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Bovine Babesiosis: A Clinical Review

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ABSTRACT

Bovine babesiosis is a significant tick-borne disease of cattle, second only to trypanosomiasis among parasitic infections. Primarily caused by *Babesia bovis* and *Babesia bigemina*, and transmitted by *Rhipicephalus (Boophilus) microplus*, the disease leads to fever, anemia, hemoglobinuria, jaundice, and often death, with *B. bovis* being the most pathogenic. Diagnosis typically involves Giemsa-stained blood smears, though molecular and serological techniques are increasingly employed. Treatment includes imidocarb dipropionate and diminazene aceturate, while control strategies focus on vector management, chemotherapy, and vaccination. This review explores the disease's epidemiology, clinical features, pathogenesis, host factors, diagnostic approaches, and control challenges. It also emphasizes economic impact, public health relevance, one health perspectives, and integrated strategies for effective management.

Keywords: B*abesia*, Tick-Borne Disease, *Rhipicephalus*, Cattle Health, One Health.

INTRODUCTION

Bovine babesiosis is a tick-borne disease of cattle, caused by protozoan parasites belonging to the *Babesia* genus, within the order Piroplasmida and phylum Apicomplexa. *Babesia* species are among the most widespread blood parasites, second only to trypanosomes, and have a significant economic, medical, and veterinary impact worldwide [1-5]. Babesiosis is also referred to by several other names, including piroplasmosis, cattle fever, tick fever, Texas fever, and red water disease [5-7]. The most common *Babesia* species responsible for causing bovine babesiosis are *Babesia* bovis, *B. bigemina, B. divergens* and *B. major* [1,3-5]. Other *Babesia* species that can infect cattle include *B. major, B. ovata, B. occultans,* and *B. jakimovi* [3,5]. Babesiosis is characterized by high fever, rapid onset of hemolysis, and varying degrees of anemia [8], along with clinical signs such as increased heart and respiratory rates, inappetence, cessation of ruminal contractions, icterus, reduced

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milk production, and signs of weakness or lethargy [9]. In more severe cases, the disease may progress to emaciation, ataxia, profound hemolytic anemia, circulatory shock, and respiratory distress due to sequestration of infected red blood cells in cerebral capillaries [6].

Babesia *bovis* and *B. bigemina* are the most common and important species in tropical and subtropical areas of the world, respectively [4]. The disease poses a considerable threat to cattle production, particularly affecting adult animals with low immunity rather than young calves.

THE OVERALL PREVALENCE

Babesia bovis and *B. bigemina* are prevalent in regions such as Asia, Africa, Southern Europe, and the Americas, with both species being particularly common in Asia and *B. bigemina* more widespread in Africa [9,10]. This disease poses significant economic, medical, and veterinary challenges, being highly lethal and leading to considerable financial losses for farms, especially due to the high mortality rates associated with these species [5,11]. The economic impact is most pronounced in areas where tick populations are susceptible to fluctuations driven by environmental conditions, such as temperature, humidity, and rainfall, which influence tick activity and disease transmission dynamics [12,13]. The incidence of bovine babesiosis exhibits seasonal variation, with peaks occurring after the tick population reaches its maximum density [3]. Furthermore, the feeding behavior of adult ticks—shaped by environmental conditions—plays a critical role in disease transmission [14]. Two distinct seasonal infection peaks have been reported, from April to June and August to October, with nymphs, adults, and larvae contributing to transmission [15,16]. The global burden of bovine babesiosis threatens approximately half a billion cattle, leading to substantial losses, particularly among adult animals, resulting in higher mortality rates in infected livestock [11]. This disease significantly hinders the productivity of local livestock, especially dairy cattle, particularly those imported from *Babesia*-free regions [14].

Infection with *Babesia* divergens can cause anal sphincter spasms, leading to distinctive pipe-stem feces [17]. The virulence of different strains varies, with *B. bovis* generally exhibiting greater pathogenicity compared to *B. bigemina* and *B. divergens* [14]. Continuous exposure to pathogens in endemic regions helps maintain immunity, making clinical cases relatively rare among the general population, while newly introduced animals or those with insufficient early-life exposure are more susceptible [18,14].

Recent meta-analyses have highlighted the global prevalence of bovine babesiosis, with the highest incidence in South America (64%), followed by Australia (61%), North America (52%), Africa (27%), Europe (22%), and Asia (19%) [19]. The analysis also revealed an increase in prevalence from 23% during 2001–2009 to 25% during 2016–2019. Although this 2% rise may appear modest, some paper emphasized that it reflects a concerning trend, suggesting an expanding vector distribution and inadequate control measures, which could pose a growing threat to global cattle health if not addressed [19]. Subgroup analyses showed *B. bigemina* had the highest prevalence at 22%, followed closely by *B. bovis* at 20%, with lower prevalence rates for B. occultans (16%), *B. major* (15%), and *B. divergens* (12%) [5,19,20]. These findings further underscore the influence of environmental factors on disease spread, as suitable climatic conditions facilitate tick proliferation and subsequent outbreaks in susceptible hosts [21]. In Asia, the impact of bovine babesiosis is exacerbated by insufficient molecular identification tools, low clinical testing capabilities, and limited disease awareness, despite the presence of specific *Babesia* species responsible for infections in the region [14,22]. Notable pathogens in Asia include *Babesia microti* and *Babesia* sp. *KO1*, linked to infections in Japan, Korea, Taiwan, and mainland China. Recent research highlights the significant economic impact of babesiosis in Nepal [23]. However, comprehensive data on the prevalence of zoonotic babesiosis and its species distribution remains lacking, particularly in Asia [5,24] (Figure 1).

Figure 1. Geographical map showing the global prevalence (percentages) of bovine babesiosis according to a Meta-analysis [19].

VECTOR ECOLOGY AND SEASONAL VARIATION

Babesia divergens and *B. venatorum* are primarily harbored in cattle, roe deer, and other ruminants, while species like B. microti are commonly maintained by small mammals, including white-footed mice and cottontail rabbits [5,25]. *Babesia* species have a global presence, with geographic limitations dictated by the range of their specific tick vectors [26]. Tick populations tend to surge during hot weather or summer months due to increased temperatures [5]. Although these species often occupy overlapping areas, their vector preferences result in minor differences in their geographic distribution [27]. For instance, *Babesia bigemina* is more widely found than *B. bovis* in Asia [28]. In the past, *B. bigemina* and *B. bovis* were enzootic in much of the southern United States, but their presence is now restricted to a quarantine zone along the Mexican border [3,29].

EPIDEMIOLOGY

The epidemiology of babesiosis is influenced by a variety of factors, including the availability of susceptible hosts, competent tick vectors, and environmental conditions that support parasite transmission [3]. The primary vectors for *Babesia* species are *Rhipicephalus* (formerly *Boophilus*) ticks, found in regions between 32°N-30°S, including much of Asia [3,5]. In Europe, *Babesia* divergens is transmitted by *Ixodes ricinus*, which inhabits forests, shrubs, and woodlands and is found from Northern Scandinavia to the Mediterranean [9,14,26].

The severity of the disease in both wild and domestic animals is influenced by the host's immune status, strain virulence, infectious dose, and tick burden [5,24]. Adults are generally more susceptible to infection than calves, who are protected by maternal antibodies [30,31]. However, younger animals may still experience mild infections due to their immature immune responses, a phenomenon referred to as "inverse age resistance."

Risk factors for babesiosis include both intrinsic factors (such as age, breed, and stress) and extrinsic factors (such as climate and housing) [14,32]. Environmental conditions, such as humidity, temperature, and rainfall, significantly influence tick populations and disease transmission dynamics, with the disease typically peaking during spring and autumn due to increased tick activity [33-35].

Babesiosis is often maintained by subclinically infected cattle acting as reservoirs. The introduction of infected ticks into previously unaffected regions can lead to new outbreaks [3]. Morbidity and mortality rates vary based on regional differences in treatment availability, vaccine use, and prior exposure to the parasite [10].

HOST SUSCEPTIBILITY AND BREED RESISTANCE

Babesia bovis and *B. bigemina* are primarily found in cattle, the main reservoir hosts, but they also affect Water buffalo (*Bubalus bubalis*) and African buffalo (*Syncerus caffer*) [1,3,4]. Breeds of *Bos taurus* are generally more susceptible to babesiosis than *Bos indicus*, likely due to an evolutionary relationship with specific tick and *Babesia* species [14]. Native cattle (*Bos indicus*), particularly in Africa, exhibit

greater resistance due to their better adaptation to local climatic and feeding conditions and higher genetic diversity, including numerous allelomorphic genes [34,36]. In contrast, exotic and crossbreed cattle, developed for productivity and with more limited genetic variation, are more vulnerable, especially during summer when tick activity is high [5].

Susceptibility to *Babesia* spp. infection decreases with age, but the severity of clinical disease often increases due to reduced maternal antibody protection and declining innate immunity [1,4,5,14]. Calves born to immune mothers are temporarily protected for up to six months by maternal antibodies. However, young calves with poor antibody transfer and older or immunocompromised animals—particularly those under stress due to pregnancy or poor condition—remain highly vulnerable to infection [1,4,5].

Clinical bovine babesiosis is characterized by haemolysis of red blood cells, persistent fever, anaemia, and haemoglobinuria, which gives urine a reddish-brown colour—hence the common name "redwater" (Figure 2). The disease causes high mortality and morbidity in susceptible livestock, especially in exotic and crossbreed cattle [29].

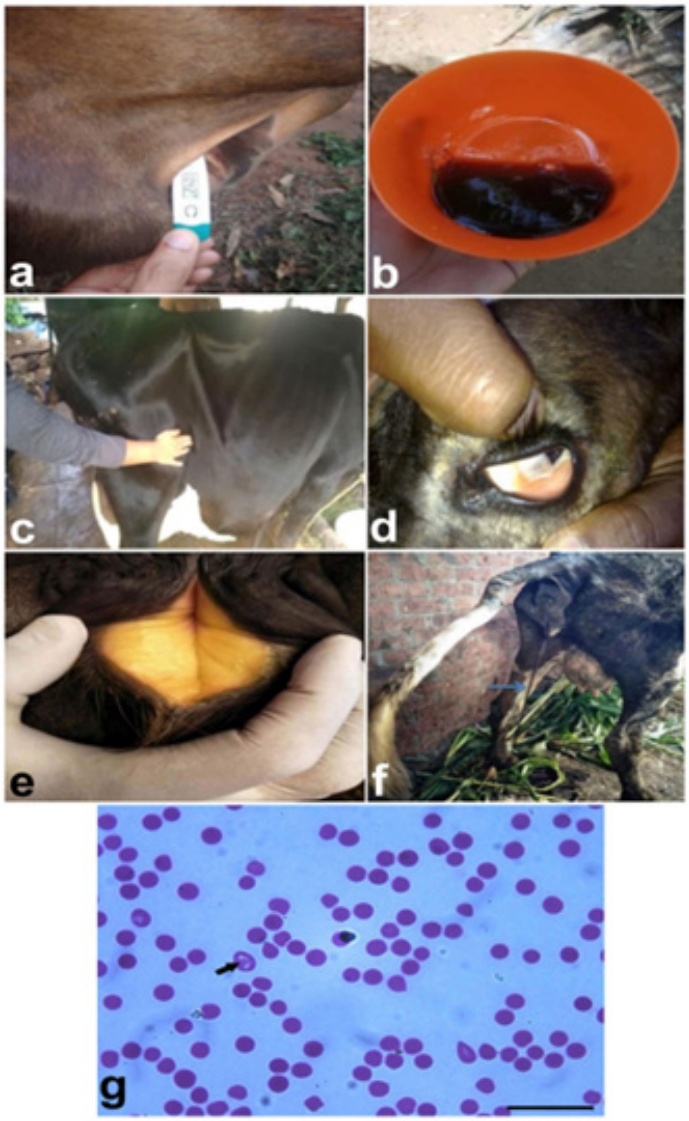

Figure 2. Obvious clinical signs of bovine babesiosis. a) A cow elucidated a high fever (104.2 F). b) A characteristic coffee-colored urine. c) An Animal with a swollen lymph node. d) *Babesia bigemina*-infected animal with a pale mucous membrane (Hemaswathy, Selvam, & Sunilkumar, 2020). e) A cow showed icteric vaginal mucous membrane. F) A marked babesiosis with a dark red to brown-colored urine. g) Giemsa-stained blood film showing intra-erythrocytic *Babesia* species of clinically infected cattle showing large intra-erythrocytic double pyriform (pear-shaped) *Babesiabigemina* joined with an acute angle. Scale bar = 20 µm.

TRANSMISSION AND LIFE CYCLE

All *Babesia* species are naturally transmitted between animals through tick bites. Within ticks, infection can be passed from the female to her offspring via transovarial transmission (through the eggs), and maintained across life stages—egg to larva, to nymph, and adult—by transstadial transmission [1,5,9]. The principal vectors of *Babesia bovis* and *B. bigemina* are *Rhipicephalus* species. In contrast, *Ixodes ricinus* serves as the primary vector for *B. divergens* [37].

Babesia bigemina is commonly transmitted to animals younger than one year, whereas *B. bovis* tends to infect animals older than two years, with the highest infection rate seen in the 6–12-month age group [5]. Transmission of *Babesia bigemina* typically occurs via one-host ticks such as *Rhipicephalus annulatus* (formerly *Boophilus annulatus*), *R. microplus* (formerly *Boophilus microplus*), *R. geigyi, R. decoloratus,* and *R. evertsi. Babesia bovis* is primarily transmitted by *Rhipicephalus annulatus* and *R. microplus*. Besides tick transmission, babesiosis can also be spread between animals via biting flies or contaminated fomites carrying infected blood [9,37]. Subclinically infected cattle that have recovered from the disease play a key role in maintaining bovine babesiosis in endemic areas [5].

Both *Babesia bovis* and *B. bigemina* are transmitted transovarially by this one-host tick, with sporozoite development occurring in the salivary glands—at the larval stage for *B. bovis*, and at the nymphal and adult stages for *B. bigemina* [38]. Notably, *Babesia bovis* infection does not persist in *Rhipicephalus* microplus beyond the larval stage, while *B. bigemina* can be passed trans generationally, even when ticks feed on non-susceptible hosts [5].

During infection, *Babesia* sporozoites penetrate the erythrocyte membrane, initiating development and eventually producing two merozoites. The developmental stages of *Babesia* include trophozoites [39]. Gametocytes ingested by the tick in the host's blood develop into two populations of ray bodies in the tick's midgut [40]. These multiply and fuse into a zygote, which invades the tick's gut epithelial cells. The zygote develops into kinetes that escape into the hemolymph and infect multiple tissues, including the oocytes [4]. Inside the oocytes, secondary schizogony occurs, leading to transovarial transmission as larvae develop. Eventually, kinetes invade the salivary glands and transform into sporozoites. At this point, tick development often halts until a vertebrate host is infected [4] (Figure 3).

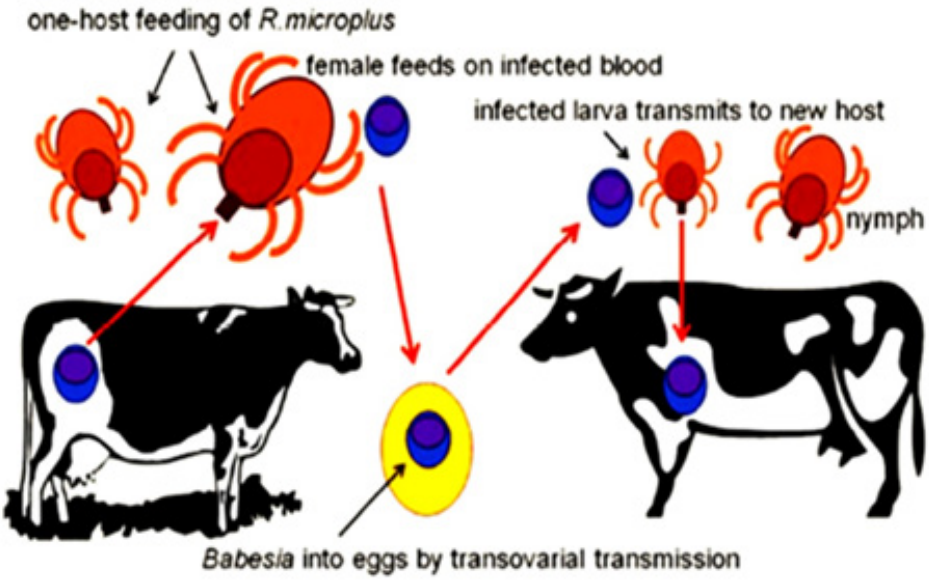

Figure 3. Transmission of *Babesia bovis* by the ixodid vector, *Phipicephalus Microplus* (Source: Joan Kleynhans).

PATHOGENESIS

In vertebrate hosts, *Babesia* spp. induce disease through direct erythrocyte damage and immune-mediated responses [40,41]. In acute infections, *Babesia bovis* is highly pathogenic due to proinflammatory cytokine release and erythrocyte destruction, causing immune-mediated hemolytic anemia [42]. This triggers macrophage activation and parasiticidal molecule release, leading to microcirculatory disruption, especially in renal and cerebral capillaries, and contributing to respiratory distress and cerebral babesiosis [9,43,44].

Host defense mechanisms involve intravascular hemolysis—resulting in hemoglobinemia, hypoxia, and anemia—and complement activation, leading to coagulation disturbances, electrolyte imbalances, and organ damage, notably in the liver and kidneys [45,46]. *Babesia bovis* targets visceral vessels and *B. bigemina* affects peripheral vessels, the latter producing visible hemolysis. Survivors may suffer ischemic damage, with chronic infections promoting vasoactive substance release, causing vasodilation and vascular leakage [47].

Severe *Babesia bovis* infections may lead to shock, disseminated intravascular coagulation, pulmonary thrombosis, and cerebral babesiosis, whereas *B. bigemina* primarily causes hemolysis without major vascular or coagulation effects [9,48]. Differences in biology also explain pathogenicity: *Babesia bovis* alters erythrocyte structure, causing cytoadhesion and sequestration in microvasculature—leading to cerebral involvement and multi-organ failure—while *B. bigemina* lacks these effects [49,50]. Moreover, *Babesia bovis* is transmitted by larvae and can cause acute disease with parasitemia as low as 1%, whereas *B. bigemina* requires over 10% parasitemia and is transmitted by nymphs [50] (Figure 4).

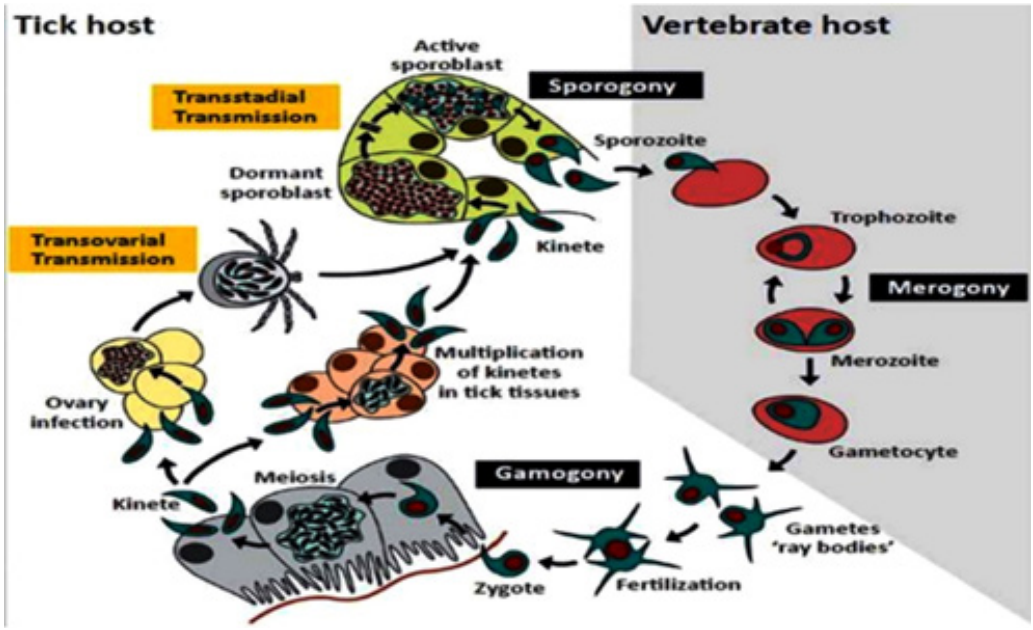

Figure 4. The life cycle of *Babesia* species [47].

CLINICAL SIGNS

The incubation period of bovine babesiosis ranges from 8 to 15 days, followed by varied clinical presentations [37]. Mortality can reach 60% in fully susceptible animals [1,4]. Clinical signs depend on age, species, parasite strain, host immunity, co-infections, genetics, and parasite dose [7,9]. While acute cases may present with severe symptoms, milder infections show intermittent parasitemia over 1–3 weeks. Calves under nine months often remain asymptomatic, likely due to maternal antibody protection [7], whereas older cattle exhibit more severe disease [4].

Classic clinical signs include hemoglobinuria (i.e., 'coffee-colored' urine), high fever, tachycardia, tachypnea, anorexia, and reduced rumen motility. Advanced stages may cause jaundice, emaciation, anemia, dyspnea, ocular issues, decreased milk yield, abortions, and reduced fertility [9]. In dairy cows, agalactia and abortion are often early signs. Mortality may reach 30% for *Babesia bigemina* and 70–80%

for *B. bovis* [29]. Anemia can develop rapidly, leading to pale mucous membranes, lethargy, and weakness [9].

Babesia bigemina typically causes anemia and hemoglobinuria without neurological involvement, while *B. bovis* can cause cerebral symptoms due to RBC aggregation in brain capillaries—resulting in incoordination, bruxism, and respiratory distress [51]. Though rare, *Babesia bigemina* and *B. divergens* may cause neurologic signs secondary to hypoxia from severe anemia [8,52]. *Babesia* divergens infections may also present with early "pipe-stem" diarrhea, later progressing to dehydration and recumbency [7,8]. Recovery from acute anemia usually occurs within a week, although weakness and poor body condition may persist.

Babesia bovis is generally more pathogenic than *B. bigemina*, often causing severe nervous signs and acute/subacute disease with rapid progression and high fatality [1,2,29]. *Babesia bigemina* causes disease at low parasitemia (<1%), while *B. bovis* often exceeds 10%, with RBC sequestration in cerebral vessels [29]. Animals recovering from acute babesiosis remain lifelong carriers, posing risks for reactivation under stress and ongoing transmission via ticks, making it a costly endemic disease [29] (Figure 5).

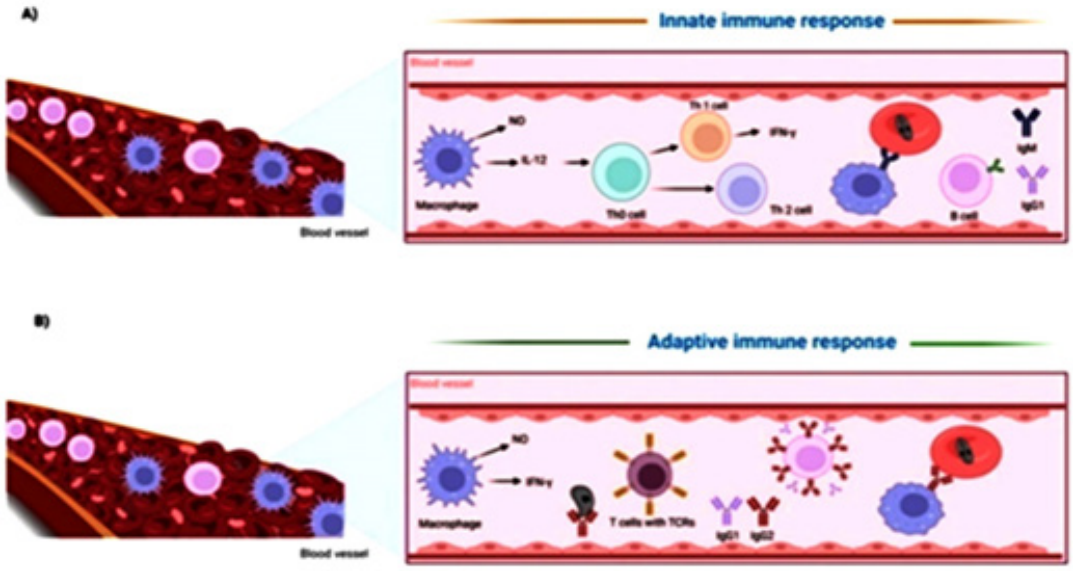

Figure 5. Schematic representation of protective immune responses in bovine infections with *Babesia* parasites. (A) This representation of innate immunity in young calves, characterized by the rapid activation of macrophages and a significant release of interferon-γ (IFN-γ) and nitric oxide (NO). Young, naïve calves exhibit greater natural resistance to infection and typically survive exposure to *Babesia*-infected ticks in endemic areas, a phenomenon referred to as pre-immunization. In contrast, adult cattle are more susceptible to *Babesia* infection and often develop acute and potentially fatal babesiosis. However, animals that survive acute infections may develop chronic babesiosis and establish lifelong protective immune responses. Additionally, innate immune responses are generally more robust in young animals compared to adults. (B) Representation of adaptive immunity observed in persistently infected or vaccinated animals, where macrophages and protective neutralizing antibodies play crucial roles in controlling parasitemia [49].

DIAGNOSIS

Several diagnostic and epidemiological techniques have been developed for bovine babesiosis, though diagnosis is often initially based on clinical signs, animal history, and seasonal occurrence [2]. Suspected cases can be confirmed via direct microscopic examination of blood smears, ideally from capillary blood at the ear or tail tip [1,4]. Thick and thin smears remain standard for detecting parasites in acute stages. In ticks, *Babesia* infection is identified through hemolymph and egg smears. For chronic or carrier animals—often showing low parasitemia and no hemoglobinuria—transmission tests can aid in confirmation [4].

Diagnosis of active babesiosis cases relies on the following major techniques:

Microscopic examination

The most common method for verifying tick fever is a microscopic examination of blood and organ smears from sick or dead animals [4]. This is accomplished by examining thick and thin films and then staining them with Giemsa or Romanovsky stain [7]. *Babesia bigemina* is commonly seen on Giemsa-stained thin blood smears in cases of acute infection. Detection is more likely with thick smears. While thick smears improve the chances of detecting the causative organism, they make identifying the characteristic morphology more difficult [4]. The best place to gather capillary blood is at the end of the tail. Organ smears, which can be made from animals that have been dead for up to 24 hours [4,53]. Microscopic examination is still the most cost-effective and time-efficient technique for identifying *Babesia* parasites. Giemsa-stained thin blood smears are the traditional and gold standard for identification and serve as an ideal method for species differentiation. It is adequate for detecting acute infections but has lower effects in cases of low parasitemia in carriers [7].

Serological examination

Since *Babesia* organisms often disappear or exist in very low numbers shortly after the acute phase, diagnosing chronic infections typically relies on serological tests to detect specific antibodies [4]. The Indirect Fluorescent Antibody Test (IFAT) and Enzyme-Linked Immunosorbent Assay (ELISA) are commonly used in subclinical cases to overcome the limitations of microscopy [7]. IFAT identifies antibodies to *Babesia bovis* and *B. bigemina*, while ELISA serves as a practical diagnostic and epidemiological tool, especially for screening large sample sets [4].

However, both methods have limitations. Their sensitivity is relatively low, and they often fail to distinguish between acute and chronic infections. Cross-reactive antibodies can lead to false-positive or false-negative results, and since antibodies can persist for months post-infection, these tests may not reflect active infection or current prevalence accurately [7].

Molecular diagnosis

Molecular diagnosis is used to identify nucleic acids which is considered as an indirect identification. However, both sensitivity and specificity are very high. The most sensitive and specific technique for the detection of babesiosis is Polymerase chain reaction (PCR) and useful for the detection of infection in the early stage [54]. It has been reported that the PCR technique is much more sensitive than microscopy for the identification of babesiosis. It is an important test for confirmation in some cases for regulatory testing [7].

Differential diagnosis

Differential diagnoses for bovine babesiosis include other hemoparasitic and systemic diseases, such as anaplasmosis, theileriosis, trypanosomiasis, leptospirosis, rapeseed poisoning, chronic copper poisoning, bacillary hemoglobinuria, post-parturient hemoglobinuria, and enzootic bovine pyelonephritis [7]. Additionally, it is essential to differentiate cerebral babesiosis from other central nervous system disorders, such as rabies and plant toxicosis, due to similarities in clinical presentation [4].

Immunity and Disease Resistance

Babesia bovis causes acute and often fatal infections in adult cattle, while animals that recover may remain persistently infected yet resistant to reinfection through a mechanism known as concomitant immunity [55]. Young calves are generally less susceptible to severe disease due to strong spleen-dependent innate immune responses that last for approximately six months after birth [56]. In contrast, protection in adult cattle relies on effective adaptive immune responses [57].

Mechanism of Innate Immunity

Innate immunity refers to non-specific defense mechanisms, which include factors such as host-parasite specificity, genetic traits, the age of the host, and the response of host cells—particularly the mononuclear phagocyte system and polymorphonuclear leukocytes [58]. The innate immune response to *Babesia bovis* has been partially characterized through studies examining the production of macrophage mediators in response to *B. bovis*-infected erythrocytes and merozoite components, with a focus on their role in inhibiting parasite growth and ensuring host survival [55]. Evidence suggests a transient role for nitric oxide in innate immunity, marked by brief induction of inducible nitric oxide synthase (iNOS) in the spleens of calves—a response absent in adult cattle [56]. In calves, iNOS expression follows early induction of interleukin (IL)-12 and interferon-gamma (IFN-γ), while in adults, IL-12 and IFN-γ expression is delayed and occurs only after IL-10 induction. Resistance to bovine babesiosis is associated with IFN-γ-mediated responses, where CD4+

T cells and macrophages serve as the primary effector cells responsible for pathogen clearance [55,56].

Mechanism of Acquired Immunity

Animals that are successfully immunized or survive the acute stage of infection and control parasitemia rely on antigen-specific CD4+ T cells producing IFN-γ. This cytokine is essential for macrophage activation, parasite clearance, and stimulation of IgG2 antibody production [55]. The persistence of *Babesia* infection in clinically recovered cattle is likely attributed to a matured immune response involving high-affinity antibodies and regulatory CD4+ and CD8+ T lymphocytes that suppress parasite replication. However, under stress or immunosuppressive conditions, this balance can be disrupted, potentially resulting in a resurgence of acute disease [49].

Treatment

Of the various methods of treatment, pharmacotherapy (treatment with drugs) is the most frequently used, cost-effective, and preferred method [59]. In endemic areas, sick animals should be treated as soon as possible with an antiparasitic drug. Chemotherapy plays an important role in controlling bovine babesiosis, and several drugs and combinations have been reported to be effective against the parasite [60,61]. In addition to chemotherapy, supportive treatment is also given, such as anti-inflammatory drugs, antihistamines, fluid therapy, and haematinics [62].

In European markets, three babesicides—quinuronium sulfate (Ludobal [Bayer Ltd.] and several generics), amicarbalide isethionate (Diampron; May and Baker Ltd.), and diminazene aceturate (Berenil, Hoechst Ltd.)—were in use for many years. With the introduction of imidocarb dipropionate (Imizol; Schering Plough), it rapidly became the product of choice in countries that licensed it, due to its therapeutic utility and its effective prophylactic use at twice the therapeutic dose [63]. However, subtherapeutic use of these drugs in cattle can result in the development of resistance, making them unresponsive to subsequent treatments with higher doses [64].

There is well-documented evidence of drug resistance development in *Babesia* species, which are intraerythrocytic parasites belonging to the Apicomplexa phylum [65]. Studies suggest that combining diminazene aceturate and imidocarb dipropionate could be an effective approach for treating bovine babesiosis, reducing the risks of resistance, and minimizing host toxicity that can occur with higher doses of these drugs [66].

CURRENT CONTROL METHODS

Vaccination

Vaccination of calves under one-year-old with attenuated live *Babesia* parasites is the primary strategy for controlling and preventing acute bovine babesiosis in endemic countries like Israel, Argentina, and Brazil [67]. Solid immunity develops after infection, which is utilized through live attenuated organisms as immunogens, providing durable immunity against heterologous challenges after a single vaccination. Advancements in production methods ensure compliance with good manufacturing practices, addressing concerns related to quality control, contamination risks, and antigenic drift [68].

In Australia, live attenuated vaccines are produced using splenectomized calves, while in South America, the successful in vitro culture of *Babesia* parasites has facilitated vaccine development [69]. Att-S74-T3Bo has shown promise as a sustainable candidate for controlling acute bovine babesiosis in highly susceptible adult cattle. Future studies should focus on expanding the vaccination cohort, assessing the duration of immunity, and evaluating its efficacy against heterologous virulent strains [70]. Studies on *Babesia bovis* proteins such as AMA-1, MSA-2c, and RAP-1 reveal that antibodies against these proteins have neutralizing effects, highlighting the role of B and T-cell epitopes in the immune response, with implications for vaccine development [71].

Live attenuated vaccines containing viable *Babesia*-infected red blood cells have limitations, including the risk of transmitting contaminating blood-borne pathogens and the potential for the parasite to revert to a virulent phenotype [57]. Despite advancements in genomics and proteomics, effective non-living vaccines are yet to be developed, requiring the continued use of live vaccines in tick and tick-borne disease control strategies tailored to regional conditions [72]. Vaccines using live *B. bovis* have not eliminated the parasite but instead created disease-resistant carriers that can serve as reservoirs for tick transmission [63].

While vaccination with live attenuated *Babesia* parasites remains crucial for controlling bovine babesiosis in endemic

regions, further research is needed to better understand cattle immune responses to *Babesia* bovis, particularly the roles of T cells and cytokines in protective immunity, to improve vaccine efficacy and safety [49].

Anti-tick control strategy

Acaricides, used for centuries to mitigate the harmful effects of ticks and tick-borne diseases on vertebrate hosts, are effective in controlling tick populations but have drawbacks such as contamination of animal products and environmental harm, making them a strategy for reducing or preventing tick infestations in susceptible hosts to combat babesiosis [73, 74, 75]. In addition to traditional acaricides, macrocyclic lactones and benzoylphenylureas, such as Ivermectin, Moxidectin, Doramectin, and difluorobenzoylurea (Fluazuron®), are effective alternatives for controlling *Rhipicephalus (Boophilus) microplus*, the primary vector of *Babesia* bovis, by disrupting tick development or targeting various endo- and ectoparasites, although concerns remain regarding their cost and potential residue in milk and meat [76].

The frequent use of acaricides, particularly those with similar modes of action, along with their misuse, has led to the emergence of resistant tick populations (Ticks and Acaricides Resistance – a Ticking Time Bomb for Livestock, WHO, n.d.). To enhance the effectiveness of tick control strategies against bovine babesiosis, an integrated approach that combines chemical treatments with biological control methods and sustainable practices is essential to minimize environmental impact and reduce the risk of resistance development [77].

CASE STUDIES AND CLINICAL REPORTS

A clinical case describes *Babesia bigemina* infection in a four-year-old crossbred cow, three months into lactation and kept at the ICAR Research Complex for the NEH Region in Umiam, Meghalaya. The cow exhibited clinical signs of high fever (106.4°F), hemoglobinuria, anorexia, reduced milk production, anemia, and diarrhea [78] Diagnosis was confirmed through Giemsa-stained blood smears and polymerase chain reaction (PCR) utilizing *Babesia bigemina*-specific primers, with the presence of *Boophilus microplus* ticks noted on the animal. Treatment with a single intramuscular injection of 4, 4' Diamidine diazoamine benzene diaceturate (Berenil) at 3.5 mg/kg body weight was effective, as the parasite was no longer detectable in both blood smears and PCR tests 48 hours post-treatment [78].

Another study on thirty crossbred female cows aged two to four years in Sherbeen city, Dakahlia Governorate, which presented with clinical signs of fever, anorexia, anemia, and red urine, confirmed the diagnosis of bovine babesiosis through microscopic examination of Giemsa-stained blood films and polymerase chain reaction (PCR) amplification targeting the 18S rRNA gene [79]. The study revealed significant hematological abnormalities, including decreased erythrocyte counts and hematocrit values, alongside biochemical changes such as elevated serum liver enzyme activities and increased bilirubin levels. Treatment using imidocarb dipropionate led to notable improvements in both clinical and laboratory parameters, highlighting the efficacy of molecular methods over traditional microscopy for diagnosing *Babesia bigemina* infections [79].

Four crossbred cows, aged 4–6 years, presented with symptoms such as fever, anorexia, dark urine, reduced milk production, depression, and reluctance to move. Clinical evaluation showed high temperatures (103°F–104.2°F), rapid heart and respiratory rates, breathing difficulty, halted rumination, and yellowish mucous membranes, alongside mild to moderate tick infestation, enlarged lymph nodes, and hemoglobinuria. Blood smears revealed *Babesia* spp. in 40% of red blood cells, and the hemogram indicated low levels of hemoglobin, packed cell volume, erythrocytes, and platelets. Serum analysis showed hyperglycemia, hyperbilirubinemia, elevated blood urea nitrogen, and aspartate aminotransferase, as well as hypoproteinemia. The coffee-colored urine tested positive for hemoglobin, glucose, and bile pigments. Treatment using diminazene aceturate (Berenil) at 3 mg/kg body weight, along with supportive care, proved effective for three cows, but one cow that was brought in later succumbed to severe anemia due to delayed treatment [80].

Economic impact

Bovine babesiosis is a global threat due to the significant economic losses it causes to the livestock industry in many countries [87]. In India, annual economic losses due to babesiosis are estimated at approximately 57.2 million USD [81], while in Tanzania, the figure stands at around 47.32 million USD [82]. Combined losses from bovine babesiosis and anaplasmosis are estimated at 16.9 million

USD in Australia, 21.6 million USD in South Africa, and 57.2 million USD in China [83, 84]. These losses encompass not only livestock mortality but also reduced milk and meat production, reproductive losses (such as abortions), diagnostic expenses, and increased costs for disease control measures like tick management, vaccination, and treatment [16].

One study estimated a direct annual milk loss of 0.81 million tons (0.43% of total production) due to bovine babesiosis, with the cost of acaricide application ranging from 2,883.05 to 12,108.79 million INR (37.13 to 155.97 million USD), averaging 7,207.49 million INR (92.95 million USD). The total leather damage loss was estimated at 7,141.74 million INR (92.10 million USD), with cattle contributing 5,386.13 million INR (69.49 million USD) and buffaloes 1,755.6 million INR (22.61 million USD) [84].

As a major initiative to control ticks, the U.S. Cattle Fever Tick Eradication Program (CFTEP), launched in 1906, aimed to eliminate bovine babesiosis and cattle fever ticks from the national herd. Since the U.S. was declared free of CFT and bovine babesiosis, the program has yielded estimated annual savings of at least 3 billion USD at today's currency rate [85].

Given the significant economic impact, effective control measures and continued research into prevention and treatment strategies are crucial for safeguarding animal health and ensuring the sustainability of livestock production systems worldwide.

Public Health Considerations

Babesia divergens, *B. microti*, and *B. venatorum* are the three primary *Babesia* species responsible for zoonotic babesiosis in many parts of the world [1]. *Babesia* divergens, which poses a major disease threat to cattle in Great Britain, can also cause severe illness in humans [87]. Approximately 40 cases of *Babesia* divergens infection have been reported in Europe, mostly among splenectomized individuals from cattle-farming regions such as France, Ireland, and Great Britain, with sporadic cases in other countries. Farmers and rural vacationers are the primary risk groups, as cattle serve as the main reservoir [87].

While most healthy adults experience mild to moderate illness, immunocompromised individuals—including those with cancer, HIV, without a spleen, on immunosuppressive drugs, or over the age of 50—are at the highest risk of developing severe disease [88]. Common symptoms include headache, chills, intense sweating, muscle pain, and abdominal discomfort. More than half of cases may rapidly progress to kidney failure and pulmonary edema. Severe manifestations such as bruising, petechiae, heart failure, coma, and even death or prolonged recovery have been reported in about one-third of patients [87].

some papers indicate diagnoses of babesiosis occurred from May to December, with a notable rise during summer and a peak in August and September (see Figure 6) [86]. In comparison, tick-borne fever showed earlier seasonality, with 64.3% (9/14) of diagnoses reported between May and July [32].

In conclusion, the rising incidence of *Babesia* divergens infections, especially among high-risk groups, highlights the urgent need for greater awareness and the implementation of preventive measures in both animal and human health sectors to manage this emerging zoonotic threat effectively (see Figure 6).

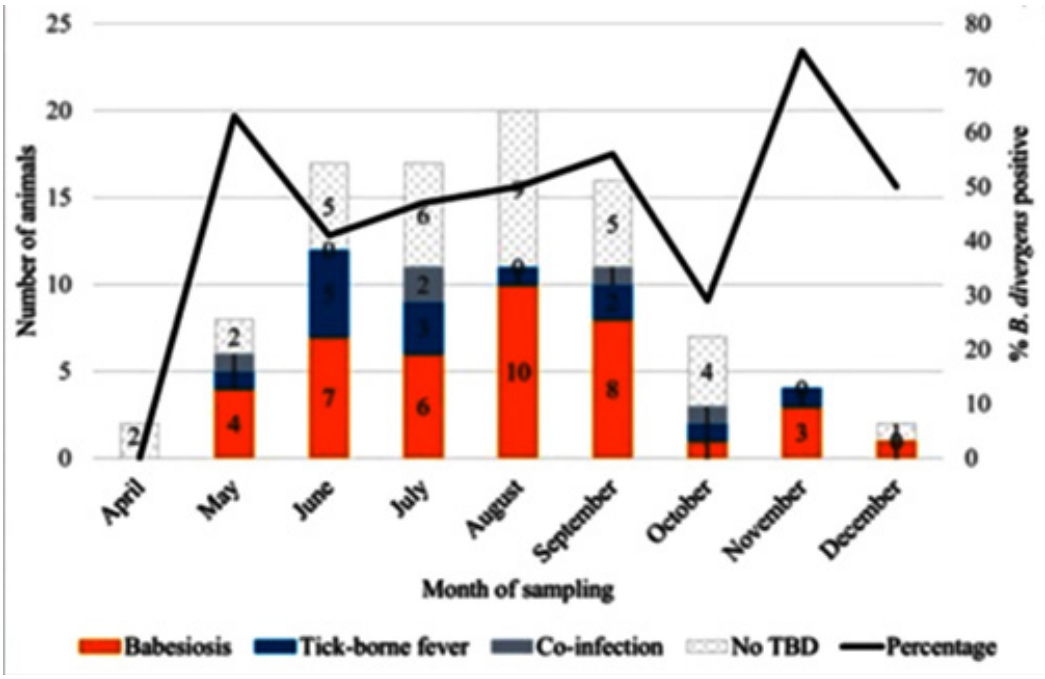

Figure 6. Seasonal distribution and frequency of diagnoses carried out in 95 sampled animals. Line represents proportion of total samples per month that tested positive for *Babesia* divergens [86].

Molecular toolkits and future research trends

Important advances in our understanding of *Babesia* biology can be directly and indirectly attributed to the sequencing of relevant *Babesia* spp. genomes, beginning with the publication of the first complete *B. bovis* genome in 2007 [89]. The recent adaptation of CRISPR/Cas9 genome editing in *B. bovis* has enhanced efforts to dissect the parasite's genome and improve our understanding of both its erythrocytic and tick stages. Additionally, the glmS ribozyme system offers a conditional knockdown approach for studying essential genes [90].

The ves1 gene family, which is large and antigenically variable, plays an important role in host immune evasion. Genomic advances have enabled complete characterization of this gene family and other critical genes involved in the parasite's sexual development [91].

The use of "omic" techniques, such as transcriptomics, has facilitated comparisons between virulent and attenuated *Babesia* spp. strains to identify virulence factors and attenuation markers. These approaches also help identify peptides presented by major histocompatibility complex (MHC) class II molecules to CD4+ T cells and detect differentially expressed genes throughout the parasite's life cycle, thereby aiding in the discovery of novel vaccine targets [49].

A deeper understanding of the mechanisms behind strong innate immunity in young animals is crucial for adjuvant selection and vaccine design [92]. This knowledge helps induce effective immune responses to control parasitemia while minimizing the risk of excessive inflammation caused by overproduction of soluble mediators. Therefore, evaluating protective immune mechanisms—such as the spleen-mediated clearance of infected red blood cells (iRBCs) and maintaining a balanced type 1 immune response—is essential for the development of effective subunit vaccines [93].

Overall, these advancements and ongoing research efforts offer promising avenues for developing effective vaccines and control strategies against *Babesia* infections in livestock.

CONCLUSION

Bovine babesiosis remains a critical threat to cattle health and productivity, particularly in tropical and subtropical regions where tick vectors thrive. The disease imposes substantial economic losses through decreased milk yield, reproductive failures, and treatment costs. While conventional diagnostic tools and chemotherapeutics remain central to disease management, the growing challenge of acaricide resistance

and limitations of current vaccines demand innovative and sustainable control measures. Future efforts should focus on advancing molecular diagnostics, developing safer and more effective vaccines, and implementing integrated vector management strategies. Adopting a One Health framework that bridges veterinary, environmental, and human health perspectives is essential for comprehensive disease surveillance and control. Continued research into host immunity, pathogen biology, and climate-driven vector dynamics will be key to mitigating the global impact of this zoonotic and economically significant disease.

ANIMAL ETHICS

This work involves no direct experimentation on animals. All clinical cases reviewed in the manuscript were managed in compliance with ethical veterinary practices and under the supervision of licensed veterinarians. Hence, it is not applicable.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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