



The Tick-Borne Pathogens: An Overview of China's Situation

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Abstract

Background Ticks are important medical arthropods that can transmit hundreds of pathogens, such as parasites, bacteria, and viruses, leading to serious public health burdens worldwide. Unexplained fever is the most common clinical manifestation of tick-borne diseases. Since the emergence of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the surge of coronavirus disease 2019 (COVID-19) cases led to the hospital overload and fewer laboratory tests for tick-borne diseases. Therefore, it is essential to review the tick-borne pathogens and further understand tick-borne diseases.

Purpose The geographic distribution and population of ticks in the Northern hemisphere have expanded while emerging tick-borne pathogens have been introduced to China continuously. This paper focused on the tick-borne pathogens that are threatening public health in the world. Their medical significant tick vectors, as well as the epidemiology, clinical manifestations, diagnosis, treatment, prevention, and control measures, are emphasized in this document.

Methods In this study, all required data were collected from articles indexed in English databases, including Scopus, PubMed, Web of Science, Science Direct, and Google Scholar.

Results Ticks presented a great threat to the economy and public health. Although both infections by tick-borne pathogens and SARS-CoV-2 have fever symptoms, the history of tick bite and its associated symptoms such as encephalitis or eschar could be helpful for the differential diagnosis. Additionally, as a carrier of vector ticks, migratory birds may play a potential role in the geographical expansion of ticks and tick-borne pathogens during seasonal migration.

Conclusion China should assess the risk score of vector ticks and clarify the potential role of migratory birds in transmitting ticks. Additionally, the individual and collective protection, vector control, comprehensive surveillance, accurate diagnosis, and symptomatic treatment should be carried out, to meet the challenge.

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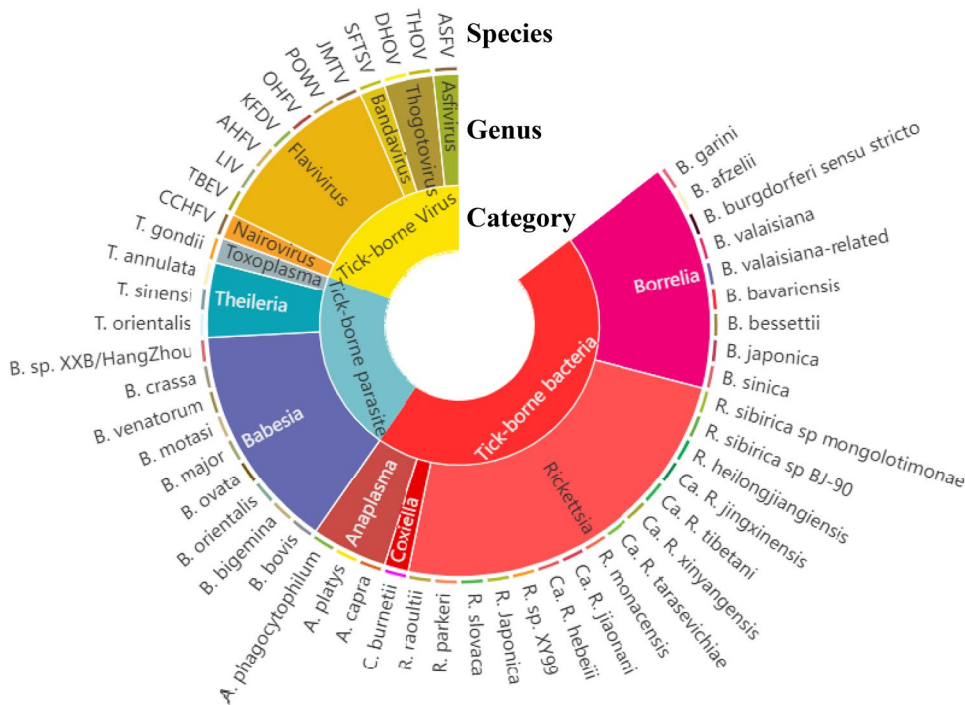
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Graphical Abstract



Keywords Tick · Pathogen · Tick-borne pathogens · Parasite · Bacteria · Virus

Introduction

Ticks (Acarina Ixodoidea) are obligate hematophagous arthropod ectoparasites, which can be distinguished by their morphology and divided into 3 families: Ixodidae (hard ticks), Argasidae (soft ticks) and Nuttalliellidae. At present, a total of 9 genera, and 124 species of ticks have been identified in China [1]. They can not only bite their hosts and suck their blood but also spread pathogens via their saliva. Tick-borne infections are zoonoses. Humans are usually considered the occasional hosts for ticks and have no role in maintaining tick-borne pathogens in the natural cycles [2]. The pathogens, spread by ticks, are called tick-borne pathogens. The diseases, caused by tick-borne pathogens, are called tick-borne diseases.

Ticks and tick-borne pathogens are one of the biggest public health threats and veterinary problems in the world. First, tick-borne pathogens, such as *Babesia*, *Theileria*, and *Anaplasma phagocytophilum*, are threatening over 80% of the cattle population. The reproduction of meat, milk, and leather and the death of infected animals have brought significant economic loss. According to the statistics of the Food and Agriculture Organization of the United Nations (FAO), the gross economic loss in the world is annually USD 13.9–18.7 billion [3], with the average loss being USD 7.3 for each animal per year. Moreover, the cost of the

prevention and the control of tick-borne diseases are high. For example, the reported cost for cattle alone, which are in areas at risk of being affected by ticks, has reached USD 380 million [4]. Second, tick-borne pathogens have also significantly threatened public health. On the one hand, the expense of medical treatment is high and has led to a considerable burden on society. According to the statistics of the National Institutes of Health (NIH), the expense for tick-borne diseases totaled USD 56 million in the United States in 2020 [5]. The reported cost for Lyme disease reached USD 40 million in Germany and 20 million in Holland in 2017, respectively [6]. On the other hand, a multitude of pathogens is usually harbored by one tick. Given this, it is unsurprising to observe the co-infection with genetically distinct pathogens in human beings. A plethora of studies reported seropositivity against multiple pathogen combinations [7–9]. However, our understanding of the interactions of these agents remains poor. Various pathogen combinations might behave synergistically, indifferently, or antagonistically within hosts, and thus modulate disease severity [10]. Challenges have been presented during diagnosis and treatment.

In recent years, reported tick-borne pathogens have shown a resurgence trend while emerging tick-borne pathogens have been continuously identified from the tick population, which have attracted extensive attention from medical and veterinary

personnel. The purpose of this review is to summarize the research progress of tick-borne pathogens, including their epidemiology, species of vector ticks, clinical manifestations, diagnosis, treatment, prevention, and control dynamics. Additionally, tick load has been detected in a variety of migratory birds [11]. They can easily cross the mountains, glaciers, deserts, and oceans, and transport ticks and tick-borne pathogens from epidemic countries to China. Therefore, further understanding of ticks and tick-borne pathogens will help to detect, monitor, prevent, and control these public health threats and challenges in China comprehensively.

Tick-Borne Parasite

Piroplasma

Piroplasma (class: Apicomplexa, order: Piroplasmida) is the causative agent of piroplasmosis, which mainly consists of parasites in the family Babesiidae and Theileriidae. *Ixodes ricinus* is predominantly responsible for the transmission of *Piroplasma* in Europe, while *Ixodes persulcatus* is predominant in China. Through trans-ovarial and transstadial transmission, their larval, nymphal, and adult ticks can transmit the parasite to mammals (including human beings) during a blood meal. Additionally, other tick species have been proven to be vectors of *Piroplasma*: *Rhipicephalus microplus*, *Rhipicephalus decoloratus*, *Rhipicephalus australis*, *Rhipicephalus sanguineus*, *Rhipicephalus annulatus*, *Dermacentor reticulatus*, *Haemaphysalis elliptica*, and *Haemaphysalis longicornis* [12]. It should be noted that the distribution of tick vectors is far more extensive than that of the relevant piroplasmosis. The threat of this agent may be underestimated.

Babesiosis is a tick-borne parasitic disease endangering the world, which is caused by protozoan parasites of the genus *Babesia*. So far, more than 100 species of *Babesia* have been identified in domestic and wild animals, among which *Babesia bigemina*, *Babesia Bovis*, and *Babesia divergens* mainly infect livestock animals, while *Babesia microti*, *B. divergens*, *Babesia Duncanii*, and *Babesia venatorum* are the causative agents of human babesiosis [13]. Bovine babesiosis could lead to severe economic loss, which is associated with apopleisis, low feed conversion efficiency, reduced production, abortion, and death of cattle. The clinical symptoms of human babesiosis are similar to malaria, including but not limited to fever, chills, and sleepiness. Additionally, the incidence of hemolytic anemia can be observed in severe cases. However, the severity of babesiosis depends on the species of *Babesia* and the immune status of the patients [14].

In China, the distribution of *Babesia* is shown in Fig. 1. It was previously thought that the responsible species of

human infections were *B. microti* and *B. venatorum* in Eastern and Northeastern China. However, two emerging *Babesia* species, *Babesia crassa*, and *Babesia* sp. XXB/Hangzhou, have been identified in Heilongjiang province and Zhejiang province respectively [15]. Additionally, an initial report of human infection with *B. divergens* in Gansu province has raised medical awareness [16]. It was the first report of *Babesia* infections in Gansu province. Interestingly, as the etiological agent of bovine babesiosis, *B. divergens* has not been identified in cattle in China. In the United States, the number of human infection cases has rapidly increased in the past 20 years. Therefore, the US government has included babesiosis as a nationally notifiable consideration [17]. This suggested that China should pay increased attention to this emerging threat and carry out systematic epidemiological surveys. In the prevalent regions, local physicians should be aware of the differential diagnoses for babesiosis and the risk for transfusion-transmitted babesiosis.

Theileria is an intracellular protozoan parasite, which could lead to bovine theileriosis and constrain cattle production in developing countries, whereby ticks are their natural vectors. The cattle infected with *Theileria* exhibit fever, anemia, jaundice, and superficial lymphadenopathy. In China, *Theileria* infection is common (Fig. 1). The causative agents are *Theileria orientalis*, *Theileria sinensis*, and *Theileria annulata*. *T. orientalis* is a blood protozoan transmitted by *Haemaphysalis* ticks and clustered into the benign *Theileria* spp. group. This group has low pathogenicity to cattle and buffalo, leading to only inconspicuous clinical symptoms. However, the *T. orientalis* Ikeda genotype is a newly identified genotype with strong virulence. It can lead to erythrocyte lysis, causing cause anemia and hypoxia in cattle [18]. Additionally, even if the pregnant cows are cured, they are still at risk of abortion. *T. sinensis*, transmitted by *H. qinghaiensis*, was initially isolated from cattle in Gansu province in China. It showed solid host specificity and can only infect cattle, yaks, and buffalo. However, due to its low pathogenicity, farmers usually pay insufficient attention to this agent, leading to constant invisible losses to the cattle industry. *T. annulata* is the causative agent of tropical theileriosis and has brought a significant impact on the cattle industry. It is transmitted by *Hyalomma* ticks and is prevalent in the arid and semi-arid areas in Northern China. The diagnosis is based on clinical symptoms (such as jaundice, severe anemia, anterior shoulder, and posterior bone lymphadenopathy) and the results of blood and lymph node smear. However, in the case of chronic or subclinical infection, the parasitemia level is extremely low and the parasites might not be detected via these methods [19].

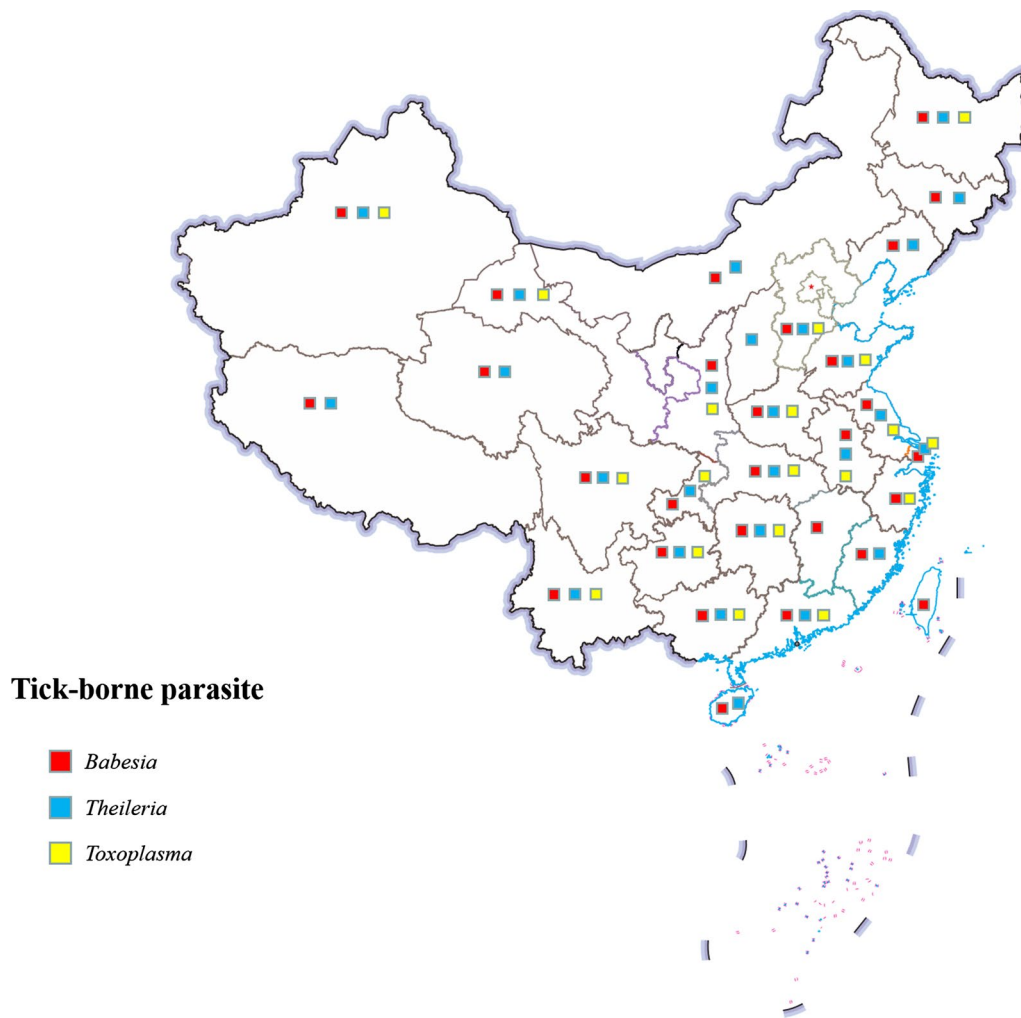


Fig. 1 Geographic distribution of Tick-borne parasite prevalence

Toxoplasma gondii

T. gondii, in the family Apicomplexa, is an obligate intracellular parasite. The majority of warm-blooded animals (from birds to mammals, including human beings) can be infected as intermediate hosts, while only cats can be the definitive hosts. It is generally believed that *T. gondii* is acquired from the ingestion of water, soil, and/or food that is contaminated indirectly by feline feces. However, the oral infection route cannot explain the infection of herbivores, birds, and wild rodents. These animals would not actively eat raw meat nor come into contact with water and food contaminated from feline feces. Thus, some scholars have suggested that arthropods may be alternative vectors for the transmission of *T. gondii*. So far, *T. gondii* has been detected in *Dermacentor variabilis*, *Dermacentor Andersoni*, *D. reticulatus*, *I. ricinus*, *H. longicornis*, *Amblyomma americanum*, *Amblyomma Cajennense*, and *Ornithodoros moubata* [20]. It has been proved that *T. gondii* could survive and remain infective in

H. longicornis for more than 15 days. Nevertheless, it could not be transmitted to hosts during a blood meal [21]. Overall, the presupposition needs more experimental data to confirm.

Toxoplasmosis, a neglected cousin of malaria, is a parasitic zoonosis with approximately a 30% infection rate in the world's human population. However, the seroprevalence has obviously regional characteristics, which can nearly reach 90% in African populations, whereas 60% in Europe [22]. It is generally believed that acute infections of immunocompetent adults are asymptomatic or subclinical, manifesting as influenza-like symptoms. As for immunocompromised demographic groups, such as patients diagnosed with AIDS or cancer, their brains will be damaged [23]. Epilepsy, insanity, ataxia, schizophrenia, and cranial nerve palsy are some common symptoms. Pregnant women can transmit *T. gondii* to the fetus vertically, which leads to obstetric diseases for the fetus and newborns, including abortion and serious congenital anomalies such as hydrocephalus, microcephaly, and calcifications [24]. According to the latest

sero-epidemiological investigations in China, the seropositivity of *T. gondii* antibodies in the general population is 5.1% [25]. The distribution of toxoplasmosis is nationwide (Fig. 1), whereby most of the infected people were in contact with cats. Therefore, eating well-cooked meat, drinking boiled water, and managing feline feces are key interventions for reducing the incidence of toxoplasmosis [26].

Tick-Borne Bacteria

Borrelia Burgdorferi Sensu Lato

B. burgdorferi sensu lato species complex, of order Spirochaetales and family Spirochaetaceae, is distributed throughout the Northern hemisphere. At present, a total of 21 species have been identified, of which 3 are associated with

different clinical manifestations in afflicted human beings: *B. burgdorferi* sensu stricto, *Borrelia garini*, and *Borrelia afzelii*. Relying on the basic metabolic function of *Ixodes* ticks, *B. burgdorferi* could interact with the intestinal and salivary proteins of vector ticks to colonize, survive, and finally exit the ticks successfully [27]. This may be due to evolving stiffer peptidoglycan, as an adaptation to obligate parasitization of vector ticks [28]. *Ixodes* ticks are primarily responsible for the transmission of *B. burgdorferi*: *I. scapularis* mainly transmits the agent on the Eastern coast of the United States, while *I. ricinus* in Europe, and *I. persulatus* in Asia [17]. In Northern China, *B. burgdorferi* is transmitted by *I. persulatus*. As for Southern China, it is transmitted by *Ixodes sinensis* and *Ixodes granulolatus*. However, ticks can only transmit *B. burgdorferi*, *B. garini*, and *B. afzelii* transstadially as opposed to trans-ovarially [29].

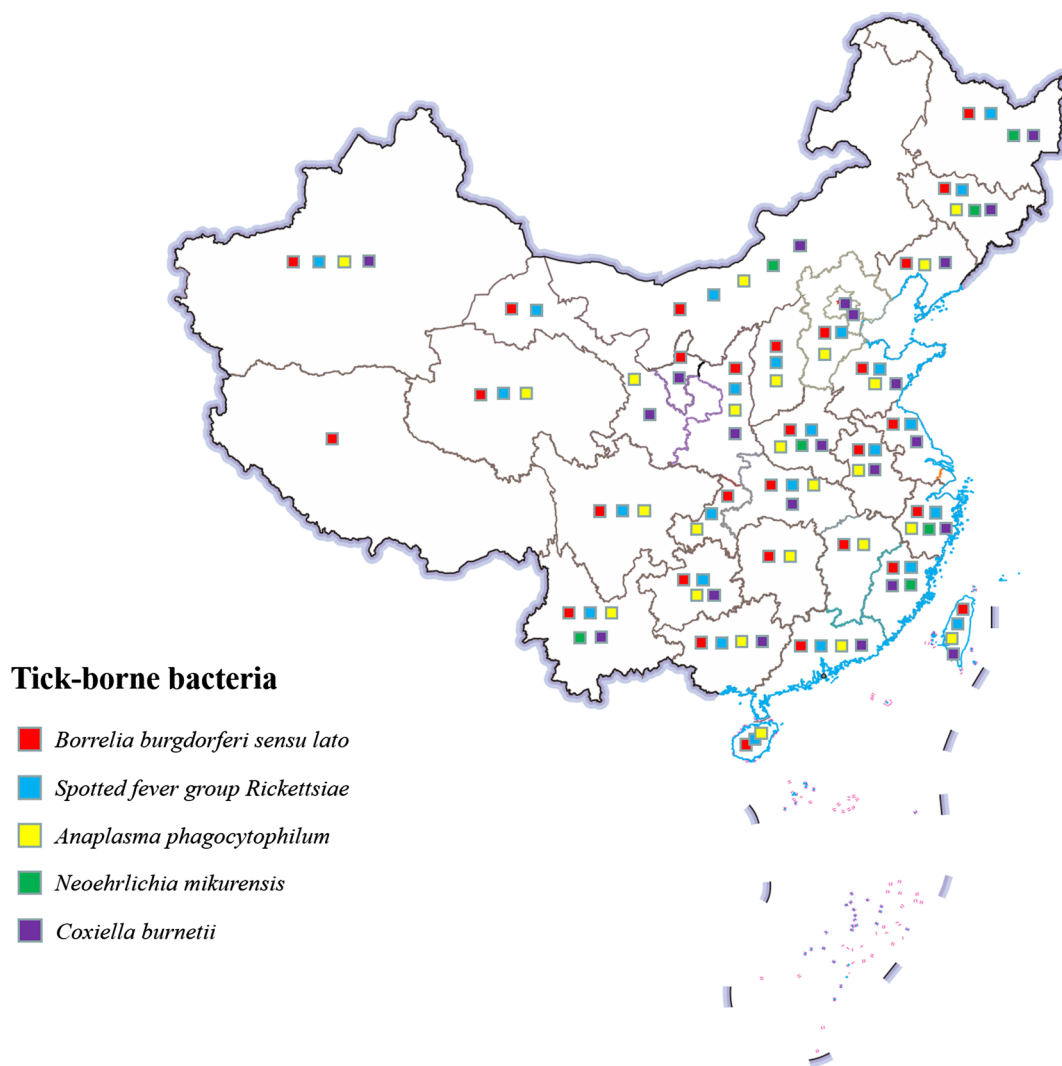


Fig. 2 Geographic distribution of Tick-borne bacteria prevalence

Lyme disease is the most common zoonosis caused by *B. burgdorferi*, of which the incidence peak is in late spring and summer every year (because nymphal ticks are most abundant and active during that time). At present, more than 30 provinces in China have reported cases of Lyme disease (Fig. 2). Acute infection in dogs is characterized by fever, claudication, lymphadenopathy, and multiple arthritis. In addition to the above symptoms, weight loss and laminitis could also be observed in infected horses and cattle. Due to the high invasion capability of *B. burgdorferi*, the number of human cases is far more than that of any other tick-borne bacteria in Europe, North America, and Asia. Human infection is often characterized by a complicated multisystem illness, including erythema migrans (localized skin inflammation) [30], Bannwarth syndrome, and typical acrodermatitis chronica atrophicans. The skin, joints, heart, and nervous system are often damaged. The diagnosis is based on the standard two-tier testing (STTT) that consists of an enzyme immunoassay (EIA) or a chemiluminescence immunoassay (CIA) as an initial test, followed by Western blotting if the result is positive or equivocal. However, if a patient is in the early phase of Lyme disease, the EIA result may be negative or equivocal. Hence, an alternative test should be considered [31].

As for infected patients, antibiotics, such as penicillin, amoxicillin, ceftriaxone, doxycycline, and azithromycin, should be given as soon as possible. Otherwise, the lesion advanced to an early disseminated stage, and finally reaching the late stage with myocarditis, neuritis, or arthritis. Additionally, Hygromycin A, a compound produced by *Streptomyces hygroscopicus*, could be selectively taken up by *B. burgdorferi* and clear the infection in mice [32]. This compound holds the promise of providing a more selective antibiotic for Lyme disease. As for the vaccine, VLA15 is the only Lyme disease vaccine candidate that is reported to undergo phase-3 clinical trials [33]. It targets the outer surface protein A (OspA) of *B. burgdorferi*, which is one of the most important surface proteins, and induces the bacterium's ability to leave the tick and infect human beings. Blocking OspA means that the transmission of *B. burgdorferi* is blocked. Additionally, OspA-based animal vaccines can effectively reduce nymphal infection in white-footed mice (*Peromyscus leucopus*), which are reservoirs of *I. scapularis* [33]. Interestingly, a new vaccine targeting the vector ticks instead of the pathogen has also been under development [34]. The vaccine contains 19 distinct mRNA snippets, which can order host cells to produce important tick salivary proteins. In turn, when faced with a tick bite, the immune system will rapidly react causing redness, inflammation, and itchiness around the bite for people to notice and pull the tick off. Within 36 h after the ticks attach, pulling the ticks off could effectively block the transmission of *B. burgdorferi*.

Table 1 Main groups of tick-borne SFGs and diseases

Pathogens	Disease	Characteristics	Prevalent Regions	Vector Ticks
<i>Rickettsia rickettsii</i>	Rocky Mountain spotted fever	Fever, headache, myalgia, arthralgia, nausea, abdominal pain, and rash	Northern Mexico and southwestern United States	<i>Rhipicephalus Sanguineus</i> , <i>Dermacentor variabilis</i> , and <i>Dermacentor andersoni</i>
<i>Rickettsia conorii</i>	Mediterranean spotted fever	Fever, headache, skin rash, and black eschar	The Mediterranean basin	<i>Rhipicephalus Sanguineus</i>
<i>Rickettsia sibirica</i>	North Asia tick-borne spotted fever	Headache, nausea, fatigue, arthralgia, and myalgia	China, Mongolia, Kazakhstan, and Russia	<i>Dermacentor Nuttalli</i> , <i>Dermacentor sinicus</i> , <i>Dermacentor silvarum</i> , and <i>Haemaphysalis yeni</i>
<i>Rickettsia philipii</i>	Pacific Coast tick fever	Eschar, fever, and headache	California of the United States	<i>Dermacentor occidentalis</i>
<i>Rickettsia africae</i>	African tick bite fever	Multiple taches noires, lymphadenopathy, lymphangitis, and edema	Africa, West Indies, and Oceania	<i>Amblyomma</i> ticks
<i>Rickettsia Japonica</i>	Japanese spotted fever	Fever, erythema, and eschar	Southwest and central Japan, and Pacific coast	<i>Haemaphysalis longicornis</i> , <i>Haemaphysalis flava</i> , and <i>Dermacentor taiwanensis</i>
<i>Rickettsia parkeri</i>	<i>Rickettsia parkeri</i> rickettsiosis	Fever, erythema, and eschar	The United States, Argentina, Brazil, Uruguay and Colombia	<i>Amblyomma maculatum</i>

Spotted Fever Group Rickettsiae

Rickettsia (order: Rickettsiales, family: Rickettsiaceae) is an obligate intracellular Gram-negative bacterium, which is transmitted by arthropods such as ticks, mites, and fleas. At present, a total of 25 pathogenic species have been identified and can be phylogenetically divided into three groups: spotted fever, typhus, and transition groups. The spotted fever group Rickettsiae (SFGR) is one of the emerging tick-borne pathogens identified in mainland China. Through both transovarial and transstadial transmission, Ixodidae ticks could reserve and transmit SFGR, which is distributed geographically, possibly expanding their distribution range through vector ticks [35].

Spotted fever is the general name for clinical diseases caused by SFGR. Different *Rickettsia* species will lead to various endemic diseases (Table 1). In the United States, reported Rocky Mountain spotted fever (RMSF) cases have dramatically increased tenfold over the past 20 years [36]. Emerging SFGR subspecies have also been discovered. Additionally, several *Rickettsia* species, which were previously considered non-pathogenic for decades, have been definitively reported to associate with human disease in Italy [37].

In recent years, an increasing number of emerging SFGRs have been reported in China, including *Rickettsia parkeri* [38], *Rickettsia Japonica* [39], *Rickettsia* sp. XY99 [40], *Candidatus Rickettsia xinyangensis* [41], *Candidatus Rickettsia jingxinensis* [42], *Candidatus Rickettsia tibetani* [43], *Candidatus Rickettsia jiaonani* [44], and *Candidatus Rickettsia tarasevichiae* [45]. This indicated that there might be more unknown species of SFGR in China, which have become a growing threat to both animals and human beings. China should first carry out a broad epidemiological investigation to identify unknown species of SFGR, especially in a geographic region where no information is available. China should then consider the data as starting point to assess the possible risk for human beings, including pathogenicity, tick vectors, and sensitive antibiotics.

Anaplasma phagocytophilum

A. phagocytophilum (order: Rickettsiales, family: Anaplasmataceae), an emerging tick-borne pathogen found in recent years, is the causative agent of human granulocytic anaplasmosis (HGA). HGA is a moderately severe febrile illness with variable symptoms and is commonly reported in the Northern hemisphere. Subclinical symptoms include fever, cough, headache, diarrhea, and vomiting. While critical symptoms include sepsis, multiple-organ failure syndromes, and acute nephritis [46]. Granulocytic anaplasmosis in dogs is characterized by acute fever, lethargy, and further gastrointestinal and/or musculoskeletal symptoms. As for domestic

ruminants, infection of *A. phagocytophilum* could cause so-called tick-borne fever, which is associated with high fever, reduced milk production, decreased weight gain, respiratory symptoms, abortions, and immunosuppressive effects.

It is generally believed that *I. ricinus* is the transmission vector of *A. phagocytophilum*. The extracellular vesicles of *I. ricinus* not only favor tick feeding but also promote the infection of *A. phagocytophilum* [47]. In return, *A. phagocytophilum* could modulate the metabolism of vector ticks and the autophagy of host cells to exploit host nutritional supplies, further adapting to the host [48, 49]. Additionally, *A. phagocytophilum* has also been detected in *I. persuleatus*, *Ixodes hexagonus*, *Ixodes trianguliceps*, *Ixodes ventralloi*, *Rhipicephalus bursa*, *D. reticulatus*, *Haemaphysalis punctata*, *H. longicornis*, and *Haemaphysalis qinghaiensis* [50]. However, the transmission capacity of these tick species has not been fully elucidated.

So far, *A. phagocytophilum* has been detected in over 26 provinces in China (Fig. 2). The first case of HGA in China was reported in Anhui Province in 2008 [51]. However, the clinical and laboratory findings were different from reported HGA cases in the United States. First, all of China's cases were positive for *A. phagocytophilum* DNA according to polymerase chain reaction (PCR). However, the morulae could not be observed on a blood smear. Second, China's cases showed significantly less headache, more diarrhea, leukopenia, and thrombocytopenia. Finally, all of China's cases had a unique symptom: relative bradycardia, which was never reported in the United States. Interestingly, a novel bunyavirus, named severe fever with thrombocytopenia syndrome virus (SFTSV) was identified in a coincident region with the earlier report of HGA [52]. The clinical symptoms were much more similar to those of HGA cases, including relative bradycardia. Therefore, some scholars have proposed that previous HGA cases could have been misdiagnosed [53]. Whether misdiagnosed or not, it highlights that HGA should be cautiously diagnosed in areas where it has never been reported. We recommend that the diagnosis should rely not only on the symptoms of fever, headache, diarrhea, and vomiting but also on the establishment of a microbiological standard for culturing *A. phagocytophilum* and validation using PCR [54].

Coxiella burnetii

C. burnetii (order: Legionellales, family: Coxiellaceae) is an intracellular bacterium with highly zoonotic potential. This small coccobacillus could infect human beings and mammals, such as cattle, buffalo, sheep, goats, horses, and pigs, and lead to a zoonosis called query (*Q*) fever. *C. burnetii* could regulate its cholesterol levels to promote intracellular survival [55] and metabolize sugar to subvert host immunity

and promote its infection [56]. *Q* fever in mammals is generally asymptomatic; however, pregnant livestock will manifest reproductive disorders, such as abortion, stillbirth, and mastitis. Large amounts of pathogens are not only shed during abortion or normal parturition, but also through milk, vaginal mucus, and feces for months [57]. The routes of human infection include direct contact with shedders, eating raw meat and milk of infected ruminants, or inhalation of contaminated aerosols [58]. Human-to-human transmission is visible, but rare [59].

Acute *Q* fever in human beings generally manifests hepatitis, pneumonia, endocarditis, and influenza-like symptoms such as fever, headache, and muscle soreness. Once diagnosed, doxycycline plus hydroxychloroquine should be given to patients as soon as possible. Without complete treatment, it may turn into chronic *Q* fever or persistent focalized infection, whose intervals can reach more than 9 years [60]. It should be noted that the use of the term, chronic *Q* fever, seems to be questioned as this term may be misleading and confused with endocarditis, pericarditis, lymphadenitis, vascular infections, osteo-articular infections, and genital infection. Thus, some scholars argued that the concept of chronic *Q* fever should be evolved to persistent focalized *C. burnetii* infection [61]. With low serological titer, the persistent focalized infection may be asymptomatic. Therefore, it needs to be diagnosed using an 18F-FDG-PET/CT scan and fluorescence in situ hybridization. Additionally, the IgG titers cannot predict the prognosis during treatment and follow-up of the persistent focalized infection [62].

In addition to aerosols, ticks could also be a source of *Q* fever infection. It is generally believed that *D. andersoni*, *Ixodes holocyclus*, *Hyalomma aegypticum*, *Hyalomma asiaticum kozlovi*, *R. sanguineus*, *Ornithodoros lahorensis*, and *Ornithodoros hermsi* are responsible for the trans-ovarial and transstadial transmission of *C. burnetii*. In China, *C. burnetii* have been detected in *Dermacentor nuttalli*, *Dermacentor pavlovskyi*, *Dermacentor silvarum*, *Dermacentor niveus*, *Haemaphysalis rufipes*, *Hyalomma anatolicum anatolicum*, *H. asiaticum kozlovi*, *H. punctata*, and *R. sanguineus* [63]. These vector ticks are widely distributed in Northwest China, which suggested that there might be a wide range of endemic foci for *Q* fever. Therefore, the prevention and control of *Q* fever are of great necessity and significance. First, in some situations, *Q* fever is regionally restricted and occupational. Abattoir workers, farmers, and veterinary personnel should follow proper procedures when handling birth products and animal carcasses, such as wearing appropriate protective masks and clothing. All the experimental manipulations of *C. burnetii* should be made at biosafety level 3 laboratories. Second, high-risk occupational groups should be given the commercial vaccine Q-VAX[®] (Seqirus, Australia) as a preventive measure [64]. However, given that severe local and systemic reactogenic

responses have been observed in previously sensitized individuals, a cutaneous skin test for *Q* fever is required before vaccination. A novel recombinant protein subunit vaccine candidate, which is combined with novel TLR triagonist adjuvants, could reduce local reactogenic responses, generating protective immunity against *C. burnetii* infection [65].

Neoehrlichia mikurensis

N. mikurensis (order: Neoehrlichia, family: Anaplasmataceae) is an emerging tick-borne intracellular bacterium, which is similar to the genus *Ehrlichia*. It was initially isolated on the Japanese island of Mikura and named *Candidatus Neoehrlichia mikurensis* [66]. The term, Candidatus, indicated that the bacterium was uncultivable. So far, 7 species of ticks have been reported to be infected by *Ca. N. mikurensis*: *I. ricinus*, *I. persulcatus*, *Ixodes ovatus*, *Ixodes frontalis*, *I. hexagonus*, *D. reticulatus*, and *Haemaphysalis concinna* [67]. The infection rates of *Ca. N. mikurensis* were the highest among *I. ricinus* and *I. persulcatus*, which indicated that these ticks were the primary vectors. However, the transmission capacity of other ticks remains disputable, as they rarely carry *Ca. N. mikurensis*. Until 2019, *Ca. N. mikurensis* has been successfully propagated in *I. ricinus* and *I. scapularis* cell lines [68], hence losing the prefix: Candidatus. Human vascular endothelial cells have been reported to be the target of infection [68].

N. mikurensis is widely distributed in Asia and Europe, and has been detected in China, Japan, Russia, Mongolia, the Czech Republic, Slovakia, Moldova, Hungary, Germany, Switzerland, Poland, Romania, France, Belgium, Italy, Spain, the Netherlands, and the Scandinavian countries. The first report of *N. mikurensis* infection in human beings was published in Europe in 2010 [69], whereby the disease was named neoehrlichiosis. Clinical manifestation of neoehrlichiosis in immunocompromised patients is rather dramatic, which includes high fever, chills, nightly sweats, and arthromyalgia [70]. In many cases, severe pain may affect the neck, elbows, temporal or mandibular joints, knees, and ankles. Skin rashes that resemble erysipelas or erythema nodosum could also be observed. Additionally, thromboembolic events had a remarkably high incidence in immunocompromised patients [70]. Deep vein thrombosis of the extremities and/or pulmonary embolism were reported to occur in the venous circulation. In arterial circulation, transient ischemic attacks have also been reported leading to mental confusion, weakness, and numbness. This suggested tropism for endothelial cells.

Although neoehrlichiosis mainly infects immunocompromised individuals, China reported 7 infection cases in non-immunocompromised persons in 2012 [71]. Therefore, it is too early to define *N. mikurensis* as an opportunistic pathogen. Currently, the only method of diagnosing *N. mikurensis*

Table 2 Reported clinical symptoms of CCHF

Period	Symptoms	Duration days
Incubation	Asymptomatic or limited symptoms	3–7 days
Pre-hemorrhagic	Unspecific symptoms: high fever, myalgia, headache, retro-orbital pain, neck stiff, nausea, vomiting, and diarrhea	1–7 days
Hemorrhagic	Hemorrhagic symptoms: epistaxis, petechiae, ecchymosis, melena, gingival bleeding, hematemesis, hematuria, and hematoma; Other symptoms: melena, hemoptysis, and hematuria	2–3 days
Convalescence	Marked fatigue, tachycardia, labile blood pressure, temporary alopecia, and memory impairment	10 days

infection is through PCR, which requires blood (including plasma, serum, and whole blood) and/or bone marrow samples. When diagnosed, patients are recommended Doxycycline as a treatment. All known cases of immunocompromised patients who were treated with adequate antibiotics improved rapidly, and a follow-up PCR analysis of their blood samples was negative [70].

Tick-Borne Virus

Bunyaviridae: Crimean–Congo Hemorrhagic Fever Virus

Hard ticks could transmit RNA viruses in the families of Bunyaviridae and Flaviviridae. Crimean–Congo hemorrhagic fever virus (CCHFV) is a member of the genus *Nairovirus*, family Bunyaviridae. With high invasiveness, CCHFV has the second widest geographical distribution of all arboviruses, just after the Dengue virus (a mosquito-borne virus). The infection has been reported in over 30 countries in Europe, Asia, Africa, and the Middle East [72]. *Hyalomma* ticks are primary vectors of CCHFV, which can transmit it through trans-ovarial and transstadial methods.

Crimean–Congo hemorrhagic fever (CCHF) is one of the most serious viral hemorrhagic fevers in human beings. There are 4 distinct periods for CCHF in total: incubation, pre-hemorrhagic, hemorrhagic, and convalescence (Table 2). The incubation period generally lasts 3–7 days, with the virus replicating and disseminating. In the pre-hemorrhagic period, the main symptom is a high fever that can reach 39–41 °C [73]. This period is generally short but can last up to 7 days, after which it will enter the hemorrhagic period whereby the viral load peaks with an average mortality rate of 30% [74]. Strict barrier precautionary measures should be taken to prevent secondary and nosocomial spread. High levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) could predict a poor outcome. Due to the lack of specific drugs or approved vaccines, care for CCHF patients is based on supportive measures, including correcting electrolyte imbalance and replacing blood volume (usually with intravenous fluids), which is caused by

gastrointestinal disorders. Fresh frozen plasma and platelets may be transfused to counter the coagulation abnormalities. Ribavirin, a nucleoside analog, has been proven to be effective in suppressing viral loads and has been highly recommended for post-exposure prophylaxis [75]. Favipiravir has been reported to suppress viral replication and synergistically act with ribavirin *in vitro* [76]. Additionally, research on the neutralization mechanism of antibodies against CCHFV provides the molecular basis, which is essential for developing specific medical countermeasures. ADI-37801 and ADI-36121, two neutralizing antibodies, can recognize and bind CCHFV epitopes by blocking membrane fusion [77]. Following binding, DVD-121-801, a bispecific antibody, can provide therapeutic protection and become a strong candidate for therapeutic antibody cocktails [78].

In China, Xinjiang province is the only region that has reported the outbreak of CCHF (Fig. 3) and isolated CCHFV strains. It has been reported that *H. asiaticum kozlovi*, *Hyalomma detritum*, and *D. nuttalli* are vector ticks of CCHFV [79]. Recently, two novel strains have been isolated from *Hyalomma asiaticum asiaticum* ticks in Xinjiang [80]. This indicated that Xinjiang province may be an important epidemic focus of CCHFV, which has been a great threat to residents. Additionally, CCHFV is globally resurging and gradually spreading to unreported regions [81]. Therefore, China should strengthen the active monitoring of the population of vector ticks, as well as the passive monitoring of hemorrhagic fever cases in case CCHFV is imported from the broader. Additionally, Italian scholars have confirmed that migrating birds could be potential vectors by introducing CCHFV from African endemic areas to Central Italy [82]. This further highlighted the importance of China paying attention to the migratory birds and strengthening virus monitoring along the migration trajectory.

Flaviviridae: Tick-Borne Encephalitis Virus

Tick-borne encephalitis virus (TBEV) is a member of the genus *Flavivirus*, family Flaviviridae, which has been classified into three subtypes: European (Eu-TBEV), Siberian (Sib-TBEV), and Far-Eastern (FE-TBEV). Their variation in amino sequences acid is 5–6%, however, further



Fig. 3 Geographic distribution of Tick-borne virus prevalence

bioinformatic analysis revealed that Eu-TBEV is a distinct species unit [83]. In recent years, two novel subtypes of TBEV have been isolated, named Himalayan (Him-TBEV) [84] and Baikalian (Bkl-TBEV) [85] respectively. At present, it has been reported that Eu-TBEV is mainly transmitted by *I. ricinus*, while Sib-TBEV and FE-TBEV are both transmitted by *I. persulcatus*. Additionally, *D. reticulatus* could also transmit the virus [86].

Most TBEV infections in human beings are asymptomatic. However, neurological symptoms, including encephalitis, meningitis, and meningoencephalitis can be observed in one-third of infection cases. The disease caused by TBEV is called tick-borne encephalitis (TBE), which is the most serious tick-borne neurological disease prevalent across the

Eurasian continent from Japan to France, even in the United Kingdom [87]. The incidence and mortality rate are dependent on the subtype of the virus. The mortality of Eu-TBEV and Sib-TBEV is about 2%, associated with neurological sequelae and long-term infection. However, the mortality of FE-TBEV is up to 30% [88]. At present, there is no specific drug for TBEV. Therefore, active vaccination is a practical measure to prevent TBEV infection. Two safe and effective vaccines have been approved: FSME-IMMUN[®] (Pfizer, USA) and Encepur[®] (GlaxoSmithKline) [89]. The vaccines are generally safe with rare serious adverse events [90].

In China, a total of 3364 TBE cases have been reported from 2007 to 2018 [91]. It is mainly endemic in Northern and Western China (Fig. 3). Most cases involved people

living or working in forests. Recently, evidence of TBEV in 2 areas of the United Kingdom attracted our attention [92]. According to the climatic forecasts, TBEV was thought to be incapable of establishing itself in the United Kingdom, as their vector ticks could not overcome the temperature limit. However, they challenged the climate, which was speculated to be carried by migratory birds [93]. This suggested that the contribution of migratory birds for TBE is substantial, particularly for medium- and long-distance dispersal. Hence, the threats might be potentially extensively underestimated.

Phenuiviridae: Severe Fever with Thrombocytopenia Syndrome Virus (Dabie bandavirus)

In 2009, researchers have detected a novel virus in Henan, Hubei, Shandong, Anhui, Jiangsu, and Liaoning provinces in China [52]. The virus could infect human beings and cause a febrile disease called severe fever with thrombocytopenia syndrome (SFTS). The clinical manifestations mainly include fever, thrombocytopenia, and leukopenia syndromes. Therefore, the virus was initially named severe fever with thrombocytopenia syndrome virus (SFTSV) and classified into the genus *Phlebovirus* and family Phenuiviridae. However, it was later renamed by the International Committee on Taxonomy of Viruses (ICTV) in 2019. This novel virus was finally denominated Dabie bandavirus and reclassified into the genus *Bandavirus*, family Phenuiviridae, and order Bunyavirales.

H. longicornis and *I. sinensis* have been proven to transovarially and transstadially transmit Dabie bandavirus [93]. While *D. silvarum* could transmit the virus transovarial rather than transstadial [94]. Additionally, *Haemaphysalis flava*, *R. microplus*, *Amblyomma testudinarium*, *D. nuttalli*, *H. asiaticum kozlovi*, *H. concinna*, *I. persulcatus*, and *Ixodes nipponensis* can harbor the virus [95]. Distributed in the Asia Pacific region, *H. longicornis* is the primary vector for Dabie bandavirus. However, recently, the United States reported the invasion of *H. longicornis* with increasing numbers infesting sheep [96], in addition to human beings bitten as well [97]. Migratory birds, as the natural hosts of *H. longicornis* have been suspected to indirectly expand the distribution of *H. longicornis* by carrying ticks during long-distance migration. There is evidence supporting the relationship between *H. longicornis* and the flyways of migratory birds [98]. However, according to the ecological niche modeling, *H. longicornis* have also been predicted to threaten more extensive regions, including Europe, South America, and Africa [99]. It suggested that authorities and healthcare workers should pay more attention to this emerging threat and enhance surveillance, as well as further investigations globally.

In addition to China, infected patients have also been reported in South Korea [100], Japan [101], and Vietnam [102], with a mortality rate ranging from 2.8–47%. SFTS has three distinct phases: fever, multiple-organ dysfunction, and convalescence. The fever stage is characterized by marked thrombocytopenia, leukocytopenia, and lymphadenopathy. Additionally, high fever, headache, myalgia, and gastrointestinal symptoms could also be observed. In the multiple-organ dysfunction stage, the symptoms will develop into hemorrhagic manifestation, sustained thrombocytopenia, disseminated intravascular coagulation, and neurological symptoms. High serum viral load can be continuously detected in fatal illnesses. As of now, there is still a lack of comprehensive understanding of the immune interactions between the virus and hosts. It has been proved that B cells in secondary lymphoid organs were the targets for Dabie bandavirus at the end stage of lethal infection. The virus could inhibit the secretion of plasma B cells and the maturation of high-affinity neutralizing antibodies, thereby allowing significant virus replication, leading to death [103]. Moreover, a human plasmablastic lymphoma cell line, PBL-1, has a similar immuno-phenotype to that of target cells and can provide a potential *in vitro* model to extend the understanding of human lethal infection [104].

At present, there is no available vaccine or specific antiviral drugs for this disease. Therefore, the treatment of SFTS mainly relies on extensive antiviral drugs. Previously, Ribavirin was considered to have potential therapeutic effects on SFTS. However, it has been proven that Ribavirin could be effective in patients only before the virus load reaches 1×10^6 copies/mL [105]. Favipiravir, developed by Toyama Chemical Co., Ltd, has been proven to provide a better therapeutic effect than Ribavirin in animal models. All infected mice survived by dosing Ribavirin within 3 days, whereas the survival rate exhibited 83 and 50% by dosing Ribavirin at 4 and 5 days, respectively [106]. Calcium channel blockers, such as Benidipine hydrochloride and Nifedipine, could effectively inhibit virus infection by impairing virus internalization and replication [107]. Nifedipine was reported to enhance virus clearance and remarkably reduce case mortality by more than fivefold. Additionally, there are three studies for developing Dabie bandavirus vaccines. A recombinant vesicular stomatitis virus expressing the Gn/Gc glycoproteins could completely protect mice from Dabie bandavirus infection [108]. A DNA vaccine expressing the same antigens could induce the production of neutralizing antibodies and an immune response of specific T cells. Aged ferrets were protected from the lethal Dabie bandavirus infection [109]. Additionally, recombinant vaccinia virus expressing envelope glycoprotein precursor could also completely protect mice from lethal challenges with Dabie bandavirus [110].

Flaviviridae: Jingmenvirus

Since the discovery of the Dabie bandavirus, Chinese researchers have carried out extensive detection and screening for tick-borne viruses, and accidentally found a novel virus [111], named Jingmen tick virus (JMTV). Subsequently, JMTV and JMTV-like viruses were detected in Africa [112], South America [113], and Europe [114] in succession. According to the genetic sequence analysis, JMTV and JMTV-like viruses were finally classified into the genus *Flavivirus*, family Flaviviridae, with a collective name: Jingmenvirus [111].

The genome of Jingmenvirus consists of 4 separate segments of linear, single-stranded positive-sense RNA, named fragments S1, S2, S3, and S4. Fragments S1 and S3 could encode nonstructural proteins (NSP1 and NSP2), which are similar to other flaviviruses. While fragments S2 and S4 encode structural proteins (VP1, VP2, and VP3), which present no homology with any known viral sequence [111]. Therefore, Jingmenvirus is the first example of a segmented RNA virus with a genome acquired partly from as-yet-unidentified viral ancestors. At present, the virus has been detected in *I. sinensis*, *I. granulatus*, *I. ricinus*, *H. flava*, *Haemaphysalis hystricis*, *H. longicornis*, *Haemaphysalis inermis*, *Haemaphysalis parva*, *Hyalomma marginatum*, *R. microplus*, *Rhipicephalus geigy*, *R. sanguineus*, *R. bursa*, *Rhipicephalus turanicus*, *Amblyomma Javanense*, and *A. testudinarium* ticks [115]. In recent years, the host range of JMTV has rapidly expanded, which has been detected in mosquitoes, rodents, cattle, dogs, and goats in China [116]. Additionally, a variant of Jingmenvirus (RC27) was observed in a non-human primate from the Republic of Uganda [112], suggesting a potential threat to human beings. China and Kosovo have reported human cases of Jingmenvirus infection [117, 118]. The patients had an itchy or painful eschar with a history of tick bites. Clinical presentations of the patients included fever, headache, and myalgia. These reports indicated the potential pathogenicity for human beings and efficient transmission by vector ticks. Its public significance should be of utmost importance.

In 2017, according to the surveillance for tick-borne diseases, another unknown virus has been identified in a patient with unexplained febrile illness in Inner Mongolia [119]. The novel zoonotic virus was named Alongshan virus (ALSV) and is prevalent in Heilongjiang and Inner Mongolia province, China. According to the genetic sequence analysis, the homology between JMTV and ALSV is 57.4–74.5% [120]. Therefore, ALSV is considered a JMTV-like virus and classified as a Jingmenvirus. Interestingly, according to the phylogenetic analysis of NS3 and NS5, the tick isolates (JMTV-SY84, GXTV, MGTV, and ALSV) are closely related to mammalian isolates (JMTV-XJ58/voles, JMTV-RC27/monkey, ALSV/human, and JMTV/human) despite their distant location. It suggested that the mammalian isolates are probably transmitted by ticks [121]. At present, it is generally believed that *I. persulcatus* could naturally carry ALSV infection to human beings. The clinical manifestations were unspecific, such as headache, fever, and tiredness. Additionally, petechial, rash, nausea, coma, arthralgia, myalgia, or other indicators could rarely be observed. Therefore, it needs to be distinguished from SFTS, TBE, HGA, and spotted fever (Table 3).

It should be noted that recently, ALSV RNA has been detected in *I. ricinus* in France [122], *I. persulcatus* in Russia [123], and *A. testudinarium* in Japan [115], suggesting that Jingmenvirus might have a wider geographical distribution than expected. Therefore, the priority is to carry out further epidemiological surveillance and etiological studies to assess the status and risk of Jingmenvirus infection. Second, it is necessary to construct mouse or primate models of Jingmenvirus infection to verify the virus's ability to horizontal and vertical transmission, and to guide the comprehensive prevention and control of the diseases.

Asfarviridae: African Swine Fever Virus

African swine fever virus (ASFV), the only member of the genus *Asfivirus* and family Asfarviridae, is the most important virus devastating the global pork industry. The virus could infect domestic pigs and wild boars, leading to

Table 3 Differential diagnosis of HGA, SFTS, TBE, spotted fever, and Jingmenvirus infection

Disease	Common symptoms	Unique symptoms
Human granulocytic anaplasmosis Severe fever with thrombocytopenia syndrome	High fever, headache, myalgia, and gastrointestinal symptoms	Leukopenia and thrombocytopenia Leukopenia, thrombocytopenia and relative bradycardia
Tick-borne encephalitis		Neurological symptoms: encephalitis, meningitis and meningoencephalitis
spotted fever		Typical skin rash on the hands and feet
Jingmenvirus infection		Untypical skin rash in other parts of the body

a hemorrhagic fever disease, named African swine fever (ASF). The morbidity and mortality of this disease are both high. ASFV was confined to African countries in the early 1900s. However, the virus was first introduced into Portugal via infected pork products in 1957 but was soon eradicated. Subsequently, the virus was second introduced into Portugal in 1960 and rapidly spread to other European, Caribbean, and American countries, including the Iberian Peninsula, Belgium, the Netherlands, Italy, Malta, France, the Dominican Republic, Haiti, Brazil, and Cuba. By the mid-1990s, ASFV was eradicated in all countries except the Italian island of Sardinia [124]. In 2007, a new transmission era was heralded as ASFV was introduced into the Republic of Georgia. The virus rapidly spread to the Russian Federation, Ukraine, and Belarus, and subsequently to the West, including Belgium, the Czech Republic, Hungary, Bulgaria, Romania, Slovakia, and Serbia. In 2018, ASFV spread into China and worsened the situation [125], as China contains half the world's swine population. Then, South Korea, Mongolia, Cambodia, the Philippines, Indonesia, Laos, Myanmar, Timor Leste, and Vietnam also reported the presence of the ASFV endemic.

ASFV is a giant, complex, enveloped DNA virus, which comprises more than 50 structural proteins and could induce the production of more than 150 proteins in infected cells. The infectious virion possesses a 5-layered structure and an overall icosahedral morphology [126]. Monocytes and alveolar macrophages in both domestic pigs and wild boars are the targets for ASFV, while lymphocyte infection was never reported. Additionally, ASFV could also infect HEK293T cells and replicate efficiently after continuous passaging [127]. The molecular mechanism of ASFV adaptation to different cell lines may be associated with the deletions of *MGF300* and *MGF360* genes.

In the absence of treatment and commercial vaccines, further understanding ASFV epidemiology is important to limit the spread of the virus. At present, ASFV can be transmitted through 3 modes: (i) Direct contact, including the oral–nasal route and skin abrasions, which are the most common among wild boars and domestic pigs. A high virus level present in the blood, saliva, nasal secretions, and urine, facilitates direct infection. Aerosol transmission is only considered to occur over short distances [128]. Additionally, contact with infected carcasses is an alternative route for ASFV transmission between wild boars, as the virus could remain infectious over long periods. (ii) Human activities could result in both short- and long-distance transmission of ASFV. Feeding domestic pigs with swill, which contain infected pork product, is the main cause of ASFV transmission [129]. Other contaminated materials, such as clothing, boots, labor tools, and transport vehicles of farmers, could also indirectly transmit ASFV to domestic pigs. Additionally, the movement of

infected pigs could lead to the virus's long-distance jump. (iii) As the only known DNA arbovirus, ASFV could be transmitted by the *Ornithodoros erraticus* complex transstadially, transsexually, and transovarially. The *Ornithodoros* ticks and warthogs (*Phacochoerus africanus*) are thought to play important roles in the ASFV sylvatic cycle. However, due to the limited transmission capacity of vector ticks, the indirect transmission from warthogs and bushpigs to domestic pigs is thought to be relatively infrequent.

At present, the transmission capacity of vector ticks and their potential roles in European and Asian epidemics have not been fully understood. Ticks in the *O. erraticus* complex have been reported to spread 4 ASFV strains: Tomar/87, OurT88/1, ASFV/P99, and NH/P68. However, they could not transmit the Eurasia circulating strain, Georgia 2007/1 [130]. Additionally, a suspected vector, *O. moubata*, was proven capable of transmitting Georgia 2007/1. *Ornithodoros verrucosus* could maintain the infectious virus for 2 or more months [131]. These results emphasized the importance of identifying vector competence and assessing their transmission risks. Recently, the United States systematically aggregated the published data on vector competence, host competence, and tick–host interactions, to identify the local species which could potentially transmit ASFV into the USA [131]. Three species of *Ornithodoros* ticks (*O. coriaceus*, *O. turicata*, and *O. puertoricensis*) were identified as the highest risk species. Additionally, 18 kinds of soft ticks were identified with low risk, and 16 other species were identified with unknown risk due to the lack of vector competence and host association data. In China, 4 species of *Ornithodoros* ticks (*O. tartakovskyi*, *O. papillipes*, *O. lahorensis*, and *O. capensis*) have been found and reported to distribute in 38 counties [1]. However, their vector competence has not been evaluated.

Due to the complexity of eco-social systems and the interconnectedness of pork industries around the world, interrupting the global spread of ASFV is quite difficult. The present strain in China was genotype I ASFV, which shared high similarity with NH/P68 and OURT88/3 [132]. Current control strategies rely on classic sanitary measures, which include the restriction of swill feeding, rapid detection, comprehensive epidemiological surveillance, strict biosecurity measures, and quarantine and slaughter policies. In infected pig farms, emergency response measures, such as compartmentalization, zoning, culling all affected pigs, safe disposal of dead pigs and products, and restriction of pig movement should be immediately employed. Additionally, appropriate import policies should also be implemented, such as proper disposal of swill from aircraft, ships, or vehicles coming from endemic countries, and policing illegal imported pigs and pork products.

Prospect

In the past several decades, the distribution of tick populations in Asia, Europe, and North America has gradually expanded [133]. The prevalence of tick-borne diseases has been increasing and become an important public health issue. However, since the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2019, the laboratory tests and case reports for tick-borne diseases were reduced. Conceivably, the decrease may be a result of limited access to specialized diagnostics due to the surge of the coronavirus disease 2019 (COVID-19) patients. Additionally, the infection of SARS-CoV-2 might influence the course of tick-borne diseases in a bad manner and lead to further complications. Therefore, the prevention of tick-borne diseases should be highlighted.

At the first line of tick-borne pathogen surveillance and control, medical and veterinary personnel should implement adequate personal protection. Before entering the high grass, low-lying bushes, and dense forests, clothing should be replaced with long-sleeved clothes and trousers in bright colors. Other individual preventive measures include tightening the cuffs, tucking trousers inside socks, treating clothing with repellent, and wearing a cap if necessary. Additionally, working duration in high-risk areas should be reduced as much as possible. After returning to the room, wet and humid parts of the body, such as the belly button, skin folds, genitals, ears, and scalp, should be checked carefully to avoid the attachment of ticks.

Farmers (living in tick-prevalent areas) should consider the management of the environment and livestock. First, they should get rid of falling leaves, mow lawns around the house and place the woodpile away from the house. Second, livestock should be prohibited from entering living quarters and regularly dipping acaricide on their body surface. Once a tick bite is observed with an unexplained fever, the patient should immediately go to the hospital for medical diagnosis and treatment. Due to the lack of a suitable environment for tick survival, urban residents are at low risk. However, the management of their pets is significant. After dogs or cats enter the grass and bushes, tick repellents should be given on their surface.

Vaccines have been proven to be helpful to prevent the tick-borne pathogens. According to the One Health concept [134], human beings, animals, and the environment are like the 3 arms of a triangle, whereby their relationship and interaction should be tackled. This highlighted the synergistic benefit of closer cooperation. Therefore, 3 vaccine frameworks need to be developed. Framework I vaccines are intended for the protection of economically valuable animals. Framework II vaccines are used to protect domestic

animals and human beings. Finally, framework III vaccines are applicable for the protection of wild animals. This relies on further basic research of tick-borne pathogens' epitopes and therapeutic antibodies. With ready-made vaccines and abundant basic research, the prevention and control of emerging and re-emerging tick-borne pathogens will be rapid and accurate.

However, relying solely on vaccines is not enough. The comprehensive prevention and control of tick-borne pathogens are also dependent on individual and collective protection, vector control, comprehensive surveillance, accurate diagnosis, and symptomatic treatment. So far, 124 tick species and 103 tick-borne pathogens have been reported in China. A total of 29 tick-borne pathogens were associated with human infections, and the number is still increasing. This further highlighted the importance of assessing the transmission risk of vector ticks. Additionally, according to the assessment of vector ticks and tick-borne pathogens' distributions [1], the suitable habitats were 14–476% larger than reported areas, indicating that the detection is seriously insufficient. At last, the possible role of migratory birds in China should also be identified to realize the comprehensive prevention and control of ticks and tick-borne pathogens.

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