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TICKS

Spread of ticks and tick-borne diseases in Germany due to global warming

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Abstract Tick-transmitted diseases like tick-borne encephalitis and Lyme Borreliosis have been well known in Germany for decades. Global climate changes may influence the emergence and reemergence of diseases. Ongoing research now gives an additional focus on other tick-borne pathogens such as *Coxiella burnetii*, *Rickettsia conorii, Anaplasma phagocytophilum* and *Babesia* spp., the causative agents of Q-fever, Mediterranean spotted fever, Anaplasmosis and Babesiosis, respectively. The epidemiology of these pathogens was investigated on ticks as well as on rodents, the main hosts. Therefore adults of *Dermacentor* spp. (n = 862) and rodents (n = 119) were collected and examined for the existence of *C. burnetii* and *Rickettsia* spp. by polymerase chain reaction (PCR). In none of the ticks and rodents *C. burnetii* could be detected, in contrast to *Rickettsia* spp. where the infection rate in ticks was about 20%. Over and above that, nymphs and adults of *Ixodes ricinus* were also collected and investigated by PCR for *A. phagocytophilum* (n = 5,424), *Rickettsia helvetica* (n = 1,187) and *Babesia* spp. (n = 3,113). Thereby infection rates of 1%, 8.9% and 1%, respectively, could be determined. The prevalence in rodents was 5.3% for *A. phagocytophilum* and 0.8% for *Babesia microti*. None of the rodents was *R. helvetica* positive.

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Introduction

In Central Europe, Lyme Borreliosis and tick-borne encephalitis are the most important tick-transmitted diseases. In the last years, further human pathogenic microorganisms were detected in ticks, but the role of ticks as vectors for these pathogens has not yet been clarified sufficiently. This involves Q-fever as the most important infection, followed by Rickettsiosis, Anaplasmosis and Babesiosis. Global change may influence the infective cycle of these infections, therefore the number of cases will increase.

Coxiella burnetii, the causative agent of Q-fever, is a small obligate intracellular bacterium, which infects macrophages. The microorganism has an outer lipopolysaccharid membrane similar to that of gram-negative bacteria. According to molecular taxonomy, *C. burnetii* belongs to gamma-proteobacteria and therefore is related to the family *Legionella*. However, *Coxiella* is the only genus in the family *Coxiellaceae*. Furthermore, *C. burnetii* has a special feature of producing spore-like bodies (small cell variants or SCV), budded by vegetative cells (large cell variants or LCV) (Fig. 1). The SCV are of great importance for the epidemiology of Q-fever because they have a high resistance against environmental influences and can be transmitted by the aerosol route especially under hot and dry conditions (Maurin and Raoult 1999).

Q-fever infections of humans usually remain asymptomatic or present as a flu-like illness with fever, headache and malaise. In about 2–5% of cases atypical pneumonia and/or granulomatous hepatitis occur. About 1% of the patients develop a chronic Q-fever, e.g. with endocarditis, which may be lethal. Endocarditis affects mainly patients with artificial heart valves. Pregnant women are especially at risk because they are highly susceptible to infection and it may

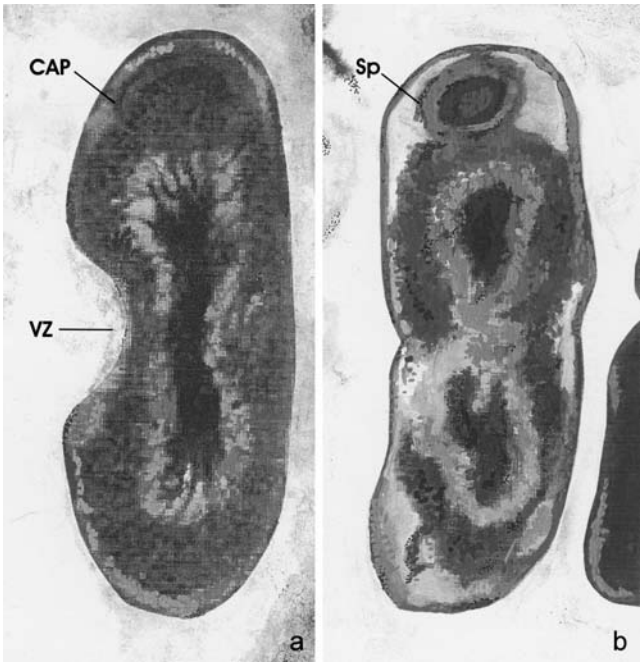

Fig. 1 *Coxiella burnetii* vegetative cells producing spore-like bodies. *CAP* capping, *VZ* vegetative cell, *Sp* spore-like body (Bergey's Manual of Systematic Bacteriology, Williams &Wilkins, Vol. 1, modified; illustrated by C. Lüttich, Gera)

lead to abortion during the first trimester. Moreover, the percentage of chronification may be higher than 30% (Raoult et al. 2002).

Rickettsia spp. are obligate intracellular bacteria belonging to the family *Rickettsiaceae*. They are divided into two groups, the typhus group and the spotted fever group. These two groups can be differentiated serologically, but inside each group, greater antigenic similarities exist which result in cross reactions. *Rickettsia* spp. are not able to form permanent stages, therefore they can be transmitted only by vectors. The vectors of the typhus group are insects (lice, fleas), whereas the species of the spotted fever group are transmitted by different tick species.

Rickettsia spp. mainly live in endothelial cells of small blood vessels which can be damaged by the infestation. This leads to bleedings in the skin, visible as small "spots", or in other organs such as heart or brain, which can be lethal (Raoult and Roux 1997).

Ehrlichia spp. are small, immobile, pleomorphic, gram-negative, obligate intracellular bacteria. They have been associated with illnesses of veterinary importance. Furthermore, they are currently considered as emerging human pathogens.

The former genus *Ehrlichia* was divided into three groups based on the nucleotide sequence of the 16S rDNA gene. Because of this reorganization, all representatives of the *Ehrlichia phagocytophila* genogroup are now described as *Anaplasma phagocytophilum*. It multiplies in granulocytes. According to their target cells they cause human granulocytic anaplasmosis.

Normally, 60% of infections with *A. phagocytophilum* are asymptomatic. After an incubation period of two to 7days, the infection starts with a flu-like illness with fever, arthralgia and malaise. Typical signs are suppression of the bone marrow and failure of liver function. Complications appear in the form of secondary infections such as Candidiasis and pneumonia. Lethality is about 7% to 10% and depends on the age and the immune system of the patient. Therapy with antibiotics is possible.

Babesia spp. are obligate intracellular parasites which reside in erythrocytes. The taxonomic classification places them in the phylum *Apicomplexa*, order *Piroplasmida*.

Babesiosis is a well-known disease of veterinary importance and is gaining increasing attention as an emerging tick-borne disease in humans (Homer et al. 2000; Kjemtrup and Conrad 2000). More than 100 *Babesia* species have been reported, but only a few have been identified as causing human infections. In Europe, human infections are mainly caused by *Babesia divergens*, in America by *Babesia microti.*

Normally, most of the infections remain subclinical. In the past, clinical manifestations were mainly observed in immunocompromised patients, for instance after a splenectomy. But in the last years, there are increased numbers of infections in healthy persons. After an incubation period of one to 3 weeks, a flu-like illness with fever, arthralgia and weakness emerges. The main symptoms are haemoglobinaemia and haemoglobinuria. Often hepatosplenomegaly and renal failure are observed.

In most of the cases, the disease is self-limited. Complications may occur in immunocompromised, splenectomised and elderly persons.

B. microti, which persists in rodents, has been shown to cause human infections in North America even in immunocompetent hosts (Granström 1997; Kjemtrup and Conrad 2000).

To evaluate the impact of climate changes, it is important to know the status quo of the agents mentioned above. For southern Germany, only a few epidemiological data exist. Therefore it is necessary to determine the prevalence of *C. burnetii, Rickettsia* spp., *A. phagocytophilum* and *Babesia* spp. in ticks and in their potential reservoir hosts.

Material and methods

Tick sampling

Ixodes ricinus (nymphs and adults) and *Dermacentor* spp. (adults) were collected in different areas of Baden-Wuerttemberg by blanket-dragging (Fig. 2).

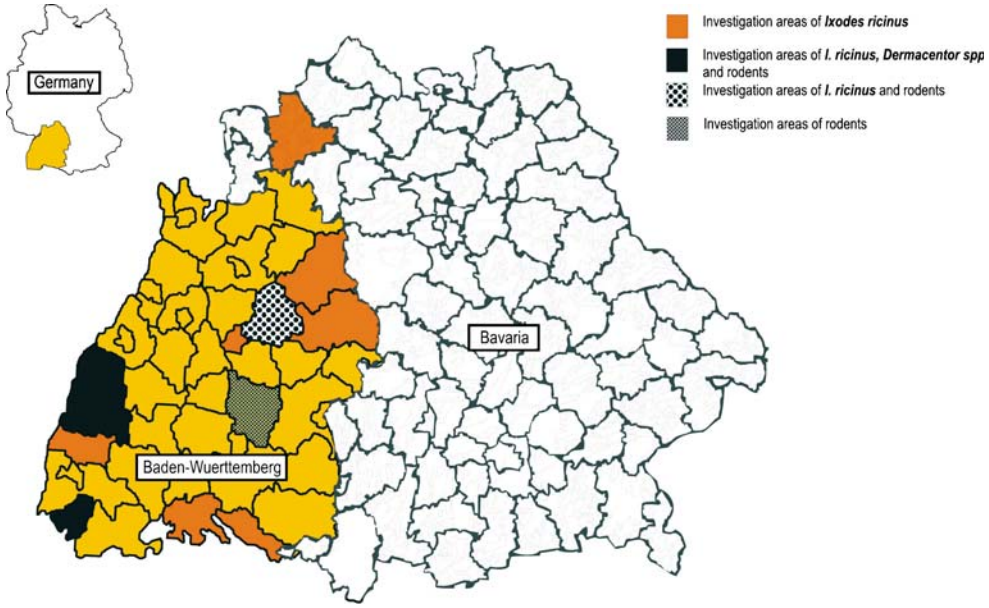

Fig. 2 Investigation areas of ticks and rodents in Baden-Wuerttemberg and Bavaria

Rodent sampling

Rodents originated also from Southern Germany (Fig. 2).

DNA extraction of ticks and rodents

DNA was extracted from *I. ricinus* using the Chelex-based method which is a fast DNA extraction procedure (Walsh et al. 1991). The method was modified as described by Hartelt et al. (2004).

DNA from *Dermacentor* spp. was extracted with the Maxwell instrument (Promega), which uses size-fractionated silica particles to bind the DNA in the presence of guanidinium isothiocyanate (Boom et al. 1990). After washing in a guanidinium-containing buffer, the DNA was eluted in nuclease-free water and was either used immediately for polymerase chain reaction (PCR) or stored at −70°C.

Rodent DNA was extracted from a 0.5 × 0.5-cm piece of the lung using also size-fractionated silica particles as described above.

Detection of *A. phagocytophilum, Rickettsia helvetica* and *Babesia spp.* by PCR

The detection of *A. phagocytophilum*, *R. helvetica* and *Babesia* spp. in *I. ricinus* was performed as described by Hartelt et al. (2004).

Detection of *Rickettsia* spp. and *C. burnetii* by PCR

The detection of *Rickettsia* spp. and *C. burnetii* was performed by PCR. These data will be published elsewhere.

DNA sequencing

All positive PCR products, used for DNA sequencing, were purified with Qiaquick purification kit (Qiagen). For DNA sequencing reactions, the fluorescence-labelled didesoxy-nucleotide technology was used. The sequenced fragments were separated, and the data were collected with an ABI PRISM 310 Genetic Analyzer (Applied Biosystems). Sequencing analysis was performed using BLAST (http://www.ncbi.nlm.nih.gov/blast/Blast.cgi).

Results and discussion

Q-fever has a worldwide distribution and is transmitted by more than 40 tick species. In Central Europe, the sheep tick *Dermacentor marginatus* is the most important vector. Germany has not always been an endemic area for Q-fever; probably, the pathogen and its vector have been imported from endemic areas after the second world war (Liebisch 1977).

The epidemiology of Q-fever is very complex. For Central Europe, Liebisch (1977) has developed an infective pathway, which consists of two cycles (Fig. 3): a basic part that takes place in natural foci, where the infection circulates between larvae and nymphs of *D. marginatus* and rodents. Twice a year, the adults of *D. marginatus* emerge and transmit the infection to large wild and domestic animals, mainly sheep. This is the second part of the cycle. Additional infections can occur by inhalation of contaminated material such as dried tick faeces or parturient fluids of infected sheep. Humans are infected almost exclusively by the aerosol route of the second cycle.

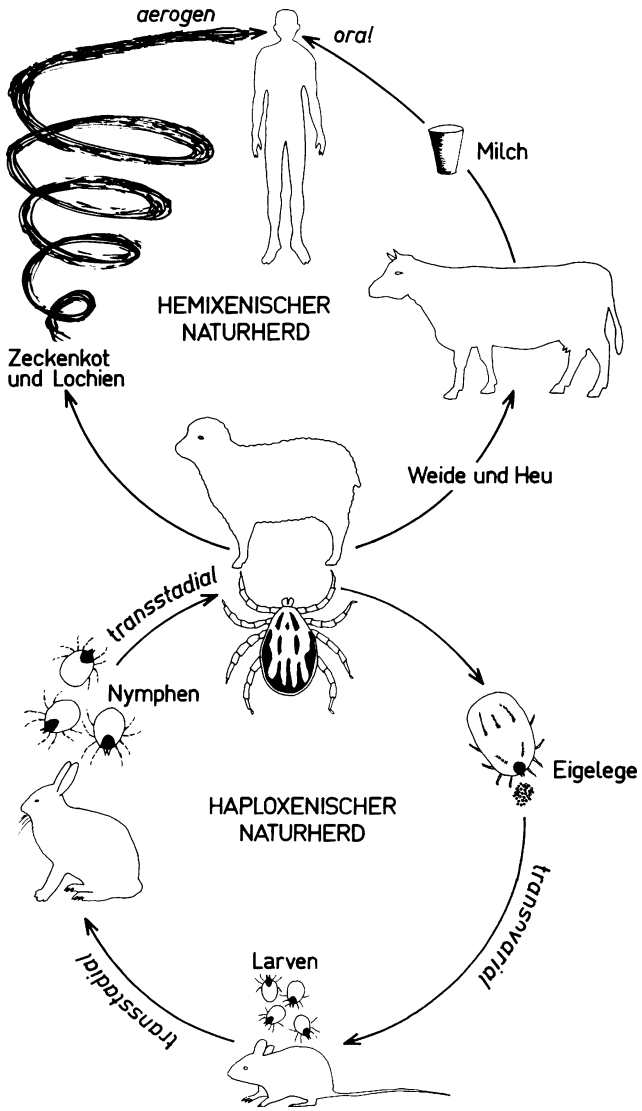

Fig. 3 Transmission of *Coxiella burnetii* (Liebisch 1977)

There are no exact data of the frequency and actual distribution of *D. marginatus*. Therefore, more than 1,000 engorged *D. marginatus* ticks and 50 tick faeces samples were collected from sheep and investigated for *C. burnetii* by PCR in a cooperation study. Interestingly, *C. burnetii* could be detected only in one tick and one faeces sample from Loerrach, in the southern Rhine valley (Sting et al. 2004).

Furthermore, 422 free-living *Dermacentor* spp. ticks from the Kinzig valley (county of Ortenau), 440 ticks from the southern Rhine valley (county of Loerrach) as well as 119 small rodents, collected in the same counties as the ticks, were tested for *C. burnetii* infections by PCR. In these studies, *C. burnetii* could not be isolated in any case (Dezfuli 2006; Pluta 2008). Therefore, it may be assumed that the natural foci are very small and were not found in our investigation. The vector competence of *Dermacentor* spp. is beyond question, because after an outbreak in Hammelburg (Unterfranken, Bavaria) a tick infection rate of 9% was found (Thoms 1996).

Q-fever is a notifiable disease but usually only outbreaks are registered. Therefore, seroepidemiological studies would be important to find out the frequency of Q-fever infections. In southern France, Maurin and Raoult (1999) found a seroprevalence of 30% in a rural population (n = 22,500). In former investigations from Germany percentages of 19% (n = 715) near Tuebingen (Baden-Wuerttemberg) (Heinrich et al. 1983) and 23% in Rollshausen (Hesse) (Lyytikainen et al. 1998) were found following an outbreak. In a cooperation study in 2007, a cross-sectional survey was made in Leutkirch (Baden-Wuerttemberg) (n = 2,447) where a seroprevalence of 7.4% for *C. burnetii* was found (Frangoulidis et al. 2007). The district of Leutkirch is not known as an endemic region for Q-fever, and thus this may be an average percentage in Baden-Wuerttemberg. In endemic regions, the seroprevalence is higher. This could be shown, for example, in a seroepidemiological study from Stetten a. k. M. (Swabian Alb, Baden-Wuerttemberg), where prevalences of more than 40% could be detected in soldiers which stayed there for 3 years (Kilb 2007).

These investigations show that the occurrence of Q-fever in Central Europe, especially in southern Germany, is more common than results from the official notification.

It is possible that the importance of ticks as vector is overestimated. In southern Germany, a connection between distribution areas of *D. marginatus* and the temporal occurrence of adult *Dermacentor* ticks in correlation with Q-fever infections could be observed (Weise 1971). However, in the last years, the biggest human outbreaks in Germany, in Jena and Soest, were caused by the aerogenic route with direct or indirect contact to infected animals. In both areas, *D. marginatus* is not present and *I. ricinus* is not a vector for *C. burnetii*, as shown in studies from Switzerland, Hesse and Baden-Wuerttemberg (Burgdorfer et al. 1979; Fritz 1994; Dezfuli 2006). Many questions regarding the epidemiology of Q-fever in Central Europe remain open.

Rickettsia spp. are distributed worldwide. In western Europe, three species are known. *R. helvetica* in *I. ricinus* and *Rickettsia slovaca* in *Dermacentor* spp. cause mild or asymptomatic illness (Hassler 2001). In contrast, *Rickettsia conorii*, which is found in the Mediterranean area, causes a sometimes serious disease, the Mediterranean spotted fever. It is transmitted mainly by *Rhipicephalus sanguineus* and *Dermacentor* spp. (Raoult and Roux 1997).

We investigated more than 1,000 *I. ricinus* of three different areas in Baden-Wuerttemberg for *Rickettsia* spp. by PCR. The infection rate was surprisingly high, at an average of nearly 9%. The positive PCR products were sequenced and they all belonged to the species *R. helvetica* (Table 1) (Hartelt et al. 2004). Apart from ticks, potential

Table 1 Prevalence of *Rickettsia* spp., *Anaplasma phagocytophilum* and *Babesia* spp. in nymphs and adults of *Ixodes ricinus* and adults of *Dermacentor* spp.

I. ricinus examined/ *R. helvetica* pos.	*Dermacentor* spp. examined/ *Rickettsia* spp. pos.	*I. ricinus* examined/ *A. phagocytophilum* pos.	*I. ricinus* examined/ *Babesia* spp. pos.
1,187/105 (8.9%)	862/167 (19.4%)	5,424/54 (1.0%)	3,113/31 (1.0%)

reservoir hosts play an important role for the distribution of *R. helvetica*. Therefore 411 rodents were investigated (Table 2), but none of the 199 *Muridae* and 212 *Arvicolidae* was infected. Therefore, it may be supposed that rodents are no competent reservoir hosts for *R. helvetica.*

Dermacentor ticks of the Rhine valley (n = 440) and Kinzig valley (n = 422) were also investigated for *Rickettsia* spp. The infection rate was about 20% (Table 1). The *Rickettsia* spp. species could not be defined by sequencing of positive PCR products, but *R. conorii* could be excluded (Pluta 2008).

Commonly, *A. phagocytophilum* is transmitted to its hosts by ticks of the genus *Ixodes*. In Europe, diseases caused by *A. phagocytophilum* are uncommon (Petrovec et al. 1997; van Dobbenburgh et al. 1999), in contrast to infections. This was pointed out by seroepidemiological studies on forestry workers (n = 4,332) in Baden-Wuerttemberg, southern Germany, where seroprevalences ranged from 5% to 16%. The average prevalence was about 10.7% (Oehme et al. 2002). In a control group, prevalences are expected to be lower (Fingerle et al. 1997). Serological investigations from Switzerland, Denmark, Scandinavia and Bulgaria showed seroprevalences with more than 20% (Weber et al. 2000; Skarphédinsson et al. 2001; Bjoersdorff et al. 1999; Christova and Dumler 1999). These data indicate that *A. phagocytophilum* is present in Europe. The serological results coincide with the prevalence in ticks. The prevalence of *A. phagocytophilum* in eleven areas in Baden-Wuerttemberg was determined. Altogether, 5,424 ticks were collected and tested for *A. phagocytophilum*. The average infection rate was 1.0%. The prevalence ranged from 0% in the county of Loerrach to almost 3% in the county of Rems-Murr (Table 1) (Hartelt et al. 2004). Tick investigations were performed in Germany and in other European countries. Thereby, infection rates with more than 24% could be registered (Cinco et al. 1997; Schouls et al. 1999; Christova et al. 2003; Skarphédinsson et al. 2007).

Rodents play an important role as reservoir host for tick-borne diseases. Therefore, 512 rodents from Baden-Wuerttemberg were investigated by PCR. In *Arvicolidae*, *A. phagocytophilum* could be detected in 13.4% of red bank voles (*Myodes glareolus*, n = 149) and in 6.2% of field voles (*Microtus agrestis,* n = 97). In contrast, only one out of 259 investigated *Muridae* was *A. phagocytophilum* positive (Table 2). Therefore it can be assumed that *Arvicolidae* act as reservoir host for *A. phagocytophilum* in southern Germany. Investigations from Switzerland and England showed that deer and sheep can also be reservoir hosts (Liz et al. 2002; Odgen et al. 2003).

Numerous *Babesia* species are transmitted by ticks. Vectors for human pathogens are ticks of the genus *Ixodes*. *Dermacentor* spp. and *Rhipicephalus* spp. are important for veterinarian pathogens.

Diseases caused by *Babesia* spp. are uncommon in Central Europe, in contrast to infections. Seroepidemiological investigations from Germany, performed in healthy blood donors, show a prevalence of 1.7% (Hunfeld et al. 2002). In persons with tick exposure, prevalences of 10%

Table 2 Prevalence of *Anaplasma phagocytophilum* and *Babesia* spp. in rodents and number of rodents examined for *Rickettsia helvetica*

Family	Species	Rodents examined for *R. helvetica*	Rodents examined/*A. phagocytophilum* pos.	Rodents examined/*Babesia* spp. pos.
Arviculidae	*Myodes glareolus*	136	149/20 (13.4%)	149/2 (1.3%)
	Microtus arvalis	62	97/6 (6.2%)	97/2 (2.1%)
	Microtus agrestis	1	1/0 (0%)	1/0 (0%)
	Microtus spp.	–	6/0 (0%)	6/0 (0%)
	total	199	253/26 (10.3%)	253/4 (1.6%)
Muridae	*Apodemus flavicollis*	186	218/1 (0.5%)	192/0 (0%)
	Apodemus sylvaticus	21	32/0 (0%)	58/0 (0%)
	Apodemus spp.	5	9/0 (0%)	5/0 (0%)
	total	212	259/1 (0.4%)	255/0 (0%)
Arvicolidae and *Muridae*	total	411	512/27 (5.3%)	508/4 (0.8%)

and 15% were determined in Germany and Sweden (Hunfeld et al. 1998, 2002; Uhnoo et al. 1992). These results coincide with the prevalence in ticks. For the examination of *Babesia* species 3,113 *I. ricinus* were collected. They originated from two areas in Baden-Wuerttemberg and from one area in Bavaria. The prevalence in these ticks was 1.0% on average (Table 1). By sequencing, 90% of the positive PCR samples were identified as *B. divergens* and 10% were identified as *B. microti* (Hartelt et al. 2004). Similar infection rates exist in the southwest of Baden-Wuerttemberg and in Bavaria. Therefore it is safe to conclude that *Babesia* spp. are prevalent in southern Germany.

The original hosts for *B. divergens* are cattle. Haemoglobinuria, the so-called "Weiderot", is an important symptom of the infection and it is widespread in southern Black Forest. An obligate host change between *I. ricinus* and a vertebrate is typical for the life cycle of *Babesia*. In the USA, the most important vertebrate hosts for *B. microti* are the white foot mouse (*Peromyscus leucopus*) and prairie vole (*Microtus ochrogaster*) (Homer et al. 2000; Burkot et al. 2000). To determine the reservoir hosts in southern Germany, a total of 509 rodents were investigated for *Babesia* spp. The average infection rate was 0.8%. Interestingly, *B. microti* could be detected in 1.6% of 253 *Arvicolidae*, whereas no infections were seen in the family *Muridae* ($n = 255$) (Table 2). Similar results were obtained in northern Germany (Walter and Liebisch 1980) and Switzerland (Gern and Aeschliemann 1986), where the prevalence was about 1.6% and 3%, respectively. Only *B. microti* could be detected in *Microtus agrestis* and in *Sorex araneus* (common shrew). In eastern Europe, a shift in the reservoir host could be observed. The prevalence in rodents, which was 10% to 20%, was much higher than in western Europe. Moreover, not only *Arvicolidae* but also *Muridae* are infected (Sinski et al. 2006). These results correlate well with the high infection rate of ticks. Obviously, the reservoir host range in Western Europe, where only *Arvicolidae* are infected, is smaller. In consequence, lower infection rates of ticks could be determined.

Conclusions

It can be assumed that global changes have consequences on the described tick-borne infections. However, the reasons are different (Kimmig 2007):

Q-fever D. marginatus is a thermophilic tick. If the temperatures increase, a further distribution of this tick species is expected. This process has already begun. When Liebisch (1977) did his investigations, the ticks have been found only in the valleys of Rhine and Main. In these areas *C. burnetii* could also be isolated in ticks. Since the 1980s, the number of ticks has apparently increased (Liebisch and Rahman 1976; Dezfuli 2006; Pluta 2008). Today, *D. marginatus* can be found even at the foot of the Swabian Alb, where this tick species was not known earlier. If *D. marginatus* reaches the plateau of the Swabian Alb, considerable problems are expected because this is a region with intensive sheep breeding. The climate prognosis for Germany for the next years predicts hot and dry summers. These conditions will favour the aerogen distribution of Q-fever. In the next few years, in spite of the role of ticks in the epidemiology of Q-fever, a spread of Q-fever and an accumulation of the disease should be expected.

What can we do for prevention? To limit the risk of Q-fever there are two possibilities: To reduce an increase of *D. marginatus*, sheep can be treated with acaricides when the adult ticks appear. In consequence, the engorged adult female ticks die before reproduction and the sheep are no longer important as reservoir hosts.

The second and perhaps the better possibility is vaccination of the sheep against *C. burnetii*, which will prevent sheep from abortion. In consequence, the amount of *C. burnetii* in the environment will be reduced dramatically. For both measures, a close cooperation between physicians and veterinarians as well as legal and financial support are necessary.

Rickettsiosis At the moment, the situation regarding Rickettsiosis in Germany is without risk. But it has to be kept in mind as an effect of global warming. Then a spread of the disease is possible. The main vector *R. sanguineus*, which is often brought to Germany with dog transports, can not survive in the environment at the moment in Germany because the temperature is too low for its development. This could change with increasing temperature and it can be expected that natural foci will develop in Germany. There are already some populations of *R. sanguineus* in houses, which could present an infection risk. Furthermore, dogs represent a risk factor because they can act as reservoir hosts for *Rickettsia* spp., especially for *R. conorii* (Krauss et al. 2004). *Rickettsia* spp. could therefore be transmitted from infected dogs, which were imported from the Mediterranean area, to *Dermacentor* spp., which are distributed in Germany. Therefore infections may be easily established in free-living *R. sanguineus*. The necessary measures for prevention of Mediterranean spotted fever are difficult, with one exception: The importation of dogs from the Mediterranean area should be subjected to a better surveillance by veterinarians.

Anaplasmosis and Babesiosis In general, it can be expected that infection cycles between ticks and rodents will be intensified due to global warming. First of all, it depends on

the population density of the rodents, which increases in mild and warm winters. These data demonstrate the status quo for southern Germany. Further observations are necessary to estimate if an increase of rodent and tick populations will lead to an increase of the prevalence of *A. phagocytophilum* and *Babesia* spp.

The knowledge of the prevalence of infectious agents in ticks and in their reservoir hosts as well as the ecology of the vectors is an important prerequisite for risk assessment of human diseases. Therefore, to evaluate these effects of global warming, continuous studies are necessary in the next years.

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