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REVIEW

DIROFILARIASIS: AN EMERGING, YET NEGLECTED ZOONOSIS

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ABSTRACT

This paper addresses the main aspects of the occurrence of dirofilariasis in animals and humans, especially in cases of infections by *Dirofilaria immitis* and *D. repens*. It highlights the importance of recognizing this parasitosis as an emerging zoonosis in the Americas, with a focus on Brazil, while providing global comparisons. The biological and environmental factors that influence its maintenance in natural conditions are also discussed.

KEY WORDS: *Dirofilaria*; *Dirofilaria immitis*; *Dirofilaria repens*; zoonosis; dirofilariasis; Americas; Brazil.

INTRODUCTION

Filarids belong to a clade of Nematoda that infects mammals and other vertebrates, except fish. Adult females are viviparous, meaning they release first-stage larvae, called microfilariae, instead of eggs (Mäser, 2022). Helminths of the genus *Dirofilaria* are currently classified as follows: Phylum: Nematoda; Class: Secernentea; Order: Spirurida; Superfamily: Filarioidea; Family: Onchocercidae; Genus: *Dirofilaria* (Moreira et al., 2020).

The first known reference to the parasitism of dogs by *Dirofilaria immitis* occurred in 1626 when Francesco Birago, an Italian nobleman, described finding a worm in the heart of one of his dogs. However, the first detailed description of the disease in dogs was published in the United States

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by Osborne in 1847 (Simón et al., 2012). In Brazil, the first cases of pulmonary dirofilariasis in humans were described in Bahia in 1878 by Silva Araújo and in Rio de Janeiro in 1887 by Magalhães (da Silva & Langoni, 2009). In 1856, Joseph Leidy described adult worms removed from the hearts of dogs, naming them *Filaria immitis*. After the creation of the genus *Dirofilaria* by Railliet and Henry, two French parasitologists, this species became known as *Dirofilaria immitis* (Leidy, 1856) Railliet & Henry, 1911 (Knauer, 1998).

The genus *Dirofilaria*, subdivided into two subgenera (*Dirofilaria* and *Nochtiella*), currently includes 27 valid species, among which *D. immitis*, *D. repens* and *D. asiatica* (Colella et al., 2025) are considered the most relevant due to their high prevalence and ability to cause morbidity in dogs and cats. These species are also responsible for pulmonary and subcutaneous dirofilariasis in humans, respectively (Knauer, 1998; Simón et al., 2005; Perles et al., 2024). *D. immitis* belongs to the subgenus *Dirofilaria*, while *D. repens* and *D. asiatica* belong to the subgenus Nochtiella. Other species of the genus, though less frequently, have been reported infecting humans: *D*. (*Nochtiella*) striata, *D*. (*Nochtiella*) *tenuis*, *D*. (*Nochtiella*) *ursi*, *D*. (*Nochtiella*) *spectans*, and *D*. (*Nochtiella*) *magnilarvata* (Perles et al., 2024). Recent studies describe a new species, *D*. (*Nochtiella*) *asiatica* in Asia, expanding the known diversity of the genus (Baptista-Fernandes et al., 2015; Perles et al., 2024; Colella et al., 2025).

Helminths of the genus *Dirofilaria* have female mosquitoes of the family Culicidae as intermediate hosts. In the case of *D. immitis* and *D. repens*, various mammal species can act as definitive hosts; however, these filarids are better adapted to wild or domestic canids. Felids and humans are less susceptible hosts, in which the development differs from that in canids (McCall et al., 2008; Simón et al., 2012).

Dirofilariasis represents a significant health problem for dogs and cats. In South America, the infection of these animals is found in almost all countries, except Chile and Uruguay, where specific surveys to determine its occurrence have not yet been conducted (Labarthe & Guerrero, 2005; Simón et al., 2022). On the other hand, periodic surveys in this continent indicate a trend towards an increase in the prevalence of dirofilariasis (Simón et al., 2012). For humans, according to the World Health Organization, dirofilariasis is an emerging zoonosis (Kramer et al., 2007; Simón et al., 2012), with 1,782 cases reported until 2012 and about 4,000 cases documented in the literature by 2024 (Simón et al., 2012; Perles et al., 2024). It is currently a notifiable disease in Ukraine, Russia, and Belarus (Kartashev et al., 2014).

This review emphasizes the global impact of dirofilariasis, with particular attention to *D. immitis* and *D. repens* in the Americas, where data gaps persist despite high prevalence.

Dirofilariasis: Biology and Distribution

Dogs and cats can be infected by various species of filarids; in the Americas, the following species have been reported: *Acanthocheilonema reconditum*, *D. immitis*, *D. repens*, *Cercopithifilaria grassi*, *C. bainae*, and *Onchocerca lupi* (Dantas-Torres & Otranto, 2020). Among these species, *D. immitis* and *A. reconditum* are found infecting dogs and cats in Brazil, and there are numerous reports of *D. immitis* infection in humans (Sneider et al., 1986; Saad et al., 1991; Amato Neto et al., 1993; Amato et al., 1995; Campos et al., 1997; Cavallazzi et al., 2002; Rodrigues-Silva et al., 2004; Doltrário et al., 2019).

Both *D. immitis* and *D. repens* can infect various mammal species; however, they are better adapted to wild and domestic canids, which serve as their reservoirs (Simón et al., 2012). De Argôlo et al. (2018), studying the pattern of canine infection by *D. immitis* in the Amazon, found that male dogs in the Marajó Island region were more likely to acquire the infection than females, with no evidence of age influence. Felids and humans are less susceptible hosts (McCall et al., 2008), in which the helminths develop differently from canids. These two species are considered the most relevant among the genus due to their high prevalence and ability to cause significant morbidity in dogs and cats, as well as being responsible for pulmonary dirofilariasis in humans in the case of *D. immitis* and the subcutaneous form in the case of *D. repens* (Simón et al., 2005).

Dirofilaria immitis has a cosmopolitan distribution, being found in tropical, subtropical, and temperate regions across various continents; *D. repens* has been reported almost exclusively in the Old World (Simón et al., 2012). Recently, using molecular techniques, it was possible to identify the occurrence of *D. repens* infection in a dog in Colombia (Ballesteros et al., 2023). This finding reinforces the need for the use of molecular techniques in the accurate identification of *Dirofilaria* species, which could result in a better understanding of the distribution of various species within the genus (Perles et al., 2024).

In the review conducted by Anvari et al. (2020), the overall infection rate of dogs by *D. immitis* was 10.9%, varying considerably by region: 22.6% in Australia, 12.1% in Asia, 11.6% in the Americas, 10.5% in Europe, and 7.6% in Africa. In Brazil, the prevalence rates of canine infection by *D. immitis* vary according to the average humidity and temperature levels of the region (Dantas-Torres & Otranto, 2020). Thus, Soares et al. (2014) obtained a prevalence rate of 44% in the Amazon, while Labarthe et al. (2014) found rates of 29.7%, 26.3%, and 13.2% in the northeast, southeast, and south regions of the country, respectively. Other surveys referred to by Simón et al. (2012) also indicate high frequencies of infection in dogs: 44% in São Paulo, 43% in Pernambuco, and 33% in Rio de Janeiro.

Dirofilariasis in felids is commonly detected in the same areas where canine infection is found, but with lower prevalence due to the lack or scarcity of microfilaremia in these animals (Simón et al., 2012). Cats may present severe pulmonary symptoms or sudden death, emphasizing the need for preventive measures, such as monthly chemoprophylaxis and antigen testing in endemic areas (Dunn et al., 2011; AHS, 2019). This indicates that felids do not play a significant role in the transmission of dirofilariasis (McCall et al., 2008). In humans, who also do not develop microfilaremia when infected, the distribution of dirofilariasis does not necessarily coincide with that of canids, partly due to the lack of reliable epidemiological data (Simón et al., 2012).

Dirofilaria immitis inhabits the pulmonary artery and right ventricle of dogs, *D. repens* is generally found in the subcutaneous tissues of its definitive hosts, occasionally locating in muscle fascia or even the abdominal cavity (Genchi et al., 2011). Humans, who are not usual hosts for *Dirofilaria*, do not allow the parasite to complete its development. *D. immitis* can reach branches of the pulmonary artery and trigger an inflammatory reaction that destroys the worm, forming nodules containing parasitic remnants (Simón et al., 2005). *D. repens*, in turn, forms subcutaneous nodules in humans and occasionally reaches the ocular region. Incidentally, both species can be found in other regions when infecting humans (Simón et al., 2012).

Female *Dirofilaria* after copulation begin to produce and release microfilariae (L1) 6 to 9 months after infecting canids; in felids, the production of microfilariae is much lower or even nonexistent (Courtney & Zeng, 1989). In humans, the parasite does not complete its development, and microfilariae production does not occur. Microfilariae of *D. immitis* measure between 290 and 330 µm and may survive up to two years in the susceptible host; adult worms, in turn, live up to seven years (Simón et al., 2012).

There are references to the occurrence of an evening peak in the microfilaremia of dogs infected by *D. immitis* (Bowman & Wu, 2022); however, there are controversies regarding this, with records of evening periodicity in experiments conducted in Romania (Ionică et al., 2017), while in other regions this has not been proven (Lovis et al., 2017).

All species of the family Onchocercidae, to which the genus *Dirofilaria* belongs, have a symbiotic relationship with bacteria of the genus *Wolbachia*, which play a fundamental role in embryogenesis and the molting process of the cuticle at various stages of filarid development (Bandi et al., 2001; McHaffie, 2012; Mäser, 2022).

Colonies of *Wolbachia* are found in the lateral cords of both male and female *Dirofilaria*, as well as in the reproductive structures of females (Slatko et al., 2010). This type of endosymbiosis is mandatory for the development of filarids in their vertebrate hosts and their survival as adults (McGarry et al., 2004; Taylor et al., 2013). The presence of these endosymbionts encodes, through their genome, the synthesis of enzymes responsible for the biosynthesis

of heme, purines, and pyrimidines, which the *Dirofilaria* genome alone cannot accomplish (Noack et al., 2021). On the other hand, there are reports that the presence of *Wolbachia* is related to the intensity of the inflammatory response of the vertebrate host, as demonstrated in the case of human infection by *Onchocerca volvulus* (Higazi et al., 2005) and the increased inflammatory process associated with dirofilariasis that occurs with the death of the worms, whether natural or treatment-associated (Taylor et al., 2001).

About 60 species of mosquitoes have been identified as potential vectors of *D. immitis*; among these, *Aedes aegypti*, *Ae. albopictus*, *Ae. canadensis*, *Ae. sierrensis*, *Ae. trivittatus*, *Anopheles punctipennis*, *A. quadrimaculatus*, and *Culex quinquefasciatus* are considered the most important (Wang et al., 2014). In Brazil, *Ochlerotatus scapularis*, *Oc. taeniorhynchus*, and *C. quinquefasciatus* have been incriminated as the main vectors of *D. immitis* (Labarthe et al., 1998; Ahid & Lourenço-de-Oliveira, 1999). The transmission of *Dirofilaria* spp. in a given region depends on the presence of mosquitoes susceptible to filarid parasitism and the existence of a minimum number of dogs infected with microfilaremia. Thus, human behavior as dog owners and climatic factors that allow the presence of vectors have an undeniable influence on the prevalence level of dirofilariasis in a region, controlling the annual period of mosquito blood-feeding activity, reducing the time required for larval development, and thereby increasing the parasite transmission rate (Genchi et al., 2005; Brooks & Hoberg, 2007). Human activities such as urbanization of wild areas on the outskirts of cities, the construction of artificial irrigation and water distribution systems, by creating microhabitats favorable to mosquito breeding, favor the growth of vector populations and influence the level of filarid transmission (Garcez et al., 2006; Tabachnick, 2010; Simón et al., 2012; González-Miguel et al., 2020; Simón et al., 2022). It is also worth considering the role that dog migrations can play in spreading dirofilariasis to previously unaffected regions (Cuervo et al., 2013).

To enable infection with the development of adult worms, *Dirofilaria* needs to evade the immune response that, in non-susceptible hosts, limits the parasite's survival. In susceptible hosts, the immune response is subverted by various mechanisms, among which the production and release by *D. immitis* of parasite-derived molecules (PDM) stand out. These are metabolites, proteins, and microRNAs released by the parasite that act to ensure its survival (Geary, 2023).

Dirofilariasis: Clinical Aspect and Diagnosis

The infection of vertebrate hosts by *Dirofilaria* determines variable clinical aspects, depending on the filarid species and the vertebrate, with the most characteristic cases occurring in canids.

Canine dirofilariasis, caused by *D. immitis*, affects the cardiorespiratory system and can lead to the animal's death due to lesions caused by adult worms and their antigenic products (Kramer et al., 2005). The association between *Dirofilaria* and *Wolbachia* may contribute to increased morbidity (Simón et al., 2012; Kramer et al., 2005). The disease, when manifest, generally develops chronically and progressively, with symptoms of vascular and pulmonary involvement and, eventually, affects the right heart. The death of adult *D. immitis* specimens, either spontaneously or after treatment, can cause thromboembolism and inflammatory changes that endanger the animal's survival. Lesions in other organs, such as the liver, peritoneal cavity, brain, and eyes, may occur. Some dogs may present respiratory distress as the only clinical manifestation due to eosinophilic pneumonia (Simón et al., 2012).

Considering the set of most frequent signs and symptoms, dogs with *D. immitis* infection are classified into three groups by Simón et al. (2012): a. Mild manifestations: asymptomatic dogs or those with a cough; b. Moderate manifestations: dogs with a cough, exercise intolerance, altered lung sounds; c. Severe manifestations: cough, exercise intolerance, dyspnea, hepatomegaly, syncope, and, sometimes, death.

In cats, dirofilariasis is often asymptomatic; when symptomatic, the main manifestations are pulmonary, characterized by cough and respiratory difficulties; sometimes, digestive alterations occur, including vomiting. Occasionally, sudden death occurs without premonitory signs (Atkins et al., 2000; Litster & Atwell, 2008; Simón et al., 2012; Noack et al., 2021).

In humans, *D. immitis* infection has a cosmopolitan distribution and usually results in the formation of pulmonary nodules around immature worms that can be mistaken for neoplasms (Foroulis et al., 2005; Simón et al., 2005; Simón et al., 2012; Dantas-Torres & Otranto, 2013). The formation of a single nodule is more frequent; however, multiple nodules can appear (Kochar, 1985; Campos et al, 1997). Occasionally, pulmonary nodules may spontaneously disappear, suggesting that such lesions may be transient (Cordero et al., 1992). When human infection is caused by *D. repens*, subcutaneous nodules form, about 35% of which are located near the eyes: orbital region and eyelids, sometimes in the subconjunctival area or vitreous (Pampiglione & Rivasi, 2000). In total, approximately 4,000 cases of human dirofilariasis have been reported in the literature (Perles et al., 2024). A review of 576 cases of human dirofilariasis in this century revealed a predominance of *D. repens* among the species involved (416 patients or 72%); *D. immitis* was responsible for 40 cases (6.9%), and three other species (*D. tenuis*, *D. hongkongensis*, and *D. ursi*) caused the remaining cases (Simón et al., 2022). In São Paulo, Brazil, Campos et al. (1997) studied 24 patients with pulmonary dirofilariasis, of whom 75% had a single non-calcified nodule located subpleural, with a diameter ranging from 1 to 3 cm; 17 (54.1%) were asymptomatic and were diagnosed during

routine imaging for another reason. Among patients with complaints, chest pain and cough were the most frequent.

The laboratory diagnosis of canine *Dirofilaria* infection can be performed by various techniques. Detection of microfilariae in peripheral blood is among the most used (Simón et al., 2012; Noack et al., 2021) due to its ease of execution. It is worth considering that, in certain regions, an evening periodicity pattern in the presence of microfilariae in peripheral blood has been identified (Ionică et al., 2017; Bowman & Wu, 2022). There are also commercially available tests for antibody detection by enzyme-linked immunosorbent assay (ELISA) or for the detection of parasitic antigens by immunochromatography (Simón et al., 2012), with good results regarding sensitivity and specificity, in addition to molecular biology tests, especially used in dogs with suspected infection but negative microfilaremia (Henry et al., 2018). Antigen tests (e.g., SNAP 4Dx) are the gold standard for *D. immitis*, while PCR aids species differentiation (AHS, 2019; CAPC, 2020). Smith et al. (2024) recommend using the Knott method in dogs with low microfilaremia, followed by the search for parasitic DNA by PCR.

In humans, the diagnosis is generally obtained through imaging exams that reveal the presence of a pulmonary nodule, and its confirmation depends on a biopsy, which also has a curative effect in the case of single nodules (Simón et al., 2005; Simón et al., 2012).

Treatment and Prevention of Dirofilariasis

In dogs, chemoprophylaxis should ideally commence before eight weeks of age, with testing for antigen and microfilariae prior to initiation to ensure protocol adherence. Animals in endemic regions require semiannual testing followed by annual screenings, while those in non-endemic areas should be tested one month before and after mosquito season (Nelson et al., 2005). For cats, despite their partial resistance to infection, year-round prevention with macrocyclic lactones is recommended due to their aberrant host status and higher risk of severe pulmonary pathology (Venco et al., 2015). Humans, though accidental dead-end hosts, benefit indirectly from pet-focused chemoprophylaxis and mosquito control measures, which reduce zoonotic transmission. Targeted prevention in dogs, particularly in low-density populations, diminishes reservoir prevalence, thereby interrupting the parasite's life cycle. Integrated approaches, including vector control and public education, are critical in high-risk areas (Simón et al., 2012; CAPC, 2020).

The treatment of dogs is usually carried out with melarsomine dihydrochloride, in varying regimens depending on the clinical situation of the animals (da Silva & Langoni, 2009). According to da Silva & Langoni (2009), mild or moderate infections are treated with two doses of 2.5 mg/kg, 24 hours apart. For more severe disease, the drug is administered in a single dose, with a

repeat dose after 30 days. Dogs that remain positive for parasitic antigen should repeat the treatment and, if necessary, undergo ivermectin administration (50 µg/kg). According to Taylor et al. (2005), the use of ivermectin combined with doxycycline for at least 10 weeks showed blockage of microfilaremia and, after 36 weeks, the elimination of 78% of adult worms. However, other authors did not achieve the same result, although they noted a reduction in the inflammatory process (Simón et al., 2007).

It is important to consider that the destruction of adult worms can result in side effects of varying morbidity due to the release of parasitic antigens into the bloodstream; these effects can be mitigated by the administration of corticosteroids (Taylor et al., 2001; Foroulis et al., 2005). Humans, since the infection is generally limited to an inactive nodule, should not receive drug treatment; the biopsy used to confirm the diagnosis constitutes effective treatment (Foroulis et al., 2005).

FINAL CONSIDERATIONS

Despite its growing relevance as an emerging zoonosis, dirofilariasis remains underdiagnosed and neglected in various regions of the world, especially in Brazil. The increase in human cases, associated with its wide geographic distribution, reinforces the need for an integrated approach that considers the interaction between environmental, biological, and social factors. Climate change, unplanned urban expansion, and the intensification of coexistence between humans and domestic animals are determinants that increase the challenges for controlling this parasitosis.

The recognition of dirofilariasis as a public health problem should be accompanied by investments in active surveillance strategies, training of health and veterinary professionals, and the development of more accessible and sensitive diagnostic tools. Additionally, the implementation of educational programs aimed at pet owners and communities is essential to promote awareness of preventive measures, such as the use of repellents, prophylaxis in dogs, and vector control. Addressing dirofilariasis requires interdisciplinary collaboration, as only through a One Health (Singh et al., 2023) approach will it be possible to advance in mitigating the impacts of this emerging zoonosis.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest to disclose.

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