



Review Article

Monitoring human tick-borne disease risk and tick bite exposure in Europe: Available tools and promising future methods



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ABSTRACT

Ticks are the main vector for infectious disease pathogens in both humans and animals, and tick-borne diseases are currently spreading throughout Europe. Various surveillance methods have been developed to estimate the burden and risk of tick-borne diseases and host exposure to tick bites. The ultimate aims of these approaches are to determine the risk level of a tick-borne disease in a given area, determine its health priority, identify the at-risk population and propose specific countermeasures or complementary studies as needed. The purpose of this review is to present the current methods for monitoring the circulation of tick-borne diseases and to highlight the use of salivary antigens as original and recently developed serological tools that could be useful for tick bite risk assessment and could improve the current surveillance methods.

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## Background

Ticks are currently the second most important vectors for pathogens that cause diseases in humans and animals after mosquitoes (Beugnet and Marie, 2009; Raoult and Parola, 2007). These obligate hematophagous arthropods parasitize every class of vertebrate, with the exception of fishes, in almost every region of the world and can transmit pathogens, including bacteria, viruses and protozoa, to mammalian hosts during blood meals (Parola and Raoult, 2001). The emergence of new tick-borne diseases (TBDs) and the re-emergence of existing ones are public health concerns for all continents (Hubalek and Rudolf, 2012; Oteo and Portillo, 2012; Socolovschi et al., 2009). Some TBDs, such as tick-borne encephalitis (TBE), are considered public health priorities, and there are benefits from specific prevention programs such as vaccination, education and public information (Beugnet and Marie, 2009; Raoult and Parola, 2007). For the efficient transmission of tick-borne pathogens in a geographic area, the following five elements should be present and should interact: the pathogen, a natural reservoir, a natural or accidental host, a vector and a suitable biotope for vector development. Modifying even one element acting on the complex host-vector-pathogen equilibrium can change the epidemiology of TBDs in an area. For example, the introduction of a new pathogen or the mutational adaptation of an old pathogen to its vector or host (Simon et al., 2008); the introduction of a new vector; the proliferation of suitable hosts (e.g., deer for *Ixodes ricinus*) (Medlock et al., 2013); human behavior modification (e.g., mushroom collection, forestry activities); changing landscapes in wild areas; climatic changes; and tick control programs can all modify the epidemiology of TBDs in an area (Daniel et al., 2009; Estrada-Pena et al., 2010, 2012a; Godfrey and Randolph, 2011; Halos et al., 2010; Laurenson et al., 2007; Stefanoff et al., 2012). Thus, an alteration in the aforementioned factors can lead to either the (re-)emergence or the reduction of TBDs in an area. Additionally, weather and climatic changes have a direct impact on the geographic distribution and behavior of tick species (Parola et al., 2008). Recent studies have reported the colonization of new areas by tick species such as *Rhipicephalus sanguineus*, *Dermacentor reticulatus*, and *I. ricinus*, the main vectors for the causative agents of Mediterranean spotted fever (MSF), scalp eschar and neck lymphadenopathy after a tick bite (SENLAT), and Lyme borreliosis (LB) plus TBE, respectively (Allegue et al., 2009; Rizzoli et al., 2011; Rovey and Raoult, 2008).

Various surveillance methods have been developed to assess TBD risk. The most current methods focus on the following: (i) human health (i.e., the human approach: disease incidence and human exposure in general or specific populations), (ii) animal health (i.e., the animal approach: disease, natural infection and animal exposure), (iii) vector characteristics (i.e., the entomological approach: tick distribution and infection), and (iv) modeling/forecasting (i.e., the determination of suitable areas for tick-borne disease transmission, including climatic, geographic, economic, human, animal and vector data). The final aim of all of these approaches is to determine the level of TBD risk in an area, determine its health priority, identify the risk for populations and propose, if necessary, specific countermeasures or complementary studies. The purpose of this review is to present the current methods used to monitor TBD risk and to highlight novel tools that are

useful for assessing a host's tick bite and could improve or complete the current standard surveillance methods.

## Tick-borne diseases in Europe

Despite improvements in prevention, TBD cases are still being identified in new locations within endemic regions and in European countries where human cases of TBD had not been previously identified (Beugnet and Marie, 2009; Dobler, 2010; Foley and Nieto, 2010; Hubalek and Rudolf, 2012; Raoult and Parola, 2007; Ruzek et al., 2010; Socolovschi et al., 2009). Various tick genera have been found in Europe, and the most prevalent ones with medical or veterinary importance have been described, such as *Ixodes* spp., *Rhipicephalus* spp., *Dermacentor* spp., *Hyalomma* spp., and *Haemaphysalis* spp. (Heyman et al., 2010). These ticks are vectors for several causative agents of TBD, among which the most frequently encountered are LB, MSF, TBE, Crimean-Congo hemorrhagic fever (CCHF), SENLAT and other rickettsioses (Bitam and Raoult, 2009). The diversity and rapid evolution in the distribution and density of tick species and their representative TBDs in Europe have caused many difficulties for the optimal management of TBD risk. Thus, monitoring TBD risk is essential throughout Europe.

LB is a multisystem inflammatory disorder caused by spirochetes of *Borrelia burgdorferi* sensu lato (s.l.). At least eight species of the *Borrelia burgdorferi* sensu lato (s.l.) group (*B. afzelii*, *B. bavariensis*, *B. burgdorferi* sensu stricto (s.s.), *B. garinii*, *B. miyamotoi*, *B. recurrentis*, *B. spielmanii*, and *B. valaisiana*), which are mainly transmitted by *I. ricinus*, are currently known to occur in Europe (Hulinska et al., 2009; Platonov et al., 2011; Rebaudet and Parola, 2006; Ryffel et al., 1999; Stanek and Reiter, 2011; Stanek et al., 2012). Despite improvements in its prevention, diagnosis and treatment, LB is still the most common ixodid tick-borne human disease in the world (Rizzoli et al., 2011). Because LB cases have been encountered in previously disease-free areas and because an increasing number of severe forms have been reported in different parts of Europe, an increase in the LB burden in Europe is expected in the coming years (Bartosik et al., 2011; Hubalek, 2009; Palecek et al., 2010).

MSF is also known as "boutonneuse fever", is endemic to the Mediterranean area, including southern Europe and northern Africa (Parola et al., 2009b). The causative agent of this disease is *Rickettsia conorii conorii*, which is transmitted by the brown dog tick *R. sanguineus* (Parola and Raoult, 2001). Recently, MSF cases have been reported in new locations within the endemic region and in other previously disease-free central and northern European countries. Moreover, an increasing incidence within endemic regions has been noted (Parola et al., 2013), and fatal and severe cases are most often reported (Amaro et al., 2003; Papa et al., 2010).

TBE is caused by a *Flavivirus* (TBE virus) that was first isolated in Russia in 1938 (Chumakov and Seitlenok, 1940). This virus is transmitted by ticks of the *Ixodes* genus, primarily *I. ricinus*, in western and central Europe (Hubalek and Rudolf, 2012). Every year, several thousand cases of TBE are recorded in the Czech Republic, Slovenia, Estonia, Lithuania and Latvia (Hubalek and Rudolf, 2012), and the burden of the disease is increasing due to extension of the affected areas and the circulation of TBE viruses (Briggs et al., 2011; Fomsgaard et al., 2009; Kupca et al., 2010; Zimmermann, 2005). There has been much speculation that climate change is a

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