Tick Biology, Disease Transmission and Control

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PREFACE

Ticks are the most important ancient group of obligate bloodsucking ectoparasites of terrestrial vertebrates, mainly of livestock. These small-sized animals are found in tropical and subtropical regions of the world. Ticks evolved during the Cretaceous period, the most common form of fossilization being amber immersion. Ticks are widely distributed around the world, especially in warm, humid climates. Ticks rely on host blood to derive nutrition to fulfil their metabolic requirements. They possess special mouth parts to remain attached to the host skin for years. They withdraw large volumes of blood from livestock, making them anaemic and causing significant weight loss. During feeding, ticks discharge a cocktail of diverse molecules, including salivary secretions, into the host's blood. Tick saliva especially secretes anti-coagulatory molecules, mainly salivary proteins, which inhibit blood clotting and assist in uninterrupted blood feeding by rupturing host skin. Through blood feeding, these insects transfer or inject pathogens into the bloodstream, enabling them to transmit various disease-causing pathogens easily. Transmission of pathogens leads to multiple diseases and morbidities, resulting in more severe economic losses to humans and their livestock. The main factors of tick parasitism are blood-sucking and saliva secretion, host immune status, age, breed, and local ecology. Ticks are major vectors of several pathogens, i.e. viruses, rickettsiae, spirochetes, bacteria, fungi, protozoa, and filarial nematodes in humans, livestock, and wild animals. These severely affect the health and survival of both domestic and wild animals, causing severe economic losses in livestock directly through blood feeding and indirectly by transmitting protozoan, rickettsial, and viral diseases.

In the present book, the geographical distribution of important tick species has been mentioned. Various ecotypes and biotypes that are responsible for pathogenesis have been explained with their host. Currently, 904 valid tick species have been listed throughout the world. The Second chapter pertains to the tick's feeding mechanism and the modification of its mouthparts for blood feeding. A Special description is added on salivary gland secreted saliva proteins/toxins, and their role in anti-coagulatory, anti-vasoconstrictor, anti-inflammatory, and anti-platelet aggregation factors during feeding to evade human and other animal hosts. Tick saliva

is used as an invasive liquid that imposes multiple severities in the host and causes impairment of physiological health. The third chapter provides an overview of the tick life cycle, including host search and invasion, progeny maintenance, survival, and establishment of host-parasite interactions. The fourth chapter has overall information about disease transmission methods and approaches. The fifth chapter is related to various tick-borne diseases caused by host-transmitted pathogens of different microbial groups, i.e. viruses, rickettsiae, spirochete, bacteria, fungi, protozoa, and filarial nematodes.

The sixth chapter has tick saliva-induced biological effects on human hosts. All these have been highlighted as anti-inflammatory, immunosuppressant peptides, immunomodulatory, and anti-chemokine activities. This chapter has complete information on host-pathogen interactions and invasion of the host by ticks, the biological effects of tick saliva toxins, and the host's immune responses.

Chapter Seven has various tick control methods such as physical, chemical, hormonal, and prophylactic. Chapter 8 provides information on various management strategies, including disease diagnosis and control of cattle, birds, and canine ticks. Chapter 9 discusses various salivary proteins as novel tick antigens and their application in antigen preparation and in influencing host immune responses. Chapter 9th concerned with various tick-controlling vaccines and their role in feeding inhibition in ticks.

Special emphasis has been given to the control of ticks by applying different categories of acaricides, including organochlorines, organophosphates, formamidines (e.g., amitraz), synthetic pyrethroids, macrocyclic lactones, fipronil, and fluazuron. But unfortunately, ticks have developed resistance against most of them. This resistance in ticks was developed through various mechanisms, including amino acid substitutions that led to morphological changes in the acaricide target, metabolic detoxification, and reduced acaricide entry through the outer layer of the tick's body. There is a need to focus on the search for new noble antigens, biologicals, signaling molecules, complement molecules, cytokines, death programmers, feeding inhibitors, antimicrobials, antibodies, and vaccines. Lastly, new molecules could generate strong innate immune responses and break the adaptation cover created by various tick species through immune tolerance and resistance to their pathogens. There are two essential steps to control ticks and inhibit their salivary secretions so that pathogen transmission can be blocked by having “anti-tick” vaccines based on unique and novel

protein antigens. Second, to have novel therapeutics derived from tick salivary components.

Lastly, to study the biology of ticks and their control, it is essential to understand the host-parasite interaction and the process of host invasion. Saliva proteins play a vital role in the interplay between host and parasite; therefore, studying the life cycle of ticks and their parasitic interactions is crucial for controlling the tick menace and reducing economic losses worldwide.

CHAPTER 1

TICK-BORNE DISEASES, TRANSMISSION, HOST IMMUNE RESPONSES, DIAGNOSIS, AND CONTROL

Abstract

The present review article explains tick-borne diseases, transmission, host immune responses, diagnosis, and control of 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 experience significant blood and weight loss, which affects their overall health. Due to more severe illness, severe economic losses were noted in livestock. This article highlights medically necessary tick-borne diseases in humans and livestock and their pathogenesis, diagnosis, and treatment methods. The present article emphasises 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 administering protective antibodies and vaccines for disease control in human beings and livestock. The authors suggest non-chemical, environmentally safe methods for successfully controlling tick-borne diseases to kill cattle, birds, and dogs that are invaded by ticks.

Keywords: Tick-borne diseases, blood feeding, transmission, pathogenesis, diagnosis, tick control, vaccine therapy

Introduction

Ticks rely on host blood and live as ectoparasites of many terrestrial vertebrates, mainly mammals, birds, reptiles, and amphibians. Due to blood-sucking behaviours, ticks can transmit numerous human and animal bacterial, viral, or parasitic diseases. Ticks are the most significant vectors of human pathogens, contributing to increased public health concerns worldwide. Ticks are arachnids with a body length of 3 to 5 mm. Along with mites, they constitute the subclass Acari. Several medically essential arthropods include vespids, mosquitoes, flies, 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 tropical, sub-tropical, and even temperate countries [1-3]. Few wild animals, mainly vertebrates, are reservoir hosts of ticks. Ticks are vectors of several pathogenic viruses, bacteria, fungi, protozoa, and filarial nematodes. These evolved during millions of years of long evolutionary periods [4]. Ticks as ectoparasites always rely on blood feeding, and all feeding stages pass their life cycle in different hosts and generate morbidities of medical and veterinary importance [5](Table 1). Ticks maintain enzootic cycles and continuously transmit pathogens among livestock and wild animal hosts. All these tick-borne pathogens have severe consequences for humans and their livestock. Tick-borne diseases primarily affect livestock and cause economic harm to the dairy farming industry and veterinary medicine [6] (Photograph 1).

There are two prominent families of ticks, i.e. Argasidae and Ixodidae. Among them, the Ixodes genus comprises highly infectious tick species that transmit a range of pathogens, resulting in diseases in livestock [7]. Hard ticks are characterised by hard shields or scutum on their dorsal surfaces [8-11]. Adult ticks are either ovoid or possess pear-shaped bodies, which remain engorged with blood. They are found to stick to the host skin using their eight legs tightly and continuously remain involved in blood feeding. Ixodidae is a family of hard or scale ticks comprising over 700 species [12,13]. At present, more than 904 tick species are 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 the complexity of their cycle, parasite-host relationships, and the emergence of zoonotic diseases in livestock and wild animals. Specifically, tick-borne pathogens spread due to variations in the area's vector-to-host ratio, intensity of the pathogen, and ecological factors

[20]. The terminal point of epizootics never comes, and diseases spread among mammals, including livestock and humans.

Ticks continuously feed on blood, which remains attached to the host's skin for days to weeks. They secrete anticoagulants and toxins in saliva to neutralise the host defences. Ticks' salivary glands secrete toxins and pass them into the blood through feeding, making livestock anaemic and causing significant economic losses to livestock worldwide [21]. Tick saliva is an invasive liquid that imposes multiple severities on the host and impairs physiological health [22]. Ticks for blood feeding puncture the host skin, damage it, and transmit various categories of dreadful infectious agents into the host's blood, which cause serious diseases in host animals. A few newly emerged tick-borne infectious diseases are Lyme borreliosis, ehrlichiosis, and babesiosis [23]. Babesiosis and anaplasmosis are dreadful tick-borne diseases; R. *microplus* and *R. annulatus* in bovine cattle herds spread these. Ticks also transmit encephalitis virus [24], Rickettsia, and other protozoa, cattle parasites [6], Mediterranean Spotted Fever, and tularaemia (human and animal) are emerging diseases [25]. No prophylactic therapies are available to control bovine babesiosis and anaplasmosis [26].

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

Both *Borrelia burgdorferi sensu lato* and tick-borne encephalitis virus *(*TBEV) are transmitted by the *Ixodes ricinus* tick. This tick species also transmits *Anaplasma phagocytophilum*, *Babesia divergens, Babesia microti, Babesia venatorum, Borrelia miyamotoi, Neoehrlichia mikurensis*, *Rickettsia helvetica*, and *Rickettsia monacensis* [30]. *Anaplasma phagocytophilum* lives 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 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" and "Theileria annae") infect dogs in Europe [34]. The most abundant and widespread tick species in Great Britain, human relapsing fever (HRF) and African swine fever (ASF), are spread by the *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 (Acanthocheilonemiasis), and ten bacterial agents (anaplasmosis, ehrlichiosis, Aegyptianellosis, tick-borne typhus, *Candidatus Rickettsia vini*, Lyme borreliosis, tick-borne relapsing fever [TBRF], tularaemia, bartonellosis, and histoplasmosis, and four viral infections i.e. Tick-Borne Encephalitis [TBE], Crimean-Congo Haemorrhagic Fever [CCHF], Looping-Ill [LI], and lumpy skin disease [LSD])[36]. The 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 that cause neurological complications include Lyme borreliosis, Q fever, and certain rickettsial infections. The present review article critically evaluated the disease transmission by different tick species, disease-causing pathogens, host immune responses, and biological damages generated. This article also has demarcated important diagnosis methods, tick prevention, and various control programs.

Source of information

Various databases were exhaustively searched to write a comprehensive book chapter on tick-borne diseases, their transmission, host immune responses, diagnosis, and control. For finding and collecting relevant information on the present topic-specific terms, such as medical subject headings (MeSH) and keywords “tick-borne diseases”, “pathogens”, tick control methods”, and “biological effects” were used in MEDLINE to fetch out research publications published till 2021. Most especially for retrieving all articles about using VIT for tick-borne diseases, electronic bibliographic databases were searched, and abstracts of published studies with relevant information on the venom toxins/allergens were collected. Furthermore, additional references were included by searching for the references cited by the studies done on the present topic. For an extensive literature search, the most relevant terms were used individually and in combination with other keywords. Efforts have been made to collect the most recent information available on the present subject. From the database, important abstracts available on relevant research articles, books, conference proceedings, and

public health organization survey reports were searched, downloaded, and collated based on the broader objective of the review. For writing this review, essential research articles and their findings, available from databases such as SCOPUS, Web of Science, EMBASE, PubMed, PMC, Publons, Swiss-Prot, and through Google searches, were thoroughly reviewed, and an attempt was made to summarize the key conceptual points. This final review identified and summarized important discoveries, findings, and outcomes using a standard methodology.

Tick Habitat

Ticks are slow-moving, tiny creatures incapable of flying or jumping. These typically inhabit sandy soil, hardwood forests, and river-banks, often with an overstory of trees or at least shrubs. These also live in narrow spaces near animal houses, cattle yards, grassy areas, and nests, and are found inside human dwellings in the dark, where they very silently attack roosting birds. All tick species rely on blood-feeding from vertebrate hosts. 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 holes, in the spring season. After embryonic development, tiny larvae can emerge, which are seen crawling onto grass weeds found in low-lying vegetation fields. Ticks live on the side lawn's edge, where they crawl swiftly and form a tick migration zone. More than 82% of tick nymphs reside inside grass fields and lawns [38]. Ixodid ticks are also found in the vegetation grounds where antelopes and other herbivores come to forage in closed enclosures; ticks show intensive free-living in large numbers. Ticks are found in open grasslands, as well as in urban areas, including woody material, carpets, doormats, and cloth seats. They are also found in Antarctica, where they are discovered stuck on penguins and feed upon their blood [28]. In bovines, cats, and dogs, ticks are found under the sides of the ears, udders, groin, tail, and anal region. Ticks can survive temperatures in the 20–29 °F range for at least two weeks. They can withstand temperatures above 0 °F (−18 °C) for over two hours.

Tick Life cycle

Ticks complete their life cycle in four stages, i.e. egg, larva, nymph, and adult. Ixodid ticks pass their life cycle among three hosts and complete it in one year. Argasid ticks develop in seven consecutive nymphal stages (instars), each requiring blood for feeding. Tick’s early larva bears six legs after hatching, and it develops two more legs after a blood meal and moults

into the nymph stage [26]. Both nymphal and adult stages possess seven segments, a pair of claws and eight legs. Tick's soft, tiny legs have sensory or tactile hairs that help them find a suitable site on the host skin [39] (Photograph 1). Ticks attach to a host by biting. They remain engorged deep in the skin and regularly suck blood. This process may take days or weeks. Due to its strong hematophagous nature, all life stages of ticks are highly destructive and suck blood in groups. These lacerate host tissue and secrete various biologically active substances that facilitate their invasion of hosts and enable the uptake of a blood meal [40].

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

One-host ticks

Both ixodid and argasid ticks complete their life cycle through egg, larval, nymphal, and adult stages in a single host [47]. It starts with eggs being laid by females, which hatch after 4-5 days, and larvae emerge. After exclusion, they need a host for a blood meal. After feeding the larvae blood, they moult into unfed nymphs, which also need host blood for nourishment. After engorging on the host's blood, the nymphs moult into sexually mature adults that remain on the host to feed and mate. Other examples of one host tick life cycle are the Winter tick *Dermacentor albipictus* and the cattle tick *Boophilus microplus* [48]. *Dermacentor variabilis* and *D. Anderson* (Ixodidae) also pass through their life cycle in four consecutive life stages [49]. Ticks show a complex epidemiology but are of great ecological significance. They generate a more considerable impact on the clinical and socio-economic status of men due to the occurrence of pathogenic diseases [50] (Table 1) (Figure 1).

Two-host ticks

There are a few tick species, like *Hyalomma anatolicum* excavatum, that complete their life cycle between two host ticks [51]. From eggs laid by female ticks, after hatching, tiny larvae emerge, which crawl and attach to a host's skin for sucking blood. They remain attached to 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 to moult into adults. Both male and female adults seek out a host to attach, which may be the same body that served as a host during their early development. Once connected, they feed and mate. After mating, females lay eggs and oviposit them in crevices, on leaves, in clothing, and under vegetation cover (Table 1) (Figure 1).

Three-host ticks

Most ixodid ticks need three hosts to complete their life cycle. Their females lay thousands of eggs on the ground/garden soil to establish parasitism. After hatching, larvae emerge, attaching themselves to feed on the blood, primarily of small mammals and birds. After feeding, they detach from their hosts and moult to nymphs on the ground, which then attach and feed on larger hosts before dropping off again to moult 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 their eggs on the ground, while males feed very little and remain on the host to continue mating with other females [51] (Table 1) (Figure 1).

Transmission of diseases

Ticks, as ectoparasites of livestock in tropical and subtropical areas, transmit a broader range of pathogens and cause severe economic losses. Ticks transmit a wide range of viral, bacterial, and protozoan pathogens; many establish lifelong infections in the vector tick. Ticks also spread pathogens transovarially to the next generation; these pathogens include Borrelia spp., Babesia spp., Anaplasma, Rickettsia/Coxiella, and tick-borne encephalitis virus, as well as *Theileria parva*. Ticks also transmit protozoan, rickettsial, Ehrlichiasis, and viral diseases of livestock, which are of great economic importance worldwide [52]. Ticks and Tick-Borne Diseases (TBDs) impact the productivity of bovines in tropical and subtropical regions worldwide. Most poor countries have cattle farming as the primary economic source, significantly impacting the livelihoods of resource-poor farming communities [52] (Table 2).

Ticks suck blood regularly from vertebrate hosts for nutrients, survival, oviposition, and the developmental stage for completion of their life cycle. Blood feeding by ticks has a severe impact on animal health, reducing weight and inducing anaemia in domestic animals. Ticks suck blood and feed on birds, mainly on migratory birds (Table 2). Migrating birds carry ticks with them. Thus, the tick population spread through cattle trade, bird homing, and transnational trans-human movements.

The castor bean tick, *Ixodes ricinus*, transmits *Borrelia burgdorferi, 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 are also transmitted by ticks [54]. Ticks transmit potential tick-borne pathogens that affect human health, resulting in severe pathogenesis and mortality [30]. Babesial vector tick synthesises 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 that feed on *Borrelia burgdorferi Sensu* Lato-infected black-legged mites.

The distribution of the population of various tick species depends on regional ecology and climatic situation. Climatic conditions also support the growth, survival, and reproduction of vertebrate populations. Ticks also feed on blood from rodents and wild and domestic animals, primarily mammals, and infect them with various disease pathogens. Most domestic and wild mammals are reservoir hosts of tick-transmitted pathogens, mainly protozoans, bacteria, viruses, rickettsia, fungi, and others, during their feeding process on the hosts [55]. After mosquitoes, ticks are the second vector group that transmits many pathogens to humans [56]. Blood feeding by ticks is the most prevalent transmission mode as they infect humans and pets. Due to the easy dissemination of highly infectious pathogens that cause multiple infections, ticks are proven to be the most dangerous vectors worldwide. Tularaemia is a dreadful zoonotic disease caused by *Francisella tularensis,* a highly contagious Gram-negative coccobacillus. This is also used as a biological weapon for generating potential bioterrorism threats and is classified in category A of warfare agents by the CDC [57]. *Rickettsia parkeri* Luckman (Rickettsiales: Rickettsiaceae) is the tick-borne causative agent of a more severe, fatal disease, rickettsiosis [58].

Tick-borne diseases are expanding regularly and reaching new geographical locations in the northern hemisphere. This is due to the international trade of animal' food and clothes. Recent surveys indicate tick-borne diseases like

rickettsioses, Lyme borreliosis, and tularaemia are transferring from nonendemic areas due to favourable climatic conditions. Lyme disease and human ehrlichiosis have been spread geographically due to the increased movement of *Ixodes scapularis* and *Amblyomma americanum* [59]. Ticks have saliva toxins that cause paralysis in human hosts [60].

Very few tick vectors transmit arboviruses [61], but these more frequently transmit obligate intracellular bacteria from the genus Rickettsia [62]. *Ixodes* ticks are commonly infected with both *B. microti* and *B. burgdorferi* and transmit these pathogens into hosts: Lyme disease-causing spirochete, *Borrelia burgdorferi.* and *B. microtia* is also transmitted through the transfusion of blood products [63]. Various species of the genus *Ixodes* infest livestock and mainly spread diseases in grazers [64]. Tick infestations directly occur due to increased outdoor activities and the movement of humans and their pets in orchards, grassy vegetation, and lawns. Dogs are exposed to ticks and tick-borne diseases by living with infected dogs and cattle [65].

Ixodid ticks, *Ixodes pacificus, Ixodes persulcatus*, *Ixodes ricinus*, and *Ixodes scapularis* are major vectors that transmit tick-borne pathogens. For regular blood, ticks remain attached to their hosts for almost 1–2 weeks to obtain blood meals. (Table 2). *Ixodes ricinus*, a medically crucial free-living tick, transmits disease pathogens, i.e. *Amblyomma* spp, *Anomalohimalaya* spp, *Bothriocroton* spp., *Cosmiomma sp, Dermacentor spp, Haemaphysalis spp, Hyalomma spp, Ixodes spp,Margaropus spp, Nosomma sp, Rhipicentor spp, and Rhipicephalus spp*, in man and other mammalian hosts [66]. The Lyme disease spirochete (*Borrelia burgdorferi*) is transmitted to humans by the western black-legged tick (*Ixodes pacificus*) [67,68]. *Ixodes pacificus* (Acri Ixodidae) nymphs make horizontal and vertical movements in hardwood forests for searching hosts. *Ixodes hexagons* or brown Ixodid ticks parasitise domestic and wild animals (Table 2).

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 Tularaemia. Ticks can be infected with bacteria, viruses, or parasites. Tick-borne diseases are those spread by the bite of an infected tick (Table 3). Saliva-secreted toxins cause most tick-borne diseases during blood feeding on hosts; parasites spread through the blood supply in various body parts after their entry. Tick-borne diseases can also be transmitted through blood products and blood

transfusions. The transmission of tick-borne pathogens via blood transfusion is of global concern [69](Table 3) (Figure 2). A few essential tick-borne diseases that are responsible for illness and severely affect public health are the following:

Lyme disease

Ixodid ticks are notorious bloodsucking ectoparasites and depend entirely on the host's blood meals. Lyme disease is an infectious, inflammatory disease caused by *Borrelia burgdorferi*, a parasite, a spirochete, and a conserved bacterium. This pathogen is transmitted to humans by biting a black-legged tick (*Ixodes scapularis*) [70]. *Borrelia burgdorferi* parasite contains membrane protein antigens which are differentially regulated during its life cycle. During blood feeding, ticks also release anticoagulants, anti-inflammatory and anti-hemostatic compounds in saliva with this parasite [71] (Table 2). This disease is a potential health threat to the Canines, mainly dogs and livestock. Significant symptoms of Lyme disease include fever, chills, headache, joint and muscle pain, fatigue, and skin rashes with erythema migrans. It manifests with lameness, anorexia, fever, lethargy, lymph adenopathy, and, in some cases, fatal glomerulonephritis. Lyme disease patients display erythema, migraines and bullseye-like rash. It also causes long-term complications in untreated cases, including arthritis, facial palsies, meningitis, and carditis. The vaccine could be an efficient approach to decrease. For the treatment of Lyme disease, oral antibiotics are provided; however, a small percentage of patients (10 to 20%) suffer from persistent, non-specific symptoms, and after being identified post-treatment, they develop Lyme disease syndrome (PTLDS). Lyme disease is treated with vaccination by healthcare providers and public health practitioners**.** It also needs public awareness and tick control [72] (Figure 2).

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

Anaplasmosis

A bite of *Anaplasma phagocytophilum* spreads anaplasmosis, and *Anaplasma marginale* is a highly infectious hard tick. This disease is prevalent in the northeastern and upper midwestern U.S. and the Pacific coast. Many cases have been reported worldwide over the last two decades. Anaplasmosis is caused by the bites and blood feeding of infected *Ixodes scapularis,* known as the deer tick *(Ixodes scapularis*). Anaplasmosis is a hemolytic disease, and its main symptoms are chills, fever, body aches, fatigue, nausea, vomiting, and diarrhoea. Patients also feel loss of appetite**,** chills, abdominal pain, and muscle aches [78-79]. Its asymptomatic coinfection shows plus anaplasmosis SFG rickettsiosis. *Anaplasma phagocytophilum* harbours inside patient erythrocytes and was identified by cell sorting assay [80]. Parasites housed inside ticks show regional climatic-induced variations in genospecies and strain frequencies differing in pathogenicity [81]. For their identification, DNA tests are performed [80]. For human granulocytic anaplasmosis, diagnosis is essential to identify Ixodes scapularis ticks and zoonotic amplification of *Anaplasma phagocytophilum* [82] (Figure 2).

Tick-borne babesiosis

Babesiosis is a zoonotic disease caused by tick-borne intraerythrocytic hemoprotozoan parasites of the genus *Babesia*. The disease is provoked by climate change, the rising population of Ixodes ticks as vectors, and the abundance of human and other mammalian hosts [83]. Babesiosis is a significant threat to human health [84]. Both dirofilariasis and babesiosis were spread in central Europe, and it was reported in microfilaraemic dogs [85]. Babesiosis is transmitted through blood transfusion or congenitally [86]. Its pathogen mainly invades human erythrocytes and lyses red blood cells, resulting in febrile hemolytic anaemia, like human malaria [87]. The disease also occurs in dogs in tropical regions [88].

Besides, human babesiosis and canine babesiosis are spread by a tick species, *Dermacentor reticulatus* [89]. v. An ICD-9-CM diagnosis code ascertains the level of babesiosis. [90]. This disease is also reported in canines and is caused by *Babesia canis, B. vogeli, B. gibsoni,* and *B. microti*, which are transmitted from infected dogs in Europe [91]. Bovine babesiosis is caused by several species of *Babesia spp*., including *B. bovis, B. bigemina*, and *B. divergens.* Babesia microti causes human babesiosis, which is endemic in the northeastern and upper Midwestern United States (Figure 2).

Intraerythrocytic protozoan parasites, the Babesia microti, cause human babesiosis. This disease remains asymptomatic initially, and patients experience high fever, sweats, chills, nausea, headaches, and fatigue after 4-5 days of infection. Babesiosis patients lose appetite and fatigue, and their urine colour becomes dark due to jaundice and anaemia. Babesiosis patients also show few clinical symptoms like anorexia, dehydration, temperature, dullness/depression, diarrhoea/constipation, pale mucosa, hepatomegaly, vomiting/nausea, splenomegaly, distended abdomen/ascites, yellow-colored urine, emaciation/weight loss, and ocular discharge [92]. Extracellular phosphorylated proteins found in the serum of infected patients are used for diagnosis [93]. The disease is also transmitted by blood transfusion. And causes heavy mortality in high-risk populations despite antibiotic therapy (Table 2) (Figure 2) [94]. A few broad-spectrum antibiotics, such as atovaquone plus azithromycin or clindamycin and quinine, are prescribed for treating babesiosis patients.

Tick-borne encephalitis

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

Ticks also harbour endogenous viruses and modulate the growth of tick-borne pathogens. Ticks also transmit viruses with diverse genetic attributes, which are classified into two orders, comprising nine families and at least 12 genera. Tick-borne encephalitis virus (TBEV) evokes severe neurological diseases in humans in different parts of the world [100]. The salivary gland secretions of hematophagous parasites and blood-sucking arthropods, such as ticks, play a more significant role in counteracting 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* are obligate intracellular pathogenic bacteria, and fatal tick-borne diseases like hot water and monocytic ehrlichiosis in livestock [103] and man [104]. (Table 2) (Figure 2).

Powassan Encephalitis

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

Lumpy skin disease

Lumpy skin disease is caused by *Borrelia burgdorferi* in the mammalian hosts by an infected tick bite of various species of Ixodid ticks belonging to the 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 the world (Table 2). *B. hermsii* and *B. turicatae* (in the southwest) cause infantile tick paralysis [60](Figure 2).

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 that resembles the *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 their larval offspring get a natural infection and become an essential participant in the transmission cycle. Significant symptoms of *Borrelia miyamotoi* disease are fever, chills, fatigue, severe headache, and muscle/joint pain**.**

Borrelia mayonii

Borrelia mayonii is a Gram-negative spirochete that causes Lyme disease in North America and the midwestern United States. *Borrelia mayonii* infects human ticks and black-legged ticks (*Ixodes scapularis*). *I. scapularis* is a

transmission vector. The primary symptoms of the disease include fever, chills, headache, fatigue, body and joint pain, as well as cardiac, neurologic, and arthritic problems.

Alpha-Gal (Red Meat) Allergy

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

Bourbon virus

Bourbon virus infection was first identified in the Midwest and southern United States, mainly in Kansas and Oklahoma. This is a sporadic infectious disease, and its patients typically exhibit mild symptoms, including fever, fatigue, rash, and muscle and joint pain.

Colorado tick fever (CTF) is a viral infection (Colivirus) caused by bites from an infected Rocky Mountain wood tick, *Dermacentor andersoni.* The patient shows important features like fever and rash, low white blood cell counts, heart problems, and severe bleeding.

Ehrlichiosis

Human ehrlichiosis starts with mild fever associated with lymphadenopathy. 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 the star tick *Amblyomma americanum*. The disease is noted in the south-central and eastern U.S. More recently ehrlichiosis has emerged as a new infection that may be associated with neuro-meningeal complications. Broad-spectrum antibiotics are prescribed for treating ehrlichiosis; to date, no suitable vaccine has been available [106].

Mycoplasma

Mycoplasma fermentans, which is smaller than bacteria, is also transferred with the *Borrelia* bacterium via an infected tick, the Lyme disease causative

agent. It invades body cells and disrupts the immune system, causing severe fatigue, joint pain, nausea, and neuropsychiatric problems (Figure 2).

Rocky Mountain spotted fever (RMSF)

This disease 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 transmits the bacterium *Rickettsia rickettsii*, which predominantly causes outbreaks in the summer season. RMSF exhibits unique illness features, including fever, paralysis, sequelae, and chronic arthritis, as well as neurologic or cardiac problems 107].

Tick-borne paralysis

Ticks transmit pathogens through a bite, which causes loss of motor function and induces paralysis. Mainly, a few toxins are secreted by female ticks of *Amblyomma aculatum*, which interact with the host's tissues and cells, generating toxicoses [108]. *Ixodes holocyclus* also generates the same morbidity and induces 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 the host [110]. Destruxin A secreted by *Rhipicephalus* (Boophilus) *microplus* ticks (Acari: Ixodidae) causes tetanic paralysis [111] (Table 2) (Figure 2).

Rickettsioses

Rickettsiosis disease is caused by an obligatory intracellular bacterium belonging 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 the Pacific Coast tick, *Dermacentor occidentalis*. *Rickettsia conorii*, a pathogen, causes Mediterranean spotted fever, while Rickettsia parkeri and Rickettsia akari cause rickettsioses in the United States [112]. The dog transmits rickettsioses in this region, the tick *Rhipicephalus sanguineus* and the camel tick *Hyalomma dromedarii*. These are essential vectors and reservoirs of Rickettsiae. Infected male ticks spread the disease through sexual transmission. Rickettsiae have been detected in spermatogonia, spermatocytes, and maturing spermatids [70] (Table 3) (Figure 2).

Tularemia

Tularemia, also known as rabbit fever, is a dreadful zoonotic disease caused by *Francisella tularensis*, a highly infectious Gram-negative coccobacillus. In men, tularaemia is also caused by direct contact. The main vectors of the tularemia pathogen are the dog tick *(Dermacentor variabilis),* the wood tick *(Dermacentor variabilis),* and the star tick (*Amblyomma americanum*). The patient feels a fever and faces a skin ulcer at the site of the tick bite.

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 a bacterial infection, sometimes also called rabbit fever, and the development of an ulcer at the site of infection is also seen. This disease is also spread by inhalation of contaminated dust or through contaminated food and water [114]. The disease shows significant clinical symptoms, including spiking fevers, inflamed lymph nodes and eyes, pneumonia, and weight loss. This is also used as a biological weapon for generating potential bioterrorism threats and is classified in category A of warfare agents by the CDC [57] [115]. (Figure 2). The parasite is detected in various wild animals, including lagomorphs, rodents, carnivores, fish, and invertebrate arthropods [116]. *Francisella tularensis* is also detected in many animal species. [117]. *F. tularensis holarctic*, biovar I am also found in common marmosets (*Callithrix jacchus*) [118]. A few broad-spectrum antibiotic aminoglycosides, the fluoroquinolones, and the tetracyclines are recommended for the treatment of diseases [119]. The macrolides were found to be highly effective against *F. tularensis* grown in phagocytic cells than in acellular media [120]. Essential tools that are used for the diagnosis of tularaemia are PCR, ELISAs, MAT, and IFA [121] (Figure 2).

Immune responses

There is an immense need to study the tick life cycle, tick-borne pathogens, and tick-host interactions to control ticks. Numerous control methods have been employed to manage ticks in various parts of the world. These are based on biomacromolecule repositories and enzyme inhibitors, utilizing genomes, transcriptomes, and proteomes. Most methods are mechanical, chemical, genetic, repellents, pesticides, toxic baths, and environmental and community-based control mechanisms. During blood feeding, ticks secrete a plethora of biomolecules in their saliva, which are directly responsible for inflammation, vasoconstriction, and the modulation of host defense mechanisms. Saliva-secreted serine protease inhibitors are used to prepare an innate immune defense. Saliva-secreted molecules do hemolymph

coagulation and induce egg development. To date, so many enzyme inhibitors like serine protease inhibitors (SPIs), which inhibit various tick biological processes, are more appropriate. These will become effective tick control agents in the future [121].

Salivary secretions in ticks transmit pathogens to various animal hosts including man. Tick saliva is a complex mixture of multiple peptides, mainly toxins and non-peptides. These substances strongly counteract hosts' homeostasis, and immunity, and inhibit tissue repair and wound healing. The ixodid ticks' salivary glands (SG) secreted saliva contains a rich mixture of anti-haemostatic, anti-inflammatory, immune modulator, anti-coagulatory, anti-vasoconstrictor, and anti-platelet aggregation factors. Tick saliva produces itching or pain and initiates blood feeding by making incisions in skin cells. Ticks inject toxins that generate cellular and humoral responses. Tick-borne pathogens affect the immune system of other invertebrates, 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 the action of regulatory biomolecules [122]. Ticks bear antigen families evasions, Isac, DAP36, and many others on their surface. Sialostatin L (SialoL) is a cysteine protease inhibitor identified in the salivary glands of the Lyme disease vector *Ixodes scapularis*. Tick salivary glands secrete cystatin sialo statin L2, suppressing Type I interferon responses in mouse dendritic cells. Dendritic cells (DCs) secrete IFN in response to tick saliva proteins. Sialo statin L also shows immunomodulatory action on dendritic cells and obstructs autoimmunity. SialoL significantly decreases LPS-induced maturation of dendritic cells in C57BL/6 mice [123] (Table 2).

Tick salivary gland-secreted bio-molecule 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 is to evoke 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 [124]. *Borrelia species* affect the differentiation of THP-1 Cells while *Ehrlichia chaffeensis* causes monocytic ehrlichiosis in man [125]. Tick saliva More specifically salivary cystatins secreted by hard tick *Ixodes scapularis*, sialo statin L (Sialo L), and sialo statin L2 (Sialo L2) in saliva inhibits differentiation, maturation, and function of murine bone-marrow-derived dendritic cells. *Borrelia burgdorferi* pathogen interacts with Toll-like receptors and evokes immune responses (Table 2).

Ticks as vectors secrete immunosuppressant peptides, immunoreactive proteins, and antimicrobial peptides also used in host defense. Few non-coding small RNAs regulate the synthesis of these peptides at the post-transcriptional level [126]. Tick-borne rickettsiae that cause spotted fever in cattle and humans [127]. Rickettsiae produce two immunodominant outer membrane proteins: rickettsial Omp A (rOmp A) and rOmpB, potent antigens that could be used for vaccine production. Besides this, ticks secrete hundreds to thousands of proteins into the saliva of the feeding site. Tick salivary gland secreted natural substances play an essential role in modulating host defense mechanisms [127]. Few of them neutralise innate immune functions and inhibit the formation of adaptive immunity, like the Australian tick *Ixodes holocyclus*, which secretes toxins and other active components that show immunomodulatory effects. Tick salivary products exposed to *Borrelia burgdorferi and Anaplasma phagocytophilum* dihydrolipoamide dehydrogenase 1 affect host-derived immunopathology during microbial growth within hosts [128]. Similar immunomodulation is also seen in other blood-sucking arthropod vectors, mainly mosquitoes, tsetse flies, and sand flies, which also transmit pathogens during blood feeding [129]. Immunoglobulin therapy is provided for the treatment of neurological diseases [130] (Table 2).

For the treatment of tick-borne encephalitis, a thiomersal-free and albumin-free (TBE-vaccine) was developed in Australia in 2000 [131]. For neutralising paralysis-causing toxins secreted by *Rhipicephalus evertsi evertsi, Rhipicephalus appendiculatus, Boophilus microplus,* and *Ixodes holocyclus* ticks monoclonal antibodies are used [132]. A recombinant veterinary vaccine has also been developed to neutralise the effect of tick neurotoxin peptide. This vaccine is successful, cost-effective, and provides long-term protective immunity against tick-induced paralysis [133]. Similarly, a vaccine is also administered to decrease Lyme disease incidence [134]. Moreover, these proteins are administered as immunogenic components to seek protection against *Anaplasma marginale* VirB2, VirB7, VirB11, and VirD4 proteins. These show effective serological responses in men [135]. Similarly, a few outer membrane (OM) proteins are used to immunise cattle to defend them from *Anaplasma marginale* tick infestation. These provide complete protection against disease and persistent infection. Polyclonal dog antiserum is also used to treat tick paralysis (Table 2). Other approaches have also been tried to develop tick vaccines for prophylactic use [136].

However, to prepare an appropriate vaccine, complete genome sequencing of bacterial parasites of ticks and their antigens must be identified and characterised [137]. This highly distinctive type IV secretion system is found in neurotoxins found in tick saliva [138]. Specifically, surface proteins with α_3 integrin binding and channel-forming activities are responsible for *Borrelia burgdorferi* [139]. A plasminogen receptor, BosR (BB0647) released in the outer membrane of *Borrelia burgdorferi* governs virulence expression and could be used as an antigen [140]. Nitric oxide also functions 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 [141]. Ceftriaxone is recommended when parenteral antibiotic therapy against tick-borne microbial pathogens [142]. More specifically, oral doxycycline, amoxicillin, and cefuroxime are used against the Lyme disease pathogen.

Diagnosis

Methods are used to diagnose tick-borne diseases. Among them, enzyme immunoassay (EIA) is the most frequent method, followed by western blot test(s). Various microscopy methods are used to diagnose blood specimens of HGA and babesiosis patients [143]. Babesiosis-generated plasminogen is tested using an achromogenic assay. Besides these 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 [143]. The Babesia pathogen is also identified in clinical samples by staining with Giemsa stain in blood smears. Besides this, PCR and anti-Babesia antibody titers are also used to identify *Babesia* sp.[144]. There is a need for diagnostic methods, vaccine development, “omics” analysis, and gene manipulation techniques of local *Babesia* strains [145].

Skin biopsy specimens are diagnosed with lesions by using immunohistochemical stains. For the diagnosis of rickettsiae, polymerase chain reaction (PCR) is used [146]. For testing samples from asymptomatic anaplasmosis cases, PCR and an indirect immunofluorescence assay (IFA) are performed to identify tick-borne infectious diseases [147]. Serology provides low specificity and high sensitivity and is used for testing acute and convalescent samples. However, PCR and immunofluorescence assay tests were found to be more appropriate for anaplasmosis diagnosis as both provide more authentic results [148].

SDS–PAGE gel electrophoresis is used to identify and characterise the essential functions of tick saliva proteins. More specifically, pathogen-specific proteins of Lyme disease are determined by SDS–PAGE gel electrophoresis, ELISA (Enzyme-Linked Immunosorbent Assay), and immunoblotting [149]. These are also diagnosed by measuring the level of Immunoglobulin G1 isotype [150]. More specifically, spotted fever caused by rickettsiosis can be identified by the LPS lipopolysaccharide antigenicity. *Theileria lestoquardi*, *T. Ovis* and *T. annulata* are detected using molecular methods in the blood of Goats and Ticks. Mast cells and IgE levels are used to detect tick-borne allergies.

Effect of climate on the emergence of tick-borne diseases

Tick-borne illnesses are found in almost all climatic regions because of the wide distribution and occurrence of various tick species adapted to the local environment. More often, climate cycles determine genetics, adaptability, host-parasite interaction, and pathogen multiplication. The main endemic areas of tick-borne diseases are forest sites and high-density urban and rural habitats. Tick infestation is a significant animal health problem worldwide, and its higher endemicity is noted in the Middle East and North Africa, as well as tropical and subtropical countries[151]. The disease prevalence, infestation, and invasion accelerate with climatic favourability, and tick-borne pathogens spread very fast and cause heavy economic losses to livestock farming and wildlife. The emergence of tick-borne zoonotic diseases also severely affects human health, as morbidity and deaths are higher in the Northern Hemisphere due to regional variations, climatic variations, and rising resistance in ticks and tick-borne pathogens. More often, hydroclimatic changes occur due to unstable weather conditions, affecting the range of some infectious diseases, including tularaemia. Tularaemia incidences are directly related to climate variables, and assessment can be done for future disease outbreaks by analysing these variables, rainfall, humidity, latitudinal gradient, temperature, and photoperiod [151]. In the Middle East and North African countries, domestic livestock are more severely attacked by multiple tick species due to harsh environmental conditions. These areas have the most suitable climate and vegetation for tick population growth and easy availability of many mammalian hosts [152]. Hence, there is an immense need to map tick-borne diseases based on the area's ecology, evoked across their geographic distribution to evaluate the burden of pathogens transmitted by ticks [153].