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PROTOZOOLOGY - REVIEW

Human Babesiosis in China: a systematic review

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Abstract

Human babesiosis, a worldwide emerging tick-borne disease, is caused by the intraerythrocytic apicomplexan parasite, babesia. In recent years, the number of infected patients globally has continued to rise, and thus human babesiosis poses a significant public health threat. Therefore, stronger initiatives should be undertaken to prevent further spread and development of this disease. In the present review, we summarize the epidemiology of reported human babesiosis cases in China from 1993 until now. The data show that *Babesia microti* is the dominant species causing human babesiosis in China and has led to more than 100 human infections thus far, where *Babesia crassa*-like is the second-most common. Moreover, Guangxi province is the second-most infected area after the Heilongjiang province. We also review the babesia life cycle, manifestation, diagnosis, and treatment. Additionally, we discuss babesiosis prevention strategies to raise public awareness, and also provide suggestions for improved babesiosis control.

Keywords Human babesiosis · *Babesisa* spp. · Epidemiology · Treatment · Prevention · China

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Introduction

Babesia, an intraerythrocytic protozoan, was first identified in cattle and sheep erythrocytes by Victor Babes in 1888 (Babes 1888). As an apicomplexan parasite, *Babesia* spp. belongs to the suborder Piroplasmida and family Babesiidae, which is the second-most common blood-borne parasite (Conrad et al. 2006; Gray et al. 2010). Interestingly, this parasite can potentially infect all vertebrate mammals, including humans, and causes a zoonotic vector-borne disease—babesiosis—which can lead to both livestock losses and significant harm to general public health (Farber et al. 2015; Schnittger et al. 2012). As a tick-borne pathogen, babesia has invaded new geographic areas in tandem with the expansion of tick habitats, causing babesiosis to become an increasing global problem (Beugnet and Moreau 2015). Human babesiosis is not well known to many physicians, so it is difficult for them to come up with the diagnosis. Several patients have been identified with babesia infection; however, in China, few received standard treatment. In recent years, the number of human babesiosis cases in China has been increasing, but relatively little importance is attached to the disease. In the present review, we summarize the reported human cases of babesiosis in China from 1993 until now, which we hope will provide practical information for clinicians, and which may help with diagnosis.

Etiology of human babesiosis

Among *Babesia* species, four phylogenetic clades can cause human infections. The first is *Babesia microti* and *B. microti*-like parasites, which mostly infect humans (Goethert 2003). The second clade consists of *Babesia duncani* and *B. duncani*-type parasites, which mainly infect dogs (Conrad et al. 2006; Kjemtrup and Conrad 2000). The third clade is composed of *Babesia divergens*, *B. divergens*-like parasites, and *Babesia venatorum*; the former two mainly infect cattle, and the latter mainly causes deer infection (Herwaldt et al. 2003; Jiang et al. 2015). These three clades are all small parasites (trophozoites found in erythrocytes that measure less than 3 μm); however, the third is also phylogenetically related to large babesia (trophozoites larger than 3 μm). The last clade comprises large babesia, such as *Babesia bovis* and *Babesia bigemina*, which mainly infect ungulates (Criado-Fornelio et al. 2003). Since the first human *B. divergens* infection was confirmed in the former Yugoslavia in 1956, increasing numbers of *B. divergens* and *B. microti* human infections have been reported worldwide, including in the America, Europe, Africa, and Asia (Gray et al. 2010; Hunfeld et al. 2008; Skrabalo and Deanovic 1957; Vannier and Krause 2012).

Babesia life cycle

Babesia has a complex lifecycle with developmental stages occurring both within the mammalian host and the tick vector (Fig. 1). One of its critical developmental steps initially takes place within mammalian host red blood cells, where babesia sporozoites attach to erythrocytes by docking onto glycosaminoglycans and sialoglycoproteins (Lobo et al. 2012; Yokoyama et al. 2006). There, they mature into trophozoites and pullulate to form merozoites. Upon leaving the erythrocytes, the progeny merozoites again invade new erythrocytes and thus an asexual growth cycle is formed (Kumar et al. 2004; Yokoyama et al. 2002). When ticks take blood meals from an infected mammalian host, the parasite enters the tick gut together with the blood in the form of gametocytes, which cannot be commonly found in human erythrocytes. Then, it completes its life cycle within tick vectors to enable effective transmission. In the tick gut, the parasites develop into gametes and fuse to form zygotes, which subsequently migrate across the tick gut barrier into the hemolymph via unknown mechanisms, where they mature into ookinetes (Liu and Bonnet 2014). Finally, they arrive at the salivary glands with the flow of hemolymph and become dormant sporoblasts (Karakashian et al. 1986). When the infected ticks feed on mammalian host, the sporoblasts become active and enter the host's bloodstream, which may result in a host babesia infection. Interestingly, humans are accidental hosts and are most commonly infected via bites of ixodid ticks, the predominant babesia vector. In addition, blood transfusions and trans-placental transmission can also play significant roles in the infection process (Spielman et al. 1985; Swanson et al. 2006).

Epidemiology of human babesiosis in China

According to the reported cases, *B. microti*, *B. venatorum*, and *B. divergens* are thought to be the main pathogens causing human babesiosis in China, including in Zhejiang, Yunnan, and Guangxi provinces (Table 1 and Fig. 2). It is asserted that the first Chinese case of babesiosis could happen in 1944 (Qu 2007); subsequently, antibody against *B. microti* was detected by serological test in Taiwan in the year of 1977 (Hsu and Cross 1977). No actual human babesiosis cases were reported, until two patients were diagnosed with non-identified babesiosis in China in 1993 and 2000 (Shi et al. 1996; Su et al. 2002).

Over the past 20 years, more than 100 patients from Zhejiang, Yunnan, and Guangxi provinces have contracted *B. microti* babesiosis; therefore, *B. microti* appears to be the dominant pathogen causing human babesiosis in China. The first confirmed human *B. microti* infection was reported in 2011 in Zhejiang province, and was confirmed with blood smears and PCR (Yao et al. 2012). *B. microti* has since been identified in ten patients residing along the China-Myanmar border in 2012 and 2013; interestingly, two patients were also co-infected with *Plasmodium* (Zhou et al. 2013). In 2013, it was reported that the positive *B. microti* infection rate in blood donors from Guangxi province was 2.53% (48/1900) (Wang et al. 2016). In addition, *B. microti* infection was also investigated in Guangxi province citizens, with a 33.6% (40/121) infection rate (Qiao et al. 2015). Moreover, two sporadic cases in southern Taiwan and Yunnan with an unknown species resembling *B. microti* infection were also reported (Shih et al. 1997; Wang and Huang 2014).

Babesia crassa-like, ranking only second to *B. microti*, is a novel pathogen that causes human babesiosis in Heilongjiang, China, during 2015 and 2016. Jia and colleagues recruited 1125 participants with a recent history of tick bites, and found 58 people were infested by *B. crassa*-like, among which, 27 were suspected cases for the subclinical symptoms (Jia et al. 2018). It is the first time to identify babesiosis caused by *B. crassa*-like pathogen in China.

B. venatorum is another pathogen that causes human babesiosis in China. Of 2912 individuals from Heilongjiang province who sought medical care after a tick bite, Jiang and colleagues reported that 48 people had contracted a *B. venatorum* infection. Among them, 32 were confirmed and 16 were probable cases (Jiang et al. 2015). An additional case of *B. venatorum* infection concerned an 8-year-old boy in

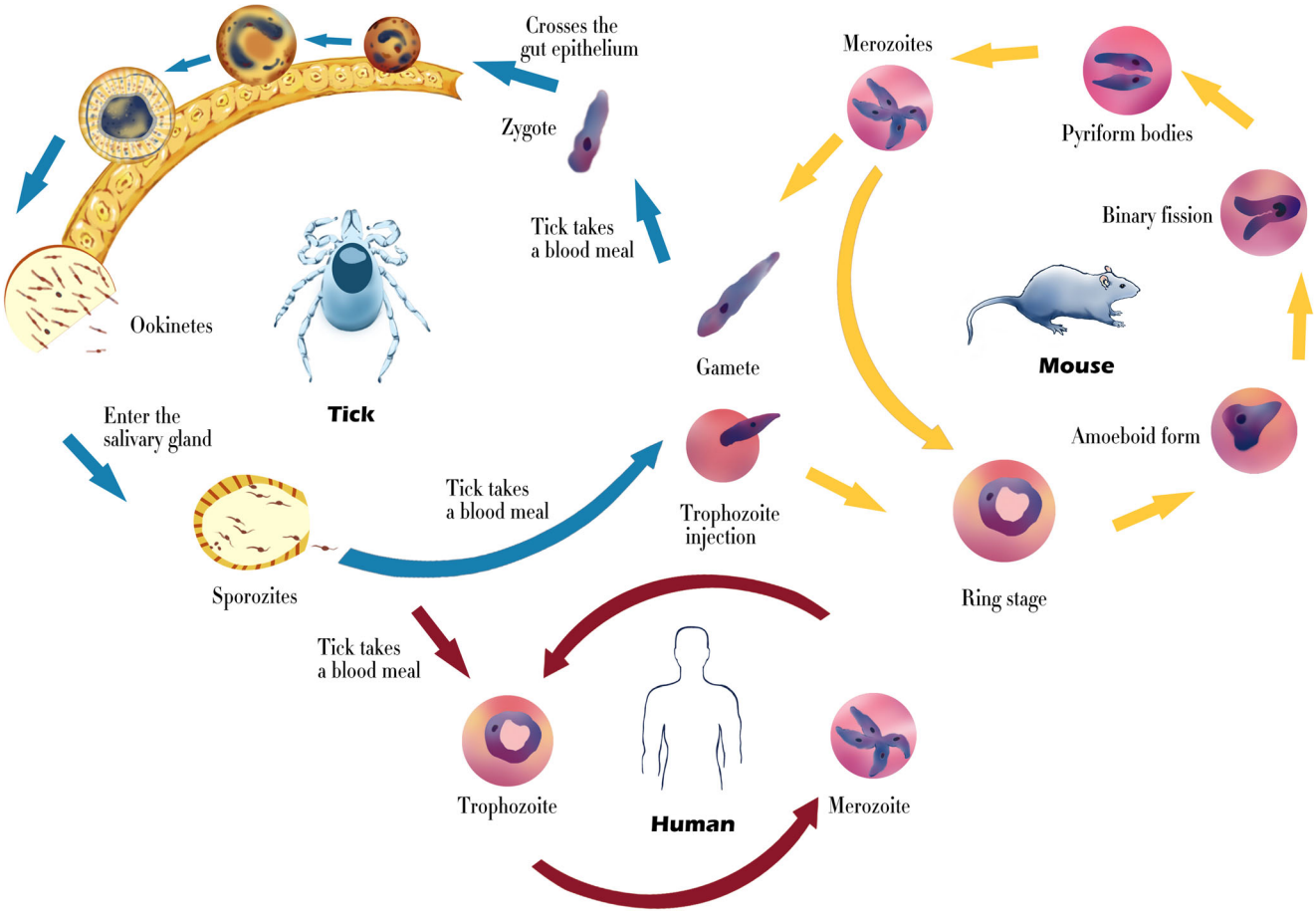

Fig. 1 A schematic diagram of human-infecting *Babesia* spp. life cycle

Xinjiang Uygur Autonomous Region, diagnosed using microscopy, PCR, and animal inoculation (Sun et al. 2014).

Thus far, *B. divergens* has been a rare cause of human babesiosis infection in China. Only two males from Shandong province have had a *B. divergens* infection, which was confirmed by PCR amplification and sequence analysis (Qi et al. 2011). In addition to the more common babesia species that can infect humans, a 42-year-old male in Hangzhou, Zhejiang province, was diagnosed with a novel babesia species infection in 2015, which was subsequently named *Babesia* sp. XXB/Hangzhou (Man et al. 2016).

A common geographical feature linking these widely distributed human babesiosis cases is abundant vegetation. The southern rural areas of Zhejiang and Guangxi have significant vegetative cover, the China-Myanmar border is hilly and extensively covered by primary and secondary rainforests, and Heilongjiang in northeastern China is a forested mountainous area (Jiang et al. 2015; Zhou et al. 2013), which all provide a natural habitat for ticks. In addition, most patients with babesiosis had a history of tick bite or blood transfusion (Jiang et al. 2015; Su et al. 2002; Yao et al. 2012; Zhou et al. 2013), consistent with the established human babesiosis transmission route.

Clinical manifestations of human babesiosis

Clinical symptoms do not manifest immediately after babesiosis infection, and the incubation period depends upon the infection route. Patients often present symptoms 1–4 weeks following a bite from an infected tick. Interestingly, the appearance of symptoms can take 1–9 weeks or longer when infection occurs via the transfusion of contaminated blood products (Vannier et al. 2008). Infected individuals often exhibit malaise and fatigue, followed by sporadic fever which is the most consistent and obvious symptom, and which can last 10 years with repetitive occurrences and/or reach 40.9 °C in some individuals (Man et al. 2016). Moreover, chills and sweats are also common symptoms, which can be accompanied by headache, myalgia, anorexia, cough, sore throat, arthralgia, and nausea (Krause et al. 1996b). Occasional symptoms such as breathing difficulties, eye redness, and dark-colored urine are also reported. However, these symptoms are non-specific and could be related to other similar diseases, resulting in unsuitable treatment (Reubush 2nd et al. 1977).

Parasitemia is the main laboratory finding in babesia-infected individuals, and can persist for several months

Table 1 Human babesiosis cases in China

Year	Species	Geographical location	Number	Technique employed	Potential transmission route	Gender	Age (years)	Drug regimens	Prognosis	Ref.
1993	*B.* sp.	Xilin Hot, IM	1	Microscopy	–	Male	39	Chloroquine	Uncertain	(Shi and Gao, 1996)
1994	*B. microti*-like	Southern TW	2[a]	Microscopy, IFA, inoculation	–	Female	51, –	Quinine, clindamycin, azithromycin	Recovered	(Shih et al. 1997)
2000	*B.* sp.	Hangzhou, ZJ	1	Microscopy	Blood transfusion	Male	36	Clindamycin	Recovered	(Su et al., 2002)
2009	*B. divergens*	Tai'an SD	2	PCR	–	Male	–	–	–	(Qi et al. 2011)
2010	*B. microti*-like	YN	1	Microscopy, IFA	Tick bites	Female	46	Artemether, azithromycin, clindamycin, atovaquone	Recovered	(Sun et al. 2014)
2011	*B. microti*	Southern ZJ	1	Microscopy, PCR	Blood transfusion, tick bites	Female	48	Artesunate, chloroquine phosphate, clindamycin	Recovered	(Yao et al. 2012)
2012–2013	*B. microti*	Tengchong, YN	10	Microscopy, PCR	Blood transfusion, tick bites	6 males	22–45	–	–	(Zhou et al. 2013)
2012	*B. venatorum*	Pishan, XJ	1	Microscopy, PCR, inoculation	Tick bites	Male	8	Azithromycin, atovaquone	Recovered	(Sun et al. 2014)
2011–2014	*B. venatorum*	HL	48[b]	PCR, microscopy, FISH, inoculation	Tick bites	–	0.6–75	13(4 Clindamycin, 8 benzylpenicillin, 5 cephalosporin)	Uncertain	(Jiang et al. 2015)
2015	*B.* sp. XXB/Hangzhou	Hangzhou, ZJ	1	Microscopy, PCR	–	Male	42	Azithromycin, doxycycline, moxifloxacin, atovaquone	Recovered	(Man et al. 2016)
2014	*B. microti*	GX	41[c]	Microscopy, PCR	–	–	–	–	–	(Qiao et al., 2015)
2013–2015	*B. microti*	GX	48	Microscopy, PCR, IFA	–	–	–	–	–	(Wang et al., 2016)
2015–2016	*B. crassa*-like	HL	58[d]	Microscopy, PCR	Tick bites	19 males	4–72	Benzylpenicillin, Cephalosporin, roxithromycin, doxycycline, clindamycin	Recovered	(Jia et al. 2018)

[a] One was asymptomatic

[b] 16 were probable cases

[c] 40 were asymptomatic

[d] 27 were suspected cases

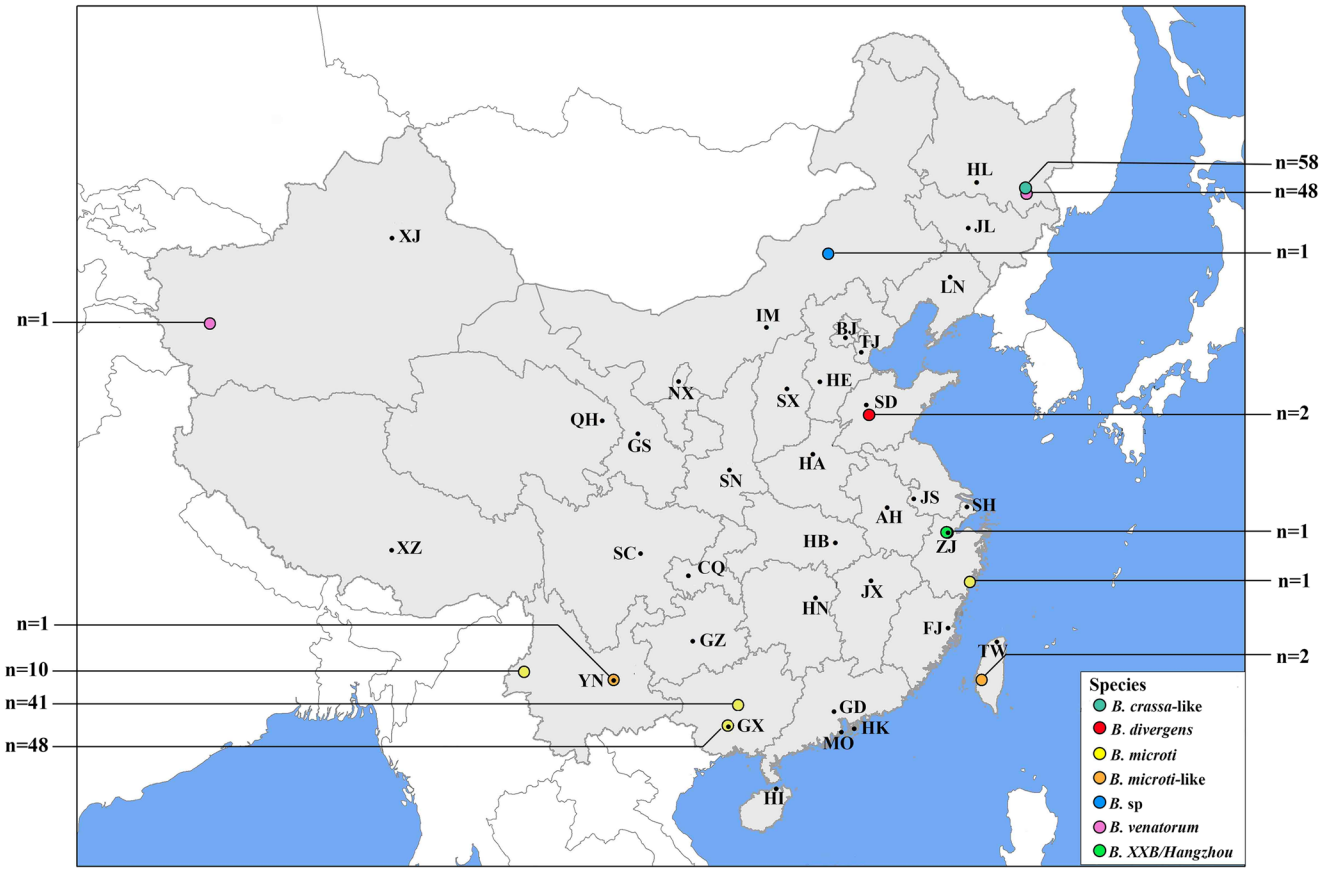

Fig. 2 The geographic distribution of reported human babesiosis cases in China

following the initiation of standard therapy in asymptomatic individuals, and may continue for more than a year in those who do not receive proper treatment. Additionally, parasitemia is often difficult to detect in immunocompetent patients (Martinot et al. 2011). In contrast, immunocompromised individuals, who have undergone splenectomy, been troubled by cancer or chronic liver or heart disease, and who have taken immunosuppressive drugs, always suffer from severe infection and present typical clinical symptoms such as high fever, high parasitemia, and severe anemia (Hunfeld et al. 2008). In addition, parasitemia is usually associated with hemolytic anemia, characterized by decreased hematocrit, low hemoglobin and haptoglobin levels, elevated reticulocyte count, and elevated lactate dehydrogenase levels (Joseph et al. 2011). Moreover, raised liver enzymes, variable leukocyte count, and thrombocytopenia are beneficial in facilitating the differentiation of babesiosis from other diseases that also cause fever (Vannier and Krause 2012).

Diagnosis of human babesiosis

Individuals with unexplained febrile illness who have settled in or traveled to areas with endemic babesiosis, or who have received a blood transfusion within the last 6 months, should be considered for a babesiosis diagnosis (Krause et al. 2002). Diagnostic methods mainly involve blood smear microscopy, parasite culture, serological tests, and molecular detection; their respective advantages and disadvantages are summarized in detail in Table 2.

Blood smear microscopy

Blood smear microscopy is the classic effective diagnostic method for human babesiosis. After Giemsa staining, parasites can be identified within erythrocytes as pleomorphic ring forms, such as round, oval, pear-shaped, amoeboid, and arranged in singles, pairs, or rarely in tetrads—termed as the "Maltese-cross appearance"—with light blue cytoplasm (Hildebrandt et al. 2013). Interestingly, infected erythrocytes remain normal size, and the cytoplasm of the ring form remains clear, especially in the infection of large babesia due to vacuole presence (Parija et al. 2015). The most pathognomonic characteristics of *B. microti* and *B. duncani* merozoites is the Maltese cross pattern, while *B. divergens* and *B. venatorum* merozoites typically appear as paired pear-shaped forms and only occasionally as tetrads (Conrad et al. 2006; Herwaldt et al. 2003). However, it is difficult to identify specific babesia species with blood smear microscopy (Hoare 1980). Parasitemia generally ranges from 1 to 10%, but can

Table 2 Advantages and disadvantages of babesiosis diagnosis techniques

Technique	Advantages	Disadvantages	Ref.
Microscopic evaluation	Easy and rapid	Possible misdiagnosis and unable to identify which species	(Parija et al. 2015)
Serological tests	Quantitative	Cross-reactivity may lead to incorrect results	(Hildebrandt et al. 2013)
Culture	Effective in identifying asymptomatic/low-parasitemic individuals and direct viewing	Requires more than a week and unable to detect some fastidious species	(Schuster 2002)
Polymerase chain reaction (PCR)	Sensitive and specific	Requires specialized techniques and reference laboratory	(Sanchez et al. 2016)

also reach 80% in severe infections. In the early stages of illness, parasitemia is often less than 1%, and parasites may not be noticed; thus, smears from serial blood collections must be investigated in at least 300 microscopic fields to avoid overlooking the parasite (Bruckner et al. 1985). *Babesia* spp. ring forms in erythrocytes are also quite similar to those of *Plasmodium* spp. and requires careful observation for correct identification. Compared to *Plasmodium*, babesia possesses pleomorphic ring forms in infected erythrocytes but lacks hemozoin pigments, identifiable gametocytes, and schizonts (Pruthi et al. 1995). Altogether, blood smear microscopy is the first step of diagnosis and additional evaluation should be performed to increase detection sensitivity and specificity.

Parasite culture

Parasite cultivation could be divided into two types including animal inoculation (in vivo) and artificial medium cultivation (in vitro). And cultivation has been used in the diagnosis of babesiosis in animals but not typically used for human babesia infections because it is time-consuming and unable to give precise results (Parija et al. 2015). However, cultivation can be helpful in the identification of asymptomatic/low-parasitemic individuals, defining phylogenetic relationships, and antimicrobial susceptibility testing. Following the appearance of visible parasitemia, the cultivation period usually takes 7–10 days by animal inoculation (Parija et al. 2015). Gerbils, splenectomized calves and hamsters, and SCID (severe combined immunodeficiency) mice have been used to detect the infection of *Babesia* spp., e.g., *B. duncani*, *B. divergens*, and *B. microti* (Bloch et al. 2012; Entrican et al. 1979; Wei et al. 2001). In addition, M199, NCTC-135, and RPMI 1640 supplied with various factors including HEPES and TES have also been used as medium for cultivation of *Babesia* spp., e.g., *B. bigemina*, *B. bovis*, and *B. divergens* (Erp et al. 1980; Grande et al. 1997; Levy and Ristic 1980; Vega et al. 1985). Interestingly, *B. microti* can only be cultured in vitro for short term and not applicable for diagnostic purposes (Shikano et al. 1995).

Serological tests

Serological tests are also widely used to examine asymptomatic or low-parasitema blood donors who are infected by *Babesia* spp., and include immunofluorescence assays (IFA), enzyme linked immune-sorbent assay (ELISA), immunoblot, and immunochromatography (Hildebrandt et al. 2013). Although IFA is the gold standard for diagnosing babesia infection (Krause et al. 1996a), there is currently no universal antigen to enable screening for all babesia species that infect humans, and antigen cross-reactivity also exists between different *Babesia* species, and between *Babesia* spp. and other parasites (Hildebrandt et al. 2013). The closer the phylogenetic relationship, the more frequent the chance of non-specific cross-reactivity (Gabrielli et al. 2012). Hence, a seropositive result would indicate babesia infection, but would not be able to identify which species. It is worth noting that lowered antibody production states may provide a serologically negative escape hatch, especially in immunocompromised patients. False-negative test results can also be obtained in the early stages of *B. microti* and *B. venatorum* infection (Herwaldt et al. 2011; Hunfeld et al. 2008). Therefore, seronegative results may result in unsuitable treatment or delay appropriate antimicrobial therapy. Serological tests are thus unable to confirm the diagnosis under most circumstances due to no available universal antigen and the presence of false negatives; therefore, patients should undergo further investigation.

Molecular detection

Polymerase chain reaction (PCR) is one of the most common molecular detection methods and has been widely used in *Babesia* spp. phylogeny identification and epidemiology studies, and especially for discovering new babesia species (Hildebrandt et al. 2008; Johnson et al. 2012). PCR is more sensitive and specific for babesia detection than the above described methods (Krause 2003). Babesia PCR identification is often based on amplified 18S RNA, and the limits of pathogen identification are ~100 gene copies, equivalent to

approximately 5–10 parasites/μL (Bloch et al. 2013; Teal et al. 2012). PCR detection of babesia DNA strongly supports an active and therefore ongoing infection (Haselbarth et al. 2007; Krause et al. 1998). In the future, molecular detection will play an even greater role in *Babesia* spp. diagnosis.

Treatment of human babesiosis

Anti-babesia drugs

Two classical combinations of different drugs can effectively treat human babesiosis, including azithromycin in combination with atovaquone, and clindamycin combined with quinidine (Weiss 2002; Wormser et al. 2006). For immunocompetent patients with mild to moderate babesiosis symptoms, oral azithromycin and atovaquone is a good choice for fewer side effects, and is also effective for moderate to severe babesiosis (Kletsova et al. 2017; Krause et al. 2000). Clindamycin and quinidine is only recommended for patients with severe clinical manifestations, although it was traditionally the first choice for all degrees of babesiosis (Krause et al. 2000). It is noteworthy that in critical cases, clindamycin or azithromycin is more effective when administered intravenously instead of orally (Simonsen et al. 2011; Wormser et al. 2006). In severely immunocompromised patients who have undergone splenectomy or an immunocompromising therapy, the antimicrobial treatment regimen should persist for at least 6 weeks, and then continue for another 2 weeks after parasites are no longer apparent in blood smears (Krause et al. 2008; Ord and Lobo 2015). Atovaquone-proguanil or artesunate therapy could also be an option when prescribing a treatment course (Goo et al. 2010; Vyas et al. 2007). Unfortunately, the standard treatment course is seldom applied in China.

Blood transfusion

Exchange transfusion partially removes babesia-infected erythrocytes and reduces vasoactive elements such as cytokines or procoagulant substances in the circulation, which can improve symptoms (Krause 2003). Blood transfusion should be considered in individuals with severe babesiosis who are not reacting to various drug combinations, as well as in patients with high-grade parasitemia (≥ 10%), significant hemolysis, or who are in danger of renal, hepatic, or pulmonary injury (Wormser et al. 2006). Moreover, blood transfusion may contribute to rapid clinical improvement in severe and sudden cases (Dorman et al. 2000). Blood transfusion is an important adjuvant therapy when treating infants with babesiosis. Simonsen and colleagues suggested that double-volume exchange blood transfusion is necessary for premature infants suffering from fulminant babesiosis with nearly 20% parasitemia (Simonsen et al. 2011).

Prevention of human babesiosis

To prevent human babesiosis, two main pathways based on the *Babesia* spp. transmission route—tick bite and blood transfusion—should be considered. Tick bites are the most common cause of *Babesia* spp. infection; thus, to limit tick bite risk, it is necessary to reduce the amount of exposed skin when traveling to tick-infested areas (Piesman and Eisen 2008). Furthermore, applying DEET-containing tick repellent to the skin and impregnating protective clothing with acaricides are also worthwhile preventative measures (Appel et al. 2008).

Blood transfusion can also expose recipients to *Babesia* spp. infection risk. With the number of babesiosis cases increasing, it is vital to strengthen the supervision and management of blood sample screening tests. The Guangxi study which identified babesia in multiple blood donor samples is a potent reminder about blood sample safety (Wang et al. 2016). It is therefore imperative to implement rigorous standardized blood sample babesia detection procedures in blood banks.

Conclusion

Human babesiosis, an emerging tick-borne disease, poses a significant public health threat worldwide. In China, *B. microti*, *B. venatorum*, and *B. divergens* are thought to be the main pathogens causing human babesiosis, which are distributed in a variety of areas including Zhejiang, Yunnan, and Guangxi provinces. In the present review, we summarized the epidemiology of reported human babesiosis cases in China from 1993 until now. And we also review the babesia life cycle, manifestation, diagnosis, treatment, and prevention strategies, which provide suggestions for improved babesiosis control in China.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests

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