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

Li-Qun Fang*, Kun Liu*, Xin-Lou Li, Song Liang, Yang Yang, Hong-Wu Yao, Ruo-Xi Sun, Ye Sun, Wan-Jun Chen, Shu-Qing Zuo, Mai-Juan Ma, Hao Li, Jia-Fu Jiang, Wei Liu, X. Frank Yang, Gregory C. Gray, Peter J. Krause, Wu-Chun Cao

*Contributed equally

State Key Laboratory of Pathogen and Biosecurity, Beijing Institute of Microbiology and Epidemiology, Beijing, P. R. China (L-Q Fang PhD, K Liu MS, X-L Li MS, H-W Yao MS, R-X Sun BS, Y Sun BS, W-J Chen BS, S-Q Zuo PhD, M-J Ma PhD, H Li PhD, J-F Jiang PhD, Prof W Liu PhD, Prof W-C Cao PhD); College of Public Health and Health Professions, and Emerging Pathogens Institute, University of Florida, Florida, USA (S Liang PhD, Y Yang PhD); Department of Microbiology and Immunology, Indiana University School of Medicine, Barnhill, Indianapolis, USA (Prof X-F Yang PhD); Duke University School of Medicine, Durham, North Carolina, USA (Prof GC Gray MD); and Department of Epidemiology of Microbial Diseases, Yale School of Public Health and Departments of Medicine and Pediatrics, Yale School of Medicine, 60 College Street, New Haven, CT 06520, USA (PJ Krause MD)

Correspondence to:
Prof Wu-Chun Cao, State Key Laboratory of Pathogen and Biosecurity, Beijing Institute of Microbiology and Epidemiology, 20 Dongda Street, Fengtai District, Beijing 100071, P. R. China, caowc@bmi.ac.cn.

© 2015. This manuscript version is made available under the Elsevier user license http://www.elsevier.com/open-access/userlicense/1.0/
Summary

A total of 33 emerging tick-borne agents have been identified in mainland China since
the beginning of the 1980s, 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. The geographic distributions of human cases were
mapped. Fifteen of the 33 emerging tick-borne agents have been reported to cause
human disease, clinical characteristics of which were described. The other 18 have
been detected in ticks or animals but their pathogenicity in humans is yet to be
determined. Various factors have contributed to the emergence of tick-borne diseases
in China. Advances in and application of modern molecular techniques should
facilitate identification of emerging tick-borne pathogens and improve laboratory
diagnosis of human infections. We anticipate that more novel tick-borne infections in
ticks and animals will continue to be identified and additional emerging tick-borne
diseases in humans will be discovered.
Introduction

Ticks were the first arthropods to be recognized as vectors that can transmit pathogens to humans 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. Humans are occasional hosts for ticks and usually viewed as “dead-end” hosts, which play no role in maintaining tick-borne agents in nature.2 Different tick species favor distinct biotopes or environments, which determine their geographic distribution and consequently the areas of risk for human tick-borne infections. In the past three decades, tick-borne pathogens have been emerging worldwide and becoming significant threats to human health.1,3

China, as the largest developing country in the world, has made tremendous progress in the control and prevention of infectious diseases but is facing a great challenge from emerging infectious diseases.4 While outbreaks of severe acute respiratory syndrome and H5N1 and H7N9 avian influenza virus infections have attracted great attention, emerging tick-borne diseases generally have been neglected by primary health care providers and clinicians. Although an increasing number of tick-borne infections have been reported in mainland China, there has been no comprehensive review of this significant public health problem. We now provide an overview of the type and distribution of emerging tick-borne infections in tick vectors, animal hosts, and humans, describe 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, a total of 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 a *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 figure S1.
Most (19/33) were initially detected in ticks, six 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 summarized in table 1.

Among the 33 newly recognized tick-associated agents, 15 have been reported to cause human infection, including four species of SFGR, two Anaplasma, and Candidatus Neoehrlichia mikurensis in the family Anaplasmataceae, three genospecies of B. burgdorferi sensu lato, three species of Babesia, and SFTSV (table 2). Six of the tick-borne pathogens were first identified in febrile patients (Candidatus Rickettsia tarasevichiae, Candidatus Neoehrlichia mikurensis, Borrelia garinii, Borrelia afzelii, “Babesia venatorum”, and SFTSV) and then found to be associated with ticks (table 1). The other nine human pathogens were initially detected in ticks or animals and subsequently shown to infect humans (Rickettsia heilongjiangiensis, Rickettsia sibirica sp. BJ-90, Rickettsia raoultii, Ehrlichia chaffeensis, Anaplasma phagocytophilum, “Anaplasma capra”, Borrelia valaisiana-related, Babesia microti, and Babesia divergens). Among these 15 emerging tick-borne diseases, severe fever with thrombocytopenia syndrome (SFTS) was first identified in mainland China, and subsequently reported in South Korea and Japan. A disease similar to SFTS also has been reported in the USA. Human infections with R. sibirica sp. BJ-90, Candidatus R. tarasevichiae, “A. capra” and B. valaisiana-related have been exclusively diagnosed in mainland China. Human infections with Candidatus Neoehrlichia mikurensis, “B. venatorum”, and R. raoultii in China were first reported outside Europe. Five tick-borne pathogens have been found in ticks and/or reservoir hosts but not yet been reported to cause infection in humans in China. They include Rickettsia monacensis, Rickettsia slovaca, Rickettsia sibirica sp. mongolotimonae, Borrelia valaisiana, and Borrelia burgdorferi sensu stricto. In addition, a Rickettsia species (Candidatus Rickettsia hebeiii), two Ehrlichia species (Ehrlichia canis, 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, Babesia sp. Xinjiang), have been identified in ticks or animals, but their pathogenicity to humans remain to be determined.

Emerging SFGR infections
As mentioned above, eight novel species of SFGR have been found in mainland China since 1982 (table 1). They are mainly distributed in northern China (north of 36° north latitude).

Tick and animal infections
The eight emerging species as well as uncharacterised species of SFGR have been shown to be associated with 16 tick species (figure 1). *R. heilongjiangiensis* has been proven to infect a variety of tick species, three rodent species, and goats (figure S2 in the appendix). In northeastern China, *R. heilongjiangiensis* was detected in nine tick species and two rodent species from Heilongjiang Province, and in *Haemaphysalis* spp. ticks from Jilin Province. In Inner Mongolia, *R. heilongjiangiensis* has been reported in *Haemaphysalis asiaticum kozlovi*, *Rhipicephalus pumilio* and *Detmacentor nuttalli* ticks. In northwestern China, *R. heilongjiangiensis* has been detected in *Dermacentor silvarum* ticks from Qinghai Province. In southern China, *R. heilongjiangiensis* has been detected in *Haemaphysalis longicornis* ticks from Guangdong Province, in goats from Yunnan Province, and in Chestnut white bellied rats from Hainan Province. In central and eastern China, it was identified in *Haemaphysalis flava* ticks from Henan, Anhui, and Hubei provinces, and in *H. longicornis* from Zhejiang Province. *R. sibirica* sp. BJ-90 was detected in *Dermacentor sinicus* from Beijing suburb. *R. raoultii* was found in *Dermacentor* ticks including *D. silvarum* and *Dermacentor marginatus*, and distributed in western China, and in *H. verticalis* collected from Inner Mongolia, in *D. silvarum* from Heilongjiang Province, and in *H. longicornis* from Liaoning Province. Four species, including *R. sibirica* sp. *mongolotimonae*, *R. monacensis*, *R. slovaca* and *Candidatus R. hebeiii*, have not been found to infect humans. Data regarding infected ticks and animal hosts are shown in
Human infections

Four species of emerging SFGR have been reported to infect humans, including \textit{R. heilongjiangiensis}, \textit{Candidatus R. tarasevichiae}, \textit{R. sibirica} sp. BJ-90, and \textit{R. raoultii} (table 2 and figure 2). Thirty four cases have been infected with \textit{R. heilongjiangiensis}, of which 19 were diagnosed in forested areas of northeastern China in the 1990s.\textsuperscript{35, 72} The other 15 cases were reported in the island of Hainan Province in 2008.\textsuperscript{57} We conducted an active surveillance for human SFGR infections at Mudanjiang Forestry Central Hospital of Heilongjiang Province in northeastern China in 2012, and eight cases (including five infected by \textit{Candidatus R. tarasevichiae}, one by \textit{R. sibirica} sp. BJ-90, and two by \textit{R. raoultii}) were identified by molecular detection and sequence determination. The diagnosis of SFGR infection was supported by the presence of IFA antibody against SFGR antigen in sera.\textsuperscript{36,37} In addition, 37 cases infected with uncharacterised species of SFGR were reported, including one in Inner Mongolia, one in Xinjiang Autonomous Region, 29 in Hainan Province, and six in Heilongjiang Province (figure 2).\textsuperscript{63,73-77} Clinical manifestations of patients with SFGR infections mainly included fever, eschar, headache, malaise, asthenia, anorexia, nausea, and lymphadenopathy. A few patients had rash and neurologic manifestations such as coma, neck stiffness, and Kernig’s sign.\textsuperscript{11,35-37,57,72-77} Detailed information on clinical and laboratory characteristics of patients infected with each of the emerging SFGR species are summarized in table S1 in the appendix.

Emerging infections with agents in the family Anaplasmataceae

Seven species in the family Anaplasmataceae have been identified in mainland China, including \textit{E. chaffeensis}, \textit{E. canis}, \textit{Ehrlichia} sp. Tibet, \textit{A. phagocytophilum}, “\textit{A. capra}”, \textit{A. platys}, and \textit{Candidatus Neoehrlichia mikurensis} (table 1).

Tick and animal infections

Seventeen tick species are known to be associated with the seven emerging agents in the family Anaplasmataceae (figure 1). \textit{E. chaffeensis} was first detected in \textit{Amblyomma testudinarium} ticks from Yunnan Province in 1996.\textsuperscript{12} Several surveys
demonstrate that it infects various tick species, and is widely dispersed in mainland China. It was also detected in dogs from Shandong Province, in long-tailed ground squirrel (*Citellus undulates* Pallas) and gerbils from Xinjiang Autonomous Region, in striped field mouse (*Apodemus agrarius*) from Heilongjiang Province, and in rodents (*Rattus norvegicus, Rattus losea, Rattus flavipes, R. niviventer, Mus musculus, Niviventer confucianus, and Rattus edwardsi*) and hares (*Lepus sinensis*) from Fujian and Zhejiang provinces (figure S2 in the appendix). A. *phagocytophilum* was first detected in *I. persulcatus* from Heilongjiang Province in 1997, and now is the most commonly encountered species in the family Anaplasmataceae over broad areas where multifarious tick species are vectors (figure 1). In addition, *A. phagocytophilum* was found to infect domestic and wild animals, including cattle, sheep, goats, horses, dogs, hare, yaks, and 24 species of rodents (figure S2 in the appendix). “*A. capra*” was first recognized in goats (*Capra aegagrus hircus*) and provisionally nominated by us, and then detected in *I. persulcatus* ticks in Heilongjiang Province. Although *Candidatus Neoehrlichia mikurensis* was initially identified in *I. persulcatus* and *Haemaphysalis concinna* ticks, it was subsequently found in *D. silvarum* and *H. longicornis* as well as various rodents from many areas of mainland China. Three other species, including *E. canis, Ehrlichia* sp. Tibet, and *A. platys*, have not been found to infect humans. Data regarding infected ticks and animal hosts are shown in figure 1 or figure S2 in the appendix.

**Human infections**

Four species of Anaplasmataceae have been identified to cause human infections in mainland China: *E. chaffeensis, A. phagocytophilum, “A. capra”, and Candidatus Neoehrlichia mikurensis*. The first human monocytic ehrlichiosis (HME) case was diagnosed in a forested area of Inner Mongolia in 1999. A total of 12 HME cases have been reported, including four in Inner Mongolia, two in Beijing, two in Tianjin, and four in Shandong Province (figure 2). A cluster of ten human granulocytic anaplasmosis (HGA) cases due to nosocomial transmission was identified in Anhui Province in 2006. An additional 94 HGA cases 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, Hubei provinces and Inner Mongolia (figure 2). A series of 28 cases infected with “A. capra” have recently been reported in Heilongjiang Province. Seven cases with Candidatus Neoehrlichia mikurensis infection were identified from 622 febrile patients in the same location in 2010. The patients with the Anaplasmataceae species infections showed undifferentiated clinical manifestations, mainly including fever, malaise, myalgia, arthralgia, and gastrointestinal symptoms (diarrhea, nausea, vomiting and anorexia). Laboratory abnormalities include leukopenia, thrombocytopenia, elevated hepatic aminopherase, lactate dehydrogenase and blood urea nitrogen (table S2 of the appendix).

Emerging infections with *Borrelia burgdorferi* sensu lato

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

Tick and animal infections

Twenty-six tick species have been shown to carry *B. burgdorferi* sensu lato (figure 1) over a wide geographic distribution of 25 provinces in mainland China. *B. garinii* is the most common genospecies and has been identified in multiple tick species (figure 1). It is found in rodents from many endemic areas, in dogs from Yunnan Province, in sheep keds (*Melophagus ovinus*) from Tibet, and in hares from Gansu Province (figure S2 in the appendix). *B. afzelii* is the second most common genospecies, and is found in the same ticks and rodents with a similar distribution as *B. garinii*. *B. valaisiana*-related (a genetically related but distinct genospecies of *B. valaisiana*) was detected in *I. granulatus* and *H. longicornis* from Guizhou Province, and in rodents from Guizhou and Zhejiang provinces. Three other genospecies that have not been found to infect humans include *B. 
valaisiana, B. sinica, and B. burgdorferi sensu stricto. Data regarding infected ticks and animal hosts are shown in figure 1 or figure S2 in the appendix.\textsuperscript{20,23,108,112-121}

**Human infections**

After identification of B. burgdorferi sensu lato in ticks and animals, human cases 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 have been found to cause human infections (table 2).\textsuperscript{19,21,23,39,122-124}

The genospecies causing thousands of Lyme disease cases in mainland China have not been characterized.\textsuperscript{125-130} We have summarized all the uncharacterised cases as infected with B. burgdorferi sensu lato regardless of its actual genospecies in figure 2. Infections with different genospecies of B. burgdorferi sensu lato may result in slightly different clinical manifestations, mainly including erythema migrans, arthritis or arthralgia, fever, headache and fatigue.\textsuperscript{19,21,23,39,122-130} Generally, clinical manifestations in mainland China are relatively mild as compared with those in USA and Europe.\textsuperscript{39}

**Emerging Babesia infections**

A total of 11 Babesia species have been discovered in mainland China since 1982, including Ba. ovis, Ba. major, Ba. ovata, Ba. orientalis, Ba. motasi, Ba. caballi, Babesia sp. Kashi, Babesia sp. Xinjiang, Ba. mircroti, Ba. divergens, and “Ba. venatorum” (table 1).

**Tick and animal infections**

Thirteen tick species have been shown to be involved in transmission of Babesia (figure 1). Those that have been shown to infect humans include Ba. microti, Ba. divergens, and “Ba. venatorum”. Ba. mircroti was found 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.\textsuperscript{32,50,131-133} Ba. divergens was detected in I. persulcatus, H. concinna, Haemaphysalis japonica ticks and striped field mice in several areas of Heilongjiang Province.\textsuperscript{32,50} “Ba.
venatorum” was reported in *I. persulcatus* ticks from forested areas of northeastern China. Other species of *Babesia* that have not been shown to infect humans 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 or figure S2 in the appendix.

**Human infections**

*Ba. microti, Ba. divergens,* and “*Ba. venatorum*” have been reported to cause human infections in mainland China (figure 2). A case of *Ba. microti* infection was diagnosed by peripheral blood and bone marrow smears as well as PCR assay in Zhejiang Province in 2011. An additional 10 patients were identified by *Ba. microti* PCR among 449 febrile persons with malaria-like symptoms in Yunnan Province during 2012-2013. One of these cases was found to be co-infected with *Plasmodium vivax* and another was co-infected with *Plasmodium falciparum*. Two cases of *Ba. divergens* infection were detected from 377 anemic patients in Shandong Province in 2009. A pediatric case of “*Ba. venatorum*” infection was reported from Xinjiang Autonomous Region. A series of 48 cases with “*Ba. venatorum*” infection were found through our active surveillance at a sentinel hospital in forested areas of northeastern China between 2011 to 2014. Among them, 32 were confirmed cases, and 16 were probable cases. This was the first report of endemic human “*Ba. venatorum*” disease anywhere in the world. In addition, two babesiosis cases with uncharacterised *Babesia* species were reported in Yunnan Province of southwestern China in 1982 and one case in 2008 (figure 2). Clinical manifestations for these patients with *Babesia* infections included fever, fatigue, anemia, chills, elevated hepatic aminopherase and C-reactive protein. Detailed information of clinical manifestations for patients with each of these species of *Babesia* infections is summarized in table S3 of the appendix.

**Emerging SFTSV infections**

SFTSV is a novel member of the genus *phlebovirus* in the *Bunyaviridae* family. It was first identified in China and made possible by an enhanced active surveillance in
selected provinces of China. Because a systematic review on the epidemiology,
clinical signs, pathogenesis, diagnosis, treatment, and prevention of human infection
with SFTSV has been published, we provide only a brief description and some new
information of the infection.

*Tick and animal infections*

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

*Human infections*

As of 2013, a total of 2543 human SFTS have been reported to the China CDC,
including 154 deaths. Incidence hotspots are located in Henan, Hubei, Anhui,
and Shandong provinces of middle-eastern China, as well as Liaoning Province of
northeastern China (figure S3 in the appendix). Clinical manifestations of the SFTS
patients are nonspecific with major symptoms that include respiratory tract symptoms,
sudden onset of fever up to 38–41°C, headache, fatigue, myalgia, and gastrointestinal
symptoms (lack of appetite, nausea, vomiting, and diarrhoea). Multiple organ failure
develops rapidly in most patients (with elevated levels of serum alanine
aminotransferase, aspartate aminotransferase, creatine kinase, and lactate
dehydrogenase; proteinuria and hematuria); and is usually accompanied by
thrombocytopenia, leukocytopenia and lymphadenopathy.

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

Beyond doubt, advances in and application of molecular technologies have led to the
discoveries of novel agents and facilitated the identification of human infections with
agents previously identified 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. On the other hand, it is likely
that various biologic factors causing an increase in the transmission and dissemination
of tick-borne zoonotic diseases have been the main causative factors of “emergence”.³

Changes in land use have affected emergence of tick-borne zoonotic diseases by
altering the interactions and abundance of ticks, wild and domestic hosts, and human
exposure to pathogens.¹⁵⁹ An example is the emergence of Lyme disease in the
northeastern USA. Reforestation of this region during the 20th century is thought to
have increased the population of white-tailed deer, which serve to greatly amplify the
number of I. scapularis. Consequentially, vector tick densities grew and expanded,
contributing significantly to the emergence of Lyme disease in the USA.¹⁶⁰

Fragmentation of forests in eastern regions of Canada and the USA may have
increased the relative abundance of small mammals due to a decrease in predator
communities, leading to elevated B. burgdorferi sensu lato infection rates in I.
scapularis nymphs. Ultimately, people in these areas were confronted with a higher
risk of Lyme disease.¹⁶¹,¹⁶²

Since the mid-1990s, the Chinese central government has initiated the “Greening”
Program to regain forests and grasslands from former agricultural lands.¹⁶³
Reforestation and grass-replanting with high quality vegetative cover probably results
in increased abundance and diversity of ticks and animal hosts, and favors the
reestablishment of pre-existing tick vector enzootic cycles in these areas. One
example was described in our study of the most severely endemic region of SFTS.
Our findings indicate that high risk of SFTS incidence is significantly associated with
vegetation-rich lands. A 10% increase in shrub, forest and rain-fed cropland areas
causes increased human SFTS incidence rates of 51%, 51% and 90%, respectively.¹⁶⁴

Urbanization also has influenced the emergence and increasing incidence of
tick-borne diseases. Studies in Europe indicate that encroachment into forested and
uncultivated areas, as well as protection of existing green spaces in the process of
urbanization, 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 as well as pathogen reservoirs, may facilitate tick transmission of
various human and animal pathogens.\textsuperscript{165,166} China has gone through the most rapid urbanization in its history in the past three decades. This rapid urbanization, followed by extensive 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.\textsuperscript{167} All of these changes in human activity, together with the increase in contact of humans and their pets with nature likely have contributed to the increasing abundance of tick exposure, as observed in other developed countries.\textsuperscript{165} Further investigation is needed to reveal the relationship between emerging tick-borne diseases and urbanization in mainland China.

Global climate change has been thought to have had less importance in the recent emergence of most vector-borne zoonotic diseases (including tick-borne diseases) than changes in land use, animal host communities, human living conditions, and societal factors.\textsuperscript{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 have been largely determined by climate conditions, which might further influence the seasonal pattern of tick-borne diseases. An increase in winter temperatures has been recognized to be responsible for the northward extension and increased abundance of \textit{Ixodes ricinus} with consequent elevated risk of tick-borne diseases dissemination.\textsuperscript{168-170} Although this topic is not settled, climatic change may be playing a role in the emergence of tick-borne diseases in China. Further studies are required to better elucidate this issue.

\textbf{Perspectives}

Ticks are currently considered second only to mosquitoes as vectors of human infectious diseases in the world.\textsuperscript{171} Up to now, more than 120 tick species have been identified in China, including over 100 species in the Ixodidae “hard tick” family and 19 species in Argasidae “soft tick” family.\textsuperscript{172} They transmit a number of pathogens while feeding on a variety of animals, including humans as accidental hosts. Approximately 30 tick species have been found to feed on humans.\textsuperscript{173,174} The diverse
geographic distribution and abundance of ticks are most dependent on optimal
environmental conditions and biotopes for each tick species, which determine the risk
areas for corresponding tick-borne zoonoses. In addition to the emerging tick-borne
infections described above, previously documented and well established tick-borne
diseases are also an ongoing threat to human health, including tick-borne encephalitis
in northeastern China, Crimean-Congo hemorrhagic fever in northwestern China,
tularemia and North-Asia tick-borne spotted fever in northern China, and Q-fever that
is widely distributed throughout China.175-184

The non-specific clinical manifestations caused by the tick-borne pathogens
described in this review, such as SFGR, *Anaplasma*, *B. burgdorferi* sensu lato,
*Babesia*, and SFTSV, present a major diagnostic challenge. Most physicians are
unfamiliar with the numerous tick-borne diseases that present with nonspecific
symptoms in the early stages of the illness. The wide distributions of the 33 emerging
tick-associated agents and their tick vectors, as well as the diversity of tick species
throughout mainland China, imply that reported cases might be only the tip of the
iceberg in regard to the actual number of tick-borne diseases. In order 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 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 recognized due to unavailability of
laboratory tests for etiological diagnosis and inadequate surveillance activities.

As described above, there are 18 tick-borne agents have been detected in ticks or
animals in China including four *Rickettsia* species, two *Ehrlichia* species, an
*Anaplasma* species, three genospecies of *B. burgdorferi* sensu lato and eight *Babesia*
species, but the full impact of their pathogenicity to humans is yet to be determined.
Despite increasing knowledge in 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. It may take many years to identify human infections after potentially pathogenic agents are found in ticks, in part because the microbial loads are much lower in human blood than in arthropods. For example, *R. sibirica* sp. BJ-90 was first identified in *D. sinicus* ticks in China in 1990, but not found to infect humans until 22 years later. Similarly, *A. phagocytophilum* was initially detected in China in 1997, but nosocomial transmission of human granulocytic anaplasmosis was recognized 10 years later. As such, the 18 tick-associated agents that have been recognized 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 remains essential for discovery of emerging tick-borne diseases in humans.

**Conclusion**

As summarized in figure 1, a total of 33 tick species belonging to six genuses have been found to be naturally infected with the emerging pathogenic agents described in this review. 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. chaffensis*, *A. phagocytophilum* and *B. garinii*, can infect several tick species. In addition, tick-borne pathogens that currently infect domestic animals may eventually cause human disease. A representative example is *B. divergens*, which has been long recognized to cause cattle babesiosis in Europe, and was subsequently identified as a human pathogen. In China, a wide range of emerging tick-borne agents are known to infect various domestic animals (figure S2 in the appendix), and their potential capability to infect human warrants great attention and further investigation. As tick-borne diseases continue to emerge in mainland China, it is critical for China and for the rest of the world to improve our understanding of the existence and health burden of these diseases.

**Contributors**
LQF, SL, XFY, GCG, PJK and WCC initiated ideas for the review. KL, XLL, HWY, RXS, YS and WJC contributed to searching literature and extracting data. KL, XLL, HWY, YY, SL, SQZ, MJM, HL, JFJ and WL assessed data. LQF, KL, XLL, HWY, RXS, YS, WJC and WCC created figures. LQF, GCG and WCC wrote the draft, and all authors contributed to the review and revision of the paper.

Conflicts of interest
We declare that we have no conflicts of interest.

Acknowledgments
This work was supported by the Natural Science Foundation of China (81290344, 81130086 and 81172728), the Special Program for Prevention and Control of Infectious Diseases in China (No. 2013ZX10004218), the Basic Work on Special Program for Science & Technology Research (2013FY114600), and NIH-NIAID (5R01AI083640 to XFY). The funders had no role in study design, data collection and analysis, decision to publish, or reparation of the manuscript.
Search strategy and selection criteria

We searched PubMed and ISI Web of Science for literature published in English, and WanFang database, China National Knowledge Infrastructure, and Chinese Scientific Journal Database for literature published in Chinese through the date of May 31, 2015. We used the following search terms: “tick-borne disease” or “tick-borne zoonosis” or “tick-borne zoonotic disease” or “tick-associated agent” or “tick-associated microbe”, and “China”, in combination with each of the five genera of tick-borne agents. A secondary manual search of the references cited in these articles was also performed to find relevant articles. We investigated all the articles related to detection, identification, or infections of these five genera of tick-borne microbes in humans, ticks and animals. We also 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.
Table 1: The first identification and origin of emerging tick-borne infections in mainland China since 1982

| Species | First identified origin* | First identified province (year)† | Reference (subsequent investigations) |
|---------|--------------------------|-----------------------------------|----------------------------------------|
| **Spotted fever group rickettsiae** | | | |
| *R. heilongiangiensi*s | *Dermacentor silvarum* | Heilongjiang (1982) | 5 (6,8,35,50-58,72) |
| *R. sibirica* sp. BJ-90 | *D. sinicus* | Beijing (1990) | 7 (36) |
| *R. sibirica* sp. mongolotimonae | *Hyalomma asiaticum kozlovi* | Inner Mongolia (1991) | 7 |
| *R. monacensis* | *Ixodes persulcatus* | Henan, Anhui, and Hubei provinces (2006) | 8 (58,68) |
| *R. raoultii* | *D. silvarum* | Xinjiang (2011) | 9 (37,59,60) |
| *R. slovaca* | *D. silvarum* | Xinjiang (2011) | 9 (60,61) |
| Candidatus *R. hebeii* | *H. longicornis* | Hebei (2011) | 10 (62) |
| Candidatus *R. tarasevichiae* | Human (*I. persulcatus*) | Heilongjiang (2012) | 11 |
| **Agents in the family Anaplasmataceae** | | | |
| *E. chaffeensis* | *Amblyomma testudinarium* | Yunan (1996) | 12 (32,38,50,67,78-85) |
| *E. canis* | *Rhipicephalus sanguineus sensu stricto* | Guangdong (1997) | 13 (16,80,97) |
| *E. sp. Tibet* | *Rhipicephalus microplus* | Tibet (2000) | 14 |
| *A. phagocytophilum* | *I. persulcatus* | Heilongjiang (1997) | 15 (38,50,61,67,78,85-94,98-100) |
| *A. platys* | Dog | Guangdong (1998) | 16 (97) |
| “*A. capra*”* | Goat | Heilongjiang (2014) | 17 |
| Candidatus Neoehrlichia mikurensis | Human (*I. persulcatus*) | Heilongjiang (2010) | 18 (95,96) |
| **Borrelia burgdorferi sensu lato** | | | |
| *B. garinii* | Human (*I. persulcatus*) | Heilongjiang (1986) | 19 (21,23,39,50,67,101-111,122,124) |
| *B. valaisiana* | *I. granulatus (Apodemus agrarius)* | Zhejiang (1997) | 20 (108,113) |
| *B. sinica* | *Niviventer confucianus* | Chongqing (1997) | 20 |
| Babesia | Host  | Species                  | Location     | Year | Reference Ranges |
|---------|-------|--------------------------|--------------|------|------------------|
| B. afzelii | Human | Heilongjiang (2000)      | Heilongjiang (2000) | 21 (39,50,101,103,105-107,122) |
| B. valaisiana-related | I. granulates, H. longicornis (A. agrarius) | Guizhou (2006) | Guizhou (2006) | 22 (39,105,108,110) |
| B. burgdorferi sensu stricto | Caprolagus sinensis | Hunan (2010) | Hunan (2010) | 23 (113) |
| Babesia | Sheep | Sichuan (1982) | Sichuan (1982) | 24 (135) |
| Ba. major | H. longicornis (cattle) | Henan (1988) | Henan (1988) | 25 (136) |
| Ba. ovata | Cattle | Henan (1990) | Henan (1990) | 26 (137) |
| Ba. orientalis | Buffalo | Hubei (1997) | Hubei (1997) | 27 (138,139) |
| Ba. motasi | Sheep | Gansu (1997) | Gansu (1997) | 28 (140,141) |
| Ba. caballi | D. silvarum, D. nuttalli | Gansu (1998) | Gansu (1998) | 29 (142-144) |
| Ba. sp. Kashi | Hy. anatolicum | Xinjiang (2005) | Xinjiang (2005) | 30 (145) |
| Ba. sp. Xinjiang | R. sanguineus sensu stricto, Hy. anatolicum | Xinjiang (2007) | Xinjiang (2007) | 31 (145) |
| Ba. microti | I. persulcatus, H. concinna | Heilongjiang (2007) | Heilongjiang (2007) | 32 (41,50,131-133,146) |
| Ba. divergens | I. persulcatus, H. concinna, H. japonica (A. agrarius) | Heilongjiang (2007) | Heilongjiang (2007) | 32 (40,50) |
| “Ba. venatorum” | Human | Xinjiang (2012) | Xinjiang (2012) | 33 (134) |
| SFTSV† | Human | Henan (2009) | Henan (2009) | 34 (150-158) |

*To indicate the first-identified origin of each emerging tick-associated agent, including human, domestic animal, rodent and tick. The agent which was simultaneously identified from other hosts or ticks, is shown in parentheses. †Provinces include autonomous regions and metropolis. “A. capra”and “Ba. venatorum” have not been formally described in taxonomic papers and thus their names are in quotation marks. ‡SFTSV indicates severe fever with thrombocytopenia syndrome virus.
| Emerging tick-borne disease | Pathogen | No. of patients | Diagnostic methods* (reference) |
|-----------------------------|----------|----------------|---------------------------------|
| Rickettsiosis               | *Rickettsia heilongjiangiensis* | 34 | A&B (35), B&C (57), A&C (72) |
| Rickettsiosis               | *R. sibirica* sp. BJ-90 | 1 | A&B (36) |
| Rickettsiosis               | *R. raoultii* | 2 | A&B (37) |
| Rickettsiosis               | Candidatus *Rickettsia tarasevichiae* | 5 | B (11) |
| Rickettsiosis               | Uncharacterised *Rickettsia* | 37 | C (63,74,75), B (76), A&C (73), E (77) |
| Human monocytic ehrlichiosis| *Ehrlichia chaffeensis* | 12 | B (38,78) |
| Human granulocytic anaplasmosis | *Anaplasma phagocytophilum* | 104 | B (38,78,99,100), A&B&C (98), A&B (86), E (93) |
| Human infection with “A. capra” | “A. capra” | 28 | A&B&C (17) |
| Human infection with Candidatus Neoehrlichia mikurensis | Candidatus Neoehrlichia mikurensis | 7 | B (18) |
| Lyme disease                | *Borrelia garinii* | 30 | B (21,23,39,122,124) |
| Lyme disease                | *B. afzelii* | 8 | B (21, 23, 39, 122), C (123) |
| Lyme disease                | B. valaisiana-related | 1 | B (39) |
| Lyme disease                | Uncharacterised *B. burgdorferi sensu lato* | 2691 | A(125,126,128–130), E(127) |
| Babesiosis                  | *Babesia divergens* | 2 | B (40) |
| Babesiosis                  | *Ba. microti* | 11 | B&D (41,146) |
| Babesiosis | “Ba. venatorum” | 49 | A&B&C (33), B&C&D (134) |
|------------|-----------------|----|------------------------|
| Babesiosis | Uncharacterised Babesia | 3  | D (147,148)             |
| SFTS†    | SFTSV‡          | 2543 | A&B&C (34,157), A or B or C (153,158), A or B (154), B&C (155), B (156) |

*Diagnostic methods: (A) a 4-fold increase in titer 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. †SFTS indicates severe fever with thrombocytopenia syndrome. ‡SFTSV indicates severe fever with thrombocytopenia syndrome virus.
Figure legends:

**Figure 1: The matrix of emerging tick-associated agents and tick species in mainland China**
SFTSV indicates the severe fever with thrombocytopenia syndrome virus.

**Figure 2: Geographic distributions of emerging tick-borne diseases in mainland China**
Human cases with spotted fever group rickettsiae (SFGR) infections are indicated in blue; cases infected with agents in the family Anaplasmataceae in red; cases infected with agents in the complex *Borrelia burgdorferi* sensu lato (*B.b.s.l.*) in purple; and cases infected with *Babesia* agents in black.
References

1. Dantas-Torres F, Chomel BB, Otranto D. Ticks and tick-borne diseases: a One Health perspective. *Trends Parasitol* 2012; 28:437–46.

2. Socolovschi C, Mediannikov O, Raoult D, Parola P. The relationship between spotted fever group rickettsiae and ixodid ticks. *Vet Res* 2009; 40: 34.

3. Kilpatrick AM, Randolph SE. Drivers, dynamics, and control of emerging vector-borne zoonotic diseases. *Lancet* 2012; 380:1946–55.

4. Wang LD, Wang Y, Jin SG, Wu ZY, Chin DP, Koplan JP, et al. Emergence and control of infectious diseases in China. *Lancet* 2008; 372:1598–605.

5. Lou D, Wu YM, Wang B. A new specie in *Rickettsia*: isolation and identification of *Rickettsia heilongjiangii*. *Chin J Microbiol Immunol* 1985; 5:250 (in Chinese).

6. Zhang L, Raoult D, Fournier PE. ‘*Rickettsia hulinii*’ belongs to the *Rickettsia heilongjiangensis* species. *Clin Microbiol Infect* 2009; 15(Suppl.2):340–2.

7. Yu X, Jin Y, Fan M, Xu G, Liu Q, Raoult D. Genotypic and antigenic identification of two new strains of spotted fever group rickettsiae isolated from China. *J Clin Microbiol* 1993; 31:83–8.

8. Li W, Liu L, Jiang X, Guo X, Garnier M, Raoult D, et al. Molecular identification of spotted fever group rickettsiae in ticks collected in central China. *Clin Microbiol Infect Dis* 2008; 15:279–80.

9. Tian ZC, Liu GY, Shen H, Xie JR, Luo J, Tian MY. First report on the occurrence of *Rickettsia slovaca* and *Rickettsia raoultii* in *Dermacentor silvarum* in China. *Parasit Vectors* 2012; 5:19.

10. Zou YX, Wang QY, Fu ZX, Liu PP, Jin HT, Yang HH, et al. Detection of spotted fever group *Rickettsia* in *Haemaphysalis longicornis* from Hebei Province, China. *J Parasitol* 2011; 97:960–2.

11. Jia N, Zheng YC, Jiang JF, Ma L, Cao WC. Human infection with *Candidatus Rickettsia tarasevichiae*. *N Engl J Med* 2013; 369:1178–80.

12. Cao WC, Gao YM, Zhang PH, Zhang XT, Dai QH, Dumler JS, et al. Identification of *Ehrlichia chaffeensis* by nested PCR in ticks from southern China. *J Clin Microbiol* 2000; 38:2778–80.

13. Pan H, Chen XR, Ma YH, SunY, Yu Q, Tong SD, et al. *Ehrlichia canis* DNA found in ticks in the south of China. *Chin J Zoonosis* 1999; 15:3–6 (in Chinese).

14. Wen BH, Jian R, Zhang YZ, Chen R. Simultaneous detection of *Anaplasma marginale* and a new *Ehrlichia* species closely related to *Ehrlichia chaffeensis* by sequence analyses of 16S ribosomal DNA in *Boophilus microplus* ticks from Tibet. *J Clin Microbiol* 2002; 40:3286–90.

15. Cao WC, Zhao QM, Zhang PH, Dumler JS, Zhang XT, Fang LQ, et al. Granulocytic ehrlichiae in *Ixodes persulcatus* ticks from an area in China where
Lyme disease is endemic. *J Clin Microbiol* 2000; 38:4208–10.

Pan H, Ma YH, Tong SD, Sun Y, Wen BH, Cheng XR. Canine ehrlichiosis caused simultaneously by *Ehrlichia canis* and *Ehrlichia platys*. *Microbiol Immunol* 2000; 44:737–9.

Li H, Zheng YC, Ma L, Jia N, Jiang BG, Jiang RR, et al. Human infections with a novel tick-borne *Anaplasma* species in China: a surveillance study. *Lancet Infect Dis* 2015; 15:663–70.

Li H, Jiang JF, Liu W, Zheng YC, Huo QB, Tang K, et al. Human infection with *Candidatus* Neoehrlichia mikurensis, China. *Emerg Infect Dis* 2012; 18:1636–9.

Ai CX, Wen YX, Zhang YG, Wang SS, Qiu QC, Shi ZX, et al. Clinical manifestations and epidemiological characteristics of Lyme disease in Hailin county, Heilongjiang Province, China. *Ann N Y Acad Sci* 1988; 539:302–13.

Masuzawa T, Takada N, Kudeken M, Fukui T, Yano Y, Ishiguro F, et al. *Borrelia sinica* sp. nov., a Lyme disease-related *Borrelia* species isolated in China. *Int J Syst Evol Microbiol* 2001; 51:1817–24.

Shi CX, Zhang ZF, Wan KL. Analyzing clinical samples of Lyme disease with 5s-23s rRNA gene spacer RFLP analysis. *Chin J Zoonoses* 2000; 16:21–3 (in Chinese).

Chu CY, Liu W, Jiang BG, Wang DM, Jiang WJ, Zhao QM, et al. Novel genospecies of *Borrelia burgdorferi* sensu lato from rodents and ticks in southwestern China. *J Clin Microbiol* 2008; 46:3130–3.

Hao Q, Hou X, Geng Z, Wan K. Distribution of *Borrelia burgdorferi* sensu lato in China. *J Clin Microbiol* 2011; 49:647–50.

Chen DM. Investigation report on sheep babesiosis with *Piroplasma ovis* infection. *Chin J Vet Sci Tech* 1982; 12:31–2 (in Chinese).

Lv WS, Yin H, Lv WX, Yu F, Zhang QC, Dou HF. Detection of *Babesia major* and the identification of its tick vector in mainland China. *Chin J Vet Sci Tech* 1988; 18:11–4 (in Chinese).

Bai Q, Liu GY, Zhang L, Zhang JY. Discovery and isolation of *Babesia ovata* in China. *Chin J Vet Sci Tech* 1990; 20:2–4 (in Chinese).

Liu ZL, Zhao JL, Ma LH, Yao BA. *Babesia orientalis* sp. nov. parasitized in buffalo *bubalus bubalis* in China (*Piroplasmida: Babesiidae*). *Acta Veterinaria et Zootechnica Sinica* 1997; 28:84–9 (in Chinese).

Yin H, Luo JX, Lv WS, Lv WX, Zhang QC, Wang YY, et al. Isolation and configuration observation of *Babesia motasi* and *Babesia ovis* in mainland China. *Chin J Vet Sci Tech* 1997; 27:7–9 (in Chinese).

Li YZ, Lu WY, Song JG. Studies on etiology and integrated control measures of difficult equine diseases in Gansu Province, China. *J Chin Agric University*
1998; S2:130 (in Chinese).

30 Luo JX, Yin H, Liu ZJ, Yang DY, Guan GQ, Liu AH, et al. Molecular phylogenetic studies on an unnamed bovine Babesia sp. based on small subunit ribosomal RNA gene sequences. Vet Parasitol 2005; 133:1–6.

31 Liu AH, Yin H, Guan GQ, Schnittger L, Liu ZJ, Ma ML, et al. At least two genetically distinct large Babesia species infective to sheep and goats in China. Vet Parasitol 2007; 147:246–51.

32 Yang LW, Hou Y, Li M, Wen ZQ, Yang J, Fan DH. Study of tick-borne pathogens at Heilongjiang Port. Chin Front Health Quar 2007; 30:77–82 (in Chinese).

33 Sun Y, Li SG, Jiang JF, Wang X, Zhang Y, Wang H, et al. Babesia venatorum infection in child, China. Emerg Infect Dis 2014; 20:896–7.

34 Yu XJ, Liang MF, Zhang SY, Liu Y, Li JD, Sun YL, et al. Fever with thrombocytopenia associated with a novel bunyavirus in China. N Engl J Med 2011; 364:1523–32.

35 Wu YM, Wei AM, Hu LM, Zhang YG, Zhang JZ, Zhang ZQ, et al. Study on aetiology of Rickettsia heilongianggii tick borne spotted fever. Chin Public Health 2001; 7:28–30 (in Chinese).

36 Jia N, Jiang JF, Huo QB, Jiang BG, Cao WC. Rickettsia sibirica subspecies sibirica BJ-90 as a cause of human disease. N Engl J Med 2013; 369:1176–8.

37 Jia N, Zheng YC, Ma L, Huo QB, Ni XB, Jiang BG, et al. Human infections with Rickettsia raoultii, China. Emerg Infect Dis 2014; 20:866–8.

38 Gao DQ, Cao WC, Zhang XT. Investigations on human Ehrlichia infectious people in Daxingan Mountains. Chin J Epidemiol 2001; 22:137–41 (in Chinese).

39 Ni XB, Jia N, Jiang BG, Sun T, Zheng YC, Huo QB, et al. Lyme borreliosis caused by diverse genospecies of Borrelia burgdorferi sensu lato in northeastern China. Clin Microbiol Infect 2014; 20:808–14.

40 Qi C, Zhou D, Liu J, Cheng Z, Zhang L, Wang L, et al. Detection of Babesia divergens using molecular methods in anemic patients in Shandong Province, China. Parasitol Res 2011; 109:241–5.

41 Lei YL, Wang XG, Yao LN, Mei JH, Lan JQ, Zeng CY, et al. Case report of human Babesia infections. Chin J Health Lab Tech 2012; 22:651–2 (in Chinese).

42 Kim KH, Yi J, Kim G, Choi SJ, Jun KI, Kim NH, et al. Severe fever with thrombocytopenia syndrome, South Korea, 2012. Emerg Infect Dis 2013; 19:1892–4.

43 Takahashi T, Maeda K, Suzuki T, Ishido A, Shigeoka T, Tominaga T, et al. The first identification and retrospective study of severe fever with
thrombocytopenia syndrome in Japan. *J Infect Dis* 2014; **209**:816–27.

44 McMullan LK, Folk SF, Kelly AJ, MacNeil A, Goldsmith CS, Metcalfe MG, et al. A new phlebovirus associated with severe febrile illness in Missouri. *N Engl J Med* 2012; **367**:834–41.

45 Jado I, Oteo JA, Alda’miz M, Gil H, Escudero R, Ibarra V, et al. *Rickettsia monacensis* and human disease, Spain. *Emerg Infect Dis* 2007; **13**:1405–7.

46 Sousa RD, Pereira BI, Nazareth C, Cabral S, Ventura C, Crespo P, et al. *Rickettsia slovaca* infection in humans, Portugal. *Emerg Infect Dis* 2013; **19**:1627–9.

47 Pretorius AM, Birtles RJ. *Rickettsia mongolotimonae* infection in South Africa. *Emerg Infect Dis* 2004; **10**:125–6.

48 Karine RO, Bernard R, Re S, Eric D. Scored antibody reactivity determined by immunoblotting shows an association between clinical manifestations and presence of *Borrelia burgdorferi* sensu stricto, *B. garinii*, *B. afzelii*, and *B. valaisiana* in humans. *J Clin Microbiol* 1999; **37**:4086–92.

49 van Dam AP, Kuiper H, Vos K, Widjojokusumo A, de Jongh BM, Spanjaard L, et al. Different genospecies of *Borrelia burgdorferi* are associated with distinct clinical manifestations of Lyme borreliosis. *Clin Infect Dis* 1993; **17**:708–17.

50 Hu MX, Zhang J, Fan DH, Fu WM, Sun XF, Yang LW. Detection of rodent infected by new tick pathogens in Suifenhe and Dongning Ports. *Chin J Vector Bio Control* 2009; **20**:573–6 (in Chinese).

51 Sun XF, Ding SL, Hu MX, Guo XM, Zhao G. Study on tick-borne *Rickettsia dermacentroxenus* infection at Heilongjiang Port. *Chin Front Health Quar* 2007; **30**:154–6 (in Chinese).

52 Wu YM, Liu GP, Wei AM, Hu LM, Zhang ZQ, Cai ZL, et al. Investigation of spotted fever group *Rickettsia* in the northeastern China. *Chin J Public Health* 2003; **19**:1043–4 (in Chinese).

53 Hao GF, Li H, Sun Y, Ge RP, Qiao GQ, Li B, et al. Detection of tick and tick-borne pathogen in some ports of Inner Mongolia. *Chin J Epidemiol* 2009; **30**:365–7 (in Chinese).

54 Li Y, Li ZK, Chen G, Kang M, Liu DX, Zhang YM. Identification and phylogenetic analysis of spotted fever group *Rickettsia* isolated from Qinghai province. *Chin J Vet Sci* 2014; **34**:1956-61 (in Chinese).

55 Zhang LJ, Zhang JS, Fu XP, Luan MC. First identification of a *Rickettsia* closely related to *R. heilongjiangii* and *R. massilliae* in South China. *Infect Dis Information* 2006; **19**:65–7 (in Chinese).

56 Liang CW, Li J, Chang LT, Yu HL, Zhang LX, Zhang LJ, et al. Spotted fever group *Rickettsia* in Yunnan Province, China. *Vector Borne Zoonotic Dis* 2012; **12**:281–6.
Jin YM, Zhang LJ, Sun LY, Lao SJ, Han J, Huang CH, et al. Epidemiological investigation of emerging spotted fever in Chengmai County, Hainan Province. *Dis Surveill* 2011; 26:18–22 (in Chinese).

Sun JM, Lin JF, Gong ZY, Chang Y, Ye XD, Gu SP, et al. Detection of spotted fever group Rickettsiae in ticks from Zhejiang Province, China. *Exp Appl Acarol* 2015; 65:403–11.

Sun X, Zhang GL, Liu R, Liu XM, Zhao Y, Zheng Z. Molecular epidemiological study of *Rickettsia raoultii* in ticks from Xinjiang, China. *Chin J Epidemiol* 2013; 34:756–7 (in Chinese).

Zhuang L, Wang CY, Tong YG, Tang F, Yang H, Liu W, et al. Discovery of *Rickettsia* species in *Dermacentor niveus* Neumann ticks by investigating the diversity of bacterial communities. *Ticks Tick Borne Dis* 2014; 5:564–8.

Dong X, Chen XP, Liu N, Dumler SJ, Zhang YZ. Co-circulation of multiple species of Rickettsiales bacteria in one single species of hard ticks in Shenyang, China. *Ticks Tick Borne Dis* 2014; 5:727-33.

Feng S, Wu H, Zhang LW, Lu ZX, Zhang CL, Li ZP, et al. Molecular epidemiological study of tick-borne spotted fever group *Rickettsia* in western mountain area of Hebei Province, China. *Chin J Vector Bio Control* 2013; 24:308–12 (in Chinese).

Fan MY, Walker DH, Liu QH, Li H, Bai HC, Zhang JK et al. Rickettsial and serologic evidence for prevalent spotted fever rickettsiosis in Inner Mongolia. *Am J Trop Med Hyg* 1987; 36:615–20.

Zhang HL, Yang H, Zhang PH, Cao WC, Zhang YZ, Yuan QH, et al. Spotted fever group *Rickettsia* DNA was detected in wild rodents and ticks in Dali, Yunnan Province, China. *Chin J Vector Bio Control* 2004; 15:461–2 (in Chinese).

Huang HN, Ding Z, He J, Wu XM, Jiang BG, Gao Y, et al. Study on the coinfection status of *Borrelia burgdorferi* sensu lato and spotted fever group *Rickettsia* in ticks from Hunchun, Jinlin Province. *Chin J Epidemiol* 2006; 27:379–83 (in Chinese).

Jiang LP, Mo SH, Zheng SG, Meng Z, Chen SY, Xie SY, et al. Spotted fever group rickettsiae DNA was first detected in ticks in Zhejiang Province. *Chin J Vector Bio Control* 2006; 17:484–5 (in Chinese).

Sun X, Zhang GL, Liu XM, Zhao Y, Zheng Z. Investigation of tick species and tick-borne pathogens in Hoxud County of Xinjiang Uyghur Autonomous Region, China. *Chin J Vector Biol Control* 2013; 24:5–10 (in Chinese).

Ye XD, Sun Y, Ju WD, Wang X, Cao WC, Wu MY. Vector competence of the tick *Ixodes sinensis* (*Acari: Ixodidae*) for *Rickettsia monacensis*. *Parasit Vectors* 2014; 7:512–8.
Wang Z, Liu XG, Luo Y, Li B, Yu D, Xu P, et al. Investigation of tick-borne spotted fever group *Rickettsia* in northwestern Liaoning Province, China. *Animal Husbandry Vet Med* 2015; 47:143–4 (in Chinese).

Chai CL, Sun JM, Lu QY, Ling F, Jiang LP, Ge JH, et al. A cross-sectional study on tick-borne *Rickettsiae* infections among murine-like animals. *Zhejiang Prev Med* 2014; 26:659–63 (in Chinese).

Wang Z, Yu M, Yang SJ, Qiu GB, Zhai RB, Guo ZY, et al. Epidemiological survey of spotted fever group *Rickettsia* in rodents in northeastern China. *Chin Pre Med* 2015; 16:184–6 (in Chinese).

Wu YM, Wei AM, Hu LM, Liu XX, Yang Q, Zhang ZQ, et al. Identification of spotted fever group (SFG) H-5 strain isolated from the patient's blood samples. *Chin J Zoonoses* 1998; 14:23–6 (in Chinese).

Fan MY, Wang JG, Jiang YX, Zong DG, Lenz B, Walker DH. Isolation of a spotted fever group *Rickettsia* from a patient and related ecological investigation in Xinjiang Uygur Autonomous Region of China. *Am Soc Microbiol* 1987; 25:628–32.

Lin BH, Sun XJ, Zhan ZN, Lin YZ, Li WG. Serological and etiological studies on undefined rickettsiosis on Hainan Island. *J Hainan Med College* 1997; 3:97–102 (in Chinese).

Lin YZ, Sun XJ, Zhan ZN, Li WG, Wang HM, Lin BH, et al. Serological and etiological studies on rickettsiosis in Hainan Island. *Chin J Zoonoses* 1999; 15:90–1 (in Chinese).

Shi H, Wang Y, Han H, Gao XL, Zhang YM, Zhang WJ, et al. Analysis of 92 patients with tick-borne diseases in Mudanjiang. *Chin J Vector Bio Control* 2013; 24:295–300 (in Chinese).

Wu J, Wang SL, Jin YM, Ma Y, Zeng XJ, Jia PB, et al. Detection of *groEL* gene in spotted fever group *Rickettsia* of patients with fever in Hainan province. *Mod Pre Med* 2014; 41:2417–9 (in Chinese).

Dong T, Qu ZY, Zhang LJ. Detection of *A. phagocytophilum* and *E. chaffeensis* in patient and mouse blood and ticks by a duplex real-time PCR assay. *PLoS One* 2013; 8:e74796.

Li HM, Jiang BG, He J, Niu JJ, Wang JX, Sun Y, et al. Detection and identification of *Ehrlichia* sp. in *Boophilus microplus* ticks from Xiamen of Fujian Province. *J Pathog Biol* 2006; 1:174–6 (in Chinese).

Meng QL, Qiao J, Sheng JL, Wang JW, Wang WS, Yao N, et al. Survey on tick-borne Anaplasmataceae in the south edge of Gurbantunggut desert. *Chin J Vet Sci* 2012; 32:1158–63 (in Chinese).

Chen Z, Liu Q, Liu JQ, Xu BL, Lv S, Xia S, et al. Tick-borne pathogens and associated co-infections in ticks collected from domestic animals in central
Zhang LJ, Cui F, Wang LL, Zhang LL, Zhang JS, Wang SW, et al. Investigation of anaplasmosis in Yiyuan County, Shandong Province, China. *Asian Pac J Trop Med* 2011; 4:568–72.

Zhao QL, Huang L, Yang X, Meng QL, Li R, Chen PB, et al. 16s rRNA sequence analysis of *Anaplasma* and *Ehrlichia* in rodents from parts area of Xinjiang. *Chin J Zoonoses* 2013; 29:743–7 (in Chinese).

Gao YM, Zhang XT, Cao WC, Dai QH, Zhang PH, Chen ZG, et al. Detection of *Ehrlichia chaffeensis* in ticks and rodents using semi-nested PCR. *Chin J Zoonoses* 2000; 16:25–8 (in Chinese).

Xu Z, Xu XH, Zhou YL, Feng L, Hou J, Zhou WQ, et al. Comprehensive surveillance of tick-borne diseases in Jiande, Zhejiang province, China. *Chin J Vector Biol Control* 2014; 25:350–3 (in Chinese).

Zhang LJ, Wang GQ, Liu QH, Chen CF, Li J, Long B, et al. Molecular analysis of *Anaplasma phagocytophilum* isolated from patients with febrile diseases of unknown etiology in China. *PLoS One* 2013; 8:e57155.

Zhang LJ, Liu H, Xu BL, Lu QY, Li L, Chang LT, et al. *Anaplasma phagocytophilum* infection in domestic animals in ten provinces/cities of China. *Am J Trop Med Hyg* 2012; 87:185–9.

Li GH, Yu Q, Zhang QX, Pan L, Zhang YN, Yao N, et al. Molecular epidemiology regarding, *Anaplasma phagocytophilum in Dermacentor silvarum* in Ningwu County, Shanxi Province. *Chin J Epidemiol* 2012; 33:642–3 (in Chinese).

Jiang JF, Jiang BG, Yu JH, Zhang WY, Gao HW, Zhan L, et al. *Anaplasma phagocytophilum* infection in ticks, China–Russia Border. *Emerg Infect Dis* 2011; 17:932–3.

Li Y, Kang FY, Yang JF, Sun CQ, Liu ZJ, Yin H. Prevalence and coexistence of *Anaplasma phagocytophilum and Borrelia burgdorferi sensu lato in ticks in Gansu, Hunan and Guangdong provinces, China. Chin J Zoonoses* 2013; 29:117–21 (in Chinese).

Yang JF, Liu ZJ, Guan GQ, Liu Q, Li YQ, Chen Z, et al. Prevalence of *Anaplasma phagocytophilum* in ruminants, rodents and ticks in Gansu, north-western China. *J Med Microbiol* 2013; 62:254–8 (in Chinese).

Cao WC, Zhao QM, Zhang PH, Yang H, Wu XM, Wen BH, et al. Prevalence of *Anaplasma phagocytophila and Borrelia burgdorferi* in *Ixodes persulcatus* ticks from northeastern China. *Am J Trop Med Hyg* 2003; 68:547–50.

Zhang HL, Sun Y, Wang JJ. Investigation on foci severe fever with thrombocytopenia syndrome and human granulocytic anaplasmosis in Lujiang County. *Chin J Dis Control Prev* 2015; 19:273–6 (in Chinese).
Zhang YZ, Wang Y, Yang WH, Zhu XH, Pi ZL, Feng Y, et al. Seroprevalence and molecular biological investigation of commonly known Rickettsia species in rodents in Qujing Prefecture, Yunnan Province, China. Chin J Zoonoses 2015; 31:35–40 (in Chinese).

Li H, Jiang JF, Tang F, Sun Y, Li ZD, Zhang WL, et al. Wide distribution and genetic diversity of “Candidatus Neoehrlichia mikurensis” in rodents from China. Appl Environ Microbiol 2013; 79:1024–7.

Lu QY, Cheng SY, Peng WL, Zhao JL, Jiang LP, Ge JH. Candidatus Neoehrlichia mikurensis infection on animals and related 16S rRNA gene analysis in Zhejiang Province. Chin J Epidemiol 2012; 33:993–4 (in Chinese).

Li Y, Chen Z, Liu Z, Liu J, Yang J, Li Q, et al. Molecular survey of Anaplasma and Ehrlichia of red deer and sika deer in Gansu, China in 2013. Transbound Emerg Dis 2015; doi:10.1111/tbed.12335.

Zhang L, Liu Y, Ni D, Li Q, Yu Y, Yu XJ, et al. Nosocomial transmission of human granulocytic anaplasmosis in China. JAMA 2008; 300:2263–70.

Wang S, Kou ZQ, Wang M, Ren YY, Hu B, Fang M, et al. A survey and identification of co-infection of Anaplasma phagocytophilum and Ehrlichia chaffeensis in Shandong. Dis Surveill 2012; 27:642–3 (in Chinese).

Li Z, Ding SJ, Lv H, Chen Y, Hou PQ, Wang XJ. Investigation of one case of human granulocytic anaplasmosis in Shandong Province. Infect Dis Information 2009; 22:165–8 (in Chinese).

Li MQ, Masuzawa T, Takada N, Ishiguro F, Fujita H, Iwaki A, et al. Lyme disease Borrelia species in northeastern China resemble those isolated from far eastern Russia and Japan. Appl Environ Microbiol 1998; 64:2705–9.

Jiang BG, Yao HW, Tong YG, Yang XF, Huang Y, Jiang JF, et al. Genome sequence of Borrelia garinii strain NMJW1, isolated from China. J Bacteriol 2012; 194:6660–1.

Chu CY, Jiang BG, He J, Gao Y, Zhang PH, Wu XM, et al. Genetic diversity of Borrelia burgdorferi sensu lato isolates from northeastern China. Vector Borne Zoonotic Dis 2011; 11:877–82.

Shi SG, Zhang F, Liu ZJ. Molecular epidemiological studies on Borrelia burgdorferi in ticks collected from several provinces and autonomous regions of northwestern China. Chin J Zoonoses 2011; 27:461–3 (in Chinese).

Chu CY, Jiang BG, Liu W, Zhao QM, Wu XM, Zhang PH, et al. Presence of pathogenic Borrelia burgdorferi sensu lato in ticks and rodents in Zhejiang, South-east China. J Med Microbiol 2008; 57:980–5 (in Chinese).

Wang HW, He J, Chu CY, Zhang PH, Wu XM, Huang HN, et al. Detection and genotyping of Borrelia burgdorferi sensu lato in ticks from some areas of China. J Pathog Biol 2006; 1:81–5 (in Chinese).
107 Zhang JJ, Zhang F, Li L, Liu ZJ. *Borrelia burgdorferi* infection and their genotypes in ticks and rodents collected from Maijishan region, Gansu Province, China. *Chin J Zoonoses* 2015; **31**:357–60 (in Chinese).

108 Hou J, Ling F, Chai CL, Lu Y, Yu XH, Lin JF, et al. Prevalence of *Borrelia burgdorferi* sensu lato in ticks from Eastern China. *Am J Trop Med Hyg* 2014; **2**:262–6.

109 Chu CY, He J, Zhao QM, Zhang PH, Wu XM, Jiang BG, et al. Molecular epidemiological studies on *Borrelia burgdorferi* in rodents collected in the forest area of several provinces and autonomous regions of China. *Chin J Zoonoses* 2006; **22**:817–20 (in Chinese).

110 Hou XX, Geng Z, Hao Q, Zhang Y, Wan KL. Rats, the primary reservoir hosts of *Borrelia burgdorferi* in six representative provinces, China. *Chin J Zoonoses* 2010; **26**:1034–6 (in Chinese).

111 Zhan L, Chu CY, Zuo SQ, Wu XM, Dumler JS, Jia N, et al. *Anaplasma phagocytophilum* and *Borrelia burgdorferi* in rabbits from southeastern China. *Vet Parasitol* 2009; **162**:354–6.

112 Wang DM, Hao Q, Cai XH, Wan KL, Wang ZX, Chen J. Study on ribotyping of Lyme borreliosis spirochete in Guizhou Province. *Chin J Epidemiol* 2003; **24**:1129–31 (in Chinese).

113 Zhang L, Wang ZY, Chen CF, Li YX, Zhang K, Du JY, et al. Isolation of *Borrelia burgdorferi* in *Ixodes* from four counties, in North Xinjiang. *Chin J Epidemiol* 2014; **35**:262–5 (in Chinese).

114 Yang Y, Zhang XL, Qiao S, Cao XM, Wang L, Hao GF, et al. Investigation on tick-borne pathogens at Ganqimaodu Port between Sino-Mongolia border. *Chin Front Health Quar* 2011; **34**:339–42 (in Chinese).

115 Zuo SY, Tang K, Li Y, Yu JH, Zhang Y, Ni X, et al. DNA detection and sequence analysis of *Borrelia burgdorferi* sensu lato in rodents from Helongjiang forest region. *Chin J Epidemiol* 2012; **33**:643–4 (in Chinese).

116 Yang XF, Wan KL, Lu JP, Temu QH, Zhang ZF, Han XZ, et al. Investigation of geographical epidemiology and etiological studies on Lyme disease in Inner Mongolia. *Chin J Zoonosis* 1999; **15**:98 (in Chinese).

117 Yang XJ, Wan KL, Wang CS, Hao Q, Wang YH, Hou XX, et al. Etiological studies on Lyme disease in Jilin Province. *Chin J Health Lab Tech* 2006; **16**:1355–62 (in Chinese).

118 Zhang DC, Hong Y, Zhang ZQ, Sun GJ, Dong SD, Zhang ZF, et al. Isolation of *Borrelia burgdorferi* in ticks and rodents in Liaoning Province. *Chin J Vector Bio Control* 1992; **3**:19 (in Chinese).

119 Tian WC, Moldenhauer S, Li MQ, Zhang ZK, Guo YX, Wang LN, et al. The first detection of *Borrelia burgdorferi* in *H. japonica*. *Chin J Zoonosis* 1995;
120 Zhang ZC, Tian WC, Guo YX, Wang LN, Yu QL, Li YP, et al. Investigation of Lyme disease in Hebei Province. *Chin J Public Health* 1995; **11**:253–4 (in Chinese).

121 Wang LJ, Chen ZL, Wan KL, Liu SL, Tao XY, Zhang JS, et al. First isolation and identification of Lyme disease spirochete in Shandong Province. *Chin J Vector Bio Control* 1997; **8**:127–8 (in Chinese).

122 Tan YH, Liu Y, Wan KL, Hao Q, Sun H, Yu LH, et al. Molecular epidemiological study of *Borrelia burgdorferi* infection among population in Xinjiang, China. *Chin J Vector Bio Control* 2013; **24**:297–300 (in Chinese).

123 Jiang BG, Zheng YC, Tong YG, Jia N, Huo QB, Fan H, et al. Genome sequence of *Borrelia afzelii* strain HLJ01, isolated from a patient in China. *J Bacteriol* 2012; **194**:7014–5.

124 Zhu X, Zhang L, Hou XB, Geng Z, Chen H, Chen T, et al. Investigation on Lyme disease of patients with arthrities or neurological disorders in Hainan province, China. *Chin J Zoonoses* 2015; **31**:353–6 (in Chinese).

125 Geng Z, Hou XX, Hao Q, Hu GL, Wan KL. Anti-*borrelia burgdorferi* antibody response in 827 patients with suspected Lyme disease. *Chin J Vector Bio Control* 2007; **18**:219–21 (in Chinese).

126 Zhou XY. The epidemiological and clinical analysis of Lyme disease in Mudanjiang from 1996 to 2003. *Chin J Parasit Dis Control* 2005; **18**:159 (in Chinese).

127 Jin SW, Hao Q, Tian Z, Hou XX, Geng Z, Jiang Y, et al. Analysis of surveillance on Lyme disease in Xinjiang prospecting region of Henan oil prospecting bureau. *Chin J Zoonoses* 2005; **21**:501–2 (in Chinese).

128 Peng FB, Zhang WF, Zhou GP, Zhang SY, Yuan YM, Wu YY. The detection and clinical study on Lyme disease in Beijing. *Chin J Epidemiol* 1994; **15**:10–3 (in Chinese).

129 Huang ZY, Hou XX, Wan KL. An investigation of Lyme disease in Pingjiang County, Hunan Province, China. *Chin J Vector Bio Control* 2001; **12**:293–4 (in Chinese).

130 Li YL, Hao JG, Zhang ZF, Wan KL, Xia XZ, Zhang JS, et al. The investigation of Lyme disease in Nanchuan County, Sichuan Province, China. *Chin J Vector Bio Control* 1991; **2**:54–6 (in Chinese).

131 Sun Y, Liu GP, Yang LW, Xu RM, Cao WC. *Babesia microti*-like rodent parasites isolated from *Ixodes persulcatus* (*Acari: Ixodidae*) in Heilongjiang Province, China. *Vet Parasitol* 2008; **156**:333–9.

132 Chen Z, Liu Q, Liu JQ, Xu BL, Lv S, Xia S, et al. Tick-borne pathogens and associated co-infections in ticks collected from domestic animals in central
China. *Parasit Vectors* 2014; 7:237.

133 Zhao XG, Li H, Sun Y, Zhang YY, Jiang JF, Liu W, et al. Dual infection with *Anaplasma phagocytophilum* and *Babesia microti* in a *Rattus norvegicus*, China. *Ticks Tick Borne Dis* 2013; 4:399–402.

134 Jiang JF, Zheng YC, Jiang RR, Li H, Huo QB, Sun Y, et al. Epidemiological, clinical and laboratory characteristics of 48 cases with "*Babesia venatorum*" infection in China: a descriptive study. *Lancet Infect Dis* 2015; 15:196–203.

135 Li W, Peng HS, Li XM. Diagnosis and treatment of a goat infected with *Babesia ovis*. *Contemp animal husbandary* 2015; 1:12–3 (in Chinese).

136 Luo JX, Yin H, Liu G, Guan GQ, Liu ZJ, Liu AH, et al. Collection and identification of Piroplasma infected to cattle and sheep in China. *Chin J Parasitol Parasit Dis* 2006; 24:S48–52 (in Chinese).

137 Bai Q, Liu G, Han G, Hui Y. Isolation and complementary transmission of *Babesia ovata* in Zhangjiachuan of Gansu Province. *Chin J Vet Sci Tech* 1994; 24:9–10 (in Chinese).

138 He L, Feng HH, Zhang WJ, Zhang QL, Fang R, Xia L, et al. Occurrence of *Theileria* and *Babesia* species in water buffalo (*Bubalus bavalis*, Linnaeus, 1758) in the Hubei Province, South China. *Vet Parasitol* 2011; 186:490-6.

139 Liu Q, Zhou YQ, Zhou DN, Liu EY, Du K, Chen SG, et al. Semi-nested PCR detection of *Babesia orientalis* in its natural hosts *Rhipicephalus haemaphysaloides* and bufalo. *Vet Parasitol* 2006; 143:260–6.

140 Sun CQ, Liu ZJ, Gao JL, Guan GQ, Ma ML, Luo JX, et al. Investigations into the natural infection rate of *Haemaphysalis qinghaiensis* with Piroplasma using a nested PCR. *Exp Appl Acarol* 2008; 44:107–14.

141 He SD, Che FM, Liu WQ. Investigation of *Babesia caballi* in areas around Qinghai Lake, China. *Chin Animal Health Insp* 2007; 24:28 (in Chinese).

142 Wang XS, Liu JY, Zhang L, Feng LG. Case report of horse *Babesia caballi* infection. *J quacul feed* 2014; 12:56–7 (in Chinese).

143 Yi CY, Guo QY, Xue H, Peng C, Ba YCH. Detection of pathogen DNA of *Babesia caballi* from *Rhipicephalus sanguineus* and *Dermacentor nuttalli*. *Heilongjiang Animal Sci Vet Med* 2014; 11:38–40 (in Chinese).

144 Guan GQ, Ma ML, Moreau E, Liu JL, Lu BY, Bai Q, et al. A new ovine *Babesia* species transmitted by *Hyalomma anatolicum anatolicum*. *Exp Parasit* 2009; 122:261–7.

145 Zhou X, Li SG, Chen SB, Wang JZ, Xu B, Zhou HJ, et al. Co-infections with *Babesia microti* and *Plasmodium* parasites along the China-Myanmar border.
Li JF, Meng DB, Wang QF, Dong XR, Wang JY. The discovery of human babesiosis. *Chin Vet* 1984; 6:19–20 (in Chinese).

Wang HX. A case of human babesiosis in southwest region of China. *Int J Med Parasit Dis* 2012; 39:190–2 (in Chinese).

Liu Q, He B, Huang SY, Feng W, Zhou XQ. Severe fever with thrombocytopenia syndrome, an emerging tick-borne zoonosis. *Lancet Infect Dis* 2014; 14:763–72.

Zhang YZ, Zhou DJ, Qin XC, Tian JH, Xiong YW, Wang JB, et al. The ecology, genetic diversity, and phylogeny of Huaiyangshan virus in China. *J Virol* 2011; 86:2864–8.

Zhao L, Zhai SY, Wen HL, Cui F, Chi YY, Wang L, et al. Severe fever with thrombocytopenia syndrome virus, Shandong Province, China. *Emerg Infect Dis* 2012; 18:963–5.

Li ZF, Liu JL, Bao CJ, Li PF, Qi X, Qin YF, et al. Seroprevvalence of antibodies against SFTS virus infection in farmers and animals, Jiangsu, China. *J Clin Virol* 2014; 60:185–9.

Ding F, Zhang WY, Wang L, Hu W, Soares MR, Sun J, et al. Epidemiologic features of severe fever with thrombocytopenia syndrome in China, 2011–2012. *Clin Infect Dis* 2013; 56:1682–3.

Gai ZT, Liang MF, Zhang Y, Zhang S, Jin C, Wang SW, et al. Person-to-person transmission of severe fever with thrombocytopenia syndrome Bunyavirus through blood contact. *Clin Infect Dis* 2012; 54:249–52.

Yu L, Yu P, Liu DH, Hou J, Chen YF. Surveillance of syndrome of fever with thrombocytopenia in Dalian, 2012–2013. *Study Trace Eleme Health* 2014; 31:5–6 (in Chinese).

Bao CJ, Guo XL, Qi X, Hu JL, Zhou MH, Varma JK, et al. A family cluster of infections by a newly recognized Bunyavirus in eastern China, 2007: further evidence of person-to-person transmission. *Clin Infect Dis* 2011; 53:1208–14.

Gai ZT, Zhang Y, Liang MF, Jin C, Zhang S, Zhu CB, et al. Clinical progress and risk factors for death in severe fever with thrombocytopenia syndrome patients. *J Infect Dis* 2012; 206:1095–102.

Lambin EF, Tran A, Vanwambeke SO, Linard C, Soti V. Pathogenic landscapes: interactions between land, people, disease vectors, and their animal hosts. *Int J Health Geogr* 2010; 9:54.

Barbour AG, Fish D. The biological and social phenomenon of Lyme disease.
Levi T, Kilpatrick AM, Mangel M, Wilmers CC. Deer, predators, and the emergence of Lyme disease. *Proc Natl Acad Sci USA* 2012; 109:10942–7.

LoGiudice K, Duerr ST, Newhouse MJ, Schmidt KA, Killilea ME, Ostfeld RS. Impact of host community composition on Lyme disease risk. *Ecology* 2008; 89:2841–9.

Liu JG, Li SX, Ouyang ZY, Tam C, Chen XD. Ecological and socioeconomic effects of China’s policies for ecosystem services. *Proc Natl Acad Sci USA* 2008; 105:9477–82.

Liu K, Cui N, Fang LQ, Wang BJ, Lu QB, Peng W, et al. Epidemiologic features and environmental risk factors of severe fever with thrombocytopenia syndrome, Xinyang, China. *PLoS Negl Trop Dis* 2014; 8:e2820.

Uspensky I. Tick pests and vectors (*Acari: Ixodoidea*) in European towns: introduction, persistence and management. *Ticks Tick Borne Dis* 2014; 5:41–7.

Uspensky I. Ticks (*Acari: Ixodoidea*) as urban pests and vectors with special emphasis on ticks outside their geographical range. *Proceedings of the Sixth International Conference on Urban Pests* 2008:333–47.

Gong P, Liang S, Carlton EJ, Jiang QW, Wu JY, Wang L, et al. Urbanisation and health in China. *Lancet* 2012; 379:843–52.

Parola P. Tick-borne rickettsial diseases: emerging risks in Europe. *Comp Immun Microbiol Infect Dis* 2004; 27:297–304.

Altizer S, Ostfeld RS, Johnson PT, Kutz S, Harvell CD. Climate change and infectious diseases: from evidence to a predictive framework. *Science* 2013; 341:514–9.

Harrus S, Baneth G. Drivers for the emergence and re-emergence of vector-borne protozoal and bacterial diseases. *Int J Parasitol* 2005; 35:1309–18.

Parola P, Raoult D. Ticks and tickborne bacterial diseases in humans: an emerging infectious threat. *Clin Infect Dis* 2001; 32:897–928.

Yang XJ, Chen Z, Liu JZ. Advances in systematics of ticks. *Acta Entomologica Sinica* 2007; 50:941–9 (in Chinese).

Meng YC. Ticks, acari, and human diseases (1st Edition). Hefei: *Chin Sci Tech Press*. 1995:43 (in Chinese).

Cao WC, Zhang XT, Xu RM. The medical significance of tick and tick-borne disease in public health. *Chin J Public Health* 1999; 15:221–2 (in Chinese).

Wu XB, Na RH, Wei SS, Zhu JS, Peng HJ. Distribution of tick-borne diseases in China. *Parasit Vectors* 2013; 6:119.

Zhao JW, Wang HY, Wang Y. Regional distribution profiles of tick-borne pathogens in China. *Chin J Bio Control* 2012; 18:45–8 (in Chinese).

Zhan L, Cao WC, Jiang JF, Zhang XA, Liu YX, Wu XM, et al. *Anaplasma*
phagocytophilum from rodents and sheep, China. Emerg Infect Dis 2010; 16:764–8.

178 Wang YY, Li J, Wang S, Hu M, Lu FL. Tick-borne infectious diseases. Infect Dis Information 2011; 24:58–61 (in Chinese).

179 Lu Z, Broker M, Liang G. Tick-borne encephalitis in mainland China. Vector Borne Zoonotic Dis 2008; 8:713–20.

180 Xia H, Li P, Yang J, Pan L, Zhao J, Wang Z, et al. Epidemiological survey of Crimean-Congo hemorrhagic fever virus in Yunnan, China, 2008. Int J Infect Dis 2011; 15:e459–63.

181 Wang Y, Peng Y, Hai R, Xia L, Li H, Zhang Z, et al. Diversity of Francisella tularensis Subsp. holarctica lineages, China. Emerg Infect Dis 2014; 20:1191–4.

182 Chen M, Fan MY. A review on the research of North-Asia tick-borne spotted fever. Chin Public Health 1997; 6:373–6 (in Chinese).

183 Liu YF, Zhang Y. The study progress of Q fever and Ehrlichiosis. Med Recap 2008; 6:864–7 (in Chinese).

184 Suss J. Tick-borne encephalitis 2010: epidemiology, risk areas, and virus strains in Europe and Asia—an overview. Ticks Tick Borne Dis 2011; 2:2–15.

185 Philippe P, Paddock CD, Socolovschi C, Labruna MB, Mediannikov O, Kernif T, et al. Update on tick-borne rickettsioses around the world: a geographic approach. Clin Microbiol Rev 2013; 26:657–702.

186 Colwella DD, Dantas-Torresb F, Otranto D. Vector-borne parasitic zoonoses: Emerging scenarios and new perspectives. Vet Parasitol 2011; 182:14–21.
Figure 1

| Emerging Tick-borne agents | Spotted fever group rickettsiae | The family Anaplasmataceae | Babesia |
|----------------------------|--------------------------------|-----------------------------|---------|
| Ticks                      |                                | Borrelia burgdorferi sensu lato | Babesia |
| Amblyomma                  | A. testudinarium               | Bb. major                   | Bb.orientalis |
| Dermacentor                | D. abaelis                    | Bb. ovata                   | Bb. morado |
|                           | D. dagestanicus               | Bb. ovis                    | Bb. cabali |
|                           | D. marginatus                 | Bb. sp. Xiphing             | Bb. diversus |
|                           | D. nivus                      | Bb. sp. major               | Bb. venatorum |
|                           | D. nuttasi                    | Borrelia burgdorferi sensu lato | Babesia |
|                           | D. silvarum                   | Babesia major               | Babesia orientalis |
|                           | D. sinesis                    | Babesia ovata               | Babesia morado |
|                           |                                | Babesia ovis                | Babesia cabali |
|                           |                                | Babesia sp. Xiphing          | Babesia diversus |
|                           |                                | Babesia. venatorum          | Babesia. venatorum |
|                           |                                | SFTS                        | Babesia |
|                           |                                | Borrelia burgdorferi sensu lato | Babesia |
|                           |                                | Babesia major               | Babesia orientalis |
|                           |                                | Babesia ovata               | Babesia morado |
|                           |                                | Babesia ovis                | Babesia cabali |
|                           |                                | Babesia sp. Xiphing          | Babesia diversus |
|                           |                                | Babesia. venatorum          | Babesia. venatorum |
|                           |                                | SFTS                        | Babesia |

Notes: The table represents the distribution of tick species and their associated pathogens. Each cell indicates the presence or absence of the pathogen in the tick species.
Figure 2

Click here to download high resolution image