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Review

Natural history of Zoonotic *Babesia*: Role of wildlife reservoirs



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ABSTRACT

Babesiosis is an emerging zoonotic disease on all inhabited continents and various wildlife species are the principal reservoir hosts for zoonotic *Babesia* species. The primary vectors of *Babesia* are Ixodid ticks, with the majority of zoonotic species being transmitted by species in the genus *Ixodes*. Species of *Babesia* vary in their infectivity, virulence and pathogenicity for people. Various factors (e.g., increased interactions between people and the environment, increased immunosuppression, changes in landscape and climate, and shifts in host and vector species abundance and community structures) have led to an increase in tick-borne diseases in people, including babesiosis. Furthermore, because babesiosis is now a reportable disease in several states in the United States, and it is the most common blood transfusion-associated parasite, recognized infections are expected to increase. Because of the zoonotic nature of these parasites, it is essential that we understand the natural history (especially reservoirs and vectors) so that appropriate control and prevention measures can be implemented. Considerable work has been conducted on the ecology of *Babesia microti* and *Babesia divergens*, the two most common causes of babesiosis in the United States and Europe, respectively. However, unfortunately, for many of the zoonotic *Babesia* species, the reservoir(s) and/or tick vector(s) are unknown. We review the current knowledge regarding the ecology of *Babesia* among their reservoir and tick hosts with an emphasis of the role on wildlife as reservoirs. We hope to encourage the molecular characterization of *Babesia* from potential reservoirs and vectors as well from people. These data are necessary so that informed decisions can be made regarding potential vectors and the potential role of wildlife in the ecology of a novel *Babesia* when it is detected in a human patient.

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1. Introduction

Babesia are tick-borne parasites in the Phylum Apicomplexa. Two closely related genera, *Theileria* and *Cytauxzoon*, are also tick-borne, and collectively these three genera are referred to as the piroplasms. Many species of piroplasms are significant pathogens and the Apicomplexa also includes numerous other pathogens of veterinary and medical importance including *Plasmodium* spp. (causative agents of malaria), *Cryptosporidium* spp., *Eimeria* spp., *Isospora* spp., and *Toxoplasma gondii*. Several reviews have focused on the clinical aspects of babesiosis in people and domestic animals, the pathogenesis of infection, the phylogenetic relationships of the piroplasms, piroplasm genomics, and their diagnosis and treatment, thus we will review the current knowledge regarding the ecology of *Babesia* among their reservoir and tick hosts with an emphasis of the role of wildlife as reservoirs (Florin-Christensen and Schnittger, 2009; Lau, 2009; Rosenblatt, 2009; Ayoob et al., 2010; Gray et al., 2010; Suarez and Noh, 2011; Lack et al., 2012; Lobo et al., 2012; Matijatko et al., 2012; Mosqueda et al., 2012; Schnittger et al., 2012).

Historically, *Babesia* were classified by two methods, (1) the relative size and shape of trophozoites in the erythrocytes and the number of merozoites and (2) the host of origin. Based on size, there were two groups (small and large *Babesia*), but this division is not associated with phylogenetic relatedness. Identification based on host origin was based on the assumption that these parasites are host-specific, which we now know is not the case for many species. Molecular characterization of multiple gene targets indicates that the piroplasms should be divided into at least five or six groups: one that includes small *Babesia* from various wild rodents, felids, canids, and mesomammals (called archaeopiroplasmids or *Microti* group); one that includes parasites from cervids, dogs, and people (called the western piroplasms, Duncani group or prototheilerids); one that includes primarily canine, bovine, and cervine species (babesids); another that includes primarily bovine, equine, and ovine species (unguilibabesids); and a final group that includes the *Theileria* and *Cytauxzoon* spp. (theilerids) (Criado-Fornelio et al., 2003). Some analyses suggest that the babesids and unguilibabesids are one monophyletic group and that the theilerids represent up to three separate groups. Regardless of divisions, numerous studies support that the organisms currently included in the genus *Babesia* are polyphyletic, and that new genera should be erected to clarify the phylogenetic relationships of the piroplasms (Criado-Fornelio et al., 2003; Lack et al., 2012; Schnittger et al., 2012). Interestingly, zoonotic species are found in all of the groups with *Babesia* spp. but no *Theileria* or *Cytauxzoon* spp. have been identified as zoonotic infections (Fig. 1).

Even at the species level, there is considerable confusion regarding the true number of species. For example, *Babesia microti*, the predominant cause of babesiosis in the United States and a rare cause of disease in people from Europe and Asia, has a holarctic distribution in rodents and insectivores, but recent molecular studies indicate that this species is a species complex that includes at least four 'named' types (US, Munich, Kobe, and Hobetsu (referred to as Otsu in some publications)) and an unknown number of other strains (Goethert et al., 2006; Tsuji et al., 2006; Nakajima et al., 2009). It has been suggested that *B. microti* and other *B. microti*-like species (some erroneously referred to as *Theileria annae*) reported

from some rodents and mesomammals (e.g. raccoons, foxes, skunks), *Babesia rodhaini* from rodents, and *Babesia leo* and *Babesia felis* from African felids should collectively be included in a new genus but more research is needed before a change is finalized (Uilenberg, 2006; Nakajima et al., 2009).

Babesiosis in people can range from asymptomatic infections to severe disease and death. Severity of illness depends on many factors, such as *Babesia* species and immunocompetence of the patient. Infections with *B. microti*, the most common species in North America, can result in asymptomatic infection to severe disease which sometimes results in death. Asymptomatic patients are typically diagnosed on routine testing that either identifies the organism in blood smears or during serologic testing (as conducted on some blood donors). It is estimated that about a third of patients remain asymptomatic (Krause et al., 2003). Most patients with *B. microti* infections develop mild to moderate flu-like illnesses characterized by malaise and fatigue that progress to include the following symptoms: rash, fever, chills, sweats, headache, arthralgia, myalgia, anorexia, cough, or nausea. Rarely, mild splenomegaly or hepatomegaly may be noted. Clinical symptoms may persist for weeks to months, but rarely for more than a year. A small percentage of patients (~5–10%), especially those that are immunosuppressed or splenectomized, may develop severe disease from *B. microti* infection. These patients may present with jaundice, or diffuse ecchymoses or petechiae (Rosner et al., 1984).

The most common zoonotic species in Europe, *Babesia divergens*, requires rapid diagnosis as clinical disease is often severe. Generally the parasite has an incubation period of one to three weeks during which the patients may begin to describe malaise and discomfort. Onset of serious illness is sudden, with hemoglobinuria as the most common sign (Telford and Spielman, 1993). Clinical signs of *B. divergens* infection are easily confused with those of malaria including jaundice, non-periodic fever, sweats, shaking, headache, vomiting, diarrhea, etc. (Gorenflot et al., 1998). It is estimated that most cases of *B. divergens* infection resulted in major organ failure and death within four to seven days after the onset of hemoglobinuria (Gorenflot et al., 1987; Kjemtrup and Conrad, 2000). However, prompt therapy with blood transfusion and ventilation has reduced the *B. divergens* mortality rate (Zintl et al., 2003). Recent reviews have discussed the clinical course of infection, diagnosis, and treatment option for babesiosis in detail (Gray et al., 2010; Mosqueda et al., 2012).

2. Natural history of zoonotic *Babesia*

The *Babesia* are one of the most common haemoparasites in the world, second only to trypanosomes, and have a wide host range, including hundreds of mammal species and a limited number of bird species. *Babesia* parasites are maintained in a complex system of tick vectors and animal reservoirs. People are not a natural host for any species of *Babesia* but can serve as accidental hosts for numerous species (Fig. 2, Table 1).

The complete life cycle for a large percentage of *Babesia* species is unknown, but ticks in the family Ixodidae are the only known vectors. One possible exception is *Ornithodoros erraticus*, an argasid soft tick, which may transmit *Babesia meri*, a parasite of sand rats (*Psammomys obesus*) in Africa (Gunders, 1977; René et al., 2012; Ros-García et al., 2011; Schwint et al., 2008; Razmi and Nouroozi,

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