# Heartworm Disease in Canines

Mandalyn Moore

Oklahoma State University

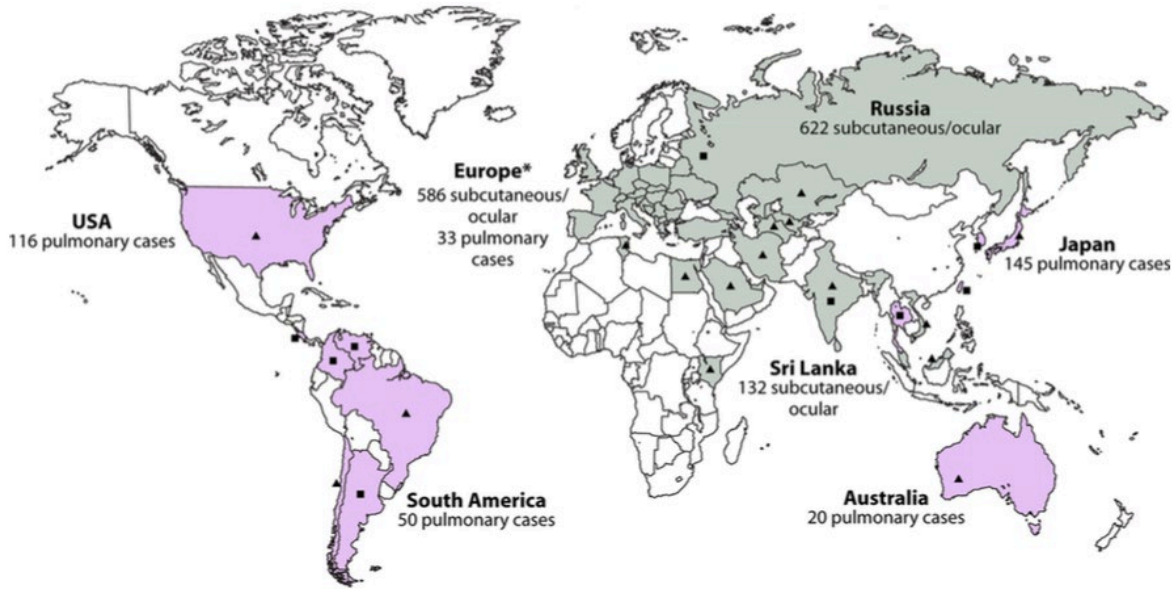
**Abstract**

Heartworm disease in canines is a complicated disease that has been diagnosed in all 50 states and in every continent excluding Antarctica. A filarial disease most commonly spread by *D. immitis* in North America, but also spread by other strains such as *D. repens* in other parts of the world. In North American infections are commonly seen in domestic and wild canids, but in many subtropical countries human infections have been diagnosed. Human infections manifest in one of four ways, pulmonary, subcutaneous, ocular, and lymphatic. Each different manifestation is accompanied by different symptoms and prognoses. Many infected dogs will be asymptomatic, but as the infection worsen and worm burden increases, dogs will show symptoms such as lethargy and decrease in exercise tolerance. As infection worsens, the symptoms will become more severe and eventually lead to right sided heart failure. Heartworm infections in canines can be diagnosed various ways depending on resources. The two most common methods of diagnosing a heartworm infection are ELISA antigen tests, many are commercially available to veterinarians, and blood smear tests to identify microfilaria. Melarsomine dihydrochloride injections have been the go to treatment for years, but due to its high cost and severe complications, many owners and veterinarians are turning to alternative treatments, such as Advantage Multi® (10% imidacloprid + 2.5% moxidectin) + doxycline, as cheaper and safer treatment option. Prevention of heartworm disease is a cheaper and safer option than treatment. Many effective heartworm preventions are on the market. In areas of high infection rates and possibly resistant strains, owners and veterinarians are turning toward a double defense protocol, utilizing heartworm preventive as well as repellent to prevent the spread of heartworm disease. With education about prevention and the heartworm life cycle, clients would be more willing to comply with recommendations regarding heartworm preventatives.

## Background

*Dirofilaria immitis* is the most common strain of filarial worm seen in North America. Transmitted by mosquitos, domestic dogs are the typical hosts, but cats and wild canines, such as coyotes and foxes, are also hosts. *D. immitis* reside in the pulmonary arterial system and heart of the host. If left untreated, the host will suffer from congestive heart failure, eventually leading to death. *D. immitis* has been diagnosed in every state in the United States, with the highest prevalence in areas surrounding the Mississippi, Missouri, and Ohio river, where prevalence can reach 48.8% (Simon et al., 2012). Different types of filarisis are found all over the world, affecting different species, and exhibiting different signs and symptoms. Humans are at risk of infections of *D. immitis* and *Dirofilaria repens*, a filarial nematode which acts similarly to *D. immitis*. Filarial infections in human present in one of two ways, pulmonary or subcutaneous/ocular. The worldwide distribution of human dirofilariasis, as research currently

Fig. 1. Distribution of human dirofilariasis cases. Purple colored countries are areas *D. immitis* diagnosis are prominent and grey colored countries are areas *D. repens* diagnosis are prevalent. (Simon et al., 2012)



shows, does not correlate with the distribution of canine dirofilariasis. This is primarily caused by a lack of data. (Simon et al., 2012). Figure 1 illustrates the distribution of human dirofilariasis cases around the world.

**Pulmonary dirofilariasis**. Pulmonary dirofilariasis is characterized by pulmonary nodules forming around immature adult worms. The dirofilariasis causes embolism and localized inflammation when it reaches a small or medium branch of the pulmonary artery. Nodules are typically found in the right lung of males with an average age of 53, but infections have been diagnosed in patients age 10-79. Most patients do not present symptoms upon infection, but when symptoms do present they are typically nonspecific, including, coughing with pleural or nonpleural thoracic pain, homotypic sputum, and fever (Simon et al., 2012). When diagnosed on radiographs, the nodule can often be confused with a malignant growth. In the rare case of multiple nodules being diagnosed via radiographs, the nodules are spherical in shape, have well defined borders, and have homogenous density, suggesting a benign profile (Simon et al., 2012). The nodules typically disappear over time, although the longest recorded presence of a single nodule is 13 years (Simon et al., 2012).

**Subcutaneous/ocular dirofilariasis.** Subcutaneous dirofilariasis is caused by adult and pre-adult *D. repens* in the subcutaneous tissue causing subcutaneous nodules. Opposite from pulmonary dirofilariasis, subcutaneous dirofilariasis is more common in women (Simon et al., 2012). Ocular dirofilariasis is the most serious of filarial infections in humans. Serious consequences of infection include damaged vision, floaters, and loss of sight.

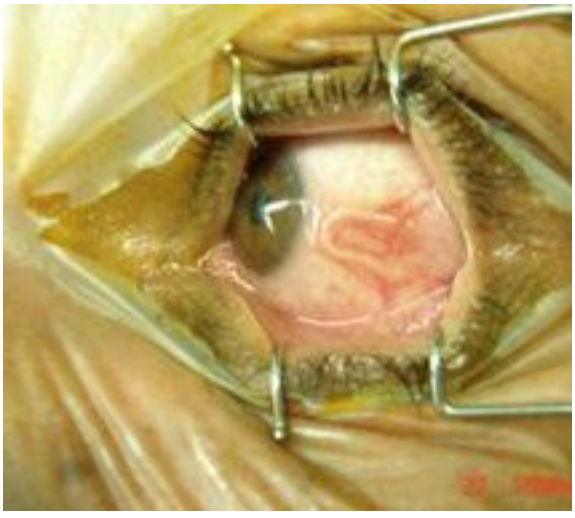


Fig 2. *D. repens* lying within scelera of human eye forming U shape granuloma

Permanent serious symptoms will occur in about 10% of infected patients, including retinal detachment, glaucoma, and other losses of visual acuity (Simon et al., 2012). Figure 2 illustrates an ocular dirofilariasis infection.

**Lymphatic Filariasis.** Lymphatic Filarial (LF) infections in humans are different than those previously mentioned because it presents in a very visible manor. Lymphatic filariasis does not present symptoms in approximately two thirds of infected individuals (Wynd, Melrose, Durrheim, Carron, & Gyapong, 2007). The other one third who do present symptoms suffer from chronic lymphedema, elephantitis, and hydrocele, due to obstruction of the lymph flow. LF is caused by several different parasitic worms, transmitted by mosquitos, namely *Wuchereria bancrofti* (NORD, 2009). Lymphatic filariasis is not caused by dirofilariasis, but rather worms in the same filariasis family. LF is present in approximately 80 tropical and subtropical countries, and extremely rare in countries with more temperate climates such as North America. Medical institutions are primarily focused on prevention of the spread of LF rather than treating those affected. Community wide doses of diethylcarbamazine and albendazole or albendazole and ivermectin are given to entire communities, once annually for a period of four to six years to prevent infection (Wynd et al., 2007). LF is different from the other filarial infections in humans not only because its symptoms present very prominently, but it also has serious social and economic effects on the infected individuals. Those affected with elphantitis and hydrocele are often marginalized and poor (Wynd et al., 2007). Women who suffer from chronic LF often do not find husbands, in a society where a woman's sole purpose is to marry and reproduce.

## Life Cycle/ Pathophysiology/ Clinical Signs

Understanding the life cycle and pathology of heartworm disease is crucial for deciding what steps to take next. The life cycle of *Dirofilaria* is comprised of a host and a vector. Both *D. immitis and D. repens*, have poor host specificity, they can infect a multitude of different hosts, most prominently canids. Other species like humans and cats can be infected, but are less susceptible hosts. Mosquitos act as the vector for *Dirofilaria*. The host and the vector must work symbiotically to support the spread of heartworm disease.

**Life Cycle in Canine Host.** When an infected mosquito takes a blood meal from a dog, the mosquito deposits a hemolymph on the puncture wound. The hemolymph carries the "larvae 3" (L3), infective stage, of *D. immitis* which is able to penetrate the hosts skin, and enter the blood stream on its own (Simon et al., 2012). 3 to 12 days post infection, the L3 stage of larvae will molt into the L4 stage. Molting to the fifth and final stage will not occur until approximately 50 to 70 days post infection. The first preadult worms arrive in the canine host's heart at around 80 days post infection and will reach sexual maturity at 120 days. Adult worms typically reside in the pulmonary arteries of the host but may spread to the right ventricle, right atrium, and caudal vena cava in hosts with a heavy worm burden (Hoch & Strickland, 2008). Adult worms have a thread-like appearance. Male heartworms can grow to be 6 to 7 inches (15 to 18 cm) long and 0.7 to 0.9 mm in diameter. Females can reach 10 to 12 inches (25 to 30 cm) and 1.0 to 1.3 mm in diameter. Sexually mature female heartworms start producing first larvae, called microfilaria, between 6 to 9 month post initial infection (Simon et al., 2012). Microfilaria are released into the blood stream to be picked up by mosquitos during a blood meal. Microfilaria can live in the blood for up to 30 months. Adult heartworms can live in the host for over 7 years.

**Life Cycle in Mosquito Vectors.** *D. immitis* microfilaria are consumed by mosquitos during a blood meal on an infected dog. Within 24 hours of ingestion, the microfilaria molt into the L2 stage once they have reached the malpighian tubules of the mosquito's digestive tract (Simon et al., 2012).The L2 larvae molt into the infective L3 larvae three days after the initial molt. The time it takes microfilaria to molt is temperature dependent. The ideal temperature for microfilarial molting is 57° F (14° C) (Hoch & Strickland, 2008). If the ambient temperature is not met, the length of time necessary for L2 to molt to L3 will be increased. Once the L3 stage is reached, the larvae migrate to the mouthparts of the mosquito until it takes a blood meal. Upon the blood meal, the L3 larvae will be deposited on the host with a hemolymph.

**Pathophysiology.** The name "heartworm" suggests that an infection of *D. immitis* is primarily a cardiac disease, but the original damages are done to the pulmonary arteries. Heartworm disease should be considered a pulmonary disease until the last stages of infection, when worms have migrated to the right cardiac chambers. The degree of the damage done is dependent on the number of worms present, the duration of the infection, and the host's immunological response to the infection. It is believed mature worms cause damage, approximately 3 months post infection, when they arrive in the pulmonary artery (Hoch & Strickland, 2008). Adult heartworms typically reside in the caudal pulmonary vascular tree where damage is caused by the release of toxic substances, the host's immunologic response, and the mere physical trauma of the worm's presence in the arteries. The initial damage is done to the endothelial cells of the arteries by triggering of activation and attraction of leukocytes and platelets (Hoch & Strickland, 2008). These changes can eventually lead to smooth muscle cell proliferation and collagen accumulation, resulting in fibrosis. Dead or dying worms are thought to cause the most damage to the host. Damage includes, thrombosis, granulomatous inflammation, and rugose villous

inflammation (Hoch & Strickland, 2008). The affected vessels become thrombosed, thickened, and functionally incompetent. Heartworms also release substances triggering vasoconstriction and hypoxia, resulting in pulmonary hypotension and lowered cardiac output. Pulmonary hypertension can lead the thickening of the right ventricular wall, ventricular hypertrophy. Hosts with a high worm burden, may present chronic pulmonary hypertension, leading to congestive heart failure. The most severe presentation of heartworm disease is known as caval syndrome. Caval syndrome is a life threatening presentation of heartworm disease. Adult worms enter into the right ventricle of the host (Kittleson). There the worms cause tricuspid regurgitation and poor cardiac output. Pulmonary hypertension may worsen the amount of tricuspid regurgitation. The decrease of forward blood flow from the right heart back to the left, causes the left heart to become volume underloaded, and the cardiac output from the left is also decreased (Kittleson). The decrease in cardiac output results in poor blood diffusion. This is seen within the host as pale mucous membranes and decreased femoral pulse pressure. The tricuspid regurgitation causes right heart failure for those hosts with caval syndrome.

**Clinical Signs.** Heartworm disease in canines usually has a chronic progression. The majority of infected dogs will not show symptoms. A heartworm infection is usually diagnosed during a routine screening, rather than a symptomatic patient. Dogs will not show any symptoms for months or years post infection, but as the worm burden and arterial damage becomes more severe, patients will present clinical signs. Symptoms usually start as a chronic cough. Coughing is typically followed by varying severity of labored breathing, and possibly lipothymias or fainting after exercise or excitement (Venco, 2007). Other symptoms may include, weight loss, loss of exercise tolerance, lethargy, poor body condition, and abdominal distention (Hoch & Strickland, 2008). As the infection continues to worsen, abnormal pulmonary sounds can be

heard resembling a crackling sound over the caudal lung lobes. A second heart sound splitting can often be heard as well (Venco, 2007). Once the infection has progressed into right cardiac congestive failure, the infected patient can present, fluid accumulation in legs, anorexia, weight loss, and dehydration. During this stage of infection, a cardiac murmur over the right side of the thorax due to tricuspid valve insufficiency and abnormal cardiac rhythm due to atrial fibrillation can be heard (Venco, 2007). Sudden death rarely occurs in infected dogs, and usually happens in response to respiratory distress or cachexia.

## Diagnosis

**Blood Test for Adult Female Antigens.** Antigen testing using an ELISA is the most common and preferred method of heartworm diagnosis. The majority of tests available to veterinarians require a small amount of blood sample, are easy to use, and highly sensitive and specific. These test detect an antigen emitted by female worms and may provide information regarding worm burden, based on the concentration of the antigen released by female worms. The downside to the antigen tests is the fact they only can detect infections that include mature female worms emitting the antigen. The tests will produce a false negative if the infection is comprised of only male worms, or during the first 5 to 8 months post infection because female worms will not be mature (Hoch & Strickland, 2008). For this reason, other forms of diagnosis are recommended to confirm a false negative. Antigen tests have been available for use for three decades, and these tests are constantly being improved to produce more reliable, accurate, and useful results. A study was done by the University of Florida comparing the sensitivity and specificity of 5 popular patient-side kits available to veterinarians. The study compared Antigen Rapid One Step (Bio Note), SNAP 4Dx Plus Test Kit (IDEXX), WITNESS Heartworm Canine Heartworm Antigen Test Kit (Zoetis), VetScan Canine Rapid Test (Abaxis), and Solo Step CH Canine Heartworm Antigen Test (Heska). A blood sample was obtained from 250 dogs 1 hour prior to euthanasia. After euthanasia, the results of the antigen tests were compared to the dog's worm burden found via necropsy. The subjects worm burden was divided into one of five subclasses of female worms, 0, 1-5, 6-20, 21-40, and >40. Each test was performed once, side-by-side according to the manufactures directions. The overall sensitivity was ≥ 97.5 and the overall specificity was 94.0% for all five tests (Little, Saleh, Wohltjen, & Nagamori, 2018). The

sensitivity for samples from dogs with a worm burden of 1-5, 6-20, and 21-40 was between 96 and 100%. The sensitivity slightly increased in dogs with a worm burden about 41. The agreement between all five tests was between 97 and 100%. This study proves that all major commercially available kits produce accurate results allowing practitioners to make informed decisions on subsequent steps.

**Blood Test for Microfilaria.** A blood smear sample may be examined under the microscope using a Knott or Difill test, to determine the presence of microfilaria. If microfilariae are seen, it is considered to be definitive proof of an infection. False negative results may be obtained in dogs that are amicrofilaremic. 30% of dogs do not have circulating microfilaria, even though they have an infection of adult worms (Venco, 2007). An infected patient may be amicrofilaremic for multiple reasons, including previous administrations of heartworm preventative, a single sex infection, prepatent infections, or immune mediated destruction of microfilariae (Hoch & Strickland, 2008). Further diagnostic testing may be necessary in suspected positive cases who are amicrofilaremic.

**Thoracic Radiographs.** Radiographs alone are not used for diagnosing heartworm disease, but useful for detecting severity and monitoring progression of infection. Radiographs may show in very severe cases, enlargement of pulmonary artery, abnormal

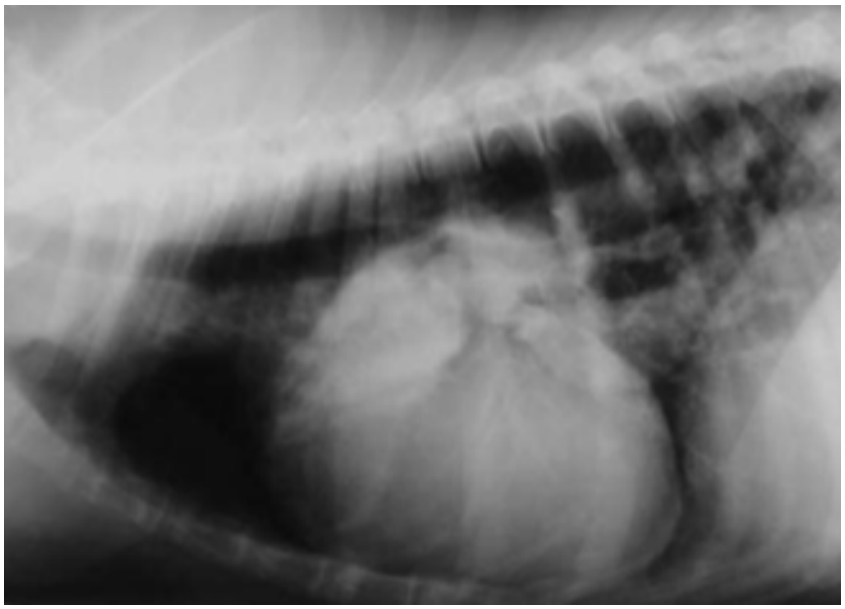


Fig 3. Thoracic radiographs of a 12-year-old infected dog with right sided cardiomegaly and severe pulmonary vascular disease.

pulmonary patterns, and in very severe cases, right-sided cardiomegaly (Venco, 2007). Radiographs are also useful for assessing the severity of pulmonary lesions, but cannot assess worm burden. Figure 3 depicts radiographs from a 12-year-old infected dog with right sided cardiomegaly and severe pulmonary vascular disease (Venco, 2007).

**Electrocardiography.** Electrocardiograms display the electrical activity from the heart. Abnormalities on electrocardiograms are typically only found in severe cases. Electrocardiography may reveal right axis deviation during the last stage of disease, when the right cardiac chamber has sustained substantial damage (Venco, 2007). Arrhythmias can also be detected via electrocardiogram but are uncommon unless cardiac enlargement is moderate to severe (Hoch & Strickland, 2008).

**Echocardiography.** Echocardiography is useful in detecting right heart dysfunction and enlargement, presence of tricuspid regurgitation, severity of pulmonary hypertension, as well as assessing worm burden (Hoch & Strickland, 2008). Heartworms will be visible as linear parallel object floating in the right cardiac chambers or in lumen of vessels. Echocardiography is performed on cases where clinical diagnostic tools suggest a severe infection. Echocardiography can also be used to confirm the diagnosis of caval syndrome. Cardiac ultrasound can increase the accuracy of staging infection by estimating worm burden, which in turn affects prognosis and treatment protocol (Venco, 2007).

## Treatment

The type of treatment varies depending on the severity of the infection. Therefore, there is no set protocol for treatment of heartworm disease. Instead, a multimodal approach must be taken. There is currently no test, nor a combination of tests that accurately predict the number of worms present in an infection. So every infected dog must be treated as if a severe immune reaction to the dead/dying worms could occur. The goal of treatment is to eliminate heartworms at all stages of life within the infected patient, with minimal post-treatment side effects.

**Adulticide Therapy.** Melarsomine dihydrochloride is the only FDA approved drug for heartworm treatment (Society, 2014). A three-dose protocol is recommended by the American Heartworm Society. The first, a deep intramuscular injection into the epaxial lumbar vertebrae (between L3 and L5) of 2.5 mg/kg of bodyweight, the second and third a month later, 24 hours apart from each other. Melarsomine is quickly absorbed and reaches maximum blood arnsenic levels around 11 minutes after injection (Page, 2008). The three injection protocol has been proven to be more effective than the previously recommended two injection protocol. The two injection only kills 90% of worms, whereas the three injection protocol kills 98% of worms. The first injection kills 90% of males and 10% of females, significantly reducing the dogs worm burden after one dose, the two subsequent injections kill the remaining worms (Simon et al., 2012). Killing the worms in two different stages reduces risks of embolic complications. It is best to perform adulticide therapy after extensive diagnostic testing, to estimate the patients worm burden and estimate the extent of possible post-treatment complications. While not ideal, it is better to treat without extensive diagnostic testing than to not treat at all. Post-injection exercise restriction is essential to minimizing cardiopulmonary complications. As the worms die and decompose, their fragments can lodge in the distal pulmonary arteries and capillary beds in

the caudal long lobes blocking blood flow and causing thromboembolism (Society, 2014). Increase in exercise or excitement resulting in increased blood flow to blocked vessels can cause capillary delamination, rupture, and fibrosis, increased pulmonary resistance, pulmonary thromboembolism, and right heart failure. Melarsomine is less effective against worms under 4 months old. Macrocylic lactones, prescription heartworm preventative, is recommend to be administered 2 months prior to adulticide treatment. This will prevent any new infections, eliminate existing larvae, and allow younger worms to mature to the age adulticide therapy would be effective (Society, 2014). Long-term macrocylic lactone administration without adulticide therapy, as a slow-kill method of treatment should not be used. Research has shown *D. immitis* are developing resistance to macrocyclic lactones. An experimental study conducted in Louisiana proved the presence of macrocyclic lactone resistance in *D. immits*, by experimentally infecting dogs with certain strains suspected of developing resistance and then treated those dogs with the macrocylic lactone drug, Ivermectin (Pulaski et al., 2014). The resistance although not currently widespread, has occurred due to selection pressure by "slow kill" method of heartworm treatment. For this reason, the extended use of macrocyclic lactones as a heartworm treatment is strongly discouraged.

**Bayer Advantage Multi® and Doxycline Treatment.** In cases where melarsomine injections are not possible, alternate treatments are available. The use of a macrocyclic lactone, like Advantage Multi®, and doxycline used together, has proven to be a cheaper and effective alternative. In a study of 16 dogs, infected with L3 larvae, all the treated dogs went from antigen positive to antigen negative (Savadelis et al., 2017). In the study, Advantage Multi® (10% imidacloprid + 2.5% moxidectin) was topically administered every 4 weeks, totaling 10 monthly treatments, to the treatment group of dogs. Doxycline was also administered at 10.0-14.1 mg/kg

for 30 days. The dogs were euthanized on days 278-282 post infection. The dogs underwent necropsy and the remaining worms were counted and sexed. By day 21 of treatment, microfilariae were not detected on a blood smear, from dogs from the treatment group. The nontreated dogs averaged 10.6 adult worms/dog at necropsy, while the treated dogs averaged 0.6 adult worms/dog. 5 of the treated dogs were not found to have any worms, the remaining 3 had either one or two worms. The overall treatment proved to be 95.9% effective (Savadelis et al., 2017). This treatment method is comparable to the two melarsomine injection treatment, with only 90% efficacy. Although the combination of Advantage Mutli® and doxycline is not as effective as the three melarsomine injections, it is cheaper, and presents less severe side effects. Treatment of Advantage Multi® and doxycline has proven to be a safe, effective, and affordable treatment of heartworm disease.

**Surgical Extraction.** Surgical extraction of worms is typically only done on patients diagnosed with caval syndrome. Diagnosis of worms present in the tricuspid or the vena cava of the heart is confirmed with echocardiograms. Caval syndrome can be fatal within two days, as adult worms partially obstruct blood flow through the tricuspid valve; surgical extraction must be pursued quickly (Society, 2014). Adulticide therapy is recommended post-surgery to kill any remaining worms that were not extracted during surgery.

## Prevention

As seen in previous sections, heartworm disease can be very severe in dogs leading to major health complications and possibly death. Treatment for heartworm disease is very expensive, and is accompanied by life threatening side effects. Administering heartworm preventative, as directed by veterinarian and manufactures directions, is a much safer and cheaper alternative.

**Comparison of Available Preventatives.** One study compared 4 commercially available heartworm preventatives., ivermectin/pyrantel pamoate (Heartgard Plus Chewables for Dogs – Merial), milbemycin oxime/spinosad (Trifexis Chewables for Dogs – Elanco Animal Health), selamectin (Revolution - Zoetis Animal Health), and imidacloprid + moxidectin (Advantage Multi® for Dogs – Bayer). Forty dogs were randomly assigned into 5 groups, 4 treated groups and 1 control group. Each dog was infected with *D. immits* L3 larvae, administered the preventative according to the manufactures directions on days 31 and 60 post infection. On days 124-126, the dogs were euthanized and necropsied for worm recovery. The control group averaged 18.4 worms/dog. By day 94 post infection, all the treated dogs were antigen negative. Percent effectiveness for, ivermectin/pyrantel pamoate, milbemycin oxime/spinosad, selamectin, and and imidacloprid + moxidectin were 29%, 52.2%, 28.8%, and 100% respectively. The high effectivity of imidacloprid + moxidectin is likely due to the unique pharmacokinetic properties of the topical formulation delivering greater and sustained drug concentrations to prevent development of *D. immits* larvae (Blagburn et al., 2016). The results of this study prove that not all available heartworm preventatives are effective against all strains of *D. immits*, pointing to a suspicion of resistance.

**Compliance and Effective Prevention.** The majority of heartworm preventative failures is not due to resistant strains, but a lack of compliance by pet owners, lack of understanding of the heartworm life-cycle, and infrequent heartworm testing. To ensure protection and the spread of any possible resistant strains, dogs should be placed on preventative as early as the manufacturer's directions allow, annual heartworm screenings should be performed, and owners should be aggressively educated about preventatives and the life cycle to increase compliance and decrease purchasing gaps.

**Prevention by Blocking Transmission.** Multimodal approaches to preventing the transmission of many vector borne human diseases, like malaria and lymphatic filarias, have been successful for decades - approaches such as bed nets, clothing, and repellents. These multimodal approaches have not received much attention regarding the transmission of heartworm disease, an industry typically focusing on prevention. A multimodal approach is an integral part in controlling the spread of heartworm disease. In one study 30 beagles were divided into four groups, group 1 a control untreated group, group 2 treated topically with DPP (dinotefuran + permethrin + pyriproxyfen – Vectra 3D) on day 0, group 3 treated orally with MBO (milbemycin oxime – Interceptor) on day 51, and group 4 treated with DPP on day 0 and MBO on day 51. Each dog was exposed to mosquitos infected with *D. immits* for 1 hour on days 21 and 28. The dogs were euthanized and necropsied on day 148-149. A total of 418 mosquitos fed on the dogs in groups 1 and 3, while only 6 mosquitos fed on the dogs in groups 2 and 4. The repellency effect in group 2 was 98.1% and 99.1% in group 4. The estimated number of L3 transmitted to control, group 2, group 3, and group 4 were 76, 2, 78, and 1 respectively. No heartworms were detected in any of the dogs treated with both DPP and MBO (McCall et al., 2017). Treating the dogs with MBO on 51 post exposure was essentially ineffective, because more L3 larvae were

transmitted to those dogs than the controls who received no protection. This study supports a "double defense protocol" in which DPP can be combined with any commercial heartworm preventative to provide a stronger protection against heartworm transmission.

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