Advances in Biological Research 10 (4): 200-212, 2016
ISSN 1992-0067

DOI: 10.5829/idosi.abr.2016.10.4.103107

Bovine Theileriosis and its Control: A Review

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Abstract: Arthropod transmitted hemoparasitic diseases are economically important vector-borne diseases of tropical and subtropical parts of the world including Ethiopia. Bovine theileriosis is a tick-borne hemoprotozoan disease of cattle caused by several theileria species and among them *T. parva*, the cause of East Coast fever and *T. annulata*, the causative agent of tropical theileriosis are the most pathogenic and economically important. The aim of this manuscript is to review currently available articles on the bovine theileriosis with a special attention to its control. Theileria have complex life cycles involving both vertebrate and invertebrate hosts. Tropical theileriosis and East Coast Fever are disease transmitted by Ixodid tick of the genus *Hyalomma* and *Rhipicephalus*, respectively. Furthermore, the sporozoites are transmitted to animals in the saliva of the feeding tick. Bovine theileriosis is characterized by high fever, weakness, weight loss, inappropriate appetite, conjunctival petechia, enlarged lymph nodes and anemia. PCR is the most beneficial molecular tool for diagnosis of infection till date than blood and lymph node smear examination and serological tests. Bovine theileriosis has global economic significance thus prevention is the best method to control losses related with the disease. Among Several control methods the most practical and widely used method is the chemical control of ticks with acaricides. However, tick control practices are not always fully effective and hence vaccination is the most sustainable option. Since there is difference in breed of cattle to tick resistance the selection of tick resistant cattle breeds is also proposed as a sustainable approach for controlling infection in developing world. Currently occurrence of tropical theileriosis is confirmed in Ethiopia thus, more research should be conducted to design and implement appropriate controland prevention strategies.

Key words: Hemoprotozoan · Theileria · Tick · Tropical theileriosis · East Coast Fever

INTRODUCTION

Arthropod transmitted hemoparasitic diseases are economically important vector-borne diseases of tropical and subtropical parts of the world including Ethiopia [1]. They are of great economic impact on livestock affecting 80% of the world cattle population and causes economic loss due to morbidity and mortality [2]. Haemoprotozoan diseases are causing devastating losses to the livestock industry and thus pose major constraints to the dairy industry throughout the world [3,4]. Theilerioses is also a tick borne protozoal disease in ruminants caused by hemoprotozoan parasites belonging to the genus *Theileria* [5]. The parasites belonging to this genus are distinguished on the basis of a distinct group of unique organelles called apical complex [6].

Theileriae are obligate intracellular protozoan parasites that infect both wild and domestic Bovidae throughout much of the world (some species also infect small ruminants). They are transmitted by ixodid ticks and have complex life cycles in both vertebrate and invertebrate hosts [7]. There are a number of species of *Theileria* spp. that infect cattle; the two most pathogenic and economically important are *T. parva* and *T. annulta* [4, 6- 8]. *Theileria parva* occurs in 14 countries [9] in sub-Saharan Africa causing East Coast fever (ECF) and still ranks first among the tick-borne diseases of cattle in sub-Saharan Africa, whilst *T. annulta* occurs in southern Europe as well as North Africa and Asia [7].

Tropical theileriosis, also known as Mediterranean coast fever, is an extremely fatal and debilitating tick-transmitted disease infecting cattle [6]. Tropical

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theileriosis is caused by *T. annulata* [10] and transmitted through Ixodid tick of genus Hyalomma. About 250 million cattle are at risk to Tropical theileriosis worldwide [11]. *Theileria parva*, is also most pathogenic species in Africa the cause of another commercially important parasitic disease called East coast fever [12] which is characterized by enlargement of superficial lymph nodes and a sustainable fever [5]. This infection causes mortality in about one million cattle annually in central, eastern and southern Africa. It threatens almost twenty five million cattle in Africa and also limits the introduction of improved breeds [6]. Hence the diseases have global serious economic impact in view of mortality, reduced milk yield, weight losses, abortions and control and prevention costs [13]. Several methodologies are currently available for the control of bovine theileriosis the most practical and widely used method is the chemical control of ticks with acaricides and vaccinations [14].

There are no clinical or serological reports of the presence of East Coast fever (*T. parva*) and its vector *R. appendiculatus* in Ethiopia. However, there is relatively uncontrolled movement of livestock from southern Sudan and Kenya, where the disease and vector (the brown ear tick) are found, suggests that there is high risk to be introduced [15]. Some of the past studies confirmed that *T. mutans*, *T. velifera*, and *T. orientalis* infect cattle in western, eastern, and southern Ethiopia [16-18]. Gebrekidan *et al*. [19] also reported a widespread distribution of Theileria spp. among domestic ruminants in northern Ethiopia in which bovine tropical theileriosis is reported for the first time.

In spite of aforementioned situation of bovine theileriosis and the economic importance of the diseases throughout the world there is paucity of well documented information specifically in Ethiopia. Accordingly, the motivation for this review arises from the recognition of global economic importance of the disease and possibility of the disease occurrence in Ethiopia. Therefore, the main objective of this paper is to review currently available articles about bovine theileriosis with a special attention to the control of the disease.

Literature Review

Etiologic Agent and Taxonomy: Theileriosis results from infection with obligate intracellular protozoa parasites in the Kingdom of Protista, Subkingdom: Protozoa, Phylum: Apicomplexa, Class: Sporozea, Subclass: Piroplasmia (piroform, round, rod-shaped parasites), Order: Piroplasmida and Family: Theileriidae, Genus: Theileria [9, 20]. Theileria are phylogenetically most closely related to members of the Babesia genus under the phylum Apicomplexa. The Phylum Apicomplexa comprises a large group of complex eukaryotic organisms known to be obligate parasites of vertebrates and invertebrates [21]. The phylum is divided into four principal groups; the Coccidia, Gregarinasina, Haemospororida and the Piroplasmorida [22]. The Piroplasmorida comprises two main genera (Babesia and Theileria) and responsible for the economically important diseases of domestic and wild animals [21].

Globally, *Theileria annulata* (cause of tropical theileriosis) and *Theileria parva* (causes of East Coast fever) are the most economically important tick-transmitted pathogenic species causing bovine theileriosis [4, 8]. These Protozoal parasites are round, ovoid, rod like or irregular shaped organism found in lymphocytes, histiocytes and erythrocytes [4]. *Theileria mutans, T. orientalis/buffeli, T. velifera* and *T. taurotragi* can also infect domesticated ruminants [7] and they are believed to cause milder and/or nonpathogenic theileriosis. However, recently, *T. orientalis complex* caused significant morbidity, economic losses and/or mortality in cattle in the Asia-Pacific region [23].

Life Cycle: The life cycle of Theileria parasite is complex, involving morphologically distinct phases in two hosts [6]. Theileria sporozoites enter their bovine host during tick feeding and they rapidly invade mononuclear leukocytes, where they mature into macroschizonts and induce proliferation in host cells [24]. Microschizonts gradually develop into macroschizonts and ultimately into merozoites, which are released from leukocytes. These merozoites invade erythrocytes and develop into piroplasms [25]. A generalized lifecycle for the genus Theileria include secretion of infective sporozoites during tick feeding into the feeding site (Figure 1). Sporozoites then infect leukocytes and multiply by merogony, after which merozoites are released, which invade red blood cells thereby establishing the piroplasm stage. During a next feeding cycle, larval or nymphal vector ticks ingest piroplasms and the released parasites undergo syngamy in the tick gut, forming a zygote, the only diploid stage. The zygote divides into motile kinetes that infect the tick gut epithelial cells and migrate to the

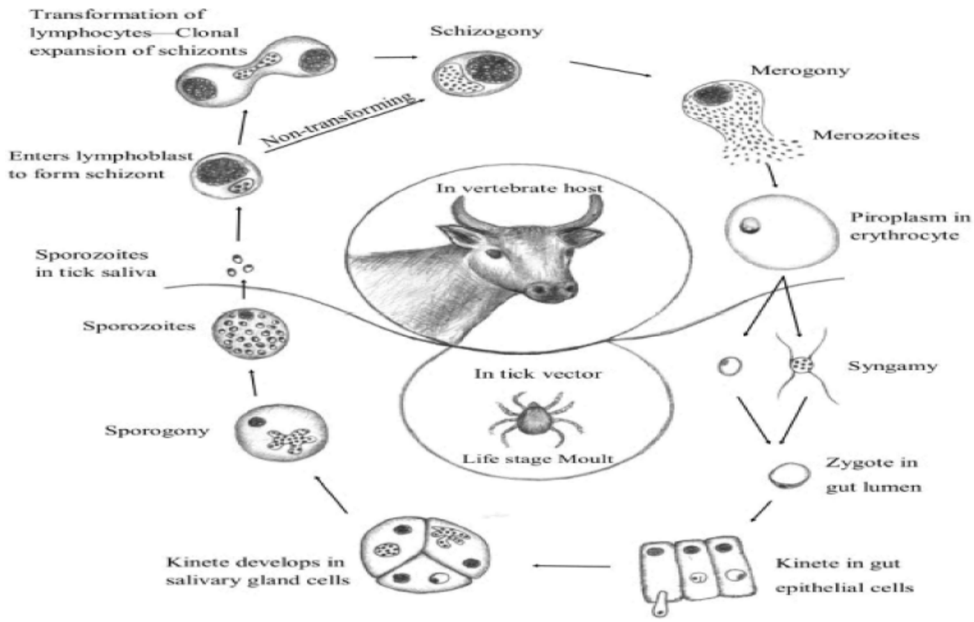

Fig. 1: A generalized life cycle of the Theileria parasite
Source: Mans *et al*. [21]

haemolymph and subsequently infect the salivary glands. After moulting and commencement of feeding by the tick, sporogony results in the multiplication of sporozoites in the salivary gland acini before injection into the feeding site by nymphs or adult ticks [21].

Epidemiology: Theileria epidemiology considers parasite and vectors distribution, mortality and morbidity of disease outbreaks, risk factors and, host range which includes host resistance and susceptibility [12].

Geographical Distribution: The geographical distribution of tropical theileriosis, is mainly determined by the location and biology of its vector, ticks of the genus Hyalomma [26]. Therefore, the incidence of the disease has a seasonal occurrence, which is modulated by the ecology of its vectors [27]. *Theileria annulata* (tropical theileriosis) occurs from southern Europe and the Mediterranean coast through the Middle East and North Africa and into parts of Asia [28]. The disease is prevalent in the South Eastern Europe, Southern Europe (Portugal, Spain, Italy, Bulgaria, Greece and Turkey) the near and Middle East, India, China and Central Asia [27]. Tropical theileriosis has also been reported in Ethiopian cattle by Gebrekidan *et al.* [19]. It is important to emphasize that endemic region of *T. annulata* and *T. parva* do not overlap [7] however, there were reports of coexistence in southern Sudan [28].

Theileria parva (East Coast fever) is found in sub-Saharan Africa (Table 1) and is prevalent in fourteen countries in Southern, Central and Eastern Africa [9]. The affected countries are Kenya, southern Sudan, Burundi, Tanzania, Malawi, Rwanda, Zaire, Mozambique, Zambia, Uganda and Zimbabwe [12]. *Theileria mutans*

Table 1: Different species of Theileria affecting domestic animals and their vectors and Distributions

Species	Host	Vector	Disease	Distribution
T. parva	Cattle and Buffalo	*R. appendiculatus* *R. zambezienesis*	East Coast Fever	East, Central Africa
T. annulata	Cattle	*Hyalomma*	Tropical theileriosis	Southern Europe, North Africa, Middle East, Sudan, central Asia and Indian subcontinent
T. mutans	Cattle buffalo	*A. variegatum*	Benign bovine theileriosis	Sub-Sahara Africa and possibly the Caribbean
T. hirci	Sheep and goat	*Hyalomma*	Malignant theileriosis of Sheep and goats.	North Africa, South Europe, Middle East. Asia

Source: Mohammed, [29]

has been found in African and on some Caribbean islands and was reported from the U.S. in 1950 and 1975. *Theileria velifera* and *T. taurotragi* occur in Africa [28]. *Theileria orientalis/buffeli* is widespread throughout the world. Infection is generally subclinical; however, disease can occur in cattle depending on a number of epidemiological factors including previous exposure to theileriae, stress or health status and variations in the species pathogenicity [7].

Host Range: Theileria species infect a wide range of both domestic and wild animals [21] *Theileria parva* can infect cattle, African buffalo (*Syncerus caffer*), water buffalo and waterbucks. Symptomatic infections are common only in cattle and water buffalo [28]. *Theileria parva* is highly virulent for European dairy cattle, however, the indigenous cattle breeds and African buffaloes in endemic areas have a natural resistance to this *Theileria* species [30]. The introduction of *T. parva* infection into a previously unexposed cattle population results in an epidemic situation with mortality up to 95% in all age categories of cattle [5].

Theileria annulata occurs in cattle (*Bos taurus* and *Bos indicus*), yaks, water buffalo and camels [26]. Mildly pathogenic and nonpathogenic species found in cattle include *T. mutans*, *T. buffeli*, *T. velifera*, *T. taurotragi* and *T. sergenti* has also been recognized. Theileria spp. has also been found in most wild Bovidae in Africa and reported in wild animals in other continents. *T. lestoquardi*, *T. separata*, *T. ovis* and other species occur in sheep and goats [28]. *Theileria annulata* sporozoites can be transmitted to goat and sheep and cause mild febrile response, however limited experimental studies indicate that schizonts and piroplasms are not produced in these host species [26].

Risk Factor: The prevalence of theileriosis depends upon geographical region and several other factors like tick density, climatic conditions, age, gender, management practices and immunity [6]. Prevalence is also influenced by cattle breed as cattle usually differ in tick resistance and innate susceptibility to infection [31]. Tropical theileriosis is more severe in exotic and cross-bred cattle (*Bos taurus*) than indigenous animals (e.g., *Bos indicus*). For example, the disease became significant in India when a program was launched to increase milk production by introducing exotic breeds. Mostly, the disease occurs in its subclinical form, leading to significant economic losses; without treatment or control, case fatality rates can reach 80 % in exotic breeds, compared with ~ 20 % in indigenous breed [32]. Age is one risk factor for example in the recent study by Saeed *et al*. [10] the prevalence of tropical theileriosis in young animals (23.4%) showed a higher prevalence than did adults (15%). Innate immunity in calves is not developed enough to combat *T. annulata*. Furthermore, in the result of reviewed study prevalence was found to be higher in females (24.6%) than male (13.1%).

Environmental Factor is also a risk factor for bovine theileriosis. The disease occurs when there is much tick activity, mainly during summer but a single tick can cause fatal infection [33]. The presence of ticks on animals an important risk factor for the spread of theileriosis [25]. Saeed *et al*. [10] reported as there is higher prevalence of *T. annulata* in hot dry summer. High ambient temperature in this season provides an environment conducive to growth and multiplication of ticks and ultimately increases the transmission of theileriosis.

Transmission: Knowledge about tick vectors, their intensity and abundance is crucial studying epidemiology of theileriosis [6]. Almost 80% of the cattle are exposed to tick infestation worldwide [34] and ticks are responsible for severe economic losses both through the direct effects of blood sucking and indirectly as vectors of pathogens and toxins. Feeding by large numbers of ticks causes reduction in live weight gain and anaemia among domestic animals [35]. Warm and moist climate is conducive for rapid growth and development of ticks [3]. Ticks are mostly found in the inguinal/groin region and external genitals as these body parts are richly supplied with blood and the thinner and short hair skin is usually preferred by tick for infestation because mouth parts can easily penetrate the vascular region for feeding [6].

Economically important Theileria species that infect cattle and small ruminants are transmitted by ixodid ticks of the genera Rhipicephalus, Amblyomma, Hyalomma and Haemaphysali. Theileria sporozoites are transmitted to animals in the saliva of the feeding tick [5]. Iatrogenic transmission can also occur via blood (e.g., on re-used needles) [28]. Developmental stages of the parasite occur in the tick and they pass transstadially through the stages of larva, nymph and adult, but there is no transovarian transmission. Consequently, larvae or nymphs become infected and transmit infection as nymphs or adults. Adults are more efficient vectors than nymphs [30].

Rhipicephalus appendiculatus is the most important vector for *T. parva,* but *R. zembeziensis* and *R. duttoni* carry this organism in parts of Africa [28]. These are three host ticks because nymph, larvae and adult may not necessarily feed on the same host. The nymph and larval instars of tick acquire infection through blood meal and leave the host before molting to the next stage. Both nymph and larvae are responsible for further transmission of infection by attaching to the new host. [6]. *Theileria annulata* is transmitted by ticks in the genus *Hyalomma* [10]. These are two host ticks because the larva molt to nymph on the same cattle. The nymph detaches and drops off of the ground to molt into an adult and seeks a new host [6]. *Theileria mutans* and *T. velifera* are transmitted by Amblyomma spp. Ticks in the genus Rhipicephalus spread *T. taurotragi* [28].

Morbidity and Mortality: Morbidity and mortality vary with the host's susceptibility and the strain and dose of the parasite. The case fatality rate for untreated East Coast fever can be as high as 100% in taurine, zebu or sanga cattle from non-endemic areas. In contrast, the morbidity rate approaches 100% among indigenous cattle, but the mortality rate is usually low. Similarly, tropical theileriosis is more severe in introduced breeds, with a mortality rate of 40-90%, while the mortality rate in indigenous cattle can be as low as 3%. Breeds of cattle that are relatively resistant to experimental infection with *T. annulata* include the Sahiwal breed of *Bos indicus* and the "Kenana" breed of *B. taurus*. Infections with Theileria spp. other than *T. parva* and *T.annulata* are rarely fatal in cattle [28].

Pathogenesis: The Theileria spp. can be grouped into schizont "transforming" and "non-transforming" species. Non-transforming Theileria are regarded as being benign but still able to cause disease as a result of anaemia induced by the piroplasm stage [21]. Pathogenesis of various forms of theileriosis is dependent on the production of schizonts in lymphocytes and piroplasms in erythrocytes [30]. The severity of infection depends upon virulence of the causative strain, the quantum of infection, the susceptibility status, age and health of the host [27]. Thus, *T. parva*, *T. annulata* and *T. hirci* produce numerous schizonts and piroplasms and are very pathogenic; *T. mutans*, *T. buffeli* and *T. avis* rarely produce schizonts but may cause varying degrees of anemia when piroplasms are many in red blood cells; and with *T. velifera* and *T. separata*, no schizonts have been described, the parasitemia is usually scanty and the infection is mild or subclinical [30].

Sporozoites of *T. parva* are injected into the bovine host by the tick in its saliva. The sporozoites then enter lymphocytes and develop into schizonts in the lymph node draining the area of attachment of the tick, usually the parotid node. Infected lymphocytes are transformed to lymphoblasts which continue to divide synchronously with the schizonts so that each daughter cell is also infected [5]. Eventually, infected lymphoblasts are disseminated throughout the lymphoid system and in non lymphoid organs where they continue to proliferate. Later, some schizonts differentiate into merozoites, are released from the lymphoblasts and invade erythrocytes which lead to development of anemia [21]. In general pathological damage is induced in cattle by schizont stage of *T. annulata* and *T. parva*. The cells infected by schizonts induce massive and uncontrolled proliferation of both specific and nonspecific T lymphocyte resulting in enlarged lymph nodes [6].

Clinical Sign: The occurrence of the disease varies depending on the parasite strain, the host's susceptibility furthermore the quantity of sporozoites inoculated and the severity of the disease is directly proportional to the initial inoculum of sporozoites injected [27]. *Theileria annulata* infection (tropical theileriosis) is characterized by high fever, weakness, weight loss, inappropriate appetite, conjunctival petechia, enlarged lymph nodes and anemia. Lateral recumbency, diarrhea and dysentery are also associated with later stages of infection [30, 36]. Unlike *T. parva*, which causes only a small reduction in circulating erythrocytes, mild to moderate anaemia is observed in tropical theileriosis, although pathology produced by the schizont stage is usually the primary cause of mortality [14].

In case of ECF cattle may also develop an extremely fatal condition referred to as turning sickness. In this disease, capillaries of central nervous system are blocked by infected cells and leads to neurologic symptoms [6]. The incubation period varies from 4 to 14 days after attachment of the infected ticks to the host. The disease may last as little as three to four days in the acute form or may be prolonged for about 20 days [27]. Studies in Japan by Chaisi *et al*. [37] indicate that some *T. orientalis* parasites can cause transient anaemia, with clinical signs in up to 2.5% of animals and occasional mortalities (<0.1%) The main clinical manifestations are fever, haemolytic anaemia of variable severity and mortality in some animals; infection is also associated with an increased incidence of abortion and stillbirths and significant reductions in milk yields in affected herds [14]. *Theileria mutans* infection can result in mild clinical signs, but pathogenic strains in eastern Africa cause severe anemia, icterus and sometimes death [18]. In general benign theileriosis is characterized by moderate to severe anemia in heavily parasitized cattle and moderate enlargement of lymph nodes [30].

Diagnosis: For routine diagnosis of bovine theileriosis, conventional methods are used, whereas serological and molecular methods are utilized for research purposes and epidemiological studies. Conventional methods involve microscopic examination of Giemsa stained thin/thick blood films for detection of piroplasms and lymph node biopsy smears for detection of schizonts. The mostly used serology tests are Indirect Immunofluorescent Antibody Test (IFAT) and Enzyme Linked Immunosorbent Assay (ELISA) [9]. Diagnosis of acute theileriosis can also be based on clinical signs (rise in body temperature, enlarged superficial lymph nodes), knowledge of disease and vector distribution as well as examination of Giemsa-stained (either in smears of needle aspirates from enlarged lymph nodes or blood smears) [7]. Definitive identification of the Theileria species involved sometimes requires the application of species-specific PCR assays [14].

Microscopic Examination: Traditional diagnosis of bovine theileriosis is mainly based on the microscopic examination of blood smears for the presence of the merozoites stage of Theileria [38]. This method is frequently used for detection as it is comparatively inexpensive. However, the method is insensitive and not suitable for carrier animals because the pathogen level is usually low in the blood stream making it an unreliable technique for accurate results [6]. Morphological differentiation of *T. annulata* and *T. parva* is also difficult, but both species are geographically separated [39]. One of important character of theileriosis is that once the animal recovered from the primary infection, the animal will become a carrier for a long time. At this stage, the animal has very low parasitemia which is difficult to detect by a microscope [38]. Therefore, high sensitivity and specific assays for detection of these pathogens from the subclinical animals are needed [6].

Serological Tests: Serological tests are reliable methods for detection of low grade or previous infections where measurement of antibody levels of a cattle herd is used for assessing the response to natural infection and also to vaccination for the purpose of disease control [9]. Serological method depends on antigens and antibodies reaction. Antibodies can be detected by different serological tests but IFAT remains the gold standard assay recommended by the OIE for most economically important parasites [7]. However, the biggest problem with the IFAT is the significant cross-reactivity observed between closely related species. Cross-reactivity between T. parva and T. taurotragi antigen and anti-sera has been observed [21].

ELISA can also be used in diagnosis of bovine theileriosis and the test is easy to perform, can diagnose a large number of samples in a short time and it is less laborious [29]. However, these methods are also not reliable due to their limitations. There are chances of cross reactivity and may confront false positive and false negative results. Theileria piroplasm may occasionally be present in the erythrocytes of long-term carriers whereas antibodies have a tendency to disappear. The animals may still be infected despite of negative serological test. Precise identification of carrier cattle is of crucial importance as they are capable of transmitting infection to non-endemic regions [6].

Molecular Tools: Molecular tools can be used to differentiate Theileria specie. The tests have proved to be highly sensitive and specific for detecting parasite DNA in blood [9]. Polymerase chain reaction (PCR) has largely superseded other methods and is widely used specie-specific molecular diagnostic assay in veterinary parasitology to determine piroplasm carrier animals. However, these methods are laborious, expensive; require specialized equipment and technical skills [6, 38]. PCR could detect parasites at 0.000001% parasitaemia, allows direct, specific and sensitive detection of parasite and differentiation of different piroplasms infecting animals [29]. Kohli *et al*. [3] reported 27.2% prevalence of theileriosis by blood smear examination while using PCR, prevalence was reported to be 32.5 %. Similarly, most recent research by Saeed *et al*. [10] used blood smear examination and PCR and Prevalence was 1.9 % and 19.3% respectively indicating that PCR is more sensitive than blood smear examination.

Preventions and Controls

Preventions: Due to the high costs of theilericidal drugs, the high prevalence of carrier state infection and the high costs of treatment, prevention is the best mean to control Thelerial infection; it consists of two types of action: (i) control of the vector tick through one or more control options [6] and (ii) vaccination [40]. Animals can be protected from both East Coast fever and tropical theileriosis by vaccination. Attenuated vaccines are used to control tropical theileriosis in some countries.

Vaccination against East Coast fever is done by simultaneously injecting virulent *T. parva* and an antibiotic (usually a long-acting tetracycline). Considerations in *T. parva* vaccination include the possibility of introducing live organisms into areas where they are not currently endemic [28]. Control of the vector tick is one of the widely used methods to prevent outbreaks. The control option for vector and vaccination will be discussed in detail in the following topics.

Control Methods: Calves infected with several other bovine tick-borne blood pathogens, including *Babesia* species and *Anaplasma marginale*, show enhanced resistance to disease in the first six months of life, enabling them to acquire immunity to these pathogens in regions where the infections are endemic. Such age-related resistance is not seen with *T. parva* or *T. annulata*, There is no any evidence that maternally derived antibodies are protective [41]. Because of the absence of such protective mechanisms and the fatal nature of the diseases in susceptible stock, control of disease caused by these highly pathogenic *Theileria* is particularly challenging [14]. So it is important to design and implement control strategies to prevent outbreaks in endemic and non-endemic regions on a priority basis [42].

Several methodologies are currently available for the control of bovine theileriosis [27] and various cost effective prophylactic measures are used to control and minimize economic losses to dairy farms globally, however, all of these need to be integrated in such a manner that they meet the specific requirements of livestock holders in different situations [6]. The most practical and widely used method is the chemical control of ticks with acaricides. However, tick control practices are not always fully effective for a number of reasons, including development of acaricide resistance, the high cost of acaricides, poor management of tick control and illegal cattle movement in many countries. Thus, vaccination using attenuated schizont-infected cell lines has been widely used [7].

Management: Good management is one control option in controlling bovine theileriosis. Management involves restriction of livestock movement and implementation of quarantine measures to keep the tick free and disease susceptible cattle apart from the tick-infested and infected animals. This is also to ensure that ticks and the pathogens they transmit are not transported to ecologically suitable but currently uninfected areas. The overall objective is to ensure that the target population is entirely free of the disease or there is endemic stability [27]. Newly purchased cattle may first be properly examined before mixing with the existing stock. If the number of ticks or tick infested cattle is small, manual removal of tick is a common practice. Forefingers are used to grasp ticks and twisted counter-clock wise. The removed ticks are, then, put on the smoldering dung cake to kill them [43].

Vector Control: Tick control is one of the most important factors influencing the epidemiology of bovine theileriosis. It has been achieved mainly by application of acaricides [27] and acaricides may be applied to kill ticks in both free living as well as parasitic stages. Tick free or acaricide treated cattle have better productivity as compared to tick infested cattle. Acaricides are applied by spraying, injections, spot-on or dipping but human safety is of utmost importance in acaricide application. Prolonged and repeated contacts with skin should be avoided. Hands and face should be properly washed before eating [43].

Dipping is considered the most effective method for acaricide application [27]. Dipping tanks are usually covered with a roof to avoid dilution by rain or evaporation. It is important to carefully adjust dip concentration according to the recommendation. Poor or incorrect application of even highly effective acaricide gives unsatisfactory results and develops acaricidal resistance. Dipping of cattle less than 3 months is not recommended. Wounds of cattle must be thoroughly checked before dipping, otherwise, it can cause discomfort and toxicity. The heads of cattle must be dipped once or twice in the solution. Cattle that are thirsty or fatigued shouldn't be dipped [43]. Despite its effectiveness Dipping become very expensive and inconsistent due to lack of facilities such as finances for rehabilitation of dip tanks, provisions of acaricides and water [9].

Acaricides can also be applied with hand spray which is environmental friendly practice, easy to operate and economical but is suitable for small herds only. For effective control, it is important to moisten the hair as well as skin with spray [6]. There are certain body parts of cattle that escape treatment by spraying and dipping. Such predilection sites include inner fringes of ear, under part of tail and legs and require special attention. Selective application of acaricides to these sites is called hand dressing and is done as a supplement to usual dipping [43]. Other options for controlling ticks are ecological and biological. Ecological control method is used for habitat and host linked treatment. Tick control in the habitat and vegetation requires modification of the plant cover by removal of vegetation that shelters ticks. Biological control, include predators like rodents, birds, ants [35].

Selection of Tick Resistant Cattle Breeds: Different breed of cattle are different in their susceptibility to theileriosi for example exotic cattle and their crossbreds are highly susceptible, while indigenous cattle are relatively resistant to tropical theileriosis [10]. Low prevalence of parasite is reported in Sahiwal cattle than European breeds suggesting that Sahiwal cattle are more resistant to tick infestation and tick borne diseases [44]. It is widely known that *Bos indicus* cattle are more resistant to ectoparasites than are *Bos taurus* animals. There are great differences between these two breeds of cattle in regard to their susceptibility to parasitism by cattle ticks [35]. In general sense rearing disease-resistant breeds play significant role in controlling bovine theileriosis. Hence selection of cattle breeds with enhanced tick resistance is proposed as a sustainable tactic for controlling infection in developing world [6].

Immunization: Control of the disease by prevention of tick infestation requires essentially continuous application of acaricides and is therefore expensive and difficult to sustain. Furthermore it can result in acaricide resistance. Because of the shortcomings of these control measures, vaccination is seen as the most sustainable option for control of the disease [14]. The attempt of immunization in cattle against tropical theileriosis was first made in Algeria in 1930s. Blood with low virulence strain was donated from infected cattle followed by mechanical passage between healthy cattle. This practice resulted in subsequent loss of parasite's ability to differentiate into merozoites with one year estimated protection in the absence of natural challenge [6].

Successful vaccination against *T. annulata* and *T. parva* has only been achieved using live parasites. A method of vaccination against *T. annulata*, based on the use of parasitised cell lines in which the parasite had been attenuated by up to 200 passages *in vitro* [14]. The vaccination for *T. parva* control is based on a method of infection and treatment (ITM) in which cattle are given a subcutaneous dose of tick-derived sporozoites and a simultaneous treatment with a long-acting tetracycline formulation. This treatment results in a mild or inapparent East Coast fever reaction followed by recovery. Recovered animals demonstrate a robust immunity to homologous challenge, which usually lasts for the lifetime of an animal [7].

The result of most recent study in Kenya by Woolhouse *et al*. [45] suggested a novel alternative approach, inoculation of young calves with more benign *T. mutans* or *T. velifera*, without the need for treatment and helping calves to survive their first exposure to *T. parva* and develop immunity. This Successful ECF control would benefit an estimated 30 million cattle in sub-Saharan Africa, reducing the costs of treatment as well as reducing demand for both antibiotics and acaricides.

Chemotherapy: Acording to OIE [7] chemotherapeutic agents such as parvaquone, buparvaquone and halofuginone are available to treat *T. annulata* and *T. parva* infections. These best Theilericidal drugs belong to the hydroxynaphtoquinones family [40]. Naphthoquinone compounds were discovered in 1970 with a wide therapeutic index [12]. These naphthoquinone compounds are not only effective for curing theileriosis but can also be used as a remarkable prophylactic measure against the disease [6]. However, according to OIE [7] treatments with chemotherapeutic agents do not completely eradicate theilerial infections leading to the development of carrier states in their hosts. Parvaquone (Parvexon ND, Bimeda) is mainly active drug against schizontes; it should be injected intramuscularly at the dose of 20 mg/kg. Buparvaquone is active against both schizontes and piroplasmes; it is injected intramuscularly at the dose of 2.5 mg/kg. Its efficacy after a single injection was estimated to 92%, which is higher than parvaquone [40].

However, these naphthoquinone compounds are not used by cattle breeders due to their high price [12] and drugs infiltrate the muscles and are not easily eliminated from the cattle's body [6]. The meat and milk products may be contaminated with drug residues leading to health hazards [46]. Drug resistance is also reported in Tunisia recently; 4 out of 7 cattle died of acute tropical theileriosis in spite of buparvaquone injections [47]. Similarly, 7 out of 8 cattle died in southern Iran, though buparvaquone treatment was given [48]. Mechanism of buparvaquone action has not been fully elucidated. However, products belonging to the hydroxynaphtoquinones probably acts by binding to cytochrome b (cyt b) inhibiting the electron transport chain in the parasite [49]. *Theileria annulata* and *T. parva* show similar disease symptoms and the symptoms include immune-depression and secondary bacterial infection e.g. pneumonia and enteritis. Antibiotic treatment is usually recommended to limit such secondary infections [6]. Tetracycline antibiotic was probably the first chemotherapeutic compound used against ECF in 1953. This antibiotic is effective only at the early stages and can't be used at later stages of infection [12].

Plant called *Calotropis procera* locally named as Thophiya (Tobia) are reported to have killing or repealing effects on tick in North Gondar, Ethiopia [50]. This plant is found as wild plant in Asia and Africa and has multipurpose chemotherapeutic activities and can be effectively used to treat bovine theileriosis [6, 51].

Economic Importance of Bovine Theileriosis: Theileriosis causes major constraints on livestock development in Africa, Asia and Middle East. The disease causes high morbidity and mortality in exotic cattle, thus inhibiting the introduction of improved cattle into endemic areas. The consequence is that the quality of cattle in endemic areas remains low, therefore impeding the development of the cattle industry and the wellbeing of producers and their families [5]. *Theileria annulata* causes severe financial losses due to live weight decrease, a drop of milk yield, abortions and in some cases deaths. Moreover, the treatment of this disease is very expensive [40]. Most important loss from *T. annulata*, representing between 22% and 38% of the overall losses, is the loss in milk yield from carriers of the disease [52]. In Eastern, Central and Southern Africa due to East Coast fever, about one million cattle per year die, with a further 28 million of the 47 million cattle in the region being at risk of contracting the disease [9].

Status of Bovine Theileriosis in Ethiopia: Similar to other countries, there are a considerable number of economically important livestock diseases occurring in Ethiopia. Among others, tick borne haemoparasitic diseases are of the major constraints to the livestock industry of the country [35]. A number of researchers are reporting presence of different Theileria species from different area of Ethiopia (Table 2). For example Gebrekidan *et al*. [19] reported a widespread distribution of Theileria spp. among domestic ruminants in northern Ethiopia. The circulation of Theileria spp. in Ethiopia is also indicated by Solomon *et al*. [16], who reported 30.9% seropositivity to *T. mutans* in cattle from the Yabelo district.

In previous studies, conducted by Sileshi *et al*. [53] *T. orientalis* and *T. velifera* were reported from Gambella region, western Ethiopia. *Theileria mutans* has been known for a long time to occur in Ethiopia [15]. Furthermore, its vectors are commonly found in different regions of Ethiopia [54]. The average seropositivity of *T. mutans* (54.2%) was reported in Ghibe valley by Feleke *et al*. [54] indicating that the population is in the state of enzootic instability. Gebrekidan *et al*. [19] reported the presence of three Theileria species in cattle in Addis Zemen, i.e. *T. velifera*, *T. mutans* and *T. orientalis complex*. The previous studies confirmed that *T. mutans*, *T. velifera*, and *T. orientalis* infect cattle in western, eastern, and southern Ethiopia [15-18].

In addition recent study conducted by Gebrekidan *et al*. [19] indicated that four species of Theileria including *T. velifera*, *T. mutans*, *T. orientalis complex* and *T. annulata* were found in northern part of Ethiopia (Table 3) (Addis Zemen, Humera and Sheraro) with infection rates of 66 %, 8%, 4%, and 2%, respectively. Furthermore the study reported the presence *T. annulata*, the cause of tropical theileriosis, in Ethiopia (Humera) for the first time. There are no clinical or serological reports of the presence of East Coast fever (*T. parva*) and its vector in Ethiopia. However, there is relatively uncontrolled movement of livestock from southern Sudan and Kenya, where the disease and vector are found ensures that a considerable risk exists.

Table 2: Report of *Theileria* species from different area of Ethiopia

Theileria species	Area	Samples	diagnostic methods test	Reference
T. mutante	southern and eastern Ethiopia	Blood	Microscopic and serology	[16, 18]
T. annulata	Northern Ethiopia	blood	PCR	[19]
T. orientalis	Northern Ethiopia	blood	MT- PCR	[8]

Table 3: Distribution of *Theileria* spp. infections in cattle in Northern Ethiopia

Study site	No. of animals	PCR+ n (%)	*T. velifera* n (%)	*T. mutans* n (%)	*T. orientalis* complex n (%)	*T. annulata* n (%)
Addis Zemen	59	48(81.4)	38 (64.4)	6 (10.2)	4 (6.8)	–
Sheraro	21	18(85.7)	17 (81)	1 (4.8)	–	–
Humera	20	14 (70)		1 (5)	–	2 (10)
Total	100	80(8)	66 (66)	8 (8)	4 (4)	2 (2)

Source: Gebrekidan *et al*. [19].

If infected ticks become established on the climatically favorable highlands of Ethiopia, close to 100% mortality of improved and indigenous cattle could occur [15].

The most recent study in Ethiopia detected and characterized *T. orientalis* in local cattle and found as most pathogenic of *T. orientalis* genotypes is low and dominant is non-pathogenic genotype. Therefore, the low intensity of infection of pathogenic genotypes of *T. orientalis* may explain why clinical oriental theileriosis is uncommon in Ethiopia [8].

CONCLUSSION

Bovine theileriosis is the most economically important diseases of bovines caused by tick-borne haemoprotozoan parasites of the genus Theileria. Two diseases caused by this parasite, with the greatest economic importance in cattle are East Coast fever and tropical theileriosis. Unlike tropical theileriosis, East Coast fever was not reported in Ethiopia. PCR is the most beneficial molecular tool for diagnosis of infection till date than blood and lymph node smear examination and serological tests. Infection by Theileria parasites limits the movement of cattle between countries as this disease is most severe in recently introduced animals. Thus, it can result in production losses and high mortality in imported and susceptible animals. Prevention and control of this disease is mainly by vector (tick) control, introducing tick resistant cattle breeds, using chemotherapeutic agents and vaccination. However, each of these methods has their own limitations and not cost effective. Even though chemotherapeutic agents such as parvaquone, buparvaquone are available as treatment option; drug resistance is reported from different countries.

Therefore, based on the above conclusion the following recommendations are forwarded:

- Continuous and programmed acaricide dipping and spraying should be implemented as a prevention and control strategy in endemic areas.
- The currently used control methods against theileriosis are expensive and have many limitations, so cost-effective and integrated control strategies should be developed.
- Since drug resistance is reported with currently available drugs, research should be extended to design new drugs having different modes of action.
- As the tropical bovine theileriosis is reported in Ethiopia, research should be conducted to design and implement appropriate disease control and prevention strategies.
- Continuous and reliable sero-surveillance should be performed on the borders to prevent and control the introduction of East coast fever to Ethiopia.

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