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Review Article

Influence of Environmental Factor on Neglected Tropical Disease: African Trypanosomiasis

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Abstract

The global health agenda has overlooked neglected tropical diseases (NTDs), leaving nearly two billion people affected by their collective burden, equivalent to that of HIV/AIDS, tuberculosis, and malaria. NTDs are prevalent among impoverished populations with poor hygiene and close contact with infectious vectors, domestic animals, and livestock, making Africa particularly vulnerable. One NTD, human African trypanosomiasis, is transmitted by the tsetse fly and affects humans and domestic animals, causing economic losses and limiting agricultural production. The tsetse fly's development, mortality, and metabolic rate are sensitive to temperature changes, and the rising population levels in sub-Saharan Africa have increased human-fly contact, posing a greater risk of contracting the disease. While controlling the tsetse fly vector and using trypanocidal drugs are effective in treating trypanosomiasis, they can lead to environmental degradation and unsustainable land use. Clearing vegetation for agriculture can reduce wild host densities and vegetative cover. This review focuses on recent advances in addressing environmental factors that affect neglected tropical diseases, including African trypanosomiasis.

Keywords: African Trypanosomiasis; Environmental Factors; Climate; Neglected Tropical Diseases; Sleeping Sickness

Introduction

Human African Trypanosomiasis (HAT), commonly known as sleeping sickness, is a blood vector-borne parasitic disease that poses a threat in sub-Saharan Africa. This infection is caused by Trypanosoma brucei rhodesiense or Trypanosoma brucei gambiense and is mainly transmitted through the bite of an infected tsetse fly of the genus *Glossina* [49].

Human African Trypanosomiasis, commonly known as sleeping sickness, is a parasitic disease transmitted by tsetse flies that poses a threat in sub-Saharan Africa. It is caused by Trypanosoma brucei rhodesiense or Trypanosoma brucei gambiense, with T. b. gambiense found in 24 countries in West and Central Africa, and T. b. rhodesiense predominantly found in 13 countries in Eastern and Southern Africa, primarily infecting humans and animals, respectively. Infection caused by these subspecies leads to a chronic infection which progresses slowly in an infected individual, with T. b. rhodesiense causing a more rapid form of the infection.

According to Simarro and colleagues (2012), about 70 million people are at risk of infection, with the first epidemic occurring between 1896 and 1906 in Uganda, the second in 1920, and the

Figure 1: Photo credit pexels.com.

most recent starting in 1970 and lasting until the 1990s. In 2012, a total of 7,216 cases were reported for both subspecies, while approximately 20,000 cases were confirmed, all caused by societal, economic, war, and political issues. However, the prevalence of the infection has decreased significantly due to various control policies and intervention programs.

The World Health Organization has classified HAT as a Neglected Tropical Disease (NTD) since it is mostly prominent in poor areas with children and adults involved in farming, fishing, and hunting. HAT is among the 17 priority NTDs recognized by WHO. It has had a huge impact on the population, thereby posing a significant threat to public health. In Africa, there have been several epidemics over the last century.

Two clinical stages evolve in the course of an infection, and symptoms are generally the same for the two parasites. The first stage is called the hemolymphatic state, where noticeable symptoms include fever, headaches, pruritus, asthenia, anemia, and hepato splenomegaly. The second stage is the meningoencephalic stage, which occurs after the parasites (trypanosomes) invade the central nervous system (CNS) and cross the blood-brain barrier (BBB). This is a very fatal stage with symptoms such as sleep disturbances, abnormal movement, hemiparesis, limb paralysis, irritability, psychotic reactions, and aggressive behavior [7].

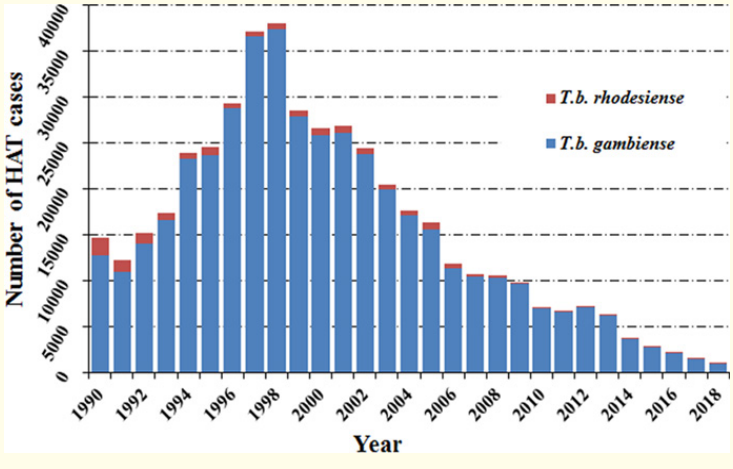

Figure 2: *Typonosoma brucei gambiense* and *rhodesiense* prevalence reported cases in edemic countries from 1999 to 2018 [48].

Life cycle of trypanosome

Trypanosomes feed on blood, which is how they are transmitted from one animal to another. In the case of *Trypanosoma brucei,* the Tsetse fly injects *T. brucei* into the bloodstream by stinging the host. *T. brucei* then multiplies by binary fission in human fluids such as blood and cerebrospinal fluid. After the multiplication of *T. brucei* in humans, the Tsetse fly bites again and ingests *T. brucei* contaminated blood meal. The parasite then multiplies further in the midgut of the Tsetse fly, eventually transforming into an infectious stage that enters the midgut of the salivary gland and produces more parasites. These parasites will then infect the next animal host. The life cycle of *Trypanosoma brucei* is illustrated below.

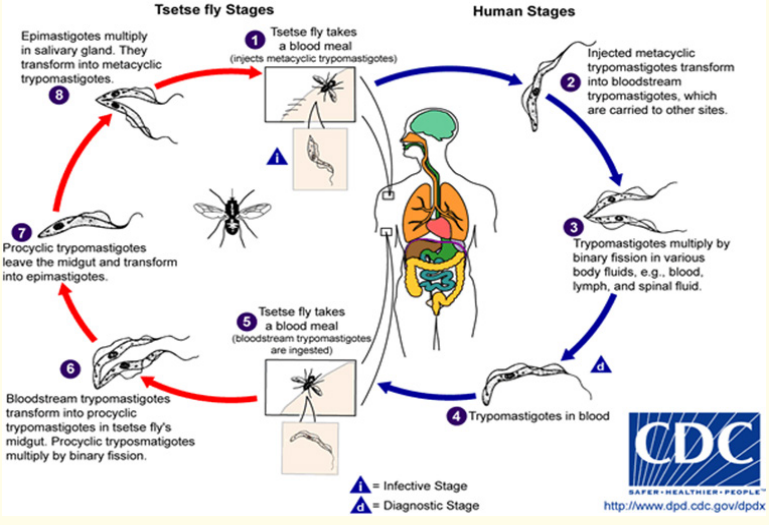

Figure 3: Life cycle of trypanosome showing the circulation and development.

Trypanosomes feed on blood, which is how they are transmitted from one animal to another. In the case of *Trypanosoma brucei*, the Tsetse fly injects *T. brucei* into the bloodstream through its bite. *T. brucei* then multiplies by binary fission in human fluids such as blood and cerebrospinal fluid. After multiplying in the human host, the Tsetse fly bites again and ingests *T. brucei*-contaminated blood. The parasite then multiplies further in the midgut of the Tsetse fly, transforms into an infectious stage, and enters the midgut of the salivary gland, where it produces more parasites. These parasites can then infect their animal host. The life cycle of *Trypanosoma brucei* is illustrated simply below.

Diagnosis of African trypanosomiasis

Figure 4: Photo credit pexels.com.

Due to the adverse effects caused by the parasites, early diagnosis is crucial to prevent the disease from progressing to the neurological stage. However, diagnosis can be a major challenge, and cumbersome treatment and diagnostic methods may be required if the disease is not detected early. Therefore, exhaustive screening is not recommended, particularly in rural areas, due to the significant investment in material resources it would require. Instead, active screening, as well as antibody and parasite detection, are necessary for proper patient examination. The Card-Agglutination Trypanosomiasis Test (CATT) is a serological test commonly used to identify suspected cases. It is carried out on blood using complete bloodstream forms of *Trypanosoma brucei gambiense* variable antigen type as the antigen. The test can also be done on plasma, which is more specific than the CATT on blood. This test is frequently used for the serological screening of *Trypanosoma brucei gambiense*. For patients with a positive CATT, parasite detection is carried out by examining the lymph nodes. The sensitivity of lymph node palpation may be affected by factors such as the type of parasite strain, stage of disease, and prevalence of other diseases. Other methods for parasitological confirmation include the Mini Anion Exchange Centrifugation Technique (mAECT) and Capillary Tube Centrifugation (CTC). After diagnosis, patients are referred to HAT treatment centers.

Treatment of African trypanosomiasis

There are two categories of treatment for Trypanosoma brucei infection. The first category involves the use of Pentamidine and Suramin during the early stages of the infection. Pentamidine is mainly used to treat Trypanosoma brucei gambiense, while Suramin is mostly administered for Trypanosoma brucei rhodesiense. Notable side effects of Pentamidine include hypoglycemia, nausea, and vomiting, while those of Suramin include allergic reactions, nephrotoxicity, hypersensitivity, and hematuria.

Figure 5: Photo credit pexels.com.

The second category of treatment involves the use of Melarsoprol, Eflornithine, and a combination of Eflornithine/Nifurtimox therapy. Melarsoprol can be used to treat both types of the disease. However, one major side effect of Melarsoprol is the risk of developing fatal encephalopathic syndrome. Nifurtimox/Eflornithine Combination Therapy remains the standard first-line treatment for the CNS stage of *Trypanosoma brucei gambiense*. For Trypanosoma *brucei rhodesiense,* Melarsoprol is the most effective first-line treatment. Clinical surveillance is necessary during the therapeutic care of these treatments.

Further studies have shown that Fexinidazole, which belongs to the class of nitroimidazole drugs, has trypanocidal properties attributed to active compounds that target trypanosomes. The drug was discovered in the 1980s by the Drugs for Neglected Diseases initiative (DNDi). Another drug used to treat the disease is Benzoxaborole, which is a by-product of the oxabrole class. However, all these approaches are hindered by a lack of vaccines and diagnostic tools, and drug treatments have led to the emergence of resistant strains of the trypanosome.

In HAT zones, these resistant strains are commonly found in domestic animals that act as reservoirs for the trypanosome, which is then spread by tsetse flies. The major reservoirs include domestic animals such as pigs and wild animals such as carnivores and primates, because the cyclical transmission of the disease depends on

the biochemical and physiological interactions occurring between the parasite and its insect host. Formal studies have shown that environmental factors, such as biotic and abiotic factors including climate change, geographical distribution, and environmental conditions of HAT foci, are responsible for the cyclical transmission.

Despite the cyclical transmission, new drug treatments and diagnostic tools are being developed for the complete elimination of the disease, thus limiting the number of new cases and decreasing the severity of the disease. Experts are making interventions towards cost-effectiveness for communities that are at risk of the disease, including community sensitization and involvement within control and elimination campaigns, with the sole purpose of completely eliminating this neglected disease in Africa. The World Health Organization (WHO) and Aventis have made their announcement known to eliminate the Trypanosoma parasite, while private partners, Non-governmental Organizations (NGOs), and other decision makers are fully committed to funding the elimination of the disease by collaborating with relevant organizations such as WHO. The aim of this review was to consider the environmental factors affecting the neglected tropical disease (HAT) and recent advances made in tackling these issues.

Environmental Stress to the *Glossina spp*

Environmental factors, such as climate change, are key variables that influence vector-borne diseases [47]. Climatic variables, such as temperature and rainfall, have a huge impact on the ecosystems of vector-borne diseases, mainly due to their impact on host behavior and development, as well as pathogen amplification. Global warming has led to an increase in surface air and ocean temperatures, which has resulted in rising sea levels and melting glaciers [18]. These conditions have worsened in recent times, and the poorest countries are hit the hardest, facing numerous infectious disease situations, such as sleeping sickness [19].

The spread of sleeping sickness is tripartite and involves the trypanosome, the tsetse fly vector and its symbionts, and the vertebrate hosts. The spread of the parasite also depends on the populations of the tsetse flies and the mammals from which they obtain their blood meal [2]. All of these require specific climatic conditions for their survival and reproduction. For instance, temperature strongly influences the reproduction and feeding habits of tsetse flies [20]. Favorable temperature conditions increase the tendency of the flies to become more infected [20].

The human population is one of the biggest factors contributing to the spread of the parasite. With an increasing population, the number of livestock and farmlands required to meet our needs will also increase, thereby increasing the distribution of tsetse flies that feed on them. To clearly understand the transmission intensity and parasite distribution, there is a need to investigate the impact of such environmental factors.

Impact of climate on the development rates of trypanosomes and tsetse flies

In central Africa, the amount of rainfall in the infested zones varies from 2.03 meters per year in the *G. bervipalpis* belts to 406 millimeters in the *G. morsitans* belt of the Bechuanaland Protectorate. Temperature values range from 40°C to just 0°C. These temperature limits are often repeated in some areas where there is a wide diurnal range that may exceed 22°C in winter months.

In some parts of East Africa, the amount of rainfall in the infested zone usually exceeds 80 inches per year. In other parts, like Kenya, where G. longipennis occurs, the rainfall may reduce to 15 inches per year. The temperature values range from 40°C to 10°C.

Previous studies in West Africa have described the habitats of *G. palpalis* and the effect of climate. In the north of Africa, the tsetse fly population is confined to a riverine forest where there is an abundance of creepers and evergreen shrubs, which cause lateral insulation. A vertical insulation is also formed by the interlocking overhead canopies. This makes the feeding ground more suitable for the tsetse flies during the dry season to obtain their food without having to migrate to neighboring savannah with its lethal temperatures. High daily maximum temperatures (34°C – 35°C) are quite dangerous for the flies when they occur for ten days. Females are quite resistant to these changes in temperature, while about 30% of male mortality was reported at a temperature of 29°C. However, 30% of female mortality occurs above 33°C over a period of ten days.

In the south, which has more humid and equable conditions, some species like *G. palpalis* are not restricted to the riverine areas. They can be found throughout the savannah woodland, even in the absence of water. Moreover, there is also a variation in seasonal density. In the north, there is an increased population of tsetse fly in the wet season (April – September) and a decrease in population density in the dry season (October – March). Although there

is a possibility of an increase during the dry season, which was a result of the intrusion of the southern rainforest along its rivers. The fly population seems to be steady at a low density; however, there could be an increase during the fourth and fifth wet months. This rise in population is due to the rise in the mean temperature. Under these conditions, there is a chance for rapid reproduction. By the end of the fourth and fifth wet months, the temperature has dropped with the saturation deficit (2.7 millibars). A decrease in population can then be expected in the north due to the decrease in the mean monthly saturation deficits of 2 millibars or less at the end of the wet season (August – September).

Some sub-genus of *Glossina spp*., such as *G. tachinoides*, show a seasonal variation in density. Their numbers rapidly increase during the early dry season, reaching a maximum in the second or third month, and then decline during the rest of the dry season. This is because the flies concentrate in favorable habitats as the dry season becomes more severe. Pupal sites become available as the water dries up during the dry season. In the wet season, the flies disperse little and are mainly found in the floodplain during the third zone.

G. morsitans also show a characteristic seasonal dispersal and concentration. During the wet season, they are dispersed into the woodland on higher ground. However, when the dry season becomes severe, they are forced back into the forest islands and thickets of the flood plains.

Temperature and food supply appear to be the main factors that affect the distribution of female tsetse flies. Warthogs are the most common source of food in the flood plains. When the diurnal temperature rises in the dry season, the flies and warthogs retreat to the forest islands where there is an adequate food supply under favorable conditions. Similarly, in wet seasons, the female population may be around 9%, which is normal. However, in hot seasons, the female population can rise from 39% to 44% due to the heat conditions that make the flies hungrier, causing females to even come to humans [24].

Control of human African trypanosomiasis

Extensive research has been conducted to understand the control of trypanosomes. However, the diagnostic framework and treatment of Human African Trypanosomiasis (HAT) have been beset with many difficulties. For instance, the use of trypanocidal drugs to combat the vector population affects the sustainability of land and promotes environmental degradation. Therefore, there is a need for new knowledge on both parasite and tsetse vector physiology, genetics, and genomics to tackle these issues and achieve more sustainable control. Below are some recent advances made towards the elimination of HAT.

Reducing vector populations

Reduction of vector populations is quite effective, especially for Rhodesiense HAT, which involves relatively cheap resources compared to Gambiense HAT. However, historical investigations, modeling, and practical interventions play a significant role in vector control of Gambiense HAT in both human and animal reservoirs. Vector control is effective during periods of low endemicity. Active surveillance campaigns may be too costly to operate during this period, but it is the only preventive measure to protect people against bites in tsetse-infested areas. Likewise, xeno-monitoring has been used to identify sleeping sickness transmission sites during low endemicity using commercially-available loop-mediated isothermal amplification (LAMP).

Furthermore, efforts have been geared towards using the Sterile Insect Technique for continent-wide vector reduction, which was suggested by the African Union after successful eradication in Zanzibar. However, there are minor difficulties associated with this approach, such as its high cost and dependence on major infrastructure such as large insectaries, irradiation facilities, and even airplanes. A more reliable, cost-efficient, and sustainable vector control method is now possible by modifying the existing insecticide-treated targets in HAT areas.

To identify the efficacy and effect of tsetse control interventions, sensitive serological tools have been created using tsetse saliva-based biomarkers. Another breakthrough in the aspect of trypanosome biology is the completion of the genome sequences of *G. morsitans* and some other vectors. The information obtained from the sequencing, such as olfactory, reproductive, and symbiotic, has been used to identify targets for population reduction. This information can be used in setting traps using their olfactory physiology. Obligate dependencies on their endosymbionts provide a weak link in the vector's ability to reproduce, making it an ideal target for new vector control mechanisms.

Population genetics of tsetse vectors in disease-endemic areas is another way to reduce the population of tsetse vectors. Identification of natural barriers to fly dispersal and routes will help provide the necessary information for field control programs using indigenous methods like traps and the Sterile Insect Technique [39,40].

Control of the parasite in the tsetse vectors

There have been recent advances in tsetse and trypanosome genomics, particularly in understanding the host-parasite relationship [41-43]. This research has uncovered new information on how parasite transmission can be disrupted in the host [32]. Studies by researchers [44,45] have reported a new approach to eliminating the parasite by engineering refractoriness in tsetse. Specifically, a commensal symbiont of the tsetse fly, Sodalis, has been identified in the midgut and genetically modified [46].

Conclusion: (Neglected African Trypanosomiasis: Challenges and Opportunities for Treatment)

The World Health Organization has identified African trypanosomiasis, caused by Trypanosoma brucei, as a neglected disease that affects both humans and animals, particularly cows. Underdeveloped Sub-Saharan African communities are particularly vulnerable to this disease. While chemotherapy remains the best option for treating trypanosomiasis, drugs such as pentamidine and suramine have limitations, and there is a need to inhibit the pathways that allow parasitic survival in a host, reduce costs, and address drug-resistant strains. Novel drug research aims to achieve these goals, but until then, it is crucial to raise awareness and provide detailed explanations in socio-economically deprived Sub-Saharan African communities.

In conclusion, African trypanosomiasis caused by Trypanosoma brucei remains a significant public health issue, affecting both humans and animals, especially in underdeveloped Sub-Saharan African communities. Although there have been recent advancements in tsetse and trypanosome genomics, as well as novel drug research to combat the disease, the diagnostic framework and treatment of Human African Trypanosomiasis (HAT) still face many difficulties. The use of trypanocidal drugs affects the sustainability of land and promotes environmental degradation, and drug-resistant trypanosoma strains are emerging. Therefore, there is a need for more sustainable and cost-effective control methods, such as reducing vector populations, using sensitive serological tools, and modifying existing insecticide-treated targets. Additionally, population genetics of tsetse vectors in disease-endemic areas could be used to reduce tsetse vector populations. Increased awareness and detailed explanation are also needed in socio-economically deprived Sub-Saharan African communities to reduce the spread of African trypanosomiasis.

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