REVIEW

Tick-borne zoonoses in Europe

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Worldwide, many infections caused by viruses, bacteria or parasites are known to be tick-transmitted zoonoses, i.e. infections transmitted from animals to humans. The present review covers zoonoses which are known to be or suspected to be tick-transmitted in large parts of Europe, i.e. Lyme borreliosis (LB), tick-borne encephalitis (TBE), ehrlichiosis and babesiosis, while other infections, which can or might be tick-transmitted or are only present in localized geographic areas, e.g. Q fever, tuleremia and Mediterranean spotted fever, are not discussed.

Tick-borne zoonoses as a cause of human disease have been known for many years but the major impact on public health in Europe and in the USA was first recognized by identification of *Borrelia burgdorferi* as the cause of Lyme disease in the early 1980s. Since then, LB has emerged as the most common and significant arthropod-transmitted zoonosis in these parts of the world.

LYME BORRELIOSIS

LB is caused by a cultivable spirochete, a new species of the genus *Borrelia* (family Spirochaetaceae), transmitted by hard ticks (Ixodidae) of the genus *Ixodes*. In Europe, the vector is *Ixodes ricinus*. Animal reservoirs are small animals (rodents) but large animals, e.g. deer, cattle and horses, are important for the life cycle of the tick. The causative agent of LB was isolated by and named after Willy Burgdorfer in the USA [1,2].

Later, it was found that LB has a wider clinical spectrum in Europe than in the USA, and this was shown to be due to the presence in Europe of at least three genospecies of *B. burgdorferi* sensu lato, i.e. *B. burgdorferi* sensu stricto, *B. garinii* and *B. afzelii*, as compared to the one genospecies, *B. burgdorferi* sensu stricto, in the USA [3–5]. Of the genospecies, *B. afzelii* has predominantly been associated with acrodermatitis chronica atrophicans, *B. garinii* with neurologic manifestations and *B. burgdorferi* sensu stricto with arthritis, while erythema migrans is caused by all three genospecies.

A majority of the clinical manifestations of *B. burgdorferi* sensu lato infection, e.g. erythema chronicum migrans or erythema migrans (EM), lymphocytoma benigna cutis, acrodermatitis chronica atrophicans (ACA), meningopolyneuritis and a connection between EM and meningitis were first described many years ago by European clinicians [6–11]. Use of penicillin for treatment of EM was described in the early 1950s by Swedish physicians [12,13]. In the same decade, German physicians established, by studies in volunteers, that both EM and ACA were caused by a transmissible agent [14,15]. These and other European physicians also suggested a spirochetal etiology, and treatment of chronic meningitis by penicillin was shown to be efficient [16]. However, it was not until a disease, dominated by the clinical manifestation of arthritis, was noted in Lyme, Connecticut, USA, that the causative agent was recognized [17].

LB has been reported from all European countries but national surveillance methods, when in place, vary between countries in Europe and do not allow for comparisons of disease incidence rates [18]. The USA, with a federal epidemiologic surveillance organization, reports a major increase in disease incidence over the past 10 years, as well as an expansion of the disease to previously less affected or unaffected areas [19]. The increase in and expansion of the disease is presumed to be due to the rapid increase in the number of white-tailed deer, with an increased presence in densely populated areas [20]. No certain data are available from

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Europe but a corresponding increase in the roe deer population has been noted, e.g. in Scandinavia [21], as well as an expansion of its distribution limits. An increase in disease incidence is, therefore, likely to have occurred also in Europe.

The incidence of LB in a general population has only been determined in one study, conducted in southern Sweden [22]. The study, conducted in an area comprising 11% of Sweden and in 24% (2.13 million) of the Swedish population, reported an average yearly incidence rate of 69 cases per 100 000 inhabitants, with a range of 26–160 cases per 100 000. The most common manifestation was EM (77% of all cases), followed by neuroborreliosis (16%) and arthritis (7%); carditis was rare.

Although the above study is the only one available on disease incidence, indirect measures such as prevalence of *Ixodes ricinus* ticks, *B. burgdorferi* sensu lato infection rate in ticks and seroprevalence studies are available from most parts of Europe [18]. All of the indirect measures have, however, weaknesses as indicators of LB. Tick prevalence data give a rough estimate of disease prevalence; for example, low tick prevalence corresponds to low incidence of disease in northern Scandinavia [23] but high tick prevalence rates may not be followed by known, high disease rates, e.g. in Ireland [24], due to a number of confounding factors. Similarly, *B. burgdorferi* sensu lato infection rates in ticks generally correspond to known disease incidence rates within a country [23] but reported rates may not be comparable between investigators, due to methodological differences. Intensity of infection in ticks seems, however, to increase from west to east in Europe (J. Gray, personal communication). Seroprevalence represents probably the best indirect measure of disease incidence but, again, these studies are difficult to interpret on a European scale, due to methodological differences and because of a lack of correlation between seroprevalence and disease incidence.

Bearing these problems in mind, the disease seems to show a gradient of increasing incidence from west to east, although pockets of high-endemic areas are present also in low-endemic countries [24–36]. Also, a gradient of decreasing incidence from south to north (and east to west) in northern Europe [37–55] and from north to south in Italy, Spain and Greece has been noted [56–71]. The highest incidence rates are reported from central and eastern Europe, e.g. an average rate of LB of 300 per 100 000 inhabitants from Austria, with 350 per 100 000 inhabitants for the eastern and southern states of Wien, Niederösterreich, Steiermark and Kärnten [72–91].

Seroprevalence and disease incidence rates are also increased in certain occupations, e.g. forestry workers [72, 74, 92–102], in some recreational occupations, e.g. orienteers [74], and in tourists to high-endemic areas both in Europe and to the east coast of the USA [24,27]. Seroprevalence in orienteers which is comparable to that found in the general population has, however, also been reported from Sweden, where the use of protective clothing is strictly enforced [23].

Seroprevalence and disease incidence rates are influenced by gender, most studies reporting higher rates for males, presumed to be due to higher occupational risks and outdoor recreational activities [103]. Seroprevalence, incidence and, most notably, disease manifestations are also influenced by age, with children showing both high incidence rates and markedly different distribution of disease manifestations from those seen in adults; for example, children have more neurologic disease than adults [103–108].

Seroprevalence studies in large proportions of the general population are not available from any European country. Some studies offer seroprevalence data from blood donors [109–111], but results are again limited to certain areas of a country and are difficult to compare between countries, or even laboratories, due to methodological differences. An ongoing seroprevalence study based on blood-donor sera in Sweden, the only country which also has a population-based incidence study, seems to yield a correlate between seroprevalence and disease incidence, which could be used for estimates of disease incidence in other countries (own unpublished data).

Treatment strategies for LB vary between countries and physicians but several regimens are useful. Prevention is currently based on protection against tick bite but two vaccines, both based on the outer surface protein A (Osp A) of *B. burgdorferi* sensu stricto, are currently undergoing efficacy trials in the USA, and preliminary data indicate that this type of vaccine is protective (S. Plotkin, personal communication). It is, therefore, likely that a similar vaccine will eventually be available also in Europe, although manufacturing will be more complex, since the vaccine will have to include Osp A from at least the other known genospecies, *B. afzelii* and *B. garinii*, in addition to the Osp A of *B. burgdorferi* sensu stricto used in the US trials.

B. burgdorferi sensu lato has been isolated from numerous tissues, e.g. skin, cerebrospinal fluid and synovial fluid but the diagnostic sensitivity of culture is low. PCRs have also been described but the results have been variable and, in many cases, conflicting [112]. The most commonly used diagnostic method in LB is serology, including antibody detection in cerebrospinal fluid. At first, immunofluorescence (IF) and, later, enzyme-linked immunosorbent assay (ELISA) were developed. These ELISAs, based on sonicate antigens,

were later followed by ELISAs based on purified antigens, e.g. a flagellar antigen or recombinant antigens [113–117]. Immunoblot or Western blot, following screening by ELISA, has recently been recommended as a confirmatory assay in the USA [118]. It should be noted, however, that neither ELISA nor immunoblot for IgG will differentiate current infection from previous clinical or asymptomatic infections; there is thus a lack of specificity for active infection, which represents a greater diagnostic problem in high-endemic areas than lack of specificity of the assays as such.

In Europe, immunoblot is used in some reference laboratories but most routine laboratories rely on ELISA. The difference in practices is probably due to the better performance of later-generation commercial ELISA kits with high cut-off levels used in Europe, which seem to have avoided diagnostic problems of similar magnitude to those encountered in the USA. Also, before immunoblot can be recommended on a larger scale, further clarification of the importance of the phenotypic heterogeneity of *B. burgdorferi* isolates in Europe and the definition of common European immunoblot criteria seems to be needed.

The European Union, recognizing the need for a joint effort in the field of Lyme disease, supported a Concerted Action on Lyme Borreliosis (EUCALB; coordinated by Dr Jeremy Gray). This network of scientists and clinicians from 17 European countries investigated disease transmission, diagnostics and clinical aspects of the disease. The network has addressed, among other issues, the need for standardization of serodiagnosis by launching a quality assurance scheme and by an immunoblot study to establish common European criteria. In collaboration with the WHO, the network contributed to serodiagnostic recommendations [119]. Also, European case definitions and laboratory support for diagnosis have been published [120] and information on different aspects of LB in Europe has been made available on the Internet (http://www.dis.strath.ac.uk/lymeeu/).

TICK-BORNE ENCEPHALITIS

The disease is caused by tick-borne encephalitis virus (TBEV) of the family Flaviviridae, genus *Flavivirus* (formally group B arbovirus), a family including many other known arthropod-borne viruses, e.g. those causing yellow fever, dengue and Japanese encephalitis. Two subtypes of TBEV are recognized, one European and one Far Eastern, transmitted by *Ixodes ricinus* and *Ixodes persulcatus*, respectively. The distributions of the two related tick species overlap in north-eastern Europe but, in general, the vector of TBEV is *I. ricinus* in western and central Europe and *I. persulcatus* in the European parts of Russia. Host reservoirs with regard to mammals and rodents are the same as for *B. burgdorferi* sensu lato. Since TBE has been the subject of two recent, extensive reviews [121,122], only some facts on the virus, i.e. the disease, epidemiology, diagnostics and prevention, will be summarized here.

TBE is a major cause of morbidity in central, eastern and northern Europe [23,78,121–142]. West of a sharp demarcation line running from mid-Sweden though mid-France, the disease is rare or non-existent. Disease incidence increases, as for LB, from west to east, with a highest reported rate of 184 per 100 000. Seroprevalence rates as high as 22–83% have been reported from some areas [23,78,127,138].

The disease with meningoencephalitic manifestations was first described from Austria in 1927 and from Russia in 1932. The virus was first isolated from human tissue in 1937 and the prototype strain for the western subtype, Neudoerfl, was isolated from a tick in Austria in 1971. TBEV has three major proteins, a structural protein C (Core or V2) and two glycoproteins of the envelope, the hemagglutinin E (or V3) and the membrane M (V1) proteins. The C and E proteins are stable and identical for both the western and the eastern subtypes, while the M protein varies with the isolates.

As for LB, most of the infections [60–70%] are subclinical. In clinical cases, the incubation period is usually 7–14 days and the first viremic stage with flu-like symptoms lasts generally for 2–8 days. This first phase of a biphasic disease is reported by some 60–70% of patients who later go on to develop the second, neurologic stage. An abortive infection after the first stage is seen in a majority of the clinical cases. The second stage is found in 5–30% of cases with clinical disease, and the manifestations vary from pure meningitis to meningoencephalitis, with or without paralysis. Reported mortality rates for the western subtype of TBEV infection vary between 0% and 4% [121,123, 125,128–130].

The disease is relatively mild in children and both the severity of the disease and the risk for permanent sequelae increase with age [121,137]. The reported rates of long-term sequelae vary between 2–11% for permanent paresis [121,124,126,131,135,138], 7–14% for hearing defects [121], and 0–24% for cerebellar dysfunction [121,124,135,138]. In carefully conducted follow-up studies, postencephalitic symptoms were found in 36–58% of patients and were classified in a majority of cases as moderate to severe [121,135,138].

Laboratory diagnosis of the disease relies mainly on serology. The first assays, still in general use, were the complement-fixation (CF) and the hemagglutination-inhibition (HI) tests, introduced in the late 1950s [123,143]. Both methods allow for confirmation of the

diagnosis within 1–2 weeks after onset of symptoms. Early diagnosis can be achieved by demonstration of IgM antibodies [144,145]. An indirect ELISA assay for IgM and IgG antibodies is commercially available [146,147]. The neutralization test (NT) can also be used but the usefulness of the assay is mainly for determination of antibody responses after vaccination. In general, these assays are considered specific and reliable for diagnosis of TBE. However, a recent study showed that significant amounts of antibodies reactive in the TBE ELISA and HI tests, but not in the NT, are induced by yellow fever vaccination and/or dengue fever infection [148].

No specific treatment is available for this devastating infection. Prophylaxis and post-exposure prophylaxis with specific immunoglobulin can be given up to the fourth day of presumed exposure [149]. Vaccine against TBEV has been available for many years but an improved version was introduced in 1980 and has a protective efficacy of 97% [150,151]. Currently, two manufacturers provide a vaccine against TBEV [150, 152]. Simultaneous administration of both immunoglobulin and vaccine has also been documented [152]. Mass vaccination campaigns have been performed in Austria and in southern Germany, and the vaccine is also widely used in other endemic countries [153]. A cost–benefit analysis of mass vaccination gave favorable results in Austria [154] and a vaccine strategy could be considered also in countries with lower disease incidence rates [121].

EHRLICHIOSIS

The genus *Ehrlichia* (family Rickettsiaceae), named in honor of the German bacteriologist Paul Ehrlich, consists of obligate intracellular pathogens that invade white blood cells. Ehrlichiae are known to cause disease in animals in Europe but were not known or considered as likely human pathogens on this continent until recent research, conducted in the USA, identified ehrlichiosis as an emergent, tick-borne zoonosis.

Monocytic ehrlichiosis

In 1986, infection with an *Ehrlichia* species was recognized in a patient at Fort Chaffee, Arkansas, USA, by characteristic morulae (inclusion bodies) in circulating mononuclear cells and by a significant antibody response to *E. canis* antigen [155]. The causative agent was isolated in 1991 [156] and was shown by 16S RNA to be closely related but not identical to *E. canis*. It was classified as a species of its own, named *E. chaffeensis*. Several recent American reviews give extensive information on the disease [157–159]. Therefore, only a summary will be presented here, with special reference to our current knowledge of the situation in Europe.

Infection in humans varies from subclinical to fulminant, with an estimated fatality rate of approximately 2% and a reported hospitalization rate of 40% for clinical cases. In the USA, more than 400 clinical cases have been recognized. However, most of the infections seem, as for LB, to be subclinical, abortive or mild. The most common clinical manifestation is a flu-like illness with fever, malaise and myalgia [160]. Common laboratory findings include leukopenia, thrombocytopenia, anemia and elevated liver transaminases [157–160]. The treatment of choice is doxycyclin.

Severe disease manifestations reported were respiratory insufficiency, i.e. adult respiratory distress syndrome (ARDS), renal failure and severe hepatic disease. Serious neurologic involvement was manifested by seizures, coma and lesions on autopsy with pleocytosis, increased protein and *E. chaffeensis* antigen by PCR in the cerebrospinal fluid [159]. A seronegative, fatal case of *E. chaffeensis* infection in an HIV-positive patient has been described [161]. Persistent infection, a characteristic of ehrlichial infections in animals, has also been demonstrated in a patient [162]. No cases of blood-transfusion-transmitted infections are known.

Annual incidence rates of 3–5 per 100 000 have been estimated in the endemic areas of the southern USA but few population-based studies are available. In a heavily tick-infested area of Arkansas, a 1.3% seroconversion rate during a period of 1–4 weeks was reported in military personnel [163]. Infection rates in ticks of up to 32.5% have been reported [164].

In Europe, virtually nothing is known of either the incidence or the prevalence of the disease, but a few cases of *E. chaffeensis* infection have been reported [165–167]. Also, two individuals with low levels of antibody to *E. chaffeensis* antigen were detected in a serosurvey on the west coast of Sweden [168]. All of these cases or infections were identified by serology alone.

In the USA, the vector most consistently associated with the disease is *Amblyoma americanum* [70], the lone star tick, which is not present in Europe. Ehrlichiae have been demonstrated by PCR in adult *Amblyoma americanum* ticks (but not in nymphs) in several states and, in one case in Arkansas, in *Dermacentor variabilis* (the American dog tick). Clinical cases occurring outside the habitats of the above ticks indicate possible additional vectors and/or related ehrlichial species.

The vector in Europe remains unknown. Also, it is unclear whether the reported human cases or seropositive individuals found in Europe were infected by *E. chaffeensis* or if these serologically diagnosed individuals were infected by other ehrlichial species,

showing immunological cross-reaction with *E. chaffeensis* antigen.

The animal reservoirs and susceptible hosts are, as yet, not fully identified in the USA. The white-tailed deer is susceptible to experimental infection, and populations of deer show high rates of antibodies to *E. chaffeensis* in endemic areas. Experimentally infected dogs, like the white-tailed deer, show persistent infection. The role of rodents in the transmission cycle remains to be elucidated [159].

The first laboratory assays using IF used *E. canis*-infected mononuclear cells but, when slides with *E. chaffeensis* antigen became available, *E. canis* was found to be less sensitive. Currently, *E. chaffeensis*-infected cells are used for IF and reagents are commercially available [156,169]. Patients infected with *E. chaffeensis* seem to seroconvert during the second week of the disease and, unlike antibodies to LB, the antibodies to *E. chaffeensis* measured by IF return to baseline levels within 2 years after disease (S. Standaert, personal communication). Immunoblot studies indicate immunodominant proteins of 120, 29, 28 and 22 kDa [170]. No ELISA has been described for *E. chaffeensis*. PCR was introduced early for diagnosis of human disease and represents a valuable method for rapid confirmation of the disease in suspected cases [159].

Granulocytic ehrlichiosis

In 1994, human infection with a granulocytic ehrlichia was described from the northern, midwestern USA [171,172]. IF and PCR demonstrated that the disease was caused by an agent related to or identical with *E. equi* and *E. phagocytophila*, two well-known agents of veterinary diseases both in the USA (*E. equi*) and in Europe (both agents). DNA homology studies have shown 99.9% and 99.8% homology to these agents, respectively. The homology of the new agent to the monocytic *E. chaffeensis* was only 92.5% [172].

The agent of human granulocytic ehrlichiosis (HGE) is currently unnamed, since it remains unclear whether it represents a new species or whether the human infection is caused by *E. equi*/*E. phagocytophila*. The relation between the three agents causing granulocytic ehrlichiosis is also unclear. The main difference between *E. equi* and *E. phagocytophila* seems to reside in host specificity [173], but small differences in the 16S rRNA sequences between the three have also been noted [174,175]. A horse experimentally infected with the HGE agent developed symptoms as of *E. equi* infection and was resistant to subsequent challenge with *E. equi* [176].

As for *E. chaffeensis* infection, recent American reviews give extensive information on granulocytic ehrlichiosis [157–159]. Therefore, only a summary will be presented here, with special reference to our current knowledge of the situation in Europe. Since HGE was described recently, only some 70 clinical cases have been diagnosed in the USA. Also as for *E. chaffeensis* infection, clinical disease seems to vary from subclinical to fulminant, with an estimated fatality rate of approximately 7–10% in clinical cases. The most common clinical manifestation of HGE is, as for *E. chaffeensis* infection, a flu-like disease [159]. In addition, infection causes thrombocytopenia, leukopenia and elevated transaminases in a majority of clinical cases.

Cases of HGE have been described from the north-midwestern and north-eastern states of the USA. A recent report indicates an incidence rate of 9–15% in patients with symptoms compatible with HGE in the midwestern USA or an estimated minimum incidence of 3 per 100 000 [177]. The vector seems to be the same as for LB, i.e. *I. scapularis*, in the eastern and midwestern USA. Tick-infection rates with the HGE agent of 10% in the midwest and up to 50% on the east coast have been reported [159,164].

The transmission cycle of the HGE agent has not been fully elucidated. The white-tailed deer seems to represent a likely reservoir [159] but the role of rodents remains to be clarified. Also, modes of transmission other than tickbites, e.g. from blood of deer, have been suggested [178].

Infection of humans with the HGE agent has recently been reported from Europe, where 12 of 70 (17.1%) Swiss LB patients were found to be seropositive for the HGE agent [179]. HGE agent infection in LB patients and in tick-exposed individuals in the UK has been shown [180]. A study from Norway showed 10.2% seropositives among LB patients [181]. Similarly, 3.8% of LB patients from Denmark were seropositive for the HGE agent (K. Hansen, personal communication). A seroprevalence study [168] in a tick-infested area of south-western Sweden showed 21 of 185 (11.4%) HGE seropositives in a general population where the rate for LB seropositives was 25 of 185 (13.5%). These studies indicate that HGE is a common tick-borne infection in Europe.

In Europe, the vector of the HGE agent has not been previously identified, although *I. ricinus* is a likely candidate. *I. ricinus* is the known vector of *E. phagocytophila* in Europe. Also, *I. ricinus* is closely related to *I. scapularis*, the vector of LB in Europe and in the USA, respectively. We have recently demonstrated, by PCR and 16S rRNA sequence analysis, the presence of the agent in Swedish *I. ricinus* ticks at a similar rate as in the mid-western USA (own unpublished data). The animal reservoirs have not yet been established but the HGE agent has been identified as a common cause of clinical disease in Swedish dogs and horses [174,182].

The diagnosis of HGE is based on IF with *E. equi* or *E. phagocytophila* antigen for antibodies to the HGE agent [159]. Antibodies measured by IF seem to return, as for *E. chaffeensis*, to baseline level within 2 years of infection (S. Dumler, personal communication). Currently published studies have been done by investigators using their own slides, prepared by experimental infection of horses or sheep. Commercial slides are available but are not useful for diagnosis of human infection (own observations). The recent in vitro culture of the HGE agent in HL60 cells, a human leukemia cell line, will facilitate serodiagnosis and experimental studies [183]. PCR is a useful tool for the diagnosis of current infection [159]. Immunoblot studies of HGE show a specific band at 44 kDa, identified in all human convalescent sera, and additional bands at 100, 42 and 25 kDa [184]. ELISA has not been used for diagnosis of human disease but an ELISA has been described for antibody response to *E. equi* infection in horses [185].

BABESIOSIS

The causative agents, *Babesia* species (phylum Apicomplexa), which are pear-shaped, malaria-like, protozoan parasites, represent a major veterinary pathogen worldwide [186]. The parasite was named after Victor Babes, a Hungarian naturalist, who in 1888 described an intraerythrocytic pathogen causing febrile hemoglobinuria in cattle in Transsylvania, present-day Rumania [187]. The piroplasms are represented by two families, the Babesiidae and the Theileriidae. The two differ in target cells, most *Babesia* species multiplying only in erythrocytes, while *Theileria* species first invade lymphocytes before invading erythrocytes. They also differ in the mode of replication in ticks. Recent phylogenetic analyses indicate that some of the agents currently classified as babesiae are more closely related to theileriae, and reclassifications have been proposed [188,189].

More than 100 *Babesia* species are known but only two, *Babesia divergens* in Europe and *Babesia microti* in the USA, have until recently been shown to cause disease in humans. Of these, *Babesia divergens* belongs to the classical *babesiae*, while *Babesia microti* is a more *Theileria*-like organism. In 1991, a *Babesia* species causing human disease, designated WA1, was described from California and was subsequently shown to be a new species, related to but different from *Babesia gibsoni* [190]. Then, in 1996, a strain resembling but not identical to *Babesia divergens*, designated MO1, was isolated from a fatal case in a splenectomized patient in Missouri, USA [191].

Babesia divergens

The first human case of babesiosis was described in 1957 from Yugoslavia, a fatal case of *Babesia divergens* infection in a splenectomized farmer [192]. Since then, some 25 clinical cases of *Babesia divergens* infections have been described from all parts of Europe [193,194]. A majority, or some 85%, has occurred in splenectomized patients and the mortality rate has been about 50%. The disease is characterized by fever, myalgia, hemolytic anemia and hemoglobulinuria, with renal failure and sometimes pulmonary edema in the most severe cases. The disease has recently been successfully treated by exchange transfusion in severe cases, in combination with quinine and clindamycin.

Although *Babesia divergens* is an important pathogen in cattle all over Europe, *Babesia divergens* infection in immunocompetent individuals has hardly been looked for. A congress report from western France indicated 8% asymptomatic seropositives in 408 individuals but the rate was 2 of 408 (0.5%) if a more conservative cut-off level of ≥1/80 was used [195]. In a case report of the first case of *Babesia divergens* infection in a splenectomized patient in Sweden, the authors mention that 13% (2 of 15) of Swedish LB patients were found to be seropositive to *Babesia divergens* [196]. Since the infection rate in immunocompetent individuals has not been investigated, it is not known if blood-transfusion transmission could occur.

I. ricinus, the vector of *Borrelia burgdorferi*, is also a vector for *Babesia divergens* but others cannot be ruled out. Cattle represent the obvious reservoir.

Diagnosis of *Babesia divergens* infection can be made by identifying intraerythrocytic parasites on blood smears (to be differentiated from malarial plasmodiae) in severe cases with a high degree of parasitemia, as seen in splenectomized patients. Inoculation of gerbils, which are highly susceptible to *Babesia divergens*, can also give the diagnosis. Serologic diagnosis of *Babesia divergens* is made by IF on smears from experimentally infected animals [196]. Antibodies seem to decrease to base-line levels within a year in the few followed-up cases [196]. *Babesia divergens* has recently been cultured in human and animal erythrocytes [197] and in a serum-free medium supplemented with human high-density lipoproteins [198]. ELISA for *Babesia divergens* has been reported to measure antibodies in bovine sera [199] but not in human sera. No PCR results for *Babesia divergens* have been published.

Babesia microti

The European situation, with a rare but severe infection in immunocompromised individuals, differs markedly from that in the USA, where more than 400 cases

of *Babesia microti* infections have been described, the majority in immunocompetent individuals [200].

Recent seroepidemiologic studies in the eastern USA have indicated infection rates for *Babesia microti* varying from 2% in asymptomatic individuals to 7.5% in individuals with a history of tick bite and fever [200]. Another population study showed seroprevalence rates for *Babesia microti* infection of 9% in adults and of 12% in children [201]. Although babesial infection had not been diagnosed in any of these individuals, 20–25% of both adults and children had had clinical symptoms compatible with the disease during the previous year.

In Europe, virtually nothing is known about *Babesia microti* infections. Sporadic reports have claimed asymptomatic seropositives for *Babesia microti* in Europe (France, southern Germany) but no systematic studies have been conducted. It is likely that the infection occurs in immunocompetent individuals also in Europe, especially as *Babesia microti* was isolated, several decades ago, from rodents in both Germany and the UK [202,203].

In the USA, the most severe, often fatal, infections of *Babesia microti* have been described in splenectomized patients, as for *Babesia divergens* infections in Europe. *Babesia microti* has been found to cause more severe disease in older immunocompetent individuals than in children, which parallels to the clinical spectrum seen in veterinary medicine. The symptoms in immunocompetent individuals are uncharacteristic or flu-like as in ehrlichiosis, with malaise, fatigue, fever, headache, myalgia, arthralgia, vomiting, depression and emotional lability as major symptoms [186]. Dark urine is common, as are mild increases in transaminases. Babesiosis has been associated with a late-onset adult respiratory distress syndrome (ARDS) [204]. Chronic infections in untreated or inadequately treated patients are not uncommon.

Asymptomatic cases of *Babesia microti* appear to recover spontaneously, but the severely ill patients need treatment with a combination of clindamycin and oral quinine, which seems to be the most effective regimen.

Chronic infection in asymptomatic individuals with a low-grade parasitemia has been shown to be transmitted by blood transfusion [205,206]. Ten cases have until now been documented from the USA, including a fatal case of blood-transmitted infection with a late-onset ARDS.

The vector for *Babesia microti* is *I. scapularis* in the USA, the same as for *Borrelia burgdorferi* and for HGE. Rodents have been shown to comprise a major reservoir of *Babesia microti* in endemic areas. In Europe, one of the known vectors of *Babesia microti* is *I. ricinus*, alongside *I. trianguliceps*.

The diagnostic methods are the same as for *Babesia divergens*, except that the most sensitive experimental animal was found to be the hamster. Most cases are diagnosed by serology by IF, and slides are commercially available [207]. Antibodies decrease to baseline levels within a year in a majority of cases. PCR for *Babesia microti* has been described and is used in diagnosis of current infection [208]. Attempts to culture *Babesia microti* in vitro have so far been unsuccessful [188]. No ELISA for *Babesia microti* has been published.

Other babesioses

The clinical picture described for WA1 has shown the same type and range of symptoms, from asymptomatic to severe clinical disease, as has been described for *Babesia microti* [209]. The most severe clinical disease, as for other babesial infections, occurred in a splenectomized individual. The only case of MO1 was a fatal infection in a splenectomized individual [191], but the spectrum of the infection caused by this organism has not, as yet, been established.

The presence of the WA1 agent or a related agent in Europe is suggested by a study, where 14 of 132 (10.6%) of Danish LB patients and 2 of 50 (4%) of Danish blood donors were found to be seropositive (K. Hansen, personal communication). It has, however, to be noted that the specificity of IF for the WA1 piroplasm has not, as yet, been established, in contrast to IF assays for *Babesia divergens* and *Babesia microti* [207], which have been shown to be specific for the respective organism, at least in serum dilutions ≥1:40–1:80.

Co-transmission and co-infection

Co-transmission of two or several of these agents has been documented both in Europe and in the USA. Cases of co-infections with TBEV and *Borrelia burgdorferi*, resulting in a fatal infection in one case, have been documented [210–212]. As for the other agents, *Ehrlichia* and *Babesia*, clinical investigations in Europe in human medicine lag vastly behind those in the USA. In veterinary medicine, however, the aggravating effect of concurrent infection of looping-ill virus (related to TBEV) and *E. phagocytophila* has been known for a long time [213].

The immunosuppressive effects of both ehrlichial and babesial infections are well known in veterinary medicine and are most likely to play an important role in aggravating other tick-borne infections in humans. Co-infections might account for the severe, chronic infections of TBEV with only an IgM response. Also, it remains to delineate the clinical picture of TBEV infections and to identify the role of ehrlichial and babesial co-infections, e.g. for the reported thrombocytopenia, leukopenia and elevated transaminases in

TBE [214], all classical features of the two latter infections.

Co-infections with the two or three tick-borne agents, *Borrelia burgdorferi*, the HGE agent and *Babesia microti*, have recently been suggested from the USA [215–217]. In the last-quoted study, the authors estimated the risk of co-infection, if one of the three infections was diagnosed, to be nearly 1:10. Similarly, co-infections, or rather seropositives to both agents, *Borrelia burgdorferi* and the HGE agent, were also found in the serosurvey on the west coast of Sweden [168].

Several notes of caution are, however, necessary. Seropositivity in LB by no means represents current infection. Subclinical or abortive infections can spontaneously heal and leave a 'serologic scar' for many years. Similarly, late treatment of clinical LB may result in antibodies detectable for many years, if not decades, after successful treatment and recovery of the patient [218]. Seropositivity to ehrlichial antigens can persist for 2 years, while antibodies of high titer to babesial antigens seem to indicate infection within a year. In addition, a report of false-positive LB serology, both by ELISA and by immunoblot, in cases of HGE agent infections has clear implications for the diagnosis of LB and of co-infections of LB and HGE [219].

Nevertheless, there are some reports which seem to sustain the notion of aggravated infections in the presence of dual, tick-borne zoonoses. Concurrent *Babesia microti* seropositivity was found, in a well-designed study, to be associated with a more severe clinical LB, which was also of longer duration than LB alone [220]. Also, a Danish study (K. Hansen, personal communication) indicates that 2 of 14 patients with neuroborreliosis, who were also seropositive for WA1, had a prolonged disease course and one of the patients had elevated liver enzymes.

Tick-borne zoonoses, LB and TBE, are important infections in Europe, while the roles of the emergent, new pathogens, *Ehrlichia* and *Babesia*, and of co-infections need to be investigated. The effort should preferably be made as a collaborative project in Europe and the network established within the Concerted Action on Lyme Borreliosis intends to expand its scope of action to include all these tick-borne zoonoses, with the ultimate goal of providing optimal prevention and treatment to patients throughout Europe.

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