



Invited Review

Tick-borne infections of animals and humans: a common ground



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ABSTRACT

A wide variety of pathogens is transmitted from ticks to vertebrates including viruses, bacteria, protozoa and helminths, of which most have a life cycle that requires passage through the vertebrate host. Tick-borne infections of humans, farm and companion animals are essentially associated with wildlife animal reservoirs. While some flying insect-borne diseases of humans such as malaria, filariasis and Kala Azar caused by *Leishmania donovani* target people as their main host, major tick-borne infections 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. While new tick-borne infectious agents are frequently recognised, emerging agents of human tick-borne infections were probably circulating among wildlife animal and tick populations long before being recognised as clinical causes of human disease as has been shown for *Borrelia burgdorferi* sensu lato. Co-infection with more than one tick-borne infection is common and can enhance pathogenic processes and augment disease severity as found in *B. burgdorferi* and *Anaplasma phagocytophilum* co-infection. The role of wild animal reservoirs in co-infection of human hosts appears to be central, further linking human and animal tick-borne infections. Although transmission of most tick-borne infections is through the tick saliva, additional routes of transmission, shown mostly in animals, include infection by oral uptake of infected ticks, by carnivorous, animal bites and transplacentally. Additionally, artificial infection via blood transfusion is a growing threat in both human and veterinary medicine. Due to the close association between human and animal tick-borne infections, control programs for these diseases require integration of data from veterinary and human reporting systems, surveillance in wildlife and tick populations, and combined teams of experts from several scientific disciplines such as entomology, epidemiology, medicine, public health and veterinary medicine.

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1. 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)) (de la Fuente, 2003) 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 (Jongejan and Uilenberg, 2004; Guglielmine 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 (Jongejan and Uilenberg, 2004; Dantas-Torres et al., 2012).

This review aims to discuss some topics related to human and animal tick-borne infections (TBIs), with emphasis on the relationship between these TBIs. Because some tick-borne pathogens do not necessarily cause disease in all of their vertebrate hosts, the term TBI is preferred over tick-borne disease in the context of this review. Since human TBIs are overwhelmingly zoonotic and involve an animal host, there is a broad-based common ground for TBIs of humans and animals. Furthermore, the ground is also the surface to which ticks drop after engorging blood from a host, often after acquiring infection, and it is where ticks embark from,

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to attach and bite a new host, whether an animal or a human, potentially further transmitting infection.

2. 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 (US; 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). 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 donovani* and 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 (Fig. 1).

3. Increase in prevalence and geographic spread of tick-borne infections

Is the global prevalence of TBIs increasing or are improvements in the ability to detect infection using sensitive and specific new techniques, and an increased awareness, responsible for more detection of disease? In this respect, a distinction needs to be made between increased reporting of TBIs and a true increase in disease

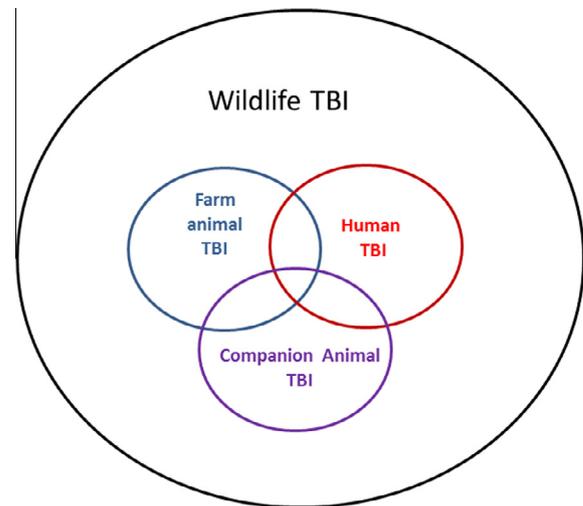


Fig. 1. Tick-borne infections of humans, farm and companion animals may overlap, infecting hosts of more than one of these categories, however they are associated with wildlife reservoirs.

incidence. Undoubtedly, increases in both true incidence and in reporting have taken place in the last decades (Hofhuis et al., 2006; Dahlgren et al., 2011). An increase in reporting stems from better communication between laboratories and diagnostic facilities using means of rapid communication such as the electronic reporting systems, electronic mail, and the internet. Furthermore, more stringent regulation on reporting of TBIs by governmental agencies and regulatory organisations such as the US Centers for Disease Control and Prevention's (CDC) National Notifiable Diseases Surveillance System (NNDSS, <http://wwwn.cdc.gov/nndss/>) and the European Centre for Disease Prevention and Control's (ECDC) European Surveillance Network Emerging and Vector-borne Diseases Program (http://www.ecdc.europa.eu/en/activities/diseaseprogrammes/emerging_and_vector_borne_diseases/Pages/index.aspx), and updated disease case definitions (<http://www.cdc.gov/nndss/script/casedefHistory.aspx>) have improved reporting.

The development of molecular diagnostic tools such as conventional PCR, realtime PCR, the reverse line blot, DNA sequencing and other methods have not only enhanced the capacity of diagnostic laboratories to detect the presence of infection, but have also expanded the capability of detecting new, previously unknown, pathogens and distinguishing between species and strains of microorganisms, which was difficult and sometimes impossible prior to the advent of molecular biological techniques. Furthermore, these molecular capabilities have become accessible and affordable to diagnostic laboratories in the last decade, and not merely restricted to research facilities.

Examples of increasing true incidence of TBIs include emergence or outbreaks of diseases such as the epidemic of Crimean–Congo haemorrhagic fever in northeastern Anatolia in Turkey during 2002–2009. This outbreak was suspected to arise due to the formation of favourable habitats for the Crimean–Congo haemorrhagic fever virus host tick, *Hyalomma marginatum*, by changes in the use of land for agriculture (Maltezou and Papa, 2010; Hubálek and Rudolf, 2012). A second example of a new TBI outbreak is the emergence of Rocky Mountain Spotted Fever in eastern Arizona, USA associated with the identification of the capability of the tick *Rhipicephalus sanguineus* to serve as a vector of this infection (Demma et al., 2006).

Several factors contribute to the change in geographic ranges of TBIs. These mostly relate to changes in the range of tick vectors or the capability of ticks present in a region to vector a new pathogen

introduced into the area. Ticks cannot fly or move long distances by themselves and, therefore, their transfer from one location to another depends mostly on movement of hosts including birds which can fly long distances (Mathers et al., 2011; Hasle, 2013), migrating wild animal species such as jackals, animals introduced into new areas by humans such as farm animals imported into areas where they were not present before, rodents travelling accidentally with ships or trucks, or imported pet animals (Pietzsch et al., 2006). Changes in wildlife populations can contribute to the spread of TBIs, for instance the spread of Lyme disease has been attributed to the increase in the deer population in the eastern US (Barbour and Fish, 1993).

Environmental factors are associated with the geographic ranges of ticks of medical and veterinary importance (Estrada-Peña et al., 2013). Climate change may also facilitate migration of vertebrate tick hosts, allowing dispersal of ticks and pathogens into new territories. Prediction of the results of climate change have included assessments of the potential distribution and spread of various tick species under different climate scenarios (Estrada-Peña et al., 2012). Mathematical models have been devised to estimate the changes in the geographic ranges of ticks and their fitness to transmit pathogens. A model which estimates the basic reproduction number which is an index of the rate of reproduction of a species or strain under certain ecological conditions, considers the number of tick vectors, number of susceptible reservoir hosts, pathogen transmission coefficients which include transtadial and transovarial transmission in the tick and vertebrate host, to tick transmission, vector daily survival probability, development duration for ticks, daily rate of loss of infectivity of host, host daily mortality rate, probability that a tick would feed on an individual of a host species, and the tick birth rate (Randolph, 1998; Ogden et al., 2013).

Transmission of TBIs can also occur by contaminated blood transfusions and needles. *Babesia* of different species have been shown to be transmitted by blood transfusion in both humans and dogs (Stegeman et al., 2003; Lobo et al., 2013). Such artificial transmission may result in spread of TBIs to new areas, if competent tick vectors and reservoir hosts are found in those areas.

To conclude the evaluation of the increase in prevalence of TBIs, it is most likely that both an increase in the spread of TBIs and an improved capability of detection are accountable for the global rise in reporting of TBIs.

4. Emerging or newly recognised tick-borne pathogens

Emerging pathogens include infectious agents that were previously unrecognised and have been identified and associated with a new disease or an illness with a previously unknown aetiology; organisms that have been described in other regions and imported into areas where they were previously unknown, or agents that were constantly present in the affected area at a low level or in a different host and due to some change have become more widely spread in the population under concern (Harrus and Baneth, 2005). Important tick-borne zoonoses such as Lyme disease, human granulocytic anaplasmosis (HGA) caused by *A. phagocytophilum*, human monocytic ehrlichiosis (HME) caused by *Ehrlichia chaffeensis*, and human babesiosis caused by *B. microti* were all described in the US during the second half of the 20th century. Although these TBIs emerged in the eastern US, they were subsequently also detected in other countries and continents. Lyme disease caused by *B. burgdorferi* s.l. was initially documented in Lyme, Connecticut, US in 1975, and has since then been described in more than 70 countries on five continents (Wu et al., 2013). Similarly, HGA, HME and *B. microti* babesiosis were initially reported in humans in 1994 (Chen et al., 1994), 1991 (Anderson et al., 1991)

and 1970 (Western et al., 1970), respectively. The causative agents of these diseases have probably been circulating for centuries among rodent and tick populations in North America and possibly in other continents, as shown for the borrelial agents of Lyme disease found in rodent and tick museum specimens in the US and Europe (Marshall et al., 1994; Matuschka et al., 1996; Hubbard et al., 1998).

'*Candidatus* Neoehrlichia mikurensis' is an intracellular bacterium member of the Anaplasmataceae family which causes severe disease with fever and septicemia in humans (Fehr et al., 2010; von Loewenich et al., 2010). It was first isolated and described from wild rats (*Rattus norvegicus*) and *Ixodes ovatus* ticks in Japan (Kawahara et al., 2004) and in the decade since its first report, it was also reported in other areas of Asia, Europe and Africa, and has been associated with *Ixodes ricinus* ticks in Europe and other *Ixodes* spp. elsewhere (Li et al., 2012; Kamani et al., 2013). '*Ca.* Neoehrlichia mikurensis' is an example of an "emerging" TBI that has been known only for a decade and appears to be dispersed in multiple regions. Similarly to other TBI agents, it is likely to have been circulating among wildlife animals and ticks long before it emerged as a recognised clinical cause of human disease.

5. Do ticks transmit infections transmitted by other arthropod vectors?

Ticks have been implicated as potential vectors of zoonotic pathogens transmitted regularly by other types of arthropod vectors. A recent scientific debate has been focused on *Leishmania infantum*, the causative agent of zoonotic canine and human visceral leishmaniasis, which is transmitted naturally by phlebotomine sand flies and whose epidemiology often overlaps with canine TBIs such as *Ehrlichia canis* and *Babesia vogeli*, transmitted by *R. sanguineus* (Dantas-Torres, 2011). *Leishmania infantum* DNA has been reported in ticks surveyed in leishmaniasis endemic areas (Trotta et al., 2012) and has also been demonstrated in engorged female ticks, their eggs and arising larvae (Dantas-Torres et al., 2011). Furthermore, hamsters experimentally inoculated i.p. or orally with macerated ticks that have fed on *L. infantum*-infected dogs have acquired infection (Coutinho et al., 2005). However, it is unlikely that ticks constitute an epidemiologically important vector for *L. infantum*. *Leishmania* are di-phasic parasites that develop from the amastigote form in which they are found in vertebrate host macrophages, to the promastigote, which attaches to specific receptors in the sand fly gut and multiplies in large quantities before being injected into the dog or human skin during the female sand fly bite. Although amastigotes may also transmit infection if injected directly into blood vessels, as in blood transfusions, the tick is unlikely to be a frequent "mechanical transmitter" which transfers infection without the transition from amastigote to promastigote (Otranto and Dantas-Torres, 2010; Dantas-Torres, 2011).

Cats are the main reservoir for *Bartonella henselae*, the bacterial causative agent of cat scratch disease, bacillary angiomatosis, ocular infection and endocarditis in humans. *Ctenocephalides felis* fleas have been shown to be responsible for the transmission of *B. henselae* between cats (Chomel et al., 1996). *Bartonella henselae* DNA, as well as other *Bartonella* spp. DNA has been frequently detected in tick surveys (Mietze et al., 2011; Bonnet et al., 2013) and has also been shown to be experimentally infectious to *I. ricinus* ticks feeding on blood on membrane, to be passed transstadially, reach the tick's salivary glands and excreted back through membranes upon a second blood meal (Cotté et al., 2008). However, despite this evidence, the question of transmission of *B. henselae* by ticks under natural conditions and its epidemiological importance remains uncertain (Chomel and Kasten, 2010; Telford and Wormser, 2010).

In summary, although tick transmission of common zoonotic pathogens biologically vectored by arthropods other than ticks may be possible under certain circumstances, it is questionable whether these pathogens have developed the adaptations to be transmitted successfully. Proof of transmission with an epidemiological importance requires both experimental evaluation of transfer as well as strong evidence for its frequent occurrence under natural settings.

6. Co-infections

Concurrent infection by several TBIs is common and frequently detected and managed in clinical situations in human and veterinary medicine. The pathogenesis and pathological consequences of co-infection are often not well understood and involve multiple mechanisms related to transmission, host and cell invasion, immune responses, pathogen multiplication and dissemination mechanisms. Co-infection can enhance pathogenic processes, parasite transmission and augment disease severity (Belongia, 2002; Rojas et al., 2014). Transmission and introduction into the host of several pathogenic agents elicits more diverse host responses which may conflict or override each other, allowing the pathogens to synergistically colonise the infected host more successfully. *Borrelia burgdorferi* spirochetes can spread to the skin, joints, heart, eyes and the nervous system, causing a multitude of clinical manifestations in humans (Grab et al., 2007). Co-infection that results in simultaneous clinical manifestations of Lyme disease and HGA has been documented in humans and studies have provided evidence that co-infections contribute to more severe morbidity and a longer duration of clinical manifestations than reported with either disease alone (Krause et al., 2002; Steere et al., 2003). Similarly, experimental infections in rodent models have shown that co-infection is associated with higher bacterial loads, prolonged persistence and more severe disease (Thomas et al., 2001; Holden et al., 2005). The synergistic effects of co-infection with the *Ixodes*-transmitted *A. phagocytophilum* and *B. burgdorferi* have been studied and their mechanisms elucidated (Grab et al., 2007). *Anaplasma phagocytophilum*-infected neutrophils release endothelial cell-derived matrix metalloproteases, cytokines and chemokines which increase vascular permeability and facilitate trans-endothelial cell migration of *B. burgdorferi* and its invasion into tissues including traversing the blood–brain barrier (Nyarko et al., 2006). *Anaplasma phagocytophilum*–*B. burgdorferi* co-infection has also been shown to enhance chemokine, cytokine and endothelial cell-derived matrix metalloprotease expression by human brain microvascular endothelial cells, thus potentially increasing vascular permeability and augmenting the inflammatory response in affected brain tissues (Grab et al., 2007). These studies have shown that tick-borne pathogens, which commonly also affect animals including dogs, have a complex synergistic relationship that can provide insights into the reasons for the severe and sometimes fatal disease reported in cases of co-infection.

Co-infections may be transmitted by vector ticks simultaneously during the same blood meal or be caused by one infection preceding the other. The introduction of a new infection to the host may facilitate the dissemination of a latent infection already present, or the presence of a previous infection may allow the establishment of new infection which would otherwise be eliminated by immune defence mechanisms. The natural reservoir hosts of many TBIs transmitted by *Ixodes* spp. ticks, including *B. burgdorferi*, *A. phagocytophilum* and *B. microti*, are rodents which are often co-infected with more than one infectious agent and may transfer infections to nymph stage ticks (Johnson et al., 2011). Co-infected ticks may infect humans or domestic animals such as dogs during their next blood meal and transmit two or more TBIs at the same time. Alternatively,

hosts may be co-infected by bites of separate ticks and at different times. Co-infection can rarely be associated with the actual ticks which transmitted it and it is difficult to learn on which animal host did the particular transmitter tick feed. However, the role of local wild animal reservoirs in co-infection of human hosts appears to be central, further linking human TBIs and animals.

7. Non-salivary transmission of tick-borne infections

Although the majority of TBIs are transmitted via the tick saliva during the course of the blood meal, there are some pathogens of veterinary importance which are transmitted naturally by other mechanisms. *Hepatozoon* spp. are protozoa that belong to the Apicomplexa and infect vertebrates by oral ingestion of an arthropod host containing infective sporozoites. Two different species of *Hepatozoon* infect dogs, *Hepatozoon canis*, prevalent in warm and temperate regions all over the world and associated with hemolympoid tissue infection, and *Hepatozoon americanum* which causes myositis and is prevalent in the southern US. The main vector of *H. canis* is the tick *R. sanguineus* whereas the Gulf Coast tick *Amblyomma maculatum* is the vector of *H. americanum* (Baneth, 2011). Both of these *Hepatozoon* spp. infect dogs that orally uptake and ingest ticks harbouring mature sporozoites. In addition, *H. americanum* is transmitted by predation on small mammals and ingestion of tissue forms in mammalian host tissues whereas *H. canis* has been shown to be transmitted transplacentally from the dam to its pups (Johnson et al., 2009a,b).

Babesia gibsoni is a small form *Babesia* sp. of dogs endemic in southeastern Asia. Although *B. gibsoni* may infect any dog, a high prevalence of infection is found in fighting dog breeds such as the Pit Bull Terrier and the Tosa (Miyama et al., 2005; Lee et al., 2009). In addition to being transmitted by tick bites similar to all other *Babesia* spp., it is also transferred directly from dog to dog (Irwin, 2009). Tick bites appear to be the most common mode of *B. gibsoni* transmission in southeastern Asia, whereas in contrast, *B. gibsoni* infection in the US (Birkenheuer et al., 2003, 2005; Yeagley et al., 2009) and Australia (Jefferies et al., 2007) is found mostly in Pit Bull Terriers and studies from these countries have indicated that direct dog to dog transmission through bites is likely to be the main mode of transmission in those countries (Birkenheuer et al., 2005; Jefferies et al., 2007; Yeagley et al., 2009).

These two examples of pathogen transmission not via tick saliva indicate that alternative routes of TBI transmission are possible, and it would be of interest to observe whether such mechanisms are revealed in the future also for TBIs involving humans.

8. Conclusions

Human TBIs cannot be described without studying and understanding their relationship to animal hosts and reservoirs. Unlike some of the major human vector-borne diseases associated with flying insect vectors, where infection could be independent of association with animals, TBIs are zoonoses and control efforts must consider this when programs are developed to limit or eradicate them. Integration of veterinary and human reporting systems, surveillance in wildlife and tick populations, and combined teams of experts from several scientific disciplines such as entomology, epidemiology, medicine, public health and veterinary medicine are needed for the formulation of regulations and guidelines for the prevention of TBIs (Dantas-Torres et al., 2012).

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