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A Review on Trypanotolerance: An Option for Trypanosomosis Control

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Abstract: Trypanosomosis is the disease of both humans and animals mainly in sub-Saharan Africa and it is the most important constraint to livestock productivity in this region. Different strategies for control of trypanosomosis and eradication of its biological vector (tsetse flies) have been practiced in Africa. Chemotherapies used as treatment and prophylactic agent, vaccine, the use of Trypanotolerant breeds, the application of insecticides, stationary insect attractants and exploitation of sterile insect techniques are among the methods of controlling both the disease and its vectors in tsetse infested and trypanosome challenged African countries. However, the development of drug resistance, environmental degradability nature of some techniques such as, removal of preferred vegetation or the destruction of host game animals and partially or entirely failure of vaccines due to antigenic variations; management of trypanosomosis still is not successful. Nowadays, because of such difficulties, the development of environmentally friendly tsetse flies control alternatives, formulation of new drugs and vaccines against trypanosomal cystein protease (congopain), trypanosomal tubulin or trypanosomal Glycosylphosphatidylinositol other than Variant surface glycoprotein and expansion of trypanotolerant livestock particularly, N'Dama cattle and Sheko (in Ethiopia) breeds in areas where under tsetse flies and trypanosomosis risk are extremely needed. Trypanotolerant cattle have the capacity to reduce severe anaemia, parasitaemia and they show good reproductive and productivity performance in low to high tsetse and trypanosome affected areas of Africa including Ethiopia.

Key words: Cattle · Control · Ethiopia · Trypanosomosis · Trypanotolerance

INTRODUCTION

Trypanosomosis is a protozoan disease affecting both humans and animals mainly, found in tropical Africa, Latin America and Asia and most of animal trypanosomosis can be considered as Neglected Tropical Diseases [1]. Species of trypanosomes infecting mammals fall into two distinct groups: Stercoraria (subgenera *Schizotrypanum, Megatrypanum* and *Herpetosoma*), in which trypanosomes are typically processed in the hindgut of the vector and are then passed on by contaminative transmission from the posterior end of the digestive tract and Salivaria (subgenera *Duttonella, Nannomonas* and *Trypanozoon*), in which transmission occurs by the anterior station and is inoculative [2]. Salivarian species are characterized by virtue of variant surface glycoprotein genes they are the only trypanosomes to exhibit antigenic variation [3].

Many agricultural and veterinary experts consider African animal trypanosomosis as the single greatest health constraint to increased livestock production in sub-Saharan Africa. Direct annual production losses in cattle are estimated at US$ 600-1200 million [4]. Estimates of the overall annual lost potential in livestock and crop production have been as high as US$ 4, 750 million [5].

Tsetse flies are appropriately referred to as Africa's pest and they are solely responsible for the cyclical transmission of trypanosomes, the causative agents of sleeping sickness' or HAT in humans and 'nagana' or AAT is in livestock. Both male and female tsetse flies are obligatory blood suckers and during feeding on an infected host, the trypanosomes are ingested by the fly together with the mammalian host's blood and they undergo a cycle of development within the insect. The duration of the cycle depends on the trypanosome species and the temperature [6]. There are currently 31 recognized species and subspecies of tsetse flies and they are normally divided into three different subgroups; the savannah (subgenus *Morsitans*), forest (subgenus *Fusca*) and riverine type (subgenus *Palpalis*)

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[7]. Only 8–10 species of tsetse flies are considered of economic (agricultural–veterinary) or human sanitary importance. Tsetse flies occur in 38 African countries infesting a total area of 10 million km^2 in sub-Saharan Africa. 60 million people are continuously exposed to the risk of infection [8]. The presence of tsetse and trypanosomosis can be considered as one of the major root causes of hunger and poverty in sub-Sahara Africa. This is exemplified by the remarkable correlation and overlap between the 38 tsetse-infested countries and the 34 heavily obliged poor countries in Africa [9]. The *Glossina palpalis* group are very difficult vectors of AAT in West Africa (*G. tachinoides, Glossina palpalis palpalis* and *Glossina palpalis gambiensis*) and HAT in Central Africa (*G. f. fuscipes* and *Glossina fuscipes quanzensis*), since they are opportunistic feeders and tolerate a high degree of disturbance of the landscape [10]. *Glossina* morsitans spp. *and Glossina* pallidipes are the most important species and are major vectors of AAT and HAT in Eastern and Southern Africa. These species are more sensitive flies to human violation and their abundance decreases when the human population exceeds 5people/km^2 [10].

Because of its high health and economic crisis controlling trypanosomosis by using different methods such as, screening and curative treatment of HAT, the prophylactic and curative treatment of AAT with trypanocidal drugs, the promotion of trypanotolerant livestock and suppression or eradication of the target vector, tsetse flies are primarily important. However, the indiscriminately application of certain drugs e.g. diminazine, isometamidium, homidium resulted increased levels of drug resistance of the parasite [11].

Thus, the expansion of trypanotolerant breeds in tsetse infested and trypanosomosis affected regions is one possible and potentially cost effective solution in the control of Trypanosomosis [12]. Therefore, the objective of this review paper is to give emphasis to the use of trypanotolerant livestock in tsetse infested and trpanosomosis affected areas to effectively control animal trypanosomosis.

Trypanosomosis Control Options

Vector Control

Sequential Aerosol Technique (SAT): Fixed wing aircraft or helicopters (in more difficult topography) are used to spray a spray of ultra-low volume (Highly concentrated formulation) of non residual insecticides such as, diazinon, malathion and parathion (Organophosphates) 10–15m above the tree covering in 5–6 subsequent spraying cycles separated by 16–18 days depending on the temperature [13]. Selection of the appropriate droplet size is of prime importance for this method to be successful i.e. the droplets should be small enough to remain suspended sufficiently long in the air and large enough to prevent upward flow. Electrically or air driven rotary atomizers are used at a speed of 16, 000 rpm to produce an aerosol of droplets of 30–40 µm [14]. This control tactic aims at killing all adult flies in each spraying cycle through direct contact with the insecticide mist and then to kill all emerging flies in the subsequent cycles before they can start reproducing. The insecticides have to be applied during periods of temperature inversion (i.e. night time) and there can be no delays or interruption in the timing of the cycles. Use of modern GPS-guided navigation and spray systems makes this tool very effective for area-wide tsetse control in dense humid forest ecosystems or eradication in open savannah-type ecosystems [15].

The disadvantages of using persistent (residual) insecticides (organochlorines) such as DDT, aldrin, endrin and chlordane over large areas in often, fragile eco-system are: (a) The potential of insects developing resistance to the insecticide, (b) the killing of beneficial non-target insects, (c) outbreaks of other pests due to the elimination of predators, (d) the general pollution of the environment due to the accumulation of the insecticide in the food chain and (e) the health hazard posed to the staff of the spray teams [16].

Stationary Attractive Devices: With this technique female tsetse flies are attracted to a device e.g. cloth traps or targets that either kill the flies through tarsal contact with insecticides applied to the surface of the target [17], or by heat or starvation after being guided to a non-return cage [18]. The method aims at exerting an additional daily mortality of 2–3% to the female segment of the population. The attractiveness of the devices can be enhanced, especially for savannah type species, by using potent odor attractants and these bait methods when applied at the appropriate densities, can suppress tsetse fly population to low numbers in a few months [19, 20]. This technique is more efficient when the targets/traps are impregnated with insecticides like pyrethroids, as only 20% of the attracted flies are generally entering the device [21].

The efficiency of traps and targets is correlated with tsetse dispersal capacities and it has been shown that dispersal for riverine species of tsetse decreases with increasing landscape fragmentation [22]. Any decrease in

tsetse distribution should be compensated by an increase of target density to obtain the same effect. Moreover, tsetse dispersal is likely positively correlated with their density, which might explain why this technique is more suitable for control than for eradication [23].

Live Bait Technique: This method is based on insecticide treatment of livestock and exploits the blood sucking behavior of both sexes of tsetse. Tsetse flies, attempting to feed on cattle or other treated domestic livestock are killed by picking up a lethal deposit of insecticide on the ventral tarsal spines and on pre-tarsi whilst feeding [24]. The success of the method depends on a relatively large proportion of feeds being taken from domestic animals and a sufficient proportion of the livestock population being treated. Pour-on formulations have the advantage over other techniques that no sophisticated equipment is needed and the insecticide application is rapid and easy [25].

Species of the *G. palpalis* group are more opportunistic feeders and suppression of the population is often followed by a new equilibrium of the population at low densities [26]. Eradication of a riverine tsetse population has to date not been demonstrated using this technique mainly due to a certain proportion of the target population feeding on alternative hosts like reptiles and at least in the case of *G. p. gambiensis* due to the tendency of the fly to return to a similar host as encountered during the first blood meal [22].

Sterile Insect Technique (SIT): The sterile insect technique relies on the production of large numbers of the target insect in specialized production centers, the sterilization of the males (or sometimes both sexes) and the sustained and systematic release of the sterile males over the target area in numbers large enough in relation to the wild male population to out-compete them for wild females. Mating of sterile insects with virgin, native female insects, results in no offspring [27]. With each generation, the ratio of sterile to wild insects will increase and the technique becomes therefore more efficient with lower population densities (inversely-density dependent) [28].

The sterile insect technique is non-invasive to the environment, has no adverse effects on non-target organisms, is species-specific and can easily be integrated with biological control methods such as parasitoids, predators and pathogens. There is no evidence of development of resistance to the effects of the sterile males provided that adequate quality assurance is practiced in the production process, but only effective when the target population density is low, it requires detailed knowledge on the biology and ecology of the target pest and the insect should be agreeable to mass-rearing [29].

Chemotherapy: Diminazene aceturate has been recommended as therapeutic agent at a dose rate 3.5 to 7 mg/kg, by intramuscular route. At 3.5 mg/kg has also been recommended against *T. congolense* in cattle, *T.vivax* in large and small ruminants and at 7 mg/kg against *T. brucei* in livestock and dogs but *diminazene aceturate* cannot be used in camels due to its high toxicity [30]. Nowadays, it seems that the theoretical dose of 3.5 mg/kg is able to get rid of the clinical signs, at least temporarily, but is most often unable to cure the infection [31].

Homidium chloride used as preventive and therapeutic agent, at the dose rate of 1 mg/kg by IM route is effective against *T. congolense* in cattle and *T. vivax* in pigs, small ruminants and horses; however it is not advised to use it because of the well known carcinogenic activity of ethidium bromide [31]. *Isometamidium* chloride can be used at dose rate of 0.25 to 0.5 mg/kg by intramuscular route as preventive and therapeutic agent for *T. vivax* and *T. congolense* in cattle and small ruminants and *T. brucei* in equines. Quinapyramine dimethylsulphate at dose rate of 3 to 5 mg/kg by subcutaneous route is recommended as therapeutic treatment against *T. congolense* in camels. Quinapyramine dimethylsulphate/chloride at dose rate of 3 to 5 mg/kg by subcutaneous route is suggested as prophylactic use for *T. vivax* in equines and *T. brucei* in pigs [32].

Treatment of *Trypanosome evansi* (Surra) is currently dependent on four drugs: polysulphonated naphtyl urea (suramin), diminazene aceturate, quinapyramine and melarsomine which are relatively expensive and not available. While the first three have been utilized for more than 50 years, melarsomine hydrochloride belonging to the family of melaminophenyl arsenicals was developed about 20 years ago. Of the drugs available only melarsomine hydrochloride and diminazene aceturate are considered safe for use in all animal species. Unfortunately, with the appearance of resistance to these drugs, their effectiveness is threatened and it is necessary to look for new drugs [33].

Trypanosoma equiperdum produces a disease called “Dourine” does not have any available drug. The disease is considered to be incurable and for that, seropositive horses should be removed or euthanized [34]. However, in vitro sensitivity of different *T. equiperdum* strains to suramin, diminazene, quinapyramine and melarsomine has been reported [35].

Vaccine: The major constraint to the development of a vaccine against trypanosomosis is the phenomenon of antigenic variation [36]. However, while the collection of these antigens generated by bloodstream forms of the parasite is large (greater than 1, 000), the range of antigens produced by metacyclic parasites following transmission through the tsetse is much more limited and would appear relatively constant [37]. Thus, it has been possible to immunize cattle and goats against tsetse-transmitted homologous (rather than heterologous) strains of *T. congolense* and *T. brucei*. African trypanosomes have developed a highly difficult and complex system of antigenic variation [38].

In the mammalian host, the whole parasite is covered with a coat of about 10^7 identical molecules of a glycoprotein, the variant surface glycoprotein (VSG). The VSG is anchored into the cell membrane via a glycolipid, glycosylphosphatidylinositol (GPI) [39]. All previous attempts to produce vaccines against African trypanosomes were only partially successful or failed entirely, because they did not deal with the stated problem of induction of immunosuppression by infecting trypanosomes however, recently a comprehensive review on previous vaccination attempts has been published [40]. There are suggestions that both macrophages and T cells might be involved immunosuppression [41]. Immunosuppression is characterized by an inhibition of the T cell proliferation due to down regulation of both IL-2 production and expression of IL-2 receptor [41].

In trypanosomosis, all conventional anti-parasitic vaccination efforts undertaken so far, that used dominant surface protein, have failed due to the antigenic variation of the trypanosomes surface coat. Therefore, an alternative strategy of the vaccination is demanding; different molecules such as trypanosomal cystein protease (congopain) [42], trypanosomal tubulin or trypanosomal GPI have been attempted [43].

The GPI-anchor of the VSG as one of the major parasitic components causing the inflammatory response associated to the infection has been identified [44]. The information has been used to evaluate GPI-based vaccination as an alternative strategy with antidisease potential using liposomes as slow delivery system, the GPI administered prior to the infection had been shown to result in a better control of the parasitemia and a longer lifespan of the infected mice [45]. The treated animals were better protected from various pathological conditions including anemia which is considered as one of the major pathological parameters of the trypanosomosis [46]. These results are related to the fact that the treatment oriented the classically activated inflammatory macrophages, to more counter-inflammatory alternatively activated macrophages, subsequently resulting in reduced TNF production and reduced pathology [47]. The needs, possibilities and requirements of further knowledge for the way to develop an anti-disease control strategy for trypanosomosis has been recently highlighted [48].

In animal trypanosomosis, the only example available of an "antidisease vaccine" is a cattle infected by *T. congolense* immunization strategy using congopain. Immunization resulted in a statistically significant beneficial effect on anemia and immunosuppression during infection. However, this protective effect proved to be too limited to be practical and other antidisease vaccine candidates are needed to enhance efficacy [42].

Trypanotolerance: an Option for Trypanosomosis Control: The term trypanotolerance was defined as the trait that confers the capacity to survive and remain productive after trypanosome infection [49]. It has been also described as the relative capacity of an animal to control the development of the trypanosome parasite and to limit its pathological effects, the most prominent of which is anaemia [50].

Comparison of infections with *T. congolense* in laboratory conditions between trypanotolerant N'Dama calves (*Bos taurus*) with more susceptible Boran calves (*B. indicus*), was confirmed that observations in the field explained that N'Dama remained productive, continued to gain weight at the same rate as the uninfected controls and females continued their oestrous cycle compared with the infected Boran cattle [51].

Mechanism of Trypanotolerance

Haemopoeitic Factor: Trypanotolerance is mediated by two independent mechanisms. The first is a better capacity to control parasitemia and the second mechanism is a better capacity to control the associated anemia and is mediated by cells from the hemopoietic system. Innate mechanisms that control parasite growth in trypanotolerant cattle are more efficient in controlling disease, making them less reliant on antibody responses [52].

The bone marrow response is a key determinant factor of trypanotolerance in cattle as it determines the animal's capacity for haematopoietic cell regeneration and control of anemia. The idea was supported by light and electron microscopic studies of sequential biopsies of bone marrow of *T. congolense* infected animals which

showed key differences between trypanotolerant N'Dama and trypanosusceptible Boran cattle. This was further maintained by some beneficial effects of macrophage activation in the bone marrow (enhanced haematopoiesis, parasite clearance and antigen processing) was found to be greater in N'Dama than in Boran, enabling the N'Dama to resist infection better than Boran cattle [53].

The cleavage of erythrocyte sialic acid of cattle infected with *T. congolense* rendered them more proned to phagocytosis by the mononuclear phagocyte system and development of anemia. However, there was return to normality of erythrocyte surface sialic acid 15 days after infection followed by improvement of anaemia. They suggested that there was accelerated replacement of sialic acid on the erythrocyte surface by the enzyme, sialytransferase known to be in the calf thyroid glands. The role of sialytransferase in trypanotolerance has not yet been reported, but sialytransferase might play a role in trypanotolerance as increased activities of this enzyme might lead to more efficient replacement of sialic acid on the erythocyte surface of trypanosome-infected animals as soon as they are being removed, thus preventing the development of anaemia. Molecular characterization of this enzyme may offer clues for enhancing its activities in other animal species to prevent the development of anemia, a cardinal pathological feature and cause of death in animals suffering from African trypanosomosis [54].

Human resistance to *T. b. brucei* is neither the result of a better acquired response nor of a better innate response, but is carried by apolipoprotein L-I (apoL-I) in human serum that is lytic to this trypanosome strain, but not to *T. b. rhodesiense* [55].

Parasite Control Factor: Trypanosome parasite control in trypanotolerance has been associated with two factors. Gutierrez [1] Compliment-dependent and clone specific lytic activities and Hoare [2] Compliment-independent trypanocidal activity that is not restricted to trypanosome clones and species [56]. Control of parasitaemia in African buffalo was correlated with a decline in catalase activity and an increase in peroxide in the plasma capable of reducing trypanosome numbers [57]. Serum xanthine oxidase, serum catalase and trypanosome specific immune responses have been reported to play roles of regulation of the level of parasitaemia in the Cape buffalo [58]. The trypanocidal activity of serum xanthine oxidase in the Cape buffalo arises from H_2O_2 generated by this enzyme during hypoxanthine and xanthine catabolism [59].

Trypanosome congolense infected N'Dama had significantly more variable surface glycoprotein (VSG)-specific IgG in blood than trypanosusceptible Boran cattle during infections [60]. There has been also a possible correlation between plasma lipid levels and trypanotolerance or susceptibility between trypanotolerant N'Dama and trypanosusceptible white Fulani cattle suggesting that plasma lipids might play roles in trypanosome growth, differentiation and pathology of disease [61].

Genetic Factor: Trypanotolerance has been described as a genetically determined complex mechanism involving factors which are not yet well known [50]. The gene-based ability is called trypanotolerance results from various biological mechanisms under multigenic control; however, the methodologies used so far have not succeeded in identifying the complete pool of genes involved in trypanotolerance. Identification of the genes involved in trypanotolerance will allow the setting up of specific micro-array sets for further metabolic and pharmacological studies and the design of field marker-assisted selection by introgression programs.

Millennia of selection had been done in tsetse-infested areas to allow in some cattle breeds (e.g.Taurine) to develop a certain degree of 'reduced susceptibility' to trypanosomosis. It is possible that genes conferring this tolerance entered the population through cross breeding with an ancient population of African cattle, whose existence could be traced by DNA analysis in breeds from the continent [62].

Several efforts have been made to identify genes that contribute to trypanotolerance and this understanding could help to discover the processes that confer resistance. In one type of approach, differential gene expression between tolerant and susceptible cattle allows the detection of genes whose up- or down-regulation is correlated with a tolerant phenotype. Using serial analysis of gene expression (SAGE), 187 genes that changed their expression were identified in N'Dama leukocytes after infection by *T. congolense* [63].

In cattle 16 phenotypes, including anaemia, body weight and parasitaemia were used in the analysis of the bovine data and 18 quantitative trait loci (QTL) were identified [64]. Trypanotolerance is thus highly polygenic, with each gene or locus explaining no more than 10–12% of the phenotypic variance of the trait. Most QTLs were linked to control of anaemia and only a few to

parasitaemia, suggesting that anaemia control is complex and of major significance. An interesting observation was that five resistance alleles in the QTL originated from the susceptible Boran grandparent, suggesting that trypanotolerance as observed in N'Dama, could be improved upon by further crossbreeding; so that genes located in a QTL and differentially expressed in tissues from trypanotolerant and susceptible animals should be particularly helpful and are potential 'resistance genes' [64].

Immune Response

Innate Immune Response: Once in the bloodstream of the mammalian host, the trypanosomes encounter the innate host immune system as the first barrier. Human and some other primates have trypanolytic factors in their serum that aid the primary defense mechanism. In a cellular innate immune response, different host cells are activated by different trypanosomal factors, initiating an acute inflammatory response [65]. Among many molecules, the trypanosomal DNA that might be released from the dead trypanosomes has been shown to activate macrophages in a process called classical activation, to secrete pro-inflammatory molecules like TNF, IL-12 and NO [66]. In this regard, involvement of toll-like receptors (TLR) and in particular the TLR9, in parasitemia control would suggest that the DNA from trypanosomes plays a role in disease progression [67]. The GPI anchor of the VSG also interacts with the macrophages (via a supposed receptor which is still indescribable) and induces secretion of pro-inflammatory cytokines [68]. So, the first response of the host immune system consists of classically activated macrophages (caM) secreting pro-inflammatory molecules such as TNF, IL-1, IL-6, NO [69]. The caMs can phagocytose antibody-opsonized parasites, as well as secrete trypanotoxic molecules such as TNF and NO that are involved in the control of the first peak of parasitemia [70].

Adaptive Immune Response: The initial inflammatory response is beneficial to the host at the early stage of the infection, but a sustained inflammation can cause pathology. Hence, it is essential for the host to reduce the inflammation which is obtained by down regulating the caM and their pro-inflammatory cytokines. Production of type II cytokines such as IL-4, IL-10, IL-5 and IL-13 which can modulate the macrophages to become more anti-inflammatory type alternatively activated macrophages (aaM) are involved in a longer survival of the host. So, a type I inflammatory response at the beginning of the infection and a shift to the type II immune response in the late stage of the infection are correlated with the capacity of the host to control the parasite and the pathology respectively. The type-I cytokine (IL-2 and IFN-γ) responses being critical during the early stage of infection while the type-II cytokine responses to be more important during the late and chronic phases of the disease [71].

Humoral Immune Response: During the trypanosome infection a dominant humoral response of the host is expected, since the location of the parasite is extra-cellular both the murine and bovine trypanosomosis is characterized by a polyclonal B cell activation as evidenced by an increased number of B cells and a significant elevation in plasma immunoglobulins [72]. Because of the polyclonal B cell activation, a significant component of the resultant antibody is either polyspecific or auto reactive [73].

Although the VSG molecules are highly immunogenic for all mouse strains upon immunization, dramatic differences in the ability of animals to mount the VSG-specific B cell response occur after infection [74]. It is shown in different independent studies that specific antibodies directed against the trypanosome VSG mediate the destruction and clearance of parasites in successive parasitemic waves and hence contribute to antibody mediated trypanotolerance [75].

Animals immunized with the irradiated trypanosomes or the VSG are successfully protected against a challenge with the homologous parasites [76]. The antibodies directed against the specific surface-exposed epitopes of the VSG coat opsonize the parasites and the immune complexes are efficiently phagocytosed and destroyed, mainly in the liver, by the macrophages (Kupffer cells) [69].

During African trypanosomosis, the VSG-specific B cell responses can occur in a T-cell independent manner [77]. Because of antigenic variation, each wave of parasitemia represents a new antigenic variant and is controlled by a variant-specific antibody response. This variant-specific immunity can be transferred by B cells but not by T cells [78].

Stability of Trypanotolerance: The stability of trypanotolerance depends on different factors such as the severity of the tsetse–trypanosomosis threat of the exposed animals, stress (work, pregnancy, parturition, lactation and suckling), intercurrent disease and poor nutrition [52]. Stability of trypanotolerance may also be related to a number of physiological factors possessed by

trypanotolerant breeds which help to survive trypanosome infection. These factors possibly include superior ability to utilize food, to tolerate heat and to conserve water [79]. N'Dama cattle can withstand higher levels of humidity than Zebu and has been reported to experience a considerable range in rectal temperature from 34.4°C at dawn to 41.1°C in late afternoon [80].

It was believed that the resistance of trypanotolerant breeds was largely the result of acquired immunity to local trypanosome populations and that "tolerance" would break down if cattle were moved and there is evidence to confirm that trypanotolerant cattle, exposed to tsetse challenge, do become more resistant, either as a result of locally acquired immunity or a primed erythropoietic response [52].

Trypanotolerance Indicators

Anaemia: The most important characteristics of infected trypanotolerant animals are they develop less severe anaemia than more susceptible breeds, a series of erythrokinetic and ferrokinetic studies of N'Dama and Zebu infected with *T. congolense* or *T. brucei* showed that the anaemia and its underlying processes broadly reflected the numbers of parasites in the blood. Consequently, it appeared that the differences in anaemia between N'Dama and Zebu were due to their capacity to control parasitaemia and could not be attributed to differences in innate erythropoietic responses [52]. Trypanosome infection in susceptible animals could have an inhibitory effect on cell production in the bone marrow and/or result in the premature destruction of developing cells [81].

Parasitaemia: The mechanism that lead to the maintenance of lower parasite loads in trypanotolerant breeds compared with susceptible breeds are not clearly understood, outcomes from laboratory experiments indicate that the killing of trypanosomes in host animals results from inhibition of the trypanosome glycolytic pathway and ATP production [82].

The degree of parasitaemia is not so easy to quantified and quantification depends on demonstration of trypanosomes in peripheral blood by parasitological techniques. The most sensitive practical field approach used to detect the presence of trypanosomes is the dark ground/phase contrast buffy coat technique (BCT) it quantifies the intensity of the infection as a parasitaemia score [83]

Productivity Performance: Trypanotolerant livestock are highly productive in greatly tsetse crowded areas compared with the larger but susceptible breeds under zero to low tsetse challenge conditions. In a recent economic analysis of production systems, the output per head of cattle in trypanotolerant herds per year was US$93 in tsetse-infested environments and was 39 percent (US$67) and 26 percent (US$74) higher than those in transhumant (seasonally migrated livestock) and sedentary mixed herds in similar environments, respectively (Table 1). The corresponding figure in tsetse free environments for output per head per year were US$99, US$75 and US$86, showing that trypanotolerant livestock were 32 percent and 15 percent more productive than susceptible transhumant and mixed herds, respectively. Thus, there is both a biological and economic justification for keeping trypanotolerant livestock [84].

Prospects and Future Exploitation Approaches: It is estimated that an area of some two million km^2 in West and Central Africa is suitable for trypanotolerant cattle without any additional control measures [85]. Certain countries, including Nigeria and Gabon, have recognized the potential contribution that trypanotolerant breeds can make to increasing their capacity to meet the growing need for food as a result, they are importing N'Dama cattle in order to establish breeding nuclei for future livestock development in tsetse-infested areas [86].

Trypanotolerant breeds offer prospects for livestock agriculture in new areas where other livestock breeds cannot survive. However, the expansion in numbers of these relatively few animal genetic resources, especially of the cattle breeds, is not guaranteed because of fear of replacement and adaptation. paradoxically, the diversity in animal genetic resources created by the presence of strains of Trypanotolerant livestock stands to erode this diversity as the more prominent among them, for example the N'Dama cattle, are more forcefully and extensively promoted at the expense of the less popular breeds [87].

For an assured future presence and use of these unique resources, a balanced utilization strategy that ensures the conservation of all breeds and strains is needed. It has been argued that genes, which do not have commercial value currently, may become important in the future [88]. Certainly, it is said that the future utilization of the genetic resources represented by trypanotolerant cattle to harvest the biomass of much of humid sub-Saharan Africa depends on their conservation, promotion and improvement. Conservation of animal genetic resources, including trypanotolerant livestock, more seriously in the future than was the case in the past is mandatory [89].

Table 1: Comparison of biological and economic performance of susceptible cattle herds (in transhumant and sedentary systems) and Trypanotolerant herds in tsetse-free and tsetse-infested environments

	System/susceptibility status of herd					
	Transhumant (fully susceptible)		Sedentary (mixed: susceptible + tolerant)		Trypanotolerant (tolerant)	
Biological or economic parameter	With *tryps*	Without *tryps*	With *tryps*	Without *tryps*	With tryps	Without *tryps*
Annual mortality (%)	6.5	5.2	5.4	4.4	10.1	9.9
Annual herd growth rate (%)	2.4	4.9	2.3	3.9	1.9	2.9
Output per head per year (US$)	67	75	74	86	93	99

Note: Tryps=Trypanosomosis. Source: (84).

Trypanotolerance in Ethiopia: In Ethiopia, approximately 15% of all arable land is under tsetse and trypanosomosis challenge. Extensive research as well as trypanosomosis controlling programs has been carried out in different parts of the country and in the Ghibe valley in particular [90]. However, despite many years of research trypanosomosis is still a major problem in many areas of Ethiopia. In the year 2000, ILRI and EIAR started a breed comparison project located in the Ghibe valley. The breeds compared were Abigar, Gurage, Horro and Sheko. The aim of the project was to investigate whether or not trypanotolerant cattle breeds exists in Ethiopia [91].

The Horro breed is a Zenga breed and it may possess some level of trypanotolerance. Nevertheless, the trypanotolerant characteristics are not altogether displayed by the Horro cattle. Instead, they have a relatively high parasitaemia (17-20 %). However, despite the higher level of parasitaemia, the Horro breed showed the best survival rate, production and reproduction. Although the Horro breed have a high level of trypanosomosis and needed more trypanocidal treatments, they still have a good and sometimes better performance. This explains that if trypanocidal drugs are readily available, the Horro breed could be a good choice in tsetse infested areas [12].

The Sheko breed classified as a humpless Shorthorn and is the only known breed of taurine type of eastern Africa [92]. The breed is found in the Bench-Maji zone of Southern Region in the south-western parts of Ethiopia. Early information claims that the Sheko possess trypanotolerant attributes [93] and later research has supported this[94].

Among four indigenous cattle breeds of Ethiopia, namely Abigar Horro, Sheko and Gurage, to natural challenge of trypanosomosis in the Ghibe valley reveled that Sheko breed has manifested very high overall average packed cell volume (PCV) values, the lowest mean trypanosome prevalence rate, the least number of trypanocidal treatments, lower mortality rate, slightly higher birth weights and highest calving rate of 51% [92].

CONCLUSION AND RECOMMENDATIONS

Trypanosomosis vector control is practical only at adult stage of tsetse flies as their eggs and larval stages remain in the soil; this condition limits the effective control of vectors. Sterile insect technique is most advisable to the environment but only effective when the tsetse population density is low, it requires full knowledge on the biology and ecology of the target vector and the insect should be willing to mass-rearing. Chemotherapy of trypanosomosis with the presently existing drugs develops resistance due to the irregularly use of those drugs by farmers. Vaccination against African trypanosomosis is either partially successful or totally failed because of very complex variant surface glycoproteins. Trypanotolerant cattle e.g. N'Dama is most effective and economical in trypanosome affected areas and their 'tolerance' resulted from some traits. In Ethiopia Sheko shows high trpanotolerant characteristics. Trypanotolerant animals have the capacity to reduce severe anaemia and parasitaemia, but the mechanism is not well understood.

Having said the above conclusion the following points are recommended for future control program:

- Molecular based researches on alteration of tsetse flies genetic materials particularly their salivary gland is encouraged together with the existing control options.
- Further studies on trypanotolerant gene(s) and haemopoeitic system should be approved to improve the productive potential of these traits in trypanotolerant animals. Moreover, policy makers and other stakeholders should cooperate to advance the important traits of trypanotolerant breeds.

- Production of trypanotolerant breeds together with other control options in tsetse infected areas is recommended until eradication is achieved.
- There is a promising situation where non variant surface glycoprotein trypanosome component targeting vaccine can be developed in the future and this helps in the fight against trypanosomosis. Therefore, the scientific community should strengthen their collective capacity towards vaccine development.

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