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Invited Review

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

Gad Baneth *

School of Veterinary Medicine, Hebrew University, P.O. Box 12, Rehovot 76100, Israel

A R T I C L E I N F O

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A B S T R A C T

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 carnivorism, 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.

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; 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 (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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* Tel.: +972 39688557; fax: +972 39604079.
E-mail address: gad.baneth@mail.huji.ac.il

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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 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://wwwn.cdc.gov/nndss/script/casedefHistory.aspx) have improved reporting.

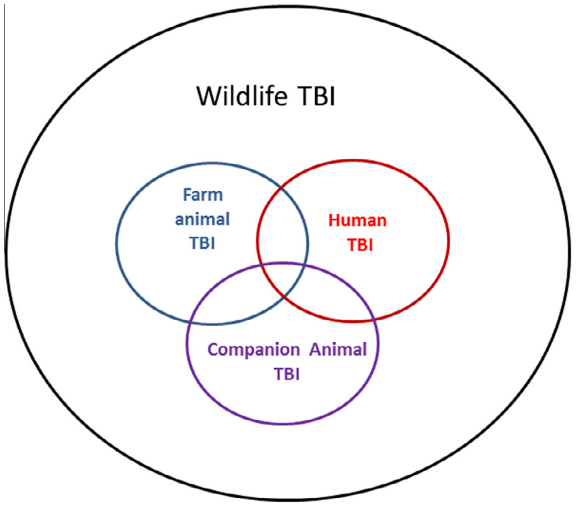

Fig. 1. Tick-borne infections of humans, farm and companion animals may overlap, infecting hosts of more than one of these categories, however they are associated with wildlife reservoirs.

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

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