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Canine Babesiosis in South Africa

A Kutyák Babesiosisa Dél-Afrikában

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Abstract

Canine babesiosis is a globally important parasitic disease in dogs. The main causative agents are *B. canis* which occurs predominantly in Europe, *B. vogeli*, and *B. rossi*, both of which occur in South Africa. In South Africa, 10% of the incoming patients in small animal clinics are infected with predominantly *B. rossi*, which is the most virulent and pathogenic of the canine babesia species. *Haemaphysalis elliptica* is the tick vector for *B. rossi.* Diagnosis of canine babesiosis is made typically by evaluating a blood smear taken from peripheral blood in conjunction with clinical signs. Most common clinical signs include lethargy, fever and pale mucous membranes. The clinical manifestations have been grouped into uncomplicated and complicated cases, the latter including conditions such as ARDS (Acute respiratory distress syndrome), IMHA (Immune mediated haemolytic anaemia), cerebral babesiosis, AKI (Acute kidney injury), pancreatitis, hepatopathy, DIC (Disseminated intravascular coagulopathy), SIRS (Systemic inflammatory response syndrome), and haemoconcentration. This paper presents up to date information on the current (2023) canine babesiosis case experiences in clinics across South Africa. According to our survey, canine babesiosis occurs year round in South Africa with peaks in the months of spring and summer. The most common complications that were experienced are IMHA (91%), ARDS (61.4%), and cerebral babesiosis (51%). The preferred treatment amongst the majority of clinicians is diminazene aceturate, however imidocarb is also widely used along with liver protectants. The differences in seasonality and in frequency of complications experienced in canine babesiosis in Hungary and South Africa may be due to different climate conditions and tick vectors and to the different pathogenicity of the dominating Babesia species.

Absztrakt

A babesiosis a kutyák világszerte jelentős parazitás betegsége. Európában a fő kórokozó a B. canis, Dél-Afrikában pedig a B. vogeli és a B. rossi. Dél-Afrikában a kisállatklinikákra érkező betegek mintegy 10%-a B. rossi-val fertőzött, amely a kutyát fertőző Babesia fajok közül a legvirulensebb és legpatogénebb. A Haemaphysalis elliptica a B. rossi kullancsvektora. A kutya babesiosisának diagnosztizálása jellemzően a perifériás vérből vett vérkenet értékelésével történik a klinikai tünetekkel összefüggésben. A leggyakoribb klinikai tünetek közé tartoznak a bágyadtság, a láz és a sápadt nyálkahártyák. A klinikai megbetegedéseket szövődménymentes és komplikált esetekre csoportosíthatjuk. Az utóbbiak között olyan állapotok szerepelnek, mint az ARDS (akut légzési distressz szindróma), az IMHA (immunmediált hemolitikus anaemia), a cerebralis babesiosis, az akut vesekárosodás, a hasnyálmirigy-gyulladás, a hepatopathia, a DIC (disszeminált intravaszkuláris koagulopátia), a SIRS (szisztémás gyulladásos válasz szindróma) és a hemokoncentráció.

Ez a dolgozat a közelmúltbeli (2023.) dél-afrikai kutya babesiosis esetekkel kapcsolatos tapasztalatokat mutatja be. Felmérésünk szerint Dél-Afrikában a kutyák babesiosisa egész évben előfordul, a járvány a tavaszi és nyári hónapokban tetőzött. A leggyakoribb szövődmények az IMHA (91%), az ARDS (61,4%) és a cerebralis babesiosis (51%) voltak. A klinikusok többségénél az előnyben részesített kezelés a diminazen-aceturát, de az imidokarbot is széles körben alkalmazták májvédő szerekkel együtt. A magyarországi és dél-afrikai babesiosis szezonalitásában és szövődményeinek gyakoriságában tapasztalható különbségek az eltérő éghajlati viszonyokból és kullancsvektorokból, valamint a domináns Babesia faj eltérő patogenitásából fakadhatnak.

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1 Introduction

Canine babesiosis is a worldwide significant tick-born disease caused by *Babesia* species which are intraerythrocytic protozoan parasites [1]. The initial discovery of *Babesia* dates back to 1888, when a Romanian pathologist named Dr. Victor Babes first described the microorganism in the erythrocytes of cattle and later in sheep [2, 3]. Soon after Dr. Babes' discovery, in 1895, an Italian veterinarian named Gian Pietro Piana first officially recorded the occurrence of *Pyrosoma bigeminum var. canis* (now known as *Babesia canis)* in a Pointer hunting dog [4]. In the 1890's, in Cape Colony of South Africa, a colonial veterinarian named Hutcheon noted signs such as hemoglobinuria, fever, and jaundice occurring in the canine population that were similar to those previously described in cattle affected with Texas fever (Redwater or Tick fever) [5, 6]. The causative agent of Texas fever was confirmed in 1893 by American microbiologist Theodore Smith to be *Pyrosoma bigeminum* (now known as *Babesia bigemina*) [6, 7]. Hutcheon wrote that these clinical signs were common and widespread in the Cape Colony and began to refer to the disease as "malignant jaundice or bilious fever". In South Africa, the first confirmation via blood smear of the "double pyrosoma resembling pyrosoma bigeminum" occurred in 1899 in Grahamstown, Eastern Cape by Dr. Carrington Purvis [5, 6]. In 1901, William Robertson, a Cape Colony veterinary surgeon, stated that "malignant jaundice is one of the most fatal diseases of the dog in the Cape Colony". Robertson goes on to describe the course of the disease, stating that at first the "dog is dull, listless, and refuses food", followed by a rise in temperature, "a yellow biliary staining of visible mucous membranes and skin", hemoglobinuria, and finally "collapse and weakness" resulting in death in most of the cases [8]. In 1989, Uilenberg proposed that the South African pyrosoma causing "malignant jaundice" was named *Babesia canis rossi* [9].

Today, canine babesiosis in South Africa is colloquially known as Biliary, Tick fever, or Bosluiskoors in Afrikaans. The South African form of canine babesiosis, primarily caused by *Babesia rossi*, is considered the most virulent form and typically presents a higher pathogenicity compared to those canine babesiosis cases experienced elsewhere that are caused by *Babesia canis, Babesia vogeli, and Babesia gibsoni* [10–12]. It is a commonly diagnosed disease in veterinary clinics across South Africa as approximately 10% of the total incoming canine patients are diagnosed with babesiosis each year. Due to the common occurrence, the disease presents a significant financial impact on the dog-owning public of South Africa in terms of treatment and prevention costs. In the early 2000's, the treatment

of canine babesiosis cost the public over 20 million Rand (982,000 Euro) [13]. Because of the significance of canine babesia occurring in South Africa, the main objective of this thesis is to provide a review of the available information regarding the etiology, clinical manifestations, diagnosis, and treatment. In addition, this thesis aims to provide current information regarding South African veterinary clinics' experiences with canine babesiosis and to compare the findings to what is experienced in Hungary.

2 Literature Review

2.1 Causative Agent

Babesia species belong to the Piroplasmida order of the Apicomplexa phylum. The *Babesia* parasites responsible for canine babesiosis can be grouped into small and large *Babesia* species based on their morphology. Small *Babesia* include *B. gibsoni*, *B. conradae* and *B. microti*-like species. *B. gibsoni* occurs in Asia, North America, Europe, Australia, Brazil, and Northern Africa [14]. The large *Babesia* species include *B. canis* which occurs primarily in Europe, *B. vogeli* occurring worldwide in tropical and subtropical areas, and *B. rossi* which occurs in Sub-Saharan Africa [1, 15]. These large *Babesia* species were formerly named *B. canis canis, B. canis rossi, and B. canis vogeli* as they were considered subspecies of *Babesia canis*. The large *Babesia* species cannot be differentiated based on morphology but is distinguishable on a molecular level by Polymerase Chain Reaction (PCR). Today, the large *Babesia* species are considered separate species due to their differences in vector specificity, pathogenicity, serology, and on a molecular level, their differences in nucleotide sequences specifically in the 18S rRNA gene [11, 16].

In South Africa, the large *Babesia* species, *B. vogeli* and *B. rossi* are the main causative agents for canine babesiosis [15, 16]. On a peripheral blood smear, they may appear as ovoid or paired 4–5µm long pyriform merozoites in the erythrocytes [17]. Babesiosis caused by *B. rossi* (Figure 1.), the more virulent species, is more prevalent than *B. vogeli*. In a 2004 study, out of 282 blood samples from dogs in South Africa, a total of 44 samples tested positive for *Babesia* where 70.5% was positive for *B. rossi* and 29.5% was positive for *B. vogeli* [18]. Unlike Asia and the United States, *B. gibsoni* is not endemic in South Africa. It's occurrence was first detected and confirmed via PCR in a 3 month old Pit-Bull terrier imported from the USA [19]. There have been no further official reports of *B. gibsoni* caused babesiosis in South Africa.

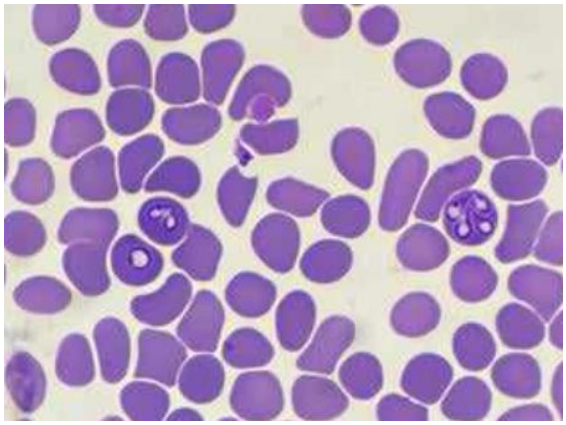

Figure 1: Various forms Babesia rossi merozoites in canine erythrocytes on blood smear.

In South Africa, Black-backed jackals (*Canis mesomelas*) has been confirmed to be the natural host and reservoir species *of B. rossi*. A study was performed to determine whether *B. rossi* occurred in free ranging Black-backed jackals, and the results confirmed via PCR and Reverse Line Blot Hybridisation (RBL) that one third of 77 *Babesia* positive samples were subclinically positive for *B. rossi* [20] .

Figure 2: Image of Black-backed Jackals photographed by Karl Svendsen

Babesiosis is a tick-born parasitic disease. In Europe, especially Central Europe, the tick vector for *B. canis* is *Dermacentor reticulatus,* preferring a cool, wet and temperate climate. *B. vogeli*'s main vector is the Brown Dog Tick, *Rhipicephalus sanguineus.* This tick prefers more tropical and subtropical environment, but can also tolerate colder climates as well[1, 21]. In South Africa, *Rhipicephalus sanguineus* prefers the warm and wet areas, but can also be found in dry parts of the country as well. Previously named *Haemaphysalis leachi*, *Haemaphysalis elliptica* also known as the Southern African Yellow Dog Tick (Figure 3.), is the vector for *B. rossi*. In South Africa, *H. elliptica* is present throughout the year, preferring high rainfall but mostly occurring where rodent hosts are present for the nymph and larval stages of the tick. Adult ticks attach mainly to the head, neck, and shoulders but may also be found between the toes and on the ears of dogs [22, 23].

Figure 3: *Haemaphysalis elliptica*, the vector of B. rossi.

2.2 Epidemiology

Canine babesiosis has a worldwide occurrence and it's endemicity depends on tick occurrence, climate, and seasonality. *Babesia canis* is endemic to Europe, particularly France, Southern Europe, and Central Europe. *Babesia vogeli* is endemic to South Africa, several Asian countries, Australia, Brazil, and the United States of America. *Babesia rossi* is endemic to South Africa but have been reported to occur in Nigeria and other Sub-Saharan countries such as Angola, Zambia, Angola, and Malawi [15]. Peak numbers of canine babesiosis are synonymous with peak tick numbers which have a strong seasonality. In Hungary, peak babesiosis cases occur in spring during the months of April and May, and in autumn during September and October. These months are associated with a milder and more wet climate which is preferred by *D. reticulatus*, the tick vector of *B. canis* [24]. In South Africa, peak canine babesiosis cases occur during the summer months of November through March especially in the summer-rainfall provinces of Gauteng, Free-State, KwaZulu-Natal, and Mpumalanga. In the Western Cape province, canine babesiosis occurs throughout the year, including the winter months of June through August as this region experiences a winter-rainfall [13].

Some breed predispositions have been noted in the occurrence of canine babesiosis. In the USA, babesiosis caused by *B. gibsoni* is most often detected in breeds associated with dog fighting such as American Staffordshire terriers, American Pitbull terriers, Tosa dogs, and their breed mixes [14]. In Hungary, a 2005 study found that German Shepherds and Komondors presented a higher prevalence of *B. canis* antibodies compared to other breeds, suggesting a genetic predisposition to babesiosis with a long term carrier status in these breeds [25]. A South African study involving 1222 *Babesia* positive cases at the Onderstepoort Veterinary Academic Hospital, found that there are no clearly identifiable individual dog breeds that are at a higher risk for canine babesiosis infection compared to

other breeds. The most common breeds diagnosed with babesiosis was the Rottweiler, Maltese Poodle, and Staffordshire Bull Terrier. The study showed that these breeds did not have a higher risk of canine babesiosis compared to the Labrador Retriever, the reference breed in this study [26]. Male dogs were reported to become infected with *Babesia* more frequently both in South Africa and Hungary, however this may be due to increased roaming behaviour of males and outdoor keeping [24, 26].

2.3 Pathogenesis

Canine babesiosis circulates in canine hosts and the tick vectors. The female tick has a blood meal from a babesiosis infected canine, usually up to a week and falls off once meal is complete. In the gut cells of the tick, the *Babesia* protozoa undergoes schizogony, an asexual reproduction. The *Babesia* enters the ovaries of the tick and transovarial infection occurs resulting in the infection of the next generation of ticks. Sporogony occurs in the salivary glands of the ticks, forming sporozoites. Once the tick attaches to the canine host, the sporozoites from the saliva enter the red blood cells of the canine host. In the red blood cells, sporozoites differentiate into trophozoites which undergo merogony to produce the merozoites. The invasion and replication the merozoites in the red blood cells causes direct damage to the cell resulting in intravascular and extravascular haemolysis. The haemolysis can result in anaemia, hypoxia, and haemoglobinuria [27]. The severity of anaemia does not correlate with the severity of parasitaemia. The severity of babesiosis depends on several factors such as the *Babesia* species, age, and immune status of the host. The most pathogenic species is *Babesia rossi*, resulting in a more severe clinical disease which is often complicated. *B. rossi* infection has a mortality of 12% while less pathogenic species such as *B. vogeli* has a 1% mortality. Infection with *B. vogeli* usually has lower levels of parasitaemia and results in a milder clinical disease, often subclinical in adults. Typically, a more severe infection occurs in puppies with any large Babesia species compared to adults. The incubation period of canine babesiosis following the tick bite is 10-21 days. Clinical signs can include fever, lethargy, anorexia, pale mucous membranes, splenomegaly, jaundice, and pigmenturia [1, 28].

2.4 Clinical Manifestations

Canine babesiosis cases can be classified as uncomplicated and complicated. Uncomplicated cases usually involve clinical signs directly related to haemolysis such as pale mucus membranes, lethargy, splenomegaly, and fever [29]. Uncomplicated cases can be further

categorized as mild (PCV ≥ 0.30 l/l), moderate (0.15 l/l ≤ PCV < 0.30 l/l) or severe (PCV < 0.15 l/l) based on the severity of anaemia. Severe uncomplicated is characterised by acute haemolytic crisis and life-threatening anaemia. Complicated babesiosis cases present clinical signs that are not directly attributable to haemolysis and can involve different organs. The complications of canine babesiosis include acute kidney injury (AKI), icterus and hepatopathy, cerebral babesiosis, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulopathy (DIC), pancreatitis, immune mediated haemolytic anaemia (IMHA), systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), and rarely cardiac dysfunction and haemoconcentration termed "red biliary" [12, 29, 30].

Acute Kidney Injury

AKI is a quite rare complication of *B. rossi* caused canine babesiosis with a prevalence of 2.2% (3/134) in hospitalized cases as found by a 1994 case overview by Jacobson at the Onderstepoort Faculty of Veterinary Science [29]. Despite AKI being a rare occurrence with *B. rossi* infection, elevated creatinine levels are found to occur more frequently, indicating a subclinical renal injury mainly limited to the renal tubules [31, 32]. In contrast, a Hungarian study found that 31% (19/61) of *B. canis* cases experienced AKI as a complication. The increased occurrence of AKI in Hungary may be explained with the difference in the pathogenicity of *Babesia* species [24]. Possible factors contributing to the development of renal injury in case of canine babesiosis include the toxic effects of haemoglobin due to haemolysis, anaemia, hypotension, and hypovolemia contributing to tissue hypoxia, In addition to this, inflammatory and immunologic processes such as immune complex deposition in the kidney due to antigenic stimulation may also contribute to kidney injury [29, 33, 34].

Diagnosis of kidney involvement and injury is based on the consistently elevated creatine level despite adequate fluid therapy and hydration [12], as well as urine volume and urinalysis [29, 30]. Clinical signs of dogs presenting with AKI include anuria or oliguria [29, 32]. Creatinine levels indicating AKI are >150µmol/l [24, 34]. In both complicated and uncomplicated cases of canine babesiosis caused by *B. rossi*, the urinalysis shows evidence of haemoglobinuria, proteinuria, and casts of renal tubular epithelial cells (RTE) [29, 32, 33]. Using urine specific gravity (USG) to evaluate kidney function may provide a false sense of security as in most babesiosis cases, the haemoglobinuria artefactually raises USG

and therefore a urine osmolality test is better indicated to gain a more accurate understanding of the kidney function [31].

On gross pathologic examination the kidneys may appear swollen with dark red-brown discoloration of the renal cortices [12, 33]. Histopathological findings from the kidneys show signs of widespread tubular necrosis (Figure 4) as well as degenerative changes in the proximal tubules including karyolysis, karyopyknosis, and vacuolar-hydropic degeneration [33]. These changes are most likely the result of hypoxic injury of the kidney and less likely due to toxic effects of haemoglobin [33, 35].

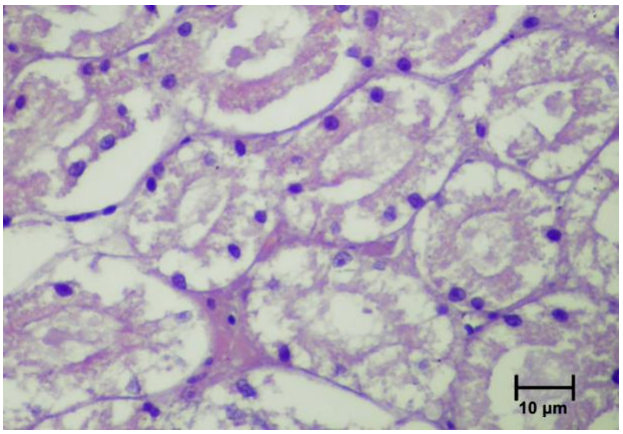

Figure 4: Section of a kidney of a dog infected with *B. canis* demonstrating tubular necrosis. Image credits to Dr. Máthé Ákos [33].

Icterus and Hepatopathy

In case of canine babesiosis, it has been stated that the sole occurrence of icterus due to haemolysis is not very likely, however it more commonly occurs in case of hepatopathy and pancreatitis in addition to the haemolysis [34, 36]. Thus icterus is both of pre-hepatic and hepatic origin [31]. Hepatopathy is characterized by marked increase of liver enzymes such as alanine transaminase (ALT) and alkaline phosphatase (ALP), bilirubinaemia, bilirubinuria, and the yellow discoloration of mucous membranes. Hepatopathy is probably caused by hypoxia, inflammatory cytokines, free radicals, and microthrombosis in the case of disseminated intravascular coagulopathy (DIC) [12, 29, 37]. Hepatomegaly has commonly been found on babesia infected dogs either post mortem or diagnostic imaging techniques such as ultrasound and radiography [12]. Histologically, characteristic changes of the liver include centrilobular congestion and necrosis of those dogs infected with babesiosis [29].

Cerebral Babesiosis

Cerebral babesiosis is not a frequently occurring complication of canine babesiosis. It is defined by the acute appearance of neurological signs as well as the related pathological findings. Reported incidence rates of central nervous system (CNS) signs occurring in canine babesiosis range from 6% to 16% [30, 34], however these signs may also occur secondary to hypoglycaemia [38]. For the diagnosis of true cerebral babesiosis, it is important to exclude hypoglycaemia in the presence of CNS signs, as it is considered a common complication occurring in 20% of babesiosis cases [38]. Cerebral babesiosis may be caused by the "sludging" of the parasitised erythrocytes in the capillaries of the brain as well as endothelial damage, perivascular oedema, and haemorrhages. Clinical signs of cerebral babesiosis include ataxia, tremors, nystagmus, anisocoria, seizure, paddling, and vocalization. Pathological findings such as macroscopic brain haemorrhages are diagnostic for cerebral babesiosis [12, 29, 30, 34]. Babesiosis with neurological signs is associated with high mortality and can result in 57 times greater chance of death [12].

Acute Respiratory Distress Syndrome

ARDS is experienced as frequent complication of canine babesiosis in South Africa with 49.7% of practices based on Collett's survey [13]. A previous study reported that ARDS is responsible for the largest proportion of fatalities (56%) amongst the complicated cases [34]. Clinical signs of ARDS include increased respiratory rate, dyspnoea, foamy nasal discharge, wet cough, and crepitating respiratory sounds. A blood-gas analysis will confirm hypoxia with an arterial partial pressure (PaO_2) < 60 mmHg [12]. ARDS is characterized by pulmonary oedema, which is caused by the increased alveolar capillary permeability. The diagnosis of babesiosis related ARDS is based on the respiratory signs, thoracic radiographs showing diffuse infiltration and atelectasis and blood gas analysis [29].

Pancreatitis

Acute Pancreatitis is a rare complication of canine babesiosis. It was previously known as the "gut form" of canine babesiosis. It is characterized by gastrointestinal clinical signs such as vomiting, melena, anorexia, abdominal pain, and icterus. In a retrospective study the incidence of acute pancreatitis as a complication of babesiosis was 1.8%. Acute pancreatitis is often accompanied by other complications such a hepatopathy, ARDS, and IMHA. Development of acute pancreatitis is associated with a higher mortality [36]. Diagnosis of

acute pancreatitis is based on elevations of pancreatic enzymes such as amylase and lipase, as well as ultrasonographic abnormalities of the pancreas.

Immune-mediated Haemolytic Anaemia

IMHA is caused by the increased destruction of erythrocytes due to membrane associated antibodies, as in case of babesiosis the surface of the red blood cells is altered and therefore is recognized as "foreign" material. Jacobson has previously reported (1994) an incidence rate of 21% (28/134) of canine babesiosis cases as IMHA positive [29]. However, a more recent (2019) study of naturally infected dogs with *B. rossi* reported an incidence rate of 10.3% [31]. The characteristic feature of babesia associated IMHA is the continuing haemolysis and anaemia despite anti-babesial treatment. The diagnosis of IMHA is based on the detection of spherocytes, Coomb's test or in-saline autoagglutination test, and a decreasing PCV [29].

Disseminated Intravascular Coagulopathy

DIC is a complication that has been frequently reported in canine babesiosis [29, 34]. A Hungarian study noted an incidence rate of 24% for the occurrence of DIC in dogs infected with *B. canis* [24]. A hallmark of canine babesiosis is the development of thrombocytopenia which can be found in both complicated and uncomplicated cases. Clinically obvious bleeding tendencies are not common, however on post-mortem examination; macroscopic haemorrhages on visceral surfaces are common [31]. The reason for the lack of obvious bleeding tendencies has been suggested to be the presence of very large and active platelets together with high fibrinogen concentrations [39]. In addition to thrombocytopenia, the haemolysis, endothelial damage, hypoxia, and acidosis in association with babesiosis may predispose to DIC. This is the systemic abnormal activation of coagulation pathways and causes the formation of microthrombi. Thrombus formation results in ischaemia and damage of parenchymal organs that may predispose to the development of MODS [29]. This complication of canine babesiosis leads to a consumption coagulopathy: affected dogs may have low platelet count, prolonged activated partial thromboplastin time, low fibrinogen concentrations as well as high D-dimer value [12].

Systemic Inflammatory Response Syndrome and Multiple Organ Dysfunction Syndrome

Canine babesiosis is associated with hypoxia, tissue damage, inflammation, and release of mediators such as inflammatory cytokines and free radicals. SIRS occurs due to overwhelming release of the inflammatory cytokines such as tumour necrosis factor (TNF),

interleukin 1, 6, and 10, as well neutrophil products and nitric oxide. SIRS is present if 2 or more of the following signs are detected: tachycardia (>120/min), tachypnoea (>30/min), either hypothermia or hyperthermia, and either leucocytosis or leukopenia with left shift [29]. In case of the acute babesiosis most often caused by *B. rossi*, Welzl et al found that 87% of infected dogs classify as positive for SIRS [34]. A more recent publication from a study at Onderstepoort Veterinary Academy Hospital reported an incidence rate of 60.5% [31]. SIRS along with hypoxia and DIC can lead to the development of MODS. MODS is defined by the presence of at least 2 or more complications such as ARDS, cerebral babesiosis, AKI, hepatopathy, and/or pancreatitis [29].

Cardiac Dysfunction

Cardiac dysfunction is a rare complication of canine babesiosis, mainly due to myocardial ischaemia and myocarditis. Electrocardiographic changes have been reported in dogs with canine babesiosis. The most frequent arrythmias include ventricular premature contraction, sinoatrial blocks, and atrioventricular block [12, 30]. Pathological findings of cardiac damage are most commonly multifocal haemorrhages of the epicardium and myocardium particularly of the left ventricle [12]. Histopathological findings include signs of inflammation, necrosis, and microthrombi [30]. Cardiac troponin I (cTnI) proved to be a reliable tool for detecting myocardial damage in canine babesiosis [40].

Haemoconcentration

Haemoconcentration or “red biliary” is a rare complication of canine babesiosis. It is characterized by the paradoxical reaction of high-normal or increased PCV with intravascular haemolysis [29]. The cause of haemoconcentration is suggested to be due to increased vascular permeability, vasculitis, and the consequent shift of protein rich fluid into the extravascular space [12, 30]. There is an ongoing debate on the cut off PCV values to suggest haemoconcentration, some authors argue for the lower normal limit (PCV > 37%) [30], while others argue the for the upper limit (PCV > 47%) [12]. Haemoconcentration is associated with other complications such as cerebral babesiosis, AKI, and higher mortality. Haemoconcentration has a more guarded prognosis [12].

2.5 Diagnosis

The diagnosis of canine babesiosis is primarily based on history of tick-exposure, clinical signs, and blood smear microscopy stained with Diff Quick. Blood sampling from peripheral capillary such as those in the ear or toe nail increases the probability to visualise the parasites

[11]. The visualisation of *Babesia* parasites in the erythrocytes is enough to confirm the diagnosis [1, 28]. However, further investigation is needed to differentiate the large babesia species. Molecular diagnosis with PCR is the most sensitive diagnostic method, especially in cases of low parasitaemia. PCR is also used to differentiate between *B. canis, B. rossi,* and *B. vogeli*. Serological tests such as the immunofluorescent antibody test (IFAT) has been used in the diagnosis of canine babesiosis for more than three decades. The drawback of IFAT is its low specificity and cross reactions with other piroplasm species. It is recommended to use IFAT in combination with PCR for a more specific diagnosis of canine babesiosis [11].

Besides the aetiologic diagnosis, laboratory examinations can be performed to determine the level of anaemia as well as aid in the diagnosis of complicated forms of babesiosis. Such laboratory exams include complete blood cell count (CBC), liver enzymes (ALT, AST), serum bilirubin, creatinine, acid-base analysis, and urinalysis [28]. An updated diagnostic flowchart presented in Figure 5 was proposed by Jacobson to better approach different clinical manifestations and their outcome [30].

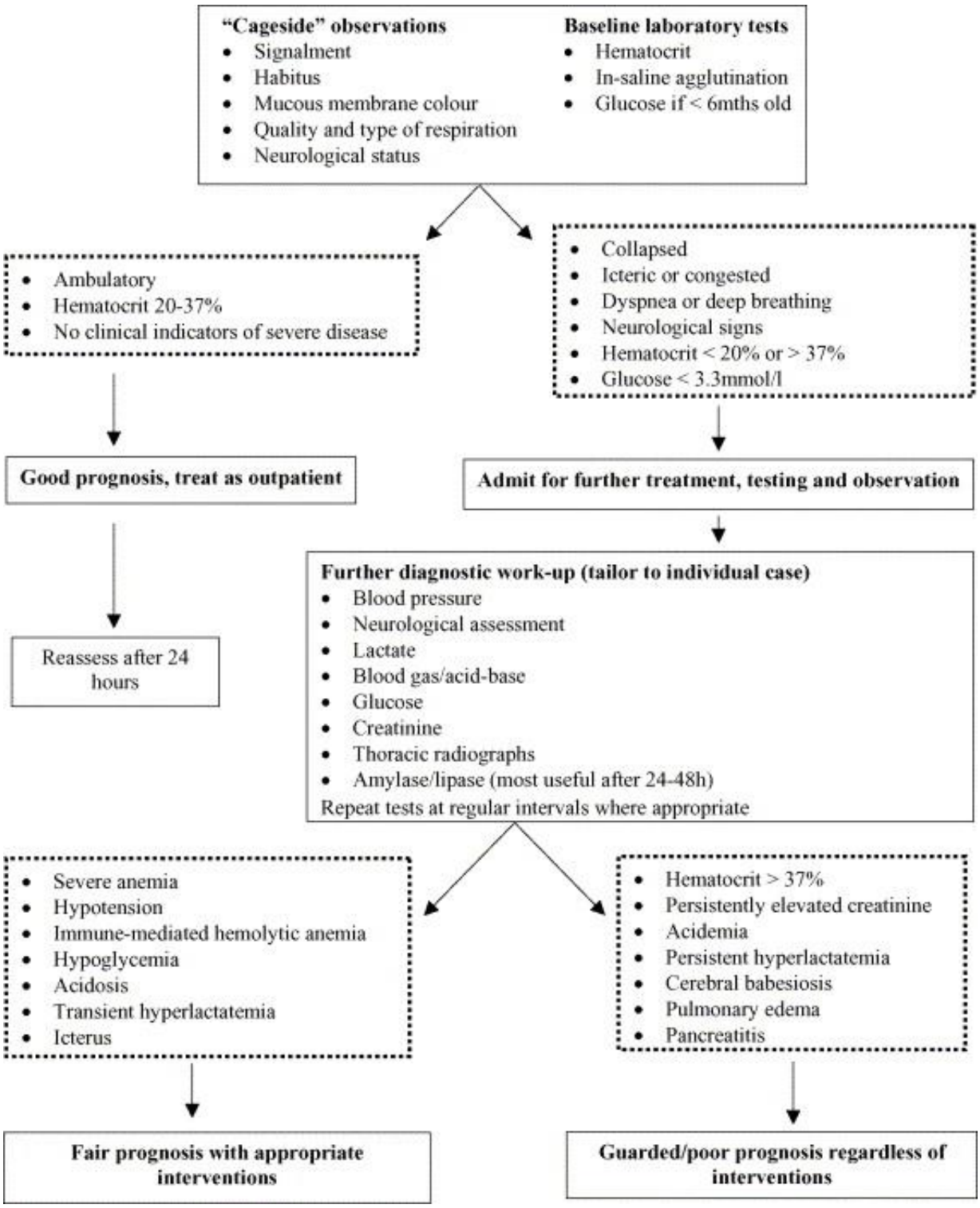

Figure 5: Diagnostic approach of confirmed canine babesiosis suggested by Jacobson [30].

2.6 Therapy

Treatment goals of canine babesiosis include alleviating the clinical signs, eliminating the parasites, and provide any additional treatment in the case of severe anaemia and complications. Anti-babesial drugs used to eliminate the *B. rossi* and *B. vogeli* infection include imidocarb and diminazene aceturate. Imidocarb is the most used drug in the United States as well as in Europe for the treatment of canine babesiosis. It is also used in South Africa. Imidocarb is given as a single dose of 7.5 mg/kg IM or 5-6.6mg/kg IM as a repeated dose 14 days after first administration [41]. Pain or swelling at the injection site may be experienced as a side effect of imidocarb [1]. Diminazene aceturate is given as single dose of 3-5mg/kg IM. Diminazene aceturate is a commonly drug used in South Africa, while it is not approved in the United States, and not available in Europe [41]. Diminazene may cause dose dependent central nervous system signs [12]. Trypan blue is an older drug that may be used in the treatment of *B. rossi* infection. It is only used in South Africa, where *B. rossi* is endemic. It is given strictly intravenously as it is tissue irritative, at a single dose of 10mg/kg. It is important to follow up trypan blue with either imidocarb or diminazene one week later to eliminate the parasites [1, 28, 42]. Severe uncomplicated as well as complicated babesiosis requires additional supportive treatment. Moderate to severe canine babesiosis may require blood transfusions depending on the clinical presentation and PCV of the patient. Several other therapies are used depending on the clinical manifestation of complicated babesiosis (Table 1) [43].

Table 1: Therapies according to the indication of complicated babesiosis

Drug / Therapy	**Indication**
Furosemide Dopamine Mannitol	AKI
Hypertonic saline infusion Diazepam Phenobarbital	Seizures, Cerebral Babesiosis
Furosemide Aminophylline	ARDS, Pulmonary oedema
Prednisolone	IMHA
Liver protectants Silymarin SAMe Vitamin B complex	Hepatopathy
Heparin	DIC
Maropitant Metoclopramide	Vomiting
IV dextrose	Hypoglycaemia

3 Methods and Materials

A short survey concerning the clinical experience of canine babesiosis was created using Google Forms. The questionnaire consisted of twenty-two questions including both open ended and various multiple choice style questions. The questions were designed in such a way that is based on available literature and for the results to be comparable to such literature and previously performed surveys. Using the South African Veterinary Council's December 2023 list of all active practicing professionals and registered facilities, a hundred clinics across all nine provinces of South Africa were chosen at random as well as a few from personal contacts. Clinics were eliminated from the survey sample if their e-mail address could not be found through a Google search, their website, or through social media such as Facebook and Instagram. The survey was made available from 10 January 2024 until 10 March 2024. An additional two more reminder emails were sent at an interval of three weeks if a response was not recorded. The results of the survey were recorded in Excel.

4 Results

Out of 100 private South African clinics, 44 responded (44%). The distribution of responses can be visualised in Figure 6. The Free State province had 9 responders, followed by 7 responders for each of the provinces of Western Cape, Gauteng, and KwaZulu-Natal, 5 responders from the North West province, 4 from the Eastern Cape, 2 responder each from the provinces of the Northern Cape and Mpumalanga, and 1 responder from Limpopo province.

Figure 6: Map of survey response distribution

43 clinics responded “Yes” when asked if they experience canine babesiosis in their clinic. The clinic which responded “No” is situated along the west coast of South Africa, and they explained that they have treated only 4 cases in the last five years with one death. When asked during which season does the clinic see ticks on their canine patients, the clinics were able to choose more than one response. All the clinics (100%) responded that they see ticks on their patients during the Summer (middle November-February), 65.91% of the clinics saw ticks during the Autumn (March-May), 50% saw ticks on their canine patients during the Winter months (June-August), and 86.36% of the clinics reported seeing ticks during Spring (September-middle November). The approximate total number of canine babesiosis cases experienced per clinic in 2023 can be seen in Table 2.

Table 2: Estimated total number of canine babesiosis cases per clinic in 2023.

	0-10	11-25	26-50	51-75	76-100	100+
Number of clinics	11	7	9	9	3	5

Responses to the question of occurrence of canine babesiosis cases experienced per season is shown in Table 3. All 44 clinics reported blood smear microscopy as main diagnostic tool of babesiosis in addition to the suspicion based on clinical signs. 2 clinics from Gauteng province reported using PCR as a diagnostic tool as well, and they ranked *B. rossi* as more frequently diagnosed than *B. vogeli*. When asked which species most commonly causes Babesiosis, 75% of the clinics reported unspecified large *Babesia* species, while 22.7 and 2.3% of clinics reported specifically *B. rossi* and *B. vogeli,* respectively.

Table 3: Approximate occurrence of Canine babesiosis cases according to season.

	0-5	6-40	40+
Summer	22.7% (10)	**61.4% (27)**	15.9% (7)
Autumn	**54.5% (24)**	43.1% (19)	2.3% (1)
Winter	**63.6% (28)**	34.1% (15)	2.3% (1)
Spring	34.1% (15)	**59.1% (26)**	6.8% (3)

The survey also inquired whether *B. gibsoni* is present in South Africa. 23% reported that it is present, 23% reported that it is not present, and 53% of clinicians did not know whether *B. gibsoni* is present or not. Participants were asked to rank the age groups of according to the most common occurrence (1) to least common occurrence (4) of babesiosis in that age group. The results can be visualized in Figure 7.

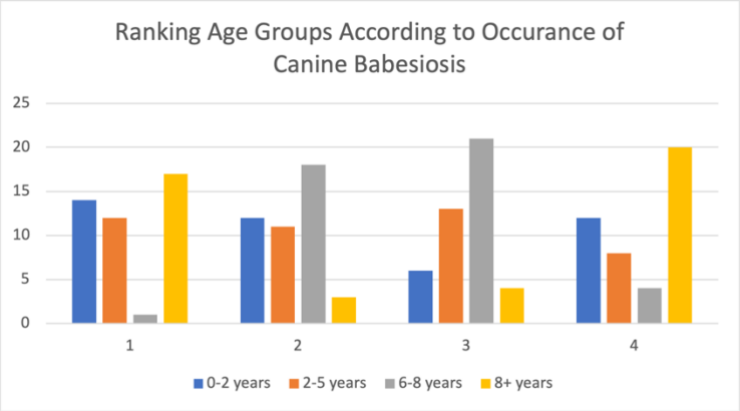

Figure 7: X-axis describes the occurance (1 most common to 4 least common) and the Y-axis depicts the number of responses.

The survey asked participants to rank the frequency of the clinical signs they experience in their canine babesiosis cases, the results of which is seen in Table 4. Participants were asked what percentage of their canine babesiosis cases they classify as complicated. 1 participant responded with 0%, 31 responded with 1-20%, 9 with 21-40%, and 3 for 41-60%. No clinics experienced 61-100% complications. In terms of the clinical manifestations of complicated babesiosis, participants were asked to select all the forms that they have experienced. All clinics experienced complications and the order of most common to least common occurrence is as follows: IMHA (91%), ARDS (61.4%), cerebral babesiosis (51%), hepatopathy (51%), AKI (54.5%), DIC (31.8%), MODS (27.3%), and SIRS (25%). In response to asking what percentage of canine babesiosis patients died, 5 participants responded 0%, 21 responded 1-5%, 10 responded 6-10%, 8 responded 11-20%, and 0 participants responded for above 20% deaths. Participants were also asked to categorize their use of antibabesial drugs, the results can be seen in Table 5.

Table 4: Ranked frequency of clinical signs experienced in babesiosis.

	1 (very rare)	2	3	4	5 (very frequent)
Fever	0	0	8	8	28
Lethargy	0	1	9	6	28
Inappetence	0	0	15	4	25
Pale mucous membranes	0	2	18	15	8
Jaundice	7	21	12	3	1
Discoloured urine	3	20	15	5	1
Vomiting	10	19	10	5	0
Collapsed (shock)	12	18	10	4	0
Abdominal Pain	19	19	3	3	0
Dyspnoea	23	12	7	2	0
Diarrhoea	23	14	6	1	0
Anuria/Oliguria	29	8	6	1	0
Seizure	40	4	0	0	0

Table 5: Categorization of antibabesial drugs usage by veterinarians in South Africa.

	Not available	Never	Rarely, sometimes	Most often	Exclusively
Diminazen aceturate	1	2	4	22	15
Imidocarb	0	11	18	11	4
Trypan blue	4	28	9	2	1

In an open-ended question, participants were asked what kind of supportive treatment are included in their canine babesiosis treatment protocol. Most common supportive treatments were IV fluid therapy, Vitamin B complex, liver supportive treatment, cortisone, prednisolone or dexamethasone and maropitant. Other therapies included blood transfusions, nonsteroidal anti-inflammatory drugs. Some clinics administer doxycycline simultaneously for *Ehrlichia* as well. The final question in the survey asked what percentage of the participant's clients used tick and flea prevention regularly: 5 participants responded 0-25%, 13 said 25-50% of clients, 22 participants reported 50-75%, and 4 replied 75-100%.

5 Discussion

Based on the results of the survey, it can be assumed that canine babesiosis is experienced in most clinics across South Africa and that it is the most commonly experienced parasitic disease in dogs. The highest number of babesiosis cases experienced in clinics in 2023 were reported from the Free State province. This may partially be due to the large response rate from this area as well as having an agricultural environment which is the ideal environment for the rodent hosts of the ticks. According to a previous South African survey conducted in 1993-1994, the province with the highest number of cases were Gauteng, Western Cape, and Kwazulu-Natal [13]. On the contrary, in our survey the responding clinics from the Gauteng province are located in the cities of Johannesburg and Pretoria, and these clinics experienced the lowest load of babesiosis cases of generally 0-10 cases a year. This may be due to the inadequate environment and lack of host for ticks in the urban areas. The canine babesiosis cases in these cities were often due to traveling to other provinces of the country or more rural areas of Gauteng. However, other studies have reported high amount of cases occurring in Gauteng [13, 44]. The one participant from Northern Cape reported low numbers of canine babesiosis, which may be due to the arid and dry environment which creates unfavourable climate conditions for the ticks. The provinces of the Western Cape and KwaZulu-Natal reported high numbers of cases in 2023. These provinces provide a more favourable environment for the ticks as they receive high rainfall and host a more subtropical environment. Based on the present survey, canine babesiosis occurs year-round in South Africa. This is not always the case in other countries such as Hungary. As for the seasonal differences of the occurrence of canine babesiosis, the highest number of cases occurred in the summer and spring months. In contrast, in Hungary the highest number of canine babesiosis cases is experienced in Spring and Autumn, and a few cases are seen also in milder winter periods [24]. The reason for this seasonal difference experienced between Hungary and South Africa may be due to the different tick vectors.

The main causative agents of babesiosis in South Africa are *B. rossi* and *B. vogeli*. South African veterinarians are not able to differentiate between the large babesia species by blood smear examination alone, however they assume that *B. rossi* is more often the cause due to the quick deterioration of the patient as well as its previously reported higher prevalence in South Africa [15, 28]. In contrast to previously published literature [11, 27, 28], based on this survey, there may be the possibility of *B. gibsoni* occurring in South Africa, however more research would be needed to determine its true occurrence. According to our results,

most clinics in South Africa confirm the diagnosis of canine babesiosis by blood smear microscopy. The clinics that opted for PCR were located in the cities and they either wanted to differentiate between the 2 large babesia species or required a more sensitive diagnostic method if low parasitaemia was suspected. Similar to what was previously reported in Hungary [24], this survey found no significant age correlation or pattern with the occurrence of canine babesiosis: 14 practices reported that it most frequently occurs in young patients while 12 practices reported it occurred more frequently in older patients. The most common clinical signs experienced were fever, lethargy and inappetence. Clinical signs of complicated babesiosis such as jaundice, dyspnoea, collapse, vomiting, and discoloured urine, have variable frequency of occurrence. Seizures were reported as a very rare clinical sign. Complications are experienced in most clinics. Only 1 clinic out of the 44, said they do not experience complications, while most of the clinics experience 1-20% of their cases as complicated. The most commonly reported complications are IMHA, ARDS, cerebral babesiosis, hepatopathy, and AKI. These findings are similar to what was reported from a previous survey from the 1990's where the most common complications experienced amongst clinics in South Africa were ARDS, cerebral babesiosis, and haemoconcentration [13]. These findings are different compared to what was reported from Hungary, where the most common complications were hepatopathy, AKI, and DIC while IMHA, ARDS, and cerebral babesiosis were rare complications [24]. This may be explained by the different pathogenicity of *B. canis*, the causative agent of most canine babesiosis cases in Hungary, compared to *B. rossi [1, 28]*. The mortality rate of canine babesiosis experienced in most practices is 1-5%, while some experience a mortality rate even above 10%. Higher mortality rates are attributed to clinics that experience complications more frequently. According to a previously published literature, the mortality rate of *B. rossi* was 12% [28], however, our results suggest a lower mortality rate. A possible explanation for reduced mortality reported in recent years (2011-2016) may be due to the reduction of treatment rates of babesia and/or reduced population of babesia infected dogs. The reduction of canine babesiosis cases presented to clinics may be due to increased host resistance, reduced pathogen virulence, or due to the increase of tick and flea prevention since the introduction of isoxazolines in 2014. The steepest decline of canine babesiosis cases were seen from 2015-2016 after the introduction of isoxazolines [44]. In this survey, half of the veterinarians reported that 50-75% of their clientele regularly use tick and flea products such as Bravecto, Simparica, and Nexgard. These products contain isooxazolines as their main ectoparasiticide agent. The veterinarians that reported that less than 50% of their clients use tick and flea prevention are

either from non-profit based practices or from private practices serving rural and low-income communities.

The most popular antibabesial drugs used in South Africa are imidocarb and diminazene aceturate. According to this survey, out of the two drugs, diminazene aceturate is the more commonly used drug to treat canine babesiosis in South Africa. This may be due to the price variation, personal preference, or availability. In the past trypan blue was a commonly used drug to treat canine babesiosis in South Africa as reported by a 1993 survey [13]. Today, South African veterinarians report that they either very rarely, or never use trypan blue. This may be due to the side effects such as a blue-green colour stain of tissues and secretions for several weeks, and its lower efficacy. Manufactures also suggest using imidocarb or diminazene aceturate to eliminate the parasites following trypan blue administration [42]. For supportive therapy; South African veterinarians today use corticosteroids, Vitamin B preparations and other liver supportive therapy, IV fluid infusions, and occasionally blood transfusion, similarly to what was surveyed in the 1990's [13].

6 Summary

Canine babesiosis is a world-wide significant parasitic disease affecting the red blood cells. Th the large babesia species affecting dogs are *B. canis, B. vogeli*, and *B. rossi*. *B. rossi* is the most pathogenic of the species and endemic to South Africa as well as having been recently found in other African countries such as Nigeria. In South Africa, canine babesiosis has a year round occurrence, with peak occurrence in the summer and winter months. The tick vector for *B. rossi* is *Haemaphysialis elliptica. B. vogeli* also occurs in South Africa, and it's tick vector is *Rhipicephalus sanguineus*. *B. canis* occurs predominantly in Europe and is vectored by *Dermacentor reticulatus*. In contrast to South Africa, canine babesiosis is not present year round in Hungary, with peak occurrences in Spring and in Autumn. The differences in seasonality and pathogenicity of canine babesiosis in Hungary and South Africa may be due to the difference in species and tick vector. *B. gibsoni*, a small babesia species, is responsible for canine babesiosis in the USA. A breed predisposition such as American Staffordshire terriers and American Pitbull terriers have been noted in *B. gibsoni.* Breed and sex predispositions have not been reported in cases of *B. rossi*, however in Hungary, German Shepards and Komondors have been proposed as predisposed breeds for *B. canis*.

Infection with babesia occurs when the tick attaches to a canine host and through the saliva the sporozoites enter the red blood cells. The replication of the parasite results in intravascular and extravascular haemolysis which results in anaemia, hypoxia, and haemoglobinuria. Based on the clinical presentation, babesia infected dogs are divided into uncomplicated and complicated cases, the latter of which include ARDS, AKI, Hepatopathy, cerebral babesiosis, pancreatitis, IMHA, DIC, SIRS, and haemoconcentration. The most common complications experience in South Africa according to our 2023 survey is IMHA, ARDS, cerebral babesiosis, and hepatopathy. The most frequently clinical signs experienced with canine babesiosis in South Africa include fever, lethargy, inappetence and pale mucous membranes. The diagnosis is usually made through visualization of the infected red blood cells on a blood smear, very rarely is PCR used, and if so, then it is used to differentiate between *B. canis* and *B. vogeli*. The preferred treatment in South Africa is predominantly diminazen aceturate, but imidocarb is also widely used. Further therapies depend on the complications experienced as well as the severity of the anaemia. The mortality rate of *B. rossi* was previously reported as 12%, however out 2023 survey suggests a lower mortality. In 2014 the use of isooxazolines were introduced in South Africa, and due to the promotion

of this tick and flea preventative products, studies have shown a decline in the number of canine babesiosis cases in recent years.

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Thesis progress report for veterinary students

Name of student: Lize-Mari Hayton

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Name and title of the supervisor: Dr. Máthé Ákos DVM, PhD, Associate Professor

Department: Department of Internal Medicine

Thesis title: Canine Babesiosis in South Africa

Consultation – 1st semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2023	09	18	Discussing topic and table of contents	
2.	2023	09	29	Establishing the topic and format of survey	
3.	2023	11	21	Reviewing the first draft of the survey	
4.	2023	12	06	Finalizing the draft and domain of survey	
5.	2024	01	02	Update on Survey	

Grade achieved at the end of the first semester: 5

Consultation – 2nd semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2024	03	20	Understanding and interpreting the results of the survey	
2.	2024	06	21	Draft 1	
3.	2024	09	11	Draft 2	
4.	2024	10	02	Draft 3	

5.	2024	10	09	Final Draft and next steps	

Grade achieved at the end of the second semester: 5

The thesis meets the requirements of the Study and Examination Rules of the University and the Guide to Thesis Writing.

I accept the thesis and found suitable to defence,

.....
signature of the supervisor

Signature of the student:

Signature of the secretary of the department:

Date of handing the thesis in: