when the central nervous system is affected.
- Trypanosoma brucei rhodeiense (T. b. r.) is found in eastern and southern Africa. This form represents less than 10 percent of reported cases and causes an acute infection. First signs and symptoms are observed after a few months or weeks. The disease develops rapidly and invades the central nervous system.

Another form of trypanosomiasis occurs in 15 Central and South American countries. It is known as American trypanosomiasis or Chagas disease. The causal organism is a different species from those causing the African form of the disease.

Animal Trypanosomiasis

Other parasite species and sub-species of the Trypanosoma Genus are pathogenic to animals and cause animal trypanosomiasis in many wild and domestic animal species (in cattle the disease is called Nagana, a Zulu word meaning “to be depressed”). Animals can host the human pathogen parasites, especially T. b. rhodesiense; thus domestic and wild animals are an important parasite reservoir. Animals can also be infected with T. b. gambiense, however the precise epidemiological role of this reservoir is not yet well known. This disease kills animals.

The disease in domestic animals and particularly cattle is a major obstacle to the economic development of the rural areas affected.

Major Human Epidemics

There have been several epidemics in Africa over the last century: one between 1896 and 1906, mostly in Uganda and the Congo Basin, one in 1920 in a number of African countries and the most recent one beginning in 1970. The 1920 epidemic was controlled thanks to mobile teams who organized the screening of millions of people at risk. By the mid 1960s, the disease had almost disappeared. After that success, surveillance was relaxed, and the disease reappeared in several areas over the last thirty years. Recent WHO efforts and those of national control programmes and non-governmental organizations (NGOs) have stopped and begun to reverse the upward trend of new cases.
Geographical Distribution of the Disease

Sleeping sickness threatens millions of people in 36 countries of sub-Saharan Africa. However, only a small fraction of them are under surveillance with regular examination, have access to a health centre that can provide diagnostic facilities, or are protected by vector control interventions.

- In 1986, a panel of experts convened by WHO estimated that some 70 million people lived in areas where disease transmission could take place.
- In 1998, almost 40,000 cases were reported, but this number did not reflect the true situation. It was estimated that between 300,000 and 500,000 more cases remained undiagnosed and therefore untreated.
- During recent epidemic periods, in several villages in the Democratic Republic of Congo, Angola and Southern Sudan, prevalence has reached 50 percent. Sleeping sickness was considered the first or second greatest cause of mortality, even ahead of HIV/AIDS, in those communities.
- By 2005, surveillance had been reinforced and the number of new cases reported throughout the continent had substantially reduced; between 1998 and 2004 the figures for both forms of the disease together fell from 37,991 to 17,616. The estimated number of cases is currently between 50,000 and 70,000.

Progress in Disease Control

- In 2000, WHO established a public-private partnership with Aventis Pharma (now sanofi-aventis) which has enabled the creation of a WHO surveillance team, providing support to endemic countries in their control activities and the supply of drugs free of charge for the treatment of patients.
- In 2006, success in curbing the number of sleeping sickness cases has encouraged a number of private partners to sustain WHO’s initial effort towards the elimination of the disease as a public health problem.

Current Situation in Endemic Countries

The prevalence of the disease differs from one country to another as well as in different parts of a single country. In 2005, major outbreaks have been observed in Angola, the Democratic Republic of Congo and Sudan. In Central African Republic, Chad, Congo, Côte d’Ivoire, Guinea, Malawi, Uganda and United Republic of Tanzania sleeping sickness remains an important public health problem. Countries such as Burkina Faso, Cameroon, Equatorial Guinea, Gabon, Kenya, Mozambique, Nigeria, Rwanda, Zambia and Zimbabwe are reporting fewer than 50 new cases per year. In countries such as Benin, Botswana, Burundi, Ethiopia, Gambia, Ghana, Guinea Bissau, Liberia, Mali, Namibia, Niger, Senegal, Sierra Leone Swaziland and Togo transmission seems to have stopped and no new cases have been reported for several decades. Nonetheless, it is difficult to assess the current situation in a number of endemic countries because of a lack of surveillance and diagnostic expertise.
Tsetse and Trypanosomiasis Information

Infection and Symptoms

The disease is transmitted through the bite of an infected tsetse fly. At first the trypanosomes multiply in subcutaneous tissues, blood and lymph. In time, the parasites cross the blood-brain barrier to infect the central nervous system. The process can take years with T. b. gambiense.

- Mother-to-child infection: the trypanosome can cross the placenta and infect the fetus.
- Mechanical transmission is possible. However, it is difficult to assess the epidemiological impact of transmission through other blood-sucking insects.
- Accidental infections have occurred in laboratories due to pricks from contaminated needles.

The first stage of the disease, known as a haemolymphatic phase, entails bouts of fever, headaches, joint pains and itching. The second stage, known as the neurological phase, begins when the parasite crosses the blood-brain barrier and invades the central nervous system. In general this is when the signs and symptoms of the disease appear: confusion, sensory disturbances and poor coordination. Disturbance of the sleep cycle, which gives the disease its name, is an important feature of the second stage of the disease. Without treatment, sleeping sickness is fatal.

Disease Management

Disease management is performed in three steps:

- Screening for potential infection. This involves the use of serological tests and/or checking for clinical signs - generally swollen cervical glands.
- Diagnosis shows whether the parasite is present.
- Staging to determine the state of progression of the disease entails examination of cerebro-spinal fluid obtained by lumbar puncture and is used to determine the course of treatment.

Diagnosis must be made as early as possible and before the neurological stage in order to avoid complicated, difficult and risky treatment procedures.

The long, asymptomatic first stage of T.b. gambiense sleeping sickness is one of the factors that requires the use of exhaustive active screening of the population at risk in order to identify patients at an early stage and reduce transmission. Exhaustive screening of exposed populations requires a major investment in human and material resources. In Africa such resources are often scarce, particularly in remote areas where the disease is mostly found. As a result, many infected individuals may die before they can ever be diagnosed and treated.
Treatment

The type of treatment depends on the stage of the disease. The drugs used in the first stage of the disease are less toxic, easier to administer and more effective. The earlier the identification of the disease, the better the prospect of a cure. Treatment success in the second stage depends on a drug that can cross the blood-brain barrier to reach the parasite. Such drugs are quite toxic and complicated to administer. Four drugs are registered for the treatment of sleeping sickness and provided free of charge to endemic countries through a WHO private partnership with sanofi-aventis (pentamidine, melarsoprol and eflornithine) and Bayer AG (suramin).

First stage treatments

- **Pentamidine**: discovered in 1941, used for the treatment of the first stage of *T. b. gambiense* sleeping sickness. Despite a few undesirable effects, it is well tolerated by patients.
- **Suramin**: discovered in 1921, used for the treatment of the first stage of *T. b. rhodesiense*. It provokes certain undesirable effects, in the urinary tract and allergic reactions.

Second stage treatments

- **Melarsoprol**: discovered in 1949, it is used in both forms of infection. It derives from arsenic and has many undesired side effects. The most dramatic being a reactive encephalopathy (encephalopathic syndrome) which can be fatal (3 percent to 10 percent). An increase of resistance to the drug has been observed in several foci particularly in central Africa.
- **Eflornithine**: this molecule, less toxic than melarsoprol, was registered in 1990. It is only effective against *T. b. gambiense*. It is an alternative to melarsoprol treatment. The regimen is strict and difficult to apply.

The resurgence of sleeping sickness since the 1970s led WHO to reinforce its Human African Trypanosomiasis programme. The objective is to coordinate activities in endemic countries and mobilize a wide range of partners.

The WHO Programme provides support and technical assistance to national control programmes. A network has been established including donor countries, private foundations, NGOs, regional institutions, research centres and universities to participate in surveillance and control, and to undertake research projects for the development of new drugs and diagnostic tools.

The objectives of the WHO Programme are:

- Strengthen and coordinate control measures and ensure field activities are sustained;
- Strengthen existing surveillance systems;
- Support monitoring of treatment and drug resistance through the network;
- Develop information database and implement training activities.
• Promote inter-agency collaboration with the Food and Agriculture Organisation (FAO) and the International Atomic Energy Agency (IAEA). This agency is dealing with vector control through flies males made sterile by radiation. In addition there is a joint Programme Against African Trypanosomiasis (PAAT) including WHO (human health), FAO (animal health) and IAEA (vector control).

THE FAO/IAEA PROGRAMME

Food and Environmental Protection Section: Work on Quality Control of Trypanocidal Drugs

African trypanosomiasis is a severe disease that is fatal if left untreated. The conventional and most prominent method to combat trypanosomiasis is by chemotherapy. Every year some 35 million doses of trypanocides are administered to domestic ruminants. Several reports indicate the widespread phenomenon of counterfeit and poor quality drugs of isometamidium based trypanocides in sub-Saharan Africa. This has severe implications for both food safety and animal health, posing problems with residues of unspecified, unwanted chemicals and their metabolites in the food chain and the induction of trypanosome resistance, an already widespread phenomenon.

In 2003, the Animal Health Service of the FAO and the International Federation for Animal Health (IFAH) developed a joint concept note on quality assurance/quality control (QA/QC) of trypanocides. The main objective is to pursue internationally and scientifically agreed standards and protocols for QA/QC of trypanocides. The specific objectives include definition of the requirements of analytical quality assurance, establishment of good laboratory practices for chemical analysis, and transfer of the methodologies and technology to laboratories in Africa. Initially, it is proposed to support two regional reference laboratories, one in west Africa and one in the east. Future extensions of this project would hopefully expand the scope to include the development and transfer of methods for QC of other veterinary pharmaceuticals such as anthelmintics, antimicrobials and acaricides/insecticides and for residues of the compounds in animal-derived foods. Discussions are ongoing with the United Nations Industrial Development Organization (UNIDO) and IFAH to secure further funding for the project.

The Agrochemicals Unit of the FAO/IAEA laboratories at Seibersdorf, Austria, and the Department of Pharmaceutical Sciences, Strathclyde Institute for Biomedical Sciences, UK, were selected as partners for the technical aspects of the project. Laboratory work to support this project commenced in 2005. The first technical activity, the validation in Strathclyde and Seibersdorf of an HPLC method for quality control of isometamidium-based trypanocides, has been completed.

Further information on the project can be obtained from the FAO Officer (Raffaele.Mattioli@fao.org) and technical details can be obtained from the FAO/IAEA Agrochemicals Unit (A.Cannavan@iaea.org).
SECTION B - ABSTRACTS

1. GENERAL (INCLUDING LAND USE)


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Despite the many decades of use of most of the current trypanocides, we know little of their mode of action. This may in part be because most of these will act on multiple targets once inside the cell, and they derive their selective action on the parasite from selective accumulation by the pathogen. Loss of this capacity for drug uptake by the trypanosome would thus be a major cause for drug resistance. We here discuss the use of current drugs against human and veterinary African trypanosomiasis, the prevalence, causes and mechanisms of drug resistance and new developments in trypanosomiasis therapy such as the introduction of niturimox and DB289.


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Animal skin separates the inner world of the body from the largely hostile outside world and is actively involved in the defence against microbes. However, the skin is no perfect defence barrier and many microorganisms have managed to live on or within the skin as harmless passengers or as disease-causing pathogens. Microbes have evolved numerous strategies that allow them to gain access to the layers underneath the epidermis where they either multiply within the dermis or move to distant destinations within the body for replication. A number of viruses, bacteria and parasites use arthropod vectors, like ticks or mosquitoes, to deliver them into the dermis while taking their blood meal. Within the dermis, successful pathogens subvert the function of a variety of skin resident cells or cells of the innate immune system that rush to the site of infection. In this review several interactions with cells of the skin by medically relevant vector-borne pathogens are discussed to highlight the different ways in which these pathogens have come to survive within the skin and to usurp the defence mechanisms of the host for their own ends.

To understand the risk of protozoa transmission by blood is critical as: (i) the world has become globalized with extensive travel, and increased immigration; (ii) blood-borne protozoa are common in inter-tropical areas; (iii) protozoa develop biological means to escape hosts’ immune systems, together with complicated detection, surveillance, and biological testing; and (iv) life threatening-parasites are inadequately controlled by treatment or prevention. This question is relevant in France, with its non-continental territories, such as French Guiana, located in the Amazon Basin, which is endemic for various *Plasmodium* ssp. responsible for malaria, and for *Trypanosoma cruzi*, which is responsible for Chagas disease. In France, specific questioning of blood donors is haphazard despite the increase in population migration over the last three decades: specific questioning must be emphasized and “at-risk” donors should be identified and subsequently excluded from donation. Donor exclusion alone would only be partially efficient, there is also a need for relevant biological testing of blood donations and in particular for *T. cruzi* through the CE-marked test to organize a coherent prevention policy; precise studies would thus define which blood donations are subjected to this additional qualifying test when available.


We derive appropriate mathematical models to assess the effectiveness of culling as a tool to eradicate vector-borne diseases. The model, focused on the culling strategies determined by the stages during the development of the vector, becomes either a system of autonomous delay differential equations with impulses (in the case where the adult vector is subject to culling) or a system of nonautonomous delay differential equations where the time-varying coefficients are determined by the culling times and rates (in the case where only the immature vector is subject to culling). Sufficient conditions are derived to ensure eradication of the disease, and simulations are provided to compare the effectiveness of larvicides and insecticide sprays for the control of West Nile virus. We show that eradication of vector-borne diseases is possible by culling the vector at either the immature or the mature phase, even though the size of the vector is oscillating and above a certain level.


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The potential impacts of climate change on human health are significant, ranging from direct effects such as heat stress and flooding, to indirect influences including changes in disease transmission and malnutrition in response to increased competition for crop and water resources. Development agencies and policy makers tasked with implementing adaptive strategies recognize the need to plan for these impacts. However at present there is little guidance on how to prioritize their funding to best improve the resilience of vulnerable communities. Here we address this issue by arguing that closer collaboration between the climate modelling and health communities is required to provide the focused information necessary to best inform policy makers. The immediate requirement is to create multidisciplinary research teams bringing together skills in both climate and health modelling. This will enable considerable information exchange, and closer collaboration will highlight current uncertainties and hopefully routes to their reduction. We recognize that climate is only one aspect influencing the highly complex behaviour of health and disease issues. However we are optimistic that climate–health model simulations, including uncertainty bounds, will provide much needed estimates of the likely impacts of climate change on human health.


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Geomatics technology has tremendous potential to address public health issues particularly under the present circumstances of global climate change and climate or technology induced human migration, which result in an increase in the geographical extent and re-emergence of vector-borne diseases. The authors present an overview of the science of geomatics, describe the potential impacts of climate change on vector-borne diseases and review the applications of remote sensing for disease vector surveillance.


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Animal models of human African trypanosomiasis, also known as sleeping sickness, have been used for many years both to investigate disease pathogenesis and to test novel drug therapies. Model systems used have included mice, rats and non-human primates such as monkeys. Whilst such animal models have some definite but unavoidable limitations, it is argued that these are outweighed by their advantages. The latter include the ability to investigate disease pathogenesis mechanistically and the mechanisms of trypanosome traversal of the blood-brain barrier, as well as the identification of new potential drug targets and staging biomarkers, new drug therapies and combinations, and potential drug toxicity.

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Trypanosomiasis remains one of the most serious constraints to economic development in sub-Saharan Africa and, as a consequence, related research has been subject to strong social and political as well as scientific influences. The epidemics of sleeping sickness that occurred at the turn of the 20th Century focussed research efforts on what became known as “the colonial disease”. This focus is thought to have produced ‘vertical’ health services aimed at this one disease, while neglecting other important health issues. Given the scale of these epidemics, and the fact that the disease is fatal if left untreated, it is unsurprising that sleeping sickness dominated colonial medicine. Indeed, recent evidence indicates that, if anything, the colonial authorities greatly under-estimated the mortality attributable to sleeping sickness. Differences in approach to disease control between Francophone and Anglophone Africa, which in the past have been considered ideological, on examination prove to be logical, reflecting the underlying epidemiological divergence of East and West Africa. These epidemiological differences are ancient in origin, pre-dating the colonial period, and continue to the present day. Recent research has produced control solutions for the African trypanosomiases of humans and livestock that are effective, affordable and sustainable by small-holder farmers. Whether these simple solutions are allowed to fulfill their promise and become fully integrated into agricultural practice remains to be seen. After more than 100 years of effort, trypanosomiasis control remains a controversial topic, subject to the tides of fashion and politics.


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Experiments were conducted to adapt the cloth Nzi trap to a format suitable for fixed applications in biting fly sampling or control. Catches of tabanids [*Tabanus* L., *Chrysops* (Meigen), and *Hybomitra* Enderlein], and stable flies [*Stomoxys calcitrans* (L.)] in painted plywood traps were compared with those in standard phthalogen blue cloth traps, and in similarly painted cloth traps. The Manitoba horse fly trap and the *Tabanus nigrovittatus* Macquart “greenhead” box trap were used as additional standards during one tabanid season. Shiny features of traps reduced catches, e.g., paint on cloth instead of wood, or use of aluminium screening instead of netting. Nevertheless, appropriately painted plywood Nzi traps caught as many biting flies as did standard cloth Nzi traps, if paint finishes were matte, and with the use of phthalogen blue colorants. Nzi traps collected about the same tabanid fauna as the Manitoba and *T. nigrovittatus* traps, but with improved catches of *Chrysops* and *Tabanus*. Recommendations are provided on appropriate colour matching, and selection of readily available materials for trap construction.

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No abstract available.


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Previous studies have shown that about 90 percent of adult *Amblyomma variegatum Fabricius* (*Ixodidae*) picked up daily by grazing cattle are still attached to the interdigital areas in the evening, when the animals return from pasture. It was therefore postulated that a targeted treatment, designed to kill the ticks attached to the feet, would limit infestation of the predilection sites. Footbaths filled with various pyrethroid formulations were used over 3 years, at the beginning of the rainy season (from mid-May to the end of July), to assess the efficacy of such a control method. It proved efficient in preventing the ticks from attaching to the predilection sites. Although five to 12 *A. variegatum* adults attached to each treated animal daily, and although the tick burden of the predilection sites of control cattle increased each day by four to 10 ticks, the average infestation of the predilection sites of treated cattle that were initially highly infested (over 100 ticks/animal) continuously decreased to reach a level of about 10-30 ticks/animal after 6-8 weeks of treatment. In herds with a lower initial tick burden (40-70 ticks/animal) this level was obtained within 2-3 weeks and the mean infestation subsequently remained consistently low. Footbath treatment carried out every other day during the adult peak infestation period should therefore greatly limit losses due to ticks. This method was appreciated by traditional livestock farmers, essentially because it is not time-consuming and because it requires only c. 200 mL aqueous formulation per animal at each passage. The cost of the acaricide needed to treat one animal during the peak infestation period was assessed at c. Euro 0.20. This control method might also have an impact on some species of tsetse flies and mosquitoes, thereby contributing to trypanosomiasis and malaria control.


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At present there is a steady rise in African sleeping sickness (trypanosomiasis) transmitted by the tsetse fly, and which if left untreated, is fatal. Thanks to many years of neglect by research, our therapeutic repertoire is limited to medications with a high level of
Tsetse and Trypanosomiasis Information

toxicity. Both WHO and international aid organizations are pushing hard for the development of new, more efficient drugs that can be readily applied in the field.


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This paper aims to review human genetic studies that are generally poorly known by parasitologists and scientists working on other pathogenic agents. The key proposals of this paper are as follows: (i) human susceptibility to transmissible diseases may often have a complex, multigenic background; (ii) recent discoveries indicate that major genomic rearrangements may be involved, possibly more so than DNA sequence; (iii) it is crucial to have a general population genetics framework of the human species based on neutral/historical markers to analyse reliably genetic susceptibility to infectious diseases; and (iv) the population level is a key factor. Ethnic diversity, a highly adaptive genetically driven phenotypic diversity, is possibly a valuable source for exploring human genetic susceptibility to transmissible diseases, since different populations have been exposed to drastically different geographic/climatic environments and different pathogens and vectors for tens of thousands of years. Studies dealing with human genetic susceptibility to transmissible diseases have mostly been based on the hypothesis that this factor is driven by only one or a few genes, and considered the individual more than the population level. Two different approaches have been developed for identifying the genes involved: (i) candidate genes and (ii) blind association studies (linkage analysis), screening the genome with a large number of high-resolution markers. Some loci involved in susceptibility to leishmaniosis, malaria and schistosomiasis, for example, have already been identified. South American trypanosomiasis (Chagas disease) is reviewed in detail to show the methodological problems of this classical approach. Current knowledge on the general impact of transmissible diseases on human genetic diversity, mainly HLA polymorphism, and the hopes raised by recent major international programmes such as the Human Genome Project (HGP), Human Genome Diversity Project (HGDP), International Human Haplotype Map Project (Hap Map) and extended databases, networks and networks of networks will also be reviewed.

2. TSETSE BIOLOGY

(a) REARING OF TSETSE FLIES

(b) TAXONOMY, ANATOMY, PHYSIOLOGY, BIOCHEMISTRY

The procyclic form of *Trypanosoma brucei* exists in the midgut of the tsetse fly. The current model of its surface glycocalyx is an array of rod-like procyclin glycoproteins with glycosylphosphatidylinositol (GPI) anchors carrying sialylated poly-N-acetyllactosamine side chains interspersed with smaller sialylated poly-N-acetyllactosamine-containing free GPI glycolipids. Mutants for *TbGPI12*, deficient in the second step of GPI biosynthesis, were devoid of cell surface procyclins and poly-N-acetyllactosamine-containing free GPI glycolipids. This major disruption to their surface architecture severely impaired their ability to colonize tsetse fly midguts but, surprisingly, had no effect on their morphology and growth characteristics *in vitro*. Transmission electron microscopy showed that the mutants retained a cell surface glycocalyx. This structure, and the viability of the mutants *in vitro*, prompted us to look for non-GPI-anchored parasite molecules and/or the adsorption of serum components. Neither was apparent from cell surface biotinylation experiments but [*3H*] glucosamine biosynthetic labelling revealed a group of previously unidentified high apparent molecular weight glycoconjugates that might contribute to the surface coat. While characterizing GlcNAC-PI that accumulates in the *TbGPI12* mutant, we observed inositolphosphoceramides for the first time in this organism.


Iron is an essential element for metabolic processes intrinsic to life, and yet the properties that make iron a necessity also make it potentially deleterious. To avoid harm, iron homeostasis is achieved via proteins involved in transport and storage of iron, one of which is transferrin. We describe the temporal and spatial aspects of transferrin (*GmmTsf*) expression and its transcriptional regulation in tsetse where both the male and female are strictly haematophagous. Using Northern, Western and immunohistochemical analysis, we show that *GmmTsf* is abundant in the haemolymph and is expressed in the adult developmental stages of male and female insects. It is preferentially expressed in the female milk gland tubes and its expression appears to be cyclical and possibly regulated in synchrony with the oogenic and/or larvigenic cycle. Although no mRNA is detected, *GmmTsf* protein is present in the immature stages of development, apparently being transported into the intruterine larva from the mother via the milk gland ducts. Transferrin is also detected in the vitellogenic ovary and the adult male testes, further supporting its classification as a vitellogenic protein. Similar to reports in other insects, transferrin mRNA levels increase upon bacterial challenge in tsetse suggesting that transferrin may play an additional role in immunity. Although transferrin expression is induced following bacterial challenge, it is significantly reduced in tsetse carrying midgut trypanosome infections. Analysis of tsetse that have cured the parasite challenge shows normal levels of *GmmTsf*. This observation suggests that the parasite in competing for the availability of limited dietary iron may manipulate host gene expression.
Reductive evolution in mitochondria and obligate intracellular microbes has led to a significant reduction in their genome size and guanine plus cytosine content (GC). We show that genome shrinkage during reductive evolution in prokaryotes follows an exponential decay pattern and provide a method to predict the extent of this decay on an evolutionary timescale. We validated predictions by comparison with estimated extents of genome reduction known to have occurred in mitochondria and *Buchnera aphidicola*, through comparative genomics and by drawing on available fossil evidences. The model shows how the mitochondrial ancestor would have quickly shed most of its genome, shortly after its incorporation into the protoeukaryotic cell and prior to codivergence subsequent to the split of eukaryotic lineages. It also predicts that the primary rickettsial parasitic event would have occurred between 180 and 425 million years ago (MYA), an event of relatively recent evolutionary origin considering the fact that *Rickettsia* and mitochondria evolved from a common alphaproteobacterial ancestor. This suggests that the symbiotic events of *Rickettsia* and mitochondria originated at different time points. Moreover, our model results predict that the ancestor of *Wigglesworthia glossinidia brevipalpis*, dated around the time of origin of its symbiotic association with the tsetse fly (50-100 MYA), was likely to have been an endosymbiont itself, thus supporting an earlier proposition that *Wigglesworthia*, which is currently a maternally inherited primary endosymbiont, evolved from a secondary endosymbiont.

Symbiotic bacterium closely related to the secondary symbiont of tsetse flies, *Sodalis glossinidius*, has been described from the bloodsucking fly *Craterina melbae* (Diptera, Hippoboscoidea) originated independently of the tsetse flies symbiont *Sodalis glossinidius*. *FEMS Microbiology Letters*, 269 (1): 131-135.

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Symbiotic bacterium closely related to the secondary symbiont of tsetse flies, *Sodalis glossinidius*, has been described from the bloodsucking fly *Craterina melbae*. Phylogenetic analysis of two genes, 16S rRNA gene and component of type three secretion system, placed the bacterium closer to the *Sitophilus*-derived branch of *Sodalis* than to the tsetse symbionts. This indicates that the *Craterina*-derived lineage of *Sodalis* originated independent of the tsetse flies symbionts and documents the capability of *Sodalis* bacteria either to switch between different host groups or to establish the symbiosis by several independent events.

The regulation of iron is critical for maintaining homeostasis in the tsetse fly (Diptera: Glossinidae), in which both adult sexes are strict blood feeders. We have characterized the cDNAs for two putative iron-binding proteins (IBPs) involved in transport and storage; transferrin (GmmTsf1) and ferritin from Glossina morsitans morsitans. GmmTsf1 transcripts are detected in the female fat body and in adult reproductive tissues, and only in the adult developmental stage in a bloodmeal independent manner. In contrast, the ferritin heavy chain (GmmFer1HCH) and light chain (GmmFer2LCH) transcripts are expressed ubiquitously, suggesting a more general role for these proteins in iron transport and storage. Protein domain predictions for each IBP suggest both the conservation and loss of several motifs present in their vertebrate homologues. In concert with many other described insect transferrins (Tfs), putative secreted GmmTsf1 maintains 3 of the 5 residues necessary for iron-binding in the N-terminal lobe, but exhibits a loss of this iron-binding ability in the C-terminal lobe as well as a loss of large sequence blocks. Both putative GmmFer1HCH and GmmFer2LCH proteins have signal peptides, similar to other insect ferritins. GmmFer2LCH has lost the 5'UTR iron-responsive element (IRE) and, thus, translation is no longer regulated by cellular iron levels. On the other hand, GmmFer1HCH maintains both the conserved ferroxidase centre and the 5'UTR IRE; however, transcript variants suggest a more extensive regulatory mechanism for this subunit.

(c) DISTRIBUTION, ECOLOGY, BEHAVIOUR, POPULATION STUDIES


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Species identification of mosquitoes (Diptera: Culicidae) based on morphological characteristics remains often difficult in field-collected mosquito specimens in vector-borne disease surveillance programs. The use of DNA barcodes has been proposed recently as a tool for identification of the species in many diverse groups of animals. However, the efficacy of this tool for mosquitoes remains unexplored. Hence, a study was undertaken to construct DNA barcodes for several species of mosquitoes prevalent in India, which included major vector species. In total, 111 specimens of mosquitoes belonging to 15 genera, morphologically identified to be 63 species, were used. This number also included multiple specimens for 22 species. The DNA barcode approach based on the DNA sequences of mitochondrial cytochrome oxidase gene could identify 62 species among these, in confirmation with the conventional taxonomy. However, two closely related species, Ochlerotatus portonovoensis (Tiwari & Hiriyan) and Ochlerotatus wardi (Reinert) could not be identified as separate species based on DNA barcode approach, their lineages indicating negligible genetic divergence (Kimura two-parameter genetic distance = 0.0043).

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We report the development and characterization of three new microsatellite markers in the tsetse fly, *Glossina pallidipes* (Diptera: Glossinidae). Fifty-eight alleles were scored in 192 individuals representing six natural populations. Allelic diversity ranged from 9 to 28 alleles per locus (mean 19.3 +/- 5.5). Averaged across loci, observed heterozygosity was 0.581 +/- 0.209, and expected heterozygosity was 0.619 +/- 0.181. Cross-species amplifications of the *G. pallidipes* loci in other tsetse fly taxa are reported.


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Metabolic rate variation with temperature, body mass, gender and feeding status is documented for *Glossina morsitans centralis*. Metabolic rate [mean +/- SE; VCO2 = 19.78 +/- 3.11 μL CO2 h^-1 in males (mean mass = 22.72 ± 1.41 mg) and 27.34 ± 3.86 μL CO2 h^-1 in females (mean mass = 29.28 ± 1.96 mg) at 24 °C in fasted individuals] is strongly influenced by temperature, body mass and feeding status, but not by gender once the effects of body mass have been accounted for. A significant interaction between gender and feeding status is seen, similar to patterns of metabolic rate variation documented in *Glossina morsitans morsitans*. Synthesis of metabolic rate-temperature relationships in *G. m. centralis*, *G. m. morsitans* and *Glossina pallidipes* indicate that biting frequency as well as mortality risks associated with foraging will probably increase with temperature as a consequence of increasing metabolic demands, although there is little evidence for variation among species at present. Furthermore, metabolic rate-body mass relationships appear to be similarly invariant among these species. These data provide important physiological information for bottom-up modelling of tsetse fly population dynamics.

**3. TSETSE CONTROL (INCLUDING ENVIRONMENTAL SIDE EFFECTS)**

[See also 30: 14027, 14031]

In Burkina Faso, we assessed the efficacy of treating cattle with a footbath containing aqueous formulations of pyrethroids to control two tsetse-fly species, *Glossina tachinoides* Westwood, 1850 (Diptera, *Glossinidae*) and *Glossina palpalis gambiensis* Vanderplank 1949. Legs were the most targeted parts of the body for tsetse-fly blood meals: 81 percent (95 percent CI: 73, 89) for *G. tachinoides* and 88 percent (81, 95) for *G. palpalis*. The in-stable efficacy of footbath treatments was compared with manual full spraying with a 0.005 percent alphacypermethrin (Dominex, FMC, Philadelphia, USA) formulation (250mL versus 2L). The proportions of knocked-down flies were the same with footbath and full spray but the latter was more protective against fly bites. In field use, the efficacy of both methods should be similar given the recommended treatment frequency: 3 days for footbath versus 7 days for full spray. Among 96 cattle drinking at the same water point in Dafinso (Burkina Faso), 68 (71 percent) were treated with a footbath containing a 0.005 percent deltamethrin formulation (Vectocid, CEVA SA, Libourne, France). We observed the effect of this live-bait technique on the one hand on released cohorts of reared, irradiated flies, and on the other hand on wild tsetse flies. In both cases, the footbath treatment was associated with a reduction of the apparent fly density probably related to an increased mortality.


Studies were conducted in KwaZulu-Natal, South Africa, to evaluate the effectiveness of netting in preventing *Glossina austeni* and *Glossina brevipalpis* from entering H-traps. Results indicated that a net of 1.5 m in height was effective in reducing catches of *G. austeni* by 59.6 percent and catches of *G. brevipalpis* by 80.9 percent. Increasing the net height to 2.5 m reduced catches by 96.6 percent and 100 percent for *G. brevipalpis* and *G. austeni*, respectively. Nets of this height also reduced catches of horse flies by 55 percent. Although the potential use of protective netting has limitations in tsetse-infested areas of rural northern KwaZulu-Natal, it is a low-technology method that can be used as part of integrated disease management strategies.


Octenol (1-octen-3-ol), acetone, 4-methylphenol, 3-n-propylphenol, and other potential attractants (human urine, stable fly faeces), as well as guiacol, creosol (potential repellents), were tested as baits for biting flies in North America using standard phthalogen
blue IF3GM cotton Nzi traps, or similar commercial polyester traps. Baits were tested during the summers of 2001-04 at a residence in Canada and during January-August 2001 at a dairy in the USA. Behaviour in the presence of octenol was also studied by intercepting flies approaching a trap through the use of transparent adhesive film. Analogous bait and/or trap comparisons were conducted in natural settings in June 1996 in Kenya and in September-December 1997 in Ethiopia. In Canada, catches of five of six common tabanids (Tabanus similis Macquart, Tabanus quinquevittatus Wiedemann, Hybomitra lasiophilalma [Macquart], Chrysops univittatus Macquart, Chrysops aberrans Philip) and the stable fly Stomoxys calcitrans L. were increased significantly by 1.2-2.1 times with octenol (1.5 mg/h).

Catches of T. quinquevittatus and S. calcitrans were 3.5-3.6 times higher on a sticky enclosure surrounding a trap baited with octenol. No other baits or bait combinations had an effect on trap catches in North America. In Ethiopia, standard Nzi traps baited with a combination of acetone, octenol and cattle urine caught 1.8-9.9 times as many Stomoxys as similarly baited epsilon, pyramidal, NG2G, S3, biconical and canopy traps, in order of decreasing catch. When baits were compared, catches in Nzi traps of six stable fly species, including S. calcitrans, were not affected by octenol (released at approximately 1 mg/h), or cattle urine (140 mg/h), used alone or in combination with acetone (890 mg/h). Acetone alone, however, significantly increased the catches of common Stomoxys such as Stomoxys niger niger Macquart, Stomoxys taeniatus Bigot, and S. calcitrans by 2.4, 1.6 and 1.9 times, respectively. Catches of Glossina pallidipes Austen were increased significantly in traps baited with acetone, urine or octenol, or any combination, relative to those in unbaited traps (1.4-3.6 times). Catches of Glossina morsitans submorsitans Newstead were increased significantly by 1.5-1.7 times, but only when baits were used individually. Unlike other studies with East African tsetse, catches of both tsetse species with the complete bait combination (acetone, urine and octenol) did not differ from those in unbaited traps. Experiments with an incomplete ring of electric nets surrounding a Nzi trap, and a new approach using a sticky enclosure made from transparent adhesive film, revealed diverse responses to artificial objects and baits among biting flies. In Kenya, daily trap efficiency estimates for traps baited with either carbon dioxide (6 L/min) or a combination of acetone, cattle urine and acetone, were 21-27 percent for Glossina pallidipes, 7-36 percent for Glossina longipennis Corti, 27-33 percent for S. n. niger, and 19-33 percent for Stomoxys niger bilineatus Grunberg, assuming 100 percent electrocution efficiency. Actual trap efficiencies may have been lower, given observed outside: inside electric net catch ratios of 0.6:1.6. Observed ratios averaged 54 percent of expected values, with 10 of 15 possible ratios less than the minimum possible value of 1.0.


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The responses of Glossina morsitans morsitans Westwood to guaiacol (2-methoxyphenol), a mild repellent constituent of bovid odours, and seven analogues comprising 2-methoxyfuran, 2,4-dimethylphenol, 2-methoxy-4-methylphenol (4-methylguaiacol), 4-ethyl-2-methoxyphenol (4-ethylguaiacol), 4-allyl-2-methoxyphenol (4-
allylguaiacol; eugenol), 3,4-methylenedioxytoluene, and 3,4-dimethoxystyrene were compared in a two-choice wind tunnel. The 4-methyl-substituted derivative (2-methoxy-4-methylphenol) was found to elicit stronger repellent responses from the flies compared with guaiacol. None of the other analogues showed significant repellent effects on flies. 4-Methylguaiacol, guaiacol, and eugenol (which were included because of previous reports of its repellency against a number of arthropods) were further evaluated in the field with wild populations of predominantly Glossina pallidipes Austen. The presence of guaiacol or eugenol near odour-baited traps caused some nonsignificant reduction in the number of tsetse catches at relatively high release rates (approximately 50 mg/hr). In contrast, the 4-methyl derivative at three different release rates (2.2, 4.5, and 9.0 mg/hr) reduced trap catches of baited traps in a dose-response manner. At 10 mg/hr release rate, it reduced the catches of baited and unbaited traps by approximately 80 and approximately 70 percent, respectively. In addition, the compound not only reduced the number of tsetse attracted to natural ox odour (approximately 80 percent), but also had an effect on their feeding responses, reducing the proportion that fed on an ox by more than 80 percent. Our study shows that the presence of a methyl substituent at the 4-position of guaiacol enhances the repellency of the molecule to savannah tsetse and suggests that 4-methylguaiacol may represent a promising additional tool in the arsenal of techniques in trypanosomiasis control.


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Studies were carried out in Zimbabwe of the responses of tsetse to cattle treated with deltamethrin applied to the parts of the body where most tsetse were shown to land. Large proportions of Glossina pallidipes Austen (Diptera: Glossinidae) landed on the belly (approximately 25 percent) and legs (approximately 70 percent), particularly the front legs (approximately 50 percent). Substantial proportions of Glossina morsitans morsitans Westwood landed on the legs (approximately 50 percent) and belly (25 percent), with the remainder landing on the torso, particularly the flanks (approximately 15 percent). Studies were made of the knockdown rate of wild, female G. pallidipes exposed to cattle treated with a 1 percent pour-on or 0.005 percent suspension concentrate of deltamethrin applied to the (a) whole body, (b) belly and legs, (c) legs, (d) front legs, (e) middle and lower front legs, or (f) lower front legs. The restricted treatments used 20 percent, 10 percent, 5 percent, 2 percent or 1 percent of the active ingredient applied in the whole-body treatments. There was a marked seasonal effect on the performance of all treatments. With the whole-body treatment, the persistence period (knockdown > 50 percent) ranged from approximately 10 days during the hot, wet season (mean daily temperature > 30 °C) to approximately 20 days during the cool, dry season (< 22 °C). Restricting the application of insecticide reduced the seasonal persistence periods to approximately 10-15 days if only the legs and belly were treated, to approximately 5-15 days if only the legs were treated and < 5 days for the more restricted treatments. The restricted application did not affect the landing distribution of tsetse or the duration of landing bouts (mean = 30 s). The results suggest that more cost-effective control of tsetse could be achieved by applying insecticide to the belly and legs of cattle at 2-week
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intervals, rather than using the current practice of treating the whole body of each animal at monthly intervals. This would cut the cost of insecticide by 40 percent, improve efficacy by 27 percent and reduce the threats to non-target organisms and the enzootic stability of tick-borne diseases.


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Bloodmeal sources of Glossina fuscipes fuscipes and G. pallidipes, from the western Kenyan foci of human African trypanosomiasis (HAT) on Mageta Island and in Busia district, were identified using an ELISA based on chicken egg-yolk (IgY) antibodies. After absorption with cross-reacting antigens, the antibodies, which were produced against representatives of eight families of vertebrate host, were capable of differentiating serum from the different families. With the ELISA, it was possible to identify the family of host for 100 percent of laboratory-fed flies tested up to 48 h post-bloodmeal but only for 12 percent of such flies tested 96 h post-feed. Subsequently, attempts were made to identify the family of host that was the source of the (most recent) bloodmeal for each of 223 wild-caught flies, and these attempts were successful for 142 (63.7 percent) of the samples. Among the flies with identified bloodmeals, most (81.9 percent) of the G. f. fuscipes caught on Mageta Island had last fed on reptiles whereas most of the G. f. fuscipes (70.4 percent) and G. pallidipes (57.1 percent) caught in Busia had last fed on bovids. Bloodmeals of human origin accounted for <2 percent of the bloodmeals identified, perhaps indicating that, in the presence of alternative hosts, humans are not attractive hosts for tsetse in the study areas. This finding may account for the low reported incidence of HAT, despite the presence of circulating human-infective trypanosomes. In Busia at least, the use of animals, especially cattle, covered in insecticide would probably be an effective method of controlling the tsetse vectors of the trypanosomes that cause human and “animal” trypanosomiasis.

4. EPIDEMIOLOGY: VECTOR-HOST AND VECTOR-PARASITE INTERACTIONS

[See also 30: 14021, 14023, 14032, 14127, 14145]


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28
Conflict and war have long been recognized as determinants of infectious disease risk. Re-emergence of epidemic sleeping sickness in sub-Saharan Africa since the 1970s has coincided with extensive civil conflict in affected regions. Sleeping sickness incidence has placed increasing pressure on the health resources of countries already burdened by malaria, HIV/AIDS, and tuberculosis. In areas of Sudan, the Democratic Republic of the Congo, and Angola, sleeping sickness occurs in epidemic proportions, and is the first or second greatest cause of mortality in some areas, ahead of HIV/AIDS. In Uganda, there is evidence of increasing spread and establishment of new foci in central districts. Conflict is an important determinant of sleeping sickness outbreaks, and has contributed to disease resurgence. This paper presents a review and characterization of the processes by which conflict has contributed to the occurrence of sleeping sickness in Africa. Conflict contributes to disease risk by affecting the transmission potential of sleeping sickness via economic impacts, degradation of health systems and services, internal displacement of populations, regional insecurity, and reduced access for humanitarian support. Particular focus is given to the case of sleeping sickness in south-eastern Uganda, where incidence increase is expected to continue. Disease intervention is constrained in regions with high insecurity; in these areas, political stabilization, localized deployment of health resources, increased administrative integration and national capacity are required to mitigate incidence. Conflict-related variables should be explicitly integrated into risk mapping and prioritization of targeted sleeping sickness research and mitigation initiatives.


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A learning capacity for feeding is described in many insect species including vectors of diseases, but has never been reported in tsetse flies (Diptera, *Glossinidae*), the cyclic vectors of human (sleeping sickness) and animal trypanosomoses in Africa. Repeated feeding on the same host species by a disease vector is likely to increase the within-species disease-transmission risk, but to decrease it between species. An experiment with cattle and reptiles in a stable provides evidence that the species of host selected for the second blood meal in tsetse flies depends on the host encountered for the first blood meal when the between-meal interval is 2 days. This preference disappears when the between-meal interval is extended to 3 days. The energetic advantages of this acquired preference and its importance in trypanosomoses epidemiology are discussed.


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Trypanosoma brucei brucei infections which establish successfully in the tsetse fly midgut may subsequently mature into mammalian infective trypanosomes in the salivary glands. This maturation is not automatic and the control of these events is complex. Utilising direct in vivo feeding experiments, we report maturation of T. b. brucei infections in tsetse is regulated by oxidants as well as environmental stimuli. Dissection of the maturation process provides opportunities to develop transmission blocking vaccines for trypanosomiasis. The present work suggests cysteine and/or nitric oxide are necessary for the differentiation of trypanosome midgut infections in tsetse.


We did cross-sectional surveys in Kwale District, Kenya to determine the epidemiology of bovine trypanosomosis and livestock owners’ perceptions of the disease. The surveys involved relative importance of trypanosomosis, examination of the current disease constraints, current control practices and drug-use patterns. Informal meetings were held with farmers and cattle census undertaken. Tsetse-fly densities and trypanosomosis prevalences in cattle were determined. A total of 132 farmers were interviewed. Trypanosomosis, anaplasmosis, East Coast fever, and foot-and-mouth disease were reported to be the major constraints to livestock production. Trypanosomosis was the most important compared to other diseases. Chemotherapy was the most widely used method of controlling the disease. Farmer-based tsetse-control technologies were poorly adopted. Respondents were quite knowledgeable on the symptoms, causes and treatment of trypanosomosis. Glossina austeni, G. brevipalpis and G. pallidipes were found in the area; the latter was the most common (0.2–738 flies/trap). Trypanosoma congolense and T. vivax were found in cattle with the former more prevalent. Infection prevalences in cattle varied between 0 and 25 percent (median: 22 percent).


The morbidity and mortality of vector-borne diseases are closely linked to exposure of the human host to vectors. Qualitative and quantitative evaluation of individual exposure to arthropod bites by investigation of the specific immune response to vector saliva would make
it possible to monitor individuals at risk of vectorial transmission of pathogens. The objective of this study was to evaluate and compare the antibody (IgG) response to saliva from uninfected Glossina species, vectors, or non-vectors of Trypanosoma brucei gambiense by detecting immunogenic proteins in humans residing in an area endemic for human African trypanosomiasis in the Democratic Republic of Congo. Our results suggest that the immunogenic profiles observed seemed specific to the Glossina species (vector or non-vector species) and to the infectious status of exposed individuals (infected or not infected). This preliminary work tends to support the feasibility of development of an epidemiologic tool based on this antibody response to salivary proteins.


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To investigate the epidemiology of human African trypanosomiasis (sleeping sickness) in Kinshasa, Democratic Republic of Congo, two entomologic surveys were conducted in 2005. Trypanosoma brucei gambiense and human-blood meals were found in tsetse fly midguts, which suggested active disease transmission. Vector control should be used to improve human African trypanosomiasis control efforts.


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To determine and compare the prevalence of trypanosome infections in different livestock species (cattle, pigs and goats) in areas where game animals are scarce and livestock constitute the main food source of tsetse, a survey was conducted on the plateau of the Eastern Province of Zambia in Katete and Petauke districts where Glossina morsitans morsitans is the only tsetse species present. Blood was collected from a total of 734 cattle, 333 goats and 324 pigs originating from 59 villages in both districts and was examined using the buffy coat method and the PCR-RFLP as diagnostic tools. The prevalence of trypanosome infections differed substantially between livestock species. Using microscopic diagnostic methods, trypanosome infections were detected in 13.5 percent of the cattle and 0.9 percent of the pigs. All goats were parasitologically negative. The PCR-RFLP analyses increased the trypanosomiasis prevalence to 33.5, 6.5 and 3.3 percent in cattle, pigs and goats respectively. The majority of the infections (91.2 percent) were due to Trypanosoma congolense. The presence of a trypanosome infection in cattle and pigs resulted in a significant decline in the packed cell volume. The outcome of the study clearly shows that despite the availability of goats and pigs, cattle seem to be the major livestock species affected by the disease in
trypanosomiasis endemic areas. The high proportion of infections in cattle could be partly attributed to their higher availability and attractiveness to tsetse.


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No abstract available.

5. HUMAN TRYPANOSOMIASIS

(a) SURVEILLANCE

[See also 30: 14054]


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In previous papers in this journal, I have described and elaborated a hypothesis for the origin and evolution of a strain of HIV that has produced a lethal pandemic. Here I address the provocative question of how the ancestral HIV-1 group M retrovirus got to Leopoldville (Kinshasa, where the pandemic clearly spawned) from south-eastern Cameroon (where the HIV-1 strains all seemed to originate from transfer of SIV (cpz) to humans). Consistent with the phylogenetic history of HIV-1 group M (e.g., by Korber et al.), I place the critical relocation of the ancestral HIV-1 in the timeframe 1920-1927. However, unlike other hypotheses, I believe that the ancestral retrovirus was already well adapted to humans and can be identified as HIV-1 Group M subtype A (pre)-1927. Based on documents from that time period (1920-1928), it can be shown that it was not unusual for native Africans to be brought as far as 500 miles for treatment at the Leopoldville clinic (national borders were no issue because health agencies had mandate to work throughout Cameroon and Congo-Brazzaville). Specifically, sleeping sickness (trypanosomiasis) was one of the diseases of most concern at the Leopoldville clinic; in the period 1926-1928 there was an outbreak of sleeping sickness in Cameroon; and one of the native African children in the pamaquine (plasmoquineTM) study that I believe was selected for the major HIV-1 group M subgroups had trypanosomiasis. Thus, this child (or other patients/relatives from Cameroon) could have brought the ancestral HIV-1 group M retrovirus to the Leopoldville laboratory and spread it among the group of children who were undergoing treatment for malaria between February and August 1927. The diagnosis and monitoring of these protozoan diseases (trypanosomiasis and malaria) involved repetitive sampling of blood, which provides many opportunities for spreading the ancestral HIV-1 infection.
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After discovery of the first recorded case of human infection with *Trypanosoma evansi*, serologic screening of 1,806 persons from the village of origin of the patient in India was performed using the card agglutination test for trypanosomiasis and *T. evansi*. A total of 410 (22.7 percent) people were positive by whole blood, but only 81 were confirmed positive by serum. However, no trypanosomes were detected in the blood of 60 people who were positive at a high serum dilution. The results probably indicate frequent exposure of the human population to *T. evansi* in the study area, which suggests frequent vector transmission of parasites to humans. Although *T. evansi* is not infective for humans, a follow-up of seropositive persons is required to observe the evolution of human infection with this parasite.


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No abstract available.

(b) PATHOLOGY AND IMMUNOLOGY

[See also 30: 14026, 14095, 14105]


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Human African trypanosomiasis (sleeping sickness) is a parasitic infection transmitted by day-biting tsetse flies. The diagnostic gold standard is microscopy of blood, lymph node aspirates or CSF. The disease is invariably fatal, if not treated. There are over 300,000 new cases of sleeping sickness each year, and approximately 100,000 deaths. We
describe a British soldier who acquired trypanosomiasis in Malawi. He gave no history of a painful insect bite but presented with classical early signs of sleeping sickness (a primary chancre, regional lymphadenopathy, circinate erythema and a cyclical fever pattern). His condition worsened in the next week and trypanosomes were observed in a blood sample. He was aeromedically evacuated to Johannesburg, where Stage One \textit{Trypanosoma brucei rhodesiense} infection was confirmed; he also had renal and liver failure, pancytopenia and heart block. He was treated with intravenous suramin. He recovered fully over the next 5 months. It is recommended that medical officers deploying to eastern and southeastern Africa must be familiar with the common presenting signs and symptoms of \textit{T. b. rhodesiense} sleeping sickness, and should have access to a reliable local microscopy service at all times. Confirmed sleeping sickness requires immediate transfer to a tertiary diagnostic and treatment centre, where suramin (for \textit{T. b. rhodesiense} infection) or pentamidine (for \textit{T. b. gambiense}) and also melarsoprol (for Stage Two disease) must be immediately available.


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No abstract available.


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Trypanosomiases are imported and rare parasitosis on the French metropolitan territory. They are re-emerging in some endemic areas, and their mode of transmission can lead to an increase of imported cases in a near future. They can be responsible for serious disease. In this paper, we describe the basic data concerning epidemiology, clinical features, diagnosis, treatment and prevention of sleeping sickness (Africa) and Chagas disease (Latin America).


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A 61-year-old white woman presented to our institution complaining of intermittent fevers, chills, and rash. Three months before presentation, she travelled to Kenya and
Tanzania on a photographic safari. Her pretravel care included vaccinations for hepatitis A, yellow fever, tetanus-diphtheria, and polio and prescription for mefloquine. The patient initially noted a small papule on her left foot that began 2 days before her departure from Africa. The fevers, which lacked periodicity, began 1 month after her return home. Her symptoms persisted despite a course of quinine and several antibacterials (levofloxacin, azithromycin, metronidazole, doxycycline, and vancomycin) that were administered at her local hospital. She had no fresh water or direct animal contact on her trip, and all of her meals were prepared in hotel kitchens. She denied insect bites, although her husband was bitten by flies on several occasions. On physical examination, she had a temperature of 39°C, and her skin revealed a large, annular, minimally elevated plaque with central clearing from the left groin ascending to the trunk and with multiple satellite patches. Laboratory investigations revealed an elevated erythrocyte sedimentation rate but no other haematological abnormalities. Lumbar puncture revealed an elevated WBC count of 164 cells/µL (normal range, 0–4 cells/µL), with 78 percent lymphocytes, 21 percent monocytes, and 1 percent neutrophils, an elevated protein level of 191 mg/dL (normal range, 14–45 mg/dL), and a normal glucose level of 41 mg/dL. Cultures of CSF samples showed no growth, and Gram stain results were normal. A peripheral blood smear was obtained at admission to our institution.

Diagnosis of human African trypanosomiasis was made on the basis of physical examination findings and the presence of *T. brucei rhodesiense* noted on a peripheral blood screen obtained at admission. Our patient was given 1 dose of intravenous pentamidine and was subsequently given 1 dose of suramin procured from the Centers for Disease Control and Prevention. Because of an elevated WBC count, an elevated total protein level, and an elevated IgM level in CSF samples, CNS involvement was presumed, although the patient had no focal findings or neurologic symptoms. She was treated with intravenous melarsoprol (trivalent organic arsenic) together with prednisone to prevent post-treatment reactive encephalopathy. During week 1 of treatment, the patient received 108 mg of melarsoprol daily for 3 days; during week 2, she received 144 mg of melarsoprol daily for 3 days; and during week 3, she received 216 mg of melarsoprol daily for 3 days. Clinical improvement was associated with resolution of fever, a progressive decrease in the WBC count in CSF samples, and the clearance of parasitaemia on serial blood smears. The patient was subsequently discharged from the hospital with resolution of her fevers and rash. Serial lumbar punctures have been performed every 6 months since discharge from the hospital to evaluate for disease recurrence; to date, results have been negative. The patient's total protein level and WBC count in CSF samples have been normal at follow-up visits.


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Apolipoprotein L-I (apoL-I) is a human high-density lipoprotein (HDL) component able to kill *Trypanosoma brucei brucei* by forming anion-selective pores in the lysosomal
membrane of the parasite. Another HDL component, haptoglobin-related protein (Hpr), has been suggested as an additional toxin required for full trypanolytic activity of normal human serum. We recently reported the case of a human lacking apoL-I (apoL-I(-/-)HS) as the result of frameshift mutations in both apoL-I alleles. Here, we show that this serum, devoid of any trypanolytic activity, exhibits normal concentrations of HDL-bound Hpr. Conversely, the serum of individuals with normal HDL-bound apoL-I but who lack Hpr and haptoglobin [Hp(r)(-/-) HS] as the result of gene deletion (anhaptoglobinemia) exhibited phenotypically normal but delayed trypanolytic activity. The trypanolytic properties of Hp(r) (-/-) HS were mimicked by free recombinant apoL-I, whereas recombinant Hpr did not affect trypanosomes. The lysis delay observed with either Hp(r) (-/-) HS or recombinant apoL-I could entirely be attributed to a defect in the uptake of the lytic components. Thus, apoL-I is responsible for the trypanolytic activity of normal human serum, whereas Hpr allows fast uptake of the carrier HDL particles, presumably through their binding to an Hp/Hpr surface receptor of the parasite.


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Humans have innate immunity against Trypanosoma brucei brucei that is known to involve apolipoprotein L-I (APOL1). Recently, a case of T. evansi infection in a human was identified in India. We investigated whether the APOL1 pathway was involved in this occurrence. The serum of the infected patient was found to have no trypanolytic activity, and the finding was linked to the lack of APOL1, which was due to frameshift mutations in both APOL1 alleles. Trypanolytic activity was restored by the addition of recombinant APOL1. The lack of APOL1 explained the patient's infection with T. evansi.

(c) TREATMENT

[See also 30: 14026, 14031, 14146, 14155, 14156, 14159, 14166]


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To compare the effectiveness of melarsoprol and efornithine in treating late-stage Gambian trypanosomiasis in the Republic of the Congo, we analysed the outcomes of death
during treatment and relapse within 1 year of discharge for 288 patients treated with eflornithine, 311 patients treated with the standard melarsoprol regimen and 62 patients treated with a short-course (10-day) melarsoprol regimen between April 2001 and April 2005. A total of 1.7 percent (5/288) of patients treated with eflornithine died compared with 4.8 percent (15/311) of those treated with standard melarsoprol and 6.5 percent (4/62) of those treated with short-course melarsoprol. Patients treated with eflornithine tended to be younger and were more likely to have trypanosomes or higher white blood cell counts in their cerebrospinal fluid. The cumulated incidence of relapse among patients who attended at least one follow-up visit 1 year after discharge was 8.1 percent (11/136) for those treated with eflornithine, 14 percent (36/258) for those treated with standard melarsoprol and 15.5 percent (9/58) for those treated with short course melarsoprol. In a multivariate analysis, when compared with eflornithine, standard melarsoprol was found to be a risk factor for both death (odds ratio (OR) = 2.87; 95 percent confidence interval (CI) = 1.03-8.00) and relapse (hazard ratio (HR) = 2.47; 95 percent CI = 1.22-5.03); when compared with eflornithine, short-course melarsoprol was also found to be a risk factor for death (OR = 3.90; 95 percent CI = 1.02-14.98) and relapse (HR = 6.65; 95 percent CI = 2.61-16.94). It is concluded that the effectiveness of melarsoprol treatment appears to have diminished. Eflornithine seems to be a better first-line therapy for treating late-stage Gambian trypanosomiasis in the Republic of the Congo.


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Treatment of second-stage sleeping sickness relies mainly on melarsoprol. Nifurtimox has been successfully used to cure melarsoprol-refractory sleeping sickness caused by Trypanosoma brucei gambiense infection. An open, randomized trial was conducted to test for equivalence between the standard melarsoprol regimen and 3 other regimens, as follows: standard melarsoprol therapy (3 series of 3.6 mg/kg/day intravenously [iv] for 3 days, with 7-day breaks between the series); 10-day incremental-dose melarsoprol therapy (0.6 mg/kg iv on day 1, 1.2 mg/kg iv on day 2, and 1.8 mg/kg iv on days 3-10); nifurtimox monotherapy for 14 days (5 mg/kg orally 3 times per day); and consecutive 10-day melarsoprol-nifurtimox combination therapy (0.6 mg/kg iv melarsoprol on day 1, 1.2 mg/kg iv melarsoprol on day 2, and 1.2 mg/kg/day iv melarsoprol combined with oral 7.5 mg/kg nifurtimox twice a day on days 3-10). Primary outcomes were relapse, severe adverse events, and death attributed to treatment. A total of 278 patients were randomized. The frequency of adverse events was similar between the standard melarsoprol regimen and the other regimens. Encephalopathic syndromes occurred in all groups and caused all deaths that were likely due to treatment. Relapses (n=48) were observed only with the 3 monotherapy regimens. It is concluded that a consecutive 10-day low-dose melarsoprol-nifurtimox combination is more effective than the standard melarsoprol regimen.

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We describe a case of human African trypanosomiasis with a number of unusual features. The clinical presentation was subacute, but the infection was shown to be due to Trypanosoma brucei rhodesiense. The infection relapsed twice following treatment and the patient developed a melarsoprol-associated encephalopathy. Magnetic resonance imaging (MRI) findings were suggestive of microhaemorrhages, well described in autopsy studies of encephalopathy but never before shown on MRI. The patient survived severe encephalopathy with a locked-in syndrome. Our decision to provide ongoing life support may be useful to physicians treating similar cases in a setting where intensive care facilities are available.


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Existing data on human African trypanosomiasis (HAT) due to Trypanosoma brucei gambiense among children are limited. Here, we described the demographic, clinical, diagnostic, treatment and outcome characteristics of HAT in pre-school children from Kajo-Keji County, South Sudan in comparison with older patients. We did a retrospective analysis of HAT patients treated at the Kiri Sleeping Sickness Treatment Centre (SSTC), Kajo-Keji County, from June 2000 to December 2002. Of 1,958 HAT patients, 119 (6.1 percent) were pre-school children (<6 years) including 56 (47 percent) in first-stage illness and 63 (53 percent) in second-stage. The proportion of children in second-stage HAT was significantly higher in very young children (<2 years). Walking and speech disturbances were more frequent in second-stage HAT but other neurological symptoms and signs were not associated with disease stage. Pentamidine treatment for first-stage illness was very safe and effective among pre-school children. In contrast, 4.9 percent of pre-school children in second-stage illness died during melarsoprol treatment and 46 percent had > or = 1 severe adverse event(s). Macular rash, jaundice and skin necrosis on injection site were significantly more frequent in this age group (p<0.05). Melarsoprol-induced encephalopathic syndrome was less frequent but more severe than in older age groups. It is concluded that the clinical features of T. b. gambiense HAT among pre-school children are insufficiently stage-specific. Therefore, laboratory-based staging is mandatory to prevent unnecessary harm to HAT patients caused by the high toxicity of melarsoprol.

Tsetse and Trypanosomiasis Information


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Human African trypanosomiasis treatment is stage-dependent, but staging is controversial. Central nervous system involvement and its relationship with suramin treatment failure were assessed in 60 patients with parasitologically confirmed *Trypanosoma brucei* (*T. b.* gambiense) infection in haemo-lymphatic stage (white blood cell count ≤ 5/μL and no trypanosomes in the CSF). The prognostic value of cerebrospinal fluid (CSF) interleukin-10, IgM (by nephelometry and point-of-care LATEX/IgM test), total protein and trypanosome specific antibodies was assessed. IgM and interleukin-10 were measured in serum and the presence of neurological signs, intrathecal IgM synthesis and blood-CSF barrier dysfunction was determined. After suramin treatment, 14 out of 60 patients relapsed (23 percent). Relapses were significantly correlated with intrathecal IgM synthesis (OR 46; 95 percent CI 8 to 260), CSF IgM ≥ 1.9 mg/l (OR 11.7; 95 percent CI 2.7 to 50), CSF end titre in LATEX/IgM ≥ 2 (OR 10.4; 95 percent CI 2.5 to 44) and CSF interleukin-10 > 10 pg/ml (OR 5; 95 percent CI 1.3 to 20). Sensitivity of these markers for treatment failure was 43 to 79 percent and specificity was 74 to 93 percent. The results show that *T.b. gambiense* patients with signs of neuro-inflammation in CSF, who are treated with haemo-lymphatic stage drugs, are at risk of treatment failure. This highlights the need for development and
evaluation of accurate point-of-care tests for staging of human African trypanosomiasis. The authors declare not to have a commercial or other association that might pose a conflict of interest. Parts of the results were presented as a poster at the 28th Meeting of the International Scientific Council for Trypanosomiasis Research and Control (ISCTRC), Addis Ababa, Ethiopia.


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Trypanosoma brucei rhodesiense and T. b. gambiense are the causative agents of sleeping sickness, a fatal disease that affects 36 countries in sub-Saharan Africa. Nevertheless, only a handful of clinically useful drugs are available. These drugs suffer from severe side-effects. The situation is further aggravated by the alarming incidence of treatment failures in several sleeping sickness foci, apparently indicating the occurrence of drug-resistant trypanosomes. Because of these reasons, and since vaccination does not appear to be feasible due to the trypanosomes’ ever changing coat of variable surface glycoproteins (VSGs), new drugs are needed urgently. The entry of Trypanosoma brucei into the post-genomic age raises hopes for the identification of novel kinds of drug targets and in turn new treatments for sleeping sickness. The pragmatic definition of a drug target is a protein that is essential for the parasite and does not have homologues in the host. Such proteins are identified by comparing the predicted proteomes of Trypanosoma brucei and Homo sapiens, then validated by large-scale gene disruption or gene silencing experiments in trypanosomes. Once all proteins that are essential and unique to the parasite are identified, inhibitors may be found by high-throughput screening. However powerful, this functional genomics approach is going to miss a number of attractive targets. Several current, successful parasiticides attack proteins that have close homologues in the human proteome. Drugs like DFMO or pyrimethamine inhibit parasite and host enzymes alike - a therapeutic window is opened only by subtle differences in the regulation of the targets, which cannot be recognized in silico. Working against the post-genomic approach is also the fact that essential proteins tend to be more highly conserved between species than non-essential ones. Here we advocate drug targeting, i.e. uptake or activation of a drug via parasite-specific pathways, as a chemotherapeutic strategy to selectively inhibit enzymes that have equally sensitive counterparts in the host. The Trypanosoma brucei purine salvage machinery offers opportunities for both metabolic and transport-based targeting: unusual nucleoside and nucleobase permeases may be exploited for selective import of salvage enzymes for selective activation of purine antimetabolites.


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According to the World Health Organization, human African trypanosomiasis (HAT) (sleeping sickness) caused the loss of approximately 1.5 million disability-adjusted life years
We describe the effect of HAT during 2000-2002 in Buma, a rural community near Kinshasa in the Democratic Republic of Congo. We used retrospective questionnaire surveys to estimate HAT-related household costs and DALYs. The HAT outbreak in Buma involved 57 patients and affected 47 (21 percent) households. The cost to each household was equivalent to 5 months’ income for that household. The total number of HAT-related DALYs was 2,145, and interventions to control HAT averted 1,408 DALYs. The cost per DALY averted was US $17. Because HAT has a serious economic effect on households and control interventions are cost-effective, considering only global burden of disease rankings for resource allocation could lead to misguided priority setting if applied without caution in HAT-affected countries.


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No abstract available.


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Our objective was to compare the efficacy and safety of three drug combinations for the treatment of late-stage human African trypanosomiasis caused by *Trypanosoma brucei gambiense*. This trial was a randomized, open-label, active control, parallel clinical trial comparing three arms. The study took place at the Sleeping Sickness Treatment Center run by Médecins Sans Frontières at Omugo, Arua District, Uganda. Stage 2 patients diagnosed in Northern Uganda were screened for inclusion and a total of 54 selected. Three drug combinations were given to randomly assigned patients: melarsoprol-nifurtimox (M+N), melarsoprol-eflornithine (M+E), and nifurtimox-eflornithine (N+E). Dosages were uniform: intravenous (iv) melarsoprol 1.8 mg/kg/d, daily for 10 d; iv eflornithine 400 mg/kg/d, every 6 h for 7 d; oral nifurtimox 15 (adults) or 20 (children <15 y) mg/kg/d, every 8 h for 10 d. Patients were followed up for 24 months. Outcomes measured were cure rates and adverse events attributable to treatment. Randomization was performed on 54 patients before enrollment was suspended due to unacceptable toxicity in one of the three arms. Cure rates obtained with the intention to treat analysis were M+N 44.4 percent, M+E 78.9 percent, and N+E 94.1 percent, and were significantly higher with N+E (p = 0.003) and M+E (p = 0.045) than with M+N. Adverse events were less frequent and less severe with N+E, resulting in fewer treatment interruptions and no fatalities. Four patients died who were taking melarsoprol-nifurtimox and one who was taking melarsoprol-eflornithine. It is concluded that the N+E combination appears to be a promising first-line therapy that may improve treatment of sleeping sickness, although the results from this interrupted study do not permit conclusive