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ARTICLE

Tick-borne Diseases, Transmission, Host Immune Responses, Diagnosis and Control

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ABSTRACT

Present review article explains tick-borne diseases, transmission, host immune responses, diagnosis and control in relation to climatic variations. Ticks are hematophagous ectoparasites which suck large volumes of blood from livestock and humans. They release large numbers of protozoans, bacteria, rickettsia and viral pathogens during blood feeding and transmit disease pathogens through saliva. Due to heavy blood sucking by ticks animals face significant blood and weight loss that affect their overall health. Due to more severe illness, high economic losses were noted in livestock. This article highlights medically important tick borne diseases in man and livestock, its pathogenesis, diagnosis and treatment methods. The present article emphasizes invasion of hosts, host-pathogen interactions, tick saliva toxin induced host immune responses and biological effects. This article highlighted various tick control methods i.e. physical killing, acaricidal, biological, hormonal, genetic and immunological methods such as administration of protective antibody and vaccines for disease control in human being and his livestock. The authors suggest non-chemical environmentally safe methods for successful control of tick borne diseases to kill cattle, bird and canine invading ticks.

1. Introduction

Ticks rely on host blood, and live as ectoparasites of so many terrestrial vertebrates mainly mammals, birds, reptiles and amphibians. Due to blood sucking behaviours, ticks are capable of transmitting numerous human and animal bacterial, viral or parasitic diseases. Ticks are the most important vectors of human pathogens, leading to increased public health problems worldwide. Ticks are arachnids, having a body length of 3 to 5 mm in size. Along with mites, they constitute the subclass Acari. There are a number of medically important arthropods including vespids, ticks, mosquitoes, flies, and fleas mites and ticks. These small sized or tiny animals produce deadly toxins and cause lethal allergic reactions.They are major vectors of arthropod-borne pathogens in the both tropical and sub-tropical and even in temperate countries [1-3]. Few wild animals mainly veretebrates are reservoir hosts of ticks. Ticks are vectors of a number of pathogenic viruses, bacteria, fungi, protozoa, and filarial nematodes. These were evolved during a million of years of long evolutionary period over millions of years [4]. Ticks as ectoparasites always rely on blood feeding and its all feeding stages pass their life cycle pass in different hosts and generate morbidities of medical and veterinary importance [5]. (Table 1). Ticks maintain enzootic cycles and make continuous transmission of pathogens among livestock and

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wild animal hosts. All these tick-borne pathogens show severe consequences in man and his livestock. Tick borne disease largely affects livestock and cause economic harms to dairy farming industry and veterinary medicine [6] (Photograph 1).

Photograph 1. 1a hard tick parasite on cattle skin, 1b-1c soft ticks, 1d-1i tick infestation on dairy cow and buffalo skin.

There are two big families of ticks i.e. Argasidae and Ixodidae. Among them Ixodes genus, contain highly infectious tick species which transmit a range of pathogens and give rise diseases in livestock [7]. Hard ticks bear a beak-shaped structure in their mouthparts; while soft ticks have their mouthparts on the underside of their bodies (Photograh 1). Adult ticks are either ovoid or possess pear-shaped bodies, which remain engorged with blood. They found tightly stick over host skin by using its eight legs and continuously remain involved in blood feeding. Hard ticks are characterized by hard shield or scutum on their dorsal surfaces [8-11]. Soft ticks do not possess hard shield hence kept in Family Argasidae. Ixodidae is the family of hard ticks or scale ticks one of the two big families of ticks. It consists of over 700 species [12,13]. At present more than 904 various tick species have been listed throughout the world [14-19] .(Table 1).

Ticks are transmission vectors of numerous pathogens which are particularly sensitive to climatic changes and spread due to anthropogenic behaviour Both affect complexity of their cycle, parasites-host relationships and emergence of zoonotic diseases in live stock and wild animals.. More specifically tick borne pathogens spread due to variation in vector to host ratio, intensity of pathogen, ecological factors of that area [20]. Terminal point of epizootic never comes and diseases spread among mammals, including livestock and humans.

Ticks continuously feed on blood, for which remain attach to the host skin for days to weeks. These secrete anticoagulants and toxin in saliva to neutralize the host defenses. Ticks salivary glands secrete toxins, and passed into the blood through feeding, make livestock anemic and cause great economic losses to them worldwide [21]. Tick saliva is used as an invading liquid that imposes multiple severities in host and do impairment of physiological health [22]. Ticks for blood feeding puncture the host skin, damage it, and transmit various categories of dreadful infectious agents into host blood which cause serious diseases in host animals. Few newly emerged tick-borne infectious diseases are Lyme borreliosis, ehrlichiosis, and babesiosis [23]. Babesiosis and anaplasmosis are dreadful tick-borne diseases, these are spread by *R. microplus and R. annulatus* in bovine cattle herds. Ticks also transmit encephalitis virus [24] Rickettsia and other protozoa cattle parasites [6], Mediterranean Spotted Fever, Turalemia (human and animal) are emerging diseases [25]. There are no prophylactic therapies are available to control bovine babesiosis and anaplasmosis [26].

Due to their worldwide distribution, ticks usually found in all types of climates from hottest to coldest climates, and show worldwide distribution. But these are widely distributed especially in warm, humid climates. *Hyalomma anatolicum* and *Haemaphysalis bispinosa* was observed inside the cattle sheds. ixodid ticks in Maharashtra, India, was undertaken during 1976 to 1978 [27]. Both show their presence throughout India, but *H. spinigera* is confined in Southern Indian states, central zones, Orissa and Meghalaya [27]. From Kerala State 23 ticks species of domestic and wild animals have reported so far [28,29].

Both *Borrelia burgdorferi sensulato* and tick-borne encephalitis virus (TBEV) are transmitted by Ixodes ricinus tick.This tick species also *perform* transmission of *Anaplasma phagocytophilum, Babesia divergens, Babesia microti, Babesia venatorum, Borrelia miyamotoi, Neoehrlichia mikurensis, Rickettsia helvetica and Rickettsia monacensis* [30]. *Anaplasma phagocytophilum* live inside ticks and various wild and domestic animals It causes human granulocytic anaplasmosis (HGA) [31]. Few tick borne diseases caused by members of Rickettsiales and Legionellales remain asymptomatic in nature and spread by silent transmission to humans [32]. Rickettsia species initiate unknown pathogenicity to vertebrate hosts during tick blood meal acquisition [33]. Both the large and small forms of *Babesia species* (*B. canis, B. vogeli, B. gibsoni,* and *B. microti*-like isolates also referred to as "*B.vulpes*"

Table 1. important bacterial diseases transmitted by various tick species

S.No.	Disease	Organism	Vector	Geographical distribution	Symptom	Treatment
1	Lyme borreoliosis disease	*Borrelia burgodorferi*	*Ixodes scapularis Ixodespacificus Ixodesricinus*	North east,Midwest and west coast states, Europe, south central U.S.	Erythema migrans, Fatigue, erythema migrans , malaise myalgias,arthralgias,headache, fever chills	Amoxicillin) or cefuroxime Doxycycline (Vibramycin, non-steroidal anti-inflammatory drugs
2	Anaplasmosis	*Anaplasmaphagocytophilum*	*Ixodesscapularis Ixodespacificus*	North east,Midwest and west coast states	Myalgias,headache, fever chills	Doxycycline Chloramphenicol (Chloromycetin) Rifampin (Rifadin)
3	Anaplasmosis	*Anaplasma platys*	*Rhipicephalussanguineus*	South central south western, U.S.	Myalgias, headache, fever chills	Doxycycline Chloramphenicol (Chloromycetin) Rifampin (Rifadin)
4	Ehrlichiosis	*Ehrlichiacanis*	*Rhipicephalussanguineus*	South central south western, U.S	myalgias,headache, fever chills	Doxycycline Chloramphenicol (Chloromycetin) Rifampin (Rifadin)
5	Ehrlichiosis	*Ehrlichiaewingii Ehrlichiachaffeensispanola mountain Ehrlichiasp*	*Amblyommaamericanum*	Cental and south eastern U.S. Extending northward along the atlantic coast	myalgias, headache,fever chills	Doxycycline Chloramphenicol (Chloromycetin) Rifampin (Rifadin)
6	Ehrlichiosis	*Ehrlichiamuris*	*Ixodesscapularis*	Upper Midwest(minnesota and Wisconsin)	myalgias, headache, fever chills	Chloramphenicol (Chloromycetin) Rifampin (Rifadin)
7	Rocky mountain spotted fever	*Rickettsia ricketsii*	*Dermacentorvariabilis Rhipicephalussanguineus*	South central and south westerna and eastern U.S.	myalgias, ,headache,fever ,malaise,vomiting , rash	Chloramphenicol tetracyclin Doxycycline
8	Tularemia	*Francisellatularensis*	*Ixodesscapularis Amblyommaamericanum Dermacentorvariabilis*	South and Midwest	myalgias, headache,fever chills vomiting fatigue, sore throat, abdominal pain , skin ulcers, diarrhea, lymphadenopathy	Chloramphenicol Streptomycin Gentamicin ,Tetracyclin, Fluroquinolones

and "*Theileria annae*") infect dogs in Europe, [34]. The most abundant and widespread tick species in Great Britain, in human relapsing fever (HRF) and African swine fever (ASF) are spread by *Ornithodoros moubata* argasid tick [35].

Ticks are responsible for the spread of diseases like Anaplasmosis, Babesiosis and Ehrlichiosis (Table 1). So far 19 tick borne diseases have been reported in animals and men, involving four protozoa (babesiosis, theileriosis, cytauxzoonosis, hepatozoonosis), one filarial nematode (acanthocheilonemasis), ten bacterial agents (anaplasmosis, ehrlichiosis, aegyptianellosis, tick-borne typhus, Candidatus Rickettsia vini, Lyme borreliosis, tick-borne relapsing fever [TBRF], tularaemia, bartonellosis, and hemoplasmosis), and four viral infections i.e. tick-borne encephalitis [TBE], Crimean-Congo Haemorrhagic Fever [CCHF], louping-ill [LI], and lumpy skin disease [LSD]) [36]. TBE virus is the most frequent virus associated with potentially severe neurological lesions. No treatment is available so far for this disease. The most frequent bacterial diseases cause neurological complications due to occurrence of Lyme borreliosis, Q fever and some rickettsial infections. In present review article we have critically *evaluated* the disease transmission by different tick species, disease causing pathogens, host immune responses, biological damages generated. This article also has *demarcated* important diagnosis methods, ticks prevention and various control programs.

2. Source of Information

For writing present comprehensive review article on tick-borne diseases, transmission, host immune responses, diagnosis, and control various databases were searched exhaustively. For finding and collection of relevant information on present topic specific terms such as medical subject headings (MeSH) and key words "tick borne diseases", "pathogens", tick control methods" and "biological effects" were used in MEDLINE to fetch out research publications published till 2021. Most specially for re-

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trieving all articles pertaining to the use of VIT for tick borne diseases, electronic bibliographic databases were searched and abstracts of published studies with relevant information on the tick borne diseases and transmission were collected. Furthermore, additional references were included through searching the references cited by the studies done on the present topic. For an extensive literature search most relevant terms were used individually and in combination to other key words. Efforts have been made to collect most recent information available on present subject. From database important abstracts, available on relevant research articles, books, conferences proceedings and public health organization survey reports were searched, downloaded and collated based on the broader objective of the review. For writing this review important research articles, its findings available from databases, including SCOPUS, Web of Science, and EMBASE, Pubmed, PMC, Publon, Swissprot, Google searches"were read well and tried to summarize the conceptual notings. By applying common methodology, important discoveries, findings and outcomes were identified and summarized in this final review.

3. Tick Habitat

Ticks are slow moving tiny creatures incapable of flying or jumping. These usually live in sandy soil, hardwood trees, and rivers, with an overt story of trees or at least shrubs. These also live in narrow spaces near animal houses, cattle yards, grassy mats, nests, found inside human dwellings in dark and very silently attacks roosting birds. All tick species rely on blood feeding from vertebrate hosts. For extensive blood feeding ticks apply all counteractive measures to weaken their hosts' immune and homeostatic mechanisms. They move by sensing carbon dioxide released in the breath of their hosts [37]. Ticks give eggs in dark places, mainly in narrow spaces or hole in the spring season. After embryonic development tiny larvae can emerge, which are seen crawling on to grass weds found in low-lying vegetation field. Ticks live on side lawn's edge where they crawl swiftly are a tick migration zone. More than 82% of tick nymphs reside inside grass fields and lawns [38]. Ixodid ticks also found in the vegetation grounds where antelopes and other herbivores come to forage in closed enclosures; where ticks show free-living intensively in large numbers. Ticks found in open grasslands to urban woody material, carpets, doormats and cloth seats. They also found in Antarctica, where they found stuck on penguins and feed upon their blood [28].

4. Tick Life Cycle

Ticks complete their life cycle in four i.e. egg, larva, nymph, and adult. Ixodid ticks pass their life cycle among three hosts, and complete single their life cycle in one year. Argasid ticks develop in consecutive seven nymphal stages (instars). Each one requires a blood for feeding. Tick's early larva just after hatching bears six legs, and it develops two more legs after a blood meal and *moulting* into the nymph stage [26]. Both nymphal and adult stages, possess seven segments and a pair of claws and possess eight legs. Tick's soft very small legs have sensory or tactile hairs which help them to find a suitable site on host skin [39] (Photograph 1). Ticks attach to a host bite. They remain engorge deep into skin and regularly suck blood this process may take days or weeks. Due to strong hematophagous nature all life stages of ticks are highly destructive and suck blood in groups. These lacerate host tissue and secrete a variety of biologically active substances which assist them in invasion of hosts and for enabling the uptake of a blood meal [40] (Photograph 1).

Ticks detect animal host by breathing carbon dioxide and body odors. They also sense through body heat, moisture, and vibrations [41]. For blood sucking ticks grasp the host skin by legs and puncture or cuts into the surface of the host's skin [42] (Photograph 1). They make tiny holes in the host's epidermis, into which insert their hypostome, and suck blood with the help of anticoagulants secreted in saliva that acts as platelet aggregation inhibitor [43,44]. Ticks mostly target marsupial and placental mammals, birds, reptiles (snakes, iguanas, and lizards), and amphibians for blood feeding [45]. Because ingestion blood, ticks are vectors of so many diseases that affect health of humans and other animals. Ticks harm largely domestic animals by making them anemic and damaging wool and hides [46] (Table 1) (Photograph 1).

4.1 One-host Ticks

Both ixodid and argasid ticks pass their life cycle in egg, larva, nymph, and adult in single host [47]. It starts with egg laying by females which after 4-5 days hatch and larvae emerge, just after eclosion they need a host for blood meal. After blood feeding larvae moult into unfed nymphs which also need host blood for their nourishment. After engorging on the host's blood, the nymphs moult into sexually mature adults that remain on the host in order to feed and mate. Other example of one host tick life cycle is Winter tick *Dermacentor albipictus* and the cattle tick *Boophilus microplus* [48]. *Dermacentor variabilis and D. anderson* (Ixodidae) also pass on their life cycle in four consequent life stages [49]. Ticks show a complex epidemiology but are of great ecological significance. They generate larger impact on clinical and socio-economic status of man due to occurrence of the pathogenic diseases [50].

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(Table 1) (Figure 1).

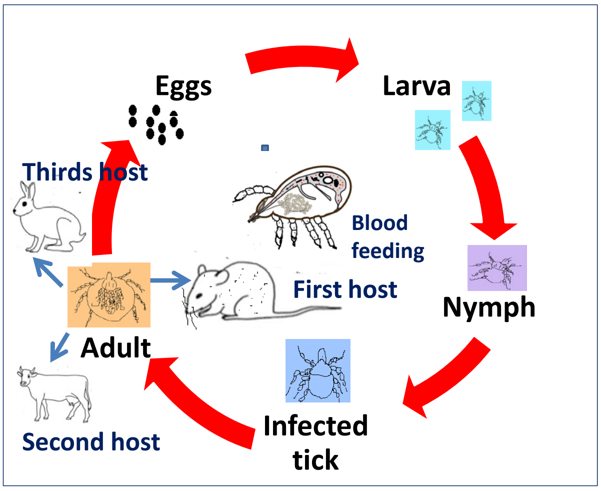

Figure 1. various stages of tick life cycle completed in different hosts

4.2 Two-host Ticks

There are few ticks species like *Hyalomma anatolicum excavatum*which complete their life cycle between two-host ticks [51]. From eggs laid by female ticks, after hatching tiny size larvae emerge, which crawl and attach to a host skin for sucking blood. They remain attached on the host after developing into nymphs which also reattach to the host for blood feeding. Once engorged, they drop off the host and find a safe area in the natural environment in which to molt into adults. Both male and female adults seek out a host on which to attach, which may be the same body that served as host during their early development. Once attached, they feed and mate. After mating tick females lay eggs and oviposit them in crevices, leaves, clothe and vegetation cover (Table 1) (Figure 1).

4.3 Three-host Ticks

Most ixodid ticks for completion of their life cycle need three hosts. For establishing parasitism their females lay eggs thousands in number on the ground/garden soil. After hatching larvae emerge, which attach themselves for feeding blood primarily on small mammals and birds. After feeding, they detach from their hosts and molt to nymphs on the ground, which then attach and feed on larger hosts before dropping off yet again in order to molt into adults. Adults seek out a third host on which to feed and mate. Female adults engorge on blood and prepare to drop off to lay her eggs on the ground, while males feed very little and remain on the host in order to continue mating with other females [51]. (Table 1) (Figure 1)

5. Transmission of Diseases

Ticks as ectoparasites of livestock in tropical and sub-tropical areas tramsmit wideranges of pathogens and cause severe economic losses. Ticks transmit a wide range of viral, bacterial and protozoan pathogens; many of them establish persistent infections of lifelong duration in the vector tick. Ticks also spread pathogens through transovarially to the next generation, these pathogens are *Borrelia spp., Babesia spp., Anaplasma, Rickettsia/ Coxiella, and tick-borne encephalitis virus and Theileria parva.* Ticks also transmit protozoan, rickettsial, Ehrlichiacasis and viral diseases of livestock, which are of great economic importance world-wide [52]. Ticks and tick-borne diseases (TBDs) affect the productivity of bovines in tropical and subtropical regions of the world. Most of the poor countries have cattle farming is main economic source, leading to a significant adverse impact on the livelihoods of resource-poor farming communities [52] (Table 2).

Ticks suck blood regularly from vertebrate hosts for nutrients, survival, oviposition and developmental stage for completion of their life cycle. Blood feeding by ticks severely impacts animal health, results in *reduction weight* and induce anemia among domestic animals. Ticks suck blood and feed on birds, mainly on migratory birds (Table 2). Migrating birds carry ticks with them. Thus ticks population spread through cattle trade, bird homing and trans-national trans-human movements.

The castor bean tick, *Ixodes ricinus*, transmit *Borrelia burgdorferi, s, Anaplasma phagocytophilum, Rickettsia helvetica, Francisella tularensis, Neoehrlichia mikurensis, Bartonella spp., Borrelia miyamotoi and Babesia spp* [53]. *However, Babesia microti, Borrelia miyamotoi (another spirochete), Anaplasma phagocytophilum, and Powassan virus* also transmitted by ticks [54]. Ticks transmit potential tick-borne pathogens that affect human health that results in severe pathogenesis and mortality [30]. Babesial vector tick synthesize defensin against *Babesia sp*. Ticks also transmit *Borrelia sp* and viral pathogens among wild canines, and white-tailed deer (Table 2). Tick borne diseases are also spread by birds which feed on *Borrelia burgdorferi Sensu Lato*-infected blacklegged mites.

Distribution of population of various tick species depends on regional ecology and climatic situation. Climatic situations also support vertebrate population growth, survival and reproduction. Ticks also feed blood on ro dents and wild and domestic animals mostly mammals and infect them with various disease pathogens. Mostly domestic and wild mammals are reservoir hosts of tick transmistted pathogens mainly protozoans, bacteria, viruses, rickettsia, fungi and others during their feeding process

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Table 2. important protozoan diseases transmitted by various tick species

S. No.	Disease	Organism	Vector	Symptom	Treatment
1	Babesiosis	*Babesia vogal*	*Rhipicephalus sanguineus*	Severe headache, nausea, abdominal pain, hemolytic anemia, fever, chills, sweats	Atovaquone PLUS azithromycin, Clindamycin PLUS quinine
2	Babesiosis	*Babesia gibsoni*	*Rhipicephalus sanguineus*	Severe headache, nausea, abdominal pain, hemolytic anemia, fever, chills, sweats	Atovaquone PLUS azithromycin, Clindamycin PLUS quinine
3	Babesiosis	*Other Babesiasp*	*Rhipicephalus sp.*	Flu like symptoms, body aches, loss of appetite, nausea, or fatigue	Antiparasitic drugs,
4	Hepatozoonosis	*Hepatozoon americanum*	*Amblyomma maculatum*	fever, lethargy, decreased appetite, weight loss, muscle pain/weakness, reluctance to move, and discharge from the eyes and nose	Trimethoprim-sulfa, clindamycin, and pyrimethamine.
5	Hepatozoon canis	*Hepatozoon americanum*	*Rhipicephalus sanguineus*	haemolymphatic tissues and causes anaemia and lethargy.	Imidocarb dipropionate at 5-6 mg/kg IM and Tab. Doxycycline
6	Tularemia	*Francisella tularensis*	*Ixodesscapularis Amblyommaamericanum Dermacentorvariabilis*	cough, chest pain, and difficulty breathing, swollen lymph nodes near the skin ulcer	Streptomycin, gentamicin, doxycycline, and ciprofloxacin
7	Rocky mountain spotted fever	*Rickettsia ricketsii*	*Dermacentorvariabilis Dermacentorandersoni Rhipicephalussanguineus*	Fever, chills, or loss of appetite, nausea or vomiting, skin rashes or red spots, eye redness, headache, rash on the palms and soles, or sensitivity to light	Doxycycline , Monodox, Vibramycin,
8	Q Fever	*Coxiella brunette*	*Dermacentor andersoni*	Pain in the abdomen or muscles, fatigue, high fever, malaise, chills, or night sweats, coughing, headache, nausea, or shortness of breath	Antibiotic doxycycline
9	Ehrlichiosis	*Ehrlichia chaffeensis*	*Amblyomma americanum, Ixodes scapularis*	Human Monocytic plasmolysis, fever, chills, malaise, nausea, diarrhoea	Doxycycline
10	Anaplasmosis	*Anaplasma phagocytophilum*	*Ixodes scapularis Ixodes pacificus*	Human Granulocytic plasmolysis, fever, headache, chills, and muscle aches.	Doxycycline, single IM injection of long-acting oxytetracycline at a dosage of 20 mg/kg.

on the hosts [55]. After mosquitoes *ticks* are second vector group that transmit large number of pathogens to humans [56]. Blood feeding by ticks is the most prevalent modes of transmission as they infect human and his pets. Due to easy dissemination of highly infectious pathogens which cause multiple infection, ticks are proved most dangerous vectors worldwide. Tularemia is a dreadful zoonotic disease caused by the *Francisella tularensis*, a highly infectious Gram-negative *Cocco-bacillus.* This is also used as biological weapons for generating potential bioterrorism threat and classified in category A of warfare agents by the CDC [57]. *Rickettsia parkeri Luckman* (Rickettsiales: Rickettsiaceae), is the tick-borne causative agent causes a more sever fatal disease rickettsiosis [58].

Tick-borne diseases are expanding regularly and these are reaching to new geographical locations in northern part of the world. This isdue *international* trade of animals and food and clothes. Recent surveys indicate tick-borne diseases like rickettsioses, Lyme borreliosis, tularemia, are transferring from *non-endemic* areas due to transmission favorable climatic conditions. Lyme disease and human ehrlichiosis have been spread in geographical locations because of increased movements of *Ixodes scapularis* and *Amblyomma americanum* [59]. Tick have saliva toxins cause paralysis in human hosts [60].

There are very few tick vectors which tansmit arboviruses [61] but these more frequently transmit obligate intracellular bacteria belong genus Rickettsia [62]. Ixodes ticks are commonly infected with both *B. microti* and *B. burgdorferi*, and transmit these pathogens together into hosts. Lyme disease-causing spirochete, *Borrelia burgdorferi.* And *B. microti* are also transmitted through transfusion of blood products A. [63]. Various species of genus Ixodes infest livestock, mainly spread diseases in grazers [64]. Tick infestation is directly occur due to increase in outdoor activities and movement of man and his pets in orchards, grassy vegetation and lawn. Dogs exposed to ticks and tick borne diseases by living with infected dogs and cattle [65].

Ixodid ticks *Ixodes pacificus, Ixodes persulcatus, Ix-*

odes ricinus and Ixodes scapularis, are major vectors which transmit tick-borne pathogens. For taking a regular blood meal ticks remain attached to their hosts for almost 1-2 weeks to obtain blood meals (Table 2). *Ixodes ricinus* a medicly important free living tick transmit disease pathogens i.e. *Amblyomma spp, Anomalohimalaya spp, Bothrio crotons spp, Cosmiomma sp, Dermacentorspp, Haemaphysalisspp, Hyalomma spp, Ixodes spp, Margaropusspp, Nosomma sp, Rhipicentorspp, and Rhipicephalusspp* in man and other mammalian hosts [66]. The Lyme disease spirochete *(Borrelia burgdorferi)* to humans is transmitted by western black-legged tick *(Ixodes pacificus)* [67,68]. Ixodes pacificus (Acriixodidae) nymphs do make horizontal and vertical movements in hardwood forest for searching hosts. *Ixodes hexagons* or brown Ixodid ticks parasitze domestic and wild animals (Table 2).

6. Major Tick Borne Diseases

Tick-borne diseases are transmitted through the bite of an infected tick. These include Lyme disease, Anaplasmosis, Ehrlichiosis, Babesiosis, Powassan (POW), Rocky Mountain Spotted Fever, and Tularemia. Ticks can be infected with bacteria, viruses, or parasites. Tick-borne diseases are those spread by the bite of an infected tick (Table 3). Most of the tick-borne diseases are caused by saliva secreted toxins during blood feeding on hosts, parasite spreads through blood supply in various body parts after its entry. Tick borne diseases are also spread through blood products and blood transfusion. The transmission of tick-borne pathogens via blood transfusion is of global concern [69]. (Table 3) (Figure 2). Few important tick brone diseases which are responsible for illness and severely affect public health are following:

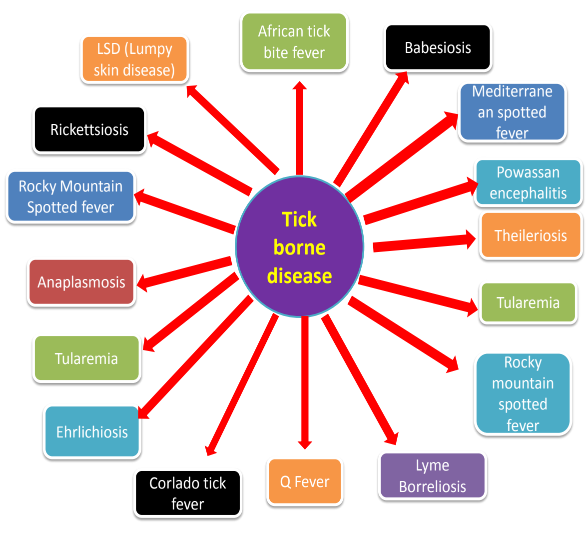

Figure 2. various tick borne diseases

6.1 Lyme Disease

Ixodid ticks are notorious bloodsucking ectoparasites and are completely dependent on blood-meals from the hosts. Lyme disease, is an infectious, inflammatory disease, this is caused by *Borrelia burgdorferi,* parasite a spirochete consulate bacteria. This pathogen is transmitted to humans by the bite of blacklegged tick *(Ixodes scapularis)* [70]. *Borrelia burgdorferi* parasite contains membrane protein antigens which are differentially regulated during its life cycle. During blood feeding tick also release anticoagulants, anti-inflammatory and antihemostatic compounds in saliva with this parasite [71]. (Table 2). This disease is a potential health threat to the Canines mainly dogs, and lives stocksriti. Important symptoms of Lyme disease are fever, chills, headache, joint and muscular pain, fatigue, and a skin rashes with erythema migrants. It manifests with lameness, anorexia, fever, lethargy, lymph adenopathy and, in some cases, fatal glomerulo-nephritis. Lyme disease patient display erythema migrans, and bullseye-like rash. It also causes long term complications in untreated cases, it imposes arthritis, facial palsies, meningitis, and carditis. The vaccine could be an efficient approach to decrease. For treatment of Lyme disease oral antibiotics are provided, but few patients (10 to 20%) suffer from persistent, non-specific symptoms and identified post-treatment they display Lyme disease syndrome (PTLDS). Lyme disease is treated by vaccination of healthcare providers and public health practitioners**.** It also needs public awareness and tick control [72] (Figure 2).

Lyme disease is also caused by multi-system bacterial infection that cause relapsing fever [73]. Important symptoms of this disease are red signs over skin, mild fever, and influenza-like symptoms with ocular manifestations [74]. Some patients also show neuro-meningeal complications and severe neurological lesions [75]. At earlier satge diagnosis remains difficult because of nonspecific symptoms [76] in endemic areas [72]. Borrelia causes Tick-borne relapsing fever (TBRF), it is transmitted spread by Ornithodoros tick vectors [77].

6.2 Anapalsmosis

Anaplasmosis is spread by a bite of *Anaplasma phagocytophilum and Anaplasma marginale* a highly infectious hard tick. This disease is prevalent in northeastern and upper midwestern U.S. and Pacific coast. Its large numbers of cases have been reported worldwide also occurs worldwide during last two decades. Anaplasmosis is caused by the bites and blood feeding of infected Ixodes scapularis, known as deer tick *(Ixodes scapularis)*. Anaplasmosis is hemolytic disease and its main symptoms are

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Table 3. Important tick borne diseases in man and livestock

S.No.	TBDs	Species	Host	Vector Tick species	Symptoms
1	Rocky Mountain Spotted fever	*Rickettsia rickettsia (Dermacentor variabilis, Dermacentorandersoni)*	Man, Dog, small mammals are the natural reservoirs in the wild	*Dermacentor variabilis and Dermacentor andersoni.*	Subclinical infection to severe or fatal multiorgan collapse. Blackened or crusted skin at the site of a tick bite.
2	Rickettsiosis	*Rickettsia parker (Amblyommamaculatum)*	Small mammals, and humans	*Dermacentor variabilis Dermacentor andersoni Rhipicephalus sanguine*	Rickettsial vasculitis, vascular inflammation
3	Pacific Coast tick fever	Rickettsia philipii (Dermacentoroccidentalis)	Horses, deer, cattle, lagomorphs, peccaries, porcupines, tapirs, desert bighorn sheep, and humans	*Dermacentor* species	Eschar or tissue necrosis
4	Mediterranean spotted fever	Rickettsia philipii (Dermacentoroccidentalis)	Man	*Dog tick Rhipicephalus sanguineus*	Headache, fever andmaculopapular rash
5	African tick bite fever	Rickettsia philipii (Dermacentoroccidentalis)	Ruminants , equids, candis, felids, rodents, human	*Rhipicephalusannulatus,Rhi. Bursa, Rhituranicus, Rh isanguineus,Hyalomma excavatum, H rufipes, H marginatum,H.dromedarii, Haemaphysalis punctate, Haeparva , Hae.sulcata, Dermacentormarginatus, D. reticulatus, Ixodesricinus*	Severe headache, nausea, abdominal pain, hemolytic anemia, fever, chills, sweats
6	Theileriosis	Rickettsia philipii (Dermacentoroccidentalis)	Ruminantsequid	*H. marginatum, H.anato licum,Hexcavatum,Hdetr itum, Haemaphysalisspp, Rhipicephalus*	Anemia and, in some cases, jaundice or hemoglobinuria.
7	Cytauxzoonosis	*Cytauxzoonfelis*	Domestic cat	*star tick, Amblyomma americanum*	Necropsy, splenomegaly, hepatomegaly, enlarged lymph nodes, and renal edema
8	Hepatozoonosis	*Hepatozooncanis*	Candis felids	*Rhi. Sanguineus*	Fever, lethargy, decreased appetite, weight loss, muscle pain/weakness, reluctance to move, and discharge from the eyes and nose
9	Canine filariosis	*Acanthocheione-mareconditum*	Dogs	?	Weight loss, cough,fatigue
10	Anaplasmosis	*Anaplasmaphag-ocytophilum, A. platys, A. marginale, Abovis, A ovis, A central*	Ruminants dogs, human	*Ixodespp, Dermacentorspp, Rhipicephalusspp,Haemaphysalisspp,Hyalommaspp,Ornithodorusspp*	Human Granulocytic plasmolysis, fever, headache, chills, and muscle aches
11	Ehrlichiosis	*Ehrlichiacanis*	Dogs	*Rhi. Sanguineus?*	Human Monocytic plasmolysis, fever, chills, malaise, nausea, diarrhoea
12	Aegypti anellosis	*Aegyptianellapullorum*	Duck	?	Parasitize the erythrocytes, infectious anemia”.
13	Tick borne typhus	*R. hoogstraali, R. aeschlimanni, R. slovaca*	Human Dogs	*H. marginatum, H. aegyptium, H excavatum, D. marginatus, Haeparva*	High fever, nausea, malaise, diarrhea, and vomiting.

14	*Candidatus R. vini*	*R. vini*	Birds	*Ixodesarboricola, Haemaphysalis longicornis ticks*	Leukopenia and elevated hepatic enzyme levels
15	Lyme Borreliosis	*Borreliaburgdorferi, Bor. Turcica sp.* Nov	Human, dogs, horses	*I .ricinus, H. aegyptium, H excavatum, D. marginatus, Haeparva*	Circular rash with red oval or bull's-eye marks appear anywhere on body, fatigue, joint pain and swelling, fever, swollen lymph nodes
16	TBRF	*Bor. Crocidurae*	Rodents	*Ornithodoroserraticus*	Fatigue, fever, loss of appetite, malaise, night sweats, or sweating, loss of muscle, phlegm, severe unintentional weight loss, shortness of breath, or swollen lymph nodes
17	Tularemia	*Francisella tularensis*	Human	?	cough, chest pain, and difficulty breathing, swollen lymph nodes near the skin ulcer
	Bartonelliosis (Cat scratch fever)	*Bartonellahenselae*	Cat	?	Fever, headaches, fatigue, poor appetite, brain fog, muscle pain, and swollen glands around the head, neck, and arms.
18	Hemoplasmosis	*Mycoplasma haemofelis*	Cat	?	Lethargy, weakness, reduced appetite, dehydration, weight loss and intermittent pyrexia
19	CCHF	CCHF virus	Human	*H. marginatum, haemaphysalisspp, Rhipicephalusspp, I .ricinus*	Stomach pain, and vomiting. Red eyes, a flushed face, a red throat, and petechiae
20	LI	LI Virus	Sheep	?	
21	LSD (Lumpy skin disease)	LSD Virus	Cattle	?	Skin nodules and oedema, enlarged lymph nodes, nasal discharge
22	Tick borne encephalitis	*TBE virus complex Ixodusricinus, Ixodus persulcatus*	Europe Asia, Middle East	Common and widespread	Swelling of the brain and/or spinal cord, confusion, and sensory disturbances
23	Powassan encephalitis	*POW virus (Ixodesscapularis, Ixodes cookie)*	Northern US / adjacent Canada far eastern Russia	Rare increasing	Swelling of the membranes surrounding the brain and spinal cord
24	Other TBEsOmsk hemorrhagic fever (OHF), Kyasanur Forest Disease(KFD) Louping ill virus, others	*OHF virus KFD Louping ill virus (IxodesDermacentor, Haemophysalis*	Europe , Russia, China, Japan , India , Southeast Asia, Middle East	Rare to common within localized range some increasiing	High-grade fever with chills, intense frontal headache, severe myalgia and body aches
Bunyavirales /Orthonairovirus					
25	Crimean - Congohemorrhagic fever (CCHF)	(CCHF) virus *(Hyalommamarginatum* other tick species	Europe Central Asia, India , Africa	Common and widespread increasing	Headache, high fever, back pain, joint pain, stomach pain, and vomiting.
	Bunyavirales /Phelbovirus				
26	Severe fever with thrombocytopenia syndrome (SFTS)	SFTS virus *(Haemophysalislongicornis , Rhipicephalusmicroplus*	China Korea Japan	Uncommon increasig	Thrombocytopenia, leukopenia, nausea, and vomiting

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27	Heartland virus disease	Heartland virus *(Amblyammaamericanum)*	Midwestern and Southwestern US	Rare	Fever, fatigue (feeling tired), decreased appetite, headache, nausea, diarrhea, and muscle or joint pain
28	Bhanja virus disease	*Dermacentor, Haemophysalis*	Africa Central Asia Southern Europe	Rare	
	Reovirdae/ Coltvirus				
29	Corlado tick fever	CTF virus *(Dermacentorandersoni)*		Rare	Photophobia, vomiting, meningoencephalitis, and slight or partial paralysis.
30	Eyach virus disease	Eyach virus *(Ixodusricinus)*		Rare	Biphasic fever, chills, headache, generalized musculoskeletal aches, and malaise.
	Orthomyxovir Idea / Thogotovirus				
31	Thogotovirus (THOV) disease, Dhori virus (DHOV)disease Bourborn virus disease	(THOV) (DHOV) disease *Bourborn virus (HyalommaAmblyomma , Rhipicephalus)*	Africa, Asia Europe, (THOV) (DHOV) USA, (Bourborn)	Rare , Bourborn virus isolated from *Amblomma americanum*	Meningitis and neuromyelitis optica

chills, fever, body and headache, fatigue, nausea, vomiting, and diarrhea. patient also feel loss of appetite, chills, abdominal pain and muscle aches [78,79]. Its asymptomatic coinfection show plus *anaplasmosis* SFG rickettsiosis. Anaplasma phagocytophilum harbors inside patient erythrocytes and was identified by cell sorting assay [80]. Parasites house inside ticks show regional climatic induced variations in genospecies and strain frequencies differing in pathogenicity [81]. For its identification DNA tests are performed [80]. For human granulocytic anaplasmosis diagnosis is important to identify *Ixodes scapularis* ticks and zoonotic amplification of *Anaplasma phagocytophilum* [82]. (Figure 2)

6.3 Tick-borne Babesiosis

Babesiosis is a zoonotic, disease that is caused by a tick-borne intra-erythrocytic hemoprotozoan parasites of genus Babesia. Disease provokes due to climate changes and rising vector population of Ixodes ticks and presence of human and other mammalian hosts in plenty [83]. Babesiosis is a major threat to human health [84]. Both dirofilariosis and babesiosis in was spread in central Europe, it was reirted in microfilaraemic dogs [85]. Babesiosis is transmitted through blood transfusion or congenitally [86]. Its pathogen mainly invade human erythrocytes and lyse red blood cells that results in febrile hemolytic anemia much similar to human malaria [87]. Disease also occurs in dogs in tropical regions [88].

Besides, human babesiosis canine babesiosis is spread by a tick species *Dermacentor reticulatus* [89]. Canine babesiosis is caused by many species of Babesia. Babesiosis disease level is ascertained by a ICD-9-CM diagnosis code [90]. This disease is also reported in canines that is caused by Babesia canis, B. vogeli, B. gibsoni, and B. *microti* from infect dogs in Europe [91]. *Bovine babesiosis* is caused by several species of *Babesia spp.,* including *B.bovis, B. bigemina, and B. divergens Human babesiosis* is caused by *Babesia microti* and it is endemic in the northeastern and the upper Midwestern United States(Figure 2).

Human babesiosis is caused by intraerythrocytic protozoan parasites the *Babesia microti*. This disease remains asymptomatic in beginning and patenint feel high fever, sweats, chills, nausea, headaches and fatigue after 4-5 days of infection. Babesiosis patient loss appetite, fatigue, urine color become dark due to jaundice and anemia. Babesiosis patients also show few clinical symptoms like anorexia, dehydration, temperature, dullness/depression, diarrhea /constipation, pale mucosa, hepatomegaly, vomiting/nausea, splenomegaly, distended abdomen/ascites, yellow coloured urine, emaciation/weight loss, and ocular discharge [92]. Extracellular phosphorylated proteins found in serum of *infected* patient are used for diagnosis [93]. Disease is also transmitted by blood transfusion and causes heavy mortality in high risk populations in spite of anti-biotic therapy [94]. (Table 2) (Figure 2) Few broad spectrum antibiotics such as atovaquone plus azithromycin or clindamycin and quinine are prescribed for the treatment of babesiosis patients.

6.4 Tick-borne Encephalitis

Ticks are important vectors of encephalitis virus (TBEV) and Omsk hemorrhagic fever virus (OHFV). These are highly pathogenic ticked-borne flaviviruses. These are leading cause of encephalitis that is an emerging disease, spreading in many regions in Eurasia in dogs. Tick-borne encephalitis virus is a dreadful pathogen. It is transmitted from nymph-to-larva and in small mammals [95]. Ticks infect domestic and wild dogs and accidental and during extensive search of vertebrate hosts. TBEV infect neural tissues in humans, while OHFV causes lysis of blood cells and evoke hemorrhagic fever [96]. Tick secrete neurotoxins HT-1, saliva ticks during blood feeding it causes paralysis in man and animals [97]. Tick bites during blood feeding transfer pathogens of Lyme disease, human granulocytic anaplasmosis and human babesiosis [98]. Powassan virus causes meningoencephalitis in North America. This is a neurovirulent flavivirus [99]. (Table 2) (Figure 2)

Tick also harbors endogenous viruses and modulation tick-borne pathogen growth. Ticks also transmit viruses with diverse genetic attributes, these are placed in two orders, nine families, and at least 12 genera. Tick-borne encephalitis virus (TBEV) evokes severe neurological diseases in humans in different parts of world [100]. The salivary gland secretions in the hematophagous parasites, blood sucking arthropods such as ticks have a greater role to counteract their vertebrate host's homeostasis, inflammation, and immunity [101]. Tick saliva contains microbiome communities of microorganisms, including viruses, bacteria and eukaryotes [102]. Both *Ehrlichia ruminantium* (ER) and *Ehrlichia chaffeensis* obligate intracellular pathogenic bacteria, and fatal tick-borne disease like hot water and monocytic ehrlichiosis in livestock [103] and man [104]. (Table 2) (Figure 2).

6.5 Powassan Encephalitis

Powassan encephalitis is spread by woodchuck tick *(Ixodes cookei)*, deer tick (*Ixodes scapularis* and squirrel tick *(Ixodes marxi)*. This is a fatal neuroinvasive disease first reported in Powassan, Ontario in 1958. Its major symptoms are mild fever, head and body pain, vomiting, aphasia, muscle weakness, seizures, confusion, loss of coordination and slurred speech. Due virus invasion on brain patient under go dementia and death. No established and effective treatment of disease is available. Its early treatment of tick-borne disease is critical and in later stage it causes severe health issues in affected patients.

6.6 Lumpy Skin Disease

Lumpy skin disease is caused by *Borrelia burgdorferi* into the mammalian hosts by an infected-tick bite of various species of Ixodid ticks belong to genera Rhipicephalus (i.e., brown dog tick), Dermacentor (i.e., American dog tick), Amblyomma (black-legged tick, Lone Star tick), and Haemophysalis yellow dog ticks in various parts of wolrd (Table 2). *B.* h*ermsii* and *B. turicatae* (in the southwest) cause infantile tick paralysis [60]. (Figure 2)

6.7 *Borrelia miyamotoi* Disease

Borrelia miyamotoi infection is spread by the black-legged tick *(Ixodes scapularis)*. It was detected in deer ticks in the eastern United States and Russia. This is a spirochete bacterium resembles with *Borrelia species*. It also spread tick-borne relapsing fever. It was first identified and isolated from ticks in Japan in 1995. Infected female ticks lay eggs, and its larval offsprings get natural infection and become an important participant in the transmission cycle. Important symptoms of *Borrelia miyamotoi* disease are fever, chills, fatigue, severe headache, muscle/joint pain.

6.8 *Borrelia mayonii*

Borrelia mayonii is Gram negative spirochete that causes Lyme disease in North America and midwestern United States. *Borrelia mayonii* infect humans and ticks, and Blacklegged ticks *(Ixodes scapularis)*. *I. scapularis* is a transmission vector. The major symptoms of the disease are fever, chills, headache, fatigue, body and joint pain and cardiac, neurologic and arthritic problems.

6.9 Alpha-Gal (Red Meat) Allergy

Alpha-gal allergy is a severe food allergy that is caused by the bite of a lone star tick. Alpha-gal allergy is caused by transfer of Alpha-gal (galactose-alpha-1,3-galactose) a sugar molecule found in red meat by the star tick to humans. Sugar molecule triggers delayed allergic reaction that persists for three to six hours. The other symptoms which are noted in patients are hives and/or severe itching, swelling of the lips, face, throat, or other body parts, shortness of breath, nausea, vomiting, diarrhea, abdominal pain, sneezing, headaches, anaphylaxis (Figure 2).

6. 10 Bourbon Virus

Bourbon virus infection was first identified in Midwest and southern United States mainly in in Kansas and Oklahoma states. This is very rare infectious disease and its patients show mild symptoms like fever, fatigue, rash, muscle and joint pain.

6.11 Colorado Tick Fever

Colorado tick fever (CTF) is a viral infection (Coltivirus) that is caused after bites made by an infected Rocky Mountain wood tick i.e. *Dermacentor andersoni.* Its patient shows important features like fever, rash, low white blood cell counts, heart problems and severe bleeding.

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6.12 Ehrlichiosis

Human ehrlichiosis starts with mild fever associated with lymphoadenopathy. It is caused by several bacterial species *Ehrlichia chaffeensis, E. ewingii, Ehrlichia* muris-like agent, Panola Mountain *Ehrlichia species*, and Anaplasma phagocytophilum [105]. This disease is transmitted to humans by star tick *Ambylomma americanum*. Disease is noted in the southcentral and eastern U.S. More recently ehrlichiosis have emerged as new infections that may be associated with neuro-meningeal complications. Borad spectrum antibiotics are prescribed for the treatment of ehrlichiosis, till the date no suitable vaccine is available so far [106].

6.13 Mycoplasma

Mycoplasma fermentans is also transferred with Borrelia bacterium via an infected tick the Lyme disease causative agent. This is smaller than bacteria, it invade body cells disrupt the immune system, causing severe fatigue, joint pain, nausea and neuropsychiatric problems (Figure 2).

6.14 Rocky Mountain Spotted Fever (RMSF)

This is spread by the American dog tick (*Dercacentor variabilis*), Rocky Mountain Wood Tick (*Dermacentor andersoni*), and Brown Dog tick (*Rhipicephalus sanguineus*).The brown dog tick also transmit bacterium Rickettsia rickettsii. This disease more predominantly outbreak in the summer season. RMSF shows unique illness features like fever, paralysis, sequel, chronic arthritis, and also impose neurologic or cardiac problems (Maureen McCollough) [107].

6.15 Tick Borne Paralysis

Ticks transmit pathogens through bite which causes loss of motor function and induce paralysis. Mainly few toxins are secreted by female ticks of *Amblyomma aculatum* which react with host's tissues and cells and generate toxicoses [108]. *Ixodes holocyclus* also generate same morbidity and induce paralysis [109]. Toxins secreted by these tick species generate positive inotropic responses in rat left ventricular papillary muscles and positive contractile responses in rat thoracic aortic rings [109]. Spirochetes are blood-borne pathogens transmitted through the saliva of soft ticks but they never evoke paralysis in host [110]. Destruxin A secreted by *Rhipicephalus (Boophilus) microplus* ticks (Acari:Ixodidae) causes tetanic paralysis [111] (Table 2) (Figure 2).

6.16 Rickettsioses

Rickettsiosis diseases is caused by an obligate intracellular bacteria belong to the genus Rickettsia. Two species *Rickettsia phillipi* and *Rickettsia parkeri* cause rickettsiosis. This disease is transmitted to humans by the Gulf Coast tick *Amblyomm amaculatum* and Pacific Coast tick Dermacentor occidentalis ticks. Rickettsia conorii, pathogen causes Mediterranean spotted fever while Rickettsia *parkeri, and Rickettsia akari* causes rickettsioses in United States [112]. Rickettsioses in this region is transmitted by dog tick *Rhipicephalus sanguineus* and the camel ticks *Hyalomma dromedarii*. These are important vectors and reservoirs of Rickettsiae. Disease is spread by infected male ticks through sexual transmission. Rickettsiae have been detected in spermatogonia, spermatocytes, and maturing spermatids [70] (Table 3) (Figure 2).

6.17 Tularemia

Tularemia is also known as rabbit fever, it is a dreadful zoonotic disease caused by the *Francisella tularensis*, a highly infectious Gram-negative coccobacillus. In man tularemia is also caused due to direct contact. The main vectors of tularemia pathogen are dog tick (*Dermacentor variabilis*), the wood tick (*Dermacentor andersoni*), and the star tick (*Amblyomma americanum*). Pateint feel fever and face skin ulcer at the site of tick bites.

Tularemia is spread in humans by the dog tick (*Dermacentorvariabilis*), the wood tick (*Dermacentorandersoni*), and the lone star tick (*Amblyommaamericanum*). Tularemia is bacterial infection sometimes it is also called rabbit fever, and development of an ulcer at the site of infection also seen. This disease is also spread by inhalation of contaminated dust or through contaminated food and water [114]. Disease shows important clinical symptoms including spiking fevers, inflamed lymph nodes and eyes, pneumonia and weight loss. This is also used as biological weapons for generating potential bioterrorism threat and classified in category A of warfare agents by the CDC [57,115]. (Figure 2). Parasite is detected in wild species, of animals lagomorphs, rodents, carnivores, fish and invertebrate arthropods [116]. *Francisella tularensis* is also detected in large number of animal species. [117]. *F. tularensis* holarctica, biovar I is also found in common marmosets (*Callithrix jacchus*) [118] Few broad spectrum antibiotic aminoglycosides, the fluoroquinolones and the tetracyclines are recommended for the treatment of this diseases [119]. The macrolides found highly effective against *F. tularensis* grown in phagocytic cells than in acellular media [120]. Important tools which are used for diagnosis of tularemia are PCR, ELISAs, MAT and IFA [121] (Figure 2).

7. Immune Responses

For control of ticks there is immense need to study tick life cycle, tick-borne pathogens, and tick-host interactions. There are so many control methods which have been used to control ticks in various parts of world. These are based on biomacromolecular repository and its enzyme inhibitors by using genomes, transcriptomes, and proteomes. Most of the methods are mechanical, chemical, genetic, repellents, pesticides, toxic baths, and environmental and community based control mechanism. During blood feeding ticks secrete plethora of biomolcules in saliva which directly responsible for inflammation, vasoconstriction and the modulation of host defense mechanisms. Saliva secreted rerine protease inhibitors are used to prepare innate immune defense. Saliva secreted molecules do hemolymph coagulation and induce egg development. Till the date so many enzyme inhibitors like serine protease inhibitors (SPIs), which inhibit various tick biological processes found more appropriate. These will become effective tick control agents in future [122].

Salivary secretions in ticks are responsible for transmission of pathogens to the various animal hosts including man. Tick saliva is a complex mixture of various peptides mainly toxins and non-peptides. These substances strongly counteract hosts' homeostasis, immunity, and inhibit tissue-repair and wound healing. The ixodid ticks salivary glands (SG) secreted saliva contains a rich mixture of anti-hemostatic, anti-inflammatory, and immune modulatoranti-coagulatory, anti- vasoconstrictory, and anti-platelet aggregation factors. Tick saliva produces itching or pain and initiate blood feeding by making incision in skin cells. Ticks inject toxins which generate cellular and humoral responses. Tick brone pathogens affect immune system of other invertebrates, and induce humoral and cellular immune responses and affect signaling pathways in higher vertebrates mainly mammals. These pathogens also affect redox metabolism, complement-like molecules and action of regulatory biomolecules [123]. Ticks bear antigen families evasions, Isac, DAP36, and many others on their surface. Sialostatin L (SialoL) is cysteine protease inhibitor identified in the salivary glands of the Lyme disease vector *Ixodes scapularis*. Tick salivary glands secrete cystatin sialostatin L2 which suppresses Type I interferon responses in mouse dendritic cells. Dendritic cells (DCs) secrete IFN in response to tick saliva proteins. Sialostatin L also shows immunomodulatory action on dendritic cells and obstruct autoimmunity. SialoL significantly decrease LPS-induced maturation of dendritic cells in C57BL/6 mice [124].(Table 2).

Tick salivary gland secreted bio-molecules ticks induce immunomodulation in hosts. These also obstruct innate immunity and inhibit the generation of adaptive immune responses. The only way to stop feeding in ticks are antigen evoked acquired immune responses in immunologically-strong animal hosts. Tick saliva toxins also act as allergens these induce severe IgE-associated allergic reactions. These also cause fatal anaphylaxis, after subsequent saliva toxin exposure to the skin cells [125]. Borrelia species affect differentiation of THP-1 Cells while *Ehrlichia chaffeensis* causes monocytic ehrlichiosis in man [93,126]. Tick saliva more specifically salivary cystatins secreted by hard tick Ixodes scapularis, sialostatin L (Sialo L) and sialostatin L2 (Sialo L2) in saliva inhibits differentiation, maturation and function of murine bone-marrow-derived dendritic cells. *Borrelia burgdorferi* pathogen interact with Toll-like receptors and evoke immune responses (Table 2).

Ticks as vectors secrete immunosuppressant peptide, and, immunoreactive proteins and antimicrobial peptides which also used in host defense. Few non-coding small RNAs regulate synthesis of these peptides at post-transcriptional level [127]. Tick harbor rickettsiae that spread spot fever in cattle and human [128]. Rickettsiae produce two immune dominant outer membrane proteins; rickettsial, Omp A (rOmp A) and rOmpB which are strong antigen and could be used for vaccine production.Besides this, ticks secrete hundreds to thousands of proteins into the feeding site in saliva. Tick salivary gland secreted natural substances play an important role in modulation of host defense mechanisms [129]. Few of them neutralize innate immune functions and inhibit the formation of adaptive immunity. Similar Australian tick *Ixodes holocyclus* secrete toxins and other active components which show immunomodulatory effects.Tick salivary products exposed to *Borrelia burgdorferi, Anaplasma phagocytophilum* dihydrolipoamide dehydrogenase 1 affect host-derived immunopathology during microbial growth inside hosts [129]. Similar immunomodulation is also seen in other blood sucking arthropod vectors mainly mosquitoes, tse-tse flies and sand flies which also transmit pathogens during blood feeding [130]. For treatment of neurologic diseases immunoglobulin therapy is provided [131]. (Table 2).

For therapeutics of tick-borne encephalitis a thiomersal-free and albumin-free (TBE-vaccine) was developed in Australia 2000 [132]. For neutralizing paralysis causing toxins secreted by *Rhipicephalus evertsi evertsi, Rhipicephalus appendiculatus, Boophilus microplus and Ixodes holocyclus ticks monoclonal antibodies* are used [133]. *A recombinant* veterinary vaccine is also developed to neutralize effect of tick neurotoxin peptide. Though, this vaccine is successful, cost-effective, and provides long-term protective immunity against tick-induced paralysis [134]. Simi-

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larly, a vaccine is also administered to decrease the Lyme disease incidences [135]. Moreover, for seeking protection against Anaplasma marginale VirB2, VirB7, VirB11, and VirD4 proteins are adminsitered as immunogenic components. These show effective serological responses in man [136]. Similarly, few outer membranes (OM) proteins are used for immunization of cattle to defend from *Anaplasma marginale* tick infestation. These provide complete protection against disease and persistent infection. Polyclonal dog antiserum is also used for treatment of tick paralysis (Table 2).Other approaches are also tried for development of tick vaccines for prophylactic use [137].

However, for preparation of an appropriate vaccine complete genome sequencing of bacterial parasites of ticks and its antigens is must be identified and charecterized [138]. This highly distinctive type IV secretion system stays as neurotoxins found in tick saliva [139]. More specifically, surface protein with α_3 integrin binding and channel forming activities responsible for *Borrelia burgdorferi* [140]. And a plasminogen receptor BosR (BB0647) released in outer membrane of Borrelia burgdorferi governs virulence expression could be used as antigen [141]. Nitric oxide also function as an antimicrobial effector molecule, it is produced by activating mouse macrophages in response to viral infection. It is implicated in antiviral defense mainly against flaviviruses [142]. Ceftriaxone is recommended when parenteral antibiotic therapy against tick borne microbial pathogens [143]. More specifically, oraldoxycycline,amoxicillin and cefuroxime axetil are used against Lyme disease pathogen.

8. Diagnosis

For diagnosis of tick brone diseases methods are used. Among them most frequently method is enzyme immunoassay (EIA), followed by western blot test(s). For diagnosing blood specimens of HGA and babesiosis patients various microscopy methods [143]. Babesiosis generated plasminogen are tested by using chromogenic assay. Besides this, and concentrations of high mobility group box-1protein (HMGB-1), intercellular adhesive molecule-1 (ICAM-1), vascular adhesive molecule-1 (VCAM-1), soluble urokinase receptor of plasminogen activator (suPAR),thrombin activatable fibrinolysis inhibitor (TAFI), soluble thrombomodulin (TM)and plasminogen activator inhibitor-1 (PAI-1) level is determined by using ELISA [144]. In clinical samples Babesia pathogen is also identified by staining with Giemsa stain in blood smears. Besides this, PCR, and anti-babesia antibody titers are also used for identification of *Babesia* sp.[145]. These is a need for development of diagnostic methods, vaccine development, "omics" analysis, and gene manipulation techniques of local *Babesia* strains [146].

Skin biopsy specimens are diagnosed for lesions by using immunohistochemical stains. For diagnosis of rickettsiae polymerase chain reaction (PCR) is used [147]. For testing samples from asymptomatic anaplasmosis cases PCR and an indirect immunofluorescence assay (IFA) is performed to identify tick-borne infectious diseases [148]. Because serology provides a low specificity and high sensitivity and used for testing acute and convalescent samples. But PCR and immunofluorescence tests were found more apparopriate for anaplasmosis diagnosis as both provide more auathentic results [149].

SDS-PAGE gel electrophoresis is used to identify and chareterize the basic functions of tick saliva proteins. Morespecifically, pathogen specific proteins of Lyme disease are identified by SDS-PAGE gel electrophoresis, ELISA (enzyme- linked immunosorbent assay) and immunoblottin [150]. These are also diagnosed by measuring the level of Immunoglobulin G1 isotype [151]. More specifically spotted fever caused by rickettsiasis can be identified by LPS lipopolysaccharides antigenicity. *Theileria lestoquardi,T. ovis and T. annulata* are detected by using molecular methods in the blood of Goats and Ticks. Mast cells and IgE levels are used to detect tick borne allergy.

9. Effect of Climate on Emergence of Tick-borne Diseases

Tick borne illness found almost in all climatic regions because of wide distribution and occurrence of various ticks species adapted in local environment. Moreoften, climate cycles determine genetics, adaptability, host-parasite interaction and pathogen multiplication. The main endemic areas of tick brone diseases are forest sites, high density urban and rural habitations.. Tick infestation is a major animal health problem world wide, its higher endemicity is noted in Middle East and North Africa, tropical and subtropical countries [152]. The disease prevalence, infestation and invasion accelerates with climatic favourability and tick borne pathogens spread very fast and make heavy economic losses to livestock farming and wild life. Emergence of tick-borne zoonotic diseases also severely effect human health, as both morbidity and deaths are noted higher Northern Hemisphere due to regional variations climatic variations and rising resistance in ticks and tick borne pathogens. Moreoften, hydroclimatic changes occur due to unstable weather conditions which also affect the range of some infectious diseases, including tularemia. Tularemia incidences are directly related to climate variables,and assessment can be done for future disease outbreaks by analyzing these varaibles rainfall, humidity, latitudinal gradient, temperature and photo period [152]. In middle east and NorthAfrican countries domestic livestock are more severely attacked by multiple tick species due to harsh environmental conditions. These areas have most suitable climate and vegetation for tick population growth and easy availability of large number mammalian hosts [153]. Hence, there is an immense need in mapping of tick borne diseases based on ecology of area evoked across their geographic distribution to evaluate burden of pathogens transmitted by ticks [154].

Tick infestation is affected by climatic conditions in mountain region and its incidences increase with increase in elevation and latitude. Temperature, rainfall, humidity, day periodicity, landscape and altitude increase risk of tick-borne diseases. Spatiotemporal conditions affect distribution of ticks in temperate climate. In cold countries dogs or cats possess broad range of tick-borne pathogens and easily transmit them and generate important public health issues. Climate mainly temperature and vegetation affect horizontal distribution of ticks and tick borne parasites in all different climatic zones. Tick borne disease mapping shows high to low density of tick and its host population and disease pathogens in agro-ecosystems and forest ecosystem. Ticks from these areas show regional variation in tick-borne disease incidence, vector abundance and pathogen prevalence. Moreoften, environmental changes and unstable climatic conditions affect tick population genetics and give rise isolation among several tick populations.

10. Use of Bioinforamtic Tools for Study of Novel Tick Antigen Proteins

For generating successful anti-tick vaccines, various known antigens from different tick species are compared and suitable gaps are identified to have new novel antigen structures. Moreover, tick aquaporin-1 (AQP1) protein is compared with other antigenic proteins by using multiple sequence alignment (MSA), motif analysis, for finding similarities and differences. Its structure analysis revealed tick-specific AQP1 peptide motifs. Moreover, for finding other identifcial features in antigenic BepiPred, Chou and Fasman-Turn, Karplus and Schulz Flexibility, and Parker-Hydrophilicity prediction models are used to predict these motifs' potential to induce B cell mediated immune responses mainly for production of antibodies for therapeutic purposes [155]. By using transcriptome studies genetically susceptible and resistant bovine hosts and their corresponding proteomes can be obtained. These will help to obstruct or modify of expression of many genes encoding mediators of parasitism in nymphs and larvae of ticks. Besides this, effect of few inhibitory proteins or enzymes can be identified in silico to certain metabolic pathways which restrict developmental stages of the tick. These insight should assist in developing novel, sustainable technologies for tick control [156].

Ticks invade cattle farm yard and severely affect farm production and economy of owners. Most of the under developed and developing countries have cattle yards, which play a paramount role in agriculture production systems, throughout the world. Hence, safety and animal health of cattle tick populations is highly important. For prevention of tick borne diseases in farm animals vaccination is done. Vaccines are also used to prevent the spread and re-introduction of tick brone zoonotic diseases in human beings [157]. *Ixodes scapularis* Tick bites use saliva toxins/proteins for modulation of the feeding site. Fibrinogen, is key protein that participate in blood clotting and wound healing. Ticks salivary secretions are anti-fibrinogen molecule [158]. Host genetics plays important role in immune responsiveness against ticks and tick-borne pathogens. Moreover, susceptible breeds display increased expression of Toll like receptors, MHC Class II, calcium binding proteins, and complement factors. These also show an increased presence of neutrophils in the skin following tick feeding. Resistant breeds had higher levels of T cells present in the skin prior to tick infestation. These also contain higher numbers of eosinophils, mast cells and basophils with up-regulated proteases, cathepsins, keratins, collagens and extracellular matrix proteins in response to feeding ticks [159].

Transmission of various pathogenic microorganisms to vertebrate hosts takes place by tick bites and blood sucking [160]. Tick salivary glands, secrete toxins or proteins which exhibit cytolytic, vasodilator, anticoagulant, anti-inflammatory, and immunosuppressive activity. For their survival ticks parasitize on number of animals as they need blood components for their survival and reproduction mainly completion of their life cycle varying among species [161]. In response to invasion of tick brone pathogens host body make defense by using innate immunity, but tick breach host cutaneous defenses prior to pathogen transmission and suck blood and become give rise infectivity [162]. As protease inhibitors obstruct blood feeding in ticks, these are thought to be good candidates for broad-spectrum anti-tick vaccines [163]. In other approach tick endogenous dsRNA corresponding to potential control targets within midgut and salivary glands are used as main target for obstrtion of tick blood feeding and lower down infectivity [164].

11. Tick Management and Control

11.1 Control of Ticks

Ticks spread various diseases i.e. viruses, bacteria,

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protozoan, in livestock and in man [165]. Because of their complex transmission its control involves multiple vertebrate hosts and variety of parasites, tick prevention is prevention very difficult [166]. Identification of factors responsible for tick survival, spread, and pathogen transmission, design and performance will help in reduction in tick population and the prevalence of tick-borne diseases [167]. In additions, there is a need of rapid diagnosis and clinical management [168]. In addition, for tick control both individual persons and professionally staffed tick-management programs mainly systematic treatment programmes for control of southern cattle fever tick (SCFT), caused by *Rhipicephalus (Boophilus) microplus* [169]. Efforts must be made to control tick populations by using multiple strategies to inhit or breakdown of pathogens transmission cycle [59]. Therefore, for controlling tick population implementation and adoption of integrated program is highly essential [73] (Figure 3). For large scale control both advanced tools and techniques must require to avoid human tick bites, and roll back tickborne diseases. Multiple infection by various fungal spores and necrotic toxins can more quickly control both ticks and tick-borne diseases.

Tick-borne diseases (TBDs) are treated by using antibiotics as prescribed to the livestock for killing ticks. Few tailor-made pesticides could be used by using dsRNAs. These affect P0 gene function in tick, *Rhipicephalus haemaphysaloides*. Use of these pesticides significantly cut down blood feeding, molting or reproduction in ticks [170]. Few noble anti-tick agents could be harvested by maintain laboratory cultures of tick cell lines. Its in vitro culture cell lines could be used for production secretory molecules against tick-borne viral, bacterial and protozoan pathogens [171]. Blood feeding inhibition is also possible by using immunological based inhibitory molecules [172]. Host-targeted new technologies and methods will prove good alternative of conventional pesticide of *Ixodes scapularis* [173]. Ethnobotanical substances were also found effective and affordable products against field and domestic tick. These natural products are highly economically affordable, environmentally safer after use. It could be adopted for community-driven tick control programs [174]. For large and massive control plant origin inhibitors for more innovative tick control [175] (Figure 3).

11.2 Use of Pesticides for Tick Killing

For successful control of tick-borne zoonotic diseases an integrated tick management program must be adopted [73]. For tick control few conventional tick control methods such as spray with chemical acaricides, fluid sprays like Jeyes, engine lubricating oil, pine and tarpene oil, latex are used. Farmers also manually remove ticks by hand picking and put them inside pouricide and ash missed cow dung for their immediate killing. *Aloe ferox* sap and solvent extracts of bark of *Ptaeroxylon obliquum* are used for killing of ticks. Farmers collect ticks by hand picking and kill by dumping them in kerosene oil or in tarpene oil. For tick control of acaricides are used. For regular tick prophylactic treatment DDT, flumethrin, Bayticol® are used at large scale. Though, synthetic pesticides are highly toxic to animals and humans.The synthetic pyrethroid insecticide phenothrin is combination with the hormone analogue methoprene topically applied to flea and ticks. Phenothrin kills adult ticks while Methoprene is used to kill ticks eggs. Flumeltrin B atical ® Peptide toxin and Nitric oxide are effective in tick killing. Bifenthrin and permethrin, both pyrethroids, are also used to control ticks measures.Besides these, few residual insecticides, FenvaStarEcoCap, Bifen IT, or Precor2000 Plus Aerosol are also to kill ticks. For quick killing of ticks' non-residual, contact space sprays that contain pyrethrins are used. These highly toxic synthetic acaricides show several negative side effects because they bio-accumulates at each stage and impose toxicity to non-target organisms/animals.

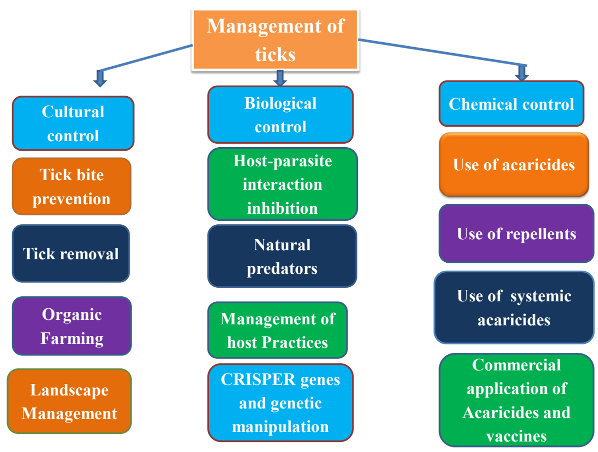

Figure 3. various methods used for management of ticks

Maxforce Tick Management System (TMS), was also used for control of field ticks. In this system bait boxes are prepared by using doxycycline *hyclate*-laden baits to attract and kill ticks. For protection of bait boxes from squirrel depredation galvanized steel shrouds are used [176]. For of flea and tick control in domestic cats fluralaner a novel isoxazoline is used, it works well as systemic ectoparasiticide [177]. For control of ticks traditional pesticides are also sprayed by using portable sprayers [178]. But due to longer exposure of pesticides tick population has developed resistance against these chemicals [179]. Therefore, to avoid harmful effects of highly toxic synthetic acaricides various latest eco-friendly strategies must be used and adopted for the prevention of tick and tick-borne illness. However, protection of environment and toxicity in hosts few tick avoidance, vector reduction programs, chemoprophylaxis, and natural repellents should be used for tick control [180]. For control of tick population Tekko Pro IGR is used to stop development in immature ticks. Ticks such as *Rhipicephalus turanicus* are controlled by using acaricidal plant products [181]. Natural tick repellents are also used for cultural management of ticks (Figure 3).

Bacillus thuringiensis (Bt) bio-insecticidal toxins are also used to kill ticks and its associating pathogens. Entomopathogenic fungi spores also control ticks mainly at enzootic or epizootic levels in their host populations. But for the use of bio-insecticides and other chemicals licensed applicators are required [182]. because they show cytotoxicity in human osteosarcoma cells, [183] damage membrane and obstruct organ functions [184]. Efforts should be made for their targeted release, low exposure period and safe use [185]. Ticks possess unique natural compounds which show multiple biological activities [186] much similar to defense molecules found in other animal groups mainly venomous [187,188]. For cultural control of ticks safe land-use pattern must be used, it reduces exposure to tick-borne pathogens and indirectly cutdown infestation (Figure 3).

Various acaricide formulations are used to control *Ixodes scapularis* nymphs a dreadful livestock tick residential areas. It successfully kills nymphal and larval stages if applied on skin topically or sprayed on grassy weds and narrow crevices or whole in doors and under neath of mats and clothes. These cutdown prevalence and intensity of parasitic interaction to small mammals [189]. Morespecifically, for long term killing of tick borne pathogen reservoirs, mild slow acting systemic acaricides must be used in endemic areas. These can do mass mortality of not only adult ticks but also nymphs and larvae successfully. These slow acting posions will prove highly useful tool for disrupting the natural cycle of the vector and pathogen. Besides this, fipronil baits made by using low dose of acracides and organic attractants can be used to control blacklegged ticks and other arthropod vectors [190]. For Lyme disease abatement besides tick control tick bites must be avoided in high risk areas [191]. However, for minimize tick attack and invasion on livestock and farm yard animals various plant orgin active constituents such as oil combinations, crude extracts, and pure compounds were also used. In addition, genetic and molecular methods which might obstruct tick feeding will prove ore safer and effective against different tick species [192]. Few antibiotics were found effective against some ticks, mainly blue ticks. A well practed method i.e. RNAi-mediated gene silencing is also used to inhibit expression of saliva toxin genes. This method genetically regulate the large tick population successfully (Table 3). But both acaricides and antibiotics they were found in milk that is again harmful for human being [193] (Figure 3).

For control of both ticks and pathogenic diseases caused by their field survey, pathogen identicfication and incidence time, status of climatic factors and interaction of host and parasite is highly important. In addition, identification of various tick species in different geographical is highly important. There is a need to use modern surveillance methods and environmental friendly methods to control ticks and tick-borne diseases [194].These must be less toxic, effective environmental friendly in order to reduce its impact on wildlife [195]. For control of ticks carbamates are also used [196]. But its low physiological dose should use because its exposure generates many numerous birth defects [197]. For tick control formamidines, is used, this a new group of acaricide-insecticides, that effectively kill ticks effectively with an uniques mode of action. For effective killing of ticks both structure--activity relations and environmental stability of compounds is very important. In additions, both toxicity and lateral transport of acarcides used for control of ticks must be explored to know its effects on physiology and metabolism on animal hosts. Most of the acaricides activate chlordimeform action by N-demethylation in vivo [198].

Pesticides put adverse effects and many of them detected organochlorine pesticides in serum concentration which lead to development of breast cancer [199]. Hence, there is a need to make and apply alternative methods, strategies and approaches to control tick and tick borne pathogen population in wild and in human surroundings. Farmers must adopt safe animal practices as use acaricides by rotation, and low toxic pesticide mixture formulations for tick killing on body surface of host animals. Manual removal of ticks, nutritional management, use of plant origin natural products, release of sterile male hybrids, are more safer methods to control ticks. Clean cultivation, pasture management, use of slow release posion baits and animal bathing cutdown chances of tick colonization. Use of multiple antigen based vaccines and antibodies obstruct tick feeding that is most safe and successful way to control population of different tick species vaccination. Among all integrated tick management methods, if two methods will be used in systematic combination with modern technological tools will provide much faster control. Such combination of methods will reduce selection pressure in parasites and may provide enlarged protection to acaricide-resistant individuals besides normal population [200] (Figure 3).

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11.3 Use of Repellents

Use of repellents repel ticks to invade wild-animal populations. Pets and wild animals should pass adequate quarantine delivery systems [201]. For protection of clothing and fabric repellents or acaricides are sprayed onto are used to deter ticks' access to human hosts [202].

11.4 Tick Control by Herbal Products

Plant natural products such as oils and other bio-organic compounds are also used for ticks [203]. Most of plant origin bio-organic compounds inhibit blood feeding in ticks [204]. These could be used to develop new highly active anti-tick agents [205]. These bioactive plant constituents need bio-evaluation process for their efficient isolation and identification [203] (Figure 3).

11.5 Natural Predators of Ticks

Red wood ants(Formica polyctena) are natural predators of Ixodes ticks and assist in reducing the local abundance of ticks [206]. Biological control agents are highly beneficial for safety of animals and protection of environment. For control of tick borne parasites and parasitism various biological agents can be employed [207]. One of the important tick controlling agent is an entomopathogenic fungi *Beauveria bassiana (B. bassiana 5197 and B. bassiana Evin)*. This fungal strain can easily grown on specific media and fungal spores are exposed to tick for inducing fungal infection [208]. Another strains of entomopathogenic fungi, the *Metarhizium spp*., also used to control tick population. *M. robertsii microsclerotia* or blastospores-granular formulations are used to control *R. microplus*, and is an important tool for control of field ticks [209] (Figure 3).

11.6 Control by Using Vaccines

For control of tick population various tick vaccines developed against saliva origin antigens have been used. Few of these vaccines have shown very high efficacy agsnat ticks as they obstruct blood feeding in ticks. These are cost-effective, sustainable and environmentally friendly and much safer alternatives of highly toxic acaricides used for tick control. SUB-MSP1vaccine is used for controlling tick population that infest cattle and sheep [210]. This vaccine is made from protective antigen, and its chimeric antigen was prepared from *Escherichia coli* membranes fused to *Anaplasma marginale* Major Surface Protein 1a (MSP1a). This SUB-MSP1a vaccine has low-cost and found highly effective for the control of cattle tick, *Rhipicephalus (Boophilus) microplus and R. annulatus* infestations in pen trials. Similarly, another SUB vaccine was developed by using recombinant subolesin in combination with other antigens for the control of cattle tick infestations [211]. Though, Subolesin (SUB)-based vaccines were found highly effective against so many tick species, but there is a need to mix and multiple antigen vaccine to curb tick infestations caused by various life stages of different tick species [212] (Figure 3).

Because tick salivary glands synthesize and release so many biomolecules which enhance transmission, and pathogenicity [213]. These tick saliva proteins involved in tick-pathogen interactions and are important targets in tick antigen-based vaccines [214]. Best example is tick midgut antigen BM86 that was used to prepare highly effective and promising vaccine for cattle tick control [215]. This Bm86 vaccines was commercialized in the 1990s (GavacTM in Cuba and TickGARDPLUS™ in Australia), only Gavac™ is available [216]. TBEV vaccines molecules from tick saliva mainly toxins are used as antigens [217]. Hence, for development of effective vaccines tick-pathogen-host interface, and identification of effective antigens is highly needful [218]. However, for preparaing development of potential anti-tick vaccines genetically modified pathogens and recombinant tick antigens could be used [219]. For generating live vaccine genetically modified viruses can be used. These may result in control of tick-vertebrate host transmission cycle in nature. But such type of vaccines will need environmental safety [220]. Further, tick-borne parasite released molecules must be identified and used for generation of potential vaccine or therapeutic candidates [221]. Few more recent methods extracellular vesicles (EVs) including exosomes that mediate transmission of flavivirus RNA and proteins to the human cells have been identified [222]. These are also used for development of novel vaccines to control ticks and tick-borne diseases [223].

Few B-cell epitopes in all the amino acid sequences are used to prepare single or arranged peptides to develop new strategies for the control and prevention of bovine anaplasmosis transmitted by ticks [224]. More specifically, after blood-feeding, tick midgut overexpresses proteins that play essential functions in tick survival and disease transmission. If salivary gland proteins/toxins responsible for tick parasitism and host interaction will be traced used for production of vaccine, these might disrupt life-cycle of ticks and eliminate tick harboring pathogens [217] .

The recombinant *B. microplus* Bm86 protective antigen was used to generate new vaccine and administer to protect cattle from tick infestations [225]. Similarly argasid chitinases and RPP0 were also used as protective antigens, for finding new vaccine targets against many tick species [226]. HlFER2 an iron-binding protein ferritin produced and secreted by hard tick *Haemaphysalis longicornis* was used to generate anti-tick vaccine antigen against multiple tick species [227]. Besides this, this aquaporin antigen found as an active ingredient in cattle vaccines targeted against infestations of *R. microplus* [228].

For control of ticks parasitize over various rodent species both oral vaccines and antibiotic baits are used [229]. It is also necessary to develop technology and antibiotics and tick controlling agents to cut down tick bites and protection of public health [230]. Though, tick invasion and infestation are regulated by many biotic and abiotic factors, and these could be manipulated to decrease tick bites. Recombinant antigens are used to generate vaccine for its effective and safe control. These vaccines successfully obstruct blood-feeding and ticks remain unfed and go on long-term starvation finally died due to antioxidant response [231]. Different levels of host anti-tick immunity affected gene expression in tick salivary glands. There is also a need to explore new drug targets for eco-friendly acaricide development. These proteins are encoded by certain genes which may be weakly expressed in ticks. These can be used to make tick resistant hosts. It will also reduce parasitism, and naturally infected bovine may develop antibodies prior to tick bites. It will also lower down the host susceptibility both ticks and easily neutralize the invasion of hosts by disease pathogen [232]. For mass vaccination of people there is a need to combine transfection technologies and the in vitro culture system prepare genetically modified live vaccines for mass vaccination [233]. For controlling babesiosis highly efficacious potential vaccine by using recent antigen technologies [234,235] (Figure 3).

11.7 International Tick Control Programs

Fro control of tick population various tick control program were launched at international level. For elimination of Cattle Fever, caused by *R. microplus* and Babesia Tick Eradication Program has been launched in Mexico and the U.S. [236]. Few countries like West Indies have launched identification and characterization of pathogens tick-borne diseases (TBDs) of human and livestock [237]. For tick eradication genetic analysis of tick population will be useful for finding types of pathogen-vector and host interrelationships. By applying genetic and molecular methods a wide array of tick and tick borne pathgen antigens could be searched world wide. These could be used to make vaccines for reduing the tick invasion on host populations [238]. MaxEnt models is best example of prediction for the occurrence of all tick species examined [239]. With this, disease diagnosis, type of invading pathogen, area wise incidence rate and climatic conditions must also study to ascertain efficacy of treatment and control method [240]. In cattle ticks acaricidal resistance is a major inderance in tick control, it could be resolved by using non-chemical methods [241]. In addition for control of ticks, study of host-parsite interactions is highly important at community level, because both community structure and the dynamics interlink ticks and its pathogenic association and host invasion [242]. For control of ticks such as Amblyomma ticks acaricide-impregnated leg-bands are tied on legs of goats [243].

11.8 Precautions

To minimize the tick infestation keep away pets from living sides. Regularly spray hosue beds, clothings curtains, grassy lawns with spray. Under side of doors and holes, crevices must be sprayed to ill tick nymphs. Apply creams to deter termites from feeding and skin penetration by infected tick larvae and nymphs. These risks can be minimized by dusting and spraying regularly the pet rooms and cattle yards with accaricides. Fumigation is also used to kill ticks inside wooden window, door mats, clothings, wooden furniture, and curtains. Regularly treat pets with anti-tick oils, sprays and provide them clean and health by regular bathing. For management of ticks in farm houses shorten and minimize grassy vegetation and use repellents to minimize tick movements.

12. Conclusions

Ticks are major vectors which transmit diverse group of pathogens and evoke diseases in livestock and make huge losses to veterinary, animal farms, pets and wild life animals worldwide. Ticks harbor a wide variety of pathogens in saliva. It is a repository of various disease pathogens including viruses, bacteria, malaria-like protozoan parasites causing babesiosis. Ticks cause direct economic losses; hence, their control is an important issue. For tick control conventional tick control methods such as household disinfectants, sprays, herbal leaf dusts, peptide toxin and Nitric oxide are effective in tick killing. Natural tick repellents are also used for cultural management of ticks. For tick control DDT, flumethrin, Bayticol®Farmers are used at large scale but these are highly toxic to animals and humans and show several negative side effects. For killing of ticks found on body surface of cattle dog, sheep, rabbit and other pats phenothrin a synthetic pyrethroids is applied topically mixed with methoprene a hormone analogue. Besides this, permethrin is also most commonly to control ticks. It is available in the market in different brand names and forms as shampoos, powders, emulsions, sprays, and coated over ribbons. But all these pesticides absorb in the skin and show lateral transport and are quite harmful for cattle. Repititive use of these acaricides against ticks is generating resistance and causing environ-

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mental contamination.

For control strict quarantine measures are enforced to prevent reintroductions of ticks with goods and materials ferried or parceled among countries. For the killing of ticks natural oils, bioinsecticides in form Bt toxins are used. For safety of man and his livestock vaccines are used. For successful control various models of tick population dynamics is required for predicting outcomes of control methods. It also needs better understanding of drivers of distribution, aggregation, stability, and density-dependent mortality. Climate-matching models, geographic information systems, and expert systems mainly subject experts and artificial intelligence are being used to identify unaffected areas in which tick pests could become established if introduced. Due to development of resistance in ticks species against conventional acaricides there is a need to opt immunological methods or vaccines to overcome the problem. Because ticks as ectoparasites suck blood from hosts and release pathogens in their blood supply. If any how blood feeding can obstruct, it will break the transmission cycle between and among hosts. If gut membrane based antigens mainly glycoproteins could be used as protective antigens tick feeding and infestations can be obstructed. Because antibodies raised against these tick antigens antibodies will be synthesized and these bind to receptor sites on the midgut of vector ticks. This close association will block tick-ingested tick-borne pathogens and their transmission. For control of ticks salivary gland extracts and various antigens isolated from tick saliva are injected to produce antibodies to obstruct feeding in ticks. For targeted control recent technologies such as transcriptomics and proteomics could be sued to discover novel genes, make expression libraries of cDNA for immunization. Do genome sequencing of expressed sequence tags, for rapid, systematic and global antigen screening. After comparison of transcriptomes and comprehensive study of various antigen types will assist in generation of more appropriate vaccines for control of ticks.. In addition, for killing of tick transmitted infectious agents broad spectrum antibiotics and vaccine doses are prescribed to control pathogenicity and deaths. There is need to apply integrated control methods and strategies for successful control of ticks.

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References

[1] Sonenshine DE. Biology of Ticks. Volume 1. Oxford University Press, New York; 1991.

[2] Guglielmone Alberto A., Richard G. Robbins, Dmitry A. Apanaskevich, Trevor N. Petney, Agustin Estrada-Pena, et al. The Argasidae, Ixodidae and Nuttalliellidae (Acari: Ixodida) of the world. A list of valid species names: Zootaxa 2010; 2528: 01-28. Guglielmone et al, 2010; Snelson 1975.

[3] Snelson JT. Animal ectoparasites and disease vector causing major reduction in world food supplies: FAO Plant Protection Bulletin 1975; 13: 103-14.

[4] Horak IG, Camicas JL, Keirans JE. The Argasidae, Ixodidae and Nuttalliellidae (Acari: Ixodida): a world list of valid tick names. Exp Appl Acarol. 2002;28:27-54.

[5] Nava S, Venzal JM, Terassini FA, Mangold AJ, Camargo LM, Labruna MB. Description of a new argasid tick (Acari: Ixodidae) from bat caves in Brazilian Amazon: J Parasitol 2010; 96: 1089-01.

[6] Holzer B, Bakshi S, Bridgen A, Baron MD. Inhibition of interferon induction and action by the nairovirus Nairobi sheep disease virus/Ganjam virus. *PLoS One*. 2011;6(12):e28594.
DOI: https://doi.org/10.1371/journal.pone.0028594.

[7] Lihou Katie, Vineer Hannah Rose, Wall Richard., Distribution and prevalence of ticks and tick-borne disease on sheep and cattle farms in Great Britain Parasit Vectors. 2020; 13: 406.

[8] Apanaskevich DA, Horak IG, Matthee CA, Matthee S. A new species of Ixodes (Acari: Ixodidae) from South African mammals: J Parasitol 2011; 97: 389-98.

[9] Peter J Krause .Human babesiosis: Int J Parasitol 2019;49:165-74.

[10] Mans BJ, De Klerk D, Pienaar R, Latif AA. .(*Nuttalliell anamaqua):* A living fossil and closest relative to the ancestral tick lineage: Implications for the evolution of blood-feeding in ticks: PloS One 2011;6: e23675.

[11] Dantas-Torres F, Venzal JM, Bernardi LF, Ferreira RL, Onofrio VC, Marcili A,, et al. Description of a new species of bat-associated argasid tick (Acari: Argasidae) from Brazil: J Parasitol 2012; 98: 36-5.

[12] Estrada-Peña A, Venzal JM, Nava S, Mangold A, Guglielmone AA, Labruna MB, et al. Reinstatement of *Rhipicephalus* (*Boophilus*) *australis*(Acari: Ixodidae) with redescription of the adult and larval stages: J Med Entomol 2012; 49: 794-02.

[13] Heath AC. A new species of soft tick (Ixodoidea: Argasidae) from the New Zealand lesser short-tailed bat, (*Mystacina tuberculata*)Gray. Tuhinga: Te Papa Museum of New Zealand 2012; 23: 29-7.

[14] Venzal J, Nava S, Mangold A, Mastropaolo M, Casás G, Guglielmone A. *Ornithodoros quilinensis* sp. nov.(Acari, Argasidae), a new tick species from the Chacoan region in Argentina: ActaParasitol 2012; 57: 329-36.

[15] Apanaskevich DA, Horak IG, Mulumba-Mfumu LK. A new species of *Rhipicephalus* (Acari: Ixodidae), a parasite of red river hogs and domestic pigs in the Democratic Republic of Congo: J Med Entomol 2013; 50: 479-84.

[16] Venzal J, Nava S, Mangold A, Mastropaolo M, Casás G, Guglielmone A. A new species of *Ornithodoros* (Acari: Argasidae), parasite of *Microlophus* spp. (Reptilia: Tropiduridae) from northern Chile: Ticks Tick-Borne Dis 2013; 4: 128-32.

[17] Oliver JH. Jr Biology and systematics of ticks (Acari: Ixodida): Annu Rev Ecol Syst 1989; 20: 397-30.

[18] Fuente Jde la, Estrada-Pena A, Venzal JM, Ticks as vectors of pathogens that cause disease in humans and animals: Front Biosci. 2008 ; 13:6938-46.

[19] FAO Ticks and ticks borne disease control. A practical field manual. Volume 1 Tick control: F.A.O. Rome. 1984 ; 299.

[20] Rizzoli A, Silaghi C, Obiegala A, et al. *Ixodes ricinus* and Its Transmitted Pathogens in Urban and Peri-Urban Areas in Europe: New Hazards and Relevance for Public Health. *Front Public Health*. 2014;2:251. Published 2014.
DOI: https://doi.org/10.3389/fpubh.2014.00251.

[21] Geevarghese G, Fernandes S, Kulkarni SMA. Checklist of Indian ticks (Acari: Ixodidae): Indian J Anim Sci.1997 ;67: 566-74.

[22] Rajamohanan K. Studies on the common ticks affecting livestock in Kerala: Ph.D. Dissertation.Kerala Agricultural University, Thrissur: (1980).

[23] Belman U P R, A M, Kamath, B U, Shenoy K A, A L U. Evaluation of health literacy status among patients in a tertiary care hospital in coastal karnataka, India. *J Clin Diagn Res*. 2013;7(11):2551-2554.
DOI: https://doi.org/10.7860/JCDR/2013/6120.3608.

[24] Boulanger P, Ruckerbauer GM, Bannister GL, MacKay RR, Peter NH. Anaplasmosis: control of the first outbreak in Canada by serological identification and slaughter. *Can J Comp Med*. 1971;35(3):249-257.

[25] Tissot Dupont H, Raoult D. Maladies transmises par les tiques [Tick-borne diseases]. Rev Med Interne. 1993;14(5):300-6. French.
DOI: https://doi.org/10.1016/s0248-8663(05)81304-9. PMID: 8235143.

[26] Almazán C, Fourniol L, Rouxel C, et al. Experimental *Ixodes ricinus*-Sheep Cycle of *Anaplasma phagocytophilum* NV2Os Propagated in Tick Cell Cultures. *Front Vet Sci*. 2020;7:40. Published 2020.
DOI: https://doi.org/10.3389/fvets.2020.00040.

[27] Prakasan K, Ramani N. Tick parasites of domestic animals of Kerala, South India: Asian J Anim Vet Adv. (2007) ; 2: 74-80.

[28] WoodwardT. E., D. H. Walker, J. S. Dumler. The remarkable contributions of S. Burt Wolbach on rickettsialvasculitis updated: Trans Am Clin Climatol Assoc. 1992; 103: 78-94.

[29] Zhou Wenshuo, Faizan Tahir, Joseph Che-Yen Wang, Woodson M, Michael B. Sherman, Karim S et al. Discovery of Exosomes From Tick Saliva and Salivary Glands Reveals Therapeutic Roles for CXCL12 and IL-8 in Wound Healing at the Tick-Human Skin Interface: Front. Cell Dev. Biol 2020; 8:554.

[30] Tal Azagi, Dieuwertje Hoornstra, Kristin Kremer, Joppe W. R. Hovius, Hein Sprong, Evaluation of Disease Causality of Rare *Ixodes ricinus*-Borne Infections in Europe, Pathogens. 2020; 9(2): 150.

[31] Ioana A. Matei, Agustín Estrada-Peña, Sally J. Cutler, Muriel Vayssier-Taussat, Lucía Varela-Castro, Aleksandar Potkonjak A review on the eco-epidemiology and clinical management of human granulocytic anaplasmosis and its agent in Europe, Parasit Vectors. 2019; 12: 599.

[32] Khamesipour Faham, O. Dida Gabriel, N. Anyona Douglas, S. Mostafa Razavi, Rakhshandehroo Ehsan, Tick-borne zoonoses in the Order Rickettsiales and Legionellales in Iran: A systematic review, PLoS Negl Trop Dis. 2018; 12(9): e0006722.

[33] Suwanbongkot Chanakan, M Langohr Ingeborg., K. Harris Emma, Dittmar Wellesley, Rebecca C. Christofferson, R. Macaluso Kevin, Spotted Fever Group Rickettsia Infection and Transmission Dynamics in *Amblyomma maculatum*Infect Immun. 2019; 87(4): e00804-18.

[34] Solano-Gallego Laia, Sainz Ángel, Roura Xavier, Estrada-Peña Agustín, Miró Guadalupe A review of canine babesiosis: the European perspective, Parasit Vectors. 2016; 9: 336.

[35] Pérez-Sánchez Ricardo , Manzano-Román Raúl, Obolo-Mvoulouga Prosper, Oleaga Ana., In silico selection of functionally important proteins from the mialome of *Ornithodoros erraticus* ticks and assessment of their protective efficacy as vaccine targets. Parasit Vectors. 2019; 12: 508.

[36] Ozubek Sezayi, G. Bastos Reginaldo. Alzan Heba F,

Inci Abdullah, Aktas Munir, Suarez Carlos E. Bovine Babesiosis in Turkey: Impact, Current Gaps, and Opportunities for InterventionPathogens. 2020; 9(12): 1041.
[37] "Common Ticks". Illinois Department of Public Health : Retrieved 11 April 2014.
[38] Nicholson WL, Sonenshine DE, Noden BH, Brown RN. Ticks (Ixodida)". In Mullen G, Durden L (eds.): Medical and Veterinary Entomology. Academic Press 2009; 483-32.
[39] "Hard ticks". CVBD: Companion Vector-Borne Diseases: Retrieved 2016.
[40] Walker JB, Keirans JE, HorakIG .The Genus *Rhipicephalus* (Acari, Ixodidae): A Guide to the Brown Ticks of the World: Cambridge University Press. (2005); p. 39.
[41] Salman MD, Tarrés-Call J, Estrada-Peña. A Ticks and Tick-borne Diseases: Geographical Distribution and Control Strategies in the Euro-Asia Region: CABI (2013); 06-12.
[42] Ann L Carr , Vincent L Salgado. Ticks home in on body heat: A new understanding of Haller's organ and repellent action: PLoS One 2019; 23: 0221659.
[43] Buysse M, Plantard O, McCoy KD, Duron O, Menard C .Tissue localization of Coxiella-like endosymbionts in three European tick species through fluorescence in situ hybridization" (PDF): Ticks and Tick-Borne Diseases 2019;10: 798-04.
[44] Balashov YS. Bloodsucking Ticks (Ixodoidea) Vectors of Disease of Man and Animals: College Park, MD: Entomol Society of America (1972).
[45] Binetruy F, Buysse M, Lejarre Q, Barosi R, Villa M, Rahola N, et al.. Microbial community structure reveals instability of nutritional symbiosis during the evolutionary radiation of *Amblyomma* ticks": Molecular Ecology. 2020; 29 : 1016-029.
[46] Duron O, Binetruy F, Noël V, Cremaschi J, McCoy KD, Arnathau C, et al. "Evolutionary changes in symbiont community structure in ticks": Molecular Ecology 2017; 26: 2905-921.
[47] Ruppert EE, Fox RS, Barnes RD. Invertebrate Zoology (7th ed.): Cengage Learning: 2004; 590-95.
[48] Smith TA, Driscoll T, Gillespie JJ, Raghavan R. A Coxiella-like endosymbiont is a potential vitamin source for the Lone Star tick. Genome Biol Evol. 2015 ;23;7:831-8.
[49] MurrayMurray W Lankester **,** W Brad Scandrett**.** Experimental transmission of bovine anaplasmosis (caused by *Anaplasmamarginale*) by means of *Dermacentor variabilis* and *D. andersoni*(Ixodidae) collected in western Canada :Can J Vet Res 2007; 71 :271-7.
[50] Sori Teshale , Dirk Geysen ,GobenaAmeni . Survey of *Anaplasma phagocytophilum* and Anaplasma sp: 'Omatjenne' infection in cattle in Africa with special reference to Ethiopia: Parasit Vectors :2018;11:162.
[51] Duron O, Sidi-Boumedine K.The Importance of Ticks in Q Fever Transmission: What Has (and Has Not) Been Demonstrated?: Trends in Parasitology 2015;31 :536-52.
[52] Jongejan F , G Uilenberg :Ticks and control methods : Rev Sci Tech 1994;13: 1201-26.
[53] Jensen BB, Bruun MT, Jensen PM, et al. Evaluation of factors influencing tick bites and tick-borne infections: a longitudinal study. *Parasit Vectors*. 2021;14(1):289. Published 2021 29.
DOI: https://doi.org/10.1186/s13071-021-04751-0.
[54] Richard S Ostfeld , Jesse L Brunner, Richard S. Ostfeld, Jesse L. Brunner., Climate change and Ixodes tick-borne diseases of humans. Philos Trans R Soc Lond B Biol Sci. 2015 5; 370(1665): 20140051.
[55] Philippe Parola Socolovschi C, Mediannikov O, Raoult D, Parola P. The relationship between spotted fever group Rickettsiae and ixodid ticks. *Vet Res*. 2009;40(2):34.
DOI: https://doi.org/10.1051/vetres/2009017.
[56] José Brites-Neto, Keila Maria Roncato Duarte, Thiago Fernandes Martins, Tick-borne infections in human and animal population worldwide Vet World. 2015; 8(3): 301-315. Published online 2015 Mar 12.
[57] Genchi Marco, Prati Paola, Vicari Nadia, Manfredini, Luciano Sacchi Andrea, Clementi Emanuela, *Francisella tularensis*: No Evidence for Transovarial Transmission in the Tularemia Tick Vectors *Dermacentor reticulatus* and *Ixodes ricinus*, PLoS One. 2015; 10(8): e0133593.
[58] Grasperge Britton J., Wolfson Wendy, R. Macaluso Kevin, *Rickettsia parkeri* Infection in Domestic Dogs, Southern Louisiana, USA, 2011, Emerg Infect Dis. 2012; 18(6): 995-997.
[59] Rochlin Ilia , Alvaro YamajiToledo.Kayoko, Aonuma Hiroka , Emerging tick-borne pathogens of public health importance: a mini-review J Med Microbiol. 2020; 69(6): 781-791.
[60] Mostafavi Ehsan, Ghasemi Ahmad, Rohani Mahdi, Molaeipoor Leila, Esmaeili Saber, Mohammadi Zeinolabedin, Molecular Survey of Tularemia and Plague in Small Mammals From Iran. Front Cell Infect Microbiol. 2018; 8: 215.
[61] Kazimírová Mária, Thangamani Saravanan, Bartíková Pavlína, Hermance Meghan, Holíková

Viera, Štibrániová Iveta, Nuttall Patricia A., Tick-Borne Viruses and Biological Processes at the Tick-Host-Virus Interface, Front Cell Infect Microbiol. 2017; 7: 339.

[62] Vincenzo Lorusso, Michiel Wijnveld, Maria S. Latrofa, Akinyemi Fajinmi, Ayodele O. Majekodunmi, Abraham G. Dogo, Augustine C. Igweh, Domenico Otranto, Frans Jongejan, Susan C. Welburn, Kim Picozzi., Canine and ovine tick-borne pathogens in camels, Nigeria Vet Parasitol. 2016; 228: 90-92.

[63] Govindasamy K, Bhanot P. Overlapping and distinct roles of CDPK family members in the pre-erythrocytic stages of the rodent malaria parasite, Plasmodium berghei. PLoS Pathog. 2020;16(8):e1008131. DOI: 10.1371/journal.ppat.1008131.

[64] Guizzo MG, Parizi LF, Nunes RD, Schama R, Albano RM, Tirloni L, et al. A *Coxiella mutualists* ymbiont is essential to the development of *Rhipicephalus microplus"*: Scientific Reports 2017;7 :17554.

[65] Ben-Yosef M, Rot A, Mahagna M, Kapri E, Behar A, Gottlieb Y et al. *Rhipicephalussanguineus* Is Required for Physiological Processes During Ontogeny": Frontiers in Microbiology. 2020;11: 493.

[66] Randolph, S.E. et al. Randolph SE, Green RM, Hoodless AN, Peacey MF. An empirical quantitative framework for the seasonal population dynamics of the tick Ixodes ricinus. Int J Parasitol. 2002; 32: 979-89.

[67] Walker, A.R. Age structure of a population of *Ixodes ricinus* (Acari: Ixodidae) in relation to its seasonal questing: Bulletin of Entomological Research 2001; 91: 69 - 78.

[68] Robert S Lane, Jeomhee Mun, Harrison A Stubbs Horizontal. Horizontal and vertical movements of host-seeking *Ixode spacificus* (Acari: Ixodidae) nymphs in a hardwood forest: J Vector Ecol 2009;34:252-66.

[69] Pantanowitz L, Telford SR, Cannon ME. Tick-borne diseases in transfusion medicine. Transfus Med. 2002;12(2):85-106.
DOI: 10.1046/j.1365-3148.2002.00358.x. PMID: 11982962.

[70] Kenedy Melisha R , Tiffany R Lenhart, Darrin R Akins. The role of *Borrelia burgdorferi* outer surface proteins: FEMS Immunol Med Microbiol 2012;66:01-19.

[71] Burgdorfer S F, W, and A Aeschlimann. Sexual transmission of spotted fever group rickettsiae by infected male ticks: detection of rickettsiae in immature spermatozoa of *Ixodes ricinus* : Infect Immuno 1980;27:638-42.

[72] Rau A, Munoz-Zanzi C, Schotthoefer AM, Oliver JD, Berman JD. Spatio-Temporal Dynamics of Tick-Borne Diseases in North-Central Wisconsin from 2000-2016. Int J Environ Res Public Health. 2020 15;17(14):5105.

[73] Fritz CL, Bronson LR, Smith CR, Schriefer ME, Tucker JR, Schwan TG. Isolation and characterization of *Borrelia hermsii* associated with two foci of tick-borne relapsing fever in California. *J Clin Microbiol*. 2004;42(3):1123-1128.
DOI: https://doi.org/10.1128/JCM.42.3.1123-1128.2004.

[74] Harish Raja, Matthew R. Starr, Sophie J. Bakri, Ocular manifestations of tick-borne diseases, Survey of Ophthalmology, 2016:61(6): 726-744.

[75] Lefebvre N, Forestier E, Farhi D, Mahsa MZ, Remy V, Lesens O, Christmann D, Hansmann Y. Minocycline-induced hypersensitivity syndrome presenting with meningitis and brain edema: a case report. J Med Case Rep. 2007 18;1:22.

[76] Choi E, Pyzocha NJ, Maurer DM. Tick-Borne Illnesses. Curr Sports Med Rep. 2016;15(2):98-104.
DOI: https://doi.org/10.1249/JSR.0000000000000238.

[77] Nusirat Elelu) Elelu Nusirat., Tick−borne relapsing fever as a potential veterinary medical problem. Vet Med Sci. 2018; 4(4): 271-279.

[78] Rodríguez-Camarillo Sergio D., Quiroz-Castañeda Rosa E., Aguilar-Díaz Hugo, Pastrana José E. Vara-, Pescador-Pérez Diego, Amaro-Estrada Itzel , Immunoinformatic Analysis to Identify Proteins to Be Used as Potential Targets to Control Bovine Anaplasmosis, Int J Microbiol. 2020; 2020: 8882031.

[79] Fernando Martínez-Ocampo, Rosa Estela Quiroz-Castañeda, Itzel Amaro-Estrada, Edgar Dantán-González, Jesús Francisco Preciado de la Torre, Camarillo Sergio Rodríguez-, Whole-Genome Sequencing of Mexican Strains of *Anaplasma marginale*: An Approach to the Causal Agent of Bovine Anaplasmosis, Int J Genomics. 2020; 2020: 5902029.
DOI: https://doi.org/10.1155/2020/5902029.

[80] Goel R, Westblade LF, Kessler DA, et al. Death from Transfusion-Transmitted Anaplasmosis, New York, USA, 2017 [published correction appears in Emerg Infect Dis. 2018 Sep;24(9):1773]. *Emerg Infect Dis*. 2018;24(8):1548-1550.
DOI: https://doi.org/10.3201/eid2408.172048

[81] Mysterud A, Heylen DJA, Matthysen E, Garcia AL, Jore S, Viljugrein H. Lyme neuroborreliosis and bird populations in northern Europe. Proc Biol Sci.

  DOI: https://doi.org/10.30564/jhp.v3i2.3788

2019 May 29;286(1903):20190759.
DOI: https://doi.org/10.1098/rspb.2019.0759. Epub 2019; 29.

[82] Elias Susan P., Bonthius Jessica, Robinson Sara, Robich Rebecca M., Lubelczyk Charles B., Smith Robert P.,., Surge in Anaplasmosis Cases in Maine, USA, 2013-2017Emerg Infect Dis. 2020; 26(2): 327-331.

[83] Young Kaitlin M., Corrin Tricia, Wilhelm Barbara, Uhland Carl, Greig Judy, Mascarenhas Mariola, Waddell Lisa A., Zoonotic *Babesia*: A scoping review of the global evidence PLoS One. 2019; 14(12): e0226781.

[84] Zhao Guo-Ping, Wang Yi-Xing, Fan Zheng-Wei, Ji Yang, Liu Ming-jin, Zhang Wen-Hui, Xin-Lou Li, Shi-Xia Zhou, Hao Li, Song Liang, Wei Liu, Yang Yang, Li-Qun Fang., Mapping ticks and tick-borne pathogens in China. Nat Commun. 2021; 12: 1075.

[85] Bajer Anna, Rodo Anna, Mierzejewska Ewa J., Tołkacz Katarzyna, Welc- Faleciak Renata., The prevalence of *Dirofilaria repens* in cats, healthy dogs and dogs with concurrent babesiosis in an expansion zone in central Europe. BMC Vet Res. 2016; 12(1): 183.

[86] Ozubek Sezayi, G. Bastos Reginaldo, Alzan Heba F, Inci Abdullah, Aktas Munir, Suarez Carlos E. Bovine Babesiosis in Turkey: Impact, Current Gaps, and Opportunities for InterventionPathogens. 2020; 9(12): 1041.

[87] Hiroki Maeda, Takeshi Hatta, M Abdul Alim , DaigoTsubokawa , FusakoMikami ,Makoto Matsubayashi, et al. Establishment of a novel tick-Babesia experimental infection model: Sci rep 2016 ; 6: 37039.

[88] Lavan Robert, Tunceli Kaan, Swardt Hendrik de, Chelchinskey Carolyn, Abatzidis Mats, Armstrong Rob., Canine babesiosis treatment rates in South African veterinary clinics between 2011 and 2016. Parasit Vectors. 2018; 11: 386.

[89] Dwunik-Szarek Dorota. Mierzejewska Ewa J, Rodo Anna, Goździk Katarzyna, Behnke-Borowczyk Jolanta, Kiewra Dorota, Monitoring the expansion of *Dermacentor reticulatus* and occurrence of canine babesiosis in Poland in 2016-2018. Parasit Vectors. 2021; 14: 267.

[90] Mikhail Menis, Barbee I Whitaker, Michael Wernecke, Yixin Jiao, Anne Eder, Sanjai Kumar, Wenjie Xu, Jiemin Liao, Yuqin Wei, Thomas E MaCurdy, Jeffrey A Kelman, Steven A Anderson, Richard A Forshee, Babesiosis Occurrence Among United States Medicare Beneficiaries, Ages 65 and Older, During 2006-2017: Overall and by State and County of Residence, *Open Forum Infectious Diseases*, 2021; 8(2). ofaa608.
DOI: https://doi.org/10.1093/ofid/ofaa608.

[91] Sainz Á, Roura X, Miró G, Estrada-Peña A, Kohn B, Harrus S, Solano-Gallego L. Guideline for veterinary practitioners on canine ehrlichiosis and anaplasmosis in Europe. Parasit Vectors. 2015;8:75.
DOI: https://doi.org/10.1186/s13071-015-0649-0.

[92] Chaudhuri S , J P Varshney. Clinical management of babesiosis in dogs with homeopathic Crotalushorridus200c: Homeopathy 2007; 96:90-4.

[93] Galán Asier, Anita Horvatić, Kuleš Josipa, Bilić Petra, Gotić Jelena, Mrljak.Vladimir, LC-MS/MS analysis of the dog serum phosphoproteome reveals novel and conserved phosphorylation sites: Phosphoprotein patterns in babesiosis caused by *Babesia canis*, a case study. PLoS One. 2018; 13(11): e0207245.

[94] NabihaHuqSaifee ,Peter J Krause , Yanyun Wu. .Apheresis for babesiosis: Therapeutic parasite reduction or removal of harmful toxins or both?: J Clin Apher 2016;31:454-8.

[95] Bournez L, Umhang G, Moinet M, Boucher JM, Demerson JM, Caillot C, et al. Disappearance of TBEV Circulation among Rodents in a Natural Focus in Alsace, Eastern France. Pathogens. 2020;9(11):930.
DOI: https://doi.org/10.3390/pathogens9110930.

[96] Safronetz David, Heinz Feldmann. Animal Models of Tick-Borne Hemorrhagic Fever Viruses Marko Zivcec :Pathogens. 2013; 2: 402-21.

[97] Sánchez M, M Venturini, A Blasco, T Lobera, B Bartolomé, J A Oteo et al. Tick bite anaphylaxis in a patient allergic to bee venom :J Investig Allergol Clin Immunol 2014; 24 :284-5.

[98] Jeremy S Gray , Olaf Kahl , Robert S Lane , Michael L Levin , Jean I Tsao. Diapause in ticks of the medically important *Ixodes ricinus* species complex: Ticks Tick Borne Dis 2016 ;7 :992-003.

[99] Syed SohebFatmi , Rija Zehra, David O Carpenter. Powassan Virus-A New Reemerging Tick-Borne Disease 2017;5:992 -003.

[100] Mizuki Sakai , Kentaro Yoshii , Yuji Sunden , Kana Yokozawa , Minato Hirano , Hiroaki Kariwa et al. Variable region of the 3' UTR is a critical virulence factor in the Far-Eastern subtype of tick-borne encephalitis virus in a mouse model: Front Public health 2014; 95: 823-35.

[101] Ivo M B Francischetti , Zhaojing Meng, Ben J Mans, Nanda Gudderra, Mark Hall, Timothy D

Veenstra, Van M Pham et al. An insight into the salivary transcriptome and proteome of the soft tick and vector of epizootic bovine abortion, *Ornithodoro scoriaceus* :J Proteomics 2008; 71 :493-12.

[102] Telleasha L Greay , Alexander W Gofton , Andrea Paparini , Una M Ryan, Charlotte L Oskam , Peter J Irwin. Recent insights into the tick microbiome gained through next-generation sequenceing :Parasit Vectors 2018;11:12.

[103] Marcelino Isabel , Miguel Ventosa , ElisabetePires , Markus Müller , Frédérique Lisacek, Thierry Lefrançois , et al . Comparative Proteomic Profiling of *Ehrlichia ruminantium* Pathogenic Strain and Its High-Passaged Attenuated Strain Reveals Virulence and Attenuation-Associated Proteins : Plos One 2015;10 :145328.

[104] Noroy Christophe Damien F Meyer. Comparative Genomics of the Zoonotic Pathogen *Ehrlichia chaffeensis* Reveals Candidate Type IV Effectors and Putative Host Cell Targets: Front Cell Infect Microbiol 2017 ;6:204.

[105] Heitman Kristen Nichols, Dahlgren F. Scott, Drexler Naomi A., R Massung obert F., Behravesh Casey BartonxIncreasing Incidence of Ehrlichiosis in the United States: A Summary of National Surveillance of *Ehrlichia chaffeensis* and *Ehrlichia ewingii* Infections in the United States, 2008-2012. Am J Trop Med Hyg. 2016 6; 94(1): 52-60.

[106] Lefebvre N, Forestier E, Farhi D, Mahsa MZ, Remy V, Lesens O, Christmann D, Hansmann Y. Minocycline-induced hypersensitivity syndrome presenting with meningitis and brain edema: a case report. J Med Case Rep. 2007 18;1:22.

[107] Maureen McCollough). McCollough M. (2018) RMSF and Serious Tick-Borne Illnesses (Lyme, Ehrlichiosis, Babesiosis and Tick Paralysis). In: Rose E. (eds) Life-Threatening Rashes. Springer, Cham.

[108] Mans B J, Gothe R, Neitz. A W H. Biochemical perspectives on paralysis and other forms of toxicoses caused by ticks : Parasitology 2004;129: 95-11.

[109] Hall-Mendelin S , S B Craig, R A Hall, P O'Donoghue, R B Atwell, S M Tulsiani, et al, Tick paralysis in Australia caused by *Ixodes holocyclus* Neumann : Ann Trop Med Parasitol 2011 ;105:95-06.

[110] William K Boyle , Hannah K Wilder , Amanda M Lawrence , Job E Lopez. Transmission dynamics of *Borrelia turicatae* from the arthropod vector: PLoS Negl Trop Dis 2014;8: 2767.

[111] Patrícia Silva Gôlo , Isabele da Costa Angelo, Mariana Guedes Camargo, Wendell Marcelo de Souza Perinotto, Vânia Rita Elias PinheiroBittencourt. Effects of destruxin A on *Rhipicephalus* (*Boophilus*) *microplus* ticks (Acari: Ixodidae) : Rev Bras Parasitol Vet 2011;20:338-41.

[112] Mariusz Piotrowski, Anna Rymaszewska., Expansion of Tick-Borne Rickettsioses in the World Microorganisms. 2020; 8(12): 1906.

[113] Hennebique A, Boisset S, Maurin M. Tularemia as a waterborne disease: a review. Emerg Microbes Infect. 2019;8(1):1027-1042.

[114] Faber M, Heuner K, Jacob D, Grunow R. Tularemia in Germany-A Re-emerging Zoonosis. Front Cell Infect Microbiol. 2018;8:40.

[115] Montales MT, Beebe A, Chaudhury A, Haselow D, Patil S, Weinstein S, Taffner R, Patil N. A Clinical Review of Tick-Borne Diseases in Arkansas. J Ark Med Soc. 2016;112(13):254-8.

[116] Esmaeili Saber, Ahmad, Naserifar Razi, Jalilian, Molaeipoor Ali Leila, Maurin Max, Mostafavi Ehsan, Epidemiological survey of tularemia in Ilam Province, west of Iran BMC Infect Dis. 2019; 19: 502.

[117] Carvalho C.L., Lopes de Carvalho I., L. Zé-Zé, M.S. Núncio, E.L. Duarte., Tularaemia: A challenging zoonosis. Comp Immunol Microbiol Infect Dis. 2014; 37(2): 85-96.

[118] Splettsoesser W.D., K. Matz-Rensing,E.Seibold, H.Tomaso,S.AL Dahouk,R. GrunowRe-emergence of *Francisella tularensis* in Germany: fatal tularaemia in a colony of semi-free-living marmosets (*Callithrix jacchus*). Epidemiol Infect. 2007; 135(8): 1256-1265.

[119] Boisset S, Caspar Y, Sutera V, Maurin M. New therapeutic approaches for treatment of tularaemia: a review. Front Cell Infect Microbiol. 2014;4:40. DOI: https://doi.org/10.3389/fcimb.2014.00040.

[120] Caspar Yvan, Maurin Max *Francisella tularensis* Susceptibility to Antibiotics: A Comprehensive Review of the Data Obtained *In vitro* and in Animal Models Front Cell Infect Microbiol. 2017; 7: 122.

[121] Yanes Hadjila, Hennebique Aurélie, Pelloux Isabelle, Boisset Sandrine, J. Bicout Dominique, Caspar Yvan, Evaluation of In-House and Commercial Serological Tests for Diagnosis of Human Tularemia., J Clin Microbiol. 2018; 56(1): e01440-17.

[122] Blisnick AA, Foulon T, Bonnet SI. Serine Protease Inhibitors in Ticks: An Overview of Their Role in Tick Biology and Tick-Borne Pathogen Transmission. *Front Cell Infect Microbiol*. 2017;7:199. DOI: https://doi.org/10.3389/fcimb.2017.00199.

[123] Santodomingo A, Cotes-Perdomo A, Foley J, Castro LR. Rickettsial infection in ticks (Acari: Ixodidae)

from reptiles in the Colombian Caribbean. Ticks Tick Borne Dis. 2018;9(3):623-628.
DOI: https://doi.org/10.1016/j.ttbdis.2018.02.003.

[124] Sa-Nunes Anderson, Andre Bafica, Lis R Antonelli, Eun Young Choi, Ivo M B Francischetti, et al. The immunomodulatory action of sialostatin L on dendritic cells reveals its potential to interfere with autoimmunity :J Immunol 2009;182:7422-9.

[125] Galli Stephen J, Philipp Stark Thomas Marichal, Mindy Tsai . Mast cells and IgE in defense against venoms: Possible "good side" of allergy?:AllergolInt 2016; 65:3-15.

[126] Noroy Christophe , Damien F Meyer. Comparative Genomics of the Zoonotic Pathogen *Ehrlichia chaffeensis* Reveals Candidate Type IV Effectors and Putative Host Cell Targets: Front Cell Infect Microbiol 2017; 25; 6:204.

[127] Wang Haiyan Fangfang Gong , Houshuang Zhang Yongzhi Zhou , Jie Cao , Jinlin Zhou. Lipopolysaccharide-Induced Differential Expression of miRNAs in Male and Female *Rhipicephalus haemaphysaloides* Ticks: Plos One 2015; 2:0139241.

[128] Noriea Nicholas F Tina R Clark , Ted Hackstadt. Targeted knockout of the *Rickettsia rickettsii* OmpA surface antigen does not diminish virulence in a mammalian model system: mBio2015; 31; 6:e00323-15.

[129] Chen Gang, Maiara S Severo, Olivia S Sakhon, Anthony Choy, Michael J Herron, Roderick F Felsheim, et al. *Anaplasma phagocytophilum* dihydrolipoamide dehydrogenase 1 affects host-derived immunopathology during microbial colonization. Infect Immuno 2012; 80:3194-05.

[130] Cavassani Karen A, Júlio C Aliberti, Alexandra R V Dias, João S Silva, Beatriz R FerreiraTick et al. Tick saliva inhibits differentiation, maturation and function of murine bone-marrow-derived dendritic cells: Immunology 2005;114:235-45.

[131] Berlit P. Immunoglobulin therapy in neurologic diseases: Klin Wochenschr 1989; 2: 967-70.

[132] MarthB Kleinhappl E . Albumin is a necessary stabilizer of TBE-vaccine to avoid fever in children after vaccination. Vaccine 2001; 20:532-7.

[133] Crause J C , J A Verschoor, J Coetzee, H C Hoppe, J N Taljaard et al.The localization of a paralysis toxin in granules and nuclei of prefed female *Rhipicephalus evertsi evertsi* tick salivary gland cells : Exp Appl Acarol 1993 ;17:357-63.

[134] Masina S, K W Broady. Tick paralysis: development of a vaccine: Int J Parasitol 1999; 29:535-41.

[135] Schnell Gilles, Nathalie Boulanger, Elody Collin, Cathy Barthel, Sylvie De Martino, Laurence Ehret-Sabatier et al. Proteomic analysis of three *Borrelia burgdorferi* sensulato native species and disseminating clones: relevance for Lyme vaccine design: Infect Immunol 2015;15:1280- 90.

[136] Sutten Eric L, JunzoNorimine, Paul A Beare, Robert A Heinzen, Job E Lopez, Kaitlyn Morse, et al. *Anaplasma marginale* type IV secretion system proteins VirB2, VirB7, VirB11, and VirD4 are immunogenic components of a protective bacterial membrane vaccine: Infect Immun 2010 ;78 :1314-25.

[137] Cupp E W Biology of ticks1991; 21:1-26.

[138] Lockwood Svetlana , Daniel E Voth, Kelly A Brayton, Paul A Beare, Wendy C Brown, et al, et al. Identification of *Anaplasma marginale* type IV secretion system effector proteins: Plos One 2011;6 :e2772.

[139] Nicholson Graham M , AndisGraudins, Harry I Wilson, Michelle Little, Kevin W Broady. Arachnid toxinology in Australia: from clinical toxicology to potential applications: Toxicon 2006 ; 1:872-98.

[140] Ristow Laura C, Halli E Miller, Lavinia J Padmore, RekhaChettri, Nita Salzman, Melissa J Caimano et al. The β_3-integrin ligand of *Borreliaburgdorferi* is critical for infection of mice but not ticks: Mol Microbiol 2012 ;85:1105-18.

[141] Ouyang Zhiming, Manish Kumar, Toru Kariu, ShaymaHaq, Martin Goldberg, Utpal Pal, et al. BosR (BB0647) governs virulence expression in *Borrelia burgdorferi:* Mol Microbiol 2009 :74:1331-43.

[142] Kreil M T R, MEibl .Viral infection of macrophages profoundly alters requirements for induction of nitric oxide synthesis: Virology 1995; 10: 212:174-8.

[143] Sanchez Edgar, Vannier Edouard, Wormser Gary P., Linden T. Hu Wormser JAMA. Author manuscript; available in PMC 2020 24.Published in final edited form as: JAMA. 2016 Apr 26; 315(16): 1767-1777.

[144] Galán Asier, Anita Horvatić, Kuleš Josipa, Bilić Petra, Gotić Jelena, Mrljak.Vladimir, LC-MS/MS analysis of the dog serum phosphoproteome reveals novel and conserved phosphorylation sites: Phosphoprotein patterns in babesiosis caused by *Babesia canis*, a case study. PLoS One. 2018; 13(11): e0207245.

[145] Sanchez Edgar, Vannier Edouard, Wormser Gary P., Linden T. Hu Wormser JAMA. Author manuscript; available in PMC 2020 24.Published in final edited form as: JAMA. 2016 Apr 26; 315(16): 1767-1777.

[146] Bajer Anna, Rodo Anna, Mierzejewska Ewa J., Tołkacz Katarzyna, Welc- Faleciak Renata., The prevalence of *Dirofilaria repens* in cats, healthy

dogs and dogs with concurrent babesiosis in an expansion zone in central Europe. BMC Vet Res. 2016; 12(1): 183.

[147] Denison Amy M., Amin Bijal D., Nicholson William L., Paddock Christopher D., Detection of *Rickettsia rickettsii*, *Rickettsia parkeri*, and *Rickettsia akari* in Skin Biopsy Specimens Using a Multiplex Real-time Polymerase Chain Reaction Assay. Clin Infect Dis. 2014 1; 59(5): 635-642.

[148] Yoo Jiyeon, Chung Jong-Hoon, Kim Choon-Mee, Yun Na Ra, Kim Dong-Min, Asymptomatic-anaplasmosis confirmation using genetic and serological tests and possible coinfection with spotted fever group *Rickettsia*: a case report, BMC Infect Dis. 2020; 20: 458.

[149] Caillot Christophe, Devillers Elodie, Boucher Jean-Marc, Hansmann Yves, Boué Franck, Moutailler Sara.,Tick-Borne Encephalitis Virus: Seasonal and Annual Variation of Epidemiological Parameters Related to Nymph-to-Larva Transmission and Exposure of Small Mammals Pathogens. 2020; 9(7): 518.

[150] AmanoK, M Fujita, T Suto .Chemical properties of lipopolysaccharides from spotted fever group rickettsiae and their common antigenicity with lipopolysaccharides from Proteus species: Infect Immun 1993 ;61 :4350-5.

[151] Arulkanthan A, Brown WC, McGuire TC, Knowles DP. Biased immunoglobulin G1 isotype responses induced in cattle with DNA expressing msp1a of *Anaplasma marginale*. Infect Immun. 1999;67:3481-7.

[152] Ghafar Abdul , Abbas Tariq, Rehman Abdul, Sandhu Zia-Ud-Din, Cabezas-Cruz Alejandro , Jabbar Abdul.Systematic Review of Ticks and Tick-Borne Pathogens of Small Ruminants in Pakistan ; Pathogens 2020 11;9(11):937.

[153] Ma Yan, Vigouroux Guillaume, Kalantari Zahra, Goldenberg Romain, Destouni Georgia., Implications of Projected Hydroclimatic Change for Tularemia Outbreaks in High-Risk Areas across Sweden. Int J Environ Res Public Health. 2020; 17(18): 6786.

[154] Nighat Perveen, Sabir Bin Muzaffar, Mohammad Ali Al-Deeb., Ticks and Tick-Borne Diseases of Livestock in the Middle East and North Africa: A Review Insects. 2021; 12(1): 83.

[155] Esteve-Gassent Maria D., Castro-Arellano Ivan, Feria-Arroyo Teresa P., Patino Ramiro, Raul F Andrew Y. Li,. Translating ecology, physiology, biochemistry and population genetics research to meet the challenge of tick and tick-borne diseases in North America-Vivas Arch Insect Biochem Physiol. 2016; 92(1): 38-64.

[156] Muhanguzi Dennis, Byaruhanga Joseph, Amanyire Wilson, Ndekezi Christian, Ochwo Sylvester, Nkamwesiga Joseph, Invasive cattle ticks in East Africa: morphological and molecular confirmation of the presence of Rhipicephalus microplus in south-eastern Uganda Parasit Vectors. 2020; 13: 165.

[157] Maruyama Sandra R. , Garcia Gustavo R., Teixeira Felipe R., Brandão Lucinda G., Anderson Jennifer M., Ribeiro José M. C. Mining a differential sialotranscriptome of *Rhipicephalus microplus* guides antigen discovery to formulate a vaccine that reduces tick infestations. Parasit Vectors. 2017; 10: 206.

[158] Laia Solano-Gallego, Ángel Sainz, Xavier Roura, Agustín Estrada-Peña, Guadalupe Miró.,A review of canine babesiosis: the European perspective, Parasit Vectors. 2016; 9: 336.

[159] Tae Kwon Kim, Lucas Tirloni, Antônio F. M. Pinto, James Moresco, John R. Yates, III, Vaz Itabajara da Silva, *Ixodes scapularis* Tick Saliva Proteins Sequentially Secreted Every 24 h during Blood Feeding. PLoS Negl Trop Dis. 2016 Jan; 10(1): e0004323.

[160] Charles Ndawula, Jr., Ala E. Tabor., Cocktail Anti-Tick Vaccines: The Unforeseen Constraints and Approaches toward Enhanced Efficacies Vaccines (Basel) 2020; 8(3): 457.

[161] Porter Lindsay M., Radulović Željko M., Albert Mulenga., A repertoire of protease inhibitor families in *Amblyomma americanum* and other tick species: inter-species comparative analyses. Parasit Vectors. 2017; 10: 152.

[162] Leal Brenda, Zamora Emily, Fuentes Austin, Thomas Donald B, Dearth Robert K, Questing by Tick Larvae (Acari: Ixodidae): A Review of the Influences That Affect Off-Host Survival. Ann Entomol Soc Am. 2020; 113(6): 425-438.

[163] Boulanger Nathalie, Wikel Stephen., Induced Transient Immune Tolerance in Ticks and Vertebrate Host: A Keystone of Tick-Borne Diseases? Front Immunol. 2021; 12: 625993.

[164] Porter Lindsay M., Radulović Željko M., Albert Mulenga., A repertoire of protease inhibitor families in *Amblyomma americanum* and other tick species: inter-species comparative analyses. Parasit Vectors. 2017; 10: 152.

[165] Grabowski JM, Tsetsarkin KA, Long D, Scott DP, Rosenke R, Schwan TG, Mlera L, Offerdahl DK,

  DOI: https://doi.org/10.30564/jhp.v3i2.3788

Pletnev AG, Bloom ME. Flavivirus Infection of *Ixodes scapularis* (Black-Legged Tick) *Ex Vivo* Organotypic Cultures and Applications for Disease Control. mBio. 2017;8(4):e01255-17.

[166] Shi J, Hu Z, Deng F, Shen S. Tick-Borne Viruses. Virol Sin. 2018 Feb;33(1):21-43.
DOI: https://doi.org/10.1007/s12250-018-0019-0. Epub 2018 ;13.

[167] Dantas-Torres F, Chomel BB, Otranto D. Ticks and tick-borne diseases: a One Health perspective. Trends Parasitol. 2013;29(10):516.
DOI: https://doi.org/10.1016/j.pt.2012.07.003.

[168] de la Fuente J, Antunes S, Bonnet S, Cabezas-Cruz A, Domingos AG, Estrada-Peña A,. Tick-Pathogen Interactions and Vector Competence: Identification of Molecular Drivers for Tick-Borne Diseases. Front Cell Infect Microbiol. 2017;7:114.
DOI: https://doi.org/10.3389/fcimb.2017.00114.

[169] Eisen Lars, Dolan Marc C.., Evidence for Personal Protective Measures to Reduce Human Contact With Blacklegged Ticks and for Environmentally Based Control Methods to Suppress Host-Seeking Blacklegged Ticks and Reduce Infection with Lyme Disease Spirochetes in Tick Vectors and Rodent Reservoirs. J Med Entomol. 2016; 20 : tjw103.

[170] Teel Hsiao-Hsuan Wang Pete D. , Grant William E., Soltero Fred, Urdaz José, Ramírez Alejandro E. Pérez, Simulation tools for assessment of tick suppression treatments of *Rhipicephalus* (Boophilus) microplus on non-lactating dairy cattle in Puerto Rico Parasit Vectors. 2019; 12: 185.

[171] Zhang Yuting, Cui Jie, Zhou Yongzhi, Cao Jie, Gong Haiyan, Zhang Houshuang, Zhou Jinlin ., Liposome mediated double-stranded RNA delivery to silence ribosomal protein P0 in the tick Rhipicephalus haemaphysaloides. Ticks Tick Borne Dis. 2018: 9(3): 638-644.
DOI: https://doi.org/10.1016/j.ttbdis.2018.01.015.

[172] Al-Rofaai Ahmed, Bell-Sakyi. Lesley, Tick Cell Lines in Research on Tick Control. Front Physiol. 2020; 11: 152.

[173] Kim, Tae Kwon Tirloni Lucas, Pinto Antônio F. M., Moresco James, Yates John R., III, Vaz Itabajara da Silva, Ixodes scapularis Tick Saliva Proteins Sequentially Secreted Every 24 h during Blood Feeding. PLoS Negl Trop Dis. 2016 Jan; 10(1): e0004323.

[174] Schulze TL, Jordan RA. Early Season Applications of Bifenthrin Suppress Host-seeking Ixodes scapularis and *Amblyomma americanum* (Acari: Ixodidae) Nymphs. J Med Entomol. 2020;57(3):797-800.

[175] Wanzala Wycliffe Potential of Traditional Knowledge of Plants in the Management of Arthropods in Livestock Industry with Focus on (Acari) Ticks. Evid Based Complement Alternat Med. 2017; 2017: 8647919.

[176] Taylor Hollmann, Tae Kwon Kim, Lucas Tirloni, Željko M. Radulović, Antônio F. M. Pinto, Jolene K. Diedrich, John R. Yates, III, Itabajara da Silva Vaz, Jr., Albert Mulenga Identification and characterization of proteins in the *Amblyomma americanum* tick cement cone Int J Parasitol. 2018; 48(3-4): 211-224.

[177] Dolan Marc C., Schulze Terry L., Jordan Robert A., Schulze Christopher J., Amy J. Ullmann, Hojgaard Andrias, Williams Martin A., Evaluation of Doxycycline-Laden Oral Bait and Topical Fipronil Delivered in a Single Bait Box to Control *Ixodes scapularis* (Acari: Ixodidae) and Reduce *Borrelia burgdorferi* and *Anaplasma phagocytophilum* Infection in Small Mammal Reservoirs and Host-Seeking Ticks .J Med Entomol. 2017; 54(2): 403-410.

[178] Baneth G. Antiprotozoal treatment of canine babesiosis. Vet Parasitol. 2018;254:58-63.
DOI: https://doi.org/10.1016/j.vetpar.2018.03.001.

[179] Meneghi Daniele De, Stachurski Frédéric, Adakal Hassane Experiences in Tick Control by Acaricide in the Traditional Cattle Sector in Zambia and Burkina Faso: Possible Environmental and Public Health Implications., Front Public Health. 2016; 4: 239.

[180] Fernandes Éverton K K , Vânia R E P Bittencourt, Donald W Roberts .Perspectives on the potential of entomopathogenic fungi in biological control of ticks: Exp Parasitol 2012;13 :300-05.

[181] Elston Dirk M.Prevention of arthropod-related disease: J Am Acad Dermtol 2004; 51:947-54.

[182] Fouche Gerda ,Olubukola T. Adenubi, Tlabo Leboho, Lyndy J. McGaw, Vinny Naidoo, Kevin W. Wellington et al .Acaricidal activity of the aqueous and hydroethanolic extracts of 15SouthAfrican plants against *Rhipicephalus turanicus* and their toxicity on human liver and kidneycells: Onderstepoort J Vet Res. 2019; 86: 1665.

[183] Stafford K C .3rd Pesticide use by licensed applicators for the control of *Ixodes scapularis* (Acari: Ixodidae) in Connecticut: J Med Entomol 1997;34: 552-8.

[184] Lu YC, W-Z Liang , C-C Kuo , L-J Hao , C-T Chou , C-R Jan et al. Action of the insecticide cyfluthrin on Ca 2+ signal transduction and cytotoxicity in human osteosarcoma cells: Hum ExpToxicol 2020;39:1268-76.

[185] Qirong Lu , Yaqi Sun , Irma Ares Arturo Anadón, Marta Martínez, María-Rosa Martínez Larrañaga, et al. Deltamethrin toxicity: A review of oxidative stress and metabolism : Environ Res 2019 ;170: 260-81.

[186] Wenbing Zhang , Gang Tang , Hongqiang Dong , Qianqian Geng , Junfan Niu , Jingyue Tang, et al. Targeted release mechanism of λ-cyhalothrinnanocapsules using dopamine-conjugated silica as carrier materials Colloids Surf B Biointerfaces:2019; 178:153-62.

[187] Kumar RB, MX Suresh. Neurotox: a unique database for animal neurotoxins. Int J Pharm Pharm Sci 2015; 7:351-4.

[188] Asawale KY, MC Mehta, P S. Uike. Drug utilization analysis of anti-snake venom at a tertiary care centre in central Maharasthtra: a 3y retrospective study. Asian J Pharm Clin Res 2018; 11:134-7.

[189] Preet P. Peptides: a new therapeutic approach. Int J Curr Pharm Res 2018; 10:29-34.

[190] Prose R, Breuner NE, Johnson TL, Eisen RJ, Eisen L. Contact Irritancy and Toxicity of Permethrin-Treated Clothing for Ixodes scapularis, *Amblyomma americanum*, and *Dermacentor variabilis* Ticks (Acari: Ixodidae). J Med Entomol. 2018;55(5):1217-1224.
DOI: https://doi.org/10.1093/jme/tjy062.

[191] Poché DM, Franckowiak G, Clarke T, Tseveenjav B, Polyakova L, Poché RM. Efficacy of a low dose fipronil bait against blacklegged tick (Ixodes scapularis) larvae feeding on white-footed mice (Peromyscus leucopus) under laboratory conditions. Parasit Vectors. 2020 ;13(1):391.
DOI: https://doi.org/10.1186/s13071-020-04258-0.

[192] Cécile Aenishaenslin, Pascal Michel, André Ravel, Lise Gern, Jean-Philippe Waaub, François Milord, Denise Bélanger .Acceptability of tick control interventions to prevent Lyme disease in Switzerland and Canada: a mixed-method study ,BMC Public Health. 2016; 16: 12.

[193] Al-Rofaai Ahmed, Bell-Sakyi. Lesley, Tick Cell Lines in Research on Tick Control. Front Physiol. 2020; 11: 152.

[194] Muhanguzi Dennis, Byaruhanga Joseph, Amanyire Wilson, Ndekezi Christian, Ochwo Sylvester, Nkamwesiga Joseph, Invasive cattle ticks in East Africa: morphological and molecular confirmation of the presence of *Rhipicephalus microplus* in south-eastern Uganda Parasit Vectors. 2020; 13: 165.

[195] (Felix Nchu, et al). []Nchu Felix, Nyangiwe Nkululeko, Muhanguzi Dennis, Nzalawahe Jahashi, Nagagi Yakob Petro, Msalya George, Development of a practical framework for sustainable surveillance and control of ticks and tick-borne diseases in Africa Vet World. 2020; 13(9): 1910-1921.

[196] Toral GM, Baouab RE, Martinez-Haro M, Sánchez-Barbudo IS, Broggi J, Martínez-de la et al. Effects of Agricultural Management Policies on the Exposure of Black-Winged Stilts (*Himantopus himantopus*) Chicks to Cholinesterase-Inhibiting Pesticides in Rice Fields. PLoS One. 2015;10(5):e0126738.
DOI: https://doi.org/10.1371/journal.pone.0126738.

[197] Schmidt RJ, Kogan V, Shelton JF, Delwiche L, Hansen RL, Ozonoff S, Ma CC, McCanlies EC, Bennett DH, Hertz-Picciotto I, Tancredi DJ, Volk HE. Combined Prenatal Pesticide Exposure and Folic Acid Intake in Relation to Autism Spectrum Disorder. Environ Health Perspect. 2017;125(9):097007.
DOI: https://doi.org/10.1289/EHP604.

[198] Addissie Yonit A., Kruszka Paul X, Troia Angela, Wong Zoë C., Everson Joshua L. , Kozel Beth A. , Prenatal exposure to pesticides and risk for holoprosencephaly: a case-control study. Environ Health. 2020; 19: 65.
DOI: https://doi.org/10.1186/s12940-020-00611-z.

[199] Hollingworth R M., Chemistry, biological activity, and uses of formamidine pesticides. Environ Health Perspect. 1976; 14: 57-69.
DOI: https://doi.org/10.1289/ehp.761457.

[200] Farooq Umar, Joshi Monika, Joshi Vinod, Cheriyath Pramil, Fischman Daniel, Graber Nora J, Self-reported exposure to pesticides in residential settings and risk of breast cancer: a case-control study Environ Health. 2010; 9: 30.

[201] Rodriguez-Vivas Roger I., Jonsson Nicholas N., Bhushan Chandra., Strategies for the control of *Rhipicephalus microplus* ticks in a world of conventional acaricide and macrocyclic lactone resistance. Parasitol Res. 2018; 117(1): 3-29.

[202] Quadros DG, Johnson TL, Whitney TR, Oliver JD, Oliva Chávez AS. Plant-Derived Natural Compounds for Tick Pest Control in Livestock and Wildlife: Pragmatism or Utopia? Insects. 2020 ;1;11(8):490.
DOI: https://doi.org/10.3390/insects11080490.

[203] Luker HA, Rodriguez S, Kandel Y, Vulcan J, Hansen IA. A novel Tick Carousel Assay for testing efficacy of repellents on *Amblyomma americanum L.* PeerJ. 2021 21;9:e11138.
DOI: https://doi.org/10.7717/peerj.11138.

  DOI: https://doi.org/10.30564/jhp.v3i2.3788

[204] Atanasov Atanas G., Waltenberger Birgit, Pferschy-Wenzig Eva-Maria, Linder Thomas , Wawrosch Christoph, Uhrin Pavel, Discovery and resupply of pharmacologically active plant-derived natural products: A review. Biotechnol Adv. Biotechnol Adv. 2015; 33(8): 1582-1614.

[205] Krushkal Julia, Negi Simarjeet, Yee Laura M., Evans Jason R., Palmisano Tanja Grkovic, Alida., Molecular genomic features associated with in vitro response of the NCI-60 cancer cell line panel to natural products. Mol Oncol. 2021; 15(2): 381-406.

[206] Thomford Nicholas Ekow, Senthebane Dimakatso Alice, Rowe Arielle, Munro Daniella, Seele Palesa, Maroyi Alfred, Kevin Dzobo., Natural Products for Drug Discovery in the 21st Century: Innovations for Novel Drug Discovery. Int J Mol Sci. 2018; 19(6): 1578.

[207] Zingg Silvia, Dolle Patrick, Voordouw Maarten Jeroen, Kern Maren.,The negative effect of wood ant presence on tick abundance. Parasit Vectors. 2018; 11: 164.

[208] Hrnková Johana, Schneiderová Irena, Golovchenko Marina, Grubhoffer Libor, Rudenko Natalie, Černý., Jiří Role of Zoo-Housed Animals in the Ecology of Ticks and Tick-Borne Pathogens—A Review. Pathogens. 2021; 10(2): 210.

[209] Abdigoudarzi M, Esmaeilnia K, Shariat., N Laboratory Study on Biological Control of Ticks (Acari: Ixodidae) by Entomopathogenic Indigenous Fungi (*Beauveria bassiana*). Iran J Arthropod Borne Dis. 2009; 3(2): 36-43.

[210] Marciano AF, Mascarin GM, Franco RFF, Golo PS, Jaronski ST, Fernandes ÉKK, Bittencourt VREP. Innovative granular formulation of *Metarhizium robertsii microsclerotia* and blastospores for cattle tick control. Sci Rep. 2021;11(1):4972.
DOI: https://doi.org/10.1038/s41598-021-84142-8.

[211] Torina A, Villari S, Blanda V, Vullo S, La Manna MP, Shekarkar Azgomi M, Di Liberto D, de la Fuente J, Sireci G. Innate Immune Response to Tick-Borne Pathogens: Cellular and Molecular Mechanisms Induced in the Hosts. Int J Mol Sci. 2020 Jul 30;21(15):5437.
DOI: https://doi.org/10.3390/ijms21155437.

[212] Almazán C, Fourniol L, Rouxel C, et al. Experimental *Ixodes ricinus*-Sheep Cycle of *Anaplasma phagocytophilum* NV2Os Propagated in Tick Cell Cultures. *Front Vet Sci*. 2020;7:40. Published 2020.
DOI: https://doi.org/10.3389/fvets.2020.00040.

[213] Kasaija PD, Contreras M, Kabi F, Mugerwa S, de la Fuente J. Vaccination with Recombinant Subolesin Antigens Provides Cross-Tick Species Protection in *Bos indicus* and Crossbred Cattle in Uganda. Vaccines (Basel). 2020;8(2):319.
DOI: https://doi.org/10.3390/vaccines8020319.

[214] Labuda M, Trimnell AR, Licková M, Kazimírová M, Davies GM, Lissina O, Hails RS, Nuttall PA. An antivector vaccine protects against a lethal vector-borne pathogen. PLoS Pathog. 2006 Apr;2(4):e27.
DOI: https://doi.org/10.1371/journal.ppat.0020027.

[215] Tae Kwon Kim, Lucas Tirloni, Antônio F. M. Pinto, James Moresco, John R. Yates, III, Vaz Itabajara da Silva, *Ixodes scapularis* Tick Saliva Proteins Sequentially Secreted Every 24 h during Blood Feeding. PLoS Negl Trop Dis. 2016; 10(1): e0004323.

[216] Couto, J.; Seixas, G.; Stutzer, C.; Olivier, N.A.; Maritz-Olivier, C.; Antunes, S.; Domingos, A. Probing the *Rhipicephalus bursa* Sialomes in Potential Anti-Tick Vaccine Candidates: A Reverse Vaccinology Approach. Biomedicines 2021:9, 363.
DOI: https://doi.org/10.3390/ biomedicines 9040363.

[217] Charles Ndawula, Jr., Ala E. Tabor., Cocktail Anti-Tick Vaccines: The Unforeseen Constraints and Approaches toward Enhanced Efficacies Vaccines (Basel) 2020; 8(3): 457.
DOI: https://doi.org/10.3390/vaccines8030457.

[218] Hodžić A, Mateos-Hernández L, Leschnik M, Alberdi P, Rego ROM, Contreras M, Villar M, de la Fuente J, Cabezas-Cruz A, Duscher GG. Tick Bites Induce Anti-α-Gal Antibodies in Dogs. Vaccines (Basel). 2019;7(3):114.
DOI: https://doi.org/10.3390/vaccines7030114.

[219] Bhowmick Biswajit , Han Qian., Understanding Tick Biology and Its Implications in Anti-tick and Transmission Blocking Vaccines Against Tick-Borne Pathogens. Front Vet Sci. 2020; 7: 319.

[220] Alvarez Dasiel Obregón, Corona-González Belkis, Rodríguez-Mallón Alina, Gonzalez Islay Rodríguez, Alfonso Pastor, Ramos Angel A. Noda, Ticks and Tick-Borne Diseases in Cuba, Half a Century of Scientific Research., Pathogens. 2020 Aug; 9(8): 616.

[221] Tsetsarkin Konstantin A., Liu Guangping, Kenney Heather, Hermance Meghan, Thangamani Saravanan, Pletnev Alexander G., Concurrent micro-RNA mediated silencing of tick-borne flavivirus replication in tick vector and in the brain of vertebrate host. Sci Rep. 2016; 6: 33088.

[222] Kendall BL, Grabowski JM, Rosenke R, Pulliam M, Long DR, Scott DP, Offerdahl DK, Bloom ME.

Characterization of flavivirus infection in salivary gland cultures from male *Ixodes scapularis* ticks. PLoS Negl Trop Dis. 2020;14(10):e0008683.
DOI: https://doi.org/10.1371/journal.pntd.0008683.

[223] Zhou Wenshuo, Faizan Tahir, Joseph Che-Yen Wang, Woodson M, Michael B. Sherman, Karim S et al. Discovery of Exosomes From Tick Saliva and Salivary Glands Reveals Therapeutic Roles for CXCL12 and IL-8 in Wound Healing at the Tick-Human Skin Interface: Front. Cell Dev. Biol 2020; 8:554.

[224] Mitchell Robert D. , Sonenshine Daniel E., León Adalberto A. Pérez de Mitchell RD 3rd, Sonenshine DE, Pérez de León AA. Vitellogenin Receptor as a Target for Tick Control: A Mini-Review. Front Physiol. 2019;10:618.
DOI: https://doi.org/10.3389/fphys.2019.00618.

[225] Rodríguez-Camarillo Sergio D., Quiroz-Castañeda Rosa E., Aguilar-Díaz Hugo, Pastrana José E. Vara-, Pescador-Pérez Diego, Amaro-Estrada Itzel, Immunoinformatic Analysis to Identify Proteins to Be Used as Potential Targets to Control Bovine Anaplasmosis, Int J Microbiol. 2020; 2020: 8882031.

[226] Almazán Consuelo, Lagunes, Villar Margarita, Canales Mario, Jongejan Rodrigo Rosario-Cruz, Frans, Fuente José de la., Identification and characterization of *Rhipicephalus (Boophilus) microplus* candidate protective antigens for the control of cattle tick infestations. Parasitol Res. 2010; 106(2): 471-479.

[227] Pérez-Sánchez Ricardo , Manzano-Román Raúl, Obolo-Mvoulouga Prosper, Oleaga Ana., In silico selection of functionally important proteins from the mialome of *Ornithodoros erraticus* ticks and assessment of their protective efficacy as vaccine targets. Parasit Vectors. 2019; 12: 508.

[228] Galay Remil Linggatong, Miyata Takeshi, Umemiya-Shirafuji Rika, Maeda Hiroki, Kusakisako Kodai, Tsuji Naotoshi, Evaluation and comparison of the potential of two ferritins as anti-tick vaccines against *Haemaphysalis longicornis*. Parasit Vectors. 2014; 7: 482.

[229] Felix D Guerrero, et al. Guerrero Felix D, Andreotti Renato, Bendele Kylie G, Cunha Rodrigo C, Robert J, Yeater Kathleen , *Rhipicephalus (Boophilus) microplus* aquaporin as an effective vaccine antigen to protect against cattle tick infestations. Parasit Vectors. 2014; 7: 475.

[230] Eisen L, Dolan MC. Evidence for Personal Protective Measures to Reduce Human Contact With Blacklegged Ticks and for Environmentally Based Control Methods to Suppress Host-Seeking Blacklegged Ticks and Reduce Infection with Lyme Disease Spirochetes in Tick Vectors and Rodent Reservoirs. J Med Entomol. 2016;53(5):1063-1092.
DOI: https://doi.org/10.1093/jme/tjw103.

[231] Buczek Alicja, Buczek Weronika.,Importation of Ticks on Companion Animals and the Risk of Spread of Tick-Borne Diseases to Non-Endemic Regions in Europe Animals (Basel) 2021; 11(1): 6.

[232] Hu Ercha, Meng Yuan, Ma Ying, Song Ruiqi, Hu Zheng xiang, Hao Min Li, Yunwei, De novo assembly and analysis of the transcriptome of the Dermacentor marginatus genes differentially expressed after blood-feeding and long-term starvation.Parasit Vectors. 2020; 13: 563.

[233] Hu Ercha, Meng Yuan, Ma Ying, Song Ruiqi, Hu Zheng xiang, Hao Min Li, Yunwei, De novo assembly and analysis of the transcriptome of the *Dermacentor marginatus* genes differentially expressed after blood-feeding and long-term starvation.Parasit Vectors. 2020; 13: 563.

[234] Alvarez J. Antonio, Rojas Carmen, Figueroa Julio V., An Overview of Current Knowledge on *in vitro Babesia* Cultivation for Production of Live Attenuated Vaccines for Bovine Babesiosis in Mexico. Front Vet Sci. 2020; 7: 364.

[235] Suarez Carlos E. Bovine Babesiosis in Turkey: Impact, Current Gaps, and Opportunities for InterventionPathogens. 2020; 9(12): 1041.

[236] Akel T, Mobarakai N. Hematologic manifestations of babesiosis. Ann Clin Microbiol Antimicrob. 2017 Feb 15;16(1):6.
DOI: https://doi.org/10.1186/s12941-017-0179-z.

[237] Esteve-Gasent Maria D., Rodríguez-Vivas Roger I, Medina Raúl F., Dee Ellis, Andy Schwartz, Research on Integrated Management for Cattle Fever Ticks and Bovine Babesiosis in the United States and Mexico: Current Status and Opportunities for Binational Coordination, Pathogens. 2020; 9(11): 871.

[238] Gondard Mathilde, Cabezas-Cruz Alejandro, Roxanne A. Charles, Vayssier-Taussat Muriel, Albina Emmanuel, Moutailler Sara. Ticks and Tick-Borne Pathogens of the Caribbean: Current Understanding and Future Directions for More Comprehensive Surveillance. Front Cell Infect Microbiol. 2017; 7: 490.

[239] Busch JD, Stone NE, Nottingham R, et al. Widespread movement of invasive cattle fever ticks (Rhipicephalus microplus) in southern Texas leads to shared local infestations on cattle and deer. *Parasit Vectors*. 2014;7:188.

DOI: https://doi.org/10.1186/1756-3305-7-188.

[240] Namgyal J, Lysyk TJ, Couloigner I, Checkley S, Gurung RB, Tenzin T, Dorjee S, Cork SC. Identification, Distribution, and Habitat Suitability Models of Ixodid Tick Species in Cattle in Eastern Bhutan. Trop Med Infect Dis. 2021;6(1):27.
DOI: https://doi.org/10.3390/tropicalmed6010027.

[241] Banović Pavle, Díaz-Sánchez Adrian Alberto, Galon Clemence, Simonin Angélique Foucault-, Simin Verica, Mijatović Dragana, A One Health approach to study the circulation of tick-borne pathogens: A preliminary study. One Health. 2021; 13: 100270.

[242] Cardoso Fernando Flores, Matika Oswald, Djikeng Appolinaire, Mapholi Ntanganedzeni, Burrow, Heather M. Yokoo Marcos Jun Iti, Multiple Country and Breed Genomic Prediction of Tick Resistance in Beef Cattle. Front Immunol. 2021; 12: 620847.

[243] Biguezoton Abel, Adehan Safiou, Adakal Hassane, Zoungrana Sébastien, Farougou Souaïbou, Chevillon Christine, Community structure, seasonal variations and interactions between native and invasive cattle tick species in Benin and Burkina Faso. Parasit Vectors. 2016; 9.

[244] Zivkovic Zorica, Nijhof Ard M, Fuente José de la, Kocan Katherine M, Jongejan Frans. Experimental transmission of *Anaplasma marginale* by male *Dermacentor reticulates* .BMC Vet Res. 2007; 3: 32.