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An Overview of Management Considerations for Mongolian Gerbils (*Meriones unguiculatus*), Cats (*Felis catus*), and Dogs (*Canis familiaris*) as Hosts for *Brugia* Infection

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Lymphatic filariasis is a mosquito-borne parasitic infection affecting an estimated 51.4 million people. *Brugia malayi* and *Brugia pahangi* are used in research because common nonprimate research species such as Mongolian gerbils (*Meriones unguiculatus*), cats (*Felis catus*), and dogs (*Canis familiaris*) can maintain the life cycle of these species of filarial nematodes. Although overall care and management of animals infected with *Brugia* spp. is relatively straightforward, there are some unique challenges and special considerations that must be addressed when managing a research colony infected with these parasites. In this review, we discuss our experience, share insight into biosafety and clinical management, and describe the expected clinical signs associated with *Brugia* infection in gerbils, cats, and dogs.

Abbreviations and Acronyms: FR3, Filariasis Research Reagent Resource Center; L3, third-stage larvae.

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Introduction

Lymphatic filariasis is a mosquito-borne parasitic infection caused by filarial nematodes. It occurs in 72 countries and affects an estimated 51.4 million people, with chronic infection resulting in lymphatic deterioration, lymphedema, and elephantiasis, the socioeconomic consequences of which are substantial.[10,25,35,42,43] While *Wuchereria bancrofti* is the most common causative agent of the disease in humans, approximately 5% to 10% of cases are due to infection with *Brugia malayi* or *Brugia timori.* Because the *B. malayi* life cycle can be maintained in commonly available nonprimate hosts, laboratory studies rely on its use.[30,41] In addition, *Brugia pahangi*, a natural parasite of felids and canids, is also used in research settings.[39]

Natural infection occurs when third-stage larvae (L3) are transmitted to the mammalian host via the bite wound produced by an infected mosquito.[20] While undergoing 2 molts in their development to the adult stage, the parasites localize to the lymphatics. Here, adults mate and the ovoviviparous females release microfilariae that enter the bloodstream, where they may be taken up by a mosquito during feeding. After approximately 10 to 14 d, depending on the species, the microfilariae develop into infective L3 that may infect another mammalian host.[15] In a laboratory environment, this infection can be maintained via injection of L3 either intraperitoneally or subcutaneously, depending on the model.[1,6,7,14,17,28]

Several nonprimate, mammalian hosts have been used as models of lymphatic filariasis or as hosts for the maintenance and production of filarial parasites for research purposes, including gerbils, cats, and dogs, all of which are maintained at the University of Georgia through the NIH–National Institute of Allergy and Infectious Diseases Filariasis Research Reagent Resource Center (FR3). While animal models for the human response to filarial infections have been developed, the primary role of laboratory infections of gerbils, cats, and dogs is for the maintenance of the parasite life cycle and the large-scale production of the parasites themselves.[18,24] Nematodes of every life cycle stage are collected and used by investigators principally for in vitro and molecular research.[30] The 3Rs (replacement, reduction, and refinement) are promoted when large numbers of parasites can be generated and harvested from a single well-maintained colony of animals, such as the FR3, then coordinated and shared with researchers around the country and world. This prevents multiple laboratories from infecting more animals than necessary or producing microfilaria and adult worms that may not be used. This valuable resource provides not only precious research materials to the scientific community, but also clinical learning opportunities for veterinary students and residents, graduate students, and animal care staff. For this review, we share our insights into common *Brugia* biosafety and animal model considerations, describe the expected clinical signs associated with experimental *Brugia* infection in gerbils, cats, and dogs, present findings from retrospective reviews of our clinical health records for these species, and discuss IACUC oversight.

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Special Considerations

Biosafety. *Brugia* spp. are considered Risk Group 2 parasitic agents due to their ability to cause disease in healthy adult humans.[33] However, the requirement of the mosquito as an intermediate host makes transmission from animal to animal or from animal to humans unlikely in a laboratory environment. Based on our risk assessment, infected animals are housed in ABSL-1 conditions. Specialized caging and personal protective equipment are not required for handling infected animals, so infected animals may remain socially housed, including with uninfected cage mates. In the authors' facilities, gerbils are housed in open-topped static housing, cats are housed in 2-over-2 quad caging, and dogs are housed in raised floor runs. In each case, animal housing is open to the room, so hazard containment is at the level of the room, not the cage. Individuals entering one of these rooms must wear gloves and either scrubs or a lab coat, which is the minimum personal protective equipment requirement for entry into research animal housing on campus. However, extra precautions are taken at the facility level to prevent exposure to mosquitoes and serve as key components of biocontainment and prevention of unintentional transmission of *Brugia* to the public. At the authors' institution, facilities housing *Brugia*-infected animals are equipped with air curtains at external entry doors to prevent intrusion of mosquitoes. In addition, infected dogs are not permitted access to outside areas. Traveling between buildings for clinical or experimental purposes is kept to a minimum. When transportation is necessary, precautions are taken to protect *Brugia*-infected animals from mosquitoes. Gerbils are moved in filter-topped enclosures, and dogs and cats are transported in crates with a cloth covering to limit potential mosquito exposure while allowing appropriate airflow.

Clinical case management. The impact of specific drug classes on *Brugia* spp. parasites must be considered before proposing treatments for *Brugia*-induced or other unrelated clinical conditions of infected animals. For example, macrocyclic lactone antiparasitic drugs such as ivermectin and moxidectin should not be used, as they can damage the *Brugia* parasites. This is important to remember when heartworm preventative is a standard treatment given to dogs and/or cats in the research facility, as animals intended for *Brugia* infection must be excluded from these preventative programs. In addition, doxycycline and tetracycline derivates should not be used. These drugs can damage the endosymbiotic bacterium, *Wolbachia*, that resides within the filarial worms. It is also important to recognize that some of these medications are excreted primarily unmetabolized in the feces, and coprophagia of feces from a cage mate receiving one of these treatments may impact microfilarial counts.[21,22] Therefore, it is important that all animals that are cohoused with *Brugia*-infected animals are excluded from heartworm prevention protocols or other uses of these medications.

Opportunities for indoor exercise. Because dogs are unable to go outdoors due to concern about mosquito exposure, primary indoor housing enclosures that exceed the floor space requirements of the Animal Welfare Regulations by at least 2-fold, a large playpen area for periodic exercise opportunities, and/or specialized exercise programs approved by the IACUC are needed.[4] For cats, periodic free range access to the housing room to encourage exercise is important. Directly relevant to the *Brugia* model, movement of all limbs may be therapeutic during episodes of lymphedema, encouraging muscle contractions to promote peripheral limb venous and lymphatic return.

Unrelated to *Brugia* spp. infection, we have found that play time outside of standard 2-over-2 quad caging, even when cats are housed socially, is helpful to their apparent psychologic wellbeing. Opportunities for scratching, running, jumping, climbing, chasing laser lights, and playing with running water while supervised may each be offered on a rotating basis.

Retrospective Review of Clinical Health Outcomes

The clinical health data presented in this review were collected from clinical health records at the University of Georgia. All animals were infected as part of IACUC-approved research protocols, and work was completed at the University of Georgia College of Veterinary Medicine, which is included in a USDA-registered, Office of Laboratory Animal Welfare–assured, and AAALAC-accredited program. All 3 species were maintained at 72 ± 2 °F and 30% to 70% relative humidity with a 12-h light/12-h dark cycle. Gerbils were housed in static polysulfone caging on a suspended shelf rack system with a wire mesh shelf design. Gerbils were maintained in groups of up to 5 per cage and received food and water ad libitum. Cats were housed in 2-over-2 quad caging (Britz, Wheatland, WY) and group housed in groups of 2 to 4 when compatible partners were available. Each quadrant had floor space of 5.0 ft^2 and was 2.5 ft tall with a raised resting platform. Dividers could be placed to separate each quadrant or removed to allow free movement between them. Individually housed cats were given access to at least 2 quadrants, while group-housed animals were given access to at least one quadrant per animal. Socially compatible cats received scheduled time to play freely in the room with cage mates and other cats from the room. They were fed once or twice daily with ad libitum access to water. Dogs were housed in raised-floor runs (Britz, Wheatland, WY) with at least twice the Animal Welfare Regulations floor space requirements and socially housed when compatible partners were available. They were fed once daily and had ad libitum access to water through autowatering devices.

The gerbil data were collected by reviewing all new or ongoing relevant clinical cases monitored during the years 2021 to 2023. The total number of gerbil infections was then determined by cross-referencing research records and including all animals infected on or after the date of the earliest infection date associated with a clinical case occurring within the above-listed parameters. The clinical health data for cats were collected via a review of all clinical health records for animals infected with *B. malayi* between the years 2020 to 2023. The clinical health data for dogs were collected via a review of health records for animals infected with *Brugia* spp. for the FR3 between 2015 and 2023.

Gerbils

Infection parameters. The Mongolian gerbil (*Meriones unguiculatus*) is a model rodent permissive to filarial infection. Both *B. malayi* and *B. pahangi* develop in the gerbil, and adults and microfilaria remain localized and can easily be collected from either the peritoneal cavity or subcutaneous tissues when L3 are injected intraperitoneally or subcutaneously, respectively.[1,6,7,28] This makes the gerbil a more useful host for parasite production than the multimammate mouse (*Mastomys* spp.), which is permissive but only via subcutaneous infection.[31] In subcutaneous infections of the gerbil, *B. pahangi* larvae have been reported to migrate to the afferent lymphatics within hours, with most having left the injection site within 3 d.[2,36] In intraperitoneal infections with *B. malayi*, the molt to the fourth larval stage occurs between 4 and 8 d postinfection, and the molt to the adult stage occurs between 21 and 34 d postinfection.[32] Microfilariae have been reported by 79 and 60 d postinfection in *B. malayi* and *B. pahangi*, respectively.[5,7,28] According to FR3 data from the 4 y prior to this writing, when infected intraperitoneally

with 400 third-stage larvae, mean recovery of microfilariae was 2.47×10^6 (SD = 2.61×10^6, $n = 192$) for *B. malayi* and 2.08×10^6 (SD = 2.21×10^6, $n = 111$) for *B. pahangi*. Mean recovery of adults was 90.6 (SD = 59.4, $n = 232$) for *B. malayi* and 152 (SD = 75.9, $n = 120$) for *B. pahangi*. Adults were 49.4% and 54.5% female for *B. malayi* and *B. pahangi*, respectively. Average time of terminal collection was 238 d postinfection (SD = 100.5 d). Due to the easily recoverable adult and microfilarial stage of these parasites in the intraperitoneal infection model, the gerbil is likely to remain crucial to filariasis research for the foreseeable future.

Clinical signs. For intraperitoneal infections, the primary clinical sign of concern is peritonitis, which is fortunately rare. Peritonitis may develop within 24 to 72 h after injection of the L3 stages. Clinical signs include a combination of lethargy, rough fur coat, ascites, potentially limited movement, and inappetence. Of the records examined from 2021 to 2023, during which 608 gerbils were acutely infected by the intraperitoneal route, only one instance of suspected peritonitis following intraperitoneal infection was reported, and the animal was promptly euthanized.

For subcutaneous infections, there are a few potential clinical signs. Interestingly, localized inflammation or granuloma at the injection site has not been observed. Occasionally, induced lymphatic disease results in transient lymphedema. Lymphedema may manifest as swelling of the limbs. This swelling normally does not affect the animal's ambulation or movement. Rarely, the lateral digits of the hind feet swell, and loss of the ungual process is possible. Of 61 gerbils infected subcutaneously from 2021 to 2023, 4 developed swelling of one or more digits on their hindlimbs, and only one of these was reported for edema of one hindlimb. No lameness has been observed in gerbils with lymphedema, and the animals appear comfortable.

Another manifestation of infection is swelling of the scrotum (Figure 1). Scrotal swelling was the clinical manifestation most commonly observed, affecting approximately 5% of gerbils infected with *Brugia* spp. by the intraperitoneal route over the last 3 y (Table 1). The species of *Brugia* did not significantly impact the risk of scrotal swelling. However, scrotal swelling was rare following subcutaneous infection, affecting only 1 of 61 animals. The degree of swelling is highly variable and may be unilateral or bilateral.

While the scrotal swelling itself does not appear to negatively affect the animals, one possible secondary effect is ulceration of the scrotal skin. These ulcerations vary in severity. Of the 45 cases of scrotal swelling reported in the last 3 y, 14 (30%) developed ulcerations on the scrotum and 4 were euthanized due to reaching humane endpoints associated with the severity of the ulceration. Frequently, the ulceration is small (less than 0.5 cm in diameter), and the animal is behaviorally normal (bright, alert, and responsive, or BAR), with no indication of pain or discomfort. These ulcerations frequently resolve when they are minor (no larger than 1 cm with no purulent discharge or bleeding). Rarely, ulcerations appear painful, with the animal becoming lethargic and/or displaying a hunched posture. If the animal has a minor ulceration and is behaviorally normal, it may be monitored at a frequency adequate to quickly identify worsening of the condition. In our experience, treatment has generally not been required for minor ulcerations. Treatment such as topical antibiotic ointment (without tetracycline or its derivatives) to prevent secondary bacterial infection could be considered. Consultation between the veterinary team and the research team should determine whether treatment is appropriate, based on the condition and the research.

Cats

Infection parameters. Cats are a competent natural host of *Brugia* spp., with *B. malayi* occurring in up to 20%, and *B. pahangi* occurring in up to 25%, of feline populations in endemic areas.[9,12,14,26,34] The domestic cat has historically been the preferred laboratory host for *B. malayi.* The cat has not been commonly used as a host for *B. pahangi* due to the high permissivity of dogs and that host's relative ease of handling. In the case of *B. malayi*, larvae are found in lymphatics proximal to the site of injection as early as 3 d postinfection. The molt to the fourth larval stage occurs 9 to 10 d postinfection and the molt to the adult stage occurs 35 to 40 d postinfection. Microfilariae are first observed between 70 and 147 d postinfection.[13,14,19] For *B. pahangi*, microfilariae appear between 69 and 96 d

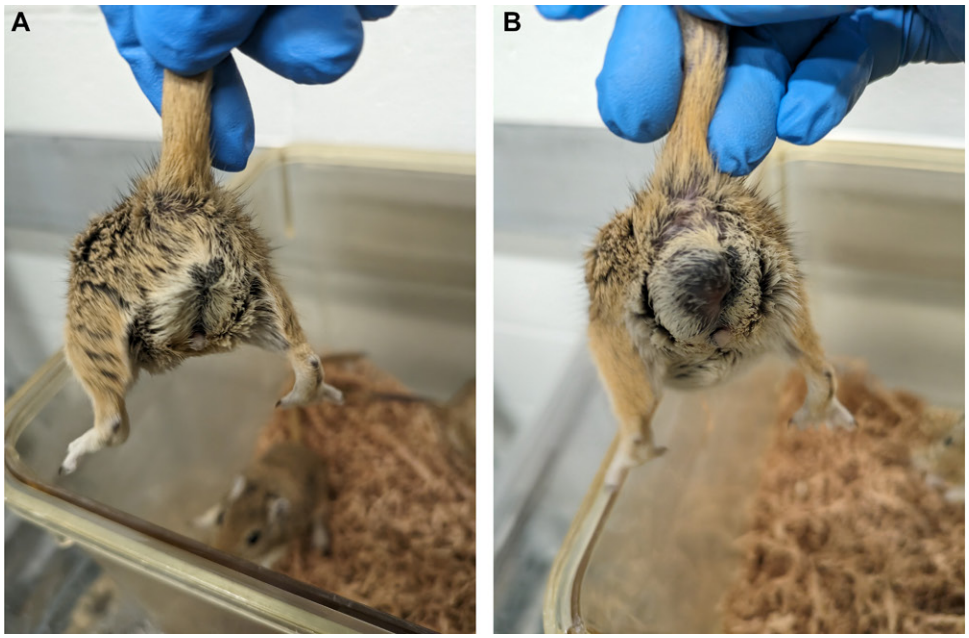

Figure 1. Normal gerbil scrotum (A) and gerbil with swelling of the left side of the scrotum following intraperitoneal infection with *Brugia pahangi* (B).

Table 1. Gerbils developing scrotal swelling after intraperitoneal infection with *Brugia* spp. from 2021 to 2023

		Scrotal swelling		Resolution	
Parasite	Number of gerbils infected[a]	Number affected (%)	Mean onset after infection ± SD (d)	Number resolved (%)	Mean duration of swelling ± SD (d)
B. pahangi	384	22 (5.7)	57.14 ± 41.82	9 (40.91)	61 ± 57.94
B. malayi	429	22 (5.1)	101.09 ± 93.67	16 (72.73)	49.38 ± 44.46

[a]Number of animals infected between 18 May 2020 and 28 Nov 2023, corresponding to the range of infection dates for animals being monitored for scrotal swelling from 01 Jan 2021 to 31 Dec 2023.

postinfection.[11] In laboratory infections, 54.5% of cats infected with *B. malayi* develop detectable microfilaremia, with one study reporting a peak peripheral blood concentration of 6,525 microfilariae/mL when 400 third-stage larvae were injected subcutaneously into the hindlimbs (200 larvae per side).[16] Studies at the authors' institution have used infections with 200 to 500 L3 SC unilaterally or bilaterally in the dorsum of the hindfoot and/or in the inguinal region to assess the effect on patency, and did not find significant differences. Cats can maintain patent infections of *B. malayi* for about 1 y.

One challenge of working with cats is the risk of personnel injury when collecting blood samples for microfilaria harvesting. Therefore, steps are taken to acclimate, socialize, and calm colony cats in several ways. After arrival from the commercial vendor, all male cats are acclimated, then castrated. They receive regular playtime and human interaction outside their cages in addition to traditional in-cage enrichment items.[40] To minimize the stress of handling during jugular vein blood collections, cats are sedated with acepromazine maleate and ketamine hydrochloride either intramuscularly (0.1 mg/kg; 10 to 12 mg/kg) or intravenously (0.02 to 0.04 mg/kg; 2.2 to 4.4 mg/kg).

Figure 2. Edema of the hind paw of a cat following infection with *Brugia malayi*. Image courtesy of the FR3.

Clinical signs. Cats with established infections are often asymptomatic, with only circulating microfilariae in the blood as evidence of infection. However, transient, mild-to-moderate lymphedema (Figure 2) for 4 wk or longer may result after experimental injection with parasite larvae. If swelling occurs, it is typically mild to moderate, cool to the touch, nonpainful, and cats continue to walk with a normal gait. In that case, no intervention is needed.

Hindlimb edema was reported in 50.6% of all cats infected with *B. malayi* from 2020 to 2023 (Table 2). Of these reported cases, approximately 76% resolved the edema, although there was significant variation in the time to resolution. Interestingly, there does appear to be a trend of more cats with occult infection (amicrofilaremic) developing edema compared with those with patent infections. However, the presence or absence of microfilaria in the blood did not appear to impact the rate of resolution.

Of the 29 cats infected with *B. malayi* from 2020 to 2023, only one developed clinical signs warranting veterinary intervention. In this case, one of the authors (M.A.M.) noted moderate-to-severe edema of the rear hocks and feet of a cat, with alopecia on the dorsal aspect of the third and fourth digits, repeated licking by the cat, and transcutaneous leakage of apparent interstitial fluid. The dependent edema was first noticed 8 wk after injection of L3 and persisted for about 6.5 mo but did not affect the cat's gait when walking. A combination of 1% topical silver sulfadiazine ointment, leg massages, and increased exercise (social playtime) was instituted to address skin and lymphatic circulatory issues. The cat appeared to respond to treatment and the transcutaneous leakage resolved within 1 wk. While the edema persisted, it improved over time and the leg massages were discontinued after 2 wk. This cat had an occult infection that did not result in detectable microfilaremia.

Dogs

Infection parameters. Owing to the ease of venipuncture and the volume of microfilaremic blood that can be safely obtained, the domestic dog is the preferred host for the largescale maintenance and production of filarial parasites as well as a research model for therapeutic development. While dogs have long been recognized as competent hosts of *B. pahangi*, natural canine infections with *B. malayi* have also been reported. More recently, canine permissivity to *B. malayi* has been demonstrated in the laboratory.[3,8,17,27,37–39] One study reports a local *B. pahangi* prevalence of 8.3% in dogs in Thailand.[23] In this host, adult worms most commonly localize to the mandibular, retropharyngeal, and axillary lymphatics following natural infection.[29]

Table 2. Prevalence of hindlimb edema in cats infected with *Brugia malayi* from 2020 to 2023

		Hindlimb edema		Resolution	
Infection status	Number of cats infected	Number affected (%)	Mean onset after infection ± SD (d)	Number resolved (%)	Mean duration of swelling ± SD (d)
Patent	17	8 (47)	90.88 ± 46.62	6 (75)	44.83 ± 14.78
Occult	12	9 (75)	74.11 ± 37.39	7 (78)	91.29 ± 70.72

Establishing the model in dogs is similar to the cat and gerbil models. In dogs the model is established by injecting 500 third-stage larvae of either *B. malayi* or *B. pahangi* subcutaneously either unilaterally or bilaterally in the inguinal region, or in the dorsal foot. Similar to the cat model, the location of the injection does not significantly impact patency. According to unpublished data collected by the FR3 during the 10 y prior to this writing, the rate of microfilaremia in dogs experimentally infected with *B. pahangi* is 100%, with patency detected as early as 10 wk postinfection with a peak peripheral blood concentration of 52,575 microfilariae/mL during the lifetime of patency ($n = 12$). In laboratory infections with *B. malayi*, one recent study reports that 50% of dogs develop microfilaremia, with an onset as early as 12 wk postinfection and a peak concentration of 9,950 microfilariae/mL.[17] The relative fecundity of *B. pahangi* in the dog is one reason it remains a model for filariasis. Dogs are typically behaviorally better suited for conscious serial blood collections than cats, and they offer the opportunity to collect larger volumes of blood. This in combination with the recently reported similar permissivity to *B. malayi* infection supports dogs as the preferred large animal model for both *B. pahangi* and *B. malayi* infection, potentially replacing the cat.[16,17]

Clinical signs. The most common finding following *Brugia* infection is intermittent hindlimb swelling, postulated to be lymphedema caused by the parasite. This swelling is ipsilateral to the site of subcutaneous injection and typically noted several weeks to months after infection, and in some cases was transient. Most cases require no veterinary intervention as they were described as mild-to-moderate swelling, with no change in gait. Hindlimb edema was reported in 1 out of 6 (16.6%) *B. pahangi*–infected animals and 2 out of 10 (20%) *B. malayi*–infected animals. Onset ranged from 29 to 61 d postinfection. Edema resolved for 2 of the dogs (one infected with *B. pahangi* and one with *B. malayi*), while the third was infected too recently to know if the edema will resolve or not.

IACUC Considerations

Overall, it is our experience that clinical signs of *Brugia* spp. infection in the model species described herein are mild and rarely require veterinary intervention. However, as a supplement to the standard daily animal observations for general wellness, a schedule to specifically monitor animals for signs of *Brugia* spp. infection and related endpoints should be established in the IACUC protocol. At our institution, weekly monitoring of uncomplicated swelling/edema has been adequate to identify cases that are starting to develop complications for any of the species discussed herein. For gerbils, monitoring is increased to twice weekly for individuals that develop ulcerations associated with scrotal swelling, and this has been sufficient to ensure that ulcerations do not progress past established humane endpoints.

In addition to periodic monitoring by the research team, it is also important for the animal care team to be aware of, and observing for, side effects of infection. Here, our animal care technicians are often the first to identify and report instances of edema, particularly in the gerbil colony since they are interacting with the animals the most frequently. Due to their training and experience, our animal care team is particularly vigilant in its monitoring of these animals and is invaluable in ensuring that clinical signs are recognized and addressed in a timely manner to ensure animal welfare. Once a report is made, the research lab initiates enhanced monitoring to assess progression of edema and/or ulcerations.

While uncommon, there are occasional instances when intervention is required. For this reason, it is important to have clear guidelines in the animal use protocol detailing when veterinary consultation should be sought, as well as humane endpoints. At the authors' institution an animal resources veterinarian must be consulted if an animal appears to be displaying signs of discomfort related to edema or swelling or if edema persists for more than 2 mo in duration. For gerbils, intervention by a veterinarian is required for ulceration of an area greater than 1 cm, ulceration of skin over both testes, purulent discharge, hunched posture, rough hair coat, and/or lethargy. Euthanasia is typically chosen if a gerbil is showing one or more of these signs. Depending on the project, severity of the signs, and prognosis, pain management and other treatments may be appropriate alternatives.

There are currently no effective diagnostic tests to ensure the permanent absence of adult *Brugia* spp. worms after anthelmintic treatment. As a result, previously infected, but currently amicrofilaremic dogs and cats are not eligible for adoption to private homes since the elimination of the human health hazard cannot be fully assured. At the authors' institution, in line with the 3Rs, dogs and cats that do not develop or maintain patent infections are eligible for transfer to another investigator to participate in research studies, reducing the total number of animals in our program. The receiving investigator is informed of their history of infection and must provide similar biosecurity conditions as described above. It is our hope that future research into the area of more specific diagnostics for the adult filarial worm as well as continued research on improved treatment protocols would not only improve the management of naturally occurring infections of both humans and animals in endemic areas, but also allow for the adoption of animals in research programs once they are determined to be definitively cleared of infection.

Conclusion

Overall, the care and maintenance of animals infected with *Brugia* spp. are straightforward and there is minimal impact on animal welfare. While some extra precautions are required to minimize the risk of exposure to mosquitoes, the lack of direct transmission makes this a relatively easy model to manage from a biosafety perspective. Animals can remain socially housed, and special personal protective equipment is not required. In addition, while edema or swelling either in the hindlimbs or scrotum is not uncommon following infection, it is rare that these side effects escalate to the point of impacting welfare or requiring veterinary intervention. Usually, animals are not in pain, and the edema resolves on its own without any treatment.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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