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African Animal Trypanosomosis and Its Control: A review

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Summary: Trypanosomes are protozoan parasites that cause debilitating diseases called trypanosomosis in animals, sleeping sickness in humans and have great socio-economic impact adversely affecting food production and economic growth in many parts of Africa, particularly in Sub-Saharan Africa. The disease caused by these extracellular hemoflagellates in domestic animals is called "Nagana" or African animal trypanosomosis. Trypanosomosis in animal is transmitted cyclically by the genus *Glossina*, but it can also be transmitted mechanically by other biting flies among which *Tabanus* and *Stomoxys* are presumed to be the most important. The distribution of the disease coincides with the habitat of the tsetse fly vector and is called the tsetse fly "belt". Trypanosomosis is controlled either by controlling the vector or the parasites or by controlling both and for many years, a large number of vector control tools have been developed and implemented. However, control of animal trypanosomosis in poor rural community has mainly been relied on the use of trypanocidal drugs. But only a small group of chemo prophylactic and chemo therapeutic trypanocidal compounds are currently in use and new compounds are unlikely to become fabricated The inevitable outcome of continued use of the same compounds for decades has resulted in drug resistance that has been largely responsible for frequently observed chemo therapeutic failures. Hence, strategic control of trpanosomosis focusing on the vector should be implemented to mitigate the problem.
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1. Introduction

Trypanosomes are protozoan parasites that cause debilitating diseases called trypanosomosis in animals and sleeping sickness in humans and have great socio-economic impact adversely affecting food production and economic growth in many parts of Africa, particularly in Sub-Saharan Africa (SSA) (Shaw *et al*., 2014; Taylor, 2015). The disease in animal is transmitted cyclically by the genus *Glossina*, but it can also be transmitted mechanically by other biting flies among which *Tabanus* and *Stomoxys* are presumed to be the most important (Truc *et al.,* 2013).

The disease caused by these extracellular hemoflagellates in domestic animals is called "Nagana" or African animal trypanosomosis (AAT). The distribution of the disease coincides with the habitat of the tsetse fly vector and is called the tsetse fly "belt" or it is sometimes referred to as "green desert" because ~10 million km^2 of potential fertile land is rendered to be unsuitable for cultivation (Shaw *et al*., 2014). Within this area, the majority of tsetse infested countries are underdeveloped, poor, heavily indebted and food-deficit due to lack of productive animals as far as meat/milk production and draft power are concerned, resulting in an annual economic loss of about 5 billion US$ (Giordani *et al*., 2016; Yaro *et al*., 2016).

The disease is controlled either by controlling the vector or the parasites or by controlling both and for many years, a large number of vector control tools have been developed and implemented (Bauer *et al*., 2012). However, control of animal trypanosomosis in poor rural community has mainly been relied on the use of trypanocidal drugs. But only a small group of chemo prophylactic and chemo therapeutic trypanocidal compounds are currently in use and new compounds are unlikely to become fabricated (De Koning *et al*., 2012). The inevitable outcome of continued use of the same compounds for decades has resulted in drug resistance that has been largely responsible for frequently observed chemo therapeutic failures (Yohannes *et al*., 2012).

In many parts of Africa, most of these trypanocidal drugs are gradually losing their efficacy due to resistance, but trypanosomes are usually not resistant to two of the drugs (DIM and ISMM) at the same time. Thus, these two compounds have been termed as sanative pair since in instances of resistance

to one drug, application of the other will control the disease (Machila *et al*., 2015). However, experimental studies conducted by Kazibwe *et al*. (2009) in Uganda, Sow *et al*. (2012) in Burkina Faso and Dagnachew *et al*. (2015) in Ethiopia showed the occurrence of resistance in trypanosomes for both DIM and ISMM which suggested that the concept of sanative pairs might no longer always be valid. Therefore, the objective of this review article is to provide highlight on African animal trypanosomosis and the problem of trypanocidal drug resistance in Africa.

2. African animal trypanosmosis

2.1 Morphology and Taxonomy

Trypanosomes are unicellular flagellated protozoal parasites that live in blood, plasma, lymph and several tissue fluids of their vertebrate hosts and characterized by one nucleus and one flagellum, either free or attached to the parasite's body by means of an undulating membrane as shown in the Figure 1. They also contain a small compact kinetoplast, a disc-shaped DNA-containing organelle, situated within a large mitochondrion (OIE, 2013; Brun *et al*., 2017). Kinetoplast DNA is arranged into a network of linked circles grouped into 20,000 minicircles and 20-50 maxicircles.

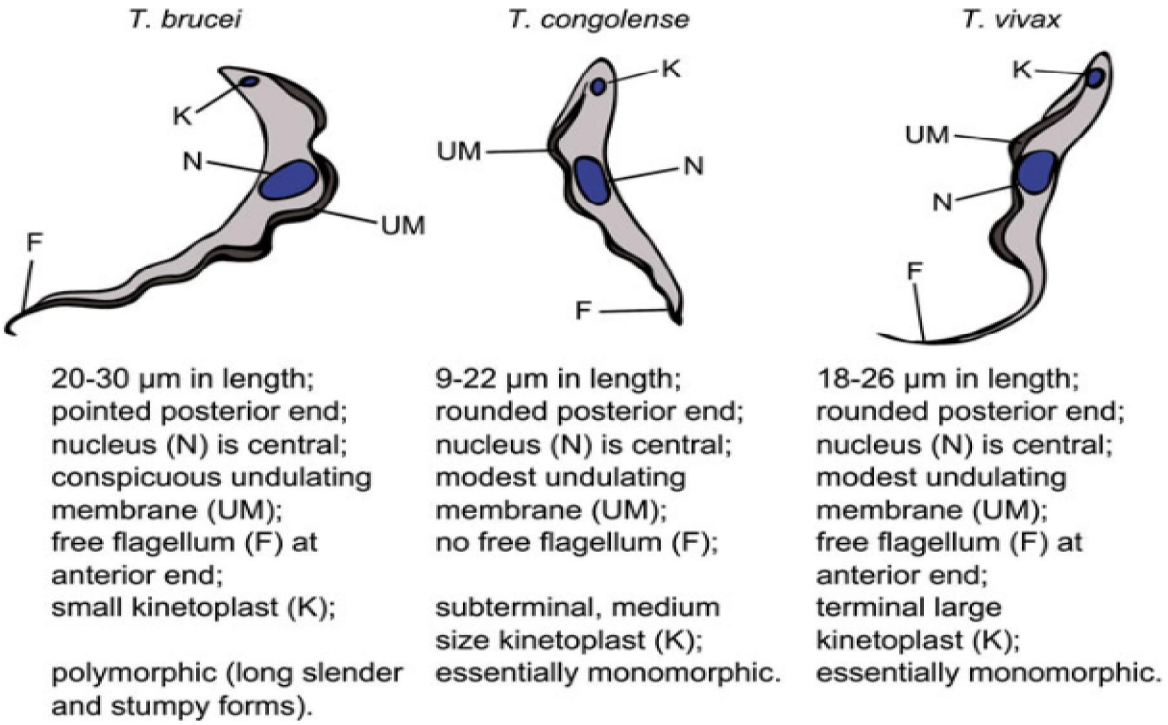

Figure 1: Morphological characteristics of blood stream form of trypanosomes
Source: (Giordani *et al*., 2016)

All trypanosomes are heteroxenous which means that they require more than one host to complete their life cycle. There are numerous different trypanosomes and the effect of their infection varies greatly based on spp. There are some spp that hardly seem to be virulent at all, as for instance *T. theileri,* where its effect can only be seen if the host is already sick. Other spp are highly virulent and cause severe diseases in their mammalian hosts (Stein *et al*., 2011).

Species of trypanosome infecting mammals fall into two distinct groups and, hence, have been divided into two sections: (i) the Stercoraria (subgenera *Schizotrypanum*, *Megatrypanum* and *Herpetosoma*), in which trypanosomes are typically produced in the hindgut of the vector and infective meta-trypanosomes can be found in the feces of the insect and are then passed on by contaminative transmission and (ii) the Salivaria, subgenera Nannomonas (*T. congolense*), Duttonella (*T. vivax*), Trypanozoon (*T. brucei*), and Pycnomonas (*T. suis*), complete their cyclical development in the anterior station of the vector and infective stages are transmitted to the mammalian host through the bite of an infected fly and/or inoculative; characteristically, salivarian spp, by virtue of their variant surface glycoprotein (VSG) genes, are the only trypanosomes that exhibit antigenic variation (Gibson *et al*., 2009; OIE, 2013).

Trypanosomes are grouped under phylum protozoa, subphylum sarcomastigophora, class zoomastigophorea, order kinetoplastida, suborder trypanostomatina, family trypanosomatidae and the genus *Trypanosoma* (OIE, 2013; Levine *et al*., 2017).

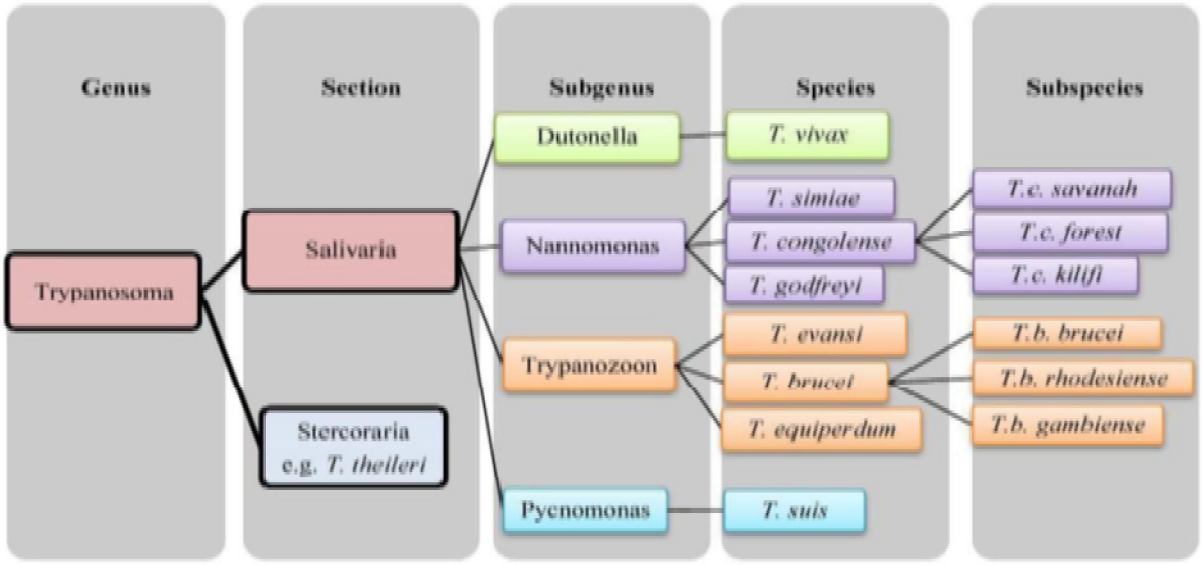

Figure 2. Schematic representation of the taxonomy of trypanosomes
Source: (Gibson *et al*., 2009)

2.2 Epidemiology

2.2.1 Distribution

African animal trypanosomosis also called Nagana, from the Zulu word 'N'gana' which means 'powerless/useless' (Steverding, 2008), is caused by three spp of trypanosomes namely *T. congolense, T. vivax* and to a lesser extent, *T. brucei*. The disease is widespread in SSA where it is cyclically transmitted by the bite of *Glossina* (Barrett *et al*., 2003). In animals, *Glossina* spp can also transmit trypanosomes mechanically when they begin a blood meal on an infected host and end it on another one, given that the time between the two meals is short enough to ensure survival of parasites in the insect mouthparts (Moloo *et al*., 2000).

Unlike other trypanosome spp, *T. vivax* does not multiply in the midgut of *Glossina* spp, but remains confined to the insect proboscis, where it completes its short life cycle. This is the reason why this spp can also be transmitted mechanically by other haematophagous flies such as horse flies (*Tabanus* spp) and stable flies (*Stomoxys* spp). Mechanical transmission has allowed *T. vivax* to spread far beyond the limits of the African tsetse belt (Osorio *et al*., 2008; OIE, 2013). Even though *T. vivax* remains enzootic in Latin America primarily due to mechanical transmission, other potential modes of transmission include perinatal and iatrogenic routes (Osorio *et al*., 2008).

Tsetse transmitted AAT is found between latitude 15°N and 29°S covering across over 37 countries mostly in Africa, from the southern edge of the Sahara desert to Zimbabwe, Angola and Mozambique. It constrains livestock production in over 37 SSA countries (Franco *et al*., 2014). It is the most economically important livestock disease in Africa especially of cattle (OIE, 2013).

Table 1: Summary on prevalence of bovine trypanosomosis in some African countries

Authors (year)	Country	Sample size	No positive	Prevalence (%)
Mattioli *et al*., 2001	Gambia	199	6	3
Abenga *et al*., 2004	Nigeria	526	48	9.1
Ohaga *et al*., 2007	Kenya	879	160	18
Jing *et al*., 2009	Uganda	1841	60	3.3
Sara, 2013	Sudan	271	13	4.8
Mekonnen *et al*., 2017	Ethiopia	384	33	8.6

There are currently 31 recognized spp and subspecies of tsetse and they are divided into three different subgroups; the savannah woodlands (subgenus *Morsitans*), riverine type (subgenus *Palpalis)* and dense-forest group (subgenus *Fusca*) (Vale *et al*., 2015). Diagrams representing cyclical and mechanical vectors of trypanosomes are indicated in Figure 3.

Tsetse flies are living for many years in proximity of wildlife constituting the sylvatic

trypanosomosis transmission cycle. Nowadays, the importance of livestock as a source of food for *Glossina* spp is increasing as a consequence of human encroachment (deforestation for cultivation) and the reduction in wildlife spp (Van den bossche *et al*., 2011). These drastic changes in their habitats and hosts availability have resulted either in their elimination or in many cases in their adaptations to those new conditions. The use of specific microclimatic niches (Takeet *et al*., 2013) and their opportunistic feeding behavior regarding the choice of the host made this adaptation possible (Kroubi *et al*., 2011).

Of the three groups of tsetse, the savannah woodland and riverine types are the most important since they inhabit areas suitable for grazing and watering of cattle (Vale *et al*., 2015). Although, the infection rate of *Glossina* spp with trypanosomes is usually low, ranging from 1-20% of the flies, each is infected for life and their presence in any number makes the rearing of cattle extremely difficult (Urquhart *et al*., 2007). When dealing with tsetse-transmitted trypanosomosis, much depends on the distribution and the capacity of the vectors, *Glossina* spp responsible for biological transmission of the disease to susceptible hosts. Considering the cyclical transmission of the parasites, diversity of tsetse habitats considerably affects the interactions among vectors (*Glossian* spp), hosts (livestock and/or wildlife) and parasites or levels of virulence (Van den bossche *et al*., 2011). For the savannah spp, the disease is widespread due to the large dispersion of these flies. For the riverine spp, the areas of contacts with hosts are limited. In this case, the risk of infection does not only depend on the density of the flies but also on the intensity of time-space interfaces between *Glossina* spp and livestock (Dale and Maudlin, 1999).

2.2.2 Mode of transmission

Most trypanosomes must develop for one to a few weeks in *Glossina* spp, which act as biological vectors before transmitted to susceptible hosts. Tsetse fly get the infection when feeding on an infected animal; after implementation of the parasitic life cycle in the fly (15-21 days), they become infective and may remain infective for the rest of their life. Transmission occurs in the early stage of blood feeding, when the fly inject some saliva before sucking the blood of its host (OIE, 2013).

Trypanosomes can also spread by fomites (needles, syringes and surgical instruments) and mechanical vectors (*Tabanus* and *Stomoxys* spp). *Trypanosoma vivax,* outside tsetse infested areas like in South America, does not require tsetse to develop; it is carried by other hematophagous flies where transmission is non-cyclical. Thus, the parasites are mechanically transmitted across vertebrate hosts, with no growth or multiplication in the insects. In this case, the fly feeds on more than one animal before repletion and remains infective for only a short time (Osorio *et al*., 2008; CFSPH, 2009). For *T. brucei* per-orale transmission can even occur after birth, when contaminated blood or other fluids are ingested by calf. Furthermore, the immune response is unable to completely eliminate trypanosomes, and animals can become in apparent carriers. These in apparent infections can be re-activated if the animal is stressed. Trans-placental transmission can also occur (CFSPH, 2009; OIE, 2013).

2.2.3 Risk factors

The epidemiology of AAT depends on three factors which include the distribution of vector, the virulence of the parasite and the response of the host (trypano-sensetivity). These factors are modulated by environmental changes that can substantially affect their dynamics and consequently influence transmission patterns of the disease. Anthropogenic environmental changes, such as increased human pressure and the simultaneous demand for arable land result in deforestation and loss of suitable habitats for tsetse spp and their hosts (Lanteri *et al*., 2008).

Host risk factor: Trypanosomes can infect all domesticated animals; clinical cases have been described in cattle, water buffalo, sheep, goats, camels, horses, donkeys, alpacas, llamas, pigs, dogs, cats and other spp of animals. In parts of Africa, cattle are the main spp affected due to the feeding preferences of *Glossina* spp. More than 30 spp of wildlife including ruminants such as white-tailed deer, duikers, antelope and African buffalo, wild equidae, lions, leopards, warthogs, capybaras, elephants, non-human primates and various rodents are also known to be susceptible to infection (CFSPH, 2009).

However, the effect of infection varies with the host in that in most wild animals, such as warthogs, bushbucks, kudus or buffalos, trypanosomes become established but do not produce the disease. This is because these animals and the parasites have evolved for many years resulting in a balanced host/parasite relationship. In domestic animals the relationship with the parasites has not fully developed leading to development of the disease (Namangala, 2011). Among the domesticated animals, humpless cattle such as N'dama of West Africa (*Bos taurus*) were the first to be introduced into northern and western Africa from about 4,500 BC, and hence they are adapted to tsetse-transmitted trypanosomes and are thus trypanotolerant (Murray *et al.,* 1998).

Trypanotolerance, the ability of some spp and breeds of livestock to survive, reproduce and remain productive under trypanosomosis risk with minimal trypanocidal drug treatment was recognized and exploited by farmers long before research on

trypanotolerance began (d'Ieteren, 2001). In cattle, trypanotolerance has been referred to as the capacity of an animal to control severe anemia development which is assumed to be independent of parasitemia levels (Berthier *et al*., 2016). N'Dama cattle acquire significant control of *T. vivax* infection, but apparently not against *T. congolense* (Trail *et al*., 1994). Due to the uncertain genetic make-up of animals within these so called trypanotolerant breeds, the level of tolerance may also vary between individual animals within a breed and it can be overcome by heavy *Glossina* challenge, malnutrition, or other stress factors (pregnancy, lactation, draught power, effect of other infections and diseases) (Murray *et al*., 1982). Some indigenous breeds of small ruminants, notably the West African dwarf sheep and goats and the East African goats also exhibit some degree of trypanotolerance (Murray *et al*., 1982).

Pathogen risk factor: All of the important livestock trypanosomes evade the host immune defenses by continuously changing their surface coat which is biologically active substances called VSG (Horn, 2014), one of the immune-evading mechanisms that essentially preclude the development of conventional vaccines (La Greca and Magez, 2011). During early stage of infection, trypanosomes release factors which alone or in concert with saliva components can impair the activation of the hosts' immune response to generate a privileged micro-environment to allow the establishment of infection (Stijleman *et al*., 2016).

The parasite's virulence, immunogenicity and response to chemotherapeutics are also important factors in the epidemiology of animal trypanosomosis as trypanosome spp occur in a remarkable variety of genotypes. Since parasitaemic animals commonly survive for prolonged periods, there are ample opportunities for fly transmission, especially for *T. congolense* and *T. brucei*. In contrast, some strains of *T. vivax* in West Africa are rapidly fatal when compared to those of East and Central Africa which kill their hosts within 1-2 weeks, so that the chances of fly infection are more limited (Urquhart *et al*., 2007) while *T. congolense* induces a more chronic disease in West Africa compared to East and Central Africa, except in the vicinity of protected game reserves (Delespaux *et al*., 2008).

Moreover, within the *T. congolense* group, the three subgroups *i.e*. savannah, kilifi and forest (Hide and Tait, 2004), that show important differences in virulence, the savannah subgroup strains are the most virulent and capable of causing severe anemia and even death of infected cattle (Auty *et al*., 2015). Even within *T. congolense* savannah subgroup, substantial differences in virulence are observed between strains (Masumu *et al*., 2006) and between transmission cycles, with significantly higher virulent strains in the sylvatic transmission cycle. These differences in virulence associated with the level of tolerance of the livestock determine the level of endemicity of the disease in a particular area (Van den bossche *et al*., 2011).

Trypanosoma brucei has a comparable host range and spatial distribution (Duffy *et al*., 2013). However, the prevalence and severity of clinical *T. congolense* infections in cattle have been reported to be higher than that of *T. brucei* (Majekodunmi *et al.,* 2013). These differences might be attributed to host's innate susceptibility modulated by the level of activity of its immune system, intrinsic differences in trypanosome virulence and the vectorial capacity of tsetse for respective parasites, food availability and co-infections, *etc* (Van den bossche *et al*., 2011; Gitonga *et al*., 2017).

Environmental risk factor: Since trypanosomosis interventions, environmental changes and encroachment of people have been an ongoing process, interactions between the host, parasite and vector would be influenced (Van den Bossche *et al.*, 2010). Agricultural and industrial developments generally lead to a lowering of tsetse density by destroying its habitat, whereas the establishment of game or forest reserves provides a large number of preferred hosts or a suitable habitat for *Glossina* spp, respectively. Herds located near such reserves are therefore at a higher risk (Moore and Messina, 2010).

The density of tsetse population in the area and the level of their contact with the host will determine the level of infection. This is further influenced by the vectorial capacity of the fly and the availability of its preferred host, which may not be livestock. Trekking of cattle through tsetse-infested vegetation is a risk nomadic farmer face from time to time and the risk is even greater where cattle routes converge, for instance, is at major bridges or watering holes (NTTICC, 2004). Furthermore, the vector for trypanosomosis, tsetse spp, requires a habitat that is strongly influenced by ecological and climatic features particularly rainfall, soil and vegetation type and temperature. Fly larvae can die as a result of drying soils. Temperature extremes, particularly above 36°C and below 10°C also lead to adult fly mortality through starvation and water loss via respiration. Moisture levels directly related to precipitation is also involved in fly mortality, even though the exact mechanism is not clear (Moore and Messina, 2010).

Cumulative effects of long rainy season or dry season are thought to be important in influencing advances and recession in tsetse population. The effect of altitude on tsetse distribution is through its effect on climate, mainly temperature. As temperature fall with increasing altitude, the geographic limitations of

different spp of tsetse may be due to their inactivity in lower temperature. Different spp of tsetse require particular vegetation type that would provide an optimal condition for growth and survival and vegetation is also important in that it provides shelter for their hosts; all environmental factors that affect tsetse spp indirectly affect the occurrence of trypanosomosis (Leak, 1999).

2.3 Diagnostic Approaches

Diagnosis of trypanosomosis in domestic livestock and Glossina spp is a basic requirement for epidemiological studies as well as for planning and implementing chemotherapy and for monitoring vector control operations. Accurate diagnosis of trypanosomosis in livestock is required for a proper appreciation of the epidemiology of the disease in any geographical locality. Besides clinical diagnosis, direct (parasitological), indirect (serological), animal inoculation and molecular diagnostic methods with varying degrees of sensitivity and specificity are available for diagnosis of the disease (IAEA, 2007).

2.3.1 Parasitological diagnosis

Parasitological diagnosis is the direct demonstration of the parasite in blood or less frequently in other body fluids using a microscope. The scarcity of the parasites and fluctuating nature of the parasitaemia limit the use of laboratory tests based on demonstration of trypanosomes in accessible body tissues such as the peripheral blood (Doyle, 2009). Hence, several techniques for the concentration of blood have been developed that increase the chance of trypanosomes detection.

Wet blood films: Through this parasitological diagnosis, the actively motile organisms of trypamastigote stage of trypanosomes are readily detected by the agitation they produce among the erythrocytes (Paris *et al.,* 1982). This method of diagnosis is simple, inexpensive and gives an immediate result, which if trypanosomes are found; the disease is diagnosed on the spot (OIE, 2008). Although, wet blood film diagnostic method has the above mentioned advantages, there are different drawbacks that include: unless the animal are brought to veterinary center or the blood (with an anticoagulant) can be taken quickly to the center, a field microscope has to be taken to the herd as the parasite loses their mobility after a limited time. It has also limited sensitivity and the spp of trypanosomes cannot be identified (*T. vivax* can often be strongly suspected if the parasites move quickly forward through the microscopic filed). The sensitivity of the method generally depends on the examiner's experience and the level of parasitaemia (OIE, 2008).

Thick blood film: This is made by placing a drop of 5-10µl blood on a clean microscope slide and the thickness of the resultant film should be such that, when dry, the figures on a wristwatch dial can just be read through it (IAEA, 2007). The smear should be kept dry and protected from dust, heat, flies and other insects. It is stained for 30 minutes with 4% diluted Giemsa stain in phosphate buffered saline of pH 7.2. Staining time and stain dilution may vary with stain and individual technique (OIE, 2013). This diagnostic method is simple and inexpensive, the trypanosomes are easily recognized by their general morphology and field microscope is not needed as the blood films are taken back to the center for processing and examination at ease. It is sometimes possible to indentify trypanosome spp seen. However, the shortcoming of this technique is that an immediate diagnosis of trypanosomes on the spot is not possible and the sensitivity of the method remains limited (OIE, 2013).

Thin blood smear: In this diagnostic method, the prepared blood smears are fixed by methanol and stained with Giemsa, or with one of the more recent test stains such as Diff-Quik, field's stain, which have the advantage of acting much faster than Giemsa. They are examined under a light microscope using x100 oil immersion objective lens, for identification of trypanosomes (Murray *et al.,* 2003).

Buffy coat technique: In mild clinical or sub clinical cases with low parasitaemia in which it is difficult to demonstrate the parasites, concentration methods become necessary. Blood is collected (70 µl) into heparinized microhaematocrit capillary tubes (75 x 1.5 mm), which are then sealed at the dry end and centrifuged for 5 minutes at 12,000 rpm. After centrifugation, trypanosomes were usually found in or just above the buffy coat layer. Then the capillary tube was cut using a diamond tipped pen 1 mm below the buffy coat to include the upper most layers of the red blood cells and 3 mm above to include the plasma. The content of the capillary tube was expressed on to a glass slide, covered with cover slip, and examined under x40 objective and x10 eye piece for movement of trypanosome spp (Murray *et al*., 1988). Trypanosome spp were identified according to their morphological descriptions as well as movement in wet film preparations (OIE, 2008).

2.3.2 Serological tests

Several antibody detection techniques have been developed to detect specific trypanosomal antibodies for the diagnosis of animal trypanosomosis, with variable sensitivity and specificity (Bengaly *et al*, 2002). The tests detect specific antibodies (which are blood proteins belonging to the immunoglobulins), developed by the host against the infection and/or to demonstrate the occurrence of circulating parasitic antigens in the blood by the use of characterized specific antibodies. The detection of antibodies indicates as there has been infection, but as antibodies

persist for sometimes (weeks or months) after all trypanosomes have disappeared from the organism (either by drug treatment or self-cure) a positive result is no proof of active infection. On the other hand, circulating trypanosomal antigens are eliminated quickly after the disappearance of the parasites and their presence therefore shows almost always that live trypanosomes are present in the animal (Uilenberg and Boyt, 1998).

2.3.3 Molecular tests

New tools developed by molecular biologists now make it possible to characterize trypanosomes both in the vectors and hosts. The use of molecular biological tools, in particular, the polymerase chain reaction (PCR), introduced an exceptional sensitivity and especially the possibility of characterization at the specific or infra-specific level. This was impossible previously (IAEA, 2007). The principle of molecular tests (DNA probes, PCR) is the demonstration of the occurrence of sequences of nucleotide which are specific for a trypanosome subgenus, spp or even types of strain. Nucleotides are the constituents of deoxyribonucleic acid (DNA) the molecules which constitutes the genes on chromosomes in the cell nucleus. A positive result indicates active infection with the trypanosomes for which the sequences are specific, as parasite DNA will not persist for long in the host after all live parasites have been eliminated. These tests are not only suitable for detecting parasites in the mammalian host, but also in the insect vector (Solano *et al.,* 2000).

2.4 Prevention and Control

All of the important livestock trypanosomes evade the host immune defenses by continuously changing their surface coat (Horn, 2014), one of the immune-evading mechanisms that essentially preclude the development of conventional vaccines (La Greca and Magez, 2011). Therefore, control of *Glossina*-transmitted animal trypanosomosis relies primarily on the use of insecticides or targets to control the vector and on the use of trypanocidal drugs to control the parasites (Holmes, 2013).

Since vector control can be expensive when used on a large scale and is not always sustainable or effective, administration of trypanocidal drugs represents the main intervention tool in most poor *rural* endemic areas, ensuring maximum effects at relatively low cost (Van den Bossche and Delespaux, 2011). The cost-effectiveness of this practice was shown both in Africa (Shaw *et al*., 2015) and elsewhere in the world (Seidl *et al*., 1999). Control of parasites with chemotherapeutic and chemoprophylactic agents has double effect; limit the losses caused by the infection and eliminate the transmissible trypanosomes reservoir (Welburn *et al*., 2015).

2.4.1 Vector control

As *Glossina* spp are sensitive to insecticides and no resistance has been developed, considerable successes were achieved in some countries. However, spraying insecticides is costly and harmful to the environment. These harmful effects are considerably reduced if the insecticides, for example, synthetic pyrethroids are applied directly on the animal in the form of spray or pour on formulation. Other effective methods involve targets impregnated with insecticides and traps that attract and catch flies. These are simple and cheap and can be constructed and maintained by local communities. Moreover, they do not pollute the environment and suitable for both small and large scale fanning (Boulange *et al*., 2002).

Another method for the control of vector is the sterile male technique. Since the female *Glossina* only mates once in a life time, this technique is theoretically able to eradicate a targeted *Glossina* spp in areas where other control methods have been used to reduce its density, but it is expensive. Furthermore, good husbandry of animals at risk and avoiding contact with *Glossina* spp also contributes much on control of the disease (OIE, 2013).

2.4.2 Host resistance and protection

Trypano-tolerant animals are being used to establish ranches in areas where *Glossina* challenge is not too heavy, but they have not been readily accepted in some countries, supposedly because they are smaller in size and they produce less milk than other indigenous breeds and crosses with exotic breeds (Radostitis *et al*., 2006). Cattle breeds, such as N`Dama and the West African shorthorn, have been in West Africa for centuries and have developed innate resistance to trypanosomes. They are infested by *Glossina* spp but do not show clinical disease (OIE, 2013).

2.4.3 Chemotherapy and chemoprophylaxis

Drugs such as ISMM and Quinapyramine sulphate or chloride can be used as prophylactic drugs during transhumance or high seasonal parasitic pressure. Diminazene aceturate and Quinapyramine methyl sulfate are drugs which can be used as curative and sanative (OIE, 2013). But, a very widely used chemotherapeutic drug is DIM, which is effective against all of the three AAT. However, chemo resistance may occur and care must be taken due to the presence of fake drugs on some markets (OIE, 2013).

Some of the documented *Glossina* and trypanosomosis control operations implemented in Ethiopia since 1980 include control measures in upper Didessa valley (4,500 km^2) by NTTICC from 1986-1989 using insecticide treated traps and targets (Regassa and Abebe, 2009) and southern Rift valley (25,000 km^2) by PATTEC using insecticide treated

traps and targets, treating cattle with insecticide, trypanocidal drugs, sequential aerial spraying, sterile insect technique, and ground spraying methods (Messele *et al*., 2012).

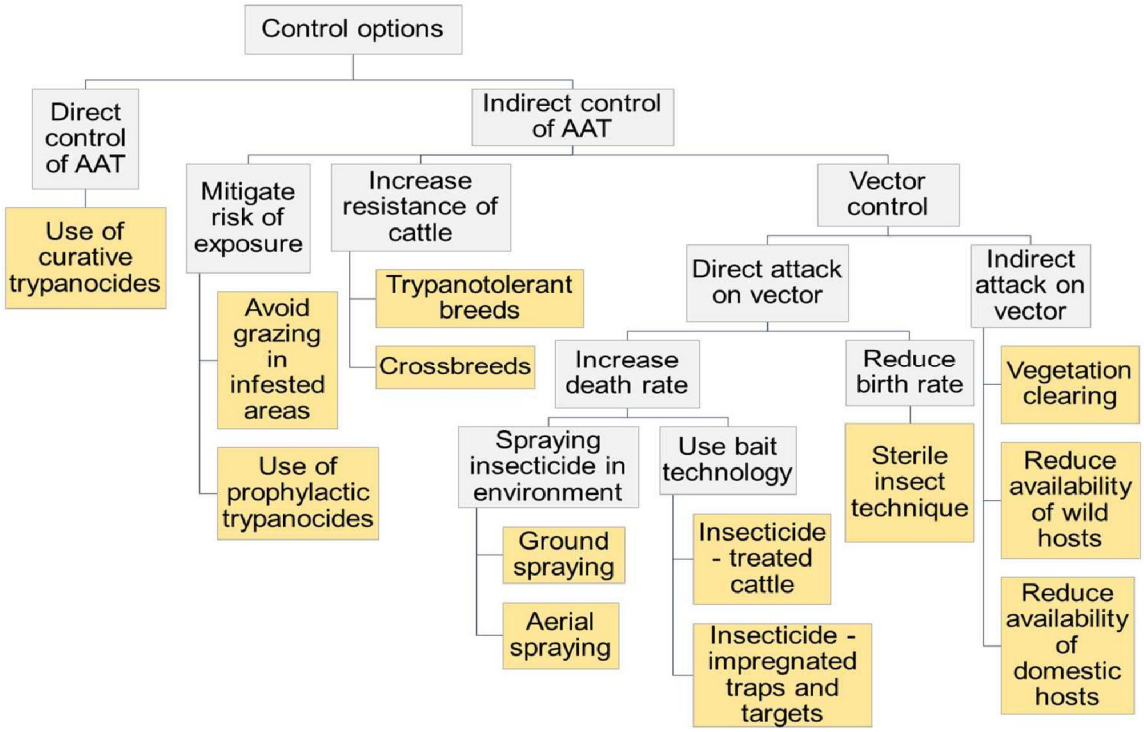

Figure 3: Summary diagram of the techniques available to control tsetse and African animal trypanosomosis
Source: (Meyer *et al*., 2016)

2.5 Drug Resistance

Infection of animals by one or more of the three most important spp of trypanosomes (*T. congolense*, *T. vivax* and *T. brucei*) results in subacute, acute or chronic diseases. The cardinal clinical sign observed in AAT is anemia, within a week of infection with *T. congolense* and *T. vivax*. Moreover, there is a pronounced decrease in PCV, hemoglobin and red blood cell count. These manifestations are observed in goats experimentally infected with *T. vivax* (Osman *et al*., 2012).

Chemotherapy and chemoprophylaxis are the major means of combating the disease. The compounds in common use for chemotherapy or chemoprophylaxis of animal trypanosomosis are DIM derivatives, suramin, quinapyramine, homidium, ISMM and pyrithidium (Mira *et al*., 1989). However, effectiveness of these drugs is limited by a factor such as parasite resistance (Melaku and Birrasa, 2013). The emergence of drug resistant trypanosome strains is considered as a serious problem in trypanosomosis control, particularly for the resource poor farmers in Africa (Kagira and Maina, 2007).

Drug resistance can be defined as the heritable loss of sensitivity of a microorganism to a drug to which it was sensitive (Sinyangwe *et al*., 2004). When trypanocides do not produce an expected cure or protection; there is a tendency to assume that drug resistance has arisen. Whilst this may be true, there are many other reasons which contribute to drug treatment failure. Only after carefully investigating the practical points of drug administration and eliminating other causes of failure, is it valid to investigate the likelihood of there being true drug resistance (Leach and Roberts, 1981).

The problem of drug resistance in animal trypanosomosis is highly spreading geographically to many regions where the disease occurs (Grace *et al*., 2009). Decades after the first case of drug resistance in trypanosomes, Clausen *et al*. (1992) confirmed multiple drugs resistant trypanosome isolates in the pastoral area of Burkina Faso. Moreover, resistance developed by trypanosomes to trypanocidal drugs has been reported from East Africa (Mulugeta *et al*., 1997).

There is a report on a five-fold increase in the prevalence of DIM resistance over a seven year period in the eastern province of Zambia, suggesting that, there might be a worsening of the problem. Trypanocidal drug resistance has been officially reported in 17 African countries (Burkina Faso, Chad, Ivory coast, Ethiopia, Kenya, Mali, Somalia, Sudan,

Tanzania, Uganda, Zimbabwe, Zambia, Mozambique, Cameroon, Nigeria, Guinea, and Central African Republic) (Delespaux *et al*., 2008). But recently, this number is increased to 21 African countries (Biniam Tsegaye *et al*., 2015).

Table 2. Trypanocidal drug resistance in some African countries

Country	Trypanosmes spp	Resistance to	References
Zambia	Tc	ID	Chitanga *et al*. (2011)
Mali	Tv/Tc	I/ID	Mungube *et al*. (2012)
Burkina Faso	Tv	ID	Sow *et al*. (2012)
Mozambique	Tc	ID	Jamal *et al*. (2005)
Uganda	Tb	ID	Kazibwe *et al*. (2009)
Zimbabwe	Tc	D	Joshua *et al*. (1995)
Kenya	Tc	I	Gray *et al*. (1993)
Ethiopia	Tc	ID	Ashenafi *et al*. (2014)
	Tv	ID	Dagnachew *et al*. (2015)

Tc = *T. congolense*, Tb = *T. brucei*, Tv = *T. vivax*, I= isometamidium; D: diminazene; ID: both isometamidium & diminazene

A report from Ethiopia has demonstrated the value of a field appraisal to determine the efficacy of trypanocidal drugs in an area where trypanocide failure occurred (Rowlands *et al*., 2008). Resistance seems to develop in a stepwise manner with trypanosomes resistant to a low dose of trypanocide being removed by a higher dose of the same compound (Connor, 2013). Nowdays, the most commonly used trypanocidal drugs for *T. congolense* and *T.vivax* infection in Ethiopia are ISMM and DIM. The current situation on the phenomenon of trypanocidal resistance particularly against *T. congolense* infection is well documented in the Ghibe valley (Yohannes, 2014).

3. Conclusion

Tsetse transmitted animal trypanosomosis is the main constraint of livestock production in parts of Africa, particularly in Sub-Saharan Africa resulting in a serious economic losses posing a significant impact on the development of the countries *T. congolense, T.vivax,* and *T.b.brucei* are responsible for tsetse transmitted animal trypanosomosis. The disease is found distributed in tsetse infested parts of Africa, although the distribution and abundance of tsetse flies and trypanosomes are affected by spatial factors such as altitude, river drainage system, temperature, local factors at peasant association level (presence of game reserves). Hence, designing and implementing prevention and control strategies of tsetse transmitted animal trypanosomosis focusing on vectors and against the parasites should be undertaken.

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