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Closer to elimination: Sleeping sickness

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In 2012 the World Health Organisation (WHO) set out to eradicate Human African Trypanosomiasis (HAT). Also known as Sleeping Sickness, it is found in 36 Sub-Saharan African countries. There has been 7 Sleeping Sickness epidemics in the past century, the most recent of which lasted between 1970s-1990s with a prevalence of 50%, making it the leading cause of mortality in affected area. HAT is caused by the Trypanosoma brucei gambiense and Trypanosoma brucei rhodiense parasites, carried by Tsetse Flies. People in rural areas who depend on agriculture, fishing, animal husbandry or hunting are most at risk of exposure.

The early-stage symptoms are generally non-specific (rash, irritation, swelling of lymph nodes) and can be mistaken for allergies until the infection worsens and symptoms become more characteristic of Sleeping Sickness, like sleeping for excessively long periods of time; seizures; difficulty talking and walking. These symptoms are late-stage indicating that infection has crossed the blood-brain barrier via leaky blood vessels and reached the brain, causing Meningoencephalitis. When left untreated, Sleeping Sickness will lead to death in under a year.

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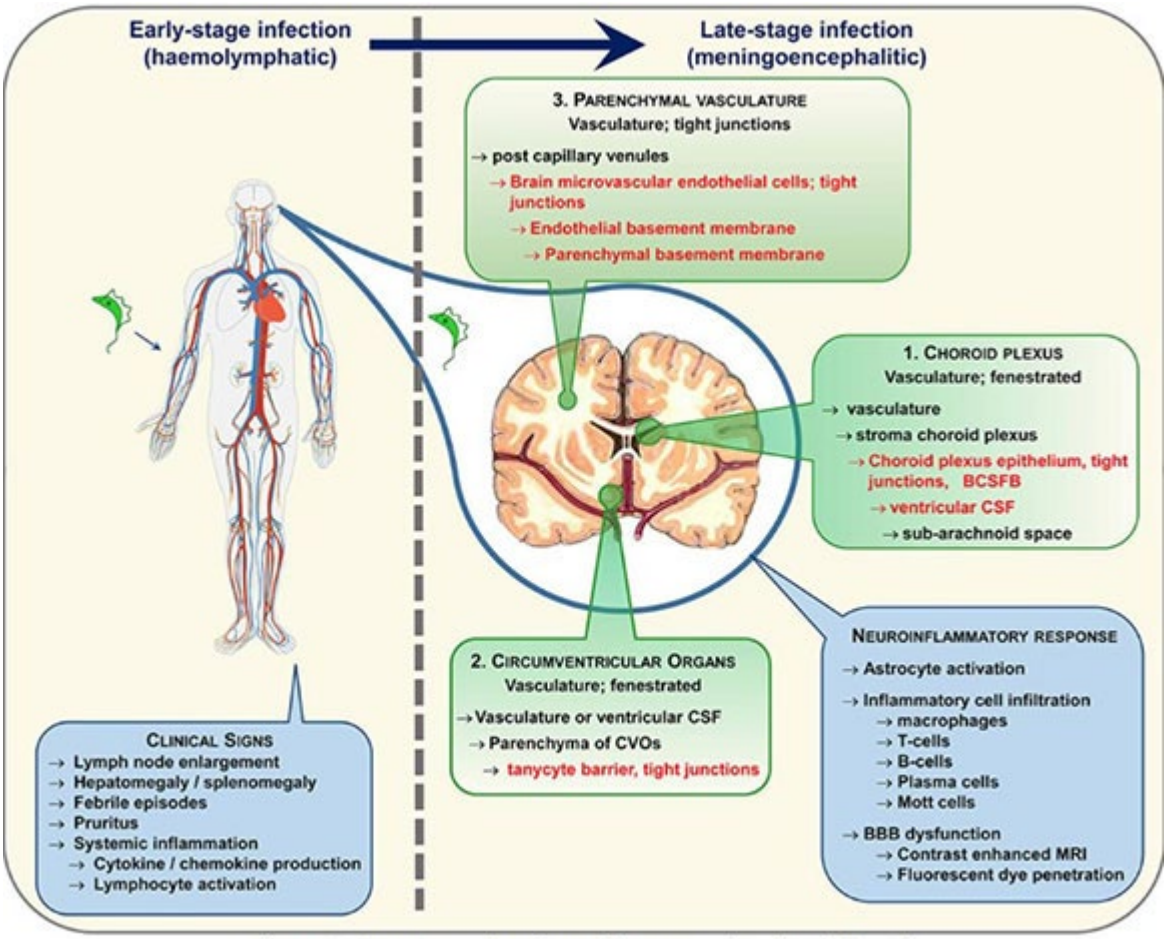

Figure 1: Symptoms of early and late stage sleeping sickness[3]

The WHO's original target was to achieve sustained elimination by 2020. Though this was not achieved, recent successes with disease surveillance sites in hospitals and clinics; quicker and more accurate diagnostic tests; and development of improved treatments, a new target has been set for 2030.

June-August 2019

Fexinidazole, the world's first completely oral treatment for both stages of Sleeping Sickness, was added to the WHO Essential Medicines List in June. Fexinidazole is a 10-day treatment that does not require patients to be in or visit hospital, meaning that healthcare workers can deliver this treatment within communities. It has been in development since 2009, and in August 2019 the WHO published new Sleeping Sickness treatment guidelines, with Fexinidazole as the first-line treatment for Trypanosoma brucei gambiense4. Fexinidazole is a 5-nitroimidazole derivative that works by creating reactive amine species that are indirectly toxic and mutagenic to trypanosomes. It is also a game changer in treatments because it does not have any of the cytotoxic effects that previously used treatments do.

January 2020

The WHO began distributing Fexinidazole in the Democratic Republic of Congo.

August 2020

Togo became the first African country to eliminate Sleeping Sickness, with a decade of no cases. Achieved through establishing surveillance sites in hospitals and rural areas to observe case numbers, provide rapid testing, and give immediate treatment with medications donated by pharmaceutical companies.

August-September 2020

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18-month post-treatment follow-up was completed for all the patients who took part in the Phase II/III clinical trials for a new drug called Acoziborole, which is a Benzoxaborole that has been in development and studied since 2009. The Drugs for Neglected Diseases Initiative reported that it can be administered orally as a single dose immediately after diagnosis; the first of its kind and a real breakthrough in treating Sleeping Sickness. Because Benzoxaboroles are a relatively new class of compounds which exhibit a large range of anti-fungal, anti-parasitic, anti-viral, and anti-bacterial, their exact mode of action is yet to be fully determined.

December 2020

WHO and pharmaceutical company Sanofi renewed their partnership, which led to a massive decrease in cases of Sleeping Sickness between the years 2000-2019; going from 33,000 to less than 1000 cases. Sanofi will provide $25m (US) for training new health professionals, disease screening, drug testing, and drug donation.

January 2021

It was proven that the FDA-approved tyrosine catabolism inhibitor, Nitisinone (NTBC), kills Tsetse Flies and could control Tsetse fly populations without harming the environment like currently used insecticides do. They found that when tsetse flies fed on rats which had been given orally administered nitisinone, 90% of flies died within 26 hours. On the other hand, when ingested by other insects such as bumblebees, NTBC had no toxic effects. Sterkel et al published a report explaining how NTBC kills Tsetse flies; “NTBC treatment causes accumulation of tyrosine and 4-hydroxyphenyl lactic acid (HPLA) metabolites, leading to fly paralysis and tissue destruction within 18 hours of a bloodmeal.” NTBC is very safe for humans, as it is currently used to treat hereditary tyrosinemia type 1 and alkaptonuria, with less than 1% of people experiencing side effects from it. They also reported that since NTBC half-life in human plasma is 54 hours; human blood would remain toxic to tsetse flies for a week after a single dose. They propose that NTBC be administered orally and/or topically to humans and livestock to reduce infections.

March 2021

Côte d'Ivoire became the second African country to achieve validated elimination status. Achieved through regular testing and providing treatment even in rural areas where people previously missed out on treatments requiring visits to hospitals out of reach. Benin and Equatorial Guinea have since applied to the WHO for certification validating their elimination of Sleeping Sickness.

May 2021

The Foundation for Innovative New Diagnostics (FIND) announced their donation of 450,000 Abbot Rapid Diagnostic Tests (SD BIOLINE HAT 2.0 tests) to endemic countries. Immunochromatographic rapid tests detect antibodies against Trypanosoma brucei gambiense. The tests do not require specialist equipment or storage - just a blood sample from a finger prick, giving a result in 15 minutes. The test is produced using recombinant parasite antigens and contains two antigens that were developed at The University of Dundee and the University of Cambridge. FIND’s donations will contribute to disease surveillance and control in rural areas10,11. Research conducted by Lumbala et al in 2017 Shows these Rapid Diagnostic Tests are more accurate (92% sensitivity) in detecting Human Trypanosomiasis than the traditional Card Agglutination Tests on both whole blood (69.1%) and on plasma diluted 1:8 (59%).

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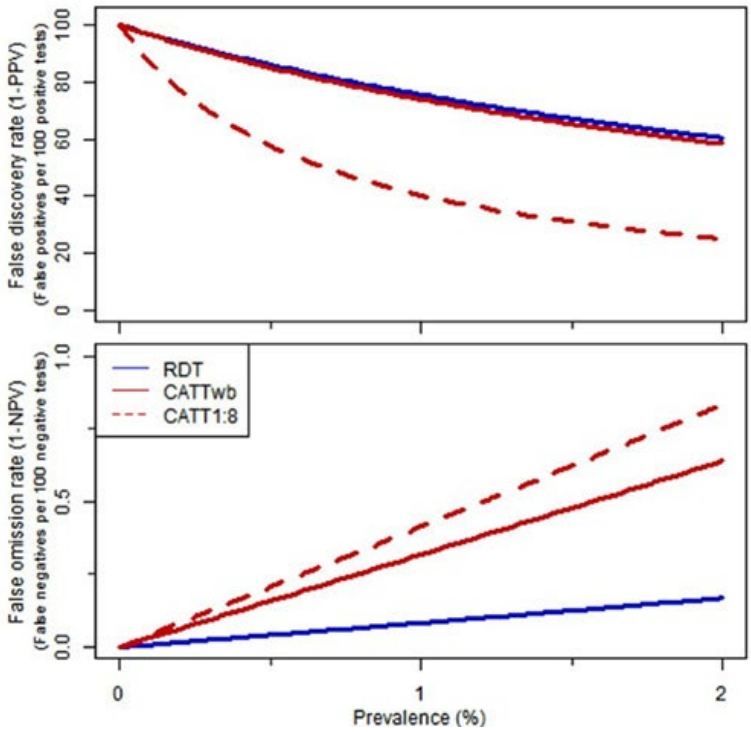

Figure 3: The False Omission Rate and False Discovery Rate of each test (RDT = SD BIOLINE HAT 2.0 Rapid diagnostic test. CATTwb = Card Agglutination Test on whole blood. CATT1:8 = Card Agglutination Test on plasma diluted 1:8)

July 2021

Fexinidazole is approved by the FDA in the US.

October 2021

The Drugs for Neglected Disease initiative announced that one of their two ‘Projects of the Year’ for 2021 is the research into Acoziborole. Recognising the colleagues who have worked on creating such all-in-one cures that can replace the existing toxic medicines available to treat Sleeping Sickness. The drug will be provided free to patients across all affected countries.

December 2021

Scientists at The University of Warwick joined an international research group and developed a new framework for identifying beneficial and cost-effective elimination strategies for HAT and other Neglected Diseases. In a paper published on the 14th December they explain that this framework will primarily focus on strategies that are more likely to meet global elimination targets and dates. In their paper they used Sleeping Sickness and the 2030 elimination target to illustrate this new framework.

Looking to the future

These achievements from the last three years show that we are on track to see Human African Trypanosomiasis be sustainably eliminated by 2030, thanks to disease surveillance and distribution of Fexinidazole and Acoziborole; which change the game for treating Sleeping Sickness quickly, and safely, in even the most rural locations.

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