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Review Article

Bovine Babesiosis; Review on its global prevalence and anticipatory control for one health

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ABSTRACT

Babesiosis is a fatal tick-borne disease infecting animals and humans, worldwide. The cattle industry is enormously affected and facing huge economic losses. *Babesia (B.) bovis* and *B. bigemina* are the common species that are responsible for babesiosis in bovines. The major vectors for *B. bovis* and *B. bigemina* are *Rhipicephalus* (*Boophilus*) species. The two major mechanisms i.e., circulatory disturbance and hemolysis are involved in causing the acute disease produced by *Babesia* species. Infected animals show a rise in body temperature, anorexia, difficulty in breathing, weakness, anemia, and jaundice. As it is a tick-borne disease, the complex relationship between causative agent, host, and vector has hindered the process of vaccine manufacturing regarding bovine babesiosis. Human babesiosis is another emerging issue that needs to be controlled. Keeping in view the drastic changes in environment is fetching increase in vector growth of ticks to spread babesiosis. This review reveals the drastic increase in the global prevalence of this disease and shows the dire need of designing effective strategies and early diagnostic methods to alleviate this disease. This disease needs proper measures to be controlled properly for the sake of one health.

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Introduction

Babesiosis is caused by intra-erythrocytic parasites of the genus *Babesia* (Hunfeld et al. 2008; Bajer et al. 2022). They are Apicomplexan protozoan parasites that belong to the suborder Piroplasmida and family Babesiadae (Sahinduran 2012; Jacob et al. 2020). The disease is also named as piroplasmosis, Texas cattle fever, Red-water, and Nantucket Tick fever around the world (Sahinduran 2012; Ozubek et al. 2020). It is considered as one of the most significant tick-borne diseases of mammals and is widely distributed among animals. It is the second most common blood-borne parasitic disease next to trypanosomiasis (Hamsho et al. 2015). The spread of disease depends on the transportation of animals and the habitat of ticks in different areas (Taylor 2014). There are six species of *Babesia* viz *Babesia (B.)*

divergens, *B. bigemina*, *B. major*, *B. argentina*, *B. bovis* and *B. occultans* but the most pathogenic is *B. bovis* while *B. bigemina* being the most prevalent one (Ibrahim et al. 2013; Elsify et al. 2015). Babesiosis is a disease with global prevalence infecting many mammalian species (Bock et al. 2004; Waked and Krause 2022) and has major economic effects on the cattle industry because of the two most important species in cattle; *B. bovis* and *B. bigemina* (Zintl et al. 2014). Among two species, *B. bigemina* causes less severe disease in cattle as compared to *B. bovis* (Bock et al. 2004). Another common specie often found in cattle is *B. divergens*. Generally, *B. bovis*, *B. bigemina* and *B. divergens* are the major well studied species that affect the cattle industry (Bock et al. 2004). Another study shows the discovery of one more spp. of *Babesia* named as *B. mymensingh* which can cause clinical disease in cattle (Taylor 2014). Additional species that can infect cattle include *B. major, B. ovata, B. occultans,* and *B. jakimovi*. All these strains of genus *Babesia* are species-specific and demand optimum conditions for their spread along with requiring the same vector i.e., ticks. *B. ovis* and *B. motasi* are known to be pathogenic agents in sheep and goats, respectively (Fakhar et al. 2012). These Babesia species affect almost all kind of vertebrate hosts and ultimately spread to the humans in result of zoonotic infections (Waked and Krause 2022).

Morphologically, *B. bovis* is found in the center of the erythrocyte and has a small size of 1-1.5µm long and 0.5-1.0µm wide. On the other hand, *B. bigemina* is long and has a size of 3.5µm long and 1-1.5µm wide, pear-shaped, paired in structure, and has two red dots in it (Mohammed and Elshahawy 2017). *B. divergens* is considered the major causative agent of bovine babesiosis in European states. Domestic babesiosis is an offensive and notorious disease of humans and animals due to the secretion of enzymes from micronemes facilitating the parasite to enter the host cells (Ozubek et al. 2020). Practically, it was observed that first case of cattle mortality due to bovine babesiosis caused by the *B. bovis*.

The first case of babesiosis was reported by Viktor Babes in 1888 when he observed the presence of round bodies within the erythrocytes in the blood of the infected cattle. In 1893, Kilborne and Smith described a factor of Texas cattle fever, by giving them the ample of genus and name *Babesia* as categorizing them as Protozoans (Kjemtrup and Conrad 2000). Parasites of the genus *Babesia* poison a wide diversity of wild mammals as well as man. *Babesia* species can be classified based on their morphology, tick prevalence, and significant symptoms that appear in the affected hosts (Jongejan et al. 2015). *Ixodes (I.) ricinus* (sheep or castor bean tick), which is present abundantly in Europe, majorly transmits *B. divergens*. However, *I. persulcatus* possibly transmit the Asian lineage of *B. divergens* (Zamoto-Niikura et al. 2018). Both of these species require three hosts and need 3-6 years in order to complete their life cycle (Sirotkin and Korenberg 2018).

Babesiosis has been a cause of huge economic losses to the dairy industry worldwide (Perez de Leon et al. 2010). In tropical and subtropical regions, bovine babesiosis is an important and wide spreading disease of cattle with major economic, medical, and veterinary impacts. Babesiosis is a very lethal disease and if enters the premises it can destroy the farms leading to huge economic losses.

Prevalence and Clinical Picture of Babesiosis:

Risking half a billion cattle around the world, bovine babesiosis causes the most serious economic loss to the livestock industry. The disease has the worst effects in the livestock industry in terms of affecting adult animals at production rather than the young, leading to the death of infected ones (Onoja et al. 2013). This disease is also a barrier to increase the productivity of local livestock due to the high mortality rate, specifically dairy cattle, which are imported from Babesia-free areas.

Being ahaemo-protozoan and host-specific disease, babesiosis is characterized by anemia, hemoglobinuria, progressive emaciation, icterus, and death mostly in the large ruminants of exotic origin and is prevalent in tropical countries of the world (Yusuf 2017). The infection of *B. divergens* can lead to the spasms of the anal sphincter leading to the passage of pipe stem feces. Whereas the major pathological factor includes virulence of strains and antigenic variations among the strains. Strains differ in pathogenicity but, *B. bigemina* and *B. divergens* are generally less virulent than *B. bovis* (Zintl et al. 2003). The repetitive contact with pathogens sustains the immunity and the ratio of clinical cases is really low in endemic areas and mostly the immune-deficient animals are being affected that are newly introduced or lack exposure to pasture in the early life years (Zintl et al. 2003). Immune compromised animals can be more prone to babesiosis.

Recently, a meta-analysis and systemic review on the global prevalence of bovine babesiosis was carried out by Jacob et al. (2020) which included a total of 163 relevant studies from 63 different countries with a total number of 81099 samples. After conducting a continent-wise analysis, the results revealed that the highest prevalence of bovine babesiosis is reported in South America (64%). However, the prevalence was 61% in Australia, 52% in North America, 27% in Africa, 22 % in Europe, and the least was 19% in Asia. The continent-wise analysis of the prevalence of bovine babesiosis is represented with the help of a heat map in Fig. 1. While analyzing the pooled prevalence, Jacob et al. (2002) found that it was higher (56%) during the period of 1967-2000 with 33 number of studies in comparison to the period 2001-2009 in which the prevalence was lower (23%) with 132 number of studies. But a rise in the prevalence of bovine babesiosis (25%) was observed during the analysis of the period 2016-2019, which is a warning bell for the cattle population in the near future. Based on the *Babesia* species, Jacob et al. (2002) also carried out subgroup analysis for estimating the prevalence of individual species and found *B. bigemina* to have the highest prevalence that was 22%, while *B. bovis* having 20%, *B. occultans* having 16%, *B. major* having 15%, and *B. divergens* with the lowest prevalence of 12% as shown in Fig 1. It can be deduced from the above data that environmental influence could be the reason for spread of disease. At different temperature and under suitable climatic conditions, ticks will grow and cause disease in susceptible animals. In Asian region due to harsh conditions, the spread rate could be lower than cold regions.

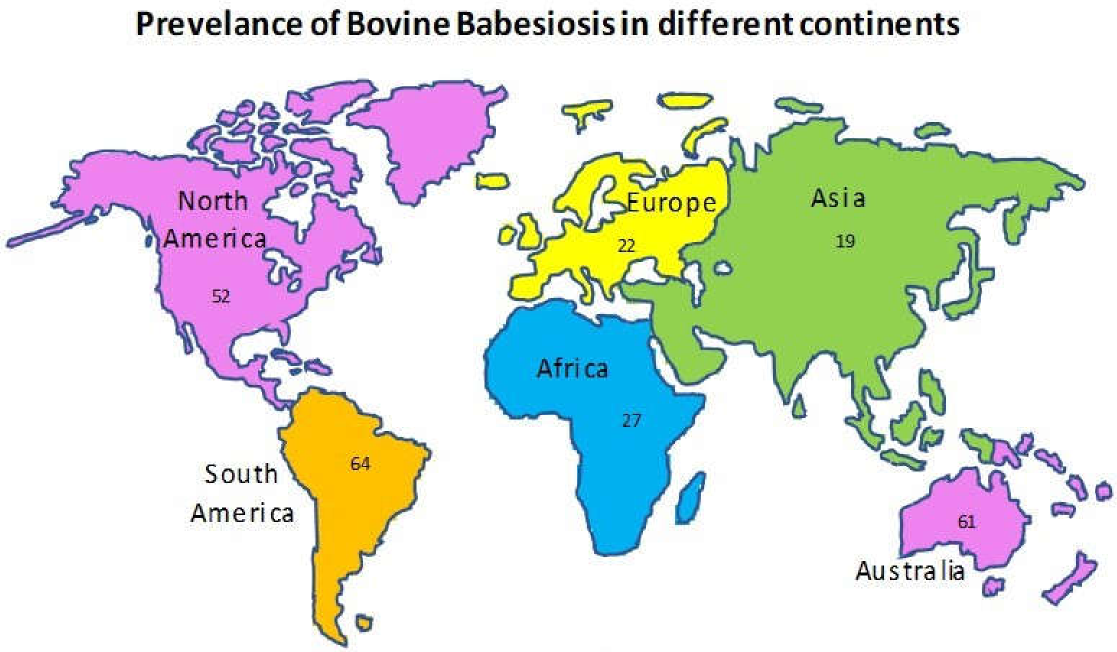

Fig. 1: Geographical map showing the prevalence of bovine babesiosis in different continents according to a metanalysis (Jacob et al. 2020)

Factors associated with clinical Babesiosis

There are two major factors associated with clinical babesiosis.

Factors that affect the infection carried by ticks

Ticks pick up the pathogen or acquire the *Babesia* infection while feeding on the blood of the infected animal. The parasite then moves into their eggs and molt into larvae. Approximately, 2000 eggs are laid by adult ticks which after shedding, hatch into larvae (Perez de Leon et al. 2010). Then larvae go to the second host (small mammals) and start developing into the nymphal stage, again shed by the host and become adults (Perez de Leon et al. 2010). The life cycle of *Babesia* is completed when the adult goes to the bovine host.

The feeding behavior of adult ticks plays a significant role in spreading the infection which may change due to unfavorable conditions i.e., <80% humidity, suitable temperature and tick season. Babesiosis has two seasonal peaks as the first one appears between April-June and the second one between August-October (Mohamed and Ebied 2014). In spring, nymphal and adult ticks actively participate in spreading the disease, while in autumn, nymphal and adults those fed in last autumn got engorged in winters and play their part in causing disease. However, in autumn and spring, the infection is spread by the larvae of the ticks (Andrews et al. 2003).

Factors that affect the immunity in animals

Calves are immune against the babesiosis till the age of 9 months and may remain immune if exposed to infection previously. That immunity can be considered as the innate immunity from the dam. Uninfected animals become more susceptible to babesial infection later. In older animals, immunity is maintained by continuous exposure to disease (Faryal et al. 2015). Babesiosis has no lifelong immunity, rough grazing behavior in native animals becomes the significant factor to expose them to the infection (Andrews et al. 2003; Zintl et al. 2003).

Epidemiology of babesiosis

Historically, the first person to detect *Babesia* and *Theileria* in cattle blood was Victor Babes who in 1888, observed disease outbreaks with the common findings of hemoglobinuria in cattle in Romania. After Victors' observation, Smith and Kilborne in 1893 revealed that *Rhipicephalus annulatus* was the vector for transmitting *B. bigemina* (Smith and Kilborne 1893). The name *Piroplasma divergens* was given to *B. divergens* by M'Fadyean and Stockman (1911) when they discovered it in the blood samples of cattle. The first case of human babesiosis was confirmed and reported in 1956 by Agoulon et al. (2012), which showed the zoonotic importance of bovine babesiosis while the contributing agent was *B. divergens*.

Bovine babesiosis occurs significantly in tropical and sub-tropical regions. The geographical and environmental conditions favoring the presence of tick vectors are directly responsible for the dissemination of causative agents (Radostits et al. 2007). The occurrence of bovine babesiosis is directly related to the presence of ticks in any area. In prevalent areas, the importance is affected as the quality of cattle remains low in numbers, so inhibiting the comfort of farmers and the growth of the livestock industry (Mosqueda et al. 2012). *Babesia* is distributed globally (Fakhar et al. 2012), however, bovine babesiosis is present in the areas populated with tick vectors and is more prevalent in the subtropical and tropical areas (Esmaeilnejad et al. 2015). The increase in the temperature leads to profound increase in the population of ticks during high temperature or summer season (Mohamed and Ebied 2014). During the past years, a remarkable change in the epidemiology of *B. divergens* in Europe is seen with a noticeable reduction in the occurrence of disease in Norway (Hasle et al. 2010), Ireland (Zintl et al. 2014), and Hungary (Hornok et al. 2006). *B. bovis* and *B. bigemina* are present remarkably in Asia, Africa, Central and South America, Southern Europe, and Austria. Table 1 shows the distribution of Babesia species in different regions of world.

Table 1: Distribution of Babesia species in different regions of world

Babesia spp.	**Domestic spp. affected**	**Major tick vector**	**Geographical distribution**	**References**
Babesia bovis	Buffalo and Cattle	*Boophilus annulatus, Boophilus microplus,* and *Boophilus geigyi*	Asia, Australia, Southern Europe, Central and South America, Africa but it is less prevalent in Africa	Criado-Fornelioet al. 2003; Silva et al. 2009
Babesia bigemina	Buffalo and Cattle	*Boophilus geigyi, Boophilus microplus, Boophilus decoloratus,* and *Boophilus annulatus*	Africa, Asia, Central and South America, Australia, and Southern Europe	Altay et al. 2008
Babesia major	Cattle	*Haemaphysalis punctate*	Asia, Africa, Europe, and Northwest Africa	I'Hostis & Seegers. 2002; Zintl et al. 2003
Babesia divergens	Cattle	*Ixodes persulcatus* and *Ixodes ricinus*	Great Britain, North-west Europe, Spain, Ireland	L'Hostis & Chauvin. 1999; Zintl et al.2003; Edelhofer et al. 2004

Considering prevalence of Babesiosis in different continents, *B. bigemina* is referred to as African red water while *B. bovis*is named as Asiatic red water. Most of the areas of the world are affected due to the presence of *B. bigemina* and *B. bovis* but the incidence is greatest in areas where the tick vector of spp. *Rhipicephalus* is commonly found. Generally, the geographical distribution of *B. bigemina* and *B. bovis*is on similar lines. However, the *B. bovis*is less distributed in Africa as compared to *B. bigemina* linked with presence of tick vectors; *Rhipicephalus evertsi* and *Rhipicephalus decoloratus*.

The species *Rhipicephalus*, formerly known as *Boophilus*, includes *R. microplus* and *R. annulatus*, while *R. decoloratus* the other one is playing role in the transmission of *B. bigemina* (Zintl et al. 2003). *B. divergens* is widespread in central and northern Europe, northern Africa, Great Britain, and Ireland (L'Hostis and Chauvin1999; Edelhofer et al. 2004) with *I. ricinus* acting as a vector (Fitzpatrick *et al.* 1968). Due to the low pathogenicity of *B. major*, it is less frequently reported and is found in some European countries (Hostis and Seegers 2002; Zintl et al. 2003; García-Sanmartín et al. 2006).

Risk factors associated with clinical Babesiosis

There have been intrinsic and extrinsic risk factors recorded in case of babesiosis studies. The major host factors responsible for babesiosis including breed, age, stress are the intrinsic factors and all other factors in the form of housing and environmental are considered as the extrinsic factors (Florin-Christensen et al. 2014). The clinical signs and symptoms in infected organisms are shown after an incubation period of 2-3 weeks. Older animals are mostly affected whereas; calves younger than 6 months are rarely affected. *Bos taurus* breeds of cattle are less resistant to babesiosis than the *Bos indicus* breeds. This is a consequence of the evolutionary association between *Bos indicus* cattle, *Boophilus* and *Babesia* species. The above-mentioned parameters are very important to reduce the risk of disease among animals (Radostits et al. 2007; Jabbar et al. 2015).

Older animals are more likely to get *Babesia* infection than young animals because of the inactive transfer of parental antibodies through colostrum in the young ones. The factor of age is the main cause of the increase in the severity of babesiosis (Taylor et al. 2007). Depending on the environmental circumstances, where the tick population is highly mutable, the heaviest losses occur in marginal areas. Clinical cases of diseases are transmitted most rapidly in the season suitable for ticks and are mostly reported in spring and autumn (Jongejan et al. 2015). The other environmental factors affecting the prevalence of babesiosis are humidity, rainfall, and temperature and this is the reason for the seasonal variation in the prevalence of babesiosis (Donnelly and MacKellar1970). Highest prevalence of babesiosis is usually reported during summer season. The higher the temperature, the higher was the tick population and as a result, there isa significant increase in the risk of disease prevalence (Mohamed and Ebied 2014). The bimodal pattern is generally observed in most of the cases of bovine babesiosis in which the peak seasons of cases are spring to early summer and autumn reflecting the behavioral peaks of *I. ricinus* (Donnelly and MacKellar 1970). It can be stated that babesiosis is more likely to cause infection in older animals, as the young ones over 6 months of age are more energetic and have strong immune systems due to maternal antibodies. Moreover, seasons have a great influence on disease occurrence as it spreads rapidly in summers.

The habitats of *I. ricinus* mainly include shrubs, forests, and woodlands while well-kept grasslands are considered secondary habitats of *I. ricinus* (Agoulon et al. 2012). Due to the "inverse age resistance" in cattle, moderate infections occur causing the immune response below the age of about 9 months (Gern et al. 1988).

Prevention and control

Due to the wide distribution of tick vectors and their increased prevalence in favorable environments, the control of bovine babesiosis is a challenge for the dairy and beef industry. Three main approaches for prevention and control of babesiosis are vaccination, vector control, and chemoprophylaxis. The proper integration of these three strategies is really important to achieve and maintain enzootic stability (Kahn 2005). Preferably, these three methods are combined to make the most profitable use of each and also to achieve the development of breed resistance and preservation of reliability. Chemotherapy has significant importance in the treatment and prevention of babesiosis. Chemoprophylaxis is not a feasible long-term substitute for operative immunization, but imidocarb and diminazens have been used to shield cattle for several months against babesiosis (Dolan1991). According to a study, 3 mg/kg imidocarb for 4 weeks in carrier animals provides protection from babesiosis (Kahn 2005).

There are several discoveries that support the effectiveness of vaccines against bovine babesiosis. Against both homologous and heterologous challenges, vaccination of cattle with natural *Babesia* antigen extracts or culture-derived supernatants containing buried *Babesia* antigens produce protective immunity (Radostits et al. 2007). Cattle already suffered from a primary *Babesia* infection are strong enough to face the repeated infections. Oral supplementation is also a good approach to fulfill the iron deficiency of cattle (Man et al. 2021). Use of acaricidal drugs on regular basis to clear the tick habitats from the farm is also being practiced globally. Proper hygiene to maintain the biosecurity measures along with regular vaccination of the susceptible herds is a way forward to control the infection (Mary et al. 2000). On the other hand, strict quarantine of the newly bought animals imported from ticks populated areas is practiced to protect the existing herd. The use of live attenuated vaccines in all uninfected animals is also advised (Jackson et al. 2001).

Future perspectives

More options for the infected farms include quitting the use of pastures for some years that may act as the source of infection or the management of herds to attain enzootic stability by confirming that calves have enough natural exposure in their early life which will help them to develop sufficient immunity (Regassa et al. 2003).

A lot of gaps are also present in research and implementation of the tick-control strategies which need to be addressed in order to limit the economic losses due to the disease. No sub-unit vaccine is available for the prevention of babesiosis and hence is a potential area that needs to be addressed in future studies. The use of machine learning procedures for the detection of differences present between structural proteins of *Babesia* spp. may be another area of interest. The administration of transfected *B. bovis* or the membrane-bounded glycoprotein named Bm86 was carried out by Mazuz et al. (2021) and the calves showed prolonged antibody (immune) response against Bm86 after presenting symptoms of mild disease. Similar approaches may be adopted for the development of new vaccines. The use of genetic modification in attenuated parasitic organisms cultured in the laboratory can give promising vaccine candidates. The development of subunit vaccines consisting of various antigens from sexual and asexual life stages of *Babesia* spp. is another strategy proposed for the control of this disease. Further research is also required to study the different possible reservoirs playing role in the spread of the tick population.

The artificial feeding systems for ticks should be discovered in order to limit the use of animals and humans for studying the effects of notorious Babesia species (Hatta 2020; Vimonish et al. 2020). The nanoparticle technology can also provide a way out to discover and prepare effective vaccines against tick populations (de la Fuente et al. 2020). Emerging sequencing techniques are also there for the rapid and efficient diagnosis of bovine babesiosis in stick endemic areas (Ozubek et al. 2020). There is a dire need to discover simple, efficient, and cost-effective diagnostic tools or kits for quick diagnosis and a better understanding of the epidemiology and prevalence of different *Babesia* spp. in different regions of the world.

Conclusion

Bovine babesiosis is among the fatal diseases for cattle. The occurrence of babesiosis among cattle and buffalo is constant among regions of the world. In order to control, manage and reduce babesiosis, there is dire need of appropriate steps at farm levels. This review provides the overview of sero-prevalence and cases according to the global perspective, having disease burden. The impact of bovine babesiosis around the world can be comprehended here. Moreover, its zoonotic perspective cannot be neglected. As the disease transmitted via vector to different hosts and ultimately spread among the humans that is the leading emerging one health concern. This public health perspective, especially for humans under one health must be considered in order to prevent and manage the disease properly. Bovine babesiosis is mainly focused as its food animal and via disease economy disturbed badly. Different manageable points have been discussed to reduce the impact of this disease at farm level.

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