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Review on Acaricide Resistant Bovine Ticks and Alternative Solutions

Dita Abebe and Assefa Kebede

Jimma University College of Agriculture and Veterinary Medicine, P.O. Box: 307 Jimma, Ethiopia

Abstract: Acaricide resistance defined as a reduction in susceptibility of bovine ticks against currently used acaricide in tick prevention and control at the recommended concentration and according to all of the recommendations for its use.Currently, acaricide resistance of livestock ticks are becoming the major challenge in fighting tick and tick borne parasites in the tropical and subtropical regions. For example, most *Rhipicephalus (Boophilus*) species are reported to be resistant for Organochlorines, organophosphates, prethroids and macrocyclic lactones. Despite this fact, there is no a compiled information on this issue;therefore, the objectives of this seminar paper are to compile information related to acaricide resistance bovine ticks and alternative solutions in mitigating the problem. Tick resistance to acaricides is an increasing problem and real economic threat to the livestock and allied industries. The mechanisms of action for acaricide resistance development include the action of detoxification enzymes or mutations at the target site of the chemical. The factors that influence the establishment and development of resistance in ticks include the frequency of the original gene mutation, mode of inheritance of the resistant allele, frequency of acaricide treatment, irrational use of acaricides and use of poor quality acaricides. A variety of bioassay methods has been developed for assessing the susceptibility of ticks to acaricides, but the once used most often for tests with organophosphates, carbamates and pyrethroids are the larval packet test and the larval immersion test. Breeding of tick resistance cattle, pasture spelling, pasture burning and some special grasses have also been considered for tick control.Information on the status and magnitude of acaricide resistance is the paramount importance in deciding the appropriate tick and tick-borne disease control strategy in different localities in the Africa including Ethiopia. Therefore, to improve the situation, development of strong national legislation in rational use of acaricide and alternative solutions should be promoted.

Key words: Acaricide · Bovine · Resistance · Tick

INTRODUCTION

Ticks and tick-borne diseases are widely distributed throughout the world, particularly in tropical and subtropical regions. It has been estimated that 80 percent of the world's cattle population is exposed to tick infestation. Although species of ticks and tick borne diseases (TBDs) differ among ecological regions, their impact on animal production is important wherever they occur. Tick control in livestock using acaricides began in the 1970s with the production of diethylethion [1]. From 1992 to the end of 1997, deltamethrin was used but the tick population was declared resistant and was replaced by amitraz. The resistance of ticks to acaricides is an inherited phenomenon and is resulted from exposure of tick populations to chemical acaricides, survival and reproduction of ticks that are less affected by the acaricide. The higher reproductive rate of ticks that have heritable resistance factors against acaricides and the resulting increase in the proportion of the tick population that carry genes for these factors is known as selection [2].

The mechanisms of acaricide resistance involve the action of detoxification enzymes or mutations at the target site of the chemical. The factors that influence the establishment and development of resistance in ticks include the frequency of the original gene mutation, mode of inheritance of the resistant allele, frequency of acaricide treatment, use of low doses and the use of poor quality acaricides [3]. There are several in-vitro tests developed for testing tick resistance against currently existing acaricide in the market. The larval packet test is

Corresponding Author: Dita Abebe, Jimma University College of Agriculture and Veterinary Medicine, P.O. Box: 307 Jimma, Ethiopia.

considered to be the most repeatable, although it is limited by the length of time that it takes. Hence it remains the test of choice for surveys and for definitive confirmation of a diagnosis of resistance. The adult immersion test with a discriminating dose has recently been recommended as a preliminary screening test for resistance because it is relatively rapid, but further work is required to determine just how sensitive and specific the test is for acaricide resistance. In the meantime, it is probably most appropriately used to provide rapid supporting evidence when control breaks down in the field [4, 5].

Since, the trend of tick resistance against existing acaricides is increasing; searching for alternative solutions is becoming the timely issues in tropical areas of the world. One of the possible solutions for this matter is selection of tick resistant breeds of cattle. Host resistance, expressed by an animal's ability to prevent the maturing of large numbers of ticks and disease immunity, are survival mechanisms for the host and for external and internal parasites. The natural tick resistance character of zebu cattle and their crosses should be given more emphasis in the tick control. Improvement of the nutrient value of pasture would allow cattle to develop a better resistance to tick infestation. Pasture alternation, pasture burning and use of certain grasses and legumes are also practiced for inhibition or killing of ticks [6].

The absence of an appropriate and effective legislation for acaricide importation, marketing and acaricide use monitoring, tick's resistance to acaricides is increasing. In Ethiopia, unconfirmed reports from different corners of the country are strongly suggesting the emerging tick acaricide-resistance in different parts of the country. Information on the status and magnitude of acaricide resistance is the paramount importance in deciding the appropriate tick and tick-borne disease control strategy in different localities in the country [7].

Currently, acaricide resistance of livestock ticks are becoming the major challenge in fighting tick and tick borne parasites in the tropical and subtropical regions. For example, most *Rhipicephalus (Boophilus*) species are reported to be resistant for Organochlorines, organophosphates, prethroids and macrocyclic lactones. Despite this fact, there no compiled information on this issue; therefore, theobjectives of this seminar paper are:

- To compile information on acaricide resistant bovine ticks
- Its alternative solutions

Literature Review:

Common Acaricides Used to Control Bovine Ticks: There are several methods being applied for controlling ticks and tick-borne diseases. The main weapon for the control of ticks at present is the use of chemical acaricides. Control of tick infestation through the use of acaricides not only reduces tick population but also it reduces tick-borne diseases. A wide range of acaricides, including arsenical, chlorinated hydrocarbons, organophosphates, carbamates and synthetic pyrethroids are being used for controlling ticks on livestock. The performance of an acaricide in the control of ticks depends not only on the activity of a product, but also on the quality and quantity of active ingredient sprayed" on cattle or delivered internally [8].

Bovine Ticks Resistance Against Acaricide

Definition of Resistance: Resistance is generally first recognized as failure of a drug to control parasitism but the formal definition of resistance is a shift in the target species susceptibility to a drug [13]. Corley*et al.* [14] has developed the definition of resistance in broad terms as "the ability of a parasite strain to survive and/or to multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within the limits of tolerance of the subject". Such a general definition could be accepted as a basis for discussions on acaricide resistance [15]. Resistance to acaricide is usually recognized because of failure to obtain a satisfactory kill of the parasitic stages on treated animal. The first tick resistance outbreak was reported from Australia on cattle tick, *Boophilus microplus*, to arsenic compounds and subsequently from South Africa and Latin America. Resistance to this chemical did not appear until after several decades of use, but resistance to chlorinated hydrocarbons appeared with far greater rapidity and is now complicated by cross-resistance between various compounds of the group [7]. Acaricides resistance are caused by treatment frequency – the more often ticks are exposed to the chemical, the more likely they will develop resistance to it, under-dosing risks tick survival, enhancing tolerance/resistance to the chemical and persistent use of one chemical group for tick control [16].

Types of Acaricide Resistance

Acquired Resistance: Is "A resistance that results from heritable resistance decreases in sensitivity to drugs through time" [17, 18].

Table 1: Common acaricides used in cattle ticks control worldwide in the history of acarines.

Acaricide group	Examples	Bovine ticks
Organochlorines	Dieldrin, aldrin and toxaphene	*Rhipicephalus* (*Boophilus*)
Macrocyclic lactones	Avermectins and milbemycins	*Rhipicephalus*(*Boophilus*)*annulatus*
Carbamates	Carbanolate and butocarb	*Hyalomma anatolicum*
Pyrethroids	Deltamethrin, permethrin	*Rhipicephalus turanicus*
Fluazuron	Di?ubenzuron and lufenuron	*Rhipicephalus* (*Boophilus*) *annulatus* and *microplus*
Organophosphates	Ethion and chlorpyrifos chlorfenvinphos and coumaphos	*Amblyomma*
Amidine	Amitraz	*Rhipicephalus* (*Boophilus*)

Source: Rajput *et al.*[9]

Table 2: Acaricides currently used in bovine tick control, mode of action and their target sites

Acaricides	Sites of action	Mode of action	Examples	References
Organophosphates	Acetylcholinesterase	Inhibiting the action of acetylcholinesterase at cholinergic synapses and at muscle end plates	Malathin, diazinon, fenthion dichlorvs	[10]
Macrocyclic Lactones	Glutamate–gated Cl- -channel	Blocking nerve signals by interfering with the glutamate gated chloride(GlCl)	Avermectin	[11]
Pyrethroids	GABA-gated chloride channel antagonists	Prolonged opening of sodium channels in nerve, muscle and other excitable cells.	Decametrina fenvalerate	[12]
Organochlorines	GABA-gated chloride channel antagonists	Binding at the picrotoxinin site in the gamma amino butyric acid chloride ionophore	Toxaphee	[6]

Cross-Resistance: Is the sharing of resistance among different acaricides with a similar mode of action. A significant pattern of cross resistance has been shown among two organophosphates (Coumaphos and diazinon) and one carbamate (Carbaryl) acaricides in several strains of *R. microplus* [19-21]. Insensitivity of AChE is considered as an important mechanism of resistance against carbamates and organophosphates. Rotation or alternation of different groups of acaricides that have no cross resistance reduces the selection pressure for resistance to any one acaricide group By other meaning, if you used acaricide A and B have the same mode of action from two different chemical groups then there is no resistance. But if you used A alone it may be resistance arise to B. [22, 23].

Multiple Resistances: Is a resistance to more than one drug, even though they have different modes of action. A significant multiple resistance occurrence in populations of *R. microplus* infesting cattle against many classes of acaricide including chlorinated hydrocarbons (DDT), pyrethroids, organophosphates and formamidines (Amitraz)[4]. Target site mutations were the most common resistance mechanism observed in the ticks for these chemicals, but multiple resistances against acaricides with different modes of action also leads to the conclusion that metabolic mechanisms are also contributing for acaricide resistance development [24, 25].

Mechanisms of Acaricide Resistance

Resistance Against Organochlorines: Organochlorines have been in use as acaricides since 1946. They were the first synthetic insecticides to be marketed and many of them were formulated for the control of ticks on cattle. The mode of action of these compounds is thought to involve binding at the picrotoxinin site in the gamma-amino butyric acid (GABA) chloride ionophore which inhibits Cl-flux into the nerve. With the function of the GABA-ergic inhibitory neurons impaired, hyperexcitation results which ultimately causes death. The mechanisms of resistance have been suggested to be primarily enhanced metabolism and reduced absorption of the chemical [6].

Resistance Against Organophosphates and Carbamates: Organophosphates were introduced around 1950, as a replacement for the chlorinatedhydrocarbons to which significant resistance had occurred. Tick resistance to organophosphates is normally associated with a single semi-dominant gene; in other words, heterozygous individuals also present resistance, although to a lesser extent than homozygous individuals. Organophosphates (OPs) were among the first chemical groups used to control arachnids. Unlike the persistent organochlorines, the organophosphate compounds that replaced them were chemically unstable and non-persistent. The organophosphates are generally categorized as the most toxic of all pesticides to vertebrates and are closely related to the nerve gases sarin, soman and tabun [26]. The development of organophosphate acaricides was primarily for the control of organochlorine-resistant *Boophilus* ticks that had become common throughout much of the cattle producing areas of the tropics and subtropics [27].

Ethion, chlorpyrifos, chlorfenvinphos and coumaphos are four of the most widely used organophosphates for the treatment of tick-infested cattle. Both Ops and carbamate acaricides exert their toxic effects on ticks by inhibiting AChE, a key enzyme vital to the function of the nervous system [28]. When ticks are poisoned with a cholinesterase inhibitor, the cholinesterase is not available to help break down the acetylcholine and the neurotransmitter continues to cause the neuron to "Fire, " or send its electrical charge. This results in over stimulation of the nervous system and ultimately arachnid dies. The first decline in the sensitivities of arachnids against OPs occurred in the early fifties. Since then, arachnids have developed resistance to more than 30 Ops and carbamates in 40 countries. Target-site insensitivity in arachnids seems to be the most common OP resistance mechanism [29, 30].

Resistance Against Amidines (Amitraz): Amitraz, triazapentadiene compound, is a member of the amidine class. Amitraz has been an effective treatment against the ticks of cattle. Amitraz has been in use for more than 30 years but resistant populations have been reported. The mode of action of amitraz is thought to be its toxic effects on a receptor for the neuromodulator, octopamine. Bioassays with synergists suggest the involvement of P450 cytochrome monooxygenases together with modification of the target site. The molecular basis of target-site resistance was two nucleotide substitutions in octopamine receptor in the resistant strains of ticks that result in amino acids different from all the susceptible strains [13]. Discovery of these mutations only in amitraz-resistant ticks provided the first evidence for the possibility of an altered target site as a mechanism of amitraz resistance in ticks [5].

Resistance Against Pyrethrin's/Pyrethroids: Resistance mechanisms for pyrethroids that act in the cattle tick are beginning to be understood at the molecular level. Voltage-gated sodium channels are the target of pyrethroid activity and resistance development [5]. Conserved point mutations in the voltage gated sodium channel gene have been associated with pyrethroid resistance in a wide range of pests and disease vectors, while metabolic resistance mediated by carboxylesterases or P450s is also well documented. *R. microplus* is resistant to active principles of decametrina and fenvalerate, both synthetic pyrethroids [29].

Resistance Against Macrocyclic Lactones: Macrocyclic lactone acaricides include the avermectins and milbemycins. Avermectins are produced by the soil microorganism, *Streptomycesavermitilis*, which was first isolated in 1976 from a soil sample in Japan. Milbemycins were first described from a culture of *Streptomyces hygroscopicus* and are structurally similar to the avermectins but lack the disaccharide at C13 [6]. Macrocyclic lactones block the transmittance of electrical activity in nerves and muscle cells by stimulating the release and binding of gamma-aminobutyric acid (GABA) at nerve endings. This causes an influx of chloride ions into the cells leading to hyperpolarisation and subsequent paralysis of the neuromuscular systems. Macrocyclic lactones have been effectively used in controlling the Southern cattle tick. Because of intensive use, partial resistance has been reported in *R. microplus*, but the exact mechanism of resistance is still unknown in ticks and parasitic mites. However, on the basis of the hypothesized mechanism of resistance in nematodes against macrocyclic lactones concluded that resistance in ticks and mites might be due to target site insensitivity of the GABA or glutamate gated chloride ion channels [31].

Order of Acaricide Resistance Developments: Use of arsenic was the first effective method for controlling ticks and tick-borne diseases and was used in many parts of the world before resistance to the chemical became a problem. Resistance to arsenicals was developed in many species of ticks and it was replaced by chlorinated hydrocarbons. Chlorinated hydrocarbon acaricides are very persistent and have been used extensively throughout the world for controlling ticks. Organophosphates were introduced around 1950, as a replacement for the chlorinated hydrocarbons to which significant resistance had occurred and have a wide range of activities against ticks at very low concentration in companion and livestock animals [9].

Factors Involved in Resistance Development

Genetic Factors: Parasite genetic factors are heritable trait and the genes that confer resistance are likely to be present in the population at low frequencies before the introduction of a new chemical [32]. It includes dominance of resistance alleles, number of genes involved, initial

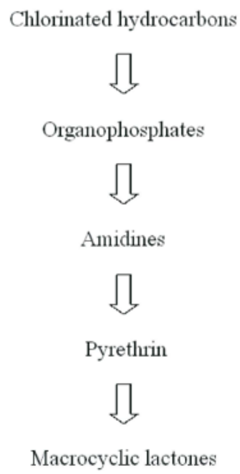

Fig. 1: Order of acaricide resistance developments
Sources: Abbas*et al*. [6]

frequency of resistance genes, genetic diversity of population, relative fitness of resistant organisms, chance of linkage disequilibrium and opportunity for genetic recombination [6].

Operational Factors: Operational aspects include chemical nature of drug, possibility of cross resistance, drug persistence in the host and drug clearance kinetics. Drug application factors include application and selection threshold, life stage(s) selected, mode of application, frequency of treatment, timing of treatments, spatial use of treatments and using other forms of control. Another contributing factor in the development of acaricide resistance may be under dosing which may be the result of poor drug quality. This may allow for the selection of mutants initially resistant to low levels of acaricides [6].

Biological Factors: Are classified as biotic or behavioral. Biotic factors include generation time, offspring per generation and breeding patterns. Behavioral aspects are those that affect gene flow and the chance of selection. These include isolation, mobility, migration, host range, fortuitous survival and refugia. The biological aspects, mainly associated with the host–parasite relationship, also influence the mechanism of selection for resistance. For example, parasites which induce effective immunity in their hosts will be under weaker selection pressure for resistance because immunity selects parasites irrespective of drug-resistance status and this reduces the chance of resistant parasites surviving and reproducing [33].

Major Bovine Tick Develop Acaricide Resistance: The history of the resistance of ticks to acaricides parallels, with a relatively few years of delay, the introduction of ew acaricide products representing several different classes of chemicals. Resistance of Boophilus microplus to tickicides is widespread in Latin America and Australia, as well as resistance of Boophilus decoloratus in Africa. It means mainly resistance to active ingredients belonging to the organochlorines, organophosphates, synthetic pyrethroids and/or amidines [34]. *Amblyomma hebraeum* and *cariegatum, Rhipicephalus appendiculatus* and *evertsi* and *Hyalomma anatolicum* arecurrently resistant to many acaricides groups [35].

Methods of Acaricide Resistance Development Identifications: Experiences of Farmers about Acaricide Resistance in the Cattle Tick. When cattle are dipped, the ticks fall off or die. After this process, the cattle emerge free of ticks. There are likely to have a problem if still find many ticks on the cattle after dipping. This is a sign that the acaricide is not working as well as it should and that the ticks may have developed resistance to it [36].

Bioassay: The fact that there are several tests in use for the diagnosis of acaricide resistance in ticks should serve to indicate that none of the tests is perfect in all circumstances [27]. A variety of bioassay methods has been developed for assessing the susceptibility of ticks to acaricides, but the ones used most often for tests with organophosphates-carbamates and pyrethroids are the larval packet test (LPT) and the larval immersion test (LIT) [37].

Larval Packet Test (LPT): This standard test is used to evaluate the acaricide resistance of ticks [38]. The larval packet test is considered to be the most repeatable, although it is limited by the length of time that it takes. Hence it remains the test of choice for surveys and for definitive confirmation of a diagnosis of resistance. In this test, tick larvae are exposed to chemically impregnated filter papers and their subsequent mortality is quantified after 24 hours. Adequate training is essential in order to achieve a high degree of confidence in this technique [27].

Larval Immersion Test (LIT): This larval bioassay is not so widely used for the diagnosis of resistance and has not been promoted by [27]. The LIT was demonstrated to be a very sensitive assay, with which it was possible to diagnose IVM resistance in some populations of cattle ticks before this resistance could be observed through

Table 3: Major Bovine Tick Develop Acaricide Resistance.

Species	Acaricide	References	Location
Boophilus microplus and *Boophilus decoloratus*	Organochlorines, organophosphates, synthetic pyrethroids and/or amidines	[34]	Latin America and Africa
Amblyomma hebraeum and *cariegatum*	Organophosphorus and Carbamate group	[8]	Latin America and Africa
Rhipicephalus appendiculatus and *evertsi*	Organophosphorus and Carbamate group	[8]	Brazil and
South Africa Hyalomma anatolicum	organochlorines and amitraz	[35]	India

efficacy failures or complains from ranchers [39]. The method provides a result in six weeks, the same time as the LPT. Comparative studies have indicated LIT results can be compared with LPT results as there is good agreement between results of the test methods. The inability of the LPT to diagnose potential resistance to fluazuron also applies to LIT [2].

Adult Immersion Test (AIT): Is a bioassay applied to engorged, female ticks. The AIT was used to determine the relative effectiveness of new acaricides against a number of tick species. Engorged adult female ticks are immersed in one of a series of dilutions of commercial acaricide in water and then incubated at room temperature for 7 days [40].

Economic Implications: Tick resistance to acaricides is an increasing problem and real economic threat to the livestock and allied industries [8]. Heavy tick burdens cause huge economic losses via blood loss, general stress and irritation, decrease in productivity, depression of immune function, damage to hides and skin and transmission of pathogens. The development of acaricide-resistant tick populations has significant implications for the infected property. The development of acaricide resistance results in the chemical being ineffective to kill and control cattle ticks. This reduces the number of available effective acaricides in the market [16].*Boophilusmicroplus* is reported to affect in excess of 75 % of the world cattle population. The economic impact has been estimated at $7 per animal per year in United State of America and at $2billion per yearin Brazil [41].

Alternative Solutions

Selection of Genetic Resistance Breeds of Cattle: Host resistance, expressed by an animal's ability to prevent the maturing of large numbers of ticks and disease immunity, are survival mechanisms for the host and for external and internal parasites. Resistance is an acquired characteristic and each animal develops its own level of resistance in response to tick challenge; the level may be high (As in most zebu cattle) or low (As in most European cattle), but a wide range of resistance occurs in all breeds of cattle [40]. Host resistance is heritable and selection and breeding for tick resistance are possible not only in Zebu×European breeds, but also within European breeds. However, selection for resistance or culling for susceptibility must at present be based on tick numbers surviving on cattle exposed either naturally or artificially to tick challenge. In general, resistant cattle require one or two treatments per season compared with three or four in susceptible breeds. A combination of resistant cattle and pasture spelling can remove the need for chemical treatment entirely. It is, therefore, suggested that the natural tick resistance character of zebu cattle and their crosses should be given more emphasis in the tick control [6].

Nutritional Management: Improvement of the nutrient value of pasture would allow cattle to develop a better resistance to tick infestation [33]. Protein–energy deficiency is an important cause of defective T-cell function and T-cells have been shown to play pivotal role in mediating acquired resistance to ticks. Hosts maintained on a low protein diet failed to acquire resistance to ticks, lost weight and developed anemia while those on a high protein diet developed resistance, maintained weight and did not develop anemia [42].

Environmental Management: Pasture alternation, pasture burning and use of certain grasses and legumes are also practiced for inhibition or killing of ticks. Burning pasture to induce a "Green flush" in the dry part of the year (Winter) is widely used practice for controlling ticks. However, the burning of pastures on a routine basis may be difficult for the resource poor livestock raisers in the developing countries [6]. Another pasture management approach consists of keeping grazing areas free of cattle until the larvae die. Pasture alternation and/or rotation combined with applications of chemical acaricides have been proved as an effective way for the control of cattle ticks. The main factors of consideration in the feedlot cattle management are good ventilation, thorough clean out on routine basis, removal of hidden sources, optimum animal density, low stress and good feed and water management [33].

Table 4: Reports of resistance in cattle ticks against acaricides in Ethiopia.

Chemical Group	Ticks	Area	References
Organochlorine	*R. (B.) decoloratus*	Bako (West shoa)	[7]
Organochlorine	*Rhipicephalus*	Borona	[43]
Chlorinated hydrocarbons	*Amblyomma*	Arsi	[44]
Organophosphate	*Rhipicephalus(Boophilus)*	Arsi	[44]
Organophosphate	*Rhipicephalus(Boophilus)*	Humbo(Wolaita)	[45]

Status of Bovine Ticks Resistance Against Acaricides in Ethiopia: An inappropriate acaricide usage, importation, marketing and monitoring led to acaricide resistance. Information on the status and magnitude of acaricide resistance is of paramount importance in deciding the appropriate tick and tick-borne disease control strategy in different localities in the country. In Ethiopia, unconfirmed reports from different corners of the country strongly suggest the emerging presence of tick acaricide-resistance[7].

CONCLUSION AND RECOMMENDATIONS

There is a trend of increment in tick resistance against the currently available acaricides recommended for cattle use. In the other side, acaricide use in control of tick and tick borne parasite is paramount important to increase production and productivity in the tropical and subtropical regions of the world.The absence of an appropriate and effective legislation for acaricide importation, marketing and acaricide use monitoring, tick's resistance to acaricides is aggravating the situation. In Ethiopia, unconfirmed reports from different corners of the country are strongly suggesting the emerging tick acaricide-resistance in different parts of the country and calls for due attention. As alternative solutions; selection and breeding of tick resistant cattle breeds, pasture alternation, pasture burning and use of certain grasses and legumes are common practiced in some parts of the world. Furthermore, a variety of bioassay methods has been developed for assessing the susceptibility of ticks to acaricides, but the one most frequently use for testing organophosphates, carbamates and pyrethroids resitance development by ticks is performed by using larval packet and larval immersion tests.

In light of the above conclusion, the following recommendations are forwarded:

- National strong legislation in acaricide importation and use should be developed
- More attention should be given to integrated control options through the use of one or more methods like selection of resistance cattle breeds, appropriate pasture management in communal grazing area and increase of good nutrition plane to get good performance of productive breeds in the area.
- Concerned government officials, nongovernment organizations and professionals should work together in developing and application of strict policy on cattle ecto-parasite control in general and tick in particular.

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