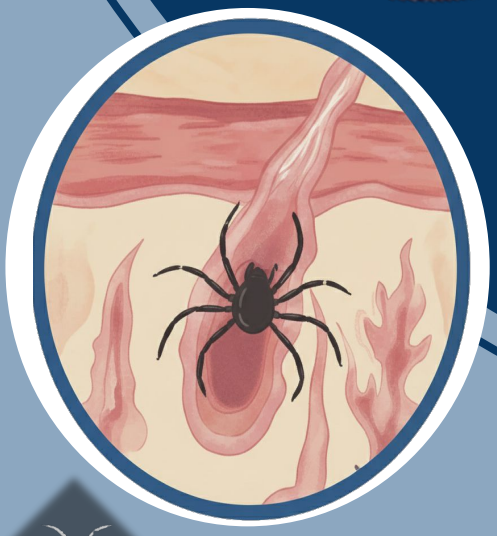


Human
Babesiosis Disease

Babesiosis is an infectious disease caused by the apicomplexan parasites of the genus *Babesia*, which infect and destroy red blood cells (RBC)

- History and Types of Babesiosis
- Epidemiology
- Environmental Impact
- Pathophysiology
- Diagnosis
- Treatment
- Disease Landscape

History of Babesiosis

Victor Babes
(1854-1926)

In the year 1888 "Victor Babes" discovered the parasite organisms that cause babesiosis in cattles red blood cells. He was a Romanian bacteriologist, physician, pathologist, and microbiologist

1957 The first human case identified in splenectomised patient (farmer) - Yugoslavian (Croatia)

1968 The first recognized in California (USA)

1969 The first case was observed in non-splenectomised patient

1976 Ixodes dammini (Ixodes scapularis) identified as vector for B. microti

1990 The first documented human case of Babesia duncani (WA1) in the Washington

2005 First human case of babisiosis reported in India, Gujarat

Types of Babesiosis

- B. microti
- B. motasi
- B. divergens
- B. venatorum
- B. Duncani
- Babesia sp. CN1
- B. crassa-like
- Babesia sp. KO1

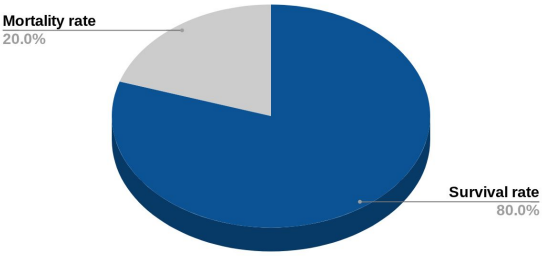
In the United States, B. microti is the agent most frequently identified in (Northeast and Midwest) and can occur in non-splenectomized individuals

In Europe, most reported cases are due to B. divergens and occur in splenectomized patients

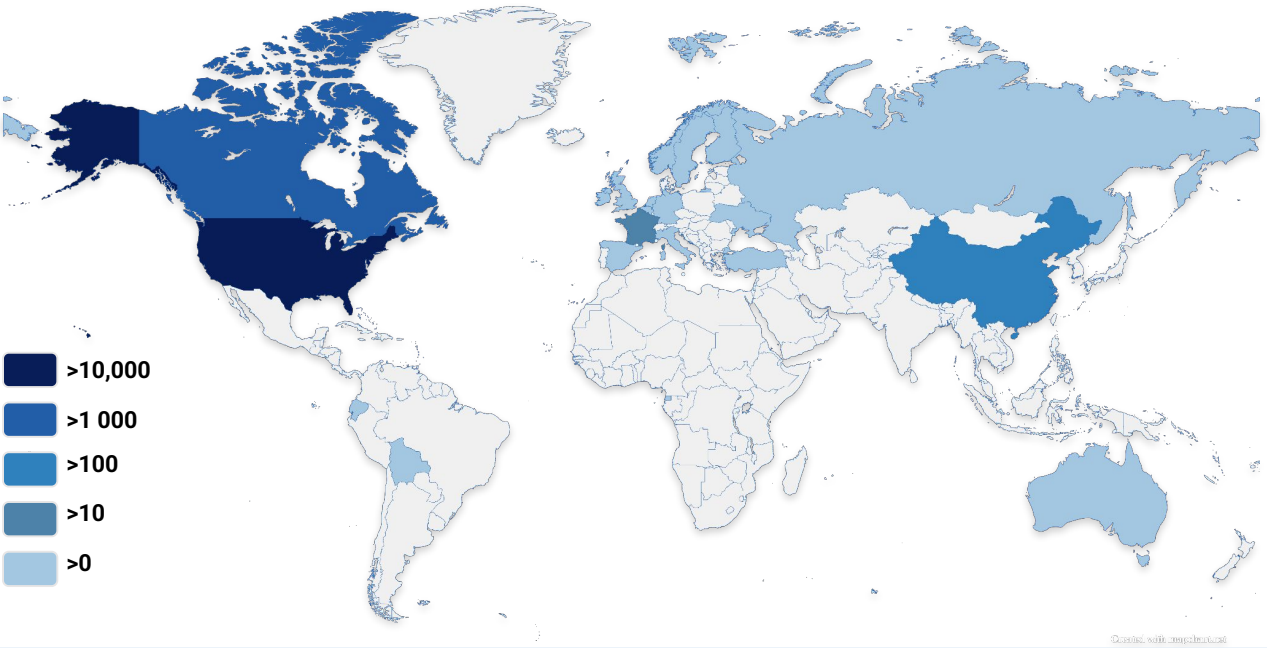
Disease Burden

Globally, the in-hospital mortality rate for Babesiosis patients is exceptionally high, with approximately one in ten (10%) dying

Babesiosis acquired from B. divergens or through transfusion transmission requires urgent attention due to the significantly increased risk of death

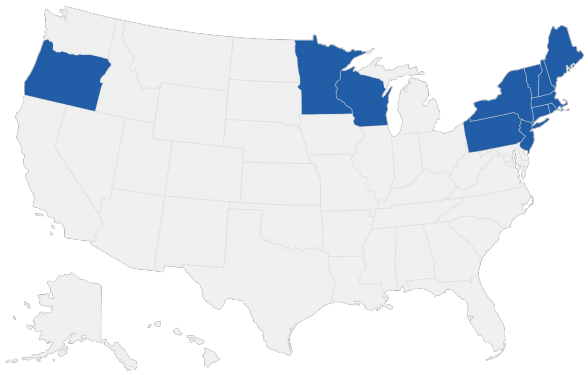


Global Epidemiology Data of Babesiosis



As of 2020, the global emergence of human babesiosis is predominantly concentrated in the USA and Canada, which together account for over 95% of reported cases, mainly caused by Babesia microti. China and France have also report cases, while all other countries have fewer than ten cases

Reported Surveillance Data for Babesiosis in US from 2011 - 2020

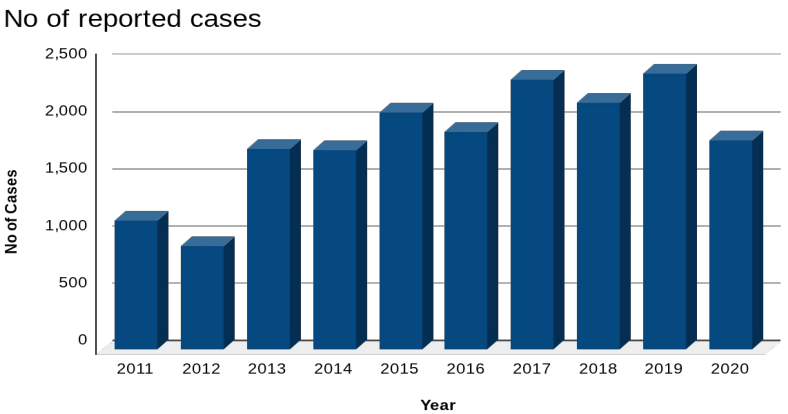


Geographic Prevalence - In United States, cases are highly concentrated in the Northeast and Upper Midwest regions

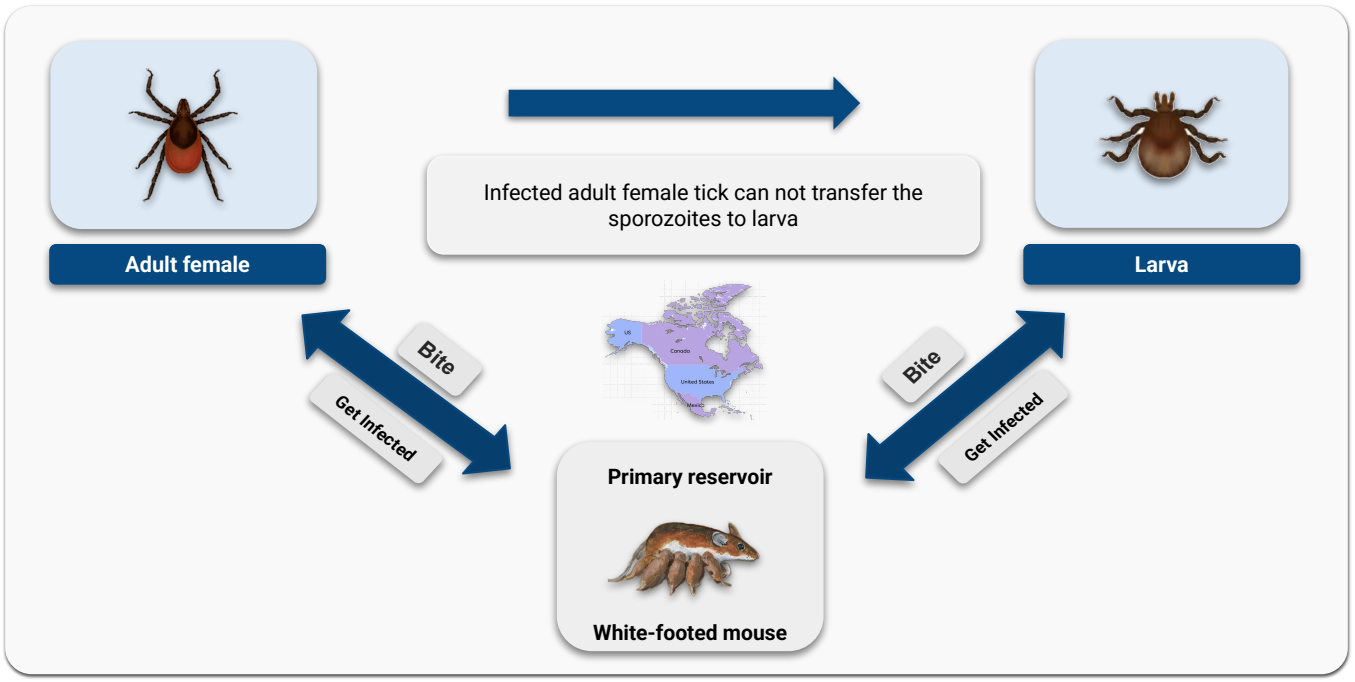
Specific "hotspots" include New England (Massachusetts, Connecticut, Rhode Island), New York, New Jersey, Wisconsin, and Minnesota (specifically the Minneapolis region)

The distribution is directly linked to the habitat of the white footed mouse and Ixodes scapularis (black-legged tick), which thrives in these wooded and coastal areas

A cumulative total of 18,294 Babesiosis cases were reported between 2011 and 2020 in United States, with the annual incidence generally trending upward over the decade, fluctuating from a low of 911 cases in 2012 to a peak of 2,418 cases in 2019

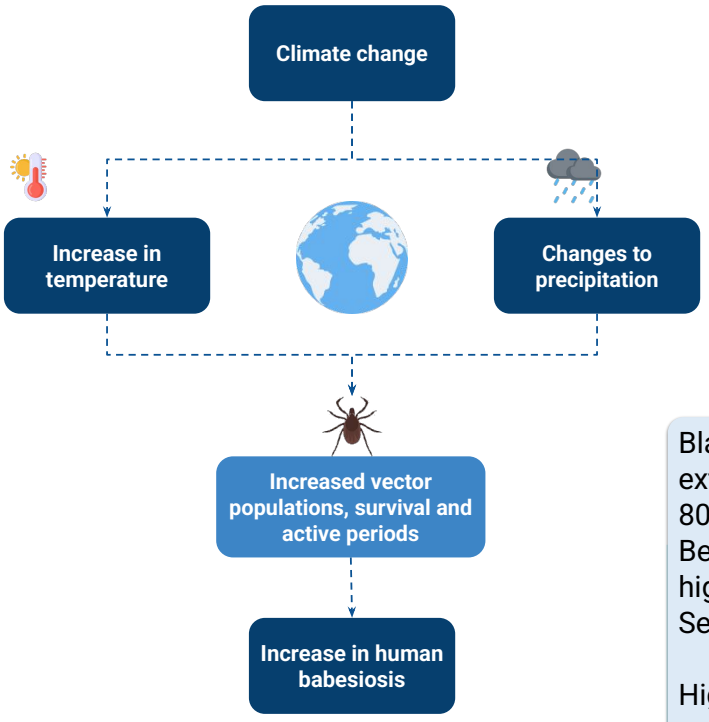


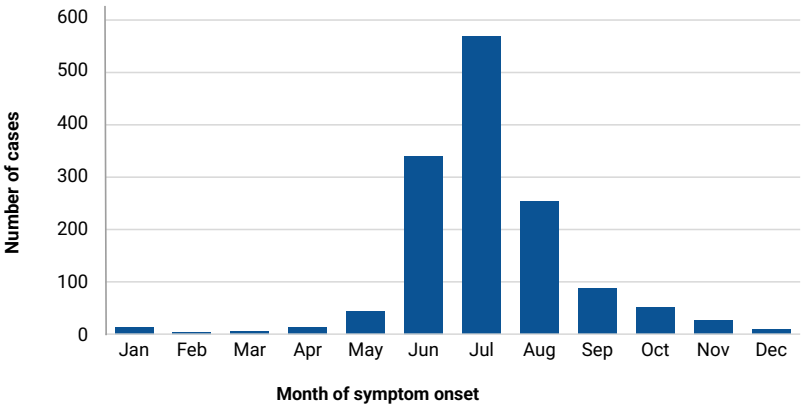
Analyzing the ecological link between white-footed mouse populations and the incidence of B. microti in North America



The majority of Babesiosis cases are caused by B. microti, a parasite primarily maintained by the white-footed mouse (the primary reservoir) inhabiting warm, dry forest and bushy areas where its high reproductive rate (up to 4-5 litters) contributes to increased population density, facilitating the infection of larval stage ticks which prefer small hosts like the mouse

Climate Impact Babesiosis Transmission





Blacklegged ticks are cold-blooded creatures which are extremely sensitive to their habitat, needing humidity above 80% and temperate weather (44.6–86°F or 7–30°C) to survive. Because of these particular environmental requirements, their highest activity levels occur during the months of May through September annually

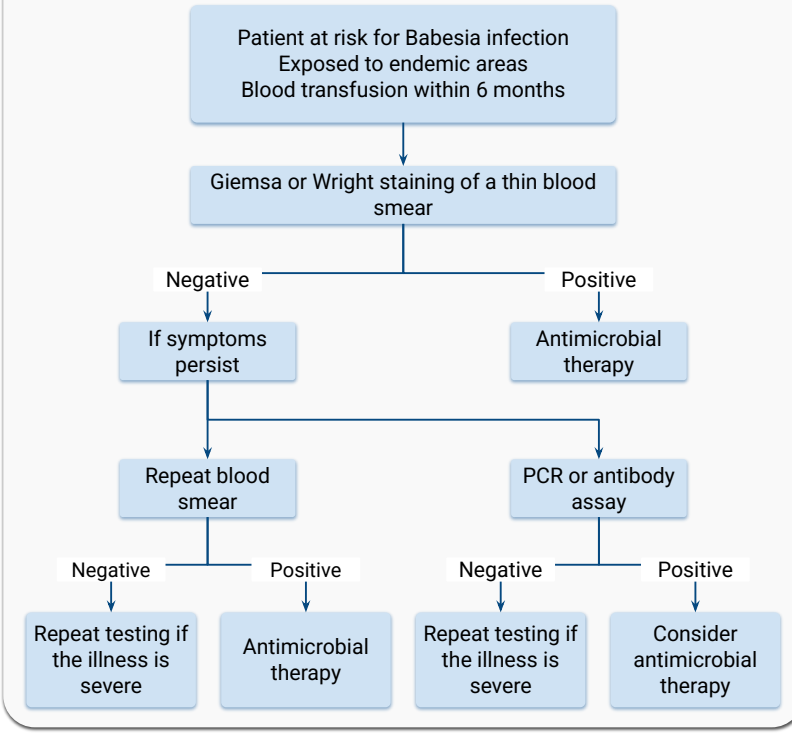
High heat and low moisture increases tick mortality, Ticks can survive freezing temperatures by sheltering in leaf litter or under snow

Diagnosis

1. **Clinical Diagnosis - Look for the signs and symptoms**
2. **Laboratory Tests**
   a. **Giemsa-Stained Blood Smear**
3. **Polymerase Chain Reaction (PCR)**
4. **Serological Tests**
   a. **Antibody testing - IgM and IgG**
5. **Biomarkers**
   a. **Elevated LDH**
   b. **Low haptoglobin**
6. **Complete Blood Count (CBC) -**
   a. **Anemia, Thrombocytopenia and Leukopenia**
7. **Other Tests for Complications**
   a. **Liver function tests**
   b. **Reticulocyte Count**

Method	Sensitivity	Specificity
Blood Smear	~55% – 93%	~99%
PCR (Active)	~96% – 100%	~99% – 100%
Serology(IFA)	~88% – 98%	~97% – 100%

Algorithm



Risk Factors

01 Geographic location
02 Summer and fall seasons
03 Pets and animals
04 Occupational exposure
05 Older adults
06 Infants and young children
07 History of previous tick-borne infections
08 Blood transfusion and organ transplant
09 Immunocompromised patients
10 Splenectomised patients

Signs and Symptoms

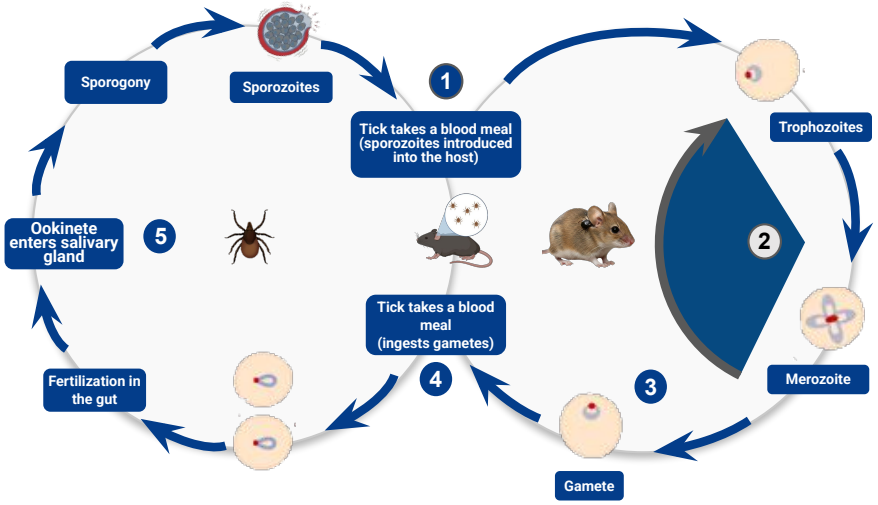
- Fatigue
- Chills
- Dizziness
- Headache
- Tachycardia
- Night sweats
- Jaundice
- Weakness
- Hemoglobinuria
- Dyspnea
- Fever
- Fainting

Complications

1. Hemolytic anemia
2. Acute kidney injury
3. Disseminated intravascular coagulation
4. Splenic rupture
5. Hepatic dysfunction
6. ARDS
7. Cardiovascular
8. Multiple organ failure

Life Cycle and Pathophysiology of Babesiosis

Step 1 - Transmission cycle from reservoir host to vector



The Ixodes tick is the definitive host and the white-footed mouse is the primary reservoir host for Babesia microti.

In Mouse: An infected tick transmits sporozoites into the mouse's bloodstream. These parasites quickly enter red blood cells, where they replicate asexually (budding). While in the blood, the parasites produce male and female gametes.

In Tick: A feeding tick ingests these gametes. Inside the tick, the gametes combine and undergo a sporogonic cycle, which produces the infectious sporozoites that are then ready to be transmitted back to a mouse/ humans.

Step 2 - Erythrocyte Invasion

During the blood meal, tick saliva delivers shielded sporozoites into the host. Once these parasites encounter an erythrocyte, they pivot their apical complex structures to face the RBC, facilitating entry

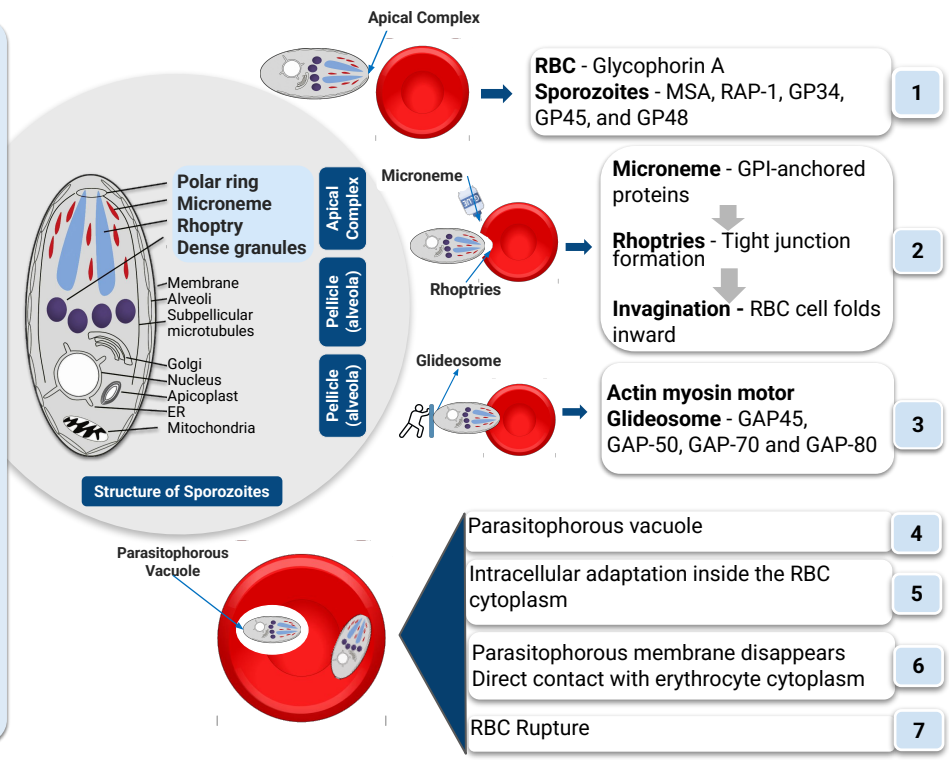
Parasite entry is triggered when its surface proteins—specifically MSA, RAP1, and GP34/45/48—lock onto the Glycophorin A proteins found on the surface of the RBC

To successfully penetrate the RBC, the parasite uses micronemes for sticking to the surface and rhoptries to lock onto the cell via RAP-1. This molecular engagement causes the RBC surface to fold inward, or invaginate, creating a path for the parasite

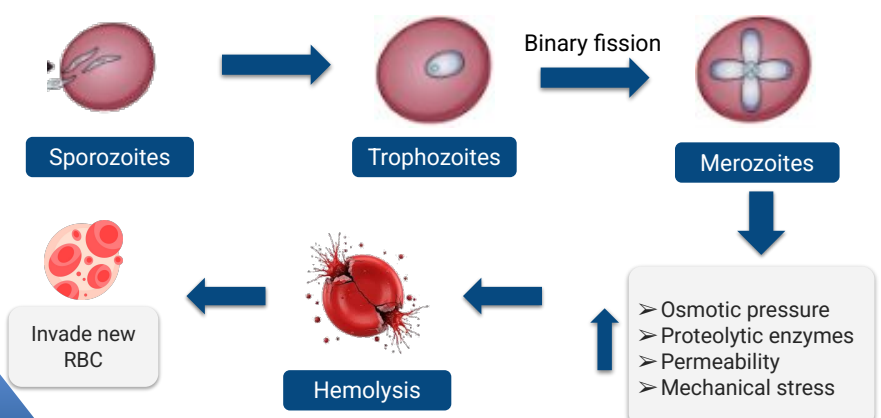
The glideosome, an actin-myosin motor complex, provides the mechanical force necessary for the parasite to propel itself into the red blood cell

Once it enters into the RBC, the parasite forms a parasitophorous vacuole to shield itself and acquire the specific nutrients needed to sustain its initial life cycle stage

Eventually parasitophorous vacuole will disintegrate which makes sporozoites to get direct contact with cytoplasm



Step 3 - Asexual reproduction in human RBC



The invaded sporozoites develop into trophozoites within the RBC

Replication: Trophozoites undergo asexual reproduction via binary fission to produce merozoites. These often form a characteristic tetrad shape known as a "Maltese Cross"

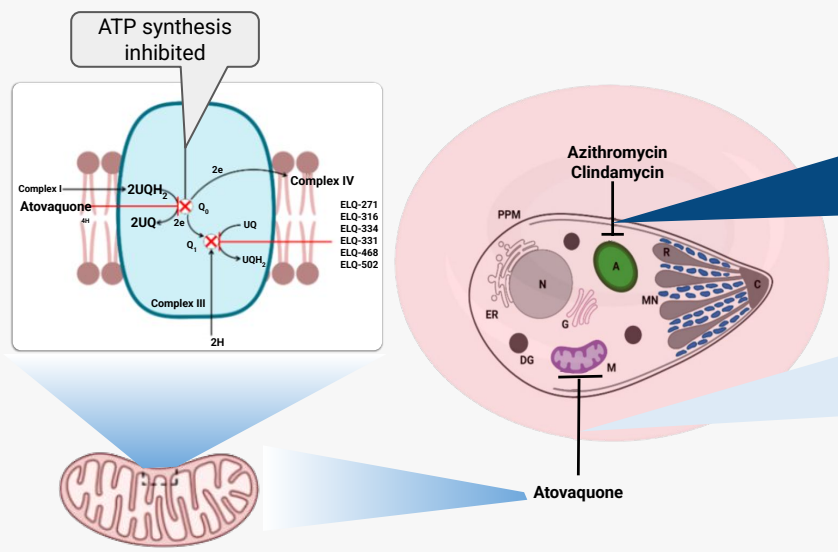
RBC Rupture: The exit of merozoites is triggered by increased osmotic pressure, proteolytic enzymes, increased permeability, and mechanical stress on the cell membrane

Propagation: The released merozoites then move on to invade new RBCs, continuing the cycle of infection

Current Treatment Regimen

B. microti	Atovaquone + Azithromycin (First-line treatment)	Mild to moderate infection	Atovaquone 750 mg orally twice a day + azithromycin 500 mg orally on Day 1, followed by 250 mg orally every day
		Hospitalized patients	Atovaquone 750 mg orally twice a day + azithromycin 500 mg IV every 24 h until symptoms improve
		Hospitalized patients	Atovaquone 750 mg orally twice a day + azithromycin 500 mg IV every 24 h until symptoms improve
	Clindamycin + Quinine (Second-line treatment)	Mild to moderate infection	Clindamycin 600 mg orally 3 times a day + quinine 650 mg orally 3 times a day
		Hospitalized patients	Clindamycin 600 mg IV 4 times a day + Quinine 650 mg 3 times a day until symptoms improve
		Hospitalized patients	Clindamycin 600 mg IV 4 times a day + Quinine 650 mg 3 times a day until symptoms improve

MOA



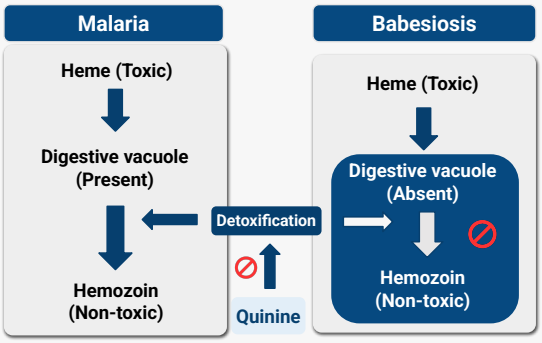
Azithromycin and Clindamycin bind to the 23S portion of the 50S ribosomal subunit within the apicoplast, inhibiting the translation of essential proteins and causing the eventual death of the parasite's offspring. This targeted disruption prevents the synthesis of isoprenoids and fatty acids that are fundamental building blocks for the membranes of new daughter cells

Atovaquone acts as a potent metabolic disruptor by targeting the parasite's mitochondrial electron transport chain (ETC). Specifically, it binds to the ubiquinol oxidizing site (Qo site) of the cytochrome bc1 complex (Complex III). By competitively inhibiting the transfer of electrons from ubiquinol to this complex, atovaquone effectively "short-circuits" the parasite's energy production

Quinine

Note - The exact mechanism of action of quinine is not known. Because in babesia species digestive vacuole is absent, due to that detoxification of heme (toxic) into hemozoin (non toxic) will not occur, as they do not degrade hemoglobin, and do not produce hemozoin. Therefore, the mode of action of quinine against Babesia parasites is likely to be different from that in Plasmodium

The hypothesized mechanism of action as per current research indicates a multi-faceted attack while quinine may physically wedge itself into the parasite's DNA to stop replication, it also appears to accumulate within the membranes of essential organelles—such as the mitochondria and endoplasmic reticulum—disrupting the vital life processes required for the parasite to survive



Side effects

Atovaquone + Azithromycin - The Atovaquone + Azithromycin combination is better tolerated because it targets structures that are unique to the parasite or vastly different from humans. Because these targets are so specific, side effects are usually mild (e.g., nausea or diarrhea), making it well-tolerated by over 85% of patients.

Quinine + Clindamycin - Quinine is a "non-selective" drug, meaning it binds to both parasite and human receptors. Blocks ion channels, leading to ear issues (ringing/hearing loss) and heart rhythm changes. It also stimulates insulin release, causing dangerously low blood sugar, while Clindamycin harsh disruption of gut flora further increases toxicity hence 72% of patients reported AE

Treatment option for babesiosis caused by non B.microti species

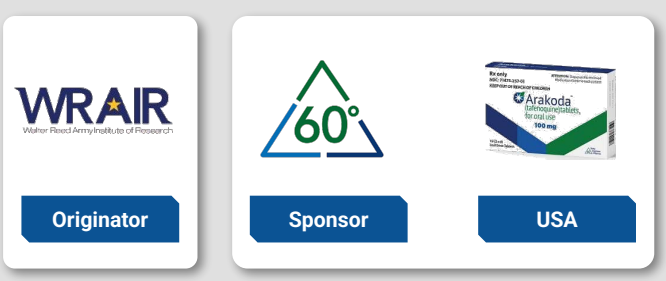
Species	Treatment Option
Babesia duncani	Clindamycin IV + Quinine oral - 7–10 days
Babesia divergens	Clindamycin IV + Quinine oral - 7–10 days
Babesia venatorum	Atovaquone + azithromycin OR clindamycin alone
Babesia crassa-like pathogen	Clindamycin alone

Babesiosis Treatment and Prophylactic Landscape

	Discovery	Preclinical	Phase 1	Phase 2
Small Molecule	Cethromycin (ALIQUANTUMRX)			Tafenoquine (Arakoda) (60°)
Vaccine		Whole parasite Babesia vaccine (Griffith University)		
Antibody	Babesiosis (KRABS Biotechnology)			

Orphan Drug Designation
Oral

Tafenoquine: An Emerging Drug Candidate for the Treatment of Babesiosis



- **Derivative -** 8-aminoquinoline derivative
- **Half-life -** Approximately 16 days
- **Current Phase -** Phase 2, study intended to confirm the high cure rate for tafenoquine in immunosuppressed patients with relapsing babesiosis
- **Regulatory Designation -** U.S. FDA granted orphan drug designation
- **MOA** - Unknown

- **Recent update -** On October 2025, the company submitted a Breakthrough Therapy application to the FDA
- **Maximum potential annual revenue**
  - Tafenoquine has three Orange Book-listed patents expiring in December 2035
  - The maximum commercial market size is estimated to be 380,000 patients/$245,000,000 in sales annually
  - Cumulative TAM - 1.17 million patients/$1.1 billion through patent expiration in 2035

Patents

Orange Book
10342791
10888558
11744828

US10342791B2

Catalyst Events

- Executing 3 trials, two babesiosis clinical trials are underway, with another anticipated to commence enrollment later this year
- Company announces positive recommendation from data safety monitoring board for B-FREE Ph2 study of Tafenoquine for Treatment of Chronic Babesiosis patients with Severe Fatigue
- The company plans to request a Type B meeting with the FDA in early 2026 to discuss requirements for a Supplemental New Drug Application (sNDA)
- Targeting profitability in 2027 based on continued commercial growth in malaria prevention, and positive Babesiosis outcome

Conclusion

The surge in human babesiosis cases is the result of a convergence between expanding host reservoirs like the white-footed mouse, increased tick density, and a rising population of immunocompromised individuals who are more susceptible to the infection.