African trypanosomiasis (sleeping sickness)

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Key facts

- Sleeping sickness occurs only in 36 sub-Saharan Africa countries where there are tsetse flies that can transmit the disease.
- The people most exposed to the tsetse fly and therefore the disease are in rural populations dependent on agriculture, fishing, animal husbandry or hunting.
- *Trypanosoma brucei gambiense (T.b.g.)* accounts for 95% of reported cases of sleeping sickness.
- After continued control efforts, the number of cases reported in 2009 has dropped below 10 000 for first time in 50 years. This trend has been maintained in 2010 with 7139 new cases reported.
- Diagnosis and treatment of the disease is complex and requires specifically skilled staff.
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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 just in sub-Saharan Africa though only certain species transmit the disease. For reasons that are so far unexplained, there are many regions where tsetse flies are found, but sleeping sickness is not. Rural populations living in regions where transmission occurs and which depend on agriculture, fishing, animal husbandry or hunting are the most exposed to the tsetse fly and therefore to the disease. The disease develops in areas ranging from a single village to an entire region. Within an infected area, the intensity of the disease can vary from one village to the next.

Forms of human African trypanosomiasis

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 currently accounts for over 95% 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 emerge, the patient is often already in an advanced disease stage where the central nervous system is affected.
- *Trypanosoma brucei rhodesiense (T.b.r.)* is found in eastern and southern Africa. Nowadays, this form represents under 5% of reported cases and causes an acute infection. First signs and symptoms are observed a few months or weeks after infection. The disease develops rapidly and invades the central nervous system.

Another form of trypanosomiasis occurs mainly in 21 Latin 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 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* and act as a reservoir. However the precise epidemiological role of this reservoir is not yet well known. The disease in domestic animals, particularly cattle, is a major obstacle to the economic development of affected rural areas.

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 epidemic occurred in 1970.

The 1920 epidemic was controlled thanks to mobile teams which organized the screening of millions of people at risk. By the mid 1960s, the disease had almost disappeared. After this success, surveillance was relaxed, and the disease reappeared in several areas over the last 30 years. The efforts of WHO, national control programmes, bilateral cooperation and nongovernmental organizations (NGOs) during the 1990's and the beginning of the 21st century stopped and reversed the upward trend of new cases.

Distribution of the disease

Sleeping sickness threatens millions of people in 36 countries in sub-Saharan Africa. Many of the affected populations live in remote areas with limited access to adequate health services, which hampers the surveillance and therefore the diagnosis and treatment of cases. In addition, displacement of populations, war and poverty are important factors leading to increased transmission and this alters the distribution of the disease due to weakened or non-existent health systems.

- In 1986, it was estimated that some 70 million people lived in areas where disease transmission could take place.
- In 1998, almost 40 000 cases were reported, but estimates were that 300 000 cases were undiagnosed and therefore untreated.
- During epidemic periods prevalence reached 50% in several villages in the Democratic Republic of Congo, Angola and Southern Sudan. Sleeping sickness was the first or second greatest cause of mortality in those communities, ahead of even HIV/AIDS.
- By 2005, surveillance was reinforced and the number of new cases reported on the continent was reduced; between 1998 and 2004 the number of both forms of the disease fell from 37 991 to 17 616. The estimated number of actual cases was between 50 000 and 70 000.
- In 2009, after continued control efforts, the number of cases reported has dropped below 10 000 (9878) for first time in 50 years. This trend has been maintained in 2010 with 7139 new cases reported. The estimated number of actual cases is currently 30 000.

In 2000 and 2001, WHO established public-private partnerships with Aventis Pharma (now sanofi-aventis) and Bayer HealthCare which 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.

The partnership was renewed in 2006 and recently in 2011. The success in curbing the number of sleeping sickness cases encouraged other private partners to sustain the 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 the last 10 years, over 70% of reported cases occurred in the Democratic Republic of Congo (DRC).
- In 2010, only the DRC declared over 500 new cases per year.
- Angola, Central African Republic, Chad, Sudan and Uganda declared between 100 and 500 new cases per year.

- Countries such as, Cameroon, Congo, Côte d'Ivoire, Equatorial Guinea, Gabon, Guinea, Malawi, Nigeria, United Republic of Tanzania, Zambia and Zimbabwe are reporting fewer than 100 new cases per year.
- Countries like Benin, Botswana, Burkina Faso, Burundi, Ethiopia, Gambia, Ghana, Guinea Bissau, Kenya, Liberia, Mali, Mozambique, Namibia, Niger, Rwanda, Senegal, Sierra Leone, Swaziland and Togo have not reported any new cases for over a decade. Transmission of the disease seems to have stopped but there are still some areas where it is difficult to asses the exact situation because the unstable social circumstances and/or remote accessibility hinders surveillance and diagnostic activities.

Infection and symptoms

The disease is mostly transmitted through the bite of an infected tsetse fly but there are other ways in which people are infected with sleeping sickness.

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

In the first stage, the trypanosomes multiply in subcutaneous tissues, blood and lymph. This is known as a haemolymphatic phase, which entails bouts of fever, headaches, joint pains and itching.

In the second stage the parasites cross the blood-brain barrier to infect the central nervous system. This is known as the neurological phase. In general this is when more obvious signs and symptoms of the disease appear: changes of behaviour, 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 considered fatal.

Disease management: diagnosis

Disease management is made in three steps.

- Screening for potential infection. This involves using serological tests (only available for *T.b.gambiense*) and checking for clinical signs - generally swollen cervical glands.
- Diagnosing whether the parasite is present.
- Staging to determine the state of disease progression. This entails examining 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, relatively asymptomatic first stage of *T. b. gambiense* sleeping sickness is one of the reasons why an exhaustive, active screening of the population at risk is required, in order to identify patients at an early stage and reduce transmission. Exhaustive screenings require 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 of lower toxicity and easier to administer. The earlier the disease is identified, 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 toxic and complicated to administer. Four drugs are registered for the treatment of sleeping sickness and provided free of charge to endemic countries.

First stage treatment:

- **Pentamidine:** discovered in 1941, used for the treatment of the first stage of *T.b. gambiense* sleeping sickness. Despite non-negligible undesirable effects, it is in general 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 treatment:

- **Melarsoprol:** discovered in 1949, it is used in both forms of infection. It is derived from arsenic and has many undesirable side effects. The most dramatic is reactive encephalopathy (encephalopathic syndrome) which can be fatal (3% to 10%). An increase in 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*. The regimen is strict and difficult to apply.
- A combination treatment of **nifurtimox and eflornithine** has been recently introduced (2009). It simplifies the use of eflornithine in monotherapy, but unfortunately it is not effective for *T.b. rhodesiense*. Nifurtimox is registered for the treatment of American trypanosomiasis but not for human African trypanosomiasis. Nevertheless, after safety and efficacy data provided by clinical trials, its use in combination with eflornithine has been accepted and included in the WHO List of Essential Medicine, and it is provided free of charge for this purpose by WHO.

WHO response

WHO provides support and technical assistance to national control programmes. An important part of the response is a WHO private partnership with sanofi-aventis (pentamidine, melarsoprol and eflornithine) and Bayer AG (suramin and nifurtimox) to provide the drugs free of charge to endemic countries. A network has been established for donor countries, private foundations, NGOs, regional institutions, research centres and universities to participate in surveillance and control, and to undertake research projects to develop new drugs and diagnostic tools.

The objectives of the WHO Programme are to:

- strengthen and coordinate control measures and ensure field activities are sustained;
- strengthen existing surveillance systems;
- ensure accessibility to diagnostic and treatment;
- support the monitoring of treatment and drug resistance throughout the network;
- develop information database and epidemiological analysis of data;
- implement training activities;
- support operational research to improve treatment and diagnostic tools;
- promote collaboration with the Food and Agriculture Organization (FAO) in charge of animal trypanosomiasis and the International Atomic Energy Agency (IAEA) dealing with vector control through male flies made sterile by radiation. The three UN agencies along with the African Union have promoted the Programme Against African Trypanosomiasis (PAAT);
- coordinate and synergize vector control activities lead by the Pan African Tsetste and Trypanosomosis Eradication Campaign of the Africa Union.