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REVIEW

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Emerging tick-borne pathogens of public health importance: a mini-review

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Abstract

Ticks are the most important vectors of human pathogens, leading to increased public health burdens worldwide. Tick-borne pathogens include viruses (e.g. tick-borne encephalitis and Powassan); bacteria, such as the causative agents of Lyme disease, spotted fever rickettsiosis and human anaplasmosis; and malaria-like protozoan parasites causing babesiosis. Tick-borne diseases are emerging due to the geographical expansion of their tick vectors, especially in the northern hemisphere. Two examples of this phenomenon are *Ixodes scapularis* and *Amblyomma americanum*, which have expanded their ranges in the USA in recent decades and are responsible for the continuous emergence of Lyme disease and human ehrlichiosis, respectively. This phenomenon is also occurring worldwide and is reflected by the increasing number of tick-borne encephalitis and haemorrhagic fever cases in Europe and Asia. In this review, we provide a concise synopsis of the most medically important tick-borne pathogen worldwide, with a particular emphasis on emerging public health threats.

INTRODUCTION

Pathogens transmitted by ticks are responsible for the majority of the vector-borne diseases in temperate North America, Europe and Asia. In the USA, ticks are responsible for over 95% of vector-borne disease cases [1]. Lyme disease is, by far, the most prevalent tick-borne disease in the northern hemisphere. According to two studies, approximately 300000 cases of Lyme disease are diagnosed annually in the USA alone, about 10-fold higher than the number of reported cases [2, 3]. Based on these estimates, Lyme disease may be among the most common infectious diseases in the USA. Additionally, around 10000 cases of other tick-borne diseases are reported annually [1], although the actual number of cases is probably significantly higher [4, 5].

The economic impact of tick-borne diseases is significant and increases every year. In the USA, the reported cost per patient diagnosed with Lyme disease totalled USD $8172 in 2002 [6], equal to USD $11838 in 2019 (CPI inflation calculator, https://data.bls.gov/cgi-bin/cpicalc.pl). A conservative approximation based on 42743 cases reported to the Centers for Disease Control and Prevention (CDC) in 2017 would result in a cost estimate of over USD $500 million annually. These costs might be even higher for patients with post-treatment Lyme disease syndrome [7]. The societal burden of Lyme disease can be very considerable, with one-quarter of the patients receiving public support or disability benefits [8]. Additional economic costs that are substantial, but difficult to quantify, are imposed on the hospitality and tourism industry in the endemic areas [9]. Public health burdens due to Lyme disease are not unique to the USA. A recent comprehensive review found Lyme disease-associated expenditures of tens of millions of euros in several European countries [10]. The combined public health impact of all tick-borne diseases remains mostly unquantified.

Although the main focus of this review is tick-borne pathogens of humans, the impact of veterinary tick-borne diseases can also be staggering, especially in developing countries [11]. Tick-borne diseases affect ~80% of the world's cattle population, with the estimated cost of between USD $13.9 billion and USD $18.7 billion [12]. For countries such as Tanzania, where the economic losses due to tick-borne disease have been quantified, the impacts were estimated at USD $364 million, with an estimated mortality of 1.3 million cattle due mostly to theileriosis (68%), anaplasmosis (13%) and babesiosis (13%) [13]. Theileriosis occurs only sporadically in the USA, but

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Keywords: tick-borne diseases; Lyme disease; *Ixodes*; *Haemaphysalis longicornis*; arboviruses.
Abbreviations: CCHFV, Crimean–Congo hemorrhagic fever virus; CDC, Centers for Disease Control and Prevention; KFD, Kyasanur Forest disease; POW, Powassan virus; RMSF, Rocky Mountain spotted fever; SFGR, Spotted fever group rickettsioses; SFTSV, Severe fever with thrombocytopenia syndrome virus; TBE, Tick-borne encephalites.

this situation could change rapidly with the recent introduction of the Asian longhorned tick, *Haemaphysalis longicornis* [14, 15]. This tick species is a competent vector of *Theileria orientalis* [16, 17], which has recently been detected on cattle farms in Virginia in the USA [18].

The expansion of tick populations, as well as the increasing incidence of tick-borne diseases, is bringing ticks to the attention of a broader range of public health professionals. The purpose of this review is to summarize the most recent advances in tick-borne diseases, with a particular emphasis on newly described or emerging diseases worldwide that present a public health threat. In this review, tick-borne pathogens are organized according to their causative agents into different taxonomic groups (Table 1). This review provides a short synopsis of a much broader topic that has been covered in depth by recent publications [1, 5, 19] for those who are interested in more details on tick-borne diseases and their vectors.

THE VECTORS

Tick-borne pathogens circulate in enzootic cycles, alternating between ticks and suitable animal hosts, mostly rodents [20]. Both the tick vector and the vertebrate host are needed to maintain tick-borne pathogens in enzootic cycles. An exception to this general rule are those pathogens that have an efficient transovarial transmission for which the tick serves as a vector as well as a host [21]. Infected ticks can transmit pathogens to humans; however, with very few exceptions (i.e. tick-borne relapsing fever caused by *Borrelia duttonii* in East Africa [22]), humans are dead-end hosts and do not play any role in the transmission and maintenance of tick-borne pathogens in enzootic cycles.

Ticks are divided into two main families, *Argasidae* or soft ticks and *Ixodidae* or hard ticks, that differ in their ecology and public health impact [20, 23]. In contrast to hard ticks, soft ticks of the family *Argasidae* feed quickly (from minutes to an hour), and can take several blood meals per stage [24]. Soft ticks have several developmental stages per moulting and typically inhabit wildlife nests, burrows,and caves. Thus, they have a more restricted habitat compared to hard ticks [25, 26]. Fewer human pathogens are transmitted by soft ticks compared to hard ticks, probably due to their behavioural traits, including short feeding times and host-seeking strategies [20].

Hard ticks, members of the *Ixodidae* family, are cosmopolitan and can be found in different natural habitats and suburban and even urban areas [25]. Hard ticks have different host-seeking behaviours and typically feed for extended periods, ranging from 3–12 days, depending on the species and tick stage [23]. Prolonged contact between ticks and their hosts facilitates the transmission of pathogens, especially bacterial pathogens that generally require over 24 h to be transmitted efficiently [27].

Hard ticks have three active feeding stages in their life cycle – larva, nymph and adult. Typically, the immature tick stages, larvae and nymphs feed on small mammals, often rodents, which are suitable animal reservoirs for many tick-borne pathogens (see Table 2 in Parola and Raoult [20] for details). Tick-borne pathogens are acquired by the vector while feeding on an infected host . These pathogens are well adapted to their vector and persist throughout moulting. This is known as transstadial transmission and is necessary for pathogen survival and transmission. Some pathogens, particularly *Rickettsia* species (see Parola and Raoult [20] for a full list), are also transmitted transovarially, from the female tick to her offspring [21].

Nymph and adult ticks are the most important stages in the transmission of human pathogens, whereas larvae only play a role in the transmission of transovarial pathogens. The most dangerous tick stage for humans are nymphs since, in contrast to adults, they are small, hard to detect and active during spring and summer, a period that concurs with the highest human outdoor activity in temperate climates. After the bite of an infected tick and a short incubation period, the initial course of infection usually presents itself as an unspecific febrile illness with symptoms including chills, sweating, headaches, myalgias, arthralgias, malaise, nausea and vomiting [28]. The severity of the illness varies among tick-borne pathogens and depends on the immune status of the patient. Some tick-borne diseases are self-limited, while others are life-threatening. For example, the course of infection for human babesiosis is often subclinical in healthy individuals but can be much more severe in immunocompromised patients [29]. While Lyme disease is not typically fatal, it may lead to debilitating and persistent conditions [30]. On the other hand, tick-borne encephalitis (TBE) or Powasan virus can be fatal or leave the patient with permanent cognitive impairment [31]. Accurate identification of ticks and their stages are essential for diagnosis, treatment and prophylaxis of tick-borne diseases [32]. Larval stages of most tick species pose little to no risk of pathogen transmission to humans. Some tick species, such as *Ixodes scapularis,* may harbour numerous pathogens, whereas other commonly encountered species may typically be associated with one major pathogen (Table 1) [33]. Successful prophylaxis of Lyme disease with preventative antibiotic treatment requires not only accurate tick species identification, but also the determination of the duration of tick feeding [32, 34].

THE PATHOGENS

Viral

Tick-borne viruses are the most taxonomically diverse group, representing four viral families or orders – *Flaviviridae*, *Bunyavirales* (formerly family *Bunyaviridae*), *Orthomyxoviridae* and *Reoviridae* (Table 1). Tick-borne flaviviruses represent a large and important group of viruses, including TBE virus, louping ill, the Asian Omsk haemorrhagic fever virus, Kyasanur Forest disease (KFD) and Powassan virus (POW). These viruses are notable for causing encephalitis and haemorrhagic symptoms [35] and are responsible for more than 10 000 cases that require hospitalization per year in Europe, Russia, China and Japan (Table 1, Fig. 1) [36]. TBE

Table 1. Main groups of tick-borne pathogens and diseases. See the main text for references

Disease or condition	Pathogen [main vector]*	Geography	Prevalence† and comments
Viral			
***Flaviviridae*/*Flavivirus* (tick-borne encephalitis group)**			
Tick-borne encephalitis (TBE)	TBE virus complex (*I. ricinus*, *I. persulcatus*)	Europe, Asia, Middle East	Common and widespread
Powassan encephalitis (POW)	POW virus (*I. scapularis*, *I. cookei*)	Northeastern USA/ adjacent Canada, Russian Far East	Rare, increasing
Other TBEs: Omsk haemorrhagic fever (OHF), Kyasanur Forest Disease (KFD), louping ill, others	OHF, KFD, other viruses (*Ixodes*, *Dermacentor*, *Haemophysalis* sp.)	Europe, Russia, China, Japan, India, Southeast Asia, Middle East	Rare to common within localized range; some increasing
Bunyavirales/*Orthonairovirus*			
Crimean–Congo haemorrhagic fever (CCHF)	CCHF virus (*Hyalomma marginatum*, other tick sp.)	Europe, Central Asia, India, Africa	Common and widespread; increasing
Bunyavirales/*Phlebovirus*			
Severe fever with thrombocytopenia syndrome (SFTS)	SFTS virus (*H. longicornis* and *R. microplus*)	China, Korea, Japan	Uncommon, increasing
Heartland virus	(*A. americanum*)	Mid-western and southern USA	Rare
Bhanja virus	(*Dermacentor*, *Haemophysalis* sp.)	Africa, Central Asia, southern Europe	Rare
Orthomyxoviridae*/*Thogotovirus			
Thogoto (THOV), Dhori (DHOV) and Bourbon virus	(*Hyalomma*, *Amblyomma*, *Rhipicephalus* sp.)	Africa, Asia, Europe (THOV and DHOV), USA (Bourbon)	Rare; Bourbon virus isolated from *A. americanum*
Reoviridae*/*Coltivirus			
Colorado tick fever (CTF)	CTF virus (*D. andersoni*)	Western USA and Canada	Rare
Eyach virus	(*I. ricinus*)	Central Europe	Rare
Bacterial			
Spirochaetales/*Borrelia* spirochetes (borreliosis and relapsing fever)			
Lyme disease	Borrelia burgdorferi (*I. ricinus* complex)	Temperate North America, Europe, Asia	Common, widespread
Relapsing fever borreliosis	B.miyamotoi (*I. ricinus* complex)	Temperate North America, Europe, Asia?	Rare
Relapsing fever borreliosis – tick-borne relapsing fever (TBRF)	Relapsing fever *Borrelia* (*Ornithodoros* and *Carios* sp.)	Worldwide (except Australia), mostly tropical and desert regions	Rare to common locally
Southern tick-associated rash illness (STARI)	Unknown (*A. americanum*)	Southern and eastern USA	Rare
Rickettsiales/*Rickettsia* (spotted fever and tick typhus)			
Rocky Mountain spotted fever (RMSF)	*Rickettsia rickettsii* (*D. variabilis, D. andersoni, R. sanguineus*)	Western hemisphere	Common
Rickettsiosis	R.parkeri (*A. maculatum*)	Southern and mid-Atlantic USA, South America	Rare, emerging in South America
Pacific Coast tick fever (PCTF)	*R. philipii*(*D. occidentalis*)	California, Pacific coast	Rare
Mediterranean spotted fever	*R. conorii* complex (*Rhipicephalus sanguineus*)	Europe, Africa, Middle East, Asia	Uncommon, imported

Continued

Table 1. Continued

Disease or condition	Pathogen [main vector]*	Geography	Prevalence† and comments
Viral			
African tick bite fever	*R. africae* (*Amblyomma* sp.)	Africa, West Indies, Oceania	Uncommon, imported
Rickettsiales/*Anaplasmataceae* (anaplasmosis and ehrlichiosis)			
Human granulocytic anaplasmosis (HGA)	*Anaplasma phagocytophilum* (*I. scapularis*, other sp.)	Northeastern and central USA	Common; emerging in Europe and Asia
Human ehrlichiosis	*Ehrlichia chaffeensis*, *E. ewingii* (*A. americanum*)	Eastern USA	Common
Human ehrlichiosis	*E. muris eauclairensis* (*I. scapularis*)	Minnesota and Wisconsin	Rare
Neoehrlichiosis	*Ca. N. mikurensis* (*Ixodes* sp.)	Europe, Asia	Rare
Other bacterial			
Tularaemia	*Francisella tularensis* (*Amblyomma, Dermacentor Ixodes and Haemaphysalis*)	North America, Europe, Asia	Uncommon by tick bite; other routes of exposure
Parasites (Protists)			
Human babesiosis	*Babesia microti*, *B. divergens*, (*I. ricinus* complex)	Northeastern and Midwestern USA Europe, China	Common; emerging in Europe and Asia
Human babesiosis	*B. duncani* (WA-1 type parasite) (*D. albipictus*, *I. pacificus*?)	Pacific Coast of North America	Emerging
Tick bite associated (non-pathogenic)			
Alpha-gal syndrome (red meat allergy)	(*A americanum, H. longicornis, Ixodes* sp.)	Worldwide	Uncommon, increasing
Tick paralysis	Various species	USA, Australia, other countries	Rare

*Generic tick names abbreviated in (): *A.*, *Amblyomma*; *D.*, *Dermacentor*; *H.*, *Haemophysalis*; *I.*, *Ixodes*; *R.*, *Rhipicephalus*.
†Prevalence, reported annual number of human cases (approximate): rare, <10; uncommon, >10–1000; common, >1000; common and widespread, ≈several thousands.

virus is expanding in Europe as a result of climate and land use changes [37]. The Asian Omsk haemorrhagic fever virus causes a febrile disease that often displays severe haemorrhagic symptoms [38]. KFD is present in the Indian subcontinent and causes encephalitis accompanied by haemorrhages [39]. The most recent and remarkable trends are the increase of TBE viruses outside of the typical temperate Eurasian range [40]. The rise of POW is an example of the current trend observed in different members of the TBE group. Once an obscure pathogen in northeastern North America, the number of human cases of POW has increased in the last decade and now is considered an emerging disease [31, 41]. The range of POW encompasses North America and Eurasia, where *I. scapularis* and *Ixodes ricinus* are widely distributed [42]. Symptomatic patients infected with POW develop neurological signs and symptoms, including encephalitis, meningitis, loss of coordination and speech difficulties, after an incubation period of 1–4 weeks, with high fever and headaches [43]. Approximately 10% of POW encephalitis cases are fatal or severe, with long-lasting neurological sequelae [41]. Another member of the TBE complex, KFD, is on the rise on the Indian subcontinent [37, 44].

TBE arboviruses are typically transmitted by members of the *I. ricinus* complex ticks, including *I. ricinus* L. in Europe, *Ixodes persulcatus* in Russia and China, and *I. scapularis* or *Ixodes pacificus* in North America [35]. Recently, *Dermacentor* species have been implicated in the transmission of TBE in those areas devoid of *Ixodes* species in East Asia [45], while *Haemaphysalis spinigera* has been proposed as the primary vector of KFD in the Indian subcontinent [44].

The order *Bunyavirales* (formerly family *Bunyaviridae*) is another crucial arboviral group and perhaps the most daunting among the emerging tick-borne viruses (Table 1, Fig. 1). This group includes the Crimean–Congo haemorrhagic fever virus (CCHFV), which has a wide range of hosts and tick vectors in Eurasia and Africa [46–48]. The transmission and life cycle of CCHFV is well-characterized; nonetheless, it remains a critical emerging pathogen over much of its range, with various modes of transmission, including tick-borne and directly from infected livestock [37, 40]. CCHFV affects the nervous system and causes neurological manifestations that precede more dramatic haemorrhagic symptoms [46]. CCHFV has a short incubation period, followed by a

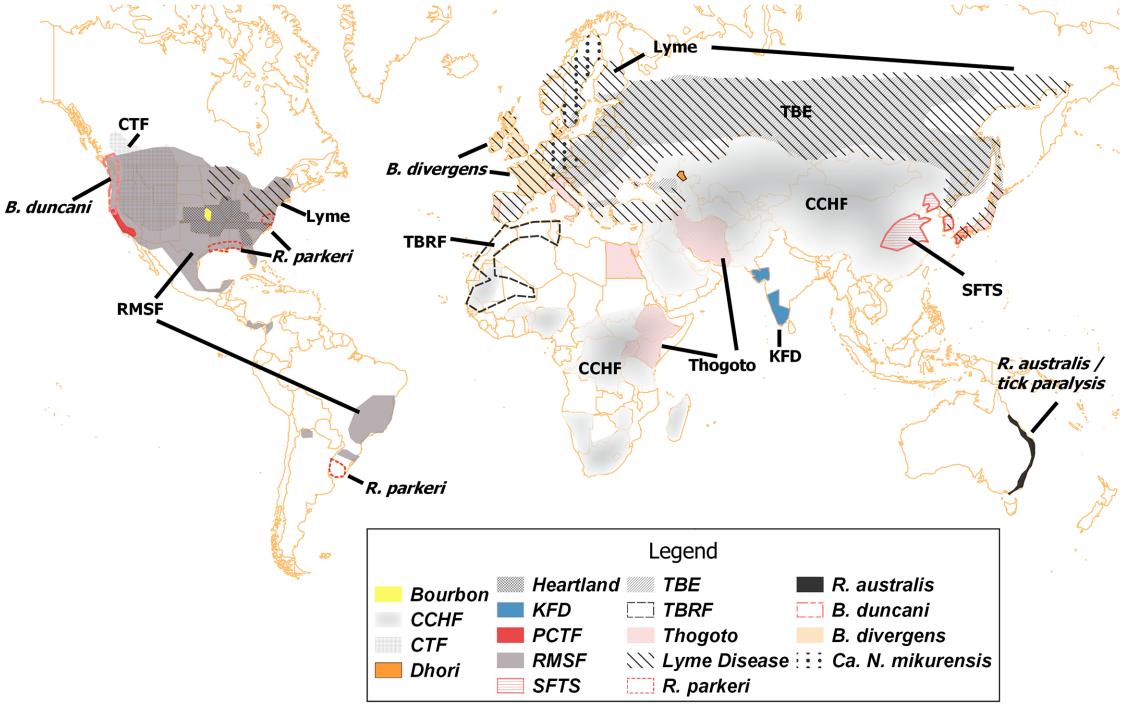

Fig. 1. Geographical distribution of selected tick-borne pathogens and diseases. All geographical boundaries are generalized and approximate. Abbreviations and descriptions are shown in Table 1. For some pathogens (Heartland virus, Thogoto virus, *B. divergens*, *Ca. N. mikurensis*), only country or state-level data were available. Only partial ranges are shown for some worldwide diseases and conditions – TBRF (tick-borne relapsing fever) in northwestern Africa, tick paralysis in Australia. Modified from previously published records and maps [29, 37, 44, 51, 53, 64, 66, 72, 83, 94, 105, 149–155]

rapid onset characterized by severe headache, dizziness, neck pain and vomiting, with high mortality rates in untreated or nosocomial infections [46, 47, 49]. CCHFV has been isolated from over 30 tick species, including *Ixodidae* and *Argasidae* ticks [50, 51]. However, the major CCHFV vectors belong to the genus *Hyalomma*, including *H. truncatum* in Africa and *H. marginatum* in southern Europe and western Asia [46, 48, 50].

Members of the genus *Phlebovirus* (*Buyanvirales*) that are closely related to CCHFV are among the newly recognized emerging pathogens, such as the severe fever with thrombocytopenia syndrome virus (SFTSV). The SFTSV was first described in 2009 and is associated with fever, thrombocytopenia, leukocytopenia and gastrointestinal symptoms [52–54]. The distribution of SFTSV is currently restricted to Asia (Fig. 1); PR China accounts for approximately 1000 cases per year with a mortality rate that ranges from 6 to 30%, while Japan and he Republic of Korea have sporadic cases [52, 53] The primary vector for the SFTSV is the Asian longhorned tick, *Haemaphysalis longicornis* Neumann [54]. The distribution of the Asian longhorned tick encompasses its original distribution in East Asia (PR China, Republic of Korea, Japan) as well as Australia, New Zealand and some Pacific Islands, where it was introduced in the past century [55]. Recently, the Asian longhorned tick was found in New Jersey [14] and neighbouring states in the USA after subsequent surveillance efforts. The Asian longhorned tick, according to suitable habitat modelling based on climatic factors, can spread throughout the eastern USA and parts of the West Coast [15]. The Midwest of the USA, which is an endemic area for the heartland virus, a novel *Phlebovirus* that is closely related to SFTSV, is a particularly suitable habitat for this tick species. The heartland virus was isolated in 2009 from two patients in Missouri, USA [56]. Since then, several more cases have been detected in nearby states [57]. The clinical manifestations of the heartland virus are similar to those of other tick-borne diseases, but it can also disseminate rapidly, causing a severe shock and multisystemic organ failure that accounts for its high mortality rate [58, 59]. The heartland virus has been isolated from lone-star ticks (*Amblyomma americanum* L.), which are considered to be its primary vector based on field isolations and laboratory studies [57, 60, 61]. Closely related to SFTSV and heartland virus are Bhanja serogroup *Phleboviruses* that are widespread in the old world. They are likely transmitted by *Haemaphysalis* ticks (Europe and Asia) or other tick species, including *Amblyomma*, *Dermacentor*, *Rhipicephalus* and *Hyalomma* ticks in Africa [62]. Reported human disease was febrile and mild [63].

The lone-star tick, *Amblyomma americanum*, likely serves as the vector for another emerging pathogen, the Bourbon

virus, from the family *Orthomyxoviridae* genus *Thogotovirus* (Table 1, Fig. 1). The Bourbon virus was isolated from multiple pools of *A. americanum* collected in Missouri, USA [64]. Although Bourbon virus infections are rare, they can be fatal [65]. This virus is the first *Thogotovirus* to be found in North America that infects humans, but other viruses such as Thogoto and Dhori are emerging in parts of Europe and Asia. In southern Russia, the Dhori virus was isolated from *Hyalomma marginatum,* and the seroprevalence in humans ranges from 4–6% [66]. Similarly, these viruses were isolated from *Hyalomma* ticks in Egypt [67]. In Japan, the recently identified Thogoto virus is likely vectored by *H. longicornis* [68]. Thogotoviruses and influenza viruses are related, and both belong to the same family, *Orthomyxoviridae*. Thus, Thogotoviruses can also be transmitted by other routes, such as aerosol [69]. Although in most patients Thogotovirus infection courses as a febrile illness, severe cases present encephalitis and other neurological disorders [70].

Similarly, Colorado tick fever (western North America, Fig. 1) and Eyach (Western Europe) viruses from the genus *Coltivirus* (family *Reoviridae*) present a self-limited flu-like illness; complications are rare but can be severe when they affect the central nervous system [71]. While Colorado tick fever is transmitted by *Dermacentor andersoni* [5, 72], the closely related Eyach virus is transmitted by *Ixodes ventalloi* and *I. ricinus* [71, 73].

Bacterial

Over 90% of bacterial species transmitted by ticks belong to two orders, *Spirochaetales* and *Rickettsiales* (Table 1) [20]. Lyme borreliosis, caused by a spirochete, is the most common tick infection, with approximately 300000 (240000 – 444000) annual cases in the USA [1–3] and 85000 cases in Europe [74] (Table 1, Fig. 1). Lyme disease is caused by different genetic species (genospecies) within the *Borrelia burgdorferi* sensu lato complex [1, 40, 75] and is transmitted by the same *I. ricinus* complex involved in TBE virus cycle – *I. ricinus* (Europe), *I. persulcatus* (Russia and Asia) and *I. scapularis* or *I. pacificus* (North America) [76–78]. The pathogenic genospecies include *B. burgdorferi* sensu stricto, *B. garinii*, *B. afzelii*, *B. spilmanii*, *B. bavariensis* and *B. mayonii,* which was recently isolated from patients, *I. scapularis* ticks, and rodents in the upper Midwest of the USA [79, 80].

The genus *Borrelia* includes other human pathogenic species that cause relapsing fever [81]. Relapsing fever is characterized by recurring febrile episodes that last around 3 days and are separated by a nonfebrile period. During these episodes, patients commonly experience high fever, headache, myalgia, chills and nausea [82]. In contrast to Lyme disease *Borrelia*, most relapsing fever spirochetes are transmitted by soft ticks from the genus *Ornithodoros*, which are present in Africa, Eurasia and the Americas [81, 83–85]. In western North America, *Ornithodoros* ticks are found in the desert and scrub regions from Texas to British Columbia [81, 84]. A notable exception in the tick-borne relapsing fever group is *Borrelia miyamotoi*, which is vectored by the same *I. ricinus* complex species that transmit Lyme borreliosis [86–88]. *B. miyamotoi* has been isolated from *I. ricinus* (Europe), *I. persulcatus* (Russia) and *I. scapularis* ticks [88]. In contrast to other relapsing fever *Borrelia* species*, B. miyamotoi* is not frequently recognized in patients, since it presents a limited febrile illness that is often subclinical. Patients display mild symptoms that are similar to those from influenza infection with high fever (98%), fatigue (98%), headache (89%), myalgia (59%), chills (35%) and nausea (30%), occasionally followed by a relapse about a week later in approximately 10% of patients [87, 88].

Tick-borne rickettsial diseases, such as spotted fever group rickettsioses (SFGR), are a group of diseases caused by members of the genus *Rickettsia*. The SFGR encompass a large number of emerging and established diseases that have a worldwide distribution (Table 1, Fig. 1) [39, 89, 90]. In the USA, Rocky Mountain spotted fever (RMSF) is vectored by *Dermacentor andersoni* Styles, the Rocky Mountain wood tick, *Dermacentor variabilis* Say, the American dog tick, and the brown dog tick (*Rhipicephalus sanguineus* Latreille) in the southwestern USA and Mexico,and is is the most severe rickettsiosis and frequently requires hospitalization [91]. A delay in diagnosis or treatment can result in complications, including amputation, cognitive disabilities, paralysis, hearing loss and even death [5, 92]. There are other forms of rickettsiosis in the USA that are caused by *Rickettsia parkeri,* which is transmitted by the Gulf Coast tick *Amblyomma maculatum* Koch and is also emerging in South America [93], and *Rickettsia philipii,* transmitted by the Pacific Coast tick *Dermacentor occidentalis* Marx. These two rickettsia species cause a less severe form of rickettsiosis with fever, diarrhoea, nausea, vomiting and an eschar, i.e., cutaneous necrosis at the site of the tick bite [92, 94].

Within the same order *Rickettsiales*, the family *Anaplasmataceae* includes emerging pathogens in the genera *Anaplasma* and *Ehrlichia*. The most important public health pathogen within this group is *Anaplasma phagocytophilum,* which is responsible for approximately 6000 cases of human granulocytic anaplasmosis (HGA) per year in the USA [95]. The vectors of HGA in the USA are *I. scapularis* and *I. pacificus* on the East and West Coasts of the USA, respectively. The onset of HGA is accompanied by unspecific symptoms, including fever, chills, malaise, headache and myalgias; appropriate treatment is essential to prevent life-threatening complications [95, 96]. HGA has also been reported in northern Europe, and Southeast Asia, including China, Mongolia and Korea [97].

Human ehrlichiosis is caused by *Ehrlichia chaffeensis* or *Ehrlichia ewingii*, which are transmitted by the American lone star tick, *A. americanum*. The symptoms are similar to those described for human anaplasmosis, and its prognosis depends on early diagnosis and treatment to avoid further complications that could potentially be fatal [98]. Human ehrlichiosis caused by *E. chaffeensis* has been detected in North America, Europe and Asia [99]. More recently, a new pathogen, *Ehrlichia muris eauclairensis,* was detected in patients from Minnesota and Wisconsin in the USA [100, 101]. Interestingly, these

Ehrlichia species are transmitted by *I. scapularis* in contrast to other *Ehrlichia* species in the USA. Another, closely related *Ehrlichia* bacterium, *Candidatus* Neoehrlichia mikurensis, is also transmitted by members of the *I. ricinus* complex, *I. ricinus* and *I. persulcatus*. It is an emerging pathogen in Europe and Asia, occasionally causing life-threatening conditions in immunocompromised patients [102–105].

Another bacterial disease, tularaemia, caused by the intracellular Gram-negative coccobacillus *Francisella tularensis*, can be transmitted by ticks. However, it is not limited to this mode of transmission and can also be acquired by many different routes, such as inhalation of contaminated aerosols, ingestion, direct contact, through deer fly, or potentially, mosquito bite [106–109]. Tularaemia is found in countries throughout the northern hemisphere in America, Europe and Asia [110].

Protozoan

Human babesiosis is an emerging tick-borne disease caused by members of the genus *Babesia*, protozoans that share many clinical features with *Plasmodium* malaria parasites, including reproduction within mammalian red blood cells [29, 40, 75, 111]. In North America, *B. microti* is the most common agent of human babesiosis and is present in the northeast and upper Midwest of the USA, where its vector, *I. scapularis,* is widely distributed. The course of human babesiosis is generally similar to a flu-like subclinical infection in healthy individuals. Older people, as well as immunocompromised and splenectomized patients, are at higher risk of developing severe symptoms and complications [29]. Human babesiosis can also be acquired through blood transfusions, a problem exacerbated by the lack of a licensed test to screen for *B. microti* in donated blood, making it the most common blood transfusion-transmitted pathogen reported in the USA [112].

Recently, a second species, *Babesia duncani,* was detected in patients along the Pacific coast of the USA and Canada [29, 113]. Until recently, the recognized vectors for *B. duncani* were *Ixodes* species, including *I. scapularis* and *I. pacificus*. A new study provided strong support for the winter tick, *Dermacentor albipictus*, and the mule deer as the respective vector and host species of *B. duncani,* suggesting that the pathogen might have a wider geographical distribution [114]. Lastly, a third species close to *Babesia divergens* has been detected sporadically in patients in the USA [113, 115, 116]. In Europe, *B. divergens* is transmitted by *I. ricinus* and is the leading cause of human babesiosis (Fig. 1) [29, 113, 117–119]. Other species vectored by *I. ricinus,* such as *Babesia venatorum* and *B. microti,* have been associated with human cases in Europe [120]. In South Asia, *B. microti* is transmitted by *Ixodes ovatus* Neumann, while *Babesia crassa* and *B. venatorum* cases have been reported from northern China, likely vectored by *I. persulcatus* [120, 121].

Tick bite-associated complications

Tick bites may cause an allergy to red meat, or alpha-gal syndrome. Alpha-gal syndrome is mediated by an IgE antibody response against an epitope present in the mammalian oligosaccharide, galactose-alpha-1,3-galactose (alpha-gal). This allergic reaction is attributed to the bite of certain tick species and is considered to be an emerging condition around the world [122, 123]. Several hundred to several thousand cases have been documented in North America, Europe, Australia and Japan; single cases have been reported from South America and Africa [124]. Some of the typical symptoms associated with the alpha-gal syndrome include urticarial or anaphylactic reactions that are generally manifested a few hours after eating red meat, including pork, lamb, beef, or kangaroo. In the USA, the lone star tick (*A. americanum*) has been often associated with reports of delayed urticaria angioedema, a painful and pruritic urticarial rash, abdominal pain, diarrhoea and sore throat [125, 126]. The bite of the Asian longhorned tick (*H. longicornis*), which was recently identified in the USA, is the most probable cause of red meat allergy in Japan [127].

Tick paralysis is a neuromuscular paralysis caused by salivary neurotoxins secreted by female hard ticks while feeding [128–131]. Worldwide, over 40 species of ticks have been implicated in tick paralysis, among them *D. andersoni* and *D. variabilis* in North America [128, 130]. The majority of reported cases have occurred in southeastern and western USA and southwestern Canada in young girls (<8 years old) with long hair where ticks are attached unnoticed [128, 129]. In Australia, tick paralysis, a rare but potentially fatal condition, is transmitted by *Ixodes holocyclus*, the aptly named Australian paralysis tick, the cause of paralysis to humans, domestic animals and wildlife [131, 132].

Tick and tick-borne disease management and control

The US Centers for Disease Control and Prevention (CDC) recommends personal protection as the best defence against tick-borne disease [133], in addition to landscaping modifications and acaricide applications to individual properties [133–136]. There is very little evidence that any of these measures are effective in reducing human–tick encounters, exposure to ticks, or disease incidence [137–139].

A prerequisite for effective personal protection is lowering tick population numbers or pathogen prevalence area-wide in highly endemic regions [140]. The only available area-wide control options to reduce tick populations target deer or mice as hosts for either adult or immature tick stages, respectively [141]. Deer population reduction was proposed as the cornerstone of integrated tick management [142], as treatments of deer and mice with topical pesticides have failed to produce a sustainable reduction in tick populations or human disease incidence [143–146].

The reasons for the failure of conventional tick control as opposed to more successful mosquito control are diverse [147]. It is clear that control of Lyme and other tick-borne diseases will require a paradigm shift emphasizing measures to reduce tick and host populations and a substantial research and development effort. At present, clinical assessment and

treatment remain the most critical tools in reducing the burden of tick-borne diseases.

CONCLUSIONS

The resurgence of tick-borne diseases is driven by the expansion of tick populations, particularly in northern America, Europe and Asia. Much of North America is endemic for a confounding variety of tick-borne pathogens, including viruses, bacteria and protozoa. In addition, tick bites can also lead to severe allergic reactions. In high-risk areas, public health practitioners are at the frontline of tick-borne diseases and should be familiar with the different tick species present in the area as well as the pathogens they transmit. Personal protection, vector control and accurate diagnosis and treatment will remain the cornerstones of coping with tick-borne diseases in the foreseeable future. While vaccine development may provide some relief, in general, relying solely on a vaccine does not work well in the multi-pathogen multi-vector systems [148] that are found in most endemic tick-borne disease areas (Fig. 1). The recent introduction of vector-borne pathogens such as West Nile virus and a new tick species, the Asian longhorned tick (*Haemaphysalis longicornis*), underscores the risk of increased expansions by vectors and pathogens in the increasingly mobile and interconnected world.

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I. R. and A. T. conceptualized the study and wrote the original draft.

Conflicts of interest
The authors declare that there are no conflicts of interest.

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