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Review Articles

Accelerating towards human African trypanosomiasis elimination: Issues and opportunities

Kingsley Uchenna Ozioko[1], Chris Ikem Okoye[1], Rose Nduka Obiezue[1], Idika Kalu Idika[2], Raymond Agbu Awudu[3], Bede Izuchukwu Ezewudo[4] & Celestine Osita Ezea[5]

[1]*Department of Zoology and Environmental Biology, University of Nigeria, Nsukka.* [2]*Department of Veterinary Parasitology and Entomology, University of Nigeria, Nsukka.* [3]*Central Laboratory Unit, Federal University Wukari, Wukari, Taraba State Nigeria.* [4]*Department of Zoology, Nnamdi Azikiwe University, Akwa Anambra State, Nigeria.* [5]*Department of Biology, Federal University of Technology Owerre Imo State, Nigeria.*

ABSTRACT

Human African trypanosomiasis (HAT) has been an alarming global public health issue. The disease affects mainly poor and marginalized people in low-resource settings and is caused by two subspecies of haemoflagellate parasite, *Trypanosoma brucei* and transmitted by tsetse flies. Progress made in HAT control during the past decade has prompted increasing global dialogue on its elimination and eradication. The disease is targeted by the World Health Organization (WHO) for elimination as a public health problem by 2020 and to terminate its transmission globally by 2030, along-side other Neglected Tropical Diseases (NTD). Several methods have been used to control tsetse flies and the disease transmitted by them. Old and new tools to control the disease are available with constraints. Currently, there are no vaccines available. Efforts towards intervention to control the disease over the past decade have seen considerable progress and remarkable success with incidence dropping progressively, reversing the upward trend of reported cases. This gives credence in a real progress in its elimination. This study reviews various control measures, progress and a highlight of control issues, vector and parasite barriers that may have been hindering progress towards its elimination.

Key words Human African trypanosomiasis; Elimination; Issues; Opportunities

INTRODUCTION

Human African trypanosomiasis (HAT) also known as human sleeping sickness is a neglected tropical disease caused by protozoan parasites, *Trypanosoma brucei* and transmitted by the bite of tsetse fly (*Glossina sp.) T. brucei* and its arthropod vector that cause HAT were discovered and identified between 1894–1910[1]. There are two subspecies that infect humans; *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*[2]. While the former is responsible for the chronic form of sleeping sickness in West and Central Africa, the latter gives rise to the acute form of the disease in East and Southern Africa. The clinical presentation of HAT appears in two phases, the first haemolymphatic phase which is associated with a febrile illness and the second meningoencephalitic phase which is characterized by the invasion of the central nervous system[3]. HAT depends solely on interaction of the trypanosome, with the vector, as well as humans for *Trypanosoma brucei gambiense*, and animals for *Trypanosoma brucei rhodesiense*[4]. HAT epidemic reached the highest in the late 1990s when approximately 25,000 new cases were reported per year. The origin of these epidemics was linked to violent disturbances, social conditions, upheaval of war combined with lack of awareness and poverty[4]. World Health Organization (WHO) had in early days put forward ambitious targets for eliminating HAT incidence globally[5]. Sustained control efforts have of late dramatically reduced the number of HAT cases to unparalleled low numbers and raised hopes for 2020 WHO roadmap target to eliminate it as a public health problem[6]. There was considerable reduction in the total number of reported new cases between 2000 and 2014[7]. In 2015, it caused around 3500 deaths, down from 34,000 in 1990[8] and in 2017 only 1447 new cases were reported to WHO as compared with 2184 in 2016. In 2018, there were 977 cases recorded[9].

Inspite of global reduction in the number of cases, the condition is still at a threatening mark in many African countries. Currently, there are no vaccines available and

treatments are antiquated, toxic, increasingly ineffective making its management difficult[10] and diagnosis complex. Various control measures are available with constraints. The global programme to control the disease relies mostly on active screening and case treatment to reduce the organisms which carried the disease as well as to distrupt the cycle of transmission by reducing the number of vectors that transmit the infection[11–13]. Significant progress has been made in recent years to achieve the goal of elimination[14]. This progress has led to continued optimism and commitments by global and regional partners to commit to HAT elimination within a generation. Despite considerable progress in HAT control, the most effective strategy for meeting up the WHO target roadmap has not yet been elucidated[15]. Successes have followed several epidemics, multiple human activities are known to be risk factors for acquiring sleeping sickness[16], and the target years are drawing nearer. In this study we review various control measures, strength and constraints that may have been hindering progress towards WHO's goals for 2020 and 2030. Those aspect of vectors and parasites adaptations that can enhance HAT transmission and its resurgence at the point of eradication are also unfolded thus, contributing to new directions for research and control.

Distribution of HAT

Sleeping sickness occurs only in 36 sub-Saharan Africa countries where there are particular vectors that transmit the disease[17]. Many of the affected populations live in highly rural poor areas with restricted access to adequate health services, which intricates the inspection, diagnosis and treatment of cases[18–19]. There are many risk factors that facilitate transmission such as civil conflict and instability in affected countries and regions[20]. *T. b. gambiense* is distributed in Western and Central Africa and causes chronic disease while *T. b. rhodesiense* is found in Eastern and Southern Africa and responsible for acute severe disease. The most affected country in the world is the Democratic Republic of the Congo which accounts for about 75% of the *Trypanosoma brucei gambiense* reported cases[4]. Strengthened control efforts have lowered the number of new cases drastically[21]. *Trypanosoma brucei gambiense* is found in 24 countries in West and Central Africa and accounts for over 98 percent of reported cases of sleeping sickness while *Trypanosoma brucei rhodesiense* is found in 13 countries in Eastern and Southern Africa and represents fewer than 2 percent of reported cases and causes an acute infection[21]. Sleeping sickness occurs in geographically characterized zones referred to as foci[22], a zone of transmission where the interaction between the parasites, vectors, hosts and environment has not yet been completely understood but offers suitable habitat for HAT transmission to occur[4].

Transmission of HAT

HAT is transmitted by the bite of an infected tsetse fly from the genus *Glossina sp*. There are other possibilities of transmission such as mechanical transmission through other blood-sucking insects[23], congenital transmission from mother to child, and accidental contamination through pricks from contaminated needles and sharp objects as well as transmission of the parasite through sexual intercourse[4, 24]. Epidemiologically, human, animal, tsetse fly and the pathogenic parasite, the trypanosome interact in space and time within a permissive environment in transmission of HAT[4]. *T. b. gambiense* form of sleeping sickness is transmitted from human to human by the tsetse fly which is the most common form of transmission[25]. Occasionally, transmission can come directly from animals to humans[26], which is believed to have epidemiological importance of such zoonotic transmission[23]. *T. b. rhodesiense* sleeping sickness transmission cycle involves to a great extent domestic and wild animals, but epidemics occasionally occur in domestic animals and humans[11]. Intensified human to human transmission occurs during epidemics. The strong zoonotic character of the *T. b. rhodesiense* form of the disease substantially complicates inspections and control issues, requiring action on the fly or on the animals hosting the parasite[7]. Within a pemissive environment, the parasites biologically complete their life cycle in two hosts: the definitive stage "in mammalian" and intermediate stage "in arthropod" [27–28].

Adaptive nature of parasites and vectors in transmission of HAT

Trypanosomiasis is transmitted to humans and animals by a blood sucking insect, the tsetse fly. Tsetse sucks blood from humans or animals, picking up parasites from an infected host or injecting parasites they carry into a host. Trypanosome has a complex life cycle in which it must adapt either to the mammalian bloodstream or to different compartments within the tsetse fly[29]. The transmission of *T. brucei* is highly dependent on the physiological interactions that occur between the parasite and its hosts (insects)[30]**.** Trypanosome suppresses various activities that saliva of tsetse fly causes when it bites humans such as anti-platelet aggregation, anti-thrombin and anti-coagulation. They do the suppression by reducing the salivary gland gene transcription in the tsetse[31]. Trypanosome makes such physiological changes in the tsetse fly so as to facilitate its own transmission. Trypanosomes have evolved to escape the immune response by several mecha-

nisms. One major trick played by trypanosomes to evade immune system is antigenic variation[32], a mechanism that enables the trypanosomes to produce a surface coat composed of another glycoprotein. Antigenic variation is a mechanism by which parasites alter its protein coat to evade the host immune system. Trypanosomes switch and express different variant surface glycoprotein (VSG) that enable an entirely different surface coat to be produced. As the immunity to the current var protein builds up and starts eliminating the parasites, some switch up another var protein to escape and maintain their survival within hosts[33]. Mechanism of antigenic variation has been a major impediment to vaccine development against African trypanosomes[34]. Instead of evading the host immune system, trypanosomes can confront it by manipulating the immune response, favoring parasite survival rather than death. Huge modifications have been observed in both innate and the adaptive immune system during infection by human-pathogen trypanosomes, which include disorders in the complement system, antigen presentation as well as defects concerning T- and B-cells[35]. *T. brucei* possess a single flagellum which is a key mediator of trypanosome transmission. Apart from its role in motility, flagellum is also a crucial host-parasite interface that mediates attachment to host tissues and provides a staging for the assembly of signaling proteins and virulence factors that function in host-parasite interactions[10]. Midgut colonization of trypanosomes in tsetse fly depends on their ability to adapt while passing from the blood of vertebrate host to the different environment of the tsetse gut**.**

Tsetse fly has a very long piercing mouth part known as proboscis which is the slender, tubular feeding and sucking organ. It is one structural adaptation which helps the flies to easily pierce the skin to suck blood[36]. When tsetse fly is feeding, it bends the mouth part low from the protective maxillary palps and points it downward. It injects saliva into the host blood when sucking blood. The saliva contains anticoagulant which breaks down blood clot, and so the tsetse ensures blood keeps flowing while feeding on human hosts[37]. They are endowed with an enlarged portion of the digestive tract, crop which allows them to take up so much blood[38]. Their sensitive antennae bear specialized cells which aids them to sense the environmental condition of its resting place and the hosts on which it lands. Their legs bear taste receptors which have been shown to be sensitive to many components of human sweat. It allows rapid assessment and selection of the host to draw blood from, resulting in more efficient feeding behaviour. The two evolutionary strategies are term r-selection, for those species that produce many cheap offspring and live in unstable environment and k-selection for those species that produce few expensive offspring and live in a stable environment. While most insects are r-selected species and so have a high growth rate and produce many eggs, few of which survive to adulthood, tsetse flies are k-selected species; they produce few offspring which have a very high survival rate[39]. They exhibit adenotrophic viviparity, a reproductive system in which the eggs hatch inside the female and the larvae are nourished by the insect equivalent of milk[40]. The larvae remain inside the female until they are mature at which point they are laid and promptly pupate. The cycle is effective in protecting the insect in most vulnerable stages of their life. The composition of the gut microbiota in invertebrate hosts has been known to influence vector competence via different approaches[30]. Endosymbiotic bacteria present within the tsetse fly gut synthesize some important nutrients that the fly doesn't get from its host and are used to support lactation and development of the young. This is a beautiful adaptation that tsetse has evolved to ensure its success. Tsetse fly posessess meshwork of chitin microfibrils in the gut, the peritrophic matrix (PM) which is a physical barrier that regulates pathogen infection outcomes, prevents poreforming microbial toxins from damaging this physiologically important tissue[41–42]. It has a low biotic potential and tends to bite hosts on parts where they are less likely to be killed. The fly's behavior can bring it into suitable microhabitats where it can survive better than if it had to suffer the general climatic conditions of the area[36]. Infected ones have been evolved to bite more than uninfected ones thereby enhancing the spread of *T. brucei* through a population. They have been adapted to be efficient blood feeders; however, trypanosome has made use of this efficiency, resulting in the infection of thousands upon thousands of humans. The parastiaemia in the mammalian host is usually very low but the fly has evolved to effectively amplify the number of parasites for its transmission. Establishment and maturation of trypanosomes within the body of tsetse (the development cycle) culminates with the metacyclic form that is infective for mammalian hosts[30].

Control of HAT

The remarkable progress in the control of HAT has relied on depleting the reservoir of parasites in humans, detecting cases and ensuring curative treatment, as well as vector control activities (Fig.1). Case detection and treatment involve screening of suspected cases and treatment to reduce the human reservoir and thus decreases transmission. Cases are detected via active screening campaigns by mobile clinics[15] or fixed screening centres where teams travel daily to areas of high infection rates. Card agglu-

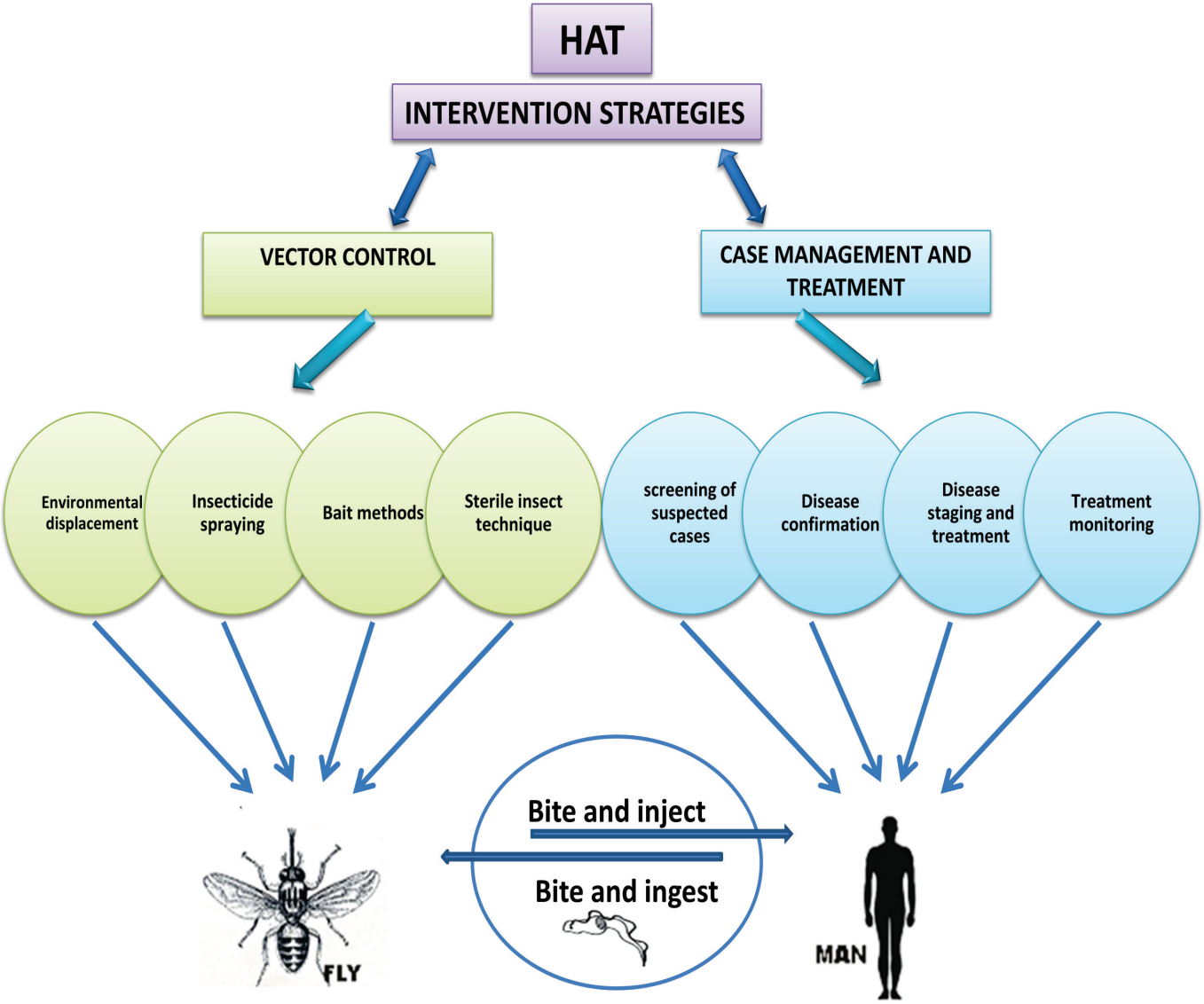

Fig. 1: A schematic diagram of intervention to control and eliminate HAT. The remarkable progress in the control of HAT has relied on depleting the reservoir of parasites in humans, detecting cases and ensuring curative treatment, as well as vector control, strategies that have proven capable of interrupting HAT transmission.

tination trypanosomiasis test (CATT) is commonly used by mobile clinics to detect suspected cases for HAT in the field[43]. Screening at-risk communities is the best approach which involves checking for clinical, and neurological signs as well as examining blood smears for signs of the parasite. This allows early-stage infection to be detected and treated immediately before the disease progresses to late stage phase of infection (meningoencephalitic). Remote nature of some HAT foci and disinclination for participation has turned out to be a challenge.

All positive results after passing through screening tests need to be confirmed using parasitological and serological test[44] to demonstrate the presence of trypanosomes in body fluid of the patient. Proper diagnosis is a resource-intensive task and requires specific training. Error-free diagnosis is also needed for an excellent result and must be repeated over and over again. Another alternative to parasitological method is molecular test, although the fomer method is still considered the "gold standard" for identifying parasites[45].

In order to decide on which treatment to be given, it is critical to determine if trypanosome infection is in stage 1 or in stage 2. The choice of treatment depends on the disease stage[46]. Treatment success in the stage 2 depends on the drugs that cross the blood-brain barrier to reach the parasites. Staging can be performed with a

lumbar puncture (spinal tap) to distinguish the early stage from the late stage of infection in which trypanosomes are present in the central nervous system (CNS) fluid[47–48]. The number of white blood cells (WBC) in the cerebral spinal fluid (CSF) is most commonly used criterion for staging and can be used to classify it[49, 44]. The stage 1 treatment for *T. b. gambiense* includes pentamidine and suramin whereas melarsoprol and eflornithine are used for stage 2. While suramin is considered for the stage 1 treatment of *T. b. rhodesiense*, melarsoprol is drug of choice for second stage[50]**.** Melarsoprol is a standard treatment and also effective for both types. A combination therapy known as nifurtimox-eflornithine combination therapy (NECT) is another significant step forward in the treatment of *T. b. gambiense*. NECT has been adopted as first line treatment for second stage *T. b. gambiense* HAT in all disease endemic countries[48]. Another better alternative to NECT is fexinidazole. It offers the following advantages over NECT; superior safety profile, easier administration, long shelf life, simplified logistics, reduced costs and better acceptance by patients[15]. Fexinidazole is used to treat both stage 1 and stage 2 of the disease. The drug has recently been approved for management of gambiense HAT[51]. The drugs used in the treatment of stage 1 of the HAT are easier to administer than that of stage 2. A few effective chemotherapies are available, all of which provoke certain undesirable effect, toxicity[52] and drug resistance that may occur. Despite all these factors, they are in general well-tolerated by patients. All drugs currently used for the treatment of HAT are donated to WHO for free distribution by the manufacturers[48]. Patients should be monitored closely for signs of treatment failure. This involves maintaining contact with (a patient) so as to monitor the effects of earlier treatments with laboratory exams of body fluids including cerebrospinal fluid. Up to 24 months post-treatment follow-up is required to declare a patient cured[53], as trypanosome may remain viable for long periods and cause relapse. Ideally, biannual clinical and laboratory evaluations including blood and cerebral spinal fluid analysis should be carried out for a period of 2 years[54]. Patients who have recovered from stage 2 of East and West Africa trypanosomiasis should undergo diagnostic check-up every three months for the first year and every six months for next 2 years. Monitoring helps determine which areas require greater effort and identify questions that might contribute to an improved response.

Vector control strategies

Transmission of HAT requires three interacting organisms: the mammalian reservoir host, tsetse fly vectors and the trypanosomes, which cause the disease. Tsetse flies (*Glossina sp*) are responsible for linking trypanosomes among the mammalian hosts and any reduction in flies density significantly reduce transmission and hence contribute to its control. Vector control remains the only available strategy capable of protecting humans from acquiring infection and when complemented with case detection and chemotherapy, lower the risk for transmission to an acceptable level. Various techniques for the parasites vector control exist.

Environmental displacement

Before most of these techniques became available, control efforts mainly involved bush-clearance (to eliminate tsetse resting sites) and wild game culling (to reduce the parasite reservoirs and host availability for tsetse[55]). Displacing tsetse from their resting and breeding place has contributed to the reduction of tsetse fly populations. After clearing vegetation, the animal reservoir hosts of the flies also move away in order to not be exposed, thus contributing to the reduction in tsetse population. Also, several animal reservoir hosts for HAT and their roles in resurgence of the trypanosomiasis have been documented in literature. Control of trypanosome infections in animals is an old method that holds prospect as a tool in disrupting the transmission among the mammalian hosts. High interaction of animals and humans increases abundance of tsetse vectors flies and hence vulnerability to vector borne diseases[56]. Elimination of animal reservoir hosts on which tsetse feed can reduce population to a very low level. Although widely effective, such a method is no longer acceptable. Indiscriminate killing of animals and large-scale bush clearing are not practiced nowadays because of environmental concerns[57]. Burning up the rangelands, smoke and avoidance of grazing have also been used to limit contact between tsetse and cattle by pastoralists[58–59].

Insecticide spraying

The use of insecticides is the major method currently employed for tsetse control[60, 17] and it is also the quickest way of reducing tsetse fly population. Insecticide use is either by ground spraying or aerial spraying[11]. While ground spraying is done by teams on the ground by selective application to the known fly resting sites, aerial spraying is done by aircraft. Ground insecticide spraying is the method of choice and has been widely used on a large scale for controlling tsetse population in many African countries. Aircraft application has the obvious advantage of covering large areas quickly but almost impossible to carry out against species living in high forest as droplets can be blown away without reaching the targeted organism. Insecticide spraying has many side-effects on non-

target organisms. Insecticides resistance, although not yet reported for tsetse also seems possible.

Bait methods

Environmental concerns about spraying large areas with insecticide led to a search for eco-friendly techniques like fly traps for tsetse control. Trap efficiency depends on ecology and behavioural pattern of the different species of tsetse[55]. Many traps have been designed for catching tsetse such as biconical trap, a first modern trap developed by Challier and Laveissiere[61]. Most of the traps being used for tsetse control today are based on biconical trap[62]. Derivative of biconical trap includes pyramidal, Vavoua and Lancien traps[61,63]. Other bait of interest includes olfactory baits (attractants) for tsetse flies designed to attract tsetse[64]. It is very effective for savannah tsetse flies. Odour-baited traps have been used in many countries and can suppress the tsetse fly population to a high extent. The technique is suitable for deployment by communities to protect small areas[60]. Traps can only be applied in some types of areas and are species specific to an extent. Animal spread with insecticide can serve as mobile baits from which flies can pick up a lethal deposit of insecticide on its body while sucking blood. Mobile baits are more attractive than the stationary traps[36] but are very expensive to maintain.

Sterile insect technique

The sterile insect technique (SIT) is another method of control in which male tsetse flies are sterilized with gamma radiation which then compete with non-sterile male to mate with females, resulting in adult female flies[17]. The essence of SIT is to overcome the biotic potential of the target tsetse population. Females inseminated by such sterile males produce no viable offsprings, resulting in a decline in the wild population. Sterile insect technique has no adverse effects on non-target organisms and is species-specific[57]. It can only be effective in laboratory or in an isolated area. Production of sufficiently large numbers of radiated, sterile males that can be used in the field is a very expensive process[65], labour intensive, requiring close supervision and detailed planning[57]. Competition with other non sessile males counterpart in the field is another big challenge. Its feasibility in areas where multiple tsetse species exist is doubtful.

Progress in research and control

WHO and its partners have continued to support the disease endemic countries in various ways. They have reinforced HAT control and surveillance activities. Screening programs have been put in place for some at-risk populations. Research is all about searching, adding new things to the research world or modifying already added ones. Research is ongoing to uncover mechanisms and compounds that could alter vectorial capacity to acquire or transmit HAT[66]. The discovery of endosymbiotic bacteria (wigglesworthia, soladis and wolbachia) present within the tsetse fly gut by researchers has provided a promising avenue in the fight against tsetse-transmitted trypanosomiasis. Those bacteria can express and release a sufficient amount of active, functional, parasite-targeting compound that when manipulated genetically could block trypanosome transmission in flies, a process known as paratransgenesis[8]. In the absence of those bacteria, tsetse flies are severely impaired in their longevity and reproduction[14]. This provides an ideal target for new vector control methods[65]. Researchers have discovered that trypanosomes are unable to survive in the bloodstream without their flagella. This insight gives them a new angle with which to attack the parasite. Trypanosomiasis vaccines are undergoing research with different vaccines candidate on development pipeline. The regional HAT Platform that focuses on strengthening clinical or operational research capacity in HAT in the most affected endemic countries has been constituted to tackle the issue of trypanosomiasis in Africa[67]. This came up with the support of international and national research groups. Its objective was to provide the population of an endemic area with diagnostic tools (simple, sensitive and adapted) and therapeutic tools (effective and adapted to both stages of the disease). Currently, the novel tools co-developed by Foundation for Innovative New Diagnostics (FIND) and other partners have contributed to the diagnosis of sleeping sickness all across Africa[67]. A number of biomarkers have been identified that accurately detect patients who have reached the neurological phase of the disease such as IgM, MMP-9 and CXCL13[68,69]. WHO has collaborated with different research institutions to seek for more appropriate diagnostic, treatment and surveillance tools. They set up a HAT specimen bank to support diagnostics research. The aim was to provide reference clinical materials to research institutions to develop and evaluate new tests for diagnosis and staging of HAT, appropriate for use in low-income countries[48]. Much progress has been made in funding to control African sleeping sickness with greatest amount directed towards basic research of the disease. The Bill and Melinda Gates foundation and United Kingdom DFID have been involved in funding research.

CONCLUSION

World Health Organisation (WHO) in collaboration with other stakeholders has made great achievements in

its control efforts through provision of high coverage of HAT prevention and curative services. Transmission of the disease seems to have been counting down to zero but there are still some gaps that have not been addressed. The gap in understanding interactions between wildlife, domestic animals and humans in the transmission cycle and also sympatric coexisting species of tsetse flies that transmit HAT as well as the level of drug resistance in the trypanosome populations in Africa. Some areas where the disease is endemic, face a variety of access barriers such as unstable security situation and/or remote accessibility to assess the exact situation. Exposed animals remain asymptomatic and play a vital epidemiologic role as reservoir of the parasite which indirectly may pose a challenge to the way the disease is being tackled on the ground in Africa. The rapid expansion of African trade and human travel coupled with war and population movement that can enhance geographical spread of pathogenic trypanosomes, tsetse flies and different animal reserviour host are still a potential problem.

Although sustained controlled measures and commitment of various stakeholders offers unique opportunity to eliminate the disease, more strategies that may contribute to the sustainability of its elimination are needed. Since parasites and vectors naturally adapt to survive and enhance transmission in any of their permissive environment, integrating vector control together with medical control strategies, seems worthwhile in meeting up Roadmap's targets for 2020 and 2030. Even at this point when we can imagine elimination of HAT as a possibility, collaboration and funding will be at the centre of any such attempt to ensure sustainability. Hence, government and other stakeholders need to respond proactively and commit to HAT control in terms of funding. Since previously sustained controlled efforts have followed a number of epidemics and risk factors are very common in Africa, focus intervention should not be relied on endemic area alone. Boundary area between endemic and unendemic population are the crucial places where pathogens spill over from one population to the other via animals reservoir host. Moreover, tsetse flies can travel a considerable distance to infect human and livestock in surrounding area. In non-endemic countries HAT is rare; control and surveillance activities may be delayed leading to potentially fatal consequences.

Despite the fact that there are so many issues converging to limit HAT elimination, control tools for HAT eradication have been tested, perfected and are currently available for use against the scourge. By the end of 2018, a major advance in the control of HAT was achieved. Considering the epidemiological situation by country, HAT distribution limit has changed in favour of eliminating the disease. For instance in Democratic Republic of the Congo, there was confirmed reduction in the number of cases from 1200 in 2017 to 650 in 2018[70,9]. The latest data released by WHO has equally confirmed decrease in the number of reported cases (<1000 in 2018)[9]. The year 2019 ushered in a period of increasing progress, great accomplishments and fresh ideas to reaching HAT elimination target. Recent introduction of fexinidazole to be included in the management of cases is a welcome development and when complemented with vector control, would ultimately eliminate both subspecies form of the disease in the future. So, it is advisable to increase and sustain the current control efforts using existing control tools while planning to achieve goal of zero transmission.

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Ethical statement: Not required

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Correspondence to: Kingsley Uchenna Ozioko, Parasitology and Public Health, Department of Zoology and Environmental Biology, University of Nigeria, Nsukka, Nigeria.
Email: ukingsley82@yahoo.com

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