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BIOLOGY, IMPORTANCE AND CONTROLL METHODS OF TICKS

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ABSTRACT

Ticks and mites are currently grouped with members of the subclass Acari, which is the largest subclass in the class Arachnida of the suborder Ixodida within the order Parasitiformes. Ticks are divided into two large families, the Argasidae and the Ixodidae, with a total of about 850 species. All ticks are obligate temporary parasites of vertebrate animals and are characterized by a complex developmental cycle. The life cycle typically includes the larva (hatching from the egg), that, after feeding, drops to the ground and molts to the nymph. As a matter of fact relatively few species of ticks have successfully adapted to livestock or feed on a human subject, and these have developed into efficient vectors of a range of pathogenic microorganisms, while virtually all human tick-borne diseases are zoonoses. Ticks and tick-transmitted infections have coevolved with various wild animal hosts which often live in a state of equilibrium with them and constitute reservoir hosts for ticks and tick-borne pathogens of livestock, pets and humans. Ticks comprise veterinary problem because they transmit diseases, produce paralysis or toxicosis, and cause physical damage to livestock.

INTRODUCTION

Ticks are haematophagous invertebrates which depend on feeding on blood from animals and have evolved in parallel and in association with the evolution of terrestrial vertebrates. Fossil records indicate that ticks have existed at least since the Cretaceous era (65–146 million years ago (mya)) (Francis E., 1929) and certainly preceded hominids and their close ancestors, as well as all domestic and most wildlife animal species prevalent today. Approximately 900

species of ticks have been described to date, of which more than 700 belong to the Ixodidae (hard ticks); approximately 200 belong to the Argasidae (soft ticks) and only one species to the Nuttalliellidae (Guglielmone et al., 2010). The lifestyle of ticks which includes uptake of blood from hosts, secretion of saliva into the host tissues, movement between different hosts and production of eggs from which a new generation of ticks develops, inevitably makes them suitable to host other organisms. Some of these are symbionts or commensals which do not induce disease, while others are able to cross into vertebrate hosts and be pathogenic to them. A wide variety of pathogens is transmitted from ticks to vertebrates including viruses, bacteria such as rickettsiae and spirochetes, fungi, protozoa and helminths, of which most have a life cycle which requires passage through the vertebrate host (Dantas-Torres et al., 2011).

Ticks transmit variety of pathogenic microorganisms, protozoa, rickettsiae, spirochaetes and viruses, more than any other arthropod vector group, and are among the most important vectors of diseases affecting livestock, humans and companion animals. Moreover, ticks can cause severe toxic conditions such as paralysis and toxicosis, irritation and allergy. The importance of tick-borne diseases for humans and companion animals is measured by morbidity and mortality. The diseases transmitted by ticks to livestock are an additional major constraint to animal production predominantly in (sub) tropical areas of the world. In general, tick-borne protozoan diseases (e.g. theilerioses and babesioses) and rickettsial diseases (e.g. anaplasmoses and heartwater or cowdriosis) are pre-eminent health and management problems of cattle and small ruminants, as well as buffalo, affecting the livelihood of farming communities in Africa, Asia and Latin America. Recently, tick-borne diseases were again ranked high in terms of their impact on the livelihood of resourcepoor farming communities in developing countries (Perry *et al*., 2002). This is particularly relevant in parts of sub Saharan Africa, Asia and Latin America where the demand for livestock products is increasing rapidly (Delgado *et al*., 1999).

Ticks and tick-transmitted infections have coevolved with various wild animal hosts which often live in a state of equilibrium with them and constitute reservoir hosts for ticks and tick-borne pathogens of livestock, pets and humans. They have only become problems of domestic livestock when these wild hosts came into contact with them, either because man moved livestock into infested regions, or moved livestock infested with the ticks into previously uninfested regions (F. Jongejan and G. Uilenberg, 2004). An example of man

moving livestock into infested regions is the introduction of cattle into Africa where they came into contact with Rhipicephalus appendiculatus, the vector of Theileria parva, the causal agent of East Coast fever and related diseases; the African buffalo is the normal host of T. parva and the infection is normally subclinical in this animal. An example of man moving ticks and tick-borne diseases with livestock is the introduction of Boophilus ticks together with the livestock diseases they transmit into the American continent. The global economic importance of ticks is particularly high for livestock, there is also a great impact on public health in the northern hemisphere, primarily due to Lyme borreliosis (LB) but also other zoonotic tick-borne illnesses, with those of viral origin, characterized by encephalitis and haemorrhagic fevers, causing the highest morbidity and mortality in man. Tick-borne pathogens of pets are of economic significance only in industrialized countries, whereas tick-borne pathogens infecting horses constitute important constraints to international trade and sporting events involving these animals (F. Jongejan and G. Uilenberg, 2004).

1. IMPORTANT TICKS OF THE WORLD

Most ticks have a preference for feeding on certain groups of wild animals, with some even being quite host specific. Consequently, the number of species pertinent to domestic animals and/or humans is limited. As a matter of fact relatively few species of ticks have successfully adapted to livestock or feed on a human subject, and these have developed into efficient vectors of a range of pathogenic microorganisms, while virtually all human tick-borne diseases are zoonoses. The following ecological criteria were used to underpin the tick–host–pathogen relationships. A tick species is considered a vector for a particular pathogen only if it (1) will feed on an infectious vertebrate host, (2) is able to acquire the pathogen during the blood meal, (3) can maintain the pathogen through one or more life stages, and (4) can pass it on to other hosts when feeding again (Kahl *et al*., 2002 none).

1.1. Ixodidae or Hard Ticks

1.1.1. ***Anatomy:*** Ticks are large-body-size (2–30 mm) acarines. Adults and nymphs have 4 pairs of walking legs, and larvae have 3. All stages have no antennae, and unlike insects, their bodies are not divided into a distinct head, thorax, and abdomen (Sonenshine, 1991 none). The anterior part of the body, the capitulum, bears the mouthparts, including sensory organs, cutting organs, and a median immobile organ (the hypostome) with numerous recurved teeth that anchor the tick to the host's skin. The ixodids are characterized by the presence of a

sclerotized plate (the scutum) on the dorsal surface of the body, and the remainder of the body is able to expand during feeding (Hillyard PD., 1996).

Ticks possess a circulatory system, and all organs and tissues are bathed by a circulating fluid, the hemolymph (Sonenshine, 1991 none). Many ticks lack eyes, and even when eyes are present, it is doubtful that they enable a detailed perception of the environment. However, ticks have a variety of peripheral sensory organs. These include hair-like structures on the body, legs, and mouthparts and a sensory complex located on the dorsal surface of the tarsus of leg I, which contains a cluster of olfactory and gustatory receptors (Haller's organ). These sensory organs are evidently important in enabling ticks to locate their hosts and also to communication with other ticks.

1.1.2. ***Life cycles and ecology:*** Typically, ixodid ticks have a 3- host life cycle, with each feeding stage of the tick (larva, nymph, and adult) having a single host (Spickett AM., 1994 none). Each stage of the tick seeks out a host, attaches, and then feeds over a period of several days. Once replete, the tick detaches and, after dropping from the host, finds a resting place where it can digest its blood meal and molt to the next feeding stage, or enter diapause, a state characterized by reduced metabolism and delayed development. In a few species, the immature forms may remain on the host during molting. Generally, adult males feed only briefly and sparingly and some do not feed at all. Mating generally occurs on the host. Thereafter, the females detach and drop off the host to digest their blood meal. They then lay their eggs, from 400 to 120,000 depending on the species (»5000 for the American dog tick, *Dermacentor variabilis*), in a sheltered environment and die (Sonenshine DE., 1993 none). Pheromones play an important role in the behavior of ticks and facilitate ticks' finding their hosts and their mates. They include assembly pheromones, which bring ticks together, and sex pheromones, which attract males to females and stimulate mounting.

The life cycle of ixodid ticks is usually completed in 2–3 years, but it may take from 6 months to 6 years, depending on environmental conditions, including temperature, relative humidity, and photoperiod. The ixodid ticks are relatively sensitive to desiccation and are especially common in grasslands and woodlands, with each species having its own particular optimal environmental conditions and biotopes that determine the geographic distribution of the ticks. For example, in Europe, the dog brown tick *R. sanguineus* is well adapted to Mediterranean vegetation and climatic conditions and is thus endemic in the Mediterranean area but is absent in the north of Europe except in human homes, where conditions enable it

to survive. On the other hand, *Ixodes scapularis* in the United States and *Ixodes ricinus* in Europe favor woods and forests with high relative humidity and are absent from dry places (Spickett AM., 1994 none).

1.1.3. ***Host seeking****:* Ixodid ticks spend 90% of their life unattached from the host (Needham GR, Teel PD. 1991), and most of them are exophilic: they live in open environments, meadows, or forests. Here they are usually seasonally active, seeking their hosts when environmental conditions are most suitable. They are highly responsive to stimuli that indicate the presence of hosts. These include chemical stimuli (such as CO2, NH3) phenols, humidity, and aromatic chemicals, and airborne vibrations and body temperatures associated with warm-blooded animals. For example, ticks are attracted by feet hitting the ground or by the CO2 emitted by a car stopped in the bush (JL Camicas, personal communication). Two typical host-seeking behavior patterns occur among exophilic ticks. In the ambush strategy, ticks climb up vegetation and wait for passing hosts, with their front legs held out in the same manner as are insect antenna (e.g., *R. sanguineus,* the brown dog tick, and *I. ricinus* adults in Europe; *I. scapularis* and *D. variabilis* in the United States; In the hunter strategy, ticks attack hosts. They emerge from their habitat and run toward their hosts when these animals appear nearby (e.g., adult and nymph *Amblyomma hebraeum* and *Amblyomma variegatum* in Africa (Sonenshine DE., 1993 none). Some species (for example, the lone star tick, *Amblyomma americanum,* in the United States) use both strategies (Sonenshine DE., 1993, Sonenshine,, 1991 none). Other species of ticks (those of the genus *Ixodes,* for example) are endophilic and exhibit a third host-seeking behavior: they remain hidden in hosts' nests and burrows awaiting their arrival.

A number of tick species are host-specific, feeding on only a limited variety of animals. Other ticks have different hosts for each feeding stage, and host specificity may vary between the different stages in the same species. Each feeding stage of *R. sanguineus,* for example, has high specificity and feeds readily on dogs. On the other hand *I. scapularis* and the American lone star tick, *A. americanum,* and adults of the European sheep tick, *I. ricinus,* usually feed on different host species, particularly large mammals but also small mammals and birds (Hillyard PD. *et al.*, 1996). Generally, habitat distribution also influences host selection, because ticks that are adapted to a habitat or vegetation type, for example woods for *I. ricinus* and *I. scapularis,* will encounter vertebrates that are adapted to the same habitat. Different species of ticks also have different affinities for people (Estrada-Pena A, Jongejan

F. 1999). Although *R. sanguineus* will feed on humans only if there are no dogs or other hosts available, *I. ricinus* in Europe, *I. scapularis* in the United States, and *A. hebraeum* in Africa feed readily on humans that enter their biotopes (Hillyard PD. *et al*., 1996).

1.1.4. ***Attachment and feeding:*** Before feeding, a tick may wander around on its host for several hours. It inserts only its hypostome into the skin and various substances produced by the salivary glands enter the host during this penetration, creating a feeding pool (Spickett AM. 1994). During the first 24–36 h of attachment, there is no or little ingestion of blood, and penetration and attachment are the predominant activity. The salivary secretions produced by ixodid ticks include a cement to anchor the mouthparts to the skin of the host; enzymes; vasodilators; and anti-inflammatory, antihemostatic, and immunosuppressive substances. These facilitate successful blood feeding, and an anesthetic in the saliva makes the bite of ixodid ticks usually painless. There may also be toxins in the saliva of some species that may cause paralysis of the host (Sonenshine DE., 1993 none). Ixodid ticks feed for long periods, and 2–15 days are required for a complete blood meal to be ingested, depending on the feeding stage, species of tick, type of host, and site of attachment. An initial slow feeding period (3–4 days) is followed by a period of rapid engorgement (1–3 days) when ticks, particularly females, may increase their body weight up to 120- fold. While feeding, there are alternating periods of sucking blood and salivation, with regurgitation occurring frequently, particularly at the end of the rapid engorgement phase *(*Parola and Raoult, 2001 none).

During the initial slow feeding period, there is continuous digestion of the blood meal in the midgut, and defecation may occur. In the period of rapid engorgement, there is reduced digestion, but this becomes continuous again after the tick is replete and detaches from the host. Ticks rapidly concentrate the blood meal by eliminating water and electrolytes in the feces, during transpiration, and in salivary gland secretions. Undigested residues from the midgut and wastes from the excretory body are eliminated through the anus (Hillyard PD. *et al*., 1996).

1.2. Argasidae or Soft Ticks

The argasids, or “soft ticks,” are quite different from the ixodids. The salivary glands of argasids do not produce cement and contain anticoagulant and cytolytic substances, because feeding only takes a brief time (Sonenshine, 19910 none). Apart from the larval stages, argasids may feed up to 10 times, during which they become replete in a few hours. The

coxal organs concentrate the blood meal, and the coxal fluid is secreted during and after the meal. The time spent on the host is relatively short, and after each meal these ticks are typically found in cracks and crevices in their habitats or just below the soil surface.

2. DAMAGES CAUSED BY TICKS

Ticks comprise veterinary problem because they transmit diseases, produce paralysis or toxicosis, and cause physical damage to livestock. Ticks' species are grouped into three families, Argasidae or soft ticks, Ixodidae or hard ticks and Nuttalliellidae (Klompen *et al.*, 1996 none). Ticks are very important to man and his domestic animals, and must be controlled if livestock production is to meet world needs for animal protein. Knowledge of the nature and habits of the tick and the disease agents it transmit helps in control (Stewart *et al*., 1981).

2.1. Losses and control

A complex of problems related to ticks and tick-borne diseases of cattle created a demand for methods to control ticks and reduce losses of cattle (George *et al*., 2004). Control of tick infestations and the transmission of tick-borne diseases remain a challenge for the cattle industry in tropical and subtropical areas of the world. Tick control is a priority for many countries in tropical and subtropical regions (Lodos *et al*., 2000). Losses due to tick infestations can be considerable. In Australia alone in 1974, losses due to cattle tick (*Boophilus microplus*) were estimated to be USD 62 million (Springell, 1983 none). Brazil loses around USD 2 billion per year (Grisi *et al*., 2002). Such losses can be cut considerably by adopting effective tick control measures. There are three major reasons for controlling ticks in domestic animals: disease transmission, tick paralysis or toxicosis, and tick-caused physical damage. The main weapon for controlling ticks at present is the use of chemical acaricides (Drummond, 1983). Ticks are responsible for severe economic losses both through direct effect of blood sucking and indirectly as vector of pathogens and toxins.

2.2. Direct effect

Feeding by large numbers of ticks causes reduction in live weight and anemia among domestic animals, while tick bites also reduce the quality of hides. Apart from irritation or anemia in case of heavy infestations, tick can cause severe dermatitis. These parasites generate direct effects in cattle in terms of milk production and reduce weight gain (L'Hostis and Seegers, 2002; Peter *et al*., 2005).

1. Tick-bite paralysis

It is characterized by an acute ascending flaccid motor paralysis caused by the injection of a toxin by certain ticks while feeding. Examples are paralysis caused by the feeding of *Dermacentor andersoni*, sweating sickness caused by *Hyalomma truncatum*, Australian tick paralysis caused by *Ixodes holocylus*, and tick toxicosis caused by *Rhipicephalus* species (Drummond, 1983). Tick paralysis is most common in late winter and spring when the adult ticks are active, but it can occur at any time if the weather is warm and humid (Stewart and de Vos, 1984). Paralysis in cattle caused by *Ixodes holocyclus* and *Dermacentor andersoni* had also been reported by Doube and Kemp (1975) and Lysyk *et al*. (2005) respectively.

2. Physical damage

Ticks are attached to the body for a blood meal and may cause irritation and serious physical damages to livestock. Included are "tick worry", irritation, unrest, and weight loss due to massive infestation of ticks; the direct injury to hides due to tick bites, loss of blood due to the feeding of ticks (Drummond, 1983).

2.3. Vector of pathogens

Ticks can be carrier, of pathogens, which they transmit from host to host during blood sucking and cause a large variety of diseases (L'Hostis and Seegers, 2002; Peter *et al*., 2005). The major diseases include Babesiosis, Anaplasmosis, Theileriosis, and heart-water, East Coast fever; in addition, other diseases of lesser importance cause severe economic losses to the livestock industry (Drummond, 1983). The presence, dynamics and amount of parasite stock in ticks exert a major influence on the kinetics of transmission of tick-borne parasitic diseases (Morel, 1980). Generally the ticks become infested with the causative organisms of diseases while they are feeding on infected animals. Then the organism may be transmitted from stage to stage in the tick (an example is *Theileria parva* transmitted by *Rhipicephalus appendiculatus*), or from the female tick through the egg to the larvae— an increase of several thousand times in vector potential (an example is *Babesia equi* transmitted by Anocentor nitens). When the next stage or generation subsequently feeds on another animal, the organism is transmitted to that animal if it is susceptible to the disease (Drummond, 1983). Tick borne diseases generally affect the blood and/or lymphatic system. Tick fever organisms, like *Anaplasma marginale*, are significant causes of cattle morbidity in Australia, USA, China and other countries (CRC-VT, 2001).

2.4. HUMAN AND ANIMAL TICK-BORNE INFECTIONS

Ticks are second only to mosquitos as vectors of human diseases (de la Fuente, 2003). In some areas where malaria is rare, such as North America and parts of Europe, Lyme disease transmitted by several species of Ixodes ticks is a main cause of human morbidity, surpassing any mosquito-borne disease. Lyme disease caused by Borrelia burgdorferi sensu lato (s.l.) is responsible for more than 90% of all vector-borne disease cases in the United States (Radolf *et al.*, 2012) and it was estimated that it may be responsible for disease in 255,000 persons annually world-wide, mostly in Europe and North America (Rudenko *et al*., 2011). Lyme disease is also prevalent in northern China where 30,000 persons are estimated to acquire this disease annually (Wu *et al.*, 2013).

Considering the large size of the global human population, the high density of humans in some areas, and the surface size of the adult human body, humans would be expected to be one of the most common blood sources for ticks. Is it reasonable to ask, therefore, if there are TBIs in which humans are the major reservoir host and which would cease to be transmitted if the human host was absent? Certainly most TBIs circulate between wildlife animals and ticks, and may affect humans or domestic animals, but do not rely on infecting people for their persistence. For example, Lyme disease circulates mostly among rodents, and humans or domestic dogs are just incidental hosts that could suffer from clinical disease but do not play an important role in the enzootic transmission and epidemiology of this infection (Radolf *et al.*, 2012). Additional pathogens transmitted by Ixodes spp. including the flavivirus Tick-borne encephalitis virus (Dobler, 2010) and the protozoon Babesia microti also circulate mostly amongst rodents and ticks in sylvatic cycles, and may occasionally infect humans who infringe into these hosts' natural habitats (Leiby, 2011). Other TBIs that infect humans and animals such as Crimean–Congo haemorrhagic fever caused by an arbovirus of the Bunyaviridae are thought to be maintained by the tick as a vector as well as a reservoir, as they can be transmitted transovarially and transstadially, and by co-feeding (Mertens *et al.*, 2013 none). It may be concluded that despite the global abundance of humans and their presence in a variety of climates and ecological conditions, they are not major reservoirs for TBIs. This is clearly different from the epidemiology of some of the most important human diseases transmitted by flying insect vectors such as malaria and lymphatic filariasis transmitted by mosquitos, and Kala Azar caused by Leishmania donovaniand spread by phlebotomine sand flies. While these diseases target humans as their main host, TBIs of humans, although potentially causing disease in large numbers of individuals, are typically an

infringement of a circulation between wildlife animal reservoirs and tick vectors. TBIs of humans, farm animals and companion animals such as dogs and cats, may overlap, and some agents such as B. burgdorferi and Anaplasma phagocytophilum are able to infect hosts belonging to more than one of these categories, however all of these zoonotic agents are associated with wildlife reservoirs (G. Baneth, 2014).

2.5. Tick Paralysis: A Noninfectious Tickborne Disease

In addition to transmitting many pathogens, including the bacteria reviewed below, prolonged attachment (5–7 days) of certain species of ticks may result in paralysis of the host (Sonenshine DE., 1993 none). This is caused by neurotoxic substances produced by the salivary glands of attached engorged ticks (particularly females). Tick paralysis was first recognized in Australia in 1824 and is now known to occur in many countries worldwide. More than 40 species of ticks from both families have been implicated in the condition, but *D. andersoni* and *D. variabilis* in North America, *I. ricinus* in Europe, *Ixodes holocyclus* in Australia, and *Rhipicephalus evertsi evertsi* in Africa are most commonly involved (Dworkin MS. *et al*., 1999 none). Tick paralysis occurs more often in children, although adults may also be affected. Clinical signs include weakness in the lower extremities, which ascends within hours or days to involve the trunk musculature, upper extremities, and head. Patients may present with ataxia or respiratory distress, and mortality rates of up to 10% have been reported (Felz MW. *et al*., 2000). Analysis of CSF samples usually reveals no abnormalities, and the diagnosis of the condition depends on a history of tick bite or finding a tick on the body of the patient. Removal of the tick leads to a rapid recovery within 24 h (Dworkin MS. *et al.*, 1999 none).

2.5.1. Causative agent and distribution: Tick paralysis is believed to be caused by a variety of proteinaceous toxins, specific to different tick species (e.g, holocyclotoxin in *Ixodes holocyclus*, the Australian paralysis tick), that are secreted into the host along with other salivary compounds during tick feeding. In humans and animals, paralytic toxins either block the release of acetylcholine at the synapses or inhibit motor-stimulus conduction. Generally, only female ticks cause paralysis, and they must be attached to a host for several (4-7) days before they begin secreting the toxin in their saliva. This malady has chiefly been reported from North America, Europe, Asia, South Africa, and eastern Australia. Historically, the greatest number of cases has occurred in North America, with highest incidence along the border between British Columbia, Canada, and the states of Washington, Idaho and Montana.

In the eastern United States, cases have been reported from seaboard areas of Virginia, the Carolinas and Georgia, but there are also records from Kentucky, Tennessee, Mississippi and Oklahoma (Felz MW. *et al*., 2000).

2.5.2. Symptoms: This affliction is characterized by an ascending flaccid paralysis. In humans, it usually begins in the legs, with muscle weakness and loss of motor coordination and sensation. Paralysis gradually progresses to the trunk, with loss of coordination in the abdominal muscles, back muscles, and eventually the intercostal muscles of the chest. Paralysis of the last-named muscle group is especially serious because it can lead to respiratory failure. Ultimately, the victim may be unable to sit up or move either arms or legs, and chewing, swallowing and speaking may become difficult. The condition progresses rapidly, and death may occur 24-48 hours after onset of symptoms. Recorded mortality rates are 10-12%. Diagnosis simply involves finding an embedded tick, usually at the nape of the neck or in the scalp. After removal of the tick, symptoms generally resolve within hours or days, which suggest that the tick toxin is either rapidly excreted or metabolized. However, if paralysis is advanced, recovery can take weeks or months. No drugs are available for treatment (Dworkin MS. *et al*., 1999 none).

2.5.3. Vectors and transmission: Worldwide at least 46 ixodid and argasid species in 10 genera have been implicated in cases of tick paralysis involving humans, other mammals, and birds. However, in North America only five tick species – *Dermacentor andersoni, D. variabilis, Amblyomma americanum, A. maculatum* and *Ixodes scapularis* – are known to cause paralysis in humans. In the Pacific Northwest, most cases occur during the spring and early summer, coincident with the adult activity period of *D. andersoni*. In the eastern United States, cases of tick paralysis in dogs and occasionally in humans have been associated with bites of *D. variabilis*, but in California this tick apparently produces paralysis only in dogs. Also in California, several mild cases of human paralysis were ascribed to *Ixodes pacificus* during the first half of the twentieth century, but these were not well documented and no new cases have since been reported. Interestingly, even in regions with a high incidence of tick paralysis, only a portion of the female tick population appears to be able to cause this condition. Paralysis ticks often attach at the nape of the neck, where they may be concealed by long hair; for this reason, most victims are girls. Among adults, men engaged in outdoor activities are more likely than women to be affected (Dworkin MS. *et al*., 1999).

2.5.4. Reservoirs: There are no reservoirs associated with tick paralysis, since the affliction does not entail the passage or maintenance of an infectious agent.

2.6. Tick-Borne Infectious Diseases

Ticks were the first arthropods to be established as vectors of pathogens and currently they are recognized, along with mosquitoes, as the main arthropod vectors of disease agents to humans and domestic animals globally. Moreover, the incidence of tick-borne diseases (TBDs) is increasing worldwide. For instance, more than 250 000 human cases of Lyme borreliosis were reported from 2000 to 2010 in the United States and the dis- ease is also increasing in Europe; where over 50 000 cases are reported each year in humans (Piesman, J. and Eisen, L., 2008).

Ticks are arthropods belonging to the order Arachnida. They are free living but require a blood meal during at least one life stage. ‘‘Soft’’ ticks (family: Argasidae) attach to the host, complete feeding within a few minutes, and promptly detach. ‘‘Hard’’ ticks (family: Ixodidae) are protracted feeders and remain attached for up to several days before reaching repletion. Successive blood meals on different hosts permit the transmission of blood-borne pathogens from one host to another. Ticks species with catholic feeding preferences can transmit microbes from evolutionarily commensal reservoir species (eg, rodents) to incidental susceptible species (eg, humans). The risk of disease transmission therefore is determined by the prevalence of infectious ticks—a function of the number and infection prevalence of the pathogen’s reservoir host—and by the likelihood of an encounter between an infected tick and a susceptible host—a function of both the numbers of ticks and susceptible hosts within a fixed area and their respective behaviors (Curtis L. Fritz, 2009). Ticks are important to human and veterinarymedicine, they act as vectors of bacterial, protozoal, rickaettsial, spirochaetal and viral diseases of humans, domestic stock and companion animals. As ectoparasites with irritating bites, they cause extensive harm to their hosts due to blood loss, damage to themskin and anorexia leading to reduction in growth. They are considered as agents of 'tick paralysis' in man and animals, probably due to the secretion of toxic substances in their saliva. Lesions can be caused by ticks (dermatophilosis) in cattle, goats and sheep (Sh Salari Lak *et al*, 2008). Ticks and tick-borne diseases affect animal and human health worldwide and are the cause of significant economic losses. Approximately 10% of the currently known 867 tick species act as vectors of a broad range of pathogens of domestic

animals and humans are also responsible for damage directly due to their feeding behavior (Jongejan and Uilenberg, 2004).

2.6.1. Tick borne encephalitis (TBE)

Tick borne encephalitis (TBE) is the most important tick-transmitted neurological disease in Central and Eastern European countries and in Russia. Endemic regions range from Northern China and Japan through far Eastern Russia to Europe (Gritsun *et al*., 2003b, Barrett *et al*., 2008 none).

TBE is caused by the TBE-virus (TBEV), a flavivirus, which is transmitted mainly by ixodic tick species and by unpasteurized dairy products, mainly goat milk. TBE morbidity has been increasing over the last decades and the disease is continuously spreading to new, formerly unaffected areas. Süss *(2008)* reports a nearly 400% increase of reported TBE morbidity in Europe between 1974 and 2004 and TBE can now be found in new regions (*Cha*rrel *et al.*, 2004*)* and at higher altitudes *(*Holzmann *et al., 2009).* Many factors contribute to this increase: expanding tick populations due to climatic factors *(Randolph, 2009; Randolph, 2010),* social and behavioural changes *(*Kriz *et al., 2004),* as well as changes in land use and leisure activities *(*Sumilo *et al., 2008*). Also, reporting of TBE cases has been improved substantially over the years and in 16 countries TBE is now a notifiable disease *(Suss, 2010 none).*

Most likely, however, TBE is still considerably underreported, and in 7 (low-) endemic countries, regular reporting of TBE cases is not required by the health authorities. On average, between 1990 and 2009, nearly 8.500 cases of TBE were reported annually in Europe including Russia, although, with considerable variability in incidence from year to year *(*Suss, *2010).* TBEV is a neurotropic virus that can cause potentially fatal meningitis, encephalitis and/or radiculitis. About one third of infected subjects develop clinical disease; of these, 75% show the classic biphasic picture of an initial short-lasting, flu-like illness starting about 2 weeks after the tick bite, and followed after a few symptom-free days by signs of central nervous system (CNS) involvement *(*Kaiser, *1999).* Men are affected twice as frequently as women.

Post encephalitic neurologic sequelae, termed "post-encephalitic TBE syndrome*" (Kaiser, 2008)* occur in 35-58% encephalitic cases, with a variety of symptoms and outcomes. Three main TBEV subtypes, closely related genetically and antigenically, are described: The

European, also called Western (TBEV- Eu), the Far Eastern (TBEV- Fe) and the Siberian (TBEV- Sib) subtypes *(*Ecker *et al., 1999).* The clinical course and the probability of death or severe neurologic sequelae depend on the age of the affected person - severity is increasing with age. Moreover, the clinical outcome may in part depend on the infecting TBEV subtype. Thus, the case fatality rate (CFR) in persons infected with TBEV- Eu or TBEV- Sib rarely exceeds 1% *(*Kaiser, *2008),* whereas with the TBE- Fe, CFRs up to 30-40% have been reported *(*Mandl, *2005).* In Western Siberia, where the TBEVSib is prominent, the reported CFR was 2-3% *(*Lindquist and Vapalahti, *2008).*

Repellents or insecticides provide unreliable protection against tick-bites *(*Ginsberg, 2005) and specific treatment options are lacking, since there is no antiviral with activity against TBE in vivo. Active immunization is currently the only option for prophylaxis against TBE. Encepur® and TBE-Immun®, the two vaccines that are manufactured in Western Europe, are based on cell cultured and inactivated TBEV, adjuvanted to aluminium hydroxide *(*Zent and Broker, 2005). Encepur®and TBE-Immun® are widely used inin TBE-endemic EU-countries. Two Russian vaccines are on the market: TBE Moscow Vaccine® is produced by the federal state enterprise Chumakov Institute of poliomyelitis and Viral encephalitides and EnceVir®, which is produced by the Russian company Microgen in Tomsk (Leonova and Pavlenko, 2009). TBE Moscow vaccine® and EnceVir® are used in Russia and some neighbouring countries. Like the Western TBE vaccines, they are based on primary cell culture of chicken fibroblasts and are using aluminium hydroxide as adjuvant (Leonova and Pavlenko, 2009).

Being a zoonosis, TBE cannot be easily eliminated from endemic areas. However, the introductions of large-scale vaccination campaigns have proven highly effective in reducing the burden of disease. In Austria, where the vaccination coverage in the general population has reached approximately 90%, the number of clinical cases could be reduced to about 10%, as compared to the prevaccination era (Heinz, 2008). In most highly TBE-endemic countries, large-scale vaccination campaigns are not implemented, however.

2.6.1.1. Transmission and vector ecology: Ticks are the main vectors and serve as virus reservoir whereas vertebrates, mainly small rodents such as the yellow-necked field mouse or voles (Charrel et al., 2004) serve as so called amplifying hosts and act as the ticks' source of infection (Large mammals such as roe, deer or goat rarely reach sufficient viremia to be infectious for ticks). In the tick population TBEV is transmitted by the trans-ovarial route and

also by highly effective trans-stadial transmission that occurs when nymphs and larvae are co-feeding on the same rodent host (Danielova et al., 2002). An infected tick remains infected for life.

Ticks become active at temperatures above 8°C and a relative humidity of 70-80%. These parameters are important for tick survival as well as for the seasonality of TBE. Hence, the forested areas of Europe and Asia provide ideal tick habitats (Gritsun *et al.*, 2003b). At least 11 tick species are capable of transmitting TBEV. However, only two species are important vectors: *Ixodes ricinus*, the common castorbean tick, acts as principal tick vector for TBEV-Eu in Central and Western Europe, Scandinavia, and in the European part of Russia. TBEV-Eu was isolated also from *Haemophysalis* species on the Korean peninsula (Ko *et al.*, 2010*). Ixodes persulcatus* is the main vector for TBEV-Sib (in Russia and Finland) and TBEV-Fe (in Russia and Far East Asa (including Chinaand Japan) (Gritsun *et al.*, 2003b). *Ixodes ovatus* is transmitting the virus only in Japan. TBEV is transferred to the host when the infected tick attaches itself to hair-covered portions of the human dermis and inserts its hypostoma into the punctured skin. As the saliva of the tick is anestetizing, the bite often passes unnoticed. Following the bite of an infected tick, the first TBEV replication usually occurs locally, in dermal cells. Further replication takes place in the regional lymph nodes; the virus has been found also in Langerhans cells. The affection of lymph nodes is followed by viraemia, during which many extraneural tissues including the reticulo-endothelial system are infected (Haglund and Gunther, 2003). At this stage, the virus also crosses the blood-brain barrier and invades the CNS where it causes inflammation, lysis and cellular dysfunction (Dumpis *et al.*, 1999; Maximova *et al.*, 2009). However, it is not fully understood by which mechanisms the acute febrile illness is driven into a severe or even fatal infection of the CNS (Toporkova *et al.*, 2008).

The clinical ssymptoms of TBE can be explained by affinity of TBEV to distinct regions of the CNS *(*Maximova *et al.*, 2009). In lethal cases, common findings include a diffuse lymphocytic infiltration of the meninges and signs of meningitis preferentially in the cerebellum. Also, edematous and hyperemic changes are found in almost all parts of the CNS; the lesions are localized in the grey matter and consist of lymphocytes and lymphocytic perivascular infiltrations as well as of an accumulation of glial cells. Changes in the cerebral cortex are restricted to the motor area with degeneration and necrosis of pyramidal cells (Kaiser, 2008). Characteristic neuropathologic changes in fatal human cases also include a

multinodular to patchy polioencephalomyelitis accentuated in the spinal cord, brain stem and cerebellum (Gelpi *et al.*, 2005; Gelpi *et al.*, 2006). Immunohistochemical visualization of TBEV demonstrates that the virus preferentially targets large neurons of the anterior horns, medulla oblongata, pons, dentata nucleus, Purkinje cells, and striatum (Gelpi *et al.*, 2005). There is an inverse topographical correlation between inflammatory change and immunohistochemical detectability of TBEV. Furthermore, a close association between cytotoxic CD8+ cells and cell membranes of TBEV-containing neurons has been demonstrated (Gelpi *et al.*, 2006).

2.6.1.2. Diagnosis: Clinically suspected cases of TBE can be confirmed only by laboratory techniques, as the clinical picture of TBE may be similar to that of other viral CNS affections. TBEV can be detected in blood and CSF during the first viremic phase of the disease using reverse transcription-polymerase chain reaction (RT-PCR) techniques. In practice, these techniques are of minor importance, since patients are mostly diagnosed in the second phase of the disease, following admission to hospital with neurologic symptoms. During this phase the virus has already been cleared from the blood (Holzmann, 2003).

During phase 2 of the disease, in parallel with the development of neurological symptoms, antibodies appear in serum and CSF, allowing etiological diagnosis to be confirmed by ELISA *(Holzmann, 2003).* Hemagglutination tests (HI- tests) are rarely used today due to lack of specificity. In the majority of TBE-patients with neurological symptoms, specific IgM and IgG antibodies can be detected in the first serum sample. In the CSF, specific antibodies occur more slowly, but within 10 days of onset of symptoms CSF-antibodies almost invariably become detectable. ELISA tests allowing rapid diagnosis of TBE are commercially available such as Immunozym FSME® Progen Biotechnik Heidelberg, Germany or Enzygnost® ELISA DADE Behring, Germany. In Russia, Vecto-TBE-IgM and Vecto-TBEIgG, VectorBest Russia, are available commercially.

2.6.1.3. Treatment and postexposure prophylaxis: No curative treatment exists for TBE. Treatment is restricted to symptomatic measures such as antifebrile and antiinflammatory medication (paracetamol, aspirin etc). Corticosteroids are not proven to be of use during the clinical course of TBE. Patients with severe neurologic manifestations have to be closely monitored.

2.6.2. Rocky Mountain spotted fever

Causative agent and distribution: Rocky Mountain spotted fever (RMSF), known over its vast range by many other names (tick fever, tick-borne typhus fever, black fever, black measles, New World spotted fever, North American tick typhus, Mexican spotted fever, Tobia fever, São Paulo fever), is the most frequently reported rickettsial disease in the United States. RMSF is the prototype of the spotted fever group of rickettsiae and is caused by *Rickettsia rickettsii*, a small (1-2µ long, 0.3µ wide), pleomorphic, obligately intracellular parasite that multiplies freely in the cytoplasm and occasionally in the nuclei of host cells. Though first described in 1872 from residents of the Bitterroot, Snake and Boise River valleys of Montana and Idaho, this disease is endemic throughout the continental United States, southern Canada, and western and central Mexico. Infection also occurs in Costa Rica, Panama, Colombia, Argentina and Brazil. In the United States, most cases are now acquired in the mid- and south Atlantic and south-central states, especially within a triangular area extending from southern New Jersey and the Carolinas westward to eastern Oklahoma (currently, North Carolina and Oklahoma report the highest incidence of RMSF). Most infections arise from exposure in rural or suburban environments, but urban foci also exist, as in some parks and vacant lots of New York City. Children are most commonly infected.

2.6.2.2. Symptoms: The incubation period, 2-5 days in severe infections and 3-14 in milder cases, is followed by abrupt moderate to high fever, malaise, deep muscle pain, severe frontal and occipital headaches, chills, conjunctival injection, and vomiting. The most characteristic and constant symptom is a maculopapular rash that appears from the second to the fifth day after the onset of other symptoms on the wrists, ankles and, less commonly, the back, later spreading to all parts of the body. Rickettsiae multiply in the epithelial linings of capillaries, smooth muscle of arterioles, and other blood vessels; therefore, death may occur at any time during the acute clinical phase (9-15 days after onset of symptoms) as a result of disseminated intravascular coagulation caused by widespread rickettsia-induced vasculitis. Sequelae in recovered patients may include cardiac abnormalities, loss of motor coordination, paralysis, and loss of fingers or toes due to gangrene. In the absence of antibiotic therapy, the case fatality rate is 15-20%, but even today 2-5% of patients die, chiefly because of misdiagnosis or failure to seek treatment.

2.6.2.3. Vectors and transmission: *Rickettsia rickettsii* is transmitted by the bite of an infected tick or, less often, by contamination of abraded skin with crushed tick tissues or

feces. The proportion of infected ticks in nature is generally small (1-5%), and most human cases stem from the bites of adult ticks in late spring and summer (nymphs occasionally transmit infection). In eastern North America, the principal vector is the American dog tick, *Dermacentor variabilis.* Pacific Coast populations of this species do not appear to play a major role in the transmission of *R. rickettsii*. *Dermacentor variabilis* is a common parasite of domestic dogs, as well as a variety of wild mammal species, including groundhogs. In western North America, the chief vector is the Rocky Mountain wood tick, *D. andersoni*, adults of which are often associated with large game animals and cattle. In 2003, cases of RMSF were reported from eastern Arizona, an area that previously had reported few cases of this disease. Subsequent investigations implicated *Rhipicephalus sanguineus* as the vector, with nymphs the likely vector to humans. In affected communities, high numbers of peridomestic *R. sanguineus* were associated with large, free-roaming stray dog populations. Significantly, *R. sanguineus* had long been known as an efficient vector of *R. rickettsii* to humans in Mexico. Other tick species that help maintain *R. rickettsii* in nature include *Haemaphysalis leporispalustris*, which feeds on birds and rabbits, and *Ixodes texanus*, which feeds on raccoons. *Amblyomma americanum* has been found infected with a spotted fever group rickettsia known as *R. amblyommii* that may produce a mild illness in humans, but this tick apparently does not play a significant role in the transmission of RMSF, although in Latin America *A. cajennense* and other *Amblyomma* species have been implicated as vectors of this disease.

2.6.2.4. Reservoirs: Ticks are long-term reservoirs, maintaining infection by transovarial and transstadial passage. Many other tick species help maintain RMSF in nature, especially *Haemaphysalis leporispalustris*, which transmits infection between rabbits throughout North America. *Rickettsia rickettsii* has been isolated from numerous small and medium-sized mammals, including members of the genera *Didelphis, Microtus, Peromyscus, Sigmodon, Spermophilus* and *Tamias*, but the period when rickettsiae are present in host blood is usually brief (< 8 days) and infections are generally subclinical. Even so, ticks feeding on infected animals may acquire rickettsiae, which then produce generalized infections in tick tissues. *Rickettsia*-infected immature ticks that feed on small mammals create a pool of infected mammalian hosts that serve as reservoirs for uninfected ticks. Given the limited home range of most small mammals, foci of hyperinfection may develop in the tick population.

2.6.3. Lyme disease

Lyme borreliosis was first recognized in 1975, when there was a cluster of cases of juvenile arthritis with an unusually high incidence of erythematous rash in the town of Old Lyme, Connecticut (Sonenshine DE., **1993)**.

2.6.3.1. Causative agent and distribution: Lyme disease, also known as Lyme borreliosis, erythema chronicum migrans, tick-borne meningopolyneuritis, and Bannwarth's syndrome, is the most common vector-borne infection of humans in the temperate Northern Hemisphere, including North America, Europe, and northern Asia. In the United States, Lyme disease was first recognized in the mid-1970s in the vicinity of Old Lyme, Connecticut; since then, thousands of confirmed cases have been reported annually, although over 90% of these have occurred along the Northeast coast (southern Maine to northern Virginia), in the upper Midwest (especially Wisconsin and Minnesota), and in northern California. The etiologic agent was not discovered until 1981, but cases of this disease have been described in the European medical literature since 1883(Gary P. *et al.*, 2006). Worldwide, the disease is caused by spirochete bacteria belonging to three pathogenic genomic groups, or genospecies: *Borrelia burgdorferi* sensu stricto (North America and Europe), *B. afzelii* (Europe and Asia), and *B. garinii* (Europe and Asia). There are also many minimally pathogenic or nonpathogenic genospecies belonging to the *Borrelia burgdorferi* sensu lato complex, such as *B. andersonii* and *B. bissettii* (United States), *B. lusitaniae*, *B. spielmanii*, and *B. valaisiana* (Europe), and *B. japonica*, *B. sinica*, *B. tanukii*, and *B. turdi* (Asia). Antigenic differences between these groups may explain some of the variation observed in principal clinical manifestations in infected persons in the United States versus those in other parts of the world. Human cases of a Lyme-like syndrome have also been reported from Mexico, South America, Australia, and the tropical portions of Africa and Asia (Philippe Parola and Didier Raoult, 2001).

2.6.3.2. Symptoms: Lyme disease has been called "the great imitator" because of its protean manifestations. Within 1-3 weeks of tickbite, a characteristic macular, erythematous, expanding lesion called erythema migrans (EM), formerly known as erythema chronicum migrans (ECM), develops at the site of tick attachment—but only in somewhat over 60% of cases. Most patients have just one EM, but 25-50% may experience multiple lesions; in either case, the rash gradually expands to a width of between several inches and a foot or more. Because an EM is flat and produces no sensation, it may not be noticed if it is located on a

part of the body that is difficult to see. Vague flu-like symptoms (low-grade fever, headache, fatigue, arthralgias, myalgias, and regional lymphadenopathy) may precede or accompany EM formation, but asymptomatic infections also occur (Gary P. *et al.*, 2006). Without antibiotic treatment, the EM and associated symptoms sometimes disappear in 3-4 weeks. Untreated patients may show no further signs of illness or they may develop late-stage disseminated Lyme disease from one to several months afterward. Disseminated disease is characterized by neurologic abnormalities (including the clinical picture of aseptic meningitis, encephalitis, chorea, cerebellar ataxia, cranial neuritis with facial palsy, motor or sensory radiculoneuritis and myelitis; 15-30% of patients), cardiac abnormalities (including atrioventricular block, acute myopericarditis or cardiomegaly; less than 10% of patients), and musculoskeletal complaints, especially arthritis of the large joints (about 60% of patients), but these manifestations apparently vary regionally with strains of the spirochete and may also be dependent on immunogenetic factors. In some patients, neurologic and/or arthritic symptoms may become chronic and debilitating (Philippe Parola and Didier Raoult, 2001).

2.6.3.3. Vectors and transmission: At least 40 species of ixodid ticks and two argasids have been found naturally infected with *B. burgdorferi* sensu lato spirochetes. However, all known primary vectors of Lyme disease are members of the tick genus *Ixodes*, subgenus *Ixodes*. In North America, these are the blacklegged tick, *I. scapularis*, in the East and upper Midwest (the northern form of *I. scapularis* was previously known as *I. dammini*), and the western blacklegged tick, *I. pacificus*, on the West Coast. In the Old World, the so-called castor bean or sheep tick, *I. ricinus*, extends across Western Europe into European Russia, where its range overlaps that of *I. persulcatus*, the principal vector in Eastern Europe and throughout Palearctic Asia, including Japan and Taiwan. Various other *Ixodes* that seldom bite humans or are not members of subgenus *Ixodes* may serve as enzootic or maintenance vectors of *B. burgdorferi*, e.g., *I. (I.) dentatus* in eastern North America, *I. (I.) jellisoni* and *I. (I.) spinipalpis* (including its junior subjective synonym *I. neotomae*) in western North America, and *I. (Partipalpiger) ovatus* in Japan. As well, certain ticks in other genera, such as the lone star tick, *Amblyomma americanum*, by virtue of their abundance, wide distribution and lack of host specificity, may occasionally become infected with and transmit *B. burgdorferi* to humans, even though experimental evidence indicates that they are inefficient or incompetent vectors. Spirochetes have also been detected in mosquitoes, deer flies and horse flies in both the northeastern United States and Europe, where there are anecdotal accounts of humans acquiring spirochetal infections from bites of blood-sucking insects (Gary P. *et al.*, 2006).

The role of insects in the transmission of *B. burgdorferi* appears to be negligible, but further investigation may be warranted. In North America, most cases of Lyme disease result from the bites of nymphal ticks, which are chiefly active during late spring and early summer and are often unnoticed because of their small size. In Asia, however, females of *I. persulcatus* are most often involved in transmitting borreliae to humans. In the eastern United States, people living in semi-forested suburban situations, with abundant white-tailed deer, are most at risk of infection from bites of nymphal *I. scapularis*, whereas in northern California only the relatively few *I. pacificus* nymphs that fed on infected dusky-footed woodrats as larvae are responsible for spirochete transmission to humans. It should be noted that simultaneous infections with *B. burgdorferi* and *Babesia microti* (the agent of babesiosis) and/or *Anaplasma phagocytophilum* (the agent of human granulocytic ehrlichiosis/anaplasmosis) have been observed in *I. scapularis*, and there is evidence that two or even three of these organisms may be transmitted during a single tick bite (Philippe Parola and Didier Raoult, 2001).

2.6.3.4. Reservoirs: Rodents, insectivores, other small mammals, and even some species of birds maintain spirochetes within their tissues for prolonged periods, if not for life, and readily infect larval ticks that feed on them. Infection is then passed transstadially to nymphs and adults. Less than 1% of unfed tick larvae have been found infected with *B. burgdorferi*, indicating that transovarial transmission is of little consequence in the maintenance of Lyme disease in nature.

In eastern North America, competent reservoirs of *B. burgdorferi* sensu lato include the white-footed mouse (*Peromyscus leucopus*), eastern chipmunk (*Tamias striatus*), short-tailed shrew (*Blarina brevicauda*) and masked shrew (*Sorex cinereus*), while in the West the dusky-footed woodrat (*Neotoma fuscipes*), California kangaroo rat (*Dipodomys californicus*), western gray squirrel (*Sciurus griseus*) and deer mice (*Peromyscus* spp.) are commonly infected. White-tailed deer (*Odocoileus virginianus*) of eastern North America, which are important hosts of adult *I. scapularis*, and western fence lizards (*Sceloporus occidentalis*) of the far West, which are the chief hosts of *I. pacificus* immatures in many biotopes, do not serve as reservoirs, but these and other vertebrates are important maintenance hosts for tick populations (Philippe Parola and Didier Raoult, 2001).

3. MAINTENANCE AND TRANSMISSION OF PATHOGENS AMONG TICKS AND HOSTS

The role of ticks and their hosts in the maintenance and transmission of pathogens cannot be determined solely by field studies, which commonly report only the detection of a sequence of nucleic acid in a number of specimens of ticks. Complementary laboratory studies should be designed to capture the essentials of the role played by each element of the system. These laboratory tests would confirm the hypotheses built upon field studies. To qualify as a true vector of a pathogen, the tick must (i) feed on infectious vertebrates (ii) acquire the pathogen during the blood meal (iii) maintain the pathogen through one or more trans-stadial molts and (iv) transmit the pathogen to previously unexposed hosts while feeding again (Kahl *et al*., 2002). Assigning vector status to a tick, based solely on the detection of nucleic acids, or reservoir status to a host species, based solely on serologic studies, is not acceptable. Detection of nucleic acids of pathogens in a tick or host indicates that it possesses carrier status (see below for definitions), and detection of antibodies in host serum merely indicates that an animal has been exposed to the pathogen. Whether or not pathogen transmission takes place from tick to host or from host to tick must be addressed experimentally in the laboratory.

After a blood meal, pathogens remain in the gut contents with the ingested blood. Each pathogen has different mechanisms of passing through the gut membrane. Laboratory studies have demonstrated that some pathogens might enter the gut cell by expressing molecules that enable the recognition of specific receptors in the cell membrane. This might be the case of Anaplasma spp., which expresses the MSP1a protein, an adhesin that is believed to binds to specific portions of tick gut cells (de la Fuente et al., 2001). In the case of the spirochaetes of the complex Borrelia burgdorferi s.l., OspA, OspB, and OspD are expressed by B. burgdorferi residing in the gut of unfed ticks, suggesting they promote the spirochete persistence in ticks between blood meals (Schwan *et al*., 1995). OspA promotes the attachment of B. burgdorferi to the tick protein TROSPA, present on tick gut epithelial cells (Pal *et al.,* 2004). OspB also has an essential role in the adherence of B. burgdorferi to the tick gut (Neelakanta *et al*., 2007). During transmission to the mammalian host, when the infected tick begins to feed and the spirochetes in the midgut begin to multiply rapidly, most spirochetes cease expressing OspA on their surfaces. Simultaneous with the disappearance of OspA, the spirochete population in the midgut begins to express an OspC and migrate to the

salivary gland of the tick. Upregulation of OspC begins during the first day of feeding and peaks 48 h after attachment (Schwan and Piesman, 2000).

Tick-transmitted viruses employ other mechanisms of dispersion. The TBE virus is internalized into gut cells by endosomes that ticks produce to digest ingested blood. After viruses are internalized into cells via endocytic pathways, they must escape from the endosome to the cytosol. Enveloped viruses, like TBEV, utilize membrane fusion to cross the membrane barrier and reach the cytoplasm (Mudhakir and Harashima, 2009). In this particular example, the virus used the class II fusion protein that dissociates in the low pH of the tick gut cell to mediate fusion with the endosomal membrane and release into the cytoplasm (Mudhakir and Harashima, 2009). The receptors and mode of entry of CCHFV into tick cells are currently unknown (Simon *et al*., 2009).

Two events in the tick life cycle are of epidemiological significance in the maintenance of transmitted pathogens. Because ticks feed once at each stage, the pathogen must to be able to persist in each new stage after molt, to pass into a new cohort of vertebrates by means of an infective bite. This is called trans-stadial passage (i.e. from stage to stage). It involves the acquisition of a pathogen by a tick while feeding on an infective reservoir host, the subsequent molt to the next active stage of the tick, and the further persistence of the pathogen in the newly molted tick. Another key feature in the life cycle of some tick-transmitted pathogens is trans-ovarial (vertical) passage, i.e. the persistence of a pathogen acquired by a tick and transferred to the cohort of eggs by the engorged female (Kahl *et al*., 2002). This is commonly regarded as a way of massive dissemination of the pathogen throughout the next generation of ticks and to a naive generation of hosts. Both mechanisms of persistence of pathogens depend on the rates at which they are passed onto the next stage of the tick, which is regulated by species-specific mechanisms (Hartemink *et al*., 2008). In the case of tick-transmitted viruses, transmission rates from the infected engorged females to eggs are negligible.

The interactions between the elements of any tick–host– pathogen system are thus key features to understand pathogen prevalence in questing ticks. The evaluation of such interactions is a necessary preliminary step in risk assessment, and it is therefore necessary to summarize the framework of relevant terminology proposed by Kahl *et al.* (2002) that was constructed to address major pitfalls in the research of the relationships among ticks, hosts and pathogens.

When hosts are fed on by infected vector ticks, they may be exposed to the pathogen, and may then become either carriers or non-carriers. As the term implies, carrier hosts are those carrying the pathogen. However, a carrier host is not necessarily infective to ticks and therefore the terms non-reservoir and reservoir must be used to define infectivity status. The former are incapable of transmitting the infection to uninfected ticks. Reservoir capacity of the hosts describes the absolute contribution made by a particular reservoir host species to the natural prevalence of infection by a given pathogen within a certain site. Such reservoir capacity may be different at different sites, because of the faunal composition of the community of hosts and their relative contribution to the epidemiological events in the transmission of the pathogen. Host infectivity denotes the efficiency with which the host transmits the infection to ticks feeding on it. Reservoir capacity is dependent upon the infectivity of the host for feeding ticks and the duration of the infective period (Kahl *et al*., 2002), which is highly variable for the different ticktransmitted pathogens, from a few days to months. By feeding on reservoir hosts, ticks are exposed to pathogens and they may become either non-carrier or carrier ticks. The former are unable to acquire the pathogen, even if they feed on viremic hosts, and they therefore have no importance in the epidemiology of such pathogens. Carrier ticks may be vectors or non-vectors after feeding on infected reservoirs.

The above definitions imply that the relationships among ticks, hosts and pathogens are quantitative instead of being simply qualitative. The first is the vector capacity, which quantitatively defines the potential of the tick to transmit a pathogen. The second is called the vector competence, which only defines the adequacy of the tick to be a vector of a pathogen. This means that such relationships have wide ranges of variability even if necessary contacts between competent tick vectors and reservoir hosts are produced on regular spatial and temporal scales. The rules governing the transmission of a pathogen may be even more complex if several species of reservoirs and ticks overlap in the same territory, each with different abilities to carry and transmit the pathogen, that may or may not overlap their periods of activity, be present at different densities, or have different sensitivity to the actions of the environmental or biotic factors (Agustin Estrada-Pena *et al.*, 2014).

4. IMPACT ON LIVESTOCK

Some other economic estimates of the cost of ticks to the livestock industry only concern certain diseases and particular regions and, although we do quote a few of them, we are under

no illusion as to their accuracy. Mukhebi *et al*. (1999) estimated that the national annual loss due to cowdriosis in Zimbabwe could attain 5.6 million US$, while a questionnaire study in 1991 by Meltzer, Perry & Donachie (1996) arrived at a figure of about 6.5 million US$ in cattle alone on large-scale commercial farms in Zimbabwe, most of this amount being the cost of dipping. Recently, Minjauw &McLeod (2003) have made a great effort at producing figures, tables and maps on the importance, the distribution, the numbers of animals at risk and the cost of the various diseases in eastern and southern Africa, also to some extent in sub-Saharan Africa as a whole, and of tropical theileriosis in India. They estimate the annual cost of tropical theileriosis in India at 384.3 million US$, of East Coast fever in the smallholder dairy system in Kenya and Tanzania at 54.4 million US$ and 4.41 million, respectively, in the traditional system in Kenya and Tanzania at 34.1 and 129.5 million, respectively. An older figure is 168 million US$ annually as the cost of Theileria parva in eastern, central and southern Africa (Mukhebi, Perry & Kruska, 1992). F. Jongejan and G. Uilenberg, 2004.

Without acting as vectors of disease, ticks can be harmful to livestock and of great economic importance simply because of their direct effects. Much depends on the circumstances, on the tick species involved, on the local climatic conditions (favourable or unfavourable to the ticks) and, to a large extent, on the susceptibility to tick infestation of the livestock in the region. Resistance to tick infestation, or at least the capability of developing an effective immunological response to infestation, is genetically determined. This is particularly important where one-host Boophilus spp. are implicated (Bekker *et al.,* 2001).

Uncontrolled Boophilus infestations in climatically favourable conditions severely affect European cattle, but have little effect on zebu cattle. Such infestations per se, even when no diseases are transmitted by the ticks, can limit productivity of European Bos Taurus cattle to the extent that a choice has to be made between simply renouncing the use of such cattle, or applying intensive and expensive chemical tick control, which usually leads rapidly to resistance against the acaricides used. For example, on the island of New Caledonia the tick Boophilus microplus has been introduced without the diseases it transmits elsewhere, namely babesioses and anaplasmosis (F. Jongejan and G. Uilenberg, 2004). However, highly favourable climatic conditions throughout the year and a large population of susceptible European beef cattle breeds have made it necessary to develop intensive acaricidal treatment programmes, which have led to an enormous problem of widespread multi-acaricide resistance, with resistance having successively developed to the various groups of chemicals

used (Bianchi, Barre´ & Messad, 2003). Hence, it may be far more economical to make more use of Bos indicus breeds, pure or cross-bred, as has been done in many instances in Australia, where zebu cattle have proved to be much more resistant to tick infestation than European cattle.

The damage caused by tick bites also diminishes the value of skins and hides for the manufacture of leather; even ticks with a short hypostome, such as Boophilus, may be important in this respect when present in large numbers on susceptible cattle. Ticks with long and massive hypostomes, such as Amblyomma and to some extent Hyalomma spp., may induce abscesses because of secondary bacterial infections. In this way Amblyomma spp. may cause loss of teats or lameness, depending on the site of attachment. In turn loss of teats will lead to increased calf mortality (Bekker *et al.*, 2001).

The saliva of certain tick species contains paralyzing toxins; examples of this are D. andersoni in Canada and the USA that can cause death even in adult cattle, I. rubicundus that induces a severe form of paralysis in sheep in southern Africa, and I. holocyclus in Australia, that usually feeds on bandicoots, but can also feed on domestic animals, tropical bats (Pteropus spp.) or humans, and is considered a very important tick with respect to tick toxicosis (Gothe, 1999). Another form of tick toxicosis is 'sweating sickness', a generalised eczema-like condition of calves and other species of livestock in Africa, induced by the saliva of certain lines of Hyalomma truncatum. A detailed account of tick salivary toxins is given in the chapter by Mans, Gothe & Neitz in this Supplement. There is also at least one example of a tickassociated disease which is not transmitted by ticks.

This is severe bovine dermatophilosis induced by the presence of adult Amblyomma variegatum which, in certain regions of the tropics, may prevent upgrading of local cattle with highly susceptible imported breeds (Ambrose, Lloyd & Maillard, 1999). The most important diseases transmitted by ticks, particularly in domestic ruminants, are babesioses, theilerioses, anaplasmoses and cowdriosis (see chapters in this Supplement on babesiosis by Bock *et al.*, theileriosis by Bishop et al. and anaplasmosis by Kocan *et al.*). Recovered animals retain the infection and remain immune for long periods, sometimes for life. In general, where such diseases are endemic, the local livestock has been exposed to a long process of natural selection and has, to various degrees, become tolerant, but not refractory to the infection. Furthermore, young animals are generally more tolerant than adults. The combination of natural tolerance and age-associated tolerance may result in an endemically

stable situation which, at best, means that the prevalence of infection may be 100% but that the disease is not clinically apparent. In other cases, endemic stability may be less perfect and there may be some mortality following primo-infections in young animals, but older stock that have survived the infection are immune. Obviously tick numbers are important as endemic stability can only be attained where adequate numbers of infected ticks are present to infect all animals while they still possess their ageassociated tolerance. For example, in regions where cowdriosis is endemic the situation may be endemically stable in local cattle, but not in local breeds of small ruminants, probably because fewer Amblyomma (at least adult ticks) feed on them. Climatic conditions are among the main factors influencing tick numbers and endemic stability is thus not attained in areas which are climatically marginal for the vector tick species (F. Jongejan and G. Uilenberg, 2004).

Exotic livestock, introduced from disease-free regions in which they have not been exposed to natural selection, are far more susceptible to most tick-borne diseases and even though mortality in young stock of such breeds is less than in adults, endemic stability can often not be achieved. This is certainly true for cattle and theilerioses (at least tropical theileriosis, Theileria annulata, and East Coast fever caused by T. parva), babesiosis caused by Babesia bovis, and cowdriosis (Ehrlichia (Cowdria) ruminantium). However, there may be little difference in susceptibility to anaplasmosis (Anaplasma marginale) and babesiosis caused by B. bigemina between local and exotic cattle. Particularly theilerioses and cowdriosis may make it impossible, or at least uneconomical, to keep exotic ruminant breeds unless management and veterinary infrastructures are adequate. The same considerations apply to indigenous breeds of animals that have never been exposed to a particular pathogen. For instance, translocations of indigenous goats from the north of Mozambique to the south into Amblyomma hebraeum-infested areas were highly risky because of cowdriosis (Bekker *et al*., 2001).

Anyone involved with livestock in tropical and subtropical areas of the world recognises that ticks and tick-borne diseases are important, but there are few if any reliable global figures of the costs involved. Young, Groocock & Kariuki (1988) considered the control of ticks and tick-borne diseases as the most important health and management problem inAfrica, presenting a problem of equal or greater magnitude than tsetse fly and trypanosomosis. Various estimates of effects are tentative, sometimes rather different, and moreover depend on variables, including annual climatic variations, fluctuating exchange rates and inflation.

The global costs of tick and tick-borne disease control has been estimated at US$ 7 milliard (=7r109) by McCosker (1979). This amount, still sometimes quoted, is certainly hugely underestimated because it was based on Australian figures taking only the tick B. microplus and its role as a vector into account, multiplied by the world cattle population exposed to ticks and tick-borne diseases (F. Jongejan and G. Uilenberg, 2004).

5. TREAT TICK BITES

5.1. Removing ticks from the skin

Patients may present with attached ticks, and removing these ticks may not be easy. It is best to use blunt, rounded forceps, and a magnifying glass may be helpful if immature ticks are found. The forceps are used to grasp the mouthparts of the ticks as close as possible to the skin, and the tick is then pulled upward, perpendicular to the skin, with a continuous and steady action (Hillyard PD., 1996**)**. Specific instruments are commercially available and may be particularly useful for removing nymphal stages. Usually any mouthparts of the ticks retained in the skin are eliminated uneventfully by the body. Shave incisions close to the skin may also be used. After removal of the ticks, a disinfectant should be applied to the bite site and the tick stored at 2207C in case the patient subsequently develops a disease that requires the tick for detection or isolation of the causative agent. Other methods of removing ticks, such as using the fingers instead of forceps or using lighted cigarettes, petroleum jelly, or suntan oil to kill the ticks in situ, should be avoided, because they may increase the risk of regurgitation by the tick and, consequently, the transmission of infectious agents (Hillyard PD., 1996**)**.

5.2. Antibiotic prophylaxis after tick bites

Most tick bites are uncomplicated and result only in benign cutaneous inflammatory reactions that may be pruritic for a few days. Sometimes a granuloma may develop, supposedly as a result of mouthparts being retained at the feeding site. As described above, the bacterial agents transmitted by ticks are susceptible to antibiotics, particularly doxycycline, which may be used prophylactically after a tick bite to reduce the risk of disease transmission. However, there are no data to indicate that antimicrobial prophylaxis is beneficial for tick-bitten patient to prevent Lyme disease, tularemia, and rickettsioses, and its efficacy in an animal model of Rocky Mountain spotted fever has not been demonstrated (Walker D., 1995**)**. Testing for the presence of antibodies against tickborne bacteria (borreliae, rickettsiae, *F. tularensis, C. burnetii*, ehrlichiae) at presentation and 3–6 weeks later, and treating it only if there is

clinical or serological evidence of infection is not recommended because of the low sensitivity, low positive predictive value, and the cost of the tests. Finally, clinicians have to observe the patient and treat only if a disease occurs. It must be kept in mind that the risk of transmission of a bacterial disease by a tick increases with the duration of attachment and generally requires 24–48 h. The degree of tick engorgement or the time since tick exposure and discovery of the tick may be used to establish the likely duration of attachment and the risk of disease transmission (Philippe Parola and Didier Raoult, 2001).

5.3. PREVENTION AND CONTROL OF TICKS AND TICK BORNE DISEASES

Tick control and TBD prevention: current practices the control of ticks is largely based on the use of chemicals on animals and in the environment. Several active ingredients with killing and/or repellent effects are com-mercially available for use on companion animals and livestock. These active ingredients might be prescribed in different formulations, such as sprays, soaps, shampoos, powders, impregnated collars, dip solutions, pour-on, and spot-on applications. Products commonly used to control ticks on companion animals are often formulated as spot-on applications, impregnated collars, and sprays (Otranto, D. and Wall, R., 2008), whereas pour-on and dip solutions are frequently used to control ticks infesting livestock (Walker, A.R., 2011). Moreover, new strategies for the control of tick on wildlife (e.g., white-tailed deer) have also been developed and studies indicate that they might be useful in reducing the level of environ-mental infestation by some tick species (e.g., A. ameri-canum and the blacklegged tick Ixodes scapularis), thus contributing to the control of certain TBDs, such as Lyme borreliosis (Schulze, T.L. *et al*., 2009). Alternative tick control strategies have been proposed, including use of anti-tick vaccines and of biological con-trol agents, such as entomopathogenic fungi (Samish, M. et al., 2008). Indeed, non-chemical approaches might be rather useful in some situations, particularly to reduce the level ofenvironmental infestation. For example, pasture man- agement and rotational grazing can help to reduce the level of tick infestation on livestock (Walker, A.R., 2011), although these approaches are not always feasible due to land availabil- ity constraints and lack of compliance by farmers. Heavy tick infestations on humans are less common; usually patients are presented with one or a few ticks attached. The treatment of choice for tick infestation on humans is the prompt removal of attached ticks using a curved forceps or fine point tweezers (Piesman, J. and Eisen, L., 2008). Ticks have barbed mouthparts and secrete a cement-like substance with saliva that allows them to firmly attach to the skin of the host. Care should be exercised to avoid crushing the tick's body, so as to prevent the contact of potentially

infectious tick fluids with skin. It is important to wash the bite wound area with antibacterial soap and water after tick removal, and the disinfection of bite wounds with ordinary antiseptics is also recommended (Dantas-Torres F., 2007). Furthermore, patients should be advised to seek medical attention if skin rash or flu-like symptoms are recorded some days or weeks after tick removal. The best preventive measure against TBDs is to stay away from ticks. For obvious reasons, this is not feasible for individuals who live in or visit tick-infested environments. In this case, the use of protective clothing should be advised as well as the use of tick repellents, which might be available for use on clothing and/or skin (Bissinger, B.W. and Roe, R.M., 2010). The prevention of TBDs can also be achieved by vaccination of individuals at risk, although only a few effective vaccines are currently available for the prevention of TBDs either in animals or in humans. Veterinarians are provided with vaccines against anaplasmosis, babesiosis, and Lymeborreliosis (Suarez, C.E. and Noh, S., 2011), but these vaccines are for species that only infect animals. A vaccine is commercially available for the prevention of tick-borne encephalitis in Europe and eastern Russia, although this has not been enough to reduce the global number of human cases of the disease (Piesman, J. and Eisen, L., 2008). A vaccine against Lyme borreliosis was approved in 1999 by the US Food and Drug Administration, but was withdrawn from the market in 2002. Because the transmission of certain tick-borne patho-gens (e.g., Borrelia burgdorferi) is not immediate (Piesman, J. and Eisen, L., 2008), the prompt removal of all attached ticks might greatly reduce the risk of infection and this should be strongly emphasized by physicians and veterinarians.

Reducing and controlling tick populations is difficult (Lane, R.S. *et al*. 2004). Habitat modifications, including vegetation management by cutting, burning, and herbicide treatment, and drainage of wet areas are one strategy for tick control, but their effects are often shortlived and they can cause severe ecological damage. In some areas, host exclusion or depopulation may result in a reduction in the density of ticks, but this is mostly impractical and is also not ecologically sound. The use of organophosphates or pyrethroids, which may be combined with pheromones to control ticks, may cause environmental contamination and toxicity for animals and humans, even when applied only to selected habitats. Acaricides, however, can be applied directly to wild or domestic hosts to kill attached ticks and disrupt tick feeding. Charrel, R.N., (2007).

Biological control methods for ticks are also available, and these include the promotion of natural predators (including beetles, spiders, and ants), parasites (insects, mites, and nematodes), and bacterial pathogens of ticks; the mass release of males sterilized by irradiation or hybridization; and the immunization of hosts against ticks (Weckesser, S., 2010). At the present time, tick control is best based on the concept of integrated pest management, in which different control methods are adapted to one area or against one tick species with due consideration to their environmental effects.

5.4. Prevention of tick bites

Tick bites are best prevented by people avoiding tick-infested areas. When this is not possible, tick bites may be prevented by the wearing of long trousers that are tucked into boots. At the present time, the best method to avoid tick bites has 2 components: application of a topical deet (*N*,*N*-diethyl-*m*-toluamide) repellent to exposed skin and treatment of clothing with permethrin. This system is currently used by the US Army and by numerous armies throughout the world to protect their soldiers (Schreck CE., *et al.*, 1986). It yields protection results at nearly 100% and is also effective against biting flies, gnats, chiggers, fleas, and mosquitoes.

Tick repellents that contain deet are the most effective and can be applied to the skin (Hillyard PD., 1996**)**. The optimal concentration ranges from 15% to 33%, which allows for high performance and a high margin of safety. The performance drops off when concentrations of 135% are used. Although subsequent uses may cause irritation in some people, there are no data to suggest long-term dangers of deet products when they are used in accordance with label directions (Qiu H, Jun HW, McCall JW., 1998). These products are available in a wide variety of formulas (such as lotions and sprays) that can address specific needs of users, including individual travelers, persons working or recreating in the outdoors, and even young children, who should use less concentrated products (<7%). Some of them provide up to 12 h of protection from 1 application, and long-acting formulations are being developed (Salafsky B., *et al*., 2000).

However, the application of repellents to exposed skin provides little protection against ticks, because they can crawl underneath clothing and bite untreated portions of the body. Thus, treating clothing with permethrin (a pyrethroid that kills ticks on contact) is recommended to complement the treated skin. It is not licensed for direct application to the skin. This chemical is virtually nontoxic to humans and can be applied to clothing in a pressurized spray

formulation. Major brands include Duranon, Sawyers, and Permanone. It can be used with any age group. Furthermore, it remains effective for up several weeks and through weekly washings. Nets can be treated with permethrin for additional protection while sleeping. Finally, checking clothing regularly while in tick-infested areas is highly recommended to back up the few hours of protection provided by the insect repellents. It is also recommended that the entire body be carefully screened for parasites by campers while they are staying in and after the leave infested areas. Any tick found should be removed immediately (Philippe Parola and Didier Raoult, 2001).

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