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The Epidemiology, Clinical Manifestations, Management, and Prevention of Common Tickborne Infectious Diseases in Returning Travellers

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Ticks are among the most versatile arthropod vectors of infectious diseases because ticks of all ages and both sexes remain infectious for generations without having to reacquire infections from reservoirs. Ticks transmit the most common arthropod-borne disease in the US and Europe, Lyme borreliosis (LB); and the most commonly fatal arthropod- borne disease in the US, Rocky Mountain spotted fever (RMSF). Ticks have become frequent vectors of re-emerging and newly emerging zoonotic diseases in travellers, including African tick bite fever, Mediterranean spotted fever, and the tickborne encephalitis viruses (TBEV). Recent environmental changes, such as milder winters, and human lifestyles, such as choosing maximum tick activity times (May- August) for outdoor trekking and leisure activity times, now place humans and ticks together for longer periods in welcoming ecosystems for blood-feeding and infectious disease transmission.[1] This review will describe existing and emerging tickborne diseases of returning travellers in order to alert clinicians to populations at increased risks of contracting tickborne diseases abroad and to describe current diagnostic and treatment strategies for tickborne diseases.

Materials and Methods

In order to describe the evolving epidemiology, clinical manifestations, management, and prevention of tickborne infectious diseases in returning travellers, data sources describing existing and newly emerging tickborne diseases were selected by Medline search, 1966-2008; by Old Medline search for articles published prior to 1966; and by Pub Med and Google Scholar® searches. Data sources included case reports and series, observational and longitudinal studies, active and passive surveillance investigations.

Tick Behaviour, Biology, and Taxonomy

Ticks are classified into 3 families: (1) Ixodidae or hard ticks; (2) Argasidae or soft ticks; and (3) Nuttalliellidae with characteristics of both.[2] Ixodid ticks have a hard dorsal plate (scutum) and mouthparts that are attached anteriorly and visible dorsally. They live in open, exposed environments, such as woodlands, grasslands, meadows, and scrub brush areas. Argasid ticks are leathery and have subterminally attached mouthparts, not visible dorsally. Argasid ticks live in sheltered environments, such as animal nests, caves, crawlspaces, and household crevices.

The Epidemiology of Tickborne Infectious Diseases in Returning travellers

Arthropod bites acquired abroad are common problems in returning travellers. In a 2006 disease surveillance study in international travellers, skin lesions were the third most common cause of health provider visits in 17,353 returning travellers, with insect bites being the most commonly presenting skin lesions.[3] In a 2009 prospective descriptive analysis of skin and soft tissue infections (SSTIs) in 60 travellers returning to Paris over a 60-month period, Hochedez and co-investigators found that most SSTIs were acquired abroad (73%); occurred on the legs (75%); and many originated in insect bites.[4] In a descriptive review of the threats to international travellers posed by tickborne diseases, Jensenius and coauthors noted that 14 tickborne diseases had

been reported in international travellers by 2006 with the following tickborne infectious diseases occurring most commonly: (1) LB in travellers returning from America and Europe; (2) African tick bite fever in travellers returning from sub-Saharan Africa; and (3) tickborne viral encephalitis (TBVE) in travelers returning from Central and Eastern Europe.[5] In a series of epidemiological and microbiological investigations, Süss and co-investigators made the following observations regarding tickborne infectious diseases in Europe. (1) By 2008, both LB and TBVE had become major public health problems with LB causing 100,000 to 150,000 reported cases per year and TBVE causing 10,000 to 15,000 cases per year.[1, 6, 7] (2) TBVE had become endemic in specific regions of 27 nations, and the number of endemic areas per nation was increasing over time.[1, 6, 7] In the US, the reported number of LB cases increased from 9,000 per year in 1991, to 23,000 per year in 2006.8 With the addition of unreported cases, the actual incidence of LB in the US would be 60,000 to 100,000 cases per year, approximating the European experience.[1,8] The global epidemiology of the tickborne SF-causing rickettsiae has also evolved significantly with (1) emerging new strains and diseases (R. parkeri or North American tick bite fever in the US; R. slovaca and R. raoultii lymphadenopathy in Europe); (2) greater understanding of the highly conserved genomes of related species (the Borrelia burgdorferi genospecies, R. africae-R. parkeri, the R. conorii subspecies); (3) wider geographic distribution of some species (R. rickettsia, R. conorii, R. slovaca); (4) new tick vectors (Rhipicephalus sanguineus for RMSF in the US); (5) cluster outbreaks in returning travelers (African tick bite fever); and (6) clusters of more virulent SFs worldwide (RMSF in the US and Latin America, Mediterranean SF [MSF] in Europe, and Queensland tick typhus [QTT] in Australia) (Figure 1).[9-18] In 2001, Raoult and co-investigators tested 415 patients for riskettsial diseases after returning to France from visits to either Africa or the West Indian island of Guadeloupe with the following results: (1) 39 patients had African tick bite fever caused by R. africae as confirmed by polymerase chain reaction (PCR); (2) 80 patients were found to have R. africae tick bite fever by serological tests; (3) infections with R. africae were acquired by visitors to 11 sub-Saharan African countries and Guadeloupe; (4) 95% of patents had tick bite eschars and of these 54% had multiple eschars; and (5) illnesses were mild and characterized by a maculopapular or vesicular, non-pruritic rashes in 46% of patients.[16] The authors concluded that the most common cause of tick-bite rickettsiosis in travelers returning to France from visits to sub-Saharan Africa or Guadeloupe was tick bite fever caused by R. africae, a mild illness characterized by low grade fever, one or more tick-bite eschars, and rash.[16] In 2002, Jensenius and co-investigators performed a seroepidemiological study of 152 first-time Norwegian travellers to sub-Saharan Africa with seropositivity determined by the detection of specific antibodies to R. africae by microimmunofluorescence and/or Western blot analysis with the following results: (1) 13 (8.6%) patients were seropositive for R. africae; (2) 8 of the 13 seropositive patients (62%) reported mild illnesses with single or multiple eschars and maculopapulovesicular rashes and were treated with oral tetracyclines; and (3) a multiple logistic regression model determined that either hunters on safaris (OR = 10.1, p = 0.019) or visitors to rural areas for a week or more (OR = 6.0, p = 0.012) were significant risk factors for R. africae infections in travelers returning to Norway from Africa.[19] In 2002, Raoult and coauthors reported the first human R. aeschlimannii infection confirmed by microimmunofluorescence and PCR in a traveler returning to France from a visit to Morocco with low grade fever, tick bite eschar (tâche noire) on the ankle, and generalized maculopapular rash.[20] In 2003,

Cazorla and coauthors reported the first human R. slovaca infection in France in a 79-year-old woman who discovered a tick on her scalp 6 days after a trip to southern Burgundy.[21] R. slovaca was identified by PCR both in the Dermacentor marginatus tick removed from the patient's scalp and in an eschar biopsy.[21] In summary, there is now significant epidemiological, microbiological, immunological, and molecular evidence to support both an increasing prevalence of tickborne infectious diseases worldwide and a rising incidence of existing and newly described tickborne infectious diseases in returning travellers from tickborne disease-endemic regions.

Some Common Tickborne Bacterial Infections in Returning travellers

Spirochete Infections (Borrelioses)

The borrelioses are a large group of tickborne spirochetal infections caused by Gram-negative bacteria of the genus Borrelia, which has over 35 known species and over 300 strains or genospecies, with over 100 strains endemic in the US and Europe. Many of the species and strains are known to cause Lyme disease or Lyme borreliosis (LB); others may cause the Southern Tick-Associated Rash Illness (STARI) or Masters' disease in the Southern US, and a variety of tickborne relapsing fevers (TBRF) worldwide. The Borrelia species and strains all exhibit unique genetic diversity, regional geographic distribution, pathogenicity, and presenting clinical manifestations. The Borrelia species and strains that can cause LB are referred to collectively as Borrelia burgdorferi sensu lato *(Table 1)*. Although Borrelia burgdorferi sensu stricto is the sole agent of LB in regional pockets of the US and has been exported to Europe, most cases of LB in Europe and Asia are caused by other B. burgdorferi s.l. species, such as B. afzelii, B. garinii, and B. spielmanii. In Europe, B. burgdorferi s.l.-infected ticks have been described in almost every country. They have also been found in North Africa, Japan, far eastern Russia, Northwest China, and Mongolia. In South America, B. burgdorferi s.l. infected ticks have been widely reported in Brazil; and seroprevalence studies have documented their antigens in patients in Bolivia and Colombia *(Figures 2 & 3)*.[11, 22] Recently, several new strains of B. burgdorferi s.l. have been identified as causing LB in Europe, including B. bissettii and B. lusitaniae. However to this date, there has been no consistent, definitive evidence of B. burgdorferi s.l.-infected ticks or other Borrelia genospecies-infected ixodid ticks endemic in and capable of transmitting the causative spirochetes of LB Australia. Nevertheless, the tickborne spirochetal spotted fevers (SF) and tick paralysis are not uncommon tickborne disease diagnoses in Australia. Since Borrelia spirochetes must migrate from the tick's midgut to the salivary gland during blood-feeding, tick attachments for less than 24 hours rarely result in LB in man.[23] After an incubation period of 1-2 weeks, the hallmark of spirochete transmission manifests as erythema migrans, a solitary and round erythematous, maculopapular rash with a bull's-eye or solid pattern at the site of tick attachment *(Figure 4)*.[23] Erythema migrans also occurs in STARI at the site Tickborne Diseases in Travellers of Amblyomma americanum (lone star tick) attachment, and results from the subcutaneous, centrifugal movement of spirochetes from bite sites to the central circulation and target organs *(Figure 4)*.[23] In a meta-analysis of 53 longitudinal studies of LB in the US and Europe, Tibbles and Edlow reported that many patients did not recall a tick bite (74% in the US, 36% in Europe); constitutional symptoms of low grade fever (< 39º C.) and headache were common, but nausea and vomiting were rare; and a single solid or target-like erythema migrans lesion was the most common initial presentation of LB (88% in Europe, 81% in the US).[24] Thus, the presenting

clinical manifestations of LB may differ somewhat on different continents and even within regions as a result of infections caused by different species and strains of B. burgdorferi s.l.-infected ixodid ticks. Although deaths from LB are rare, the greatest morbidity from target organ damage in LB occurs in patients with prolonged or untreated infections with approximately 5-8% developing cardiac manifestations, 15-20% developing neurological manifestations, and 40-60% developing chronic arthritis.[23,24] However, if LB is recognized and treated early, cure rates will exceed 90%, late manifestations will be avoided, and outcomes will be excellent.[23,24] There is substantial risk and no benefit from additional antibiotic treatment of patients with any post-infectious sequelae of LB after appropriate initial treatment for LB.[23,24] The Jarish-Herxheimer reaction (JHR), an inflammatory cytokine-mediated reaction to dying spirochetes with a worsening of presenting symptoms, vasodilation, and myocardial dysfunction, may occur during antibiotic treatment for LB, but is more common following antibiotic therapy for BRF.[23,26,27] There have been no reported deaths from JHR during antibiotic therapy for LB, and the very rare case fatalities from LB have been attributed to cardiac conduction abnormalities from myocarditis in untreated cases.[23-25]

The Tickborne Relapsing Fevers (TBRF)

The tickborne relapsing fevers (TBRF) comprise a worldwide group of Gram negative bacterial infections by Borrelia spirochetes following brief, painless, and often unnoticed bites by Ornithodoros species argasid or soft ticks *(Table 2, Figure 5)*.[26,27] In 2005, Wyplosz and co-investigators reported 3 cases of TBRF in travellers returning to France from diseaseendemic countries without prior histories of tick bites.[28] In all 3 cases, Giemsa-stained peripheral blood smears demonstrated spirochetes, later identified molecularly as B. hispanica in a patient returned from Spain and B. crocidurae in the other 2 patients returned from Africa.[28] All patients were treated with doxycycline, 100 mg twice a day for 10 days, and recovered quickly.[28] The authors concluded that travelers returning from TBRF-endemic countries were at risk of TBRF, and that initial screening with Giemsa stained blood smears for spirochetes followed by PCR confirmation of causative species were the most efficient diagnostic modalities.[28] Unlike ixodid ticks, Ornithodoros ticks feed briefly for less than 30 minutes indoors, usually at night.[2,26, 27] Unlike LB-causing spirochetes, TBRF spirochetes are already present in the salivary glands at the onset of blood-feeding, and do not need time to migrate from the gut to the mouthparts.[23,26,27] The wild animal host reservoirs of most TBRFs are maintained in mammals, most commonly rodents.[26,27,29] The painless bite of a TBRF-infected tick is marked after a few days by a small red to violaceous papule with a central eschar.[27,29] Only 1 spirochete is sufficient to initiate TBRF, and the infection rate after a single bite by an infected tick is over 50%.[27,29] The incubation period to onset of the first febrile episode is 3-12 days.[23,27] TBRF is defined clinically by the sudden onset of 1 or more episodes of high (> 39° C.) fever, spaced by afebrile periods of 4-14 days; with the first febrile episode lasting 3-6 days, and the relapsing episodes lasting 1-3 days each.[23,27,29] The first episode ends with a 15-30 minute "crisis" with tachycardia, hypertension, hyperpyrexia (as high as 43º C.), and rigors, followed by diaphoresis and defervescence.[26-29] All febrile episodes will be accompanied by nausea, headache, neck stiffness, myalgia, and arthralgia. The relapsing febrile episodes result from the growth of new spirochete populations in the blood to replace those killed by macrophages and cytokines.[26,29] Most patients will

have splenomegaly; 10% will have hepatomegaly; and most will have elevated transaminases and uncongugated bilirubin, and prolonged prothrombin and partial thromboplastin times.[26,29] Direct neurological involvement is more common than in LB and may include cranial nerve neuritis, radiculopathy, and myelopathy.[26,27,29] Myocarditis is also more common than in LB, may be complicated by adult respiratory distress syndrome (ARDS), and is often fatal.[29] Clinical presentations, and diagnostic and treatment strategies for North American LB, STARI, and TBRF are compared in Table 3.

The Spotted-Fever Biogroup of Rickettsial Infections

The rickettsiae are obligate intracellular, Gram negative bacteria that thrive in ixodid tick salivary glands and are transmitted during blood-feeding. Within 2 to 14 days rickettsiae are disseminated hematogenously to vascular endothelial lining cells of target organs, including the central nervous system (CNS), lungs, and myocardium. The tickborne SF rickettsiae are compared in descending order of clinical severity of infection by endemic tick vectors and reservoirs in Table 4. Unlike the tickborne B. burgdorferi s.l. species causing LB, the tickborne SF biogroup of Gram-negative rickettsiae do cause many common and shared features in clinical presentations of SF infections including (1) incubation periods of approximately 1 week; (2) flu-like prodromes of fever, headache, myalgia, nausea, vomiting, and abdominal pain; (3) spotty rashes within 3-5 days of fever onset; and (4) necrotic eschars at tick-bite sites. Nevertheless, some SF rickettsial diseases may remain "spotless" including RMSF in 10-15% of cases, complicating early differential diagnosis.[9,15,30] The tickborne rickettsial infections that can cause spotty rashes include R. rickettsii (RMSF), R. conorii (MSF), R. australis (QTT), and R. africae/R. parkeri (African/North American tick bite fever) in about 50% of cases.[18,30-33] The tickborne rickettsial infections that are associated with one or more necrotic eschars at tick bite sites include R. conorii, R. australis, R. africae/R. parkeri, R. japonica, R. slovaca, R. aeschlimannii, and R. honei.[13,18,20,21,30,31] The SF rickettsioses may vary in severity from causing multi-system organ failure (RMSF, MSF) to painful lymphadenopathy (R. slovaca, R. raoultii), to mild to subclinical disease (R. africae, R. parkeri, R. aeschlimannii). [13,16-18,20,21,30,31,33] After an average incubation period of 1 week, RMSF starts with a flu-like, febrile prodrome followed by a characteristic maculopapular, evolving-topetechial rash in 85-90% of cases in 3-5 days.[9,30] The pathognomonic rash starts distally on the wrists and ankles and then spreads centripetally up the limbs. The pathophysiological mechanisms of petechial rashes and target organ system damage (CNS, lungs, heart) in the SF rickettsioses include vascular endothelial cell damage by microbial replication, vascular inflammation (vasculitis), and increased widespread vascular permeability which may result in hypovolemic shock, oliguric pre-renal failure, acute tubular necrosis, cerebral edema, and noncardiogenic pulmonary edema. Distal, digital necrosis may occur in severe cases of RMSF and QTT from hypoperfusion *(Figure 6)*.[9,18,30] Cardiac vasculitis may manifest as myocarditis with intraventricular conduction blocks. CNS complications in RMSF and other severe SF infections may include ataxia, photophobia, transient deafness, focal neurologic deficits, meningismus, meningoencephalitis, seizures, and coma. Pulmonary complications may include cough, alveolar infiltrates, interstitial pneumonitis, pleural effusions, pulmonary edema, and ARDS.[9,18,30] Initially, MSF caused by R. conorii, was thought to be a much more benign disease than RMSF.[17,32] However, in 1981, severe cases of MSF

with multiple eschars and multisystem disease similar to RMSF with CNS, renal, and pulmonary complications were first reported; and now appear to be increasing across Europe.[17,32] In a 1997 outbreak in of MSF in Portugal, case fatality rates in 105 inpatients (32%) exceeded those of untreated RMSF (23%).[32] QTT, African tickbite fever (ATBF), and R. slovaca or R. raoultii-associated lymphadenopathy are generally milder diseases than RMSF and MSF. However, severe cases of QTT with RMSF-like complications, including renal insufficiency, pulmonary infiltrates, and distal digital ischemic necrosis were recently reported from Australia *(Figure 6)*.[18] The precise laboratory diagnosis of tickborne rickettsial SFs may be established by microbiological isolation of the causative organisms from skin or eschar biopsies, or blood cultures; nonspecific immunofluorescent antibody tests that will cross-react with other SF antigens; other immunocytologic techniques to demonstrate intracellular rickettsiae; and PCR to identify species-specific rickettsial DNA or RNA. Antibiotic treatment mainstays for the tickborne rickettsial SFs remain the tetracyclines for most cases and chloramphenicol for severe multi-system diseases and during pregnancy. Although short, 1-2 day courses of doxycycline have been reported to be as successful as 10-day courses in some SF infections (MSF), such treatment strategies have not be tested in randomized controlled trials in other SF infections, and are also not recommended.[30] Most authorities now recommend that tetracycline, chloramphenicol, or ciprofloxacin for tetracycline-allergic patients be continued for a minimum or 7-10 days; or until the patient has been afebrile for at least 48 hours and is improving clinically.[30]

Common Tickborne Viral Infections

The Tickborne Viral Encephalitides

Tickborne viral infections are mostly caused by flaviviruses and may be divided into 2 separate clinical presentations, each with preferred tick vectors and wild animal reservoirs: (1) the tickborne viral encephalitides (TBVE), and (2) the viral hemorrhagic fevers, which are uncommon in travellers *(Table 4)*. TBVE infections share several common clinical and epidemiological characteristics including: (1) incubation periods of approximately 1 week; (2) biphasic illnesses separated by symptom-free periods beginning with flu-like viremic stages and ending with CNS or hemorrhagic manifestations; (3) nonspecific serodiagnosis by comparing acute and convalescent sera for increased antibody titers; (4) more specific diagnoses by ELISA or nucleic acid detection from blood or CSF by real time PCR or RT-PCR; (5) no specific treatments other than supportive therapy; and (6) significantly increased mortality or post-infection morbidity compared to the borrelioses.[34] The tickborne encephalitis viruses are transmitted by the injection of infected saliva from ixodid ticks.[34-36] During blood-feeding, viruses in tick saliva will increase up to ten-fold, and render early removal of the feeding tick ineffective in preventing disease.[34-36]
The preferred wild animal reservoirs for TBEVs include rodents, insectivores (moles and voles), medium-sized mammals, deer and other ungulates (Table 5). [34-36]
Powassan (POW) encephalitis, a North American TBVE, first isolated in 1958, exhibits a confined regional distribution with a predictable seasonal occurrence in the New England states and Eastern Canada; several ixodid tick vectors; an extensive wild animal reservoir in rodents and medium-sized mammals, especially woodchucks and skunks.[35] Cases occur from May to December and peak during June- September, when ticks are most active. [35] Patients with POW will present with somnolence, headache, confusion, high fever, weakness, ataxia, and CSF lymphocytosis. [35]
Transient improvement may be followed by neurological deterioration, evidence of

ischemia or demyelination on magnetic resonance imaging (MRI), and slow recovery often with permanent deficits including memory loss, weakness, ophthalmoplegia, and lower extremity paraparesis. [35] Since there is no vaccine or specific therapy for POW, the best means of prevention are avoidance of and personal protection from tick bites. [35] In Eurasia, TBVE remains a common cause of permanent neurological morbidity from Scandanavia to Japan, with more than 10,000 cases reported per year, a third of which will result in permanent neurological deficits.[1,34] Besides tick bites, TBVE may occasionally be transmitted by ingestion of unpasteurized milk products from viremic livestock and by breastfeeding. [34] In Eurasia, TBVE is typically a biphasic illness in over 70% of cases with an initial febrile flu-like presentation followed by a 1-3 week symptom-free interval. [34] This recovery period may be followed by meningoencephalitis with CSF pleocytosis; occasional transverse myelitis; and a more frequent poliomyelitis-like flaccid paralysis that targets the arms, neck, and shoulders. [34] MRI and electroencephalographic (EEG) abnormalities are common, but nonspecific. [34] Other acute neurological complications may include altered consciousness, seizure activity, cranial nerve palsies, and an often fatal bulbar syndrome with cardiorespiratory failure. [34,36] Highly effective vaccines have now been developed for several strains of tickborne encephalitis- causing viruses, including European, Russian, Middle Eastern, and Chinese strains.

The Prevention and Control of Tickborne Infectious Diseases

There are a number of strategies that can be used in the prevention and control of tickborne infectious diseases including immunization, personal protective measures, and landscape and wildlife management. In the 1990's, a LB vaccine was developed for the US, but later withdrawn (2002) due to poor sales. Immunization strategies to prevent tickborne infectious diseases have proved far more effective in Europe, especially in Austria and Eastern Europe, and in Asia, than in the US. Current immunization programs for tickborne viral diseases now provide primary prevention of TBEV-Eu in Europe, TBEV-Sib in Russia and the Middle East, TBEV-FE in China and the Far East, and Crimean-Congo hemorrhagic fever in Bulgaria and other parts of Eastern Europe.[37] Besides immunizations, prophylactic antibiotics following presumed ixodid tick bites with erythema migrans have been recommended as prophylactic therapies strategies for the primary prevention of some tickborne infections, such as Borrelia burgdorferi s.s.-caused LB in North America. A randomized clinical trial found that a single 200 mg dose of doxycycline administered within 72 hours of a tick bite was 87% effective in preventing LB in the US. [37] However, such prophylactic strategies have not been well studied in randomized controlled trials in other countries with different species and genospecies of LB-causing B. burgdorferi s.l. Personal protective measures to prevent tick-transmitted diseases include wearing appropriate clothing, performing frequent tick checks, and applying insect repellants. Wearing long pants tucked into socks, long-sleeved shirts, and light-colored clothing can aide in keeping ticks off of the skin and in making them easier to spot on clothing. The topical application of insect repellants containing 20-50% formulations of N, N-diethyl-meta-toluamide (DEET) directly on the skin is another effective and recommended measure. A new non-DEET, topical insect repellant, 7% picardin (KBR 3023), may be effective against mosquitoes; but has not been tested in humans against ticks in randomized controlled trials. Impregnating

clothing with permethrin, routinely performed by the military, is highly effective against ticks and offers greater protection to DEET-untreated skin. Most patients with LB, TBRF, and TBEV do not recall tick bites as these diseases are often transmitted by diminutive nymphal ticks. Nevertheless, tick localization and removal as soon as possible, preferably within 24-36 hours, remain recommended strategies to prevent the borrelioses and rickettsial SFs. Ticks should always be removed with forceps (or tweezers), not fingers (as squishing ticks can transmit several tickborne diseases across dermal barriers or create infectious aerosols), and in contiguity with their feeding mouthparts; rather than burning embedded ticks with spent matches or painting them with adhesives or nail polishes. Effective landscape management strategies to prevent tickborne diseases include widespread application of effective acaricides (synthetic pyrethroids, carbamates, fipronil) over tick-preferred cosystems, removal of vegetation and leaf litter near homes, fences, trails, and other outdoor recreation sites; and the creation of dry barriers of gravel, stone, or wood chips between forested areas and yards or playgrounds. Wildlife management strategies to prevent tickborne diseases include encouraging the development of better veterinary vaccines for tickborne diseases with large domestic animal reservoirs; applying acaricides actively to domestic animals and passively to deer and cattle at baited feeding and watering stations, or salt licks; and setting out acaricide-baited rodent houses for rodents to occupy or acaricide-baited cotton balls for rodents to adopt as nesting materials, especially in crawl spaces under homes, in drainage culverts, and near playgrounds.

Conclusions

Recent environmental changes and human behaviours now place humans and ticks together outdoors for longer preferred periods in warming and welcoming ecosystems for breeding, blood-feeding, and infectious disease transmission.**1** The increasing popularity of ecotourism and adventure travel worldwide also places more tourists outdoors in tick-endemic regions more often, thereby increasing the incidence of tickborne infectious diseases in returning travellers. Better prevention and treatment strategies for tickborne diseases are indicated now before the highly conserved genomes of tick-transmitted microorganisms re-assort their nucleic acids with their hosts and develop antimicrobial resistances (especially to tetracyclines) and super-pathogen capabilities.

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TABLE 1
Some Representative *Borrelia burgdorferi* sensu lato Species Causing Lyme Borreliosis (LB)

Borrelia Burgdorferi s.l. species	Tickborne diseases	Geographic distribution	Tick vectors	Wild animal reservoirs
Borrelia afzelii	European Lyme borreliosis	Europe Scandinavia	*Ixodes ricinus*	Mammals: deer, rodents
B Burgdorferi	American Lyme borreliosis	N America: Northeast US Midwest US & Pacific Northwest US Europe	*I scapularis* (Eastern US) *I pacificus* (Western UIS)	Mammals: deer, rodents
B garinii	European Lyme borreliosis	N Europe Russia Asia	*I ricinus* (Europe) *I persulcatus* (Asia)	Mammals: rodents
B lusitaniae	European Lyme borreliosis	Western Mediterranean (Portugal) Eastern Europe (Slovenia)	*I ricinus* (Europe)	Green lizards (*Lacerta viridis*), probably rodents (mice, voles)
B spielmanii	European Lyme borreliosis	Germany, Czech Republic, Hungary, Slovenia, Eastern Europe	*I ricinus*	Garden dormouse (*Eliomys quercinus*)

TABLE 2
Some Representative *Borrelia* Species Causing Tickborne Relapsing Fever (TBRF)

Borrelia species	Tickborne diseases	Geographic distribution	Tick vectors	Wild animal reservoirs
B crocidurae	North African tickborne relapsing fever (TBRF)	North Africa, Mediterranean basin	*Ornithodorus erraticus*	Mammals: rodents, possibly birds
B duttonii	East African TBRF	East, Central & South Africa	*O moubata*	Humans
B hermsii	American TBRF	West Coast US (California) &	*O hermsii*	Mammals: rodents,

		Canada		chipmunks, squirrels
B hispanica	Hispano-African TBRF	Iberian peninsula: Spain, Portugal, NW Africa: Algeria, Morocco, Tunisia	*O marocanus*	Mamals: rodents
B latyschewii	Caucasian or Russian TBRF	Russian Caucasus(Tajikistan, Uzbekistan, Central Asia	*O tartakovskyi*	Mamals: rodents
B mazzottii	Southern TBRF	Southen US, Mexico, Central America, S America	*O talaje*	Mamals: rodents
B parkeri	Western TBRF	SW & South-central US, Mexico	*O parkeri*	Mamals: rodents
B persica	Asiatic-African TBRF	Mddle East (Egyot, Iran), Central Asia, W China, N India	*O tholozani*	Mamals: rodents
B turicatae	American Southwestern TBRF	SW & South-central US, Mexico, Central America	*O turicata*	Mamals: rodents, armadillos, opossums, pigs, monkeys
B venezuelensis	Venezuelan TBRF	Central & South America	*O rudis*	Mamals: rodents, armadillos, opossums, monkeys (Panama, Colombia)

TABLE 3
A Comparison of North American Lyme Borreliosis, Southern Tick-Associated Rash Illness and Tickborne Relapsing Fever

Infectious disease characteristis	**Lyme borreliosis**	**Southern tick-borne associated rash illness (STARI)**	**Tickborne relapsing fever**
Microbial agents	*B burgdorferi* (US, Europe), *B afzelii* (Europe), *B garinii* (Europe, Asia)	*B lonestari* has been isolated from a skin biopsy and cultured in vitro from infected *Amblyomma* ticks	Many *Ornithodoros* species of soft ticks
Preferred tick vectors	*Ixodes* spp hard ticks	*Amblyomma americana*	*Ornithodoros* spp soft ticks

Preferred animal reservoirs	Rodents (nymphs), deer (adults)	Lizards	Rodents (nymphs), man (B duttoni only), deer, birds (adults)
Endemicity	Highly endemic in US & Europe	Southeastern US	Highly endemic among vector-populated regions worldwide
Fever>_ 39^{o}C	Very uncommon	Absent, low-grade fever may occur rarely	Present in relapsing episodes 1-3 days each * may reach 43^{o}C
Relapsing fevers	Not present	Not present	Present
Erythema migrans or other rash	Present as an annular or target-like maculopapular rash with a mean diameter of 7cm; more common on extremities	Present & mimics that of Lyme disease but with a smaller mean diameter of 4.5cm; more common on trunk	Absent
Arthritis	May be present in untreated (up to 60%) late or "chronic" infections & manifesting as oligoarthritis	Arthralgia, myalgia & neck stiffness may occur, less commonly than with Lyme disease. No chronic arthritis	Neck stiffness, arthralgia, myalgia common; not arthritis
Neurological manifestations	May be rpesent in up to 15% of cases & includes headache. Cranial nerve neuritis of CN VII (Bell's palsy)	Dizziness, headache, memory loss, concentration difficulty may occur. No chronic neurological complications	Common: meningitis, meningoencephalitis, Cranila nerve neuritis of CN VII (Bell's palsy) & VIII (deafness), myelitis, radiculopathy
Other presenting manifestations	Myocarditis & conduction defects in late onset & untreated cases in up to 8% of cases	Regional lymphadenopathy may occur. Chronic complications not described	Splenolegaly in most, hepatomegaly in 10%, rarely myocarditis manifesting as prolonged QT interval
Best screening serodiagnostics	Giemsa or Wright stained peripheral smear, phase contrast or dark field microscopy for spirochaetes; ELISA, IFA	Epidemiological & clinical presentation. No presently available screening serodiagnostics. Rule out Lyme disease by ELISA,	Giemsa or Wright stained peripheral smear, phase contrast or dark field microscopy for spirochaetes; ELISA, IFA

		IFA & western immunoblot	
Best confirmatory diagnostics	In vitro cultivation; western immunoblot, PCR	PCR on skin biopsy. In vitro cultivation	In vitro cultivation (not recommended. BSL-3 lab required), rodent inoculation, PCR
Recommended antibiotic therapy	Doxycycline 100mb bid OR Amoxicillin 500mg tid For 14-21 days; Parenteral therapy for neurological involvement	Doxycycline 100mb bid OR Amoxicillin 500mg tid For 14-21 days	Tetracycline 500mg or 12.5mg/kg qid OR doxycycline 100mg bid OR Erythromycin 500mg or 12.5mg/kg qid fpr 10 days; parenteral therapy with penicillin G or ceftriaxone for cardiac or CNS involvement

TABLE 4
Some Representatives of the Spotted Fever Biogroup of Tickborne Rickettsioses

Rickettsia species	Tickborne diseases	Geogeaphic distribution	Tick vectors	Wild animal reservoirs
R rickettsiae	Rocky Mountain spotted fever (SF), Brazilian SF	Continental US, Central America (Costa Rica, Mexico, Panama), South America (Argentina, Brazil)	*Amblyomma, Dermacentor, Rhipicephalus* spp	Mammals: ungulates, rodents
R conorii (including the R conorii strain complex or genospecies)	Boutonneuse fever, Mediterranean SF, Israeli SF, Astrakhan SF, Indian tick typhus, Kenyan tick typhus	Mediterranean basin, Africa, Middle East, Asia	*Rhipicephalus* spp	Mammals: ungulates, rodents
R sibirica mongolotimonae	N Asian tick typhus (Siberian tick typhus)	N Asia (Russia, China,	*Dermacentor, Haemaphysalis, Hyalomma* spp	Mammals: ungulates, rodents

		Mongolia, Pakistan. Kazakhstan, Kirgizia, Tadjikistan, Europe (France)		
R japonica	Japanese SF	Japan & China	*Haemaphysalis* spp, *Ixodes ovatus*	Mammals: rodents
R australis	Queensland tick typhus	E Australian seaboard from Cairns (Queensland) to Gippsland (Victoria)	*Ixodes* spp especially *I holocyclus.* Less commonly *I tasmani*	Mammals: rodents
R honei	Flinders Island SF	S Australia, Thailand	*Aponomma* spp	Mammals: rodents
R africae	African tick bite fever	Sub-Saharan Africa, West Indies (Guadeloupe, seropositive ticks & cattle confirme on other islands)	*Amblyomma* spp, especially *A varigatum* in sub-Saharan Africa and Guadeloupe	Mammals, especially domestic cattle & goats
R parkeri	American tick bite fever Southern or Gulf Coast tick bite fever (*Maculatum* disease)	N American Atlantic coast Southern US, US Gulf Coast	*Amblyomma* spp *Amblyomma maculatum*	Mammals: rodents
R slovaca	Tickborne lymphadenopathy, *Dermacentor*-borne eschar, lymphadenopathy or necrosis	Europe	*Dermacentor* spp	Mammals: Ungulates, rodents
R aeschlimanniae	Not named at present	S Europe, Africa	*Hyalomma spp*	Mammals: Ungulates, rodents

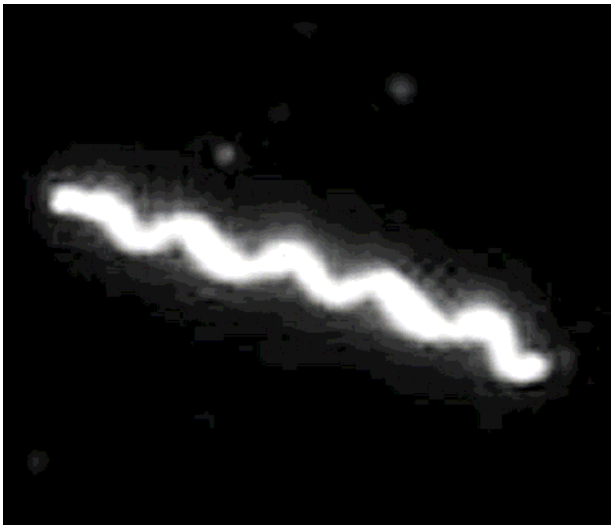
TABLE 5
Some Representative Tickborne Viral Encephalitides (TBVE)

Virus name	Geographic distribution	Tick vectors	Wild animal reservoirs
Central European tickborne encephalitis	Europe except Iberian peninsula	Ixiodid ticks, especially *Dermacentor marginatus, Ixodes persulcatus* & *I ricinus*	Mammals, especially rodents including hedgehogs, wood mice, voles. Also deer, other ungulates, birds, domestic livestock, especially goats
Powassan encephalitis	Canada, Northeast US, Far Eastern Russia	Ixodes spp, especially *I cookie, Dermacentor andersoni*	Mammals: rodents, skunks & other medium sized mammals, esp woodchucks & groundhogs
Langat	Malaysia	Ixodid ticks	Mammals: monkeys, rodents
Louping ill	UK, Scotland	Ixodid ticks	Sheep
Russian (Siberian) Spring-Summer encephalitis (TBEV-Sib)	Russia	*Ixodes* spp, *I persulcatus, I ricinus*	Mammals: rodents including hedgehogs, wood mice & voles. Also birds, deer other ungulates, domestic livestock esp goats
Far EasternTBE (TBEV-FE_	Eastern Russia, China to far Eastern Japan	*I persulcatus*	Mammals: rodents including hedgehogs, wood mice & voles. Also birds, deer other ungulates, domestic livestock esp goats
Turkish Sheep encephalitis	Turkey	Ixodid ticks	Sheep

FIGURE 1

Rhipicephalus sanguineus, the brown dog tick, male tick "questing" for a host. *R. sanguineus* is a new US vector for Rocky Mountain spotted fever (RMSF) in addition to the historical vectors, *Dermacentor andersoni*, the Rocky Mountain wood tick, and Dermacentor variabilis, the American dog tick. Source: US Centers for Disease Control and Prevention (CDC), Atlanta, GA USA. CDC Public Health Image Library (PHIL). PHIL ID # 7646. No copyright permission required.

FIGURE 2



Borrelia burgdorferi, the causative bacterium of Lyme borreliosis (LB) in the US and Eurasia, is shown here on an immunofluorescent-stained, peripheral blood smear under darkfield microscopy. Note the characteristic coiled spring appearance of a spirochete. Source: US Centers for Disease Control and Prevention, Atlanta, GA USA. Public Health Image Library. Photo by Dr. Robert D. Gilmore, CDC. No copyright permission required.

FIGURE 3

Ixodes scapularis, the black-legged ixodid deer tick; an adult female with nymphs. Ixodid ticks are common arthropod vectors of LB and the spotted fever rickettsioses worldwide, especially nymphs, whose bites are often painless and unnoticed. Source: US Centers for Disease Control and Prevention (CDC), Atlanta, GA USA. CDC Public Health Image Library (PHIL). PHIL ID # 1205. No copyright permission required.

FIGURE 4

Erythema migrans, the pathognomonic “bull’s eye” rash at the bite sites of *B. burgdorferi* sensu lato or *B. lonestari*-infected ixodid ticks, the tick vectors of LB and

Southern Tick-Associated Rash Illness (STARI) respectively in endemic regions worldwide. Source: US Centers for Disease Control and Prevention (CDC), Atlanta, GA USA. CDC Public Health Image Library (PHIL). PHIL ID # 9875. No copyright permission required.

FIGURE 5

Ornithodoros moubata, an argasid (soft) tick, is an indoor-dweller and the most common vector of tickborne relapsing fever caused by *B. duttoni* in sub-Saharan Africa, especially in East Africa and South Africa, and the Indian Ocean Islands. Source: US Centers for Disease Control and Prevention (CDC), Atlanta, GA USA. Cutler SJ. Possibilities for relapsing fever reemergence. Emerg Infect Dis 2006; 12: 369-74. Available at www.cdc.gov/ncidod/eid/vol12no03/05-0899-G1.htm.

FIGURE 6

Distal digital gangrene of the fingertips in a 45-year-old man with Queensland tick typhus (QTT) caused by *Rickettsia australis*, a spotted fever biogroup member, and transmitted to humans through the bite of ixodid ticks *(Ixodes holocylus, I. tasmani)*

along the eastern coast of Australia. Source: US Centers for Disease Control and Prevention (CDC), Atlanta, GA USA. McBride WJH, Hanson JP, Miller R, Wenck D. Severe spotted fever group rickettsiosis, Australia. Emerg Infect Dis 2007; 13: 1742-4. Available at http://www.cdc.gov/eid/contents/13/11/1742.htm.

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