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UPDATE ON TICK-BORNE BACTERIAL DISEASES IN EUROPE

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Summary:

In recent years, the prevalence of tick-borne bacterial diseases has significantly increased in European countries. The emergence and reemergence of these illnesses are attributed to changes in the environment and human behavior. Several diseases are caused by bacteria initially isolated from ticks and subsequently considered pathogenic. It is necessary to consider the bacteria found in arthropods capable of biting humans as potential human pathogens. Here we review the clinical and epidemiological data on bacterial tick-borne diseases in European countries. We focus on the epidemiological and clinical aspects of tick-borne rickettsioses and give an overview of other tick-borne illnesses as well as the emergence and re-emergence of these diseases.

KEY WORDS : Europe, ticks, Rickettsia, Tularemia, Borrelia, Anaplasma, Bartonella, Q fever.

Résumé : ACTUALITÉ SUR LES MALADIES BACTÉRIENNES TRANSMISES PAR PIQÛRE DE TIQUE EN EUROPE

Au cours des dernières années, la prédominance des maladies bactériennes transmises par piqûre de tique a sensiblement augmentée dans les pays européens. L'émergence et la réémergence de ces maladies sont attribuées aux changements de l'environnement et du comportement humain. Des bactéries initialement isolées dans des tiques ont provoqué plusieurs maladies et sont considérées maintenant comme pathogènes. Il faudrait considérer toutes les bactéries trouvées dans les arthropodes capables de piquer l'homme comme des bactéries potentiellement pathogènes. Ici, nous examinons les données cliniques et épidémiologiques des pays européens sur les rickettsioses transmises par piqûre de tique, de l'ehrlichiose, la tularémie, la maladie de Lyme, la fièvre Q, la bartonellose, de l'apparition et de la réémergence de ces maladies.

MOTS CLÉS : *Europe, tiques, rickettsies, tularémie, Borrelia, Anaplasma, Bartonella, fièvre Q.*

In European countries, Ixodid ticks are considered the main vector of human infectious diseases. Ticks transmit a number of different pathogens that cause disease in humans, including bacteria, viruses, and protozoa (Parola & Raoult, 2001b). These obligate hematophagous arthropods parasitize every class of vertebrates in almost every region of the world and occasionally bite humans (Parola & Raoult, 2001b). All species of ticks (Acaris: Ixodida) are grouped into three families: Argasidae (186 species), Ixodidae (692 species) and Nuttalliellidae (monotypic) (Nava *et al.*, 2009). Each tick species lives in optimal environmental conditions that define particular biotopes and more or less strictly adhered to a specific host; therefore, the geographic distribution of ticks is usually restricted to specific areas (small or large), which explains why tick-borne diseases are often regional (Parola & Raoult, 2001b). Tick-borne diseases are emerging zoonoses with a re-emergence of "old" diseases. The history of tick-borne illnesses is one of constant renewal, with discoveries of new pathogens associated with descriptions of novel diseases.

There are several factors in the emergence of tick-borne diseases, and among these may be climate change (Parola & Raoult, 2001a). It has been suggested that global warming has led to a northward expansion of several tick species, including *Ixodes ricinus*, the vector of Lyme disease in Europe, and *Rhipicephalus sanguineus*, the vector of Mediterranean spotted fever (MSF) (Suss *et al.*, 2008; Estrada-Pena & Venzal, 2007). However, the impact of climate change on tick-borne diseases remains a topic of much debate in the scientific literature (Suss *et al.*, 2008; Randolph, 2004). In this review, we describe the bacterial tick-borne diseases in European countries, focusing on the epidemiological and clinical aspects of tick-borne rickettsioses, with overviews of other tick-borne diseases. For diagnostic strategies, we refer to recent reviews (Brouqui *et al.*, 2004; Dana, 2009).

TICK-BORNE RICKETTSIOSES

Tick-borne rickettsioses are caused by obligate intracellular bacteria belonging to the spotted fever group (SFG) of the genus *Rickettsia* within

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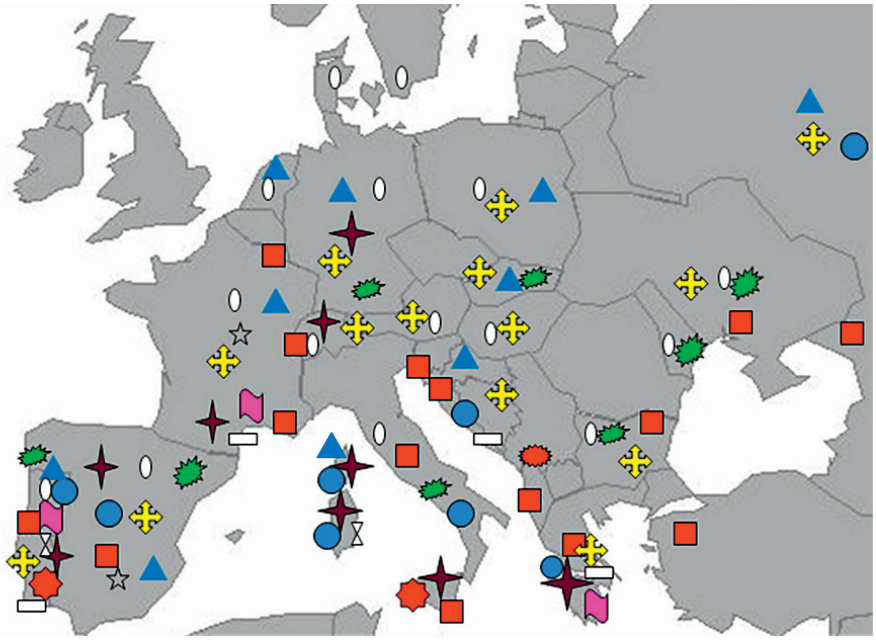
the family *Rickettsiaceae* in the order *Rickettsiales* (Parola *et al.*, 2005; Merhej *et al.*, 2009). These bacteria infect and colonize the organs of ticks, particularly the salivary glands and ovaries of adult females. This enables some species of ticks to transmit rickettsiae to vertebrate hosts during feeding and from one tick generation to the next (Socolovschi *et al.*, 2009c). The rickettsial field underwent a significant progression because of technological advances in molecular methods. In European countries, nine pathogenic for human rickettsiae can be detected in ticks in nature (one presumptively associated with a human illness), some rickettsiae are isolated from or detected only in ticks, and there are also several imported rickettsioses (Figs 1, 2).

Rickettsia conorii conorii

Rickettsia conorii conorii is the agent of Mediterranean spotted fever (MSF), which is endemic in northern Africa and southern Europe. *Rhipicephalus sanguineus*, the brown dog tick, is the vector and the probable reservoir of the disease (Parola *et al.*, 2009b; Socolovschi *et al.*, 2009a). MSF cases are still being identified in new locations within this region, and have recently been described in Turkey, Bulgaria, Ukraine, Slovenia, Croatia, Albania, Malta and Georgia (Rovery & Raoult, 2008; Tonna *et al.*, 2006). In Italy, around 1,000 cases are reported each year (Parola *et al.*, 2005). The annual MSF incidence rate in southern France is approximately 50 cases per year per 100,000 persons. In Portugal, the incidence rate from 1989-2000 was $9.8/10^5$ inhabitants, the highest rate among the Mediterranean countries (de Sousa *et al.*, 2003). In Bulgaria, a very important peak of MSF was noted in 1995 (236 cases), reaching 716 cases in 1997. A few cases have been reported sporadically across northern and central Europe, including Belgium, Switzerland, the Netherlands, Germany and the northern region of France, where *Rh. sanguineus* ticks have been imported (Parola *et al.*, 2005; Peter *et al.*, 1984; Rovery & Raoult, 2008; Dobler & Wolfel, 2009).

In Europe, most MSF cases are encountered in late spring and summer, when the tick vectors are most active. In the south of France, most cases are diagnosed during July and August. This is probably linked to the



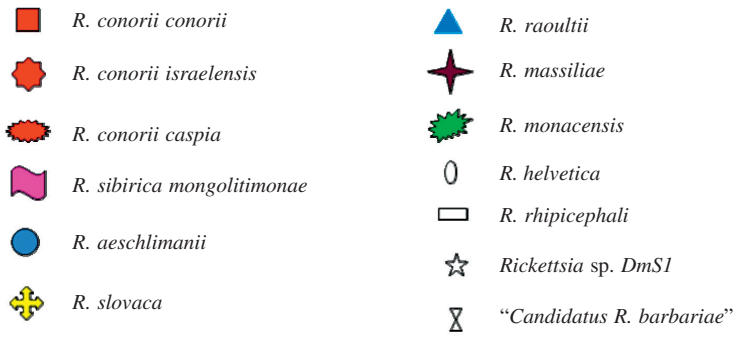


Fig. 1. – Tick-borne rickettsiae in Europe. Colored symbols indicate pathogenic rickettsiae. White symbols indicate rickettsiae of possible pathogenicity and rickettsiae of unknown pathogenicity.

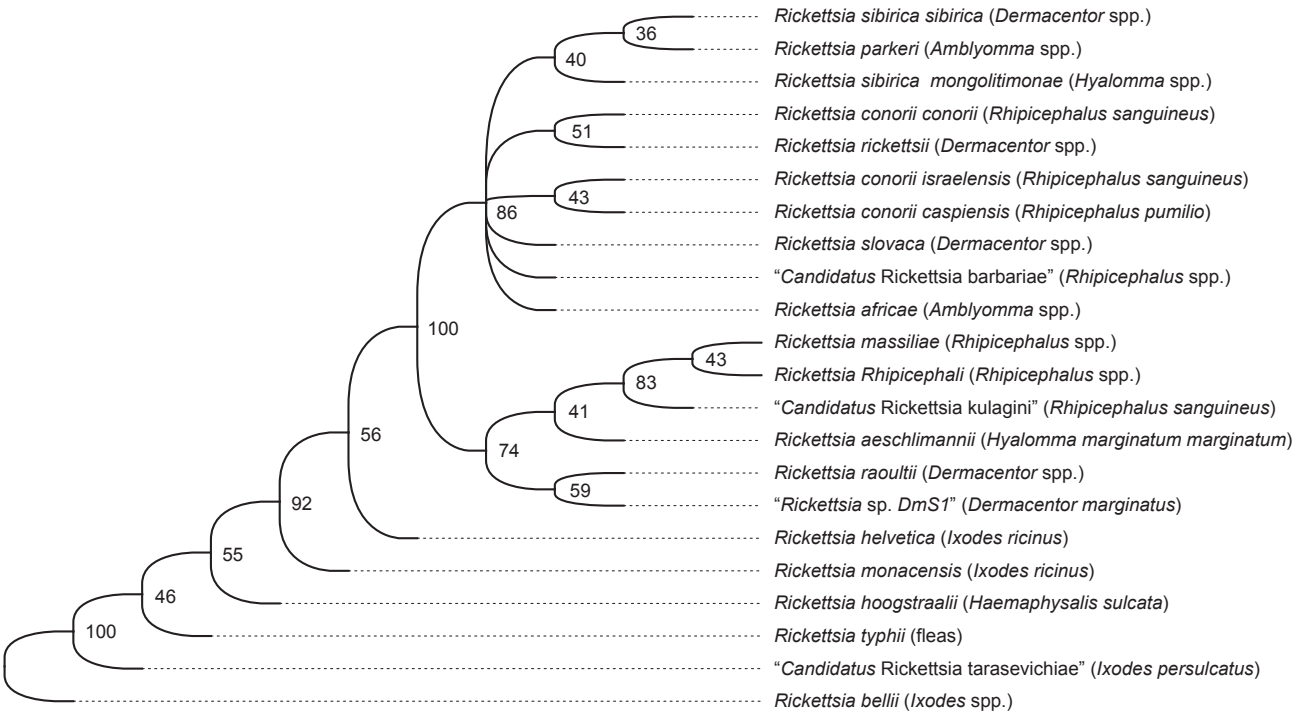


Fig. 2. – Phylogenetic trees for members of the genus Rickettsia of derived from *glt*A sequence data with Tamura-Nei genetic distance method (Tick vector of each rickettsia).

increased aggressiveness and propensity of *Rh. sanguineus* to bite hosts in warmer conditions. During the French heat wave in August 2003, which was the hottest summer of the preceding 50 years, 22 *Rh. sanguineus* (including specimens infected by *R. conorii* and *R. massiliae)* were found attached to a homeless person who died of MSF (Hemmersbach-Miller *et al.*, 2004). Recently, the investigation of a cluster of rickettsioses in southern France during the exceptionally warm months of April and May 2007 was reported. Patients suffered from severe *R. conorii* and *R. massiliae* infections, and the authors found that this group of cases resulted from the unexpected proliferation and aggressive behavior of *Rh. sanguineus* ticks infected with these rickettsiae. The authors also demonstrated experimentally that *Rh. sanguineus* readily bites humans when exposed to higher temperatures (Parola *et al.*, 2008). In Croatia, more than 80 % of cases occur between July and September, with a peak in August (Punda-Polic *et al.*, 2003). During the 1970s, an increase in MSF cases was observed in France, Italy, Spain, and Portugal. The increase was correlated with higher temperatures and lower rainfall in Spain and with a decrease in the number of days of frost during the preceding year in France (Parola *et al.*, 2008; Parola *et al.*, 2005). In Portugal, the number of positive cases of MSF doubled in 2004-2005, and the authors speculated that it was probably associated with climate change, particularly low precipitation (de Sousa *et al.*, 2006). In addition, an undetected reservoir-vector system may have emerged (Parola *et al.*, 2009b). The increased incidence of MSF could also be explained by the use of improved diagnostic methods and by new interest in several countries after reconsidering the severity and high mortality rates of the disease (Rovery & Raoult, 2008). Recently, in a prospective study conducted in Algeria, North Africa, 49 % of patients were hospitalized with a severe form of MSF, and the global death rate was 3.6 %. Furthermore, the MSF incidence was 54.5 % in patients hospitalized with major neurological manifestations and multiorgan involvement (Mouffok *et al.*, 2009).

After an incubation of around six days, the onset of MSF is abrupt. Typical patients have a high fever, flu-like symptoms, a local necrotic inflammation with a black crust called an eschar (the "tache noire") at the tick bite site and a maculopapular rash (Rovery & Raoult, 2008; Parola *et al.*, 2005). Occasionally, the eschar is not found, and it is seen rarely in multiples (Rovery & Raoult, 2008). Recently, clinical symptoms of MSF were described in 415 Sicilian children. Fever, rash and "tache noire" were present in 386 (93 %), 392 (94.5 %) and 263 (63.4 %) cases, respectively, and 18 (4.6 %) children had atypical exanthema (Colomba *et al.*, 2006). Severe forms, including major neurological manifestations and multiorgan involvement, may occur in 5 to 6 % of cases. In Portugal from 1994-2006, the case fatality rate among 71 MSF patients was 13 %,

more than five times higher than the conventionally recognized mortality rate (Sousa *et al.*, 2008; Parola *et al.*, 2005). The highest MSF mortality rate (32.3 %) was described in southern Portugal in 1997 (de Sousa *et al.*, 2003). Although one may speculate that the pathogenic strain of Israeli tick typhus isolated in 1997 could be responsible for this increase in the fatality rate, inherited patient factors might also be strongly associated with mortality. The classic risk factors for severe forms include advanced age, cirrhosis, chronic alcoholism, G6PD deficiency, immunocompromised situations, prior prescription of an inappropriate antibiotic, and delay of treatment (Parola *et al.*, 2005). Recently, a diagnostic score was established to help clinicians diagnose MSF (Raoult & Roux, 1997).

Rickettsia conorii israelensis

Israeli spotted fever (ISF) was reported in 1946 in Israel, and the number of cases increased following the development of new settlements in the rural areas of the country (Raoult & Roux, 1997). *R. conorii israelensis* has been detected in *Rh. sanguineus* specimens collected in Sicily and Portugal, and several clinical cases were described in the same countries (Giammanco *et al.*, 2003; Santos-Silva *et al.*, 2006a; Sousa *et al.*, 2008). The clinical manifestations of ISF are similar to those of other spotted fever group infections, but an inoculation eschar is rarely observed and a history of tick exposure is not always present. In Israel, eschars caused by infection with the ISF strain have been described in only 4 % of cases (Gross &Yagupsky, 1987). A prospective study in Portugal conducted during 1994-2006 identified 69 patients with ISF, confirmed either by isolation of *R. conorii israelensis* from blood cultures or detection of rickettsial DNA in skin biopsy samples by polymerase chain reaction (PCR). The clinical characteristics were statistically similar with MSF. A history of a recognized tick bite was more common in patients infected with *R. conorii conorii* than in those infected with ISF, and an eschar was observed in a significantly higher percentage of MSF patients (Sousa *et al.*, 2008).

Several fatal cases and severe forms of ISF have been described, especially in children, as well as in travelers and those with G6PD deficiency (Sousa *et al.*, 2008; Chai *et al.*, 2008; Boillat *et al.*, 2008). In the Portugal study, the case fatality rate for ISF was significantly greater than that for MSF, and a greater percentage of patients with ISF required admission to the intensive care unit compared to MSF patients. Analysis of the relationship between co-morbidities and fatal MSF outcomes demonstrated that alcoholism was a statistically significant risk factor for a fatal outcome (Sousa *et al.*, 2008). A retrospective analysis in Sicily from 1987 to 2001 identified five of 24 patients infected with *R. conorii israelensis* by molecular tools; three of them presented severe forms and one died (Giammanco *et al.*, 2005). These recently reported cases show that ISF is a severe disease.

Rickettsia conorii caspiensis

Astrakhan fever is a summer spotted fever resembling MSF that is endemic to the Astrakhan and nearby regions of Russia near the Caspian Sea. It is transmitted to humans through the bites of *Rh. pumilio* ticks. Astrakhan spotted fever was later serologically diagnosed in Kalmykia (Russia), the agent was isolated also from *Rh. pumilio* from Western Kazakhstan; however, no clinical cases have yet been reported (Tarasevich & Mediannikov, 2006). Similar rickettsiae were identified as a cause of febrile illness in a patient from Chad and detected in *Rh. sanguineus* ticks from Kosovo (Fournier *et al.*, 2003a; Fournier *et al.*, 2003b). Thus, Astrakhan fever might be a cause of spotted fever in Kosovo, and the area of distribution of this rickettsia could be wider than initially suspected in Astrakhan. Clinically, Astrakhan fever is characterized by clinical symptoms resembling those of MSF, that is, elevated fever, a maculopapular rash of the trunk, and severe myalgias. However, an inoculation eschar at the site of the tick bite is present in only 23 % of patients (Tarasevich *et al.*, 1991).

Rickettsia massiliae

In 1992, a novel rickettsial agent was isolated from *Rh. sanguineus* ticks collected near Marseille (France). It was characterized as a distinct species within the SFG group of rickettsiae and named *R. massiliae* (Beati & Raoult, 1993). In Europe, this rickettsia has been detected by molecular methods in *Rh. sanguineus* from Greece, Switzerland, Spain, and Italy; in *Rh. turanicus* from Portugal, the Greek Islands, Spain, and Italy; in *I. ricinus* from Spain and Germany; and in *Rh. pusillus* from Spain (Bernasconi *et al.*, 2002; Psaroulaki *et al.*, 2003; Fernandez-Soto *et al.*, 2006; Psaroulaki *et al.*, 2006; Mura *et al.*, 2008). The first human case of infection with *R. massiliae* was confirmed in 2005, 20 years after the isolate was obtained from the patient. In 1985, this patient was hospitalized in Palermo, Italy, with fever, a necrotic eschar on his right ankle, a maculopapular rash on his palms and soles and mild hepatomegaly. He recovered completely after receiving tetracycline (Vitale *et al.*, 2006). Recently, the second case of *R. massiliae* infection was diagnosed by serological and molecular tools. A 25-year-old man developed fever, night sweats, headache, two necrotic skin lesions on the buttocks and the thighs, and a maculopapular rash involving the palms and soles. A few days later, he complained of acute visual loss and bilateral chorioretinitis was diagnosed. The clinical course was favorable, but

three months later, the recovery of visual acuity was incomplete. During an entomological survey, dense populations of *Rh. sanguineus* were found in the house where the patient had been bitten by ticks. They were infected with new genotypes of clonal populations of *R. massiliae* (13/133; 10 %) (Parola *et al.*, 2008).

Rickettsia sibirica mongolitimonae

R. sibirica mongolitimonae causes LAR (lymphangitis-associated rickettsiosis) (Fournier *et al.*, 2005; Fournier *et al.*, 2006). This rickettsia was firstly isolated in Beijing from *Hyalomma asiaticum* ticks collected in the Alashian region of Inner Mongolia in 1991 (Yu *et al.*, 1993). In Europe, *R. sibirica mongolitimonae* was detected in *H. anatolicum excavatum* from Greece and in *Rh. pusillus* from Portugal (Psaroulaki *et al.*, 2005; De Sousa *et al.*, 2006). In 1996, the first case of human infection was diagnosed in southern France in a woman who had a febrile rash and a single inoculation eschar in the groin (Raoult *et al.*, 1996). This patient was a resident of Marseille and had no travel history; however, the patient had collected compost from a garden where migratory birds were resting.

Since January 1998, *R. sibirica mongolitimonae* infection has been diagnosed in 11 additional patients by isolation of bacteria, PCR of samples obtained from the eschar or blood, specific Western blot and cross adsorption. Seven patients lived in southern France, one patient had returned from a trip to southern Algeria, one patient was from South Africa, one patient was from Portugal, and one patient was from Greece (Fournier *et al.*, 2005; de Sousa *et al.*, 2006; Psaroulaki *et al.*, 2005; Pretorius & Birtles, 2004; Fournier *et al.*, 2000b; Raoult *et al.*, 1996). Among 12 patients with LAR, three (25 %) (from Algeria, South Africa, and Portugal) were bitten by a tick on the foot, and in the latter two patients, eschars were found between the toes. Most of the cases reported in France occurred in the spring, except for one case in early July. The Portugal case occurred in August during the peak of the MSF season, whereas the patients from South Africa and Greece were ill in winter. It is probable that the occurrence of these cases in different months could be related to the differences in seasonal activity and population dynamics of different vectors. In a study of 12 cases, *R. sibirica mongolitimonae* infection was characterized as follows: fever (100 %), headache (6/12; 50 %), rash (10/12; 83 %), eschar (11/12; 92 %), two eschars (2/12; 17 %), a draining lymph node (7/12; 58 %), and lymphangitis expanding from the inoculation eschar to the draining node (5/12; 42 %). All patients recovered without any sequelae (Fournier *et al.*, 2005; de Sousa *et al.*, 2006; Psaroulaki *et al.*, 2005; Pretorius & Birtles, 2004; Fournier *et al.*, 2000b; Raoult *et al.*, 1996).

Rickettsia slovaca and *Rickettsia raoultii*

R. slovaca has been found in *Dermacentor marginatus* and *D. reticulatus* ticks in a great majority of European countries, including France, Spain, Italy, Switzerland, Slovakia, Hungary, Ukraine, Yugoslavia, Armenia, Portugal, Russia, Greece, Germany and Poland (Parola *et al.*, 2009a; Parola *et al.*, 2005; Dobler & Wolfel 2009; Kachrimanidou *et al.*, 2009). This bacterium was isolated in 1968 from *D. marginatus* ticks in Czechoslovakia. In 1997, *R. slovaca* was described as a human pathogen and the agent of tick-borne lymphadenopathy (TIBOLA), also known as *Dermacentor*-borne necrotic erythema and lymphadenopathy (DEBONEL), which is defined as the association of a tick bite, an inoculation eschar on the scalp, and cervical lymphadenopathies (Raoult *et al.*, 2002b).

In 2008, several rickettsial isolates (*Rickettsia* sp. genotypes DnS14, DnS28 and RpA4) from *D. silvarum*, *D. reticulatus*, *D. marginatus* and *D. nuttalli* ticks collected in Russia and France were characterized using multi-gene sequencing and classified as a unique, new *Rickettsia* species named *R. raoultii* (Mediannikov *et al.*, 2008). *R. raoultii* was detected in ticks collected from several European countries: France, Russia, Poland, Slovakia, Spain, Portugal, Germany, Croatia and the Netherlands (Dobler & Wolfel, 2009; Ibarra *et al.*, 2005; Matsumoto *et al.*, 2009; Vitorino *et al.*, 2007; Nijhof *et al.*, 2007; Mediannikov *et al.*, 2008). In 2002, *R. raoultii* was detected by PCR in a *D. marginatus* tick taken from the scalp of a patient in France who had developed a typical clinical picture of TIBOLA. Later, *R. raoultii* was found by PCR in the blood of one patient in Spain with TIBOLA/DEBONEL (Ibarra *et al.*, 2006).

Recently, a retrospective French study among 86 patients diagnosed with TIBOLA/DEBONEL from January 2002 through December 2007 reported 49 cases of *R. slovaca* infection and seven new cases of *R. raoultii* infection. All of these results were confirmed by positive culture, PCR of blood or skin samples, lymph node aspirates, ticks, and Western blot with cross adsorption assays (Parola *et al.*, 2009a). The peak incidence for TIBOLA/DEBONEL occurs during March-May and September-November, which corresponds to the activity of *Dermacentor* ticks in Europe. Infection was most frequent in women and in children less than 12 years old. There is no explanation for the finding that children and women are at higher risk for TIBOLA/DEBONEL or why *Dermacentor* ticks prefer to bite persons on the scalp; it is possible that the *Dermacentor* ticks usually bite hairy domestic and wild animals, and the longer hair of women and children may attract them (Parola *et al.*, 2009a).

The clinical description of *R. slovaca* infection includes fever (21/39; 54 %), headache (16/30; 53 %), asthenia (23/33; 70 %), rash (7/30; 23 %), painful eschar (14/22; 64 %), painful adenopathies (18/26; 69 %), and face

edema (16/31; 19 %). After antibiotic treatment, all patients recovered; however, the eschar resulted in alopecia lasting for several months in 59 % (16/27) of patients, as well as prolonged asthenia in 35 % (10/29) and chronic asthenia (more than six months) in 14 % (4/28) of patients (Parola *et al.*, 2009a). Patients with *R. raoultii* infection had a painful eschar and adenopathies, headache, and asthenia. Fever occurred in 80 % (4/5). No alopecia was noted, but 50 % (2/4) of patients had prolonged asthenia (one to six months) and 25 % (1/4) had chronic asthenia (Parola *et al.*, 2009a).

R. slovaca and *R. raoultii* seem to be involved in most, but not all cases of TIBOLA/DEBONEL. Recently, other etiological agents for several cases of TIBOLA/DEBONEL syndrome were confirmed as *Bartonella henselae, Francisella tularensis*, and probably as *Borrelia burgdorferi* infection. The authors proposed the name SENLAT for this syndrome: scalp eschar and neck lymphadenopathy after tick bite (Angelakis *et al.*, 2009b; Oteo *et al.*, 2004).

Rickettsia monacensis

In 2002, *R. monacensis* was isolated and characterized from an *I. ricinus* tick collected in a city park in Munich, Germany (Simser *et al.*, 2002). Since then, it has been detected by PCR in ticks in several European countries, mainly in southern and southeastern Europe: Spain, Italy, Portugal, Slovakia, Albania, Hungary, Bulgaria, Moldova, Eastern Ukraine and Switzerland (Marquez *et al.*, 1998; Sekeyova *et al.*, 2000; Beninati *et al.*, 2002; Dobler & Wolfel, 2009; Sreter-Lancz *et al.*, 2006; de Carvalho *et al.*, 2008; Boretti *et al.*, 2009; Movila *et al.*, 2009). The prevalence of *R. monacensis* infection in *I. ricinus* ticks collected in nature varied between 2.4 % in Spain, 8.6 % in Germany, 12.2 % in Slovakia and 52.9 % in Bulgaria (Christova *et al.*, 2003; Sekeyova *et al.*, 2000). Recently, in two patients from Spain, *R. monacensis* was detected in blood samples by molecular tools and one rickettsial strain was isolated by shell vial culture. The first patient was an 84-year-old man from La Rioja who, seven days after the onset of fever, general discomfort, headache, and joint pain, developed a nonpruritic, disseminated maculopapular rash of the trunk and lower extremities, including palms and soles, with no inoculation eschar. The second patient was a 59-year-old woman from Basque country. She had a history of a tick bite one week before symptom onset. Fever, headache, and an erythematous rash with no inoculation eschar at the site of a tick bite were noted. The patients recovered without sequelae with doxycycline treatment (Jado *et al.*, 2007). This strain of *R. monacensis* was not analyzed by another laboratory.

Rickettsia aeschlimannii

R. aeschlimannii was first isolated from *H. marginatum marginatum* ticks collected from Morocco in 1992 and then characterized as a new rickettsia in 1997 (Beati *et al.*, 1997). Later, *R. aeschlimannii* was detected in ticks from Croatia, Spain, Corsica, Portugal, Italy, Greece and Russia (Oteo *et al.*, 2006; Santos-Silva *et al.*, 2006b; Shpynov *et al.*, 2009; Mura *et al.*, 2008; Punda-polic *et al.*, 2002). *H. m. marginatum* is a thermophilic tick species usually occurring in relatively dry and warm regions of southern Europe, northern Africa and some parts of Asia. It is also a vector of the Crimean-Congo hemorrhagic fever virus. The first human infection caused by *R. aeschlimannii* was in a French patient who became ill after returning from a trip to Morocco. The patient exhibited symptoms similar to those of MSF, including an eschar on his ankle, high fever, and a generalized maculopapular rash. The definitive diagnosis was made by PCR amplification of rickettsial DNA in the patient's early serum (Raoult *et al.*, 2002a). A second case was documented in a South African man who was bitten by a *Rh. appendiculatus* tick. The patient, returning from a hunting and fishing trip, discovered a tick attached to his right thigh and an eschar around the attachment site. After removing the tick, he immediately self-prescribed doxycycline. No further symptoms developed. Molecular studies of both the biopsy specimen and the tick confirmed the *R. aeschlimannii* infection (Pretorius & Birtles, 2002). Recently, two new cases were reported in Algeria (Mokrani *et al.*, 2008). The first patient, an 80-year-old man, reported contact with dogs parasitized by ticks. He had a seven-day history of high fever, headache, myalgia, and vomiting. Upon physical examination, a generalized maculopapular rash, two eschars (right shoulder and knee), and bilateral hemorrhagic signs on the retina were noticed. The second patient, a 36-year-old man, reported a 15-day history of fever with headache. A maculopapular rash and purpuric lesions on the arms were noted.

The occurrence of *R. aeschlimannii* in ticks from Spain, Italy, Portugal, and Corsica, a French island in the Mediterranean Sea, suggests that this infection is not only a risk for travelers to Africa, but may also exist in southern Europe where *H. marginatum* is prevalent (Fernandez-Soto *et al.*, 2003). In Spain, *H. marginatum* ticks represent 4 % of human-biting ticks. From January 2002 to December 2004, five patients were bitten by *H. marginatum* in Northern Spain. Of these five ticks, two (40 %) were infected by *R. aeschlimannii*, but neither of these two patients became ill (Oteo *et al.*, 2005). Furthermore, infection rates of *H. marginatum* ticks may be high, such as those reported in Croatia (64.7 %) (Punda-polic *et al.*, 2002).

Rickettsia helvetica

R. helvetica is a member of the SFG of rickettsiae presumptively associated with human illnesses. It was first isolated from *I. ricinus* in Switzerland in 1979 (Beati

et al., 1993). *R. helvetica* has been detected in *I. ricinus* in many European countries, including France, Spain, Portugal, Austria, Denmark, the Netherlands, Switzerland, Sweden, Portugal, Germany, Bulgaria, Slovenia, Poland, Hungary, Moldova, Eastern Ukraine and Italy (Nijhof *et al.*, 2007; Christova *et al.*, 2003; Dobler & Wolfel, 2009; Marquez, 2008; Parola *et al.*, 2005; Nilsson *et al.*, 1999; Movila *et al.*, 2009). In Sweden, two patients with clinical symptoms of fatal perimyocarditis were infected with *R. helvetica*, as confirmed by electron microscopy, PCR and serology (Nilsson *et al.*, 1999). Subsequently, an association between *R. helvetica* and sarcoidosis in Sweden was reported by the same researchers (Nilsson *et al.*, 2002). However, the validity of these associations has been questioned by some rickettsiologists (Walker *et al.*, 2003), and additional studies did not reveal anti-rickettsial antibodies in a group of Scandinavian sarcoidosis patients (Planck e*t al.*, 2004). In 2000, seroconversion to *R. helvetica* was described in a 37-year-old immunocompetent French man four weeks after the onset of an unexplained febrile illness with prolonged fever, fatigue, myalgias, and headache. No rash, lymphadenopathy or inoculation eschar was noted. The serology result was confirmed by cross-adsorption and Western blotting. Results of a serosurvey of forest workers from the area where the patient lived showed a 9.2 % seroprevalence against *R. helvetica* (Fournier *et al.*, 2000a). In eight of 75 patients (11 %) in Switzerland, serological findings suggested possible acute or past *R. helvetica* infection (Baumann *et al.*, 2003). In 2004, eight patients from France, Italy, and Thailand showed serological evidence of *R. helvetica* infection. The infection presented as a mild disease in the warm season and was associated with fever, headache, and myalgia but without a cutaneous rash. Only one patient developed an eschar (Fournier *et al.*, 2004). Interestingly, one case of *R. helvetica* infection was reported in Sweden with the presence of a macular rash involving the arms and legs. A 57-year-old, healthy, immunocompetent man had a fever, myalgias, arthralgias and severe headache with photophobia, but no lymphadenopathy or inoculation eschar. The infection was confirmed by PCR, blood culture, serology and Western blot assay (Nilsson, 2009). Among 4,604 clinical rickettsial cases reported in Italy from 1998 to 2002, three cases of a mild form of rickettsiosis were serologically attributed to *R. helvetica* (Ciceroni *et al.*, 2006). Additional evaluation and isolation of the bacterium from clinical samples are needed to confirm the pathogenicity of *R. helvetica*.

Other tick-borne rickettsiae

The most recently discovered rickettsiae were first detected and isolated in ticks and subsequently characterized as human pathogens, including *R. massiliae, R. aeschlimannii, R. monacensis* and *R. slovaca*. To be considered a human pathogen, a rickettsia must be either isolated in cell culture from or detected by molecular methods in blood or tissue from patients with illnesses clinically compatible with spotted fever rickettsioses who are also seropositive using standard reference laboratory methods (Parola *et al.*, 2005). Several additional rickettsiae have been detected in ticks, but their pathogenicity is not known. *R. rhipicephali* was detected in *Rh. sanguineus* ticks collected from France, Portugal, Greece and Croatia (Drancourt *et al.*, 1992). In 2000, a new rickettsial genotype, *Rickettsia* sp. DmS1, was detected in one out of 70 *D. marginatus* ticks collected from game pigs (*Sus scrofa)* in southern France. This genotype was later detected in the same tick species in Spain (Sanogo *et al.*, 2003; Fernandez-Soto *et al.*, 2006). Based on preliminary phylogenetic studies, this new rickettsia appears to be within the *R. massiliae* group. Recently, another new rickettsia was described in *Rh. sanguineus* ticks collected from Sardinia; this organism was previously identified in four *Rh. turanicus* ticks in Portugal and referred to as PoTiRb169. This new species was further characterized by amplification and sequencing of several genes, and the authors proposed the name "*Candidatus* Rickettsia barbariae" (Mura *et al.*, 2008). In addition, the existence of another novel SFG rickettsiae was demonstrated in *Haemaphysalis sulcata* ticks collected from sheep and goats in Croatia. This new rickettsia was named *R. hoogstraali*, and was isolated and deposited in two different collections (Duh *et al.*, 2009). A rickettsial genotype from the *R. massiliae* genogroup called *Candidatus* Rickettsia kulagini was identified in *Rh. sanguineus* ticks from Crimean peninsula, Ukraine (Mediannikov *et al.*, 2007). *Candidatus* Rickettsia tarasevichiae was identified in *Ixodes persulcatus* ticks with a high prevalence (Shpynov *et al.*, 2003). This tick replaces *I. ricinus* in Northern Russia and Finland (Jaaskelainen *et al.*, 2006).

Imported rickettsioses

Case reports and retrospective studies showed the importance of rickettsioses imported by international tourists. Usually, the diagnosis can be made based on the presence of flu-like symptoms following a recent visit to tick-infested areas, a history of a tick bite, the presence of an eschar and the type of rash. Severe complications and fatalities are occasionally seen.

During the last decade, approximately 400 cases of tick-borne rickettsioses have been reported in international travelers. The vast majority of these illnesses were either African tick bite fever (ATBF) caused by *R. africae* in patients returning from sub-Saharan Africa and the West Indies or Mediterranean spotted fever caused by *R. conorii* in patients retuning from the

Mediterranean area (Jensenius *et al.*, 2006). ATBF is transmitted by *Amblyomma* ticks that are aggressive and actually attack hosts, which leads to clustered cases of infection (Socolovschi *et al.*, 2009b). In more than half of the cases, multiple inoculation eschars occur. Indeed, several ticks may attack at the same time, and the rickettsiae infection rate among ticks may reach 100 % (Jensenius *et al.*, 2003a). Furthermore, thirty-eight travelers, 4.0 % of the cohort and 26.6 % of those reporting flulike symptoms, of 940 Norwegian travelers to rural sub-Equatorial Africa were diagnosed with ATBF. Game hunting, travel to Southern Africa and travel during November through April were found to be independent risk factors (Jensenius *et al.*, 2003b). Finally, all new rickettsioses described throughout the world may be imported into European countries.

HUMAN GRANULOCYTIC ANAPLASMOSIS

Human granulocytotropic anaplasmosis (HGA) is a tick-borne zoonotic infection caused by *Anaplasma phagocytophilum,* which is transmitted in Europe by *I. ricinus* ticks. *I. ricinus* is also the vector of Lyme borreliosis, it harbours *R. helvetica* and *R. monacensis*. Across Europe, the prevalence of *Anaplasma phagocytophilum* infection in *I. ricinus* ticks is variable and can be between 0.4 to 66.7 %. It is not transmitted transovarially in ticks; small mammals, particularly *Apodemus sylvaticus* (wood mouse), *A. flavicollis* (yellow-necked mouse), *Sorex araneus* (common shrew) and especially *Clethrionomys glareolus* (bank vole), have been implicated as HGA reservoirs in Europe.

A limited number of laboratory-confirmed HGA cases have been reported in Austria, Italy, Latvia, the Netherlands, Norway, Poland, Slovenia, Spain, France, Russia and Sweden, (Bakken & Dumler, 2008; Parola, 2004; Lotric-Furlan *et al*., 2006). Serologic studies also support the presence of HGA infection, much of which may be asymptomatic, in potentially exposed adults in Germany, Bulgaria, Denmark, Spain, Italy, Estonia, Greece, and France (Parola, 2004). The first patient to have recognized HGA was reported in the U.S. in 1990; the first European case was reported in Slovenia in 1997 (Petrovec *et al.*, 1997). By the end of December 2004, at least 2,871 cases of HGA were reported from 13 U.S. states to the Centers for Disease Control and Prevention (CDC) (Bakken & Dumler, 2008). In 2002, Blanco and Oteo (Blanco & Oteo, 2002) compared the clinical and laboratory features of 15 European patients to those reported for U.S. patients. Most patients report exposure to ticks or a tick bite between seven and 30 days before the onset of the disease. The majority of cases occurred between June and August (73 %), a period of higher vector activity in these areas. European HGA patients generally have a less severe course than U.S. patients, and the presence of morulae is uncommon. In most patients, the disease consists of flu-like symptoms: fever, myalgias, arthralgias, and headache. Physical examination reveals a few abnormalities, such as conjunctivitis and lymphadenopathy. Other manifestations that can accompany the illness are pneumonia (13 %) and gastrointestinal symptoms such as nausea (53 %), vomiting (20 %), diarrhea (13 %), and abdominal pain (20 %). Hepatomegaly, splenomegaly or both are also occasionally described. Laboratory tests typically show leukopenia and thrombocytopenia, as well as elevated serum hepatic aminotransferase levels, erythrocyte sedimentation rate and C-reactive protein levels. Between January 1996 and December 2004, 24 adult patients with confirmed HGA were identified in a prospective study conducted in Slovenia. The clinical characteristics and laboratory findings were similar to those reported from other European countries. All of the patients had an acute febrile illness with headache, malaise, myalgia and/or arthralgia. Laboratory findings included leukopenia (16/24; 66.7 %), thrombocytopenia (20/24; 83.3 %), abnormal liver function (23/24; 95.8 %), elevated erythrocyte sedimentation rates (18/24; 75 %), and elevated concentrations of C-reactive protein (23/24; 95.8 %) (Lotric-Furlan *et al.*, 2006). In Europe, verification of HGA has been based on PCR and immunofluorescence antibody tests, because no isolation of the etiologic agent from humans has yet been reported (Blanco & Oteo 2002).

BORRELIOSIS

Borrelia species are Gram-negative spriochetes, or helically coiled bacteria, which cause several arthropod-borne diseases in European countries, including Lyme disease and tick-borne relapsing fever (TBRF).

Lyme borreliosis (LB)

Lyme disease is caused by three of the at least 14 different *Borrelia* species belonging to the complex *B. burgdorferi*: *B. burgdorferi* sensu stricto (ss), *B. garinii,* and *B. afzelii* (Stanek & Strle, 2003).

However, *B. valaisiana, B. lusitaniae, B. spielmanii* and *B. bissettii* have been detected and isolated in samples of human origin (Rudenko *et al.*, 2009). LB is the most frequent *Ixodid* tick-borne human disease in the world, with an estimated 85,500 patients annually and 65,500 in Europe alone (Hubalek, 2009). In Europe, most cases occur in Scandinavian countries (up to 155 cases per 100,000 individuals) and in central Europe (especially Germany, Austria and Switzerland). However, LB cases have been reported throughout the region, including the United Kingdom, where many cases occur in the South

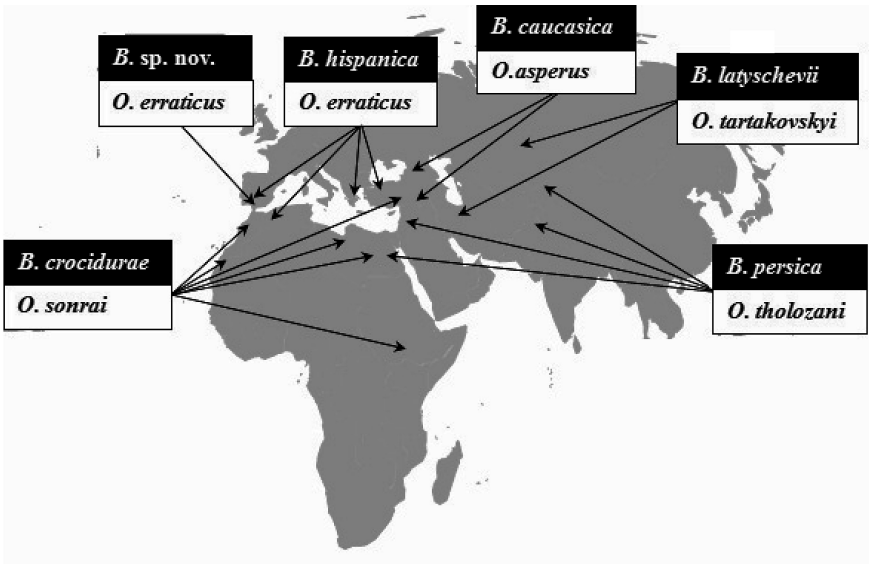


Fig. 3. – Relapsing fever borreliosis in Europe.

Downs or New Forest areas. *B. burgdorferi* ss and related *Borrelia* species exist in nature in enzootic cycles primarily involving *Ixodes* ticks and a wide range of animal hosts. In Europe, small mammals, such as mice and voles, are reservoirs of *B. afzelii, B. burgdorferi* ss and *B. garinii* serotype 4, while birds are the primary reservoirs of *B. garinii* and *B. valaisiana* (Stanek & Strle, 2003; Nadelman & Wormser, 1998). A recent study in Hungary identified green lizards (*Lacerta viridis)* as potential hosts of *I. ricinus* ticks, and therefore a possible reservoir of *Borrelia burgdorferi* sensu lato (Foldvari *et al.*, 2009). As with other spirochete infections, human Lyme disease occurs in stages, with remissions, exacerbations, and different clinical manifestations at each stage. Although infection with any of three pathogenic *Borrelia* species may occur in the skin, nervous system, or joints, the frequency, severity, and duration of these symptoms varies with each species. *B. burgdorferi* ss seems to be associated with most rheumatologic disorders, *B. garinii* appears to be the most neutropic and causes chronic borrelial encephalomyelitis, and *B. afzelii* is most strongly associated with skin manifestations, including acrodermatitis chronica atrophicans. The clinical and microbiological characteristics of LB have been recently reviewed (Nadelman & Wormser, 1998; Stanek & Strle, 2003). Microbial or serological confirmation of infection is needed for all manifestations of LB except for typical early skin lesions. The culture of *Borrelia* species from patient specimens permits definitive diagnosis, but usually is obtained only in the early stage of disease.

Relapsing fever borreliosis

Tick-borne relapsing fever (TBRF) is a zoonotic disease, caused by spirochetes of the genus *Borrelia* and transmitted to humans through the bite of soft ticks of the genus *Ornithodoros*, family Argasidae (Rebaudet & Parola, 2006). Six species of borrelia causing TBRF are known to occur in Europe, including *B. hispanica,* transmitted by the *O. erraticus* tick*; B. crocidurae,* transmitted by the *O. sonrai* tick*; B. persica,* transmitted by the *O. tholozani* tick*; B. caucasica,* transmitted by the *O. asperus* tick*; B. latyschevii,* transmitted by the *O. tartakovskyi* tick; and a new *Borrelia* species, isolated in southern Spain from three patients with TBRF and from the *O. erraticus* tick (Anda *et al.*, 1996) (Fig. 3). Two additional *Borrelia* pathogenic to humans are present in Eurasia: *B. microtii* and *B. baltazardi* were described in 1946 and 1979, respectively. No other scientific data are known at this time regarding these species (Assous & Wilamowski, 2009).

In Israel, a total of 606 cases of TBRF were confirmed by association between febrile illness and a positive peripheral blood smear. Most cases occurred during summer and fall and correlated with *Ornithodoros* tick activity, high human outdoor activity and light clothes worn during these seasons (Sidi *et al.*, 2005). TBRF is a disease characterized by relapsing or recurring episodes of fever, often accompanied by headache, muscle and joint aches and nausea. The incidence of TBRF appears to be rare in Europe. However, European physicians should be on alert for imported cases of TBRF. Several confirmed cases have been reported in the literature: immigrants from Ethiopia three months after they arrived in Israel, four French patients with unexplained fever from Senegal and a Dutch woman that developed symptoms after a two-week trip to Guatemala and Belize (Sidi *et al.*, 2005; Patrat-Delon *et al.*, 2008; Heerdink *et al.*, 2006).

TULAREMIA

Tularemia is a zoonotic infection caused by the bacterium *Francisella tularensis*. In 1923, tick-borne tularemia was reported for the first time

by physicians in Idaho, and one year later it was isolated from ticks (Petersen *et al.*, 2009). Moreover, infections with *F. tularensis* in nature have been documented in various arthropods, including fleas, lice, midges, bedbugs, mosquitoes, ticks and flies. In Europe, *F. tularensis* has been detected in *I. ricinus*, *D. reticulates* and *D. marginatus* ticks (Aberer, 2009; Hubalek *et al.*, 1996). In the U.S., Sweden, Finland and Russia, arthropod bites are a common mode of tularemia transmission to humans. In Central Europe, contact with infected animals and ingestion of contaminated food or water are more common modes of transmission (Hubalek *et al.*, 1996; Petersen *et al.*, 2009). The prevalence of tularemia in ticks is very low: only 0.01 % of 120,000 *I. ricinus* adult ticks in Russia were positive (Sjostedt, 2007a). In Slovakia, 34 *F. tularensis* strains were isolated from 4,542 starving ticks, predominantly from *D. reticulatus* (Gurycova *et al.*, 1995). Recently, a possible reservoir of *F. tularensis* was investigated in Germany. *F. tularensis* was detected in five different rodent species with carrier rates of 2.04, 6.94 and 10.87 % per trapping area, and two strains were isolated from water voles. None of the ticks tested positive for *F. tularensis* (Kaysser *et al.*, 2008). In central European foci, hares appeared to be the main carrier and source of tularemia in humans, whereas ticks harbored by hares were the perennial reservoir of *F. tularensis* (Sjostedt, 2007b).

Several outbreaks of tularemia have been reported in the literature, but they were not associated with transmission by ticks (Kantardjiev *et al.*, 2006; Reintjes *et al.*, 2002; Payne *et al.*, 2005; Perez-Castrillon *et al.*, 2001). The clinical symptoms of tularemia depend upon the route of infection. When infected by a tick, an indolent ulcer often occurs at the site of the bite followed by swelling of the regional lymph nodes. The ulcer is usually also followed by a fever.

Q FEVER

Q fever is a zoonosis caused by *Coxiella burnetii* (Raoult *et al.*, 2005). *C. burnetii* has been detected in 140 species of ticks in 12 genera throughout the word (absent in New Zealand), but the role of ticks in Q fever transmission to humans is very small (Parola & Raoult, 2001b; Tissot-Dupont & Raoult, 2008). Recently, none of 862 *Dermacentor* ticks tested positive for *C. burnetii* in Germany, and one specimen of *Haemaphysalis punctata* from 691 questing adult ixodid ticks was positive in Spain (Hartelt *et al.*, 2008; Barandika *et al.*, 2008). Q fever is usually acquired by the ingestion or inhalation of virulent organisms from infected mammals and their products, most frequently goats, sheep, and cats. Infection in humans is often asymptomatic, but it can manifest as an acute disease, such as pneumonia, hepatitis or isolated fever. Q fever can also appear in a chronic form, mainly involving endocarditis and vascular infection, as well as hepatitis and chronic infection after pregnancy (Raoult *et al.*, 2005).

BARTONELLA

Bartonella species are Gram-negative bacilli or coccobacilli belonging to the alpha 2 subgroup of *Proteobacteria*, family *Bartonellaceae*. These bacteria are transmitted by blood-sucking arthropods, including fleas, lice, sandflies and ticks (Angelakis *et al.*, 2009a). In European countries, *Bartonella* species have been detected by molecular tools in *D. reticulates* and *Ixodes* spp. ticks. The prevalence of *Bartonella*-infected ticks can vary from 1.2 % in the Czech Republic to 60 % in the Netherlands (Schouls *et al.*, 1999; Hercik *et al.*, 2007). Recently, *I. ricinus* ticks were demonstrated to be a competent vector for *B. henselae* (Cotte *et al.*, 2008). Five *Bartonella* species were found in ticks collected in European countries: *B. quintana, B. henselae, B. capreoli, B. bacilliformis*-like bacterium and *B. schoenbuchensis*. In Russia, Slovenia, Poland and France, several clinical studies confirmed *Bartonella* transmission from ticks to humans (Podsiadly *et al.*, 2009; Angelakis *et al.*, 2009b). In the study performed in Slovenia, 86 febrile children were screened with serological tools for multiple tick-borne antigens after a history of tick bite. *B. henselae* infection was detected in five children, *B. quintana* infection was found in four children, and both infections were present in one child (Arnez *et al.*, 2003). In Poland, 17 patients with clinical symptoms of neuroborrelioses were tested for *Bartonella* infection. Among these patients, *B. henselae* was detected in one case, and *B. burgdorferi* and *B. henselae* infections were found in two patients (Podsiadly *et al.*, 2003). In France, *B. henselae* infection was confirmed in three patients after a tick bite history. All patients presented scalp eschar and neck lymphadenopathy (Angelakis *et al.*, 2009b).

CONCLUSION

Tick-borne illnesses are emergent and re-emergent zoonotic diseases. The progression of tick-borne diseases and their increased morbidity is associated with outdoor activities and travels (Parola, 2004). Several climate models predict a global warming, more in the northern and altitude range, such as in Germany, with the emergence of Lyme diseases and tick-borne encephalitis in the last years (Suss *et al.*, 2008).

Increasing public education on tick-borne diseases and avoidance of tick bites (such as using protective clothing, insect repellents, and early detection and removal of ticks) are the best prevention. The early removal of ticks can reduce the spread of infectious organisms. Antibiotic prophylactic therapy after a tick bite is not generally recommended (Aberer, 2009). Europeans who have spent time in tick-endemic areas should inspect themselves frequently for ticks. Complete removal of attached ticks is indicated with tweezers or forceps close to the skin. Routine disinfection of the bite wound is recommended to avoid contamination of the bite site with skin bacteria (Bakken & Dumler, 2008; Aberer, 2009). European clinicians should be aware of the clinical signs of tick-transmitted diseases in patients with unexplained febrile illnesses, and a careful travel and tick exposure history should be taken. Empiric antimicrobial therapy (most often with doxycycline) is appropriate in most cases of significant clinical illness in which rickettsioses, anaplasmosis, tularemia, bartonelloses or borrelial infections are suspected by epidemiological and clinical manifestations, and may be lifesaving.

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