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Canine heartworm – an ever-present threat

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Introduction

Vector-borne diseases are of increasing significance to the health of human, canine and feline populations. It is estimated that 45% of the human population in Europe is exposed to the risk of helminth vector-borne diseases (Petric, Zgomba, Bellini & Becker, 2012). A number of canine vector borne diseases are increasing in prevalence and distribution in Europe and worldwide: leishmanisis, dirofilariosis and babesiosis are just three of these. The change in distribution and prevalence can be attributed to factors including, climate change, increased awareness amongst veterinary surgeons and the increase in movement of pets, both within Europe and further afield.

Canine heartworm is caused by a nematode of the genus *Dirofilaria* (**Figure 1**). The two most important species in Europe are *D.immitis and D.repens. D. Immitis* is commonly referred to as canine heartworm, but it can and does infect other species. Clinical disease has been seen in cats, wolves, coyotes, foxes and ferrets amongst others. *D.immitis and D.repens* are widespread worldwide and their distribution is evolving constantly. They are major veterinary diseases of interest from both a veterinary and zoonotic perspective (Otranto, Dantas-Torres, Brianti, Traversa, Petrić, Genchi & Capelli, 2013). The focus of this article is on *D. Immitis* in dogs.

In the UK the risk of disease lies primarily with our travelling pet population. *D. immitis* is not currently established in the UK, as our climate is not consistently warm enough, but we do have the mosquito vector, so it is possible this may change in the future. Given the increasing number of dogs travelling abroad it is important for veterinary surgeons and veterinary nurses to be aware of the disease and have a broad understanding of distribution, clinical signs, diagnosis, treatment and, importantly, prevention.

Distribution

D. immitis was initially diagnosed in the United States (**Figure 2**) and since then has been confirmed in Europe, South America, Asia and Australia. In America, the disease is endemic and autochthonous transmission has occurred in all states and nearly all of the Canadian provinces. It has been diagnosed in areas of Alaska in untravelled dogs (Rubin, Nelson, McCall, Carithers, Graham, Buzhardt…Guerrero, 2014). This has occurred in the last 50 years and demonstrates, that if conditions are right, how easily a vector-borne disease can become established, not just in a single area but across a continent. **Figure 3** illustrates where the disease has been confirmed to be endemic in Europe.

Work was carried out to establish prevalence in the shelter dog population in New Orleans after Hurricane Katrina in 2006. Of the dogs tested, 80% were found to be heartworm-positive. This contributed to the continued spread of the disease across the continent, as a large number of dogs were relocated across the different states after the hurricane (Levy, Edinboro, Glotfelty, Dingman, West & Kirkland Cady, 2007). In Europe, the disease is predominantly seen in southern countries. Northern Italy has the highest prevalence; here it has been documented that prevalence could be upwards of 80% (Otranto et al., 2013). A recent study of dogs in southern Portugal found evidence of exposure in 9.4% of dogs (Maia, Coimbra, Ramos, Cristóvão, Cardoso & Campino, 2015).

Life cycle and vector

The Culicidae family of mosquito is the vector for *Dirofilaria.* Over 60 species of the family are known to be vectors for transmission. They are continually expanding their territories, and, as they do, the number of confirmed cases rises and new endemic areas emerge (Genchi, Poglayen, Kramer, Venco & Agostini, 2001). Climate

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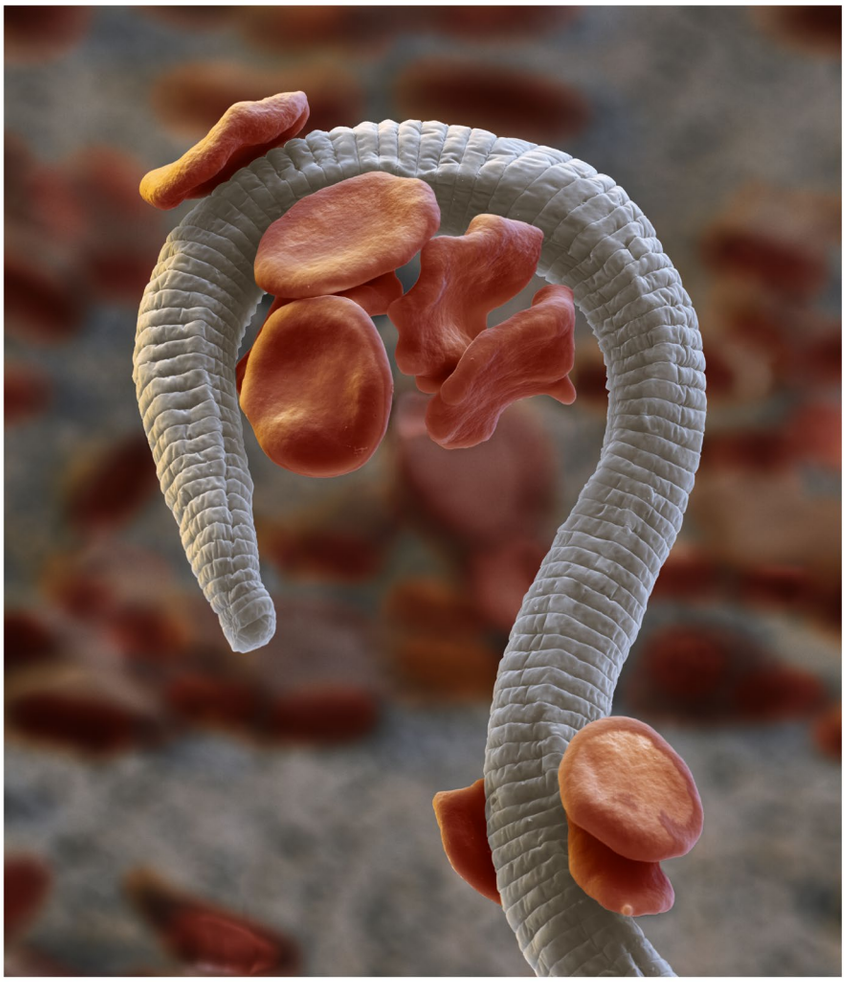
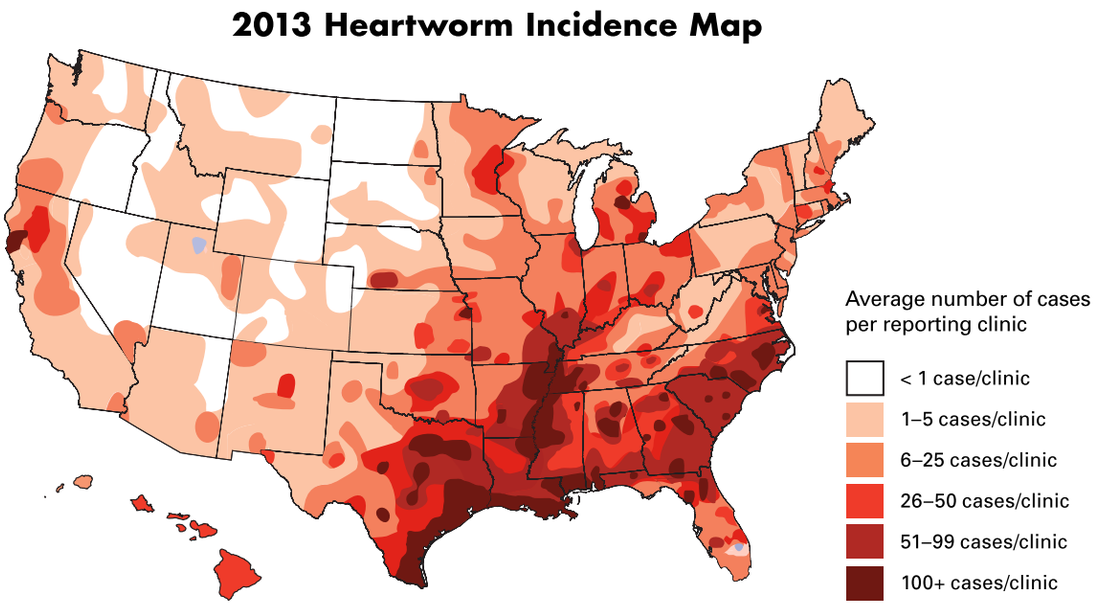


Figure 1. Adult Dirofilaria immitis © Bayer Animal Health GmbH

change is one of the factors affecting their distribution and is one of the main hypothesised factors for the northward movement of the disease in Europe. Temperature and humidity are the two main factors that are imperative for transmission, as they allow establishment of a viable mosquito population. Transmission occurs more commonly during the summer months, however, with the increase in ambient temperature and influence of factors such as micro-climates in urban areas, transmission can be year round. Certain species of mosquito, such as *Aedes quadrimaculatus,* can hibernate over winter for up to 4–5 months, which lengthens the transmission season (Otranto et al., 2013).

The life cycle of *D. immitis* is long compared to other parasitic nematodes (**Figure 4**). It takes 7–9 months and is highly temperature dependent. A host becomes infected when a mosquito carrying the infective L_3 stage takes a blood meal and transmits the infection. The infective L_3 stage remains within the skin for approximately 3–4 days before moulting to L_4. It then migrates through muscle fibres, abdominal and thoracic tissues until it reaches the pulmonary parenchyma where it moults to an L_5 immature adult measuring around 2.5–3.5 cm. Blood pressure forces the immature adults into the pulmonary vessels where they complete their final moult into a mature adult 80–120 days post infection. They



© American Heartworm Society

The severity of heartworm incidence as shown in this map is based on the average number of cases per reporting clinic. Some remote regions of the United States lack veterinary clinics, therefore we have no reported cases from these areas.

Figure 2. American heartworm incidence 2013 © American Heartworm Society

Figure 3. Dirofilaria immitis and Dirofilaria repens distribution in Europe © ESCCAP

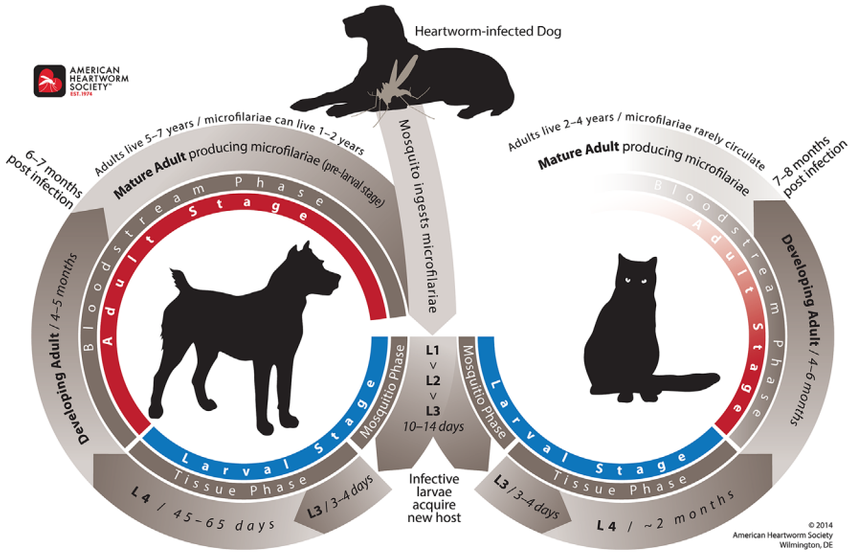


Figure 4. Lifecycle of Dirofilaria immitis © American Heartworm Society

then become sexually mature and measure around 15–30 cm in length.

Adult *Diro filaria immitis* reside in the pulmonary artery, lobar vessels and heavy burdens may be found in the right side of the heart as well. They can live for up to seven years. A patent infection develops from around 180 days post infection when, after reproduction, the female *D. immitis* releases microfilariae into the bloodstream. Occult infections are seen when single-sex infections are present and, in such cases, the host does not become a reservoir for infection.

Once the microfilaria have been released, they travel within the bloodstream into the capillaries where they can survive for up to 18 months in the systemic circulation. The lifecycle is completed when a female mosquito feeds and becomes infected through uptake of microfilariae via the blood meal. Development of the L_1 larvae within the mosquito's Malpighian tubules then occurs, but is temperature dependent. If the temperature is 27°C and humidity is around 80%, development from L_1 to infective L_3 takes 10–14 days; if temperatures are lower, however, this maturation process takes longer. When the temperature falls below 14°C maturation stops completely.

Diagnosis

Testing is carried out either to screen asymptomatic dogs or to confirm a suspected infection and usually focuses on detection of heartworm antigens and microfilariae.

Antigen testing is the most sensitive diagnostic test currently available. The American Heartworm Society currently advises that antigen detection tests can be performed from five months following infection and microfilaria can be detected from six months. The tests only pick up cases with mixed or female-only infections as the antigen detected is only secreted by female worms. Occult infections with male worms and very low-burden mixed infections can produce a false negative result, as low or no levels of antigen are present. Specificity is close to 100% with all commercially available ELISA and immunochromatographic tests. The level of antigen detected approximately correlates to the number of female worms present; the higher the burden, the higher the antigen level.

Microfilarial testing is usually performed at the same time as antigen detection. It consists of assessment of a blood smear for microfilariae using what is known as a *concentration technique*. The blood smear is examined using a microscope for the presence of microfilariae or cell movement, which has been caused by their motility. The modified Knott test is the most commonly used concentration test. Instructions for performing this test can be found in the American Canine Heartworm Society Guidelines. This is the preferred method, as it allows for the differentiation of *D.immitis* from other filarial species and has a higher specificity.

Radiography and echocardiography can be useful diagnostic tools. Radiography can help ascertain the severity of cardiorespiratory disease present, secondary to heartworm infection in dogs and cats. It is not uncommon to see interstitial disease occurring secondary to larval migration. This can persist for weeks to months post infection so may be evidence of a historical infection, which has subsequently been cleared by the animal. Pulmonary vessel enlargement is a common finding and is directly related to immature and adult worm burdens. Diaphragmatic lobes are most commonly affected. Right-sided heart enlargement can be seen with heavy burdens due to secondary congestive heart failure.

Echocardiography can be used to assess cardiac function and as a way of visualising the adult worms within the right atrium, ventricle and pulmonary artery. Observing the presence of adult worms is definitive evidence of a clinical infection. Worms seen within the tricuspid valve

confirms the presence of caval syndrome (see below) in the affected dog.

Clinical signs

The severity of clinical signs and disease in dogs is roughly related to the level of adult worms present. In cats, lower levels of adult worms can cause severe clinical disease. This is an important differentiation between canine and feline heartworm disease. Low-level infections in dogs are often asymptomatic, as they can tolerate a few worms with no clinical signs. A summary of clinical signs can be seen in **Table 1**.

Non-specific cardio-respiratory signs are most common in mild-to-moderate cases. In moderate-to-severe cases, clinical signs are more severe and often include those that may indicate pulmonary hypertension and/or congestive heart failure.

Caval syndrome may be a complicating factor in these cases; this develops when the adult worm burden is heavy and adults are present in the right chambers of the heart. They are then pushed through the tricuspid valve and valvular weakness ensues. Haemolysis may occur as can clinical signs associated with congestive heart failure and renal and hepatic dysfunction. Clinical signs often seen in moderate–to-severe cases include:

- exercise intolerance
- weight loss, lethargy, anorexia
- syncope
- pulmonary oedema
- coughing
- dyspnoea
- cyanosis
- haemoptysis, haematuria, epistaxis
- abdominal distention
- anaemia
- pale mucous membranes
- weak peripheral pulses, jugular pulse
- right-sided systolic murmur
- adventitious lung sounds on auscultation
- vomiting
- sudden death

Severe cases are often fatal, especially those where caval syndrome develops – death can occur within two days from the onset of caval syndrome. Aberrant larval and worm migration can also occur, as with other parasitic diseases. The CNS, eyes, peritoneum, subcutaneous tissues, and other areas have all been associated with this, with the potential for attendant clinical signs (Nelson & Couto, 2003).

Dirofilaria infection is also zoonotic. In Europe, most zoonotic cases are associated with *D. repens* and in the Americas with *D. immitis.* Clinical signs are usually respiratory or cutaneous. Both *D. immitis* and *D. repens* infections are rarely fatal in humans (Otranto et al., 2013).

Treatment

The main aim of treatment is to eliminate as many of the larval life stages and adults as possible, whilst minimising the side effects to the dog or cat. Treatment can be high risk, especially when worm burdens are high. Thrombo-embolic complications as a result of the death of the adults are not uncommon. Treatment of heartworm in dogs consists of adulticide and microfilaraemia treatment alongside treatment of associated clinical signs. The American Heartworm Society (AHS) produces guidelines on an annual or biannual basis, which are generally accepted as being the gold-standard treatment that one should aim to follow. **Table 2** shows the 2014 guidelines.

Adults

The trivalent arsenical, melarsomine dihydrochloride is the adulticide drug of choice. This is not available in the UK and would require a special import licence from the Veterinary Medicines Directorate. It is extremely potent against immature adults (L_5) and adult worms, but has no effect against earlier larval stages or microfilariae. It is imperative that when dogs are being treated with melarsomine they are cage rested and exercise is severely restricted. This is to reduce the likelihood of potentially fatal thrombo-embolism that may occur after the death of the adult worms.

The AHS currently recommends a three-step protocol with melarsomine, in which dogs receive one injection intra-muscularly, repeated 4–6 weeks later, with a third injection given 24 hours after the second. This is expected to kill over 98% of the adult worms that are over four months old. However, it is not always possible to kill all the adult worms in severe infections. In some circumstances the adults may also be removed surgically prior to adulticidal therapy. This is done when the burdens in the right side of the heart are particularly large and/or caval syndrome is present. It is usually performed via the right vena cava using alligator forceps.

Adult worms have a symbiotic relationship with a genus of Gram-negative obligate intracellular bacteria called *Wolbachia*. The bacteria also have the almost unique capability of altering the gender of the nematode. They can change a sterile male *Dirofilaria* into a female through gene manipulation. Recent studies have shown that it is preferable to administer a bactericidal agent with activity against these obligate bacteria prior to commencing adulticide therapy. This has been shown to improve life expectancy and also reduce pulmonary pathology. Doxycycline is the antibacterial of choice and a 28-day course should be given prior to the administration of melarsomine (AHS, 2014).

Microfilariae

Macrocyclic lactones are the therapeutic group of choice to kill the microfilariae. They are administered prior to melarsomine as this reduces the microfilaraemic burden and allows L_4 to mature to L_5 and adults; melarsomine is then more effective. Moxidectin, milbemycin and ivermectin can all be used for up to six months prior to melarsomine. In the UK, moxidectin is licensed in the preparation Advocate™ (Bayer Animal Health) for the purpose of reducing circulating

Table 1. Summary of clinical signs of canine heartworm disease (Rubin et al., 2014)

Mild	asymptomatic or cough
Moderate	cough exercise intolerance abnormal lung sounds
Severe	cough exercise intolerance dyspnoea abnormal heart and lung sounds enlarged liver (hepatomegaly) syncope (temporary loss of consciousness from reduced blood flow to the brain) ascites death
Caval Syndrome	sudden onset of severe lethargy and weakness accompanied by haemoglobinaemia and haemoglobinuria

Table 2. Treatment of heartworm disease in dogs (Rubin et al., 2014)

Day	Treatment
Day 0	Dog diagnosed and verified as heartworm positive: • Positive antigen (Ag) test verified with microfilaria (MF) test • If no microfilariae are detected, confirm with second Ag test from a different manufacturer Begin exercise restriction. • The more pronounced the signs, the stricter the exercise restriction If the dog is symptomatic: • Stabilize with appropriate therapy and nursing care • Prednisolone, prescribed at 0.5 mg/kg BID first week, 0.5 mg/kg SID second week, 0.5 mg/kg EOD third and fourth weeks
Day 1	Administer heartworm preventative • If microfilariae are detected, pretreat with antihistamine and glucocorticosteroid, if not already on prednisolone, to reduce risk of anaphylaxis • Observe for at least eight hours for signs of reaction
Days 1–28	Administer doxycycline 10 mg/kg BID for four weeks • Reduces pathology associated with dead heartworms • Disrupts heartworm transmission
Day 30	Administer heartworm preventative
Day 60	Administer heartworm preventative First melarsomine injection, 2.5 mg/kg intramuscularly (IM) Prescribe prednisolone 0.5 mg/kg BID first week, 0.5 mg/kg SID second week, 0.5 mg/kg EOD third and fourth weeks Decrease activity level even further • Cage restriction/on lead when using yard
Day 90	Administer heartworm preventative Second melarsomine injection 2.5 mg/kg IM
Day 91	Third melarsomine injection 2.5 mg/kg IM Prescribe prednisolone 0.5 mg/kg BID first week, 0.5 mg/kg SID second week, 0.5 mg/kg EOD third and fourth weeks Continue exercise restriction for six-eight weeks following last melarsomine injections
Day 120	Test for presence of microfilariae • If positive treat with a microfilaricide and retest in four weeks Establish year-round heartworm prevention
Day 271	Antigen test six months after completion Screen for microfilariae

microfilariae in clinical cases. This is a well-tolerated and efficacious treatment (McCall, Arther, Davis & Settje, 2014).

Low-dose prednisolone can be used alongside treatment for microfilariae and adults. As microfilariae die, subsequent antigen release can induce a hypersensitivity response. Prednisolone can help reduce the likelihood of this. The use of anti-coagulants such as aspirin has also been assessed but there is currently no evidence that supports their use (AHS, 2014).

Symptomatic treatment

Symptomatic treatment should be given for all presenting clinical signs as well. ACE inhibitors, diuretics, anti-hypertensive agents, positive inotropes, calcium-channel blockers, blood transfusions and a number of other therapies may often have to be utilised. Advice may need to be sought from a specialist as these are often complex cases.

Prevention

Canine heartworm disease can be prevented. This is the gold-standard in endemic countries such as America, and in southern Europe.

Previously, seasonal use of preventative products was recommended, but now year-round use is advised by the AHS in areas where the parasite is endemic. This approach improves compliance and, in some areas, due to climate changes, the transmission season is now much longer. If certain conditions such as warmer Springs and Autumns and urbanization persist, it could potentially be year round.

In endemic areas it is recommended that a preventative treatment is started at eight weeks of age. Macrocycliclactones, administered on a monthly basis, are effective against microfilariae, L_3, L_4 and, in some cases, adult heartworms.

Licensed preparations in the UK include ones containing moxidectinin combined with imidacloprid (Advocate™, Bayer Animal Health), selamectin (Stronghold, Pfizer) and milbemycinoxime (various preparations are available, consult the *NOAH Compendium*). If a dog is older than seven months of age, antigen testing should be performed before chemoprophylaxis is started. Equally, if a dog is between eight weeks and seven months of age when therapy is started, it should be tested for heartworm antigen six months after the first dose.

The AHS also recommends that in endemic areas, dogs are tested annually for heartworm antigen, regardless of the degree of compliance with chemoprophylaxis. This is particularly important as pockets of macrocyclic lactone resistance have been detected

in some states in America. Moxidectin appears to be the most effective molecule available but continual surveillance continues to be necessary (AHS, 2014). It is accepted that by far the most common reason for suspected lack of efficacy is poor compliance.

When effective prevention is implemented, it reduces the reservoir of disease, which in turn helps reduce the number of clinical cases and also the potential for zoonotic cases. However, because the movement of the vector is outside our control, it is highly unlikely that eradication of canine heartworm will ever occur. The focus must be on owner education and the importance of prevention of this potentially fatal disease. In the UK it is important for veterinary surgeons and veterinary nurses to be aware of the disease and its distribution so that appropriate comprehensive advice on prevention, diagnosis and treatment is given to owners travelling abroad with their dog and/or cat as well as for owners returning from endemic areas.

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Useful websites

Canine Vector Borne Diseases (CVBD) website. http://www.cvbd.org/

European Scientific Counsel Companion Animal Parasites (ESCCAP) website http://www.esccap.org/

Multiple Choice Questions

1. What is the most important factor influencing the efficacy of heartworm prophylaxis?

(a) Seasonal temperature variability

(b) Owner compliance

(c) Drug resistance

(d) Age when therapy is initiated

2. What antibiotic is administered for 28 days before treatment with melarsomine?

(a) Potentiated amoxicillin

(b) Cephalexin

(c) Enrofloxacin

(d) Doxycycline

3. Which of the following is FALSE regarding heartworm disease?

(a) Cats and dogs are often asymptomatic with low-level infections

(b) A negative antigen test does not necessarily mean the animal is infection-free

(c) Radiography and echocardiography are useful to determine the severity of the infection

(d) The life cycle is long and temperature-dependent

4. Why is routine antigen testing recommended in endemic areas?

(a) It reduces the possibility of zoonotic infection

(b) It can save the client money on drugs if testing is negative

(c) There is some evidence of drug resistance

(d) To evaluate owner compliance

5. Which statement regarding antigen testing is FALSE?

(a) Testing should be carried out 5 months after infection

(b) A high burden of male worms can contribute to a false negative

(c) Antigen testing is the most sensitive test available

(d) Can detect microfilariae from 6 months

6. Which of the following is FALSE regarding treatment with the adulticide melarsomine?

(a) It is effective against larvae and adults

(b) It is available in the UK only with a special VMD license

(c) Treatment is risky and it can result in thrombo-embolism

(d) Adjunctive surgical treatment is sometimes necessary