ARTICLE

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

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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 vertebrates 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 (Photograph 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 secretes 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"
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], tularemia, 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]). 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-

### Table 1. important bacterial diseases transmitted by various tick species

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Disease</th>
<th>Organism</th>
<th>Vector</th>
<th>Geographical distribution</th>
<th>Symptom</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lyme borreliosis disease</td>
<td>Borrelia burgdorferi</td>
<td>Ixodes scapularis</td>
<td>North east, Midwest and west coast states</td>
<td>Erythema migrans, Fatigue, erythema migrans, malaise myalgias, arthritis, headache, fever chills</td>
<td>Doxycycline (Vibramycin), non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>2</td>
<td>Anaplasmosis</td>
<td>Anaplasma phagocytophilum</td>
<td>Ixodes scapularis</td>
<td>North east, Midwest and west coast states</td>
<td>Myalgias, headache, fever chills</td>
<td>Doxycycline Chloramphenicol (Chloromycetin) Rifampin (Rifadin)</td>
</tr>
<tr>
<td>3</td>
<td>Anaplasmosis</td>
<td>Anaplasma platys</td>
<td>Rhipicephalus sanguineus</td>
<td>South central and western, U.S.</td>
<td>Myalgias, headache, fever chills</td>
<td>Doxycycline Chloramphenicol (Chloromycetin) Rifampin (Rifadin)</td>
</tr>
<tr>
<td>4</td>
<td>Ehrlichiosis</td>
<td>Ehrlichia canis</td>
<td>Rhipicephalus sanguineus</td>
<td>South central and western, U.S.</td>
<td>Myalgias, headache, fever chills</td>
<td>Doxycycline Chloramphenicol (Chloromycetin) Rifampin (Rifadin)</td>
</tr>
<tr>
<td>5</td>
<td>Ehrlichiosis</td>
<td>Ehrlichia ewingii</td>
<td>Amblyomma americanum</td>
<td>Cental and south eastern U.S. extending northward along the atlantic coast</td>
<td>Myalgias, headache, fever chills</td>
<td>Doxycycline Chloramphenicol (Chloromycetin) Rifampin (Rifadin)</td>
</tr>
<tr>
<td>6</td>
<td>Ehrlichiosis</td>
<td>Ehrlichia muris</td>
<td>Ixodes scapularis</td>
<td>Upper Midwest (Minnesota and Wisconsin)</td>
<td>Myalgias, headache, fever chills</td>
<td>Chloramphenicol (Chloromycetin) Rifampin (Rifadin)</td>
</tr>
<tr>
<td>7</td>
<td>Rocky mountain spotted fever</td>
<td>Rickettsia rickettsii</td>
<td>Dermacentor variabilis</td>
<td>South central and south western and eastern U.S.</td>
<td>Myalgias, headache, fever chills, malaise, vomiting, rash</td>
<td>Chloramphenicol (Chloromycetin) Tetracycline Doxycycline</td>
</tr>
<tr>
<td>8</td>
<td>Tularemia</td>
<td>Francisella tularensis</td>
<td>Amblyomma americanum</td>
<td>South and Midwest</td>
<td>Myalgias, headache, fever chills vomiting fatigue, sore throat, abdominal pain, skin ulcers, diarrhea, lymphadenopathy</td>
<td>Chloramphenicol Streptomycin Gentamicin, Tetracyclin, Fluroquinolones</td>
</tr>
</tbody>
</table>

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].

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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-
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 molting 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 \[50\].
Ticks as ectoparasites of livestock in tropical and sub-tropical areas transmit 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, *Ehrlichia* acasis and viral diseases of livestock, which are of great economic importance world-wide [55]. 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*, *Neoehrlichiacikurenensis*, *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 rodents and wild and domestic animals mostly mammals and infect them with various disease pathogens. Mostly domestic and wild mammals are reservoir hosts of tick transmitted pathogens mainly protozoans, bacteria, viruses, *rickettsia*, fungi and others during their feeding process.

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**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)
Table 2. important protozoan diseases transmitted by various tick species

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

on the hosts. After mosquitoes ticks are second vector group that transmit large number of pathogens to humans. 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. Rickettsia parkeri Luckman (Rickettsiales: Rickettsiaceae), is the tick-borne causative agent causes a more sever fatal disease rickettsiosis.

Tick-borne diseases are expanding regularly and these are reaching to new geographical locations in northern part of the world. This issue 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 ehrlichioses have been spread in geographical locations because of increased movements of Ixodes scapularis and Amblyomma americanum. Tick have saliva toxins cause paralysis in human hosts.

There are very few tick vectors which transmit arboviruses but these more frequently transmit obligate intracellular bacteria belong genus Rickettsia. 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. Various species of genus Ixodes infest livestock, mainly spread diseases in grazers. 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.

Ixodid ticks Ixodes pacificus, Ixodes persulcatus, Ix-
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 borne diseases which are responsible for illness and severely affect public health are following:

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 consolute 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 migrants, 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-meningal 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 Orni-thodoros tick vectors (77).

6.2 Anaplasmosis

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
<table>
<thead>
<tr>
<th>S.No.</th>
<th>TBDs</th>
<th>Species</th>
<th>Host</th>
<th>Vector Tick species</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rocky Mountain Spotted fever</td>
<td>Rickettsia rickettsia (Dermacentor variabilis, Dermacentor andersoni)</td>
<td>Man, Dog, small mammals are the natural reservoirs in the wild</td>
<td>Dermacentor variabilis and Dermacentor andersoni.</td>
<td>Subclinical infection to severe or fatal multiorgan collapse. Blackened or crusted skin at the site of a tick bite.</td>
</tr>
<tr>
<td>2</td>
<td>Rickettsiosis</td>
<td>Rickettsia parker (Amblyomma maculatum)</td>
<td>Small mammals, and humans</td>
<td>Dermacentor variabilis Dermacentor andersoni Rhipicephalus sanguine</td>
<td>Rickettsial vasculitis, vascular inflammation</td>
</tr>
<tr>
<td>3</td>
<td>Pacific Coast tick fever</td>
<td>Rickettsia philippii (Dermacentor occidentalis)</td>
<td>Horses, deer, cattle, lagomorphs, peccaries, porcupines, tapirs, desert bighorn sheep, and humans</td>
<td>Dermacentor species</td>
<td>Eschar or tissue necrosis</td>
</tr>
<tr>
<td>4</td>
<td>Mediterranean spotted fever</td>
<td>Rickettsia philipp (Dermacentor occidentalis)</td>
<td>Man</td>
<td>Dog tick Rhipicephalus sanguineus</td>
<td>Headache, fever and maculopapular rash</td>
</tr>
<tr>
<td>6</td>
<td>Theileriosis</td>
<td>Rickettsia philipp (Dermacentor occidentalis)</td>
<td>Ruminantsequid</td>
<td>H. marginatum, H. anato bic, Hexcavatum, H.detr itum, Haemaphysalis spp, Rhipicephalus</td>
<td>Anemia and, in some cases, jaundice or hemoglobinuria.</td>
</tr>
<tr>
<td>7</td>
<td>Cytaxxzoososis</td>
<td>Cytaxxzoofelis</td>
<td>Domestic cat</td>
<td>star tick, Amblyomma americanum</td>
<td>Necropsy, splenomegaly, hepatomegaly, enlarged lymph nodes, and renal edema</td>
</tr>
<tr>
<td>8</td>
<td>Hepatozoonosis</td>
<td>Hepatozooncanis</td>
<td>Candis felids</td>
<td>Rhi. Sanguineus</td>
<td>Fever, lethargy, decreased appetite, weight loss, muscle pain/weakness, reluctance to move, and discharge from the eyes and nose</td>
</tr>
<tr>
<td>9</td>
<td>Canine filariosis</td>
<td>Acanthocheione-mareconditum</td>
<td>Dogs</td>
<td>?</td>
<td>Weight loss, cough, fatigue</td>
</tr>
<tr>
<td>10</td>
<td>Anaplasmosis</td>
<td>Anaplassmaphagocytophilum, A. platys, A. marginale, Abovis, A ovis, A central</td>
<td>Ruminants dogs, human</td>
<td>Isodes spp, Dermacentorspp, Rhipicephalusspp, Haemaphysalis spp, Hyalommaspp, Ornithodorusspp</td>
<td>Human Granulocytic plasmosis, fever, headache, chills, and muscle aches</td>
</tr>
<tr>
<td>11</td>
<td>Ehrlichiosis</td>
<td>Ehrlichiacanis</td>
<td>Dogs</td>
<td>Rhi. Sanguineus?</td>
<td>Human Monocytic plasmosis, fever, chills, malaise, nausea, diarrhea</td>
</tr>
<tr>
<td>12</td>
<td>Aegypti anellosis</td>
<td>Aegyptianellapullorum</td>
<td>Duck</td>
<td>?</td>
<td>Parasitize the erythrocytes, infectious anemia”.</td>
</tr>
<tr>
<td>Page</td>
<td>Disease</td>
<td>Pathogen(s)</td>
<td>Hosts</td>
<td>Symptoms</td>
<td></td>
</tr>
<tr>
<td>------</td>
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<td></td>
</tr>
<tr>
<td>14</td>
<td>Candidatus R. vini</td>
<td>R. vini</td>
<td>Birds</td>
<td>Leukopenia and elevated hepatic enzyme levels</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Lyme Borreliosis</td>
<td>Borrelia burgdorferi, Bor. Tureca sp. Nov</td>
<td>Human, dogs, horses</td>
<td>Circular rash with red oval or bull’s-eye marks appear anywhere on body, fatigue, joint pain and swelling, fever, swollen lymph nodes</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>TBRF</td>
<td>Bor. Crocidarae</td>
<td>Rodents</td>
<td>Ornithodoroserraticus</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Tularemia</td>
<td>Francisella tularensis</td>
<td>Human</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Bartonellosis (Cat scratch fever)</td>
<td>Bartonella henselae</td>
<td>Cat</td>
<td>Lethargy, weakness, reduced appetite, dehydration, weight loss and intermittent pyrexia</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Hemoplasmosis</td>
<td>Mycoplasma haemofelis</td>
<td>Cat</td>
<td>Fever, headaches, fatigue, poor appetite, brain fog, muscle pain, and swollen glands around the head, neck, and arms.</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>CCHF</td>
<td>CCHF virus</td>
<td>Human</td>
<td>Stomach pain, and vomiting. Red eyes, a flushed face, a red throat, and petechiae</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>LI</td>
<td>LI Virus</td>
<td>Sheep</td>
<td>Skin nodules and oedema, enlarged lymph nodes, nasal discharge</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Tick borne encephalitis</td>
<td>TBE virus complex (Ixodes ricinus, Ixodes persulcatus)</td>
<td>Europe Asia, Middle East</td>
<td>Common and widespread Swelling of the brain and/or spinal cord, confusion, and sensory disturbances</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Powassan encephalitis</td>
<td>POW virus (Ixodes scapularis, Ixodes cookie)</td>
<td>Northern US / adjacent Canada far eastern Russia</td>
<td>Rare increasing Swelling of the membranes surrounding the brain and spinal cord</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Other TBEsOmsk hemorrhagic fever (OHF), Kyasanur Forest Disease(KFD) Louping ill virus, others</td>
<td>OHF virus KFD (Ixodes scapularis, Ixodes dammini, Haemaphysalis) Louping ill virus, others</td>
<td>Europe, Russia, China, Japan, India, Southeast Asia, Middle East</td>
<td>Rare to common within localized range some increasing High-grade fever with chills, intense frontal headache, severe myalgia and body aches</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Crimean - Congohemorrhagic fever (CCHF)</td>
<td>(CCHF) virus (Hyalomma marginatum other tick species)</td>
<td>Europe Central Asia, India, Africa</td>
<td>Common and widespread increasing Headache, high fever, back pain, joint pain, stomach pain, and vomiting.</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Severe fever with thrombocytopenia syndrome (SFTS)</td>
<td>SFTS virus (Haemaphysalis longicornis, Rhipicephalus microplus)</td>
<td>China Korea Japan</td>
<td>Uncommon increasing Thrombocytopenia, leukopenia, nausea, and vomiting.</td>
<td></td>
</tr>
</tbody>
</table>
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 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 reierted 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 patentint 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 an 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 anaphylasmosis 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 Haemaphysalis yellow dog ticks in various parts of world (Table 2). *B. hermsii* 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 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.
6.12 Ehrlichiosis

Human ehrlichiosis starts with mild fever associated with lymphoadenopathy. It is caused by several bacterial species *Ehrlichia chaffeensis*, *E. ewingii*, *Ehrlichia murrise-like* agent, Panola Mountain *Ehrlichia species*, and *Anaplasmaphagocytophilum* [105]. This disease is transmitted to humans by star tick *Amblyomma 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

*Mycoplasmafermentans* 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 (*Dermacentor 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 acaulatum* which react with host’s tissues and cells and generate toxicoses [108]. *Ixodesholocyclus* 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 intracel- lular 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 *Amblyomma maculatum* and Pacific Coast tick *Dermacentor occidentalis* ticks. Rickettsia conorii, pathogen causes Mediterranean spotted fever while Rickettsia parkeri, and *Rickettsia akari* causes rickettioses 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*). Patient feel fever and face skin ulcer at the site of tick bites.

Tularemia is spread in humans by the dog tick (*Dermacentor variabilis*), the wood tick (*Dermacentor andersoni*), and the lone star tick (*Amblyomma americanum*). 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 (*Callithrixjacchus*) [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 biomolecules in saliva which directly responsible for inflammation, vasoconstriction and the modulation of host defense mechanisms. Saliva secreted rine 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 modulator-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 borne 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 evasion, 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 secretes 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-
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 administered 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 characterized [138]. This highly distinctive type IV secretion system stays as neurotoxins found in tick saliva [139]. More specifically, surface protein with α₅ 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 

### 8. Diagnosis

For diagnosis of tick borne 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 microscopic methods [143]. Babesiosis generated plasminogen are tested by using chromogenic assay. Besides this, and concentrations of high mobility group box-1 protein (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 (TAFl), 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 appropriate for anaplasmosis diagnosis as both provide more authentic results [149].

SDS-PAGE gel electrophoresis is used to identify and characterize the basic functions of tick saliva proteins. More specifically, pathogen specific proteins of Lyme disease are identified by SDS-PAGE gel electrophoresis, ELISA (enzyme- linked immunosorbent assay) and immunoblotting [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. *Thelileria 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 borne 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 variables rainfall, humidity, latitudinal gradient, temperature and photo period [152]. In
middle east and North African 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. More often, 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 identification 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 underdeveloped 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 borne 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 borne 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 obstruction 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,
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 inhibit 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 hae-maphysaloides. 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 Pteroxylon 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 ecto-parasiticide \[177\]. 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, chemoprophyaxis, 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 neat of mats and clothes. These cutdown prevalence and intensity of parasitic interaction to small mammals [189]. More specifically, 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 acaricides 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 identification 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 acaricides used for control of ticks must be explored to know its effects on physiology and metabolism on animal hosts. Most of the acaricides activate chloridimeform 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).
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 and 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 [206] (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 [207]. 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 [208]. One of the important tick controlling agent is an entomopathogenic fungi Beauveria bassiana (B. bassiana 5197 and B. bassiana Évin). This fungal strain can easily grow on specific media and fungal spores are exposed to tick for inducing fungal infection [209]. 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 against as it 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-MSP1 vaccine 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 salivary 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 preparing 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 argasil chitinases and RPPO were also used as protective antigens, for finding new vaccine targets against many tick species [226]. HIFER2 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

For control of tick population various tick control programs 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 inter-relationships. By applying genetic and molecular methods a wide array of tick and tick borne pathogen antigens could be searched world wide. These could be used to make vaccines for reducing 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-parasite 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 house beds, clothing 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 acaricides. 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 pets 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. Repitive use of these acaricides against ticks is generating resistance and causing environ-
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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