# Emerging tick-borne infections in mainland China: an increasing public health threat

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## Abstract

Since the beginning of the 1980s, 33 emerging tick-borne agents have been identified in mainland China, including eight species of spotted fever group rickettsiae, seven species in the family Anaplasmataceae, six genospecies in the complex *Borrelia burgdorferi* sensu lato, 11 species of *Babesia,* and the virus causing severe fever with thrombocytopenia syndrome. In this Review we have mapped the geographical distributions of human cases of infection. 15 of the 33 emerging tick-borne agents have been reported to cause human disease, and their clinical characteristics have been described. The non-specific clinical manifestations caused by tick-borne pathogens present a major diagnostic challenge and most physicians are unfamiliar with the many tick-borne diseases that present with non-specific symptoms in the early stages of the illness. Advances in and application of modern molecular techniques should help with identification of emerging tick-borne pathogens and improve laboratory diagnosis of human infections. We expect that more novel tick-borne infections in ticks and animals will be identified and additional emerging tick-borne diseases in human beings will be discovered.

## Introduction

Ticks were the first arthropods to be recognised as vectors that can transmit pathogens to human beings and are second only to mosquitoes as vectors of infectious diseases in the world.[1] Tick-borne infections are zoonoses with pathogens maintained in natural cycles involving tick vectors and animal hosts. Human beings are occasional hosts for ticks and are usually viewed as dead-end hosts that have no role in maintaining tick-borne agents in nature.[2] Different tick species favour distinct biotopes or environments, which define their geographical distribution and, consequently, the areas of risk for human tick-borne infections. In the past three decades, tick-borne pathogens have emerged worldwide and become a great threat to human health.[1,3]

China is the largest developing country in the world and has made tremendous progress in the control and prevention of infectious diseases; however, emerging infectious diseases are the new challenge now facing China.[4] Although outbreaks of severe acute respiratory syndrome and H5N1 and H7N9 avian influenza virus infections have attracted great attention, emerging tick-borne diseases have generally been neglected by primary health-care providers and clinicians. Although an increasing number of tick-borne infections have been reported in mainland China, no comprehensive review of this substantial public health problem has been undertaken. We will provide an overview of the type and distribution of emerging tick-borne infections in tick vectors, animal hosts, and human beings. We will describe the clinical characteristics of human tick-borne diseases, and discuss possible factors contributing to their emergence.

## Emergence of tick-borne infections in mainland China

Since 1982, 33 emerging tick-associated agents have been identified in mainland China, including eight species of spotted fever group rickettsiae (SFGR);[5–11] three species of *Ehrlichia*,[12–14] three species of *Anaplasma*,[15–17] and *Candidatus* Neoehrlichia mikurensis[18] in the family Anaplasmataceae; six genospecies in the complex *Borrelia burgdorferi* sensu lato;[19–23] 11 species of *Babesia*;[24–33] and severe fever with thrombocytopenia syndrome virus (SFTSV).[34] The location and year in which each emerging tick-borne agent was first identified are shown in the appendix. Most (19 of 33) were initially detected in ticks; however, six were identified in domestic animals (sheep, goat, buffalo, and dog), two in wild animals (Chinese white-bellied rat and Chinese hare), and six in people. Detailed information regarding the identification of these emerging tick-borne infections is summarised in table 1.

Among the 33 newly recognised tick-associated agents, 15 have been reported to cause human infection, including: four species of SFGR;[11,35,46,48] an *Ehrlichia* species,[53] two *Anaplasma* species,[17,53] and *Candidatus* N mikurensis;[18] three genospecies of *B burgdorferi* sensu lato;[19,21,78] three species of *Babesia*;[33,104,108] and SFTSV (table 2).[34] Six of the tick-borne pathogens were first identified in febrile patients (*Candidatus* Rickettsia tarasevichiae, *Candidatus* N mikurensis, *Borrelia garinii*, *Borrelia afzelii*, *Babesia venatorum* [not yet formally described], and SFTSV) and then shown to be associated with ticks (table 1). The other nine human pathogens were initially detected in ticks or animals and subsequently

shown to infect human beings (*Rickettsia heilongjiangiensis*, *Rickettsia sibirica* sp BJ-90, *Rickettsia raoultii*, *Ehrlichia chaffeensis*, *Anaplasma phagocytophilum*, *Anaplasma capra*, *Borrelia valaisiana*-related genospecies, *Babesia microti*, and *Babesia divergens*). Among these 15 emerging tick-borne diseases, severe fever with thrombocytopenia syndrome (SFTS) was first identified in mainland China[34] and subsequently reported in South Korea and Japan.[134,135] A disease similar to SFTS has been reported in the USA.[136] Human infections with *R sibirica* sp BJ-90, *Candidatus* R tarasevichiae, *A capra*, and *B valaisiana*-related genospecies have been exclusively diagnosed in mainland China.[11,17,46,78] Human infections of *Candidatus* N mikurensis, *Ba venatorum*, and *R raoultii*, which have been detected in China, were first identified in Europe.[18,33,48] Five tick-borne pathogens have been detected in ticks or reservoir hosts, or both, but have not yet been reported to cause infection in human beings in China. They include *Rickettsia monacensis*, *Rickettsia slovaca*, *Rickettsia sibirica* sp *mongolotimonae*, *B valaisiana*, and *B burgdorferi* sensu stricto.[137–141] Additionally, a *Rickettsia* species (*Candidatus* Rickettsia hebeiii), two *Ehrlichia* species (*Ehrlichia canis* and *Ehrlichia* sp Tibet), an *Anaplasma* species (*Anaplasma platys*), a genospecies of *B burgdorferi* sensu lato (*Borrelia sinica*), and eight *Babesia* species (*Babesia ovis*, *Babesia ovata*, *Babesia orientalis*, *Babesia major*, *Babesia motasi*, *Babesia caballi*, *Babesia* sp Kashi, and *Babesia* sp Xinjiang) have been identified in ticks or animals, but their pathogenicity to human beings is unknown.

## Emerging SFGR infections

Eight novel species of SFGR have been recorded in mainland China since 1982 (table 1).[5–11] These species are mainly distributed in northern China (north of 36° north latitude).

### Tick and animal infections

The eight emerging species and uncharacterised species of SFGR have been shown to be associated with 16 tick species (figure 1). *R heilongjiangiensis* has been proven to infect a range of tick species, three rodent species, and goats (appendix). In northeastern China, *R heilongjiangiensis* was detected in nine tick species and two rodent species from Heilongjiang Province,[36–38] and in *Haemaphysalis* spp ticks from Jilin Province.[38] In Inner Mongolia, *R heilongjiangiensis* has been reported in *Haemaphysalis verticalis*, *Detmacentor niveus*, *Hyalomma asiaticum kozlovi*, *Rhipicephalus pumilio*, and *Detmacentor nuttalli* ticks.[39] In northwestern China, *R heilongjiangiensis* has been detected in *Dermacentor silvarum* ticks from Qinghai Province.[40] In southern China, *R heilongjiangiensis* has been detected in *Haemaphysalis longicornis* ticks from Guangdong Province,[41] in goats from Yunnan Province,[42] and in chestnut white-bellied rats from Hainan Province.[43] In central and eastern China, *R heilongjiangiensis* was identified in *Haemaphysalis flava* ticks from Henan, Anhui, and Hubei provinces,[8] and in *H longicornis* from Zhejiang Province.[44] *R sibirica* sp BJ-90 was detected in *Dermacentor sinicus* ticks from a Beijing suburb.[7] *R raoultii* was detected in *Dermacentor* species ticks, including *D silvarum* and *Dermacentor marginatus*, in western China,[9,49] in *H verticalis* collected from Inner Mongolia, in *D silvarum* from Heilongjiang Province, and in *H longicornis* from Liaoning Province.[48,39,50,51] Four species, including *R sibirica* sp *mongolotimonae*, *R monacensis*, *R slovaca*, and *Candidatus* R hebeiii, have not been proven to infect human beings. Data

regarding infected ticks and animal hosts are shown in figure 1 and the appendix.[7–10,47,52,54,119,142–147]

### Human infections

Four species of emerging SFGR have been reported to infect human beings, including *R heilongjiangiensis*, *Candidatus* R tarasevichiae, *R sibirica* sp BJ-90, and *R raoultii* (table 2; figure 2). Of 34 people infected with *R heilongjiangiensis*, 19 were diagnosed in forested areas of northeastern China in the 1990s.[35,45] The other 15 cases of infection were reported on the island of Hainan Province in 2008.[43] In 2012, we undertook an active surveillance for human SFGR infections at the Mudanjiang Forestry Central Hospital of Heilongjiang Province in northeastern China, and eight cases of SFGR infection (including five infected by *Candidatus* R tarasevichiae, one by *R sibirica* sp BJ-90, and two by *R raoultii*) were identified by molecular detection and sequence determination. The presence of antibody against SFGR antigen in serum samples detected by immunofluorescence assay lent support to the diagnosis of SFGR.[46,48] Additionally, 37 patients were reported to have been infected with uncharacterised species of SFGR, including one in Inner Mongolia, one in Xinjiang Autonomous Region, 29 in Hainan Province, and six in Heilongjiang Province (figure 2).[119–124] The clinical manifestations of SFGR infections mainly include fever, eschar, headache, malaise, asthenia, anorexia, nausea, and lymphadenopathy. A few patients had rash and neurological manifestations such as coma, neck stiffness, and Kernig's sign.[11,35,43,45,46,48,119–124] Detailed information about the clinical and laboratory characteristics of patients infected with each of the emerging SFGR species are summarised in the appendix.

## Emerging infections with agents in the family Anaplasmataceae

Seven species in the family Anaplasmataceae have been identified in mainland China, including *E chaffeensis*, *E canis*, *Ehrlichia* sp Tibet, *A phagocytophilum*, *A capra*, *A platys*, and *Candidatus* N mikurensis (table 1).

### Tick and animal infections

The seven emerging agents in the family Anaplasmataceae are known to be associated with 17 tick species (figure 1). *E chaffeensis* was first detected in *Amblyomma testudinarium* ticks from Yunnan Province in 1996.[12] Several surveys report that it infects various tick species, and is widely dispersed in mainland China.[31,54–58] Furthermore, *E chaffeensis* was detected in dogs from Shandong Province, in long-tailed ground squirrels (*Citellus undulates Pallas*) and gerbils from Xinjiang Autonomous Region, in the striped field mouse (*Apodemus agrarius*) from Heilongjiang Province, and in rodents (*Rattus norvegicus*, *Rattus losea*, *Rattus flavipectus*, *Rattus niviventer*, *Mus musculus*, *Niviventer confucianus*, and *Rattus edwardsi*) and hares (*Lepus sinensis*) from Fujian and Zhejiang provinces (appendix).[36,55,59–62] *A phagocytophilum* was first detected in *Ixodes persulcatus* from Heilongjiang Province in 1997,[15] and is now the most widely encountered species in the family Anaplasmataceae over broad areas where multifarious tick species are vectors (figure 1). Additionally, *A phagocytophilum* infects domestic and wild animals, including cattle, sheep, goats, horses, dogs, hare, yaks, and 24 species of rodents

(appendix).[36,51,54,55,62,64–72] *A capra* was first recognised in goats (*Capra aegagrus hircus*) and provisionally named by our group, but has since been detected in *I persulcatus* ticks in Heilongjiang Province.[17] Although *Candidatus* N mikurensis was initially identified in *I persulcatus* and *Haemaphysalis concinna* ticks,[18] it was subsequently detected in *D silvarum*, *H longicornis*, and various rodents from many areas of mainland China.[18,76,77] Three other species, including *E canis*, *Ehrlichia* sp Tibet, and *A platys*, have not been proven to infect human beings. Data regarding infected ticks and animal hosts are shown in figure 1 and the appendix.[13,14,16,57,63]

### Human infections

Four species of Anaplasmataceae have been identified to cause human infections in mainland China: *E chaffeensis*, *A phagocytophilum*, *A capra*, and *Candidatus* N mikurensis. The first human case of monocytic ehrlichiosis was diagnosed in a forested area of Inner Mongolia in 1999.[53] Of the 12 human cases of monocytic ehrlichiosis reported, four were recorded in Inner Mongolia, two in Beijing, two in Tianjin, and four in Shandong Province (figure 2).[53,55] A cluster of ten cases of human granulocytic anaplasmosis caused by nosocomial transmission was identified in Anhui Province in 2006.[73] An additional 94 cases of human granulocytic anaplasmosis have been reported, including 33 in Beijing, six in Tianjin, 41 in Shandong Province, one in Anhui Province, and four to five each in Henan and Hubei provinces and Inner Mongolia (figure 2).[53,55,64,74,75] In 2015, 28 patients were reported to be infected with *A capra* in Heilongjiang Province.[17] Seven cases of *Candidatus* N mikurensis infection were identified from 622 febrile patients in the same location in 2010.[18] Patients with infections caused by species from the Anaplasmataceae family showed undifferentiated clinical manifestations, mainly including fever, malaise, myalgia, arthralgia, and gastrointestinal symptoms (diarrhoea, nausea, vomiting, and anorexia). Laboratory abnormalities included leucopenia, thrombocytopenia, and raised hepatic aminopherase, lactate dehydrogenase, and blood urea nitrogen (appendix).[17,18,53,55,64,73–75]

## Emerging infections with *B burgdorferi* sensu lato

*B burgdorferi* sensu lato was first detected in human beings and *I persulcatus* in China (Heilongjiang Province) in 1986.[19] This isolate was later classified as *B garinii* by molecular biological methods in our laboratory. Five other genospecies were subsequently identified, including *B valaisiana*, *B sinica*, *B afzelii*, *B valaisiana*-related genospecies, and *B burgdorferi* sensu stricto (table 1).

### Tick and animal infections

Over a wide geographical distribution of 25 provinces in mainland China, 26 tick species have been shown to carry *B burgdorferi* sensu lato (figure 1). *B garinii* is the most common genospecies and has been identified in many tick species (figure 1).[54,79–86] *B garinii* has been detected in rodents from many endemic areas,[23,36,79,85,87,88] in dogs from Yunnan Province, in sheep keds (*Melophagus ovinus*) from Tibet, and in hares from Gansu Province (appendix).[89] *B afzelii* is the second most common genospecies, and has been identified in the same ticks and rodents as *B garinii* with a similar distribution.[36,79,81,83–85] *B valaisiana*-related genospecies (a genetically related but distinct genospecies of *B valaisiana*) was

detected in *Ixodes granulatus* and *H longicornis* from Guizhou Province, and in rodents from Guizhou and Zhejiang provinces.[22,83] Three other genospecies that have not been reported to infect human beings include *B valaisiana, B sinica,* and *B burgdorferi* sensu stricto. Data regarding infected ticks and animal hosts are shown in figure 1 and the appendix.[20,23,86,92,148–156]

### Human infections

After the identification of *B burgdorferi* sensu lato in ticks and animals, human cases of *B burgdorferi* sensu lato infection have been reported frequently in almost all provinces in mainland China, except for Tibet and Shanghai metropolis (figure 2). *B garinii*, *B afzelii*, and *B valaisiana*-related genospecies have been reported to cause human infections (table 2).[19,21,23,78,90,91,125] The genospecies causing thousands of cases of Lyme disease in mainland China have not been characterised.[126–131] All the uncharacterised human cases in figure 2 were classified as *B burgdorferi* sensu lato infections irrespective of their actual genospecies. Infections with different genospecies of *B burgdorferi* sensu lato might result in slightly different clinical manifestations, including erythema migrans, arthritis or arthralgia, fever, headache, and fatigue.[19,21,23,78,90,91,125–131] Generally, clinical manifestations in mainland China are mild compared with those in USA and Europe.[78]

## Emerging *Babesia* species infections

Since 1982, 11 *Babesia* species have been discovered in mainland China, including *Ba ovis*, *Ba major*, *Ba ovata*, *Ba orientalis*, *Ba motasi*, *Ba caballi*, *Babesia* sp Kashi, *Babesia* sp Xinjiang, *Ba microti*, *Ba divergens*, and *Ba venatorum* (table 1).

### Tick and animal infections

The transmission of babesia is associated with 13 tick species (figure 1). *Ba microti*, *Ba divergens*, and *Ba venatorum* have been proven to infect human beings. *Ba microti* was identified in *I persulcatus* and *H concinna* ticks and in striped field mice and reed voles (*Microtus fortis*) from forested areas of Heilongjiang Province, in *H longicornis* ticks and dogs from Henan Province, and in rodents from Fujian, Zhejiang, Henan, and Heilongjiang provinces.[32,36,58,105,106] *Ba divergens* was detected in *I persulcatus*, *H concinna*, and *Haemaphysalis japonica* ticks and striped field mice in several areas of Heilongjiang Province.[32,36] *Ba venatorum* was reported in *I persulcatus* ticks from forested areas of northeastern China.[109] Other species of *Babesia* that have not been shown to infect human beings include *Ba ovis*, *Ba major*, *Ba ovata*, *Ba orientalis*, *Ba motasi*, *Ba caballi*, *Babesia* sp Kashi, and *Babesia* sp Xinjiang. Data regarding their infected ticks and animals are shown in figure 1 and the appendix.[24–31,93–103]

### Human infections

*Ba microti*, *Ba divergens*, and *Ba venatorum* have been reported to cause human infections in mainland China (figure 2). A patient was diagnosed with *Ba microti* infection by peripheral blood and bone marrow smears and PCR assay in Zhejiang Province in 2011.[104] By use of PCR, *Ba microti* infections were identified in an additional ten patients among 449 febrile patients with malaria-like symptoms in Yunnan Province during 2012–13.[107] One

patient was co-infected with *Plasmodium vivax* and another was co-infected with *Plasmodium falciparum*. Two cases of *Ba divergens* infection were detected from 377 patients with anaemia in Shandong Province in 2009.[108] A case of babesiosis caused by *Ba venatorum* was reported in a child from Xinjiang Autonomous Region.[33] Between 2011 and 2014, 48 cases of *Ba venatorum* infection were reported through our active surveillance at a sentinel hospital in forested areas of northeastern China. Among them, 32 were confirmed cases, and 16 were probable cases.[109] These infections were the first report of endemic human *Ba venatorum* disease anywhere in the world. Additionally, two cases of babesiosis caused by uncharacterised *Babesia* species were reported in Yunnan Province of southwestern China in 1982 and one in 2008 (figure 2).[132,133] Clinical manifestations for patients with *Babesia* species infections included fever, fatigue, anaemia, chills, and high levels of hepatic aminopherase and C-reactive protein.[33,108,104,109,107,132,133] Detailed information about the clinical manifestations of each of these species of *Babesia* infections is summarised in the appendix.

## Emerging SFTSV infections

SFTSV is a novel member of the genus *Phlebovirus* in the Bunyaviridae family, and was first identified in China. The identification of SFTSV infections was made possible by enhanced active surveillance in selected provinces of China.[34] Since a systematic review on the epidemiology, clinical signs, pathogenesis, diagnosis, treatment, and prevention of human infection with SFTSV has been published,[157] we provide only a brief description and some new information about the infection.

### Tick and animal infections

SFTSV have been reported to infect *H longicornis* and *Rhipicephalus microplus* ticks, with a higher prevalence of infection in *H longicornis* (4–9%) compared with in *R microplus* (0–6%).[34,110] Various animals, including goats, cattle, dogs, pigs, rodents, chickens, geese, and hedgehogs, might be infected by this pathogen.[110,111] Studies in Shandong, Jiangsu, and Hubei provinces showed that goats and cattle had the highest seropositive rate. Furthermore, big animals usually had higher seropositive rates than small animals.[111,112]

### Human infections

As of 2013, 2543 human SFTS infections have been reported to the China Center For Disease Control And Prevention, including 154 deaths.[34,113–118] Incidence hotspots are located in Henan, Hubei, Anhui, and Shandong provinces of middle-eastern China, in addition to Liaoning Province of northeastern China (appendix). Clinical manifestations in patients with SFTS are non-specific with major symptoms including respiratory tract symptoms, sudden onset of fever up to 38–41°C, headache, fatigue, myalgia, and gastrointestinal symptoms (loss of appetite, nausea, vomiting, and diarrhoea). Multiple organ failure develops rapidly in most patients (with raised concentrations of serum alanine aminotransferase, aspartate aminotransferase, creatine kinase, and lactate dehydrogenase; and proteinuria and haematuria), and is usually accompanied by thrombocytopenia, leucocytopenia, and lymphadenopathy.[34,117]

## Factors contributing to the emergence of tick-borne infections

Beyond doubt, advances in and application of molecular technologies have resulted in the discovery of novel agents and helped to identify human infections caused by agents previously detected in ticks. Thus, to some extent, the emergence of tick-borne infections has resulted from the discovery of novel pathogens through the use of more sensitive and reliable detection methods. However, various biological factors, such as tick and host population dynamics, which have caused an increase in the transmission and dissemination of tick-borne zoonotic diseases, are probably the main reasons for the emergence of these infections.[3]

Changes in land use have affected the emergence of tick-borne zoonotic diseases by altering the interactions and abundance of ticks, wild and domestic hosts, and human exposure to pathogens.[158] An example is the emergence of Lyme disease in northeastern USA. Reforestation of this region during the 20th century is thought to have increased the population of white-tailed deer, which greatly amplified the number of *Ixodes scapularis*. Consequentially, vector tick densities grew and expanded, contributing substantially to the emergence of Lyme disease in the USA.[159] Fragmentation of forests in eastern regions of Canada and the USA might have increased the relative abundance of small mammals because of a reduction in predator communities, leading to an increase in *B burgdorferi* sensu lato infection rates in *I scapularis* nymphs. Ultimately, people in these areas were confronted with a higher risk of Lyme disease.[160,161]

Since the mid-1990s, the Chinese central government has initiated the Greening Program to regain forests and grasslands from former agricultural lands.[162] Reforestation and grass replanting with high-quality vegetative cover could have increased the abundance and diversity of ticks and animal hosts, and favoured the re-establishment of pre-existing tick vector enzootic cycles in these areas. One example described in our study was in the most severely endemic region of SFTS. Our findings showed that the incidence of SFTS is significantly associated with vegetation-rich lands. A 10% increase in shrub, forest, and rain-fed cropland areas resulted in increased human SFTS incidence rates of 51%, 51%, and 90%, respectively.[163]

Additionally, urbanisation has affected the emergence and increasing incidence of tick-borne diseases. Studies in Europe suggest that encroachment into forested and uncultivated areas, and protection of existing green spaces in the process of urbanisation, have created opportunities for ticks to survive in urban and especially suburban environments. The presence of many pets and domestic animals, which can serve as tick hosts and pathogen reservoirs, might help tick transmission of various human and animal pathogens.[164,165] In the past three decades, China has gone through the most rapid urbanisation in its history. This rapid urbanisation, followed by widespread rural-to-urban migration of the human population, intensive long-distance trade, and explosive short-term travel for shopping, has led to substantial health risks including air pollution, occupational and traffic hazards, and altered diets and activity.[166] All of these changes in human activity, together with increased contact between human beings and their pets and nature, have probably contributed to the increasing abundance of tick exposure, as reported in other developed countries.[164] Further

investigation is needed to show the relation between emerging tick-borne diseases and urbanisation in mainland China.

The effect of worldwide climate change on the emergence of most vector-borne zoonotic diseases (including tick-borne diseases) is thought to be less important than changes in land use, animal host communities, human living conditions, and societal factors.[3] Although the effects of climate on transmission of infectious diseases are thought to be non-linear and act in opposing directions in different climate regions, the seasonal dynamics of tick vectors are largely defined by climate conditions, which might further affect the seasonal pattern of tick-borne diseases. An increase in winter temperatures is known to cause the northward extension and increased abundance of *Ixodes ricinus*, which subsequently raises the risk of tick-borne disease dissemination.[167–169] Although this topic is still under debate, climatic change could have a role in the emergence of tick-borne diseases in China. Further studies are needed to better elucidate this issue.

## Perspectives

Ticks are thought to be second only to mosquitoes as worldwide vectors of human infectious diseases.[170] Up to now, more than 120 tick species have been identified in China, including over 100 species in the Ixodidae (so-called hard tick) family and 19 species in the Argasidae (soft tick) family.[171] They transmit several pathogens when feeding on a range of animals, including human beings as accidental hosts. About 30 tick species are reported to feed on human beings.[172,173] The diverse geographical distribution and abundance of ticks are dependent on optimum environmental conditions and biotopes for each tick species, which define the risk areas for corresponding tick-borne zoonoses.[3] In addition to the emerging tick-borne infections, previously documented and well established tick-borne diseases are a continuing threat to human health, including tick-borne encephalitis in northeastern China, Crimean-Congo haemorrhagic fever in northwestern China, tularaemia and north-Asia tick-borne spotted fever in northern China, and Q fever, which is widely distributed throughout China.[174–183]

The non-specific clinical manifestations caused by tick-borne pathogens, such as SFGR, *Anaplasma* species, *B burgdorferi* sensu lato, *Babesia* species, and SFTSV, present a major diagnostic challenge. Most physicians are unfamiliar with the many tick-borne diseases that present with non-specific symptoms in the early stages of the illness. The wide distributions of the 33 emerging tick-associated agents and their tick vectors, in addition to the diversity of tick species throughout mainland China, imply that reported cases of infection might be only the tip of the iceberg in regard to the actual number of tick-borne diseases. To develop a reasonable differential diagnosis and identify a specific pathogen, laboratory diagnostic methods that are rapid, convenient, and practical are urgently needed for these emerging tick-borne diseases. Although great progress has been made in mainland China in the detection and identification of various tick-borne pathogens and diagnosis of the infections they cause, the necessary technologies are still unavailable in most general hospitals. Unfortunately, the importance of tick-borne diseases to human and animal health has not been sufficiently recognised as a result of inaccessibility to laboratory tests for aetiological diagnosis and inadequate surveillance activities.

In China, 18 tick-borne agents have been detected in ticks or animals, including four *Rickettsia* species, two *Ehrlichia* species, an *Anaplasma* species, three genospecies of *B burgdorferi* sensu lato, and eight *Babesia* species; however, the full effect of their pathogenicity to human beings is still to be established. Despite increasing knowledge about their geographical distribution, the natural cycle of these agents and the natural history of their infection in tick vectors and animal hosts have yet to be elucidated. Identifying human infections after potentially pathogenic agents are identified in ticks could take many years, in part because the microbial loads are much lower in human blood than in arthropods.[184] For example, *R sibirica* sp BJ-90 was first identified in *D sinicus* ticks in China in 1990,[7] but was not discovered to infect human beings until 22 years later.[46] Similarly, *A phagocytophilum* was initially detected in China in 1997;[15] however, nosocomial transmission of human granulocytic anaplasmosis was not recognised until 10 years later.[73] As such, the 18 tick-associated agents that have been recognised in China in either ticks or animals represent potential candidates for new tick-borne human diseases. Likewise, a search for potential new pathogens in ticks is essential for the discovery of emerging tick-borne diseases in human beings.

## Conclusion

33 tick species belonging to six genuses have been reported to be naturally infected with the emerging pathogenic agents described in this Review (figure 1). Except for eight species (*Dermacentor abaensis*, *Dermacentor daghestanicus*, *Haemaphysalis bispinosa*, *H flava*, *Haemaphysalis sinensis*, *Haemaphysalis yeni*, *Ixodes myospalacis*, and *Rhipicephalus turanicus*), most species carry two or more agents. Conversely, some emerging agents such as *R heilongjiangensis*, *E chaffeensis*, *A phagocytophilum*, and *B garinii* can infect several tick species. Additionally, tick-borne pathogens that infect domestic animals might eventually cause human disease. A representative example is *B divergens*, which has long been recognised to cause cattle babesiosis in Europe, and was subsequently identified as a human pathogen.[185] In China, a wide range of emerging tick-borne agents are known to infect various domestic animals (appendix), and their potential capability to infect humans warrants great attention and further investigation. With the continued emergence of tick-borne diseases in mainland China, improving our understanding of the existence and health burden of these diseases is essential for China and for the rest of the world.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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**Search strategy and selection criteria**

We searched PubMed and ISI Web of Science for articles published in English, and WanFang database, China National Knowledge Infrastructure, and Chinese Scientific Journal Database for articles published in Chinese between Jan 1, 1980, and May 31, 2015. We used the following search terms: "tick-borne disease", "tick-borne zoonosis", "tick-borne zoonotic disease", "tick-associated agent", "tick-associated microbe", and "China", in combination with each of the five genera of tick-borne agents. We did a secondary manual search of the references cited in these articles to find relevant articles. We investigated all the articles related to detection, identification, or infections of these five genera of tick-borne microbes in human beings, ticks, and animals. We contacted the corresponding authors for detailed information such as the time of discovery, location, and origin of tick-borne agents if any of this information was missing in the articles.

**Figure 1. Matrix of emerging tick-associated agents and tick species in mainland China**
*Not yet formally described. SFTSV=severe fever with thrombocytopenia syndrome virus.

**Figure 2. Geographical distribution of emerging tick-borne diseases in mainland China**
Human cases of SFGR infections are shown in blue; patients infected with agents in the
family Anaplasmataceae in green; patients infected with agents in the complex *Borrelia
burgdorferi* sensu lato in purple; and patients infected with agents in the genus *Babesia* in
black. SFGR=spotted fever group rickettsiae. *Not yet formally described.

**Table 1**

First identification and origin of emerging tick-borne infections in mainland China since 1982

| | First identified origin[*] | First identified province (year)[†] | Reference (subsequent investigations) |
|---|---|---|---|
| Spotted fever group rickettsiae | | | |
| *Rickettsia heilongjiangiensis* | *Dermacentor silvarum* | Heilongjiang (1982) | 5 (6,8,35-45) |
| *Rickettsia sibirica* sp BJ-90 | *Dermacentor sinicus* | Beijing (1990) | 7 (46) |
| *Rickettsia sibirica* sp *mongolotimonae* | *Hyalomm asiaticum kozlovi* | Inner Mongolia (1991) | 7 |
| *Rickettsia monacensis* | *Ixodes persulcatus* | Henan, Anhui, and Hubei provinces (2006) | 8 (44,47) |
| *Rickettsia raoultii* | *D silvarum* | Xinjiang (2011) | 9 (48-50) |
| *Rickettsia slovaca* | *D silvarum* | Xinjiang (2011) | 9 (50,51) |
| *Candidatus* Rickettsia *hebeiii* | *Haemaphysalis longicornis* | Hebei (2011) | 10 (52) |
| *Candidatus* Rickettsia *tarasevichiae* | Man (*I persulctus*) | Heilongjiang (2012) | 11 |
| Anaplasmataceae | | | |
| *Ehrlichia chaffeensis* | *Amblyomma testudinarium* | Yunan (1996) | 12 (32,36,53-62) |
| *Ehrlichia canis* | *Rhipicephalus sanguineus* sensu stricto | Guangdong (1997) | 13 (16,57,63) |
| *Ehrlichia* sp Tibet | *Rhipicephalus microplus* | Tibet (2000) | 14 |
| *Anaplasma phagocytophilum* | *I persulcatus* | Heilongjiang (1997) | 15 (36,51,53-55,62-75) |
| *Anaplasma platys* | Dog | Guangdong (1998) | 16 (63) |
| *Anaplasma capra*[‡] | Goat | Heilongjiang (2014) | 17 |
| *Candidatus* Neoehrlichia mikurensis | Man (*I persulctus*) | Heilongjiang (2010) | 18 (76,77) |
| *Borrelia burgdorferi* sensu lato | | | |
| *Borrelia garinii* | Man (*I persulcatus*) | Heilongjiang (1986) | 19 (21,23,36,54,78-91) |
| *Borrelia valaisiana* | *Ixodes granulatus* (*Apodemus agrarius*) | Zhejiang (1997) | 20 (86,92) |
| *Borrelia sinica* | *Niviventer confucianus* | Chongqing (1997) | 20 |
| *Borrelia afzelii* | Man | Heilongjiang (2000) | 21 (36,78,79,81,83-85,90) |
| *Borrelia valaisiana*-related genospecies | *I granulatus, H longicornis* (*A agrarius*) | Guizhou (2006) | 22 (78,83,86,88) |
| *Borrelia burgdorferi* sensu stricto | *Caprolagus sinensis* | Hunan (2010) | 23 (92) |
| *Babesia* spp | | | |
| *Babesia ovis* | Sheep | Sichuan (1982) | 24 (93) |
| *Babesia major* | *H longicornis* (cattle) | Henan (1988) | 25 (94) |
| *Babesia ovata* | Cattle | Henan (1990) | 26 (95) |
| *Babesia orientalis* | Buffalo | Hubei (1997) | 27 (96,97) |
| *Babesia motasi* | Sheep | Gansu (1997) | 28 (98,99) |
| *Babesia caballi* | *D silvarum, Dermacentor nuttalli* | Gansu (1998) | 29 (100-102) |
| *Babesia* sp Kashi | *Hyalomma anatolicum* | Xinjiang (2005) | 30 (103) |
| *Babesia* sp Xinjiang | *R sanguineus* sensu stricto, *H anatolicum* | Xinjiang (2007) | 31 (103) |

| | First identified origin[*] | First identified province (year)[†] | Reference (subsequent investigations) |
|---|---|---|---|
| *Babesia microti* | *I persulcatus, Haemaphysalis concinna* | Heilongjiang (2007) | 32 (36,104-107) |
| *Babesia divergens* | *I persulcatus, H concinna, Haemaphysalis japonica* (*A agrarius*) | Heilongjiang (2007) | 32 (36,108) |
| *Babesia venatorum*[‡] | Man | Xinjiang (2012) | 33 (109) |
| SFTSV | Man | Henan (2009) | 34 (110-118) |

SFTSV=severe fever with thrombocytopenia syndrome virus.

[*] First identified origin of each emerging tick-associated agent, including man, domestic animal, rodent, and tick. The agent that was simultaneously identified from other hosts or ticks is shown in parentheses.

[†] Provinces include autonomous regions and metropolis.

[‡] Not been formally described in taxonomic papers.

**Table 2**

Emerging tick-borne diseases of human beings reported in mainland China as of May 31, 2015

|  | Pathogen | Number of patients | Diagnostic methods[*] (reference) |
|---|---|---|---|
| Rickettsiosis | *Rickettsia heilongjiangiensis* | 34 | A and B (35), B and C (43), A and C (45) |
| Rickettsiosis | *Rickettsia sibirica* sp BJ-90 | 1 | A and B (46) |
| Rickettsiosis | *Rickettsia raoultii* | 2 | A and B (48) |
| Rickettsiosis | *Candidatus* Rickettsia tarasevichiae | 5 | B (11) |
| Rickettsiosis | Uncharacterised *Rickettsia* spp | 37 | C (119-121), B (122), A and C (123), E (124) |
| Human monocytic ehrlichiosis | *Ehrlichia chaffeensis* | 12 | B (53,55) |
| Human granulocytic anaplasmosis | *Anaplasma phagocytophilum* | 104 | B (53,55,74,75), A, B, and C (73), A and B (64), E (71) |
| 1 Human infection with *Anaplasma capra*[†] | *A capra*[†] | 28 | A, B, and C (17) |
| Human infection with *Candidatus* Neoehrlichia mikurensis | *Candidatus* N mikurensis | 7 | B (18) |
| Lyme disease | *Borrelia garinii* | 30 | B (21,23,78,90,91) |
| Lyme disease | *Borrelia afzelii* | 8 | B (21,23,78,90), C (125) |
| Lyme disease | *Borrelia* valaisiana-related genospecies | 1 | B (78) |
| Lyme disease | Uncharacterised *Borrelia burgdorferi* sensu lato | 2691 | A (126-130), E (131) |
| Babesiosis | *Babesia divergens* | 2 | B (108) |
| Babesiosis | *Babesia microti* | 11 | B and D (104,107) |
| Babesiosis | *Babesia venatorum*[†] | 49 | A, B, and C (33), B, C, and D (109) |
| Babesiosis | Uncharacterised *Babesia* spp | 3 | D (132,133) |
| SFTS | SFTSV | 2543 | A, B, and C (34,117), A or B or C (113,118), A or B (114), B and C (115), B (116) |

SFTS=severe fever with thrombocytopenia syndrome. SFTSV=severe fever with thrombocytopenia syndrome virus.

[*] Diagnostic methods: (A) a four-fold increase in titre of specific antibodies in blood sera collected from the acute and convalescent stages of illness, or a seroconversion of specific antibodies; (B) molecular detection and sequence determination; (C) isolation of pathogens from clinical samples; (D) light or electronic micrograph identification for thin blood smear; and (E) methods were not provided.

[†] Not been formally described in taxonomic papers.