1. Introduction

Trypanosomosis in domestic livestock causes a significant negative impact in food production and economic growth in many parts of the Africa, particularly in Sub-Saharan Africa. It has greatly hampered people and animals settlement in a considerable part of the Africa. It occurs in Africa cover one third of the continent is arguably the most significant disease (Shiferaw et al., 2015). The distribution of the disease is influenced by the existing tsetse and biting flies. Tsetse transmitted trypanosomosis is encountered in many part of Ethiopia. Trypanocidal drugs remain the principal method of trypanosomiasis control in the country. An increasing number of reports of resistance to commonly used anti-trypanosomal drugs, indicate their future utility to be in danger. Therefore the purpose of this seminar paper is to review on anti-trypanosomal drugs and its resistance. Commonly used Anti-trypanosomal drug future effectiveness may severely reduce by widespread drug resistance. Because it is very unlikely that new anti-trypanosomal drugs will be released on to the market in the future, it is essential to maintain the efficacy of currently available drugs. So, proper detection method of drug resistance by in vivo and invitro methods is very important. Resistance to one or more of the common trypanocidal drugs used in cattle has been reported in at least four regional states in Ethiopia. Exposure of parasites to sub therapeutic drug concentrations, resulting from under dosing and uncontrolled use of trypanocidal drugs, and the lack of proper diagnosis, are considered the major causes of increasing drug resistance in Ethiopia. Avoidance of under dose, use of national drug policy and allowing integrated control measure to reduce number of drug treatments when resistance detected will be strongly recommended.

Trypanosomosis is one of the major protozoans and neglected tropical disease that impediments to agriculture and livestock production in Africa. Even though the rapid human population increase and urbanization in sub-Saharan Africa are believed to increase the demand for livestock products. This disease negatively affects the overall development in agriculture in general and to the food self-reliance efforts of the nation in particular. Pathogenic animal trypanosomes affecting livestock have represented a major constraint to agricultural development in Africa for centuries, and their negative economic impact is increasing in South America and Asia. Chemotherapy and chemoprophylaxis represent the main means of control. Trypanosomosis is major constraint to livestock production in sub-Saharan Africa. The economic importance of this disease is expressed by reducing fertility, decreasing young growth, affect milk yields, poor quality carcass, reducing stamina and working power of animals which ended with the death of animals usually (Lelisa, 2015).

As a result of tsetse flies infest a large area of the continent including the arable and fertile land of Africa, its prevalence increases from time that supported by resistance to trypanocidal drugs (Anene,2000). Even though there are several technologies exist for the control of trypanosomosis and tsetse flies, it is very difficult to be applied; because of economic problem as these technologies are so expensive to use and usually biologically unfriend to the environment. Although the use of trypanocidal drugs is the main method for its control, it is threatened by increasing cases of drug resistance (Geerts, 2001).

Trypanosomosis is neglected tropical disease that is the most important constraint to agricultural activities and animal production in Ethiopia. Among regions with it, Benshangul Gumuz is the most infected region by this disease (Mulatu, 2016). The economic importance of this disease is expressed by reducing fertility, decreasing young growth, affect milk yields, poor quality carcass, reducing stamina and working power of animals which ended with the death of animals usually (Lelisa, 2015). The effectiveness of trypanocidal drugs and the speed with which trypanocidal resistance develops and the type of resistance (single or multiple) depend on a multi-factorial process driven by the drug use practices, the quality of the drugs on the local market, the ability to detect resistance and the availability of strategies to minimize and control resistance at the smallholder level (Afework et al., 2000 and Motie et al., 2012).

Chemotherapy and chemoprophylaxis represent the mainstay of animal trypanosomiasis control, ensuring animal health and
production in enzootic countries. However, the available veterinary trypanocides are inadequate and outdated. Only six compounds are currently licensed, and their narrow therapeutic indices restrict their use, especially when even low-level resistance arises. By far, the most useful of these compounds, diminazene aceturate and isometamidium chloride, have been applied against animal trypanosomiasis in Africa (Holmes et al., 2004), with suramin also being relatively widely used to treat Trypanosoma evansi infections. Worryingly, an increasing number of reports of resistance to this family of effective chemicals, particularly diminazene and isometamidium, indicate their future utility to be in jeopardy (Delespaux and de Koning, 2007). Therefore, the objectives of this seminar paper is To review on anti-trypanosomal drugs and its resistance To highlight the status of anti-trypanosomal drugs resistance in Ethiopia

2. ANTI-TRYPANOSOMIAL DRUGS AND RESISTANCE

2.1. General Overview of Anti-Trypanosomal Drugs and its Mechanism of Action

The discovery of trypanocidal drugs with preventive action raised high hopes that their use would make it possible to run sub-tropical African into flourishing livestock production area. Although, these drugs do provide protection, all of them frequently give rise to the formation of drug resistant trypanosome strains. This drug resistance occurs, when the trypanosomes are in contact with a trypanocidal administered in a sub curative dose insufficient to ensure the destruction of the parasites (Das et al., 2004).

2.1.1. Prophylactic anti-trypanosomal drugs

Prophylactic treatments target all animals in a herd or a particular group of valuable or at risk' animals (Holmes et al., 2004). Isometamidium has a prophylactic properties and, since its launch in the 1960s, it has remained the only drug available for chemoprophylaxis of AAAT when quinapiramine was discontinued due to problems linked to toxicity and, particularly, the induction of multi-drug resistance (Peregrine, 1994; Geerts and Holmes, 1998).

Isometamidium (ISM) administered intramuscularly (IM) at a dose rate of 0.5-1mg/kg body weight is used as a curative and prophylactic drug up to six months of protection in cattle against T. vivax and T. congolense (Delespaux et al., 2010) as well as T. brucei in equidae and T. evansi in camels (Geerts et al., 2001), but this period may be shorter (two to four months) when challenge is given. (Das et al., 2004 and Sow, 2013).

Moreover, studies have shown that ISM can kill the trypanosomes developing in tsetse flies (Van den Bossche et al., 2006). During SIT campaigns, the incorporation of ISM in the first blood meal of sterile males will significantly reduce the ability of the released males to transmit trypanosomes (Bouyer et al., 2010). ISM, therefore, is less clear (Wilkes et al., 1997). Decreased levels of drug accumulation have been observed in drug-resistant populations of T. congolense (Sutherland et al., 1991), and later work found indirect evidence of an increased eflux of drug from resistant trypanosomes (Sutherland and Holmes, 2004).

2.1.2. Curative anti-trypanosomal drugs

Curative drugs aim to eliminate parasites from a sick animal. A drug could be regarded “curative” when the dose used is able to eliminate all parasites. The most widely used curative trypanocide against surra is diminazene aceturate. However, other drugs can be used, such as isometamidium chloride (both curative and preventive), cymelarsan (so far only recommended for curative treatment of camels), suramin, and quinapyramine (curative and/or preventive) (M.L. Dia and M. 2004).

Diminazene: is today the most commonly used trypanocide in cattle, sheep and goats, due to its activity against both T. congolense and T. vivax and its relatively low toxic side effects. (Reid, 2002). It is only as a curative agent and is not used for prophylaxis, as it is rapidly metabolized and excreted (Peregrine and Mamman, 1993).

It is administered IM at a dose rate of 3.5 mg/kg body weight. At these dose rates, DA, in addition to its curative uses, also offers short term protection of up to 2 weeks (Geerts et al., 2001). It was introduced for the treatment of babesiosis and African trypanosomiasis in livestock in 1955. It belongs to the diamidine class of compounds, a member of which (pentamidine) has also been used for HAT since the 1930s (Steverding, 2010).

The trypanocidal mode of action of diminazene has not been completely clarified. The compound binds the minor groove of the DNA at AT-rich sites (Wilson et al., 2008). In trypanosomes, the kDNA is a known target of the drug, and kDNA binding can cause inhibition of replication and kDNA loss (Shapiro and Englund, 1990). It is a known target of the drug and kDNA binding can cause inhibition of replication and kDNA loss (Shapiro and Englund, 1990). Diminazene: is today the most commonly used trypanocide in cattle, sheep and goats, due to its activity against both T. congolense and T. vivax and its relatively low toxic side effects. (Reid, 2002). It is only as a curative agent and is not used for prophylaxis, as it is rapidly metabolized and excreted (Peregrine and Mamman, 1993).

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Homidium salts: It is widely used in Africa to treat T. congolense and T. vivax infections in cattle, sheep and goats, in spite of its proven mutagenic and possible carcinogenic properties as a DNA intercalated (Sutcliffe et al., 2014). Due to its potential toxicity, the use of homidium is today highly discouraged (Sutcliffe et al., 2014).

Although, their mutagenic activity has been known for a long time (Shiferaw et al., 2015), homidium chloride and especially homidium bromide or ethidium are still widely used as trypanocidal drugs. The mechanism of their anti-trypanosomal action is not well understood. However, it has been shown that the drugs interfere with glycosomal functions, the function of an unusual adenosine monophosphate-(AMP) binding protein, trypanothione metabolism and the replication of kinetoplast minicircles (Wang, 1995).

Although used as a curative drug, homidium also possesses chemoprophylactic properties, but these are less pronounced than those of isometamidium. For both purposes, homidium is administered at the dose of 1 mg/ kg by a single deep intra muscular injection (Peregrine, 1994). It was found that homidium blocks both kinetoplast and nuclear DNA replication in T. brucei by distorting and changing the double helix topology (Roy Chowdhury et al., 2010).

Suramin sodium: It is the oldest trypanocide still in use, having been introduced in 1921 for the treatment of surra in camels. (Uilenberg, 1998). A definitive mode of action for the compound has not been determined. Suramin curbs glycolytic ATP production in T. brucei by inhibiting glycerol-3-phosphate oxidase and NAD+-dependent glycerol-3-phosphate dehydrogenase (Fairlamb and Uilenberg, 1998).

2.2. Anti-Trypanosomal Drug Resistance and Its Historical Background

Anti-trypanosomal drug resistance is the loss of sensitivity by a strain of an organism to a drug to which it had previously been susceptible and implies failure of treatment and prevention of
The three trypanocides used to control tsetse-transmitted trypanosomiasis in domestic animals in Africa have been in use for over 40 years and, not surprisingly, resistance of trypanosomes to these drugs has emerged. Because of the relatively limited market in Africa and the high costs of developing and licensing new drugs, international pharmaceutical companies have shown little interest in the development of new trypanocides for use in either animals or humans (Stanny et al., 2001).

Cases of resistance to veterinary trypanocides started to be reported in the field soon after their introduction, and their numbers have been in increasing ever since (Delespaux et al., 2008).

Over most of sub-Saharan Africa, bovine trypanosomiasis continues to be controlled primarily by trypanocidal drugs (Holmes et al., 2004). This is essential because without treatment, the outcome of African trypanosomiasis is almost always fatal (Legros et al., 2002). However, the effectiveness of these drugs is threatened by the development of widespread drug resistance (TDR) (Clausen et al., 2010).

Trypanocidal drug resistance is increasingly reported all over Africa and is now present in 21 sub-Saharan countries (Geerts et al., 2010; Chitanga et al., 2011). It is suspected that in several other African countries, resistance is present but is yet to be demonstrated (Delespaux et al., 2008).

Trypanocidal drug resistance has also been reported in South America, where the compound is the first line drug to treat these infections (Cadioli et al., 2012). Furthermore, in some instances, multiple drug resistance has been reported (Holmes et al., 2004). The origin of multiple resistances to trypanocides by trypanosomes in the field is unclear, though cross-resistance between the different compounds probably due to their closely related molecular structures was implicated (Tsegaye et al., 2015), but it can also occur between very different drugs (Delespaux and Koning, 2007).

Resistance to Isomethamidium® is attributed to synergistic combination of reduced uptake and increased efflux of the drug at the level of the mitochondrion i.e. a decrease in transport through the mitochondrial membrane (lowered mitochondrial electrical potential), the modification of a possible transporter located in the inner mitochondrial membrane, an increased efflux of the drug from the cytoplasmic compartment via a yet to be identified transporter or a combination of these into the mitochondrial processes (Delespaux et al., 2008).

Resistance to homidium chloride (ISM), homidium salts (homidium bromide (Ethidium®) and homidium chloride (Novidium®) and diminazene aceturate (DA) have been and are still in use even since their release into the market in 1950s (Holmes et al., 2004).

Two types of resistance against trypanocidal drugs are recognized: single drug resistance and multiple drug resistance. In single drug resistance, trypanosomiasis control still could be achieved by using one of the drug pairs in which resistance has not been developed through the application of the sanative pair principle (Geerts and Holmes, 1998).

The discovery of trypanocidal drugs with preventive action raised high hopes that their use would make it possible to turn subtropical Africa into a flourishing livestock production area. It must be admitted that most of these hopes have not been realized. Although, these drugs do provide protection, which in some conditions may last up to six months, all of them frequently give rise to the formation of drug-resistant trypanosome strains. This drug resistance occurs when the trypanosomes are in contact with a trypanocide administered in a sub curative dose insufficient to ensure the destruction of the parasites (Das et al., 2004).

Resistance to DA is attributed to the alteration of a membrane transporter (Delespaux et al., 2008). The accumulation of DA has been shown to be markedly reduced in arsenical-resistant T. brucei, T. evansi and T. equiperdum due to alterations in the P2-type purine transport system (de Konig and Jarvis, 1999).
Resistance to ethidium can be partly attributed to the fact that it contains a mutagenic agent (Matovu et al., 2001).

2.4. Risk Factors for Anti-trypanosomal Drug Resistance

Drug resistance or drug fastness of microorganisms manifests itself after exposure of the organisms to an anti-microbial agent either in vitro or in vivo. It is defined as the heritable, temporary or permanent loss of the initial sensitivity of the population of microorganisms against the active substance. Resistance is not necessarily indefinite at high concentrations the parasites succumb but, this may well beyond doses which can be tolerated by the host. On the other hand, tolerance is an innate lack of susceptibility, which does not result from previous exposure to the drug (Geerts and Holms, 1998).

Various methods for determination of drug sensitivities in pathogenic trypanosomes have been reported (Matovu, 2001) and the use of standardized protocols to enable comparison of data from different parts of Africa is strongly advocated. The principal factors which influence the evolution of trypanocidal resistance have been described at four levels namely the host, the vector, the drug and the parasite (Geerts and Holms, 1998).

2.4.1 host related factor

The host immune system plays a significant role in the success of chemotherapy as exemplified by treatment of trypanosomosis with α-DFMO. This drug is principally trypanostatic and requires a competent immune system to eliminate the arrested trypanosome population. In the presence of immune depression due to other parasitic diseases and trypanosomosis as well, the exposure time of trypanosomes to the drug is increased, which will favors selection for resistance. Other host-related causes may be environmental, e.g., nutritional status and stress, which will render the host unable to play its supportive role in the elimination of infections. The level and exposure time of the active metabolite will depend on the rate of activity of the liver, which may vary from host to host (Matovu et al., 2001).

2.4.2. Vector

Contribution by the vector is based on the fact that drug resistance is agenetically regulated characteristic. (Gibson, W., 1993). Trypanosome populations are basically clonal, but there is evidence for genetic exchange between different trypanosomes within the set (Degen, R., et al., 1995).

The evolution of resistance may rely on the degree of genetic exchange in the vector, as well as on transmission intensity/efficiency, which in turn determines the rate of spread within the population (Matovu, et al., 2001).

2.4.3. The nature of the drug

Its pharmacokinetics in the host and drug management has a bearing on chemotherapeutic success. Under-dosing is a significant factor mainly in animal trypanosomosis and selection for resistance is driven by presence of sub-optimal drug concentrations in the blood (Matovu et al., 2001).

2.4.4. Parasite related factor

Identification of drug targets within the parasites is an invaluable tool for rational use of drugs. This can be achieved by the detailed analysis of various aspects of metabolism in the parasite or elucidation of the mechanisms of action of proven anti-parasitic agents (Wang, 1997).

A clear understanding of the different drug targets will be vital when deciding which compound to administer faced with resistance to a given drug. Cross resistance is less likely to occur between drugs affecting unrelated metabolic pathways, which provide the basis for use of sanguine pairs in chemotherapy (Bacchi et al., 1994).

2.5. Method of Detecting Resistance

2.5.1. In vivo methods

The common in vivo tests used to identify drug resistance are tests in ruminants and tests in mice.

The tests in ruminants: consists of infecting a group of cattle or small ruminants with the isolate under investigation and later, when they are parasitaemic, treating them with various dosages of trypanocides (Holmes et al., 2004). Standardized protocols for the tests in animals have been developed, which should allow better comparisons of data on a temporal and spatial basis (Eisler et al., 2001). A minimum of 3 and preferably 6 animals in each group are inoculated with the same trypanosome isolate, as result from one animal is not always reliable (Eisler et al., 2001).

Test in mice: Tests in mice can be used as a single dose test or as a multi dose test. In the latter case, the objective is to obtain more detailed information by determining the CD50 or CD80 values for a given trypanocidal drug. In the case of a single test, a large number of trypanosome isolates is tested at a single discriminatory dosage of 1 mg/kg for ISM and 20 mg/kg for DA (Eisler et al., 2001).

The advantage of the mouse test is that it is cheaper than the test in ruminants. However, it presents several disadvantages. Firstly, most T. vivax isolates and also some T. congolense isolates do not grow in mice and for that reason, research on T. vivax isolates in particular has been hampered. Secondly, higher dose of drug must be used in mice in order to obtain results comparable to those from cattle because of the vast difference in metabolic size, in spite of the fact that there is reasonable correlation between drug sensitivity data in mice and cattle. Therefore, results in mice cannot be directly extrapolated to calculate the curative dose to be used in animals. Thirdly, a large number of mice per isolate are required in order to obtain a precise assessment of the degree of resistances. This makes it a rather labor intensive test. Finally the test takes as long as 60 days to evaluate the drug sensitivity of an isolate (Greets and Holmes, 2004).

2.5.2. In vitro Methods

Invitro assay: Laboratory cultivation of bloodstream form T. brucei transformed our ability to assess sensitivity to drugs, especially in the quantities made possible by large chemical libraries and robotic screening, resulting in new lead compounds (Diaz et al., 2014).

In vitro cultivation of bloodstream forms is only possible using pre adapted lines and not using isolates directly from naturally infected animals. In vitro assay are expensive to perform and require good laboratory facilities and well trained staff. In contrast to T. brucei, it is very difficult to cultivate T. Congolense (Holmes et al., 2004).

Molecular detection drug resistance: Given the limitations in assessing drug sensitivity levels of veterinary trypanosomes, the development of molecular tests to determine parasites’ susceptibility status would be of profound importance. For T. brucei group parasites it has been shown that mutations in TbAT1 and TbACP2 genes can underlie resistance to both melaminophenyl.
arsenicals and to diamidines such as pentamidine (Graf et al., 2015 and Munday et al., 2015a, b). Molecular methods for the diagnosis of ISM resistance were recently developed (Delespaux et al., 2005).

2.6. Strategies to Prevent and Control Anti-trypanosomal Drug Resistance

2.6.1. Reducing the number of treatments

It is widely agreed that the most efficient way to delay the development of drug resistance remains the reduction of drug selection pressure by decreasing the number of treatments, especially in case of multiple drug-resistance (McDermott et al., 2003). Reduction in drug pressure impacts drug resistance evolution in three ways; delays its appearance, reduces the likelihood of its establishment and slows its spread (Smith et al., 2010).

2.6.2. Use of the correct dose

Under dosing is one of the major causes of resistance development. Sub-therapeutic drug concentrations exert a strong selective pressure for the emergence of resistant clones that pre-exist in the trypanosome population. Unfortunately, under dosing occurs very frequently by farmers or unskilled persons in many countries of Africa due to the absence of strict rules about the utilization of veterinary drugs (Geerts and Holmes, 1998).

Furthermore, there are an increasing number of generic products available on a somewhat loosely regulated market, and some of these have questionable efficacy and many contain lower doses of drug than the stated amount (Holmes et al., 2004).

2.6.3. Avoiding exposure of the whole parasite population to a drug

In the past mass treatments are commonly used to control animal trypanosomiasis. However this form of treatment exerts a strong selection pressure on the trypanosome population. The higher the proportion of trypanosome population exposed to the drug and the lower the proportion in refugia (i.e. the proportion of trypanosomes present in the fly population or in other hosts), the higher the selection pressure. Therefore, in well monitored situations there is a strong case for limiting treatment to individual clinical cases; this is also desirable on grounds of minimizing drug residues, avoiding potential toxicity and reducing costs (Maudlin et al., 2004).

3. STATUS OF ANTI TRYPANOSOMIAL DRUG RESISTANCE DEVELOPMENT IN ETHIOPIA

Resistance to one or more of the common trypanocidal drugs used in cattle has been reported in at least four regional states (local areas) within the country. But the currently available information on drug resistance is derived from limited number of cases reports, and does not give any indication of the true situation of the resistance in a whole country (region) as systematic surveys have not been fully conducted. This problem of drug resistance in trypanosomes requires being spread geographically into many regions in which trypanosomes occur. Additionally, the spread of genetic products, some of which are of doubtful quality, may undermine farmer’s confidence using trypanocidal drugs (Holmes et al., 2004).

Chemotherapy’s and chemoprophylaxis’ effectiveness is being eroded by the emergence resistant trypanosomes. The widespread use, the irregular use of prophylactics drugs, their discontinuation while livestock remain at risk, the high incidence of trypanosomiasis and misuse of drugs has contributed to the development of drug resistance in the population of T. congolense parasites (Ermiyas and Getachew, 2001).

The magnitude of drug resistant trypanosomes across Ethiopia is not well documented. However, some study on a few isolates of T. congo alleging the potential risk for the future in the greater part of tsetse infested areas, where the proportional infection rate of cattle by T. congolense is increasing (Abbe and Jobre, 1996).

It was found that 11 of the 12 isolates tested were resistant in cattle to recommended doses of isometamidium and homidium. Since then, several other reports have emerged substantiating the widespread occurrence of trypanocidal drug resistance in many parts of the country (Afework et al., 2000, Teweide et al., 2004, Shimeles et al., 2008, Moti et al., 2012 and Shimelis et al., 2015).

The problem of drug resistance in trypanosomes requires being spreading geographically into many regions in which trypanosomes occur. Additionally, the spread of genetic products, some of which are of doubtful quality, may undermine farmer’s confidence using trypanocidal drugs (Holmes et al., 2004). Multiple and single trypanocidal drug resistance reported in Ethiopia is indicated in table as follows.

### Table1. Multiple and single trypanocidal drug resistance reported in Ethiopia

<table>
<thead>
<tr>
<th>Study region</th>
<th>Specific area</th>
<th>Drugs tested</th>
<th>Species of parasite</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNNP</td>
<td>Upper Didessa</td>
<td>ISM &amp; DA</td>
<td>Tc</td>
<td>Moti et al. (2010)</td>
</tr>
<tr>
<td>Afework et al. (1999)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ganz</td>
<td>Metekel</td>
<td>ISM &amp; DA</td>
<td>Tc</td>
<td>Afework et al. (2000)</td>
</tr>
<tr>
<td>NNPRS</td>
<td>Sodo</td>
<td>ISM &amp; DA</td>
<td>Tc</td>
<td>Afework et al. (2000)</td>
</tr>
<tr>
<td>Arbaminch</td>
<td>ISM &amp; DA</td>
<td>Tc</td>
<td>Afework et al. (2000)</td>
<td></td>
</tr>
<tr>
<td>Omo valley</td>
<td>ISM &amp; DA</td>
<td>Tc</td>
<td>Afework et al. (2000)</td>
<td></td>
</tr>
<tr>
<td>Tigray</td>
<td>Tuentent</td>
<td>ISM &amp; DA</td>
<td>Tc</td>
<td>Afework et al. (2000)</td>
</tr>
</tbody>
</table>

Source: Afework et al., 2015

CONCLUSION AND RECOMMENDATIONS

The great potential of livestock to rural farmers, in Ethiopia, can only be exploited if trypanosomiasis and the arising appearance of drug resistance are controlled. Chemotherapy and chemoprophylaxis are the most realistic method accessible for the control of animal trypanosomiasis. However, the increasing trend of drug resistant strains of trypanosomes is a serious threat to cattle production in Ethiopia. Unfortunately, farmers can purchase a variety of trypanocidal drugs in most markets, although all trypanocidal drugs are supposed to be imported and supplied through the Ministry of Agriculture. Exposure of parasites to sub therapeutic drug concentrations, resulting from under dosing and uncontrolled use of trypanocidal drugs, and the lack of proper diagnosis, are considered the major causes of increasing drug resistance in Ethiopia. Based on the above conclusion, the following recommendations are forwarded.
The effectiveness of available drugs should be ensured.

Urgent detailed experimental work in the field to monitor drug resistance.

Strict supervision on the usage of a trypanocidal drugs should be done.

Attention should be given to the adoption of control strategy.

Careful monitoring of distribution and degree of drugs.

References


