Review Article

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CLINICAL AND PARASITOLOGICAL SIGNIFICANCE OF THELAZIOSIS IN DOGS AND CATS

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Abstract

Thelaziosis is an eye disease of parasitic etiology, caused by nematodes from the genus Thelazia (Spirurida, Thelaziidae). In addition to domestic animals (cattle, horses, dogs and cats), the disease also occurs in wild animals, mammals and birds. Thelazia nematodes have zoonotic potential and can be transmitted from animals (most often dogs) to humans through the population of intermediate hosts - fruit flies from the Drosophilidae family. Infection with the species Thelazia callipaeda has an endemic character, and the disease mainly occurs Europe in the period from May to October, when the activity of the intermediate hosts of this nematode is increased. The presence of these parasites in dogs and cats in Serbia is expected, given that the climatic conditions in this epizootiological area are identical to those in the countries where autochthonous cases of thelaziosis have been reported. The disease is accompanied by increased ocular discharge, conjunctivitis and keratitis. Diagnosis of thelaziosis can be very simple in cases of high intensity infections, when the parasites are observed macroscopically in the dog's eye. In some cases, allergic or bacterial conjunctivitis, from which thelaziosis is difficult to distinguish, can complicate the diagnosis of this parasitosis.

Key Words: thelaziosis, dog, cat, ophthalmological changes, zoonosis

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INTRODUCTION

Thelazia callipaeda is a zoonotic parasitic nematode from the family Thelaziidae, and the role of vector in its indirect development cycle is performed by flies (Diptera: Drosophilidae), mostly the genus *Phortica. Phortica variegata* is the main intermediate host in Europe, and *Phortica okadai* in the Far East (Jin et al., 2021). Definitive hosts for *T. callipaeda* encompass a wide range of species, from domestic carnivores (dogs and cats), wild carnivores (red foxes, wolves, minks, wild cats and golden jackals), lagomorphs (brown rabbits and wild European rabbits) and humans (Shen et al., 2006; do Vale et al., 2019). Dogs are the most important definitive hosts, as the adult forms of *T. callipaeda*, whose females are ovoviviparous, occur in the canine orbital cavity (most often the conjunctival sac and nasolacrimal ducts) (Liao et al., 2017; Zhang et al., 2019).

Ophthalmological changes and the degree of damage caused by *T. callipaeda* do not depend on the number of adult nematodes present in an animal's eye (Maia et al., 2016; Liu et al., 2024), but they depend on mechanical effects and toxic effects of the parasite (Jin et al., 2021). The most common manifestations diagnosed during the clinical examination of infected dogs are: a combination of conjunctivitis and epiphora, the sensation of the presence of a foreign body, edema of the eyelids, purulent secretion, keratitis, uveitis, blepharitis, photophobia and ulceration of the cornea as the most severe change (Malacrida et al., 2008; Liao et al., 2017).

T. callipaeda was first described in dogs in the early 20^{th} century in Asia. During the 21^{st} century, the number of registered cases of this parasitic infection in animals in Europe has increased, and nowadays, thelaziosis has been diagnosed in 20 European countries. From the total number of reported cases of the disease in humans in Europe, the majority are autochthonous. However, the existence of a number of imported cases highlights the importance of surveillance to control and limit the transboundary spread of the parasite (do Vale et al., 2019).

The aim of this work is to highlight the importance of education and to raise awareness of thelaziosis among the veterinary profession, doctors (especially ophthalmologists) and animal owners. This review provides a clinical overview and useful information related to the etiopathogenesis, diagnosis and prophylaxis of *T. callipaeda*, which should help those involved to react in a timely manner and prevent the occurrence, maintenance and spread of this zoonosis.

ETIOPATHOGENESIS OF CANINE THELAZIOSIS

Thelaziosis in dogs in Europe and Asia is caused by the nematode *T. callipaeda* (Railliet and Henry, 1910), while the species *Thelazia californiensis* (Price, 1930) is mostly restricted to the western part of the United States of America. The parasite is known as "the oriental eyeworm", and according to taxonomic classification, it belongs to the

order Nemathelminthes, class Nematoda, subclass Secernentea, order Spirurida and family Thelaziidae (Faust, 1928; Burnett et al., 1957).

Morphological characteristics of the parasite

T. callipaeda is whitish in color and cylindrical in shape. Males are $4.5-13 \text{ mm} \times 0.255-0.7 \text{ mm}$ in size, while females are $6.2-17 \text{ mm} \times 0.3-0.855 \text{ mm}$. Adult forms have a transversely striated cuticle that causes eye irritation in the definitive host when the parasite moves along the host's conjunctiva. Females have a mouth opening with a hexagonal profile and two papillae on the oral opening. The caudal end of the female's body is rounded with two phasmids on the tip of the tail. The vulva is located before the esophagus-intestinal junction. Females are ovoviviparous and carry embryonated eggs in the proximal part and larvae in the distal part of the uterus (Zakir et al., 1999). The male has following characteristics: (1) in contrast with the female, the buccal capsule is inconspicuous, and the mouth opening has a circular or ellipsoid profile; (2) two asymmetrical spicules are present in the males on the anterior extremity, the longer left spicule and the shorter right spicule with its typical crescent shape; (3) the caudal end is ventrally curved; and (4) there are five pairs of post-cloacal papillae (Otranto et al., 2003).

Life cycle of the parasite

During the winter period, *T. callipaeda* survives in the definitive host (dogs, cats and wild carnivores). The female parasite lays the first-stage larva (L₁) in the tears of the definitive host, and when feeding on lacrimal proteins from the tears of an infected dog, the intermediate hosts, fruit flies (*P. variegata*), ingest L₁ larvae into their bodies. These larvae penetrate the intestinal wall of the fly in a few hours and remain in the abdomen for about two days, then infect the fat tissue of the female and the testicles of the male. The larvae grow, molt twice and the infective L₃ larvae are formed after 14-28 days. This period lasts about a month, so the highest frequency of thelaziosis can be expected one month after the appearance of the first intermediate hosts, i.e., in spring (from May to June in Europe). During the next feeding, the infective L₃ larva is transferred by the fly to the next susceptible definitive host, where it passes into the L₄ stage and further into the adult form of the parasite (Shen et al., 2006).

Flies of the order Diptera, Drosophilidae family, genus *Phortica* are vectors and intermediate hosts for *T. callipaeda* (Yang et al., 2006; Roggero et al., 2010). However, more than one species of Diptera, namely *Musca domestica* (Diptera: Muscidae) and *Amiot okadai* (Diptera: Drosophilidae), could be involved in the transmission of *T. callipaeda*. So far, this has not been confirmed in research conducted in experimental or natural conditions (Otranto and Traversa, 2005).

GEOGRAPHICAL DISTRIBUTION OF THE NEMATODE THELAZIA CALLIPAEDA

Infection with *T. callipaeda* has an endemic character. It was first discovered over a hundred years ago in Punjab, India (Railliet and Henry, 1910), and now has been diagnosed in other areas of Asia, i.e., Thailand (Bhaibulaya et al., 1970), Indonesia (Kosin et al. al., 1989), South Korea (Hong et al., 1995), China, Myanmar and Japan (Anderson, 2000), former USSR (Otranto and Traversa, 2005), Taiwan (Yang et al., 2006), Vietnam (Nguyen et al., 2012), Bangladesh (Akhanda et al., 2013), Nepal (Sah et al., 2018) and in 20 European countries (Otranto et al., 2021; do Vale et al., 2020). More than 20 years ago in Europe, *T. callipaeda* was mainly distributed along the southern part of Italy. In the last 10 to 15 years, this nematode has spread very quickly throughout the European continent and island countries. Since 2003, the list of endemic areas has expanded from Italy, through the countries of the former Yugoslavia, Poland, the Czech Republic, Slovakia, France, Germany, Switzerland, all the way to Scandinavia (Table 1). Human infections have been diagnosed in endemic regions of Europe, which indicates the importance of this parasitosis for public health.

The transport of pets provides a great range of opportunities for further spread of thelaziosis (Palfreyman et al., 2018). Great Britain, where only imported cases of canine thelaziosis have been reported so far (Graham-Brown et al., 2017), even though the vector is endemic, further confirms this fact. The presence of a relatively high total prevalence of T. callipaeda (35.52%) in dogs in the epizootiological area of Serbia is not surprising considering that the climatic conditions are identical to those in other countries where thelaziosis has been reported (Hadži Milić et al., 2016). The first autochthonous cases of ocular thelaziosis in dogs and cats in Serbia were diagnosed in the central, western and southern parts of the country (Gajić et al., 2014; Tasić-Otašević et al., 2016). Recently, T. callipaeda infection in wolves was documented for the first time in Serbia, with a total prevalence of 38.1% (Gajić et al., 2019). This finding indicates the importance of the epizootiological role of wolves as a reservoir of infection for Thelazia, although the importance of other wild carnivores should also be considered. Given that wild carnivores range very widely, i.e., foxes range 10 to 30 km (Doncaster and Macdonald, 1991), and wolves up to 800 km (Mech, 1970), they significantly contribute to the spread and maintenance of the infection in the environment. These wild animals are significant sources/reservoirs for T. callipaeda, both in endemic and non-endemic areas (Mihalca et al., 2016).

Country	Year	References
Italy	1989; 2000; 2007; 2008	Rossi and Bertaglia 1989; Lia et al., 2000; Otranto et al., 2007; Otranto and Dutto, 2008
Germany	2004; 2010	Hermosilla et al., 2004; Magnis et al., 2010
France	2007; 2010	Dorchies et al., 2007; Ruytoor et al., 2010
Switzerland	2008; 2014	Malacrida et al., 2008; Motta et al., 2014
Spain	2011; 2018; 2019	Miró et al., 2011; Marino et al., 2018; Deltell et al., 2019
Portugal	2012; 2016; 2018	Vieira et al., 2012; Maia et al., 2016; Seixas et al., 2018
Belgium	2013	Caron et al., 2013
Bosnia and Herzegovina	2014	Hodžić et al., 2014
Croatia	2014; 2016	Hodžić et al., 2014; Paradžik et al., 2016
Serbia	2014; 2016	Gajić et al., 2014; Hadži-Milić et al., 2016; Tasić-Otašević et al., 2016
Greece	2015; 2017	Diakou et al., 2015; Papadopoulos et al., 2017
Romania	2015; 2016; 2018	Mihalca et al., 2015; Tudor et al., 2016; Ioniță et al., 2016; Dumitrache et al., 2018;
Austria	2016; 2019	Hinney et al., 2016; Hodžić et al., 2019
Hungary	2016; 2018	Colella et al., 2016; Farkas et al., 2018
Bulgaria	2016	Colella et al., 2016
Slovakia	2017; 2018	Čabanová et al., 2017, 2018
Great Britain	2017; 2018	Graham-Brown et al., 2017; Hammond, 2018
Turkey	2019	Eser et al., 2019

Table 1. Chronological distribution of *T. callipaeda* in dogs and cats from Europe.

CLINICAL SIGNIFICANCE OF CANINE THELAZIOSIS AND DIAGNOSTIC APPROACH

In most cases, the animal owner brings the patient to a veterinary clinic or a veterinary specialist ophthalmologist because of eye problems. Usually, inflammation of the conjunctiva is suspected, but it has not healed despite topical therapy being applied. Ophthalmological diagnostic examination begins with recording anamnesis, an insight into the medical history and the implementation of a detailed ophthalmological examination in routine clinical examinations of dogs and cats (Maia et al., 2016). Ophthalmological examination in our clinic includes these examinations:

- Vision test (visual diagnosis) and Neuro OFT diagnosis (which includes palpebral, corneal, pupillary and chromatic pupilar light reflex (CPLR) of both eyes, vestibulocochlear nerve examination).
- Examination of the adnexa of the eye and the anterior segment in a lit room from a distance and at close range without additional magnification or special lighting, measurement of the aqueous portion of the tear film (Shirmer tear test), taking a swab of the conjunctival sac.
- Detailed close-up examination of the anterior segment of the eye in a darkened room using appropriate magnification (loupe 3×) and directional illumination (Finoff transilluminator), eversion of the third eyelid and examination of the lower posterior fornix using local anesthesia in the form of eye drops (Tetracaine 1%) and/or measurement of intraocular pressure using an applanation tonometer (Tono PenVet) with local (Tetracaine 1%) anesthesia of the conjunctiva and cornea.
- Examination of the eye (anterior segment) with a biomicroscope.
- Examination of the fundus with indirect and direct ophthalmoscope (Gelatt et al., 2021).

The finding of *T. callipaeda* in the eye is a condition that is defined in surgery as the presence of a foreign body in the eye. Suspicion of thelaziosis is established on the basis of anamnesis, epizootiological data, clinical manifestations and pathomorphological changes. A precise and reliable diagnosis is made by finding the adult forms of the parasite in the eye of the patient. *Thelazia* larvae can be diagnosed by microscopic examination in the tears of affected individuals. Epizootiological data on whether the animal traveled or stayed near places (oak forests, ponds, swamps, orchards, vineyards) that are biotopes for intermediate hosts of this nematode are of the particular importance for an objective diagnostic approach (Lešević, 2021). The infection can last for a long period of time with different clinical signs, different infection intensity, so different redness of the conjunctiva (hyperemia) and different kinds of discharge (serous, seromucous to purulent). Animals can be disturbed by the discomfort caused by the serrated cuticle of the nematodes irritating the conjunctiva and cornea. As a result of the infection, various complications can occur (keratitis, anterior uveitis-iridocyclitis) (Dimitrijević and Ilić, 2011).

Clinical manifestation of thelaziosis in dogs

In the early stage of infection or in cases of low-intensity infections, dogs and cats often do not show ophthalmological changes, so the disease can go unnoticed by owners and veterinarians (Motta et al., 2014). The clinical symptoms in dogs can differ, and the symptoms can be confused with other eye pathologies (blepharitis, conjunctivitis, keratitis, iridocyclitis). Detailed ophthalmological examinations are very important in order to diagnose nematodes in the eye, because treating the patient only for conjunctivitis and keratitis often does not give satisfactory results, even after two weeks. Larvae and adults of *T. callipaeda* are involved in the pathogenesis of ocular thelaziosis. The most common clinical signs in dogs infected with *T. callipaeda* are a combination of epiphora and conjunctivitis (especially follicular conjunctivitis; Figure 1), followed by purulent discharge, keratitis, uveitis and corneal ulceration as the rarest but most severe change (Otranto and Traversa, 2005; Miro et al., 2011).



Figure 1. Everted third eyelid with follicular conjunctivitis on the bulbar side in a dog with thelaziosis (original image supplied by Petar Krivokuća)

According to available data from the literature, the percentage of infected dogs with clinical symptoms is lower than the percentage of symptomless dogs. Maia et al. (2016) reported that the percentage of infected dogs with ophthalmological changes was 45.5%, and the percentage of infected dogs without ophthalmological changes was 54.5%. Miro et al. (2011) stated that the majority (84.6%) of animals were without clinical signs, while clinical signs were observed in 15.4% of animals. In 31.8% of

dogs, more than one clinical change in the eyes was diagnosed (Miró et al., 2011). The number of nematodes in one dog's eye ranged between 1 and 35 (Figure 2; Maia et al., 2016), and was not related to the severity of clinical symptoms (Miro et al., 2011; Liu et al., 2024). There are several treatment protocols for thelaziosis, and they have in common the mechanical removal of numerous nematodes from the patient's eye and the selection of adequate therapy (Calero-Bernal et al., 2013).





Clinical manifestation of feline thelaziosis

Cases of thelaziosis in cats are rarely published in the scientific literature. The first cases in Europe were described in Italy between 1997 and 2001 (Otranto et al., 2013). Cats diagnosed with *T. callipaeda* express a range of clinical signs. In milder cases, the clinical manifestation is accompanied by signs of mild conjunctivitis, eye secretions and blepharitis, while more severe cases are manifested by severe conjunctivitis, keratitis, chemosis and purulent eye secretions. Signs of mild conjunctivitis occur in the majority of thelaziosis cases in cats (Figure 3). A more severe clinical manifestation was found in cats that were infected with a larger number of nematodes (Marino et al., 2021). Cats diagnosed with thelaziosis lived outdoors and had no protection against endo and ectoparasites (Marino et al., 2021).



Figure 3. Clinical changes in the eye of a cat with thelaziosis (original image supplied by Anđelka Lešević)

SURGICAL-OPHTHALMOLOGICAL APPROACH TO THERAPY AND PROPHYLAXIS OF THELAZIOSIS IN DOGS AND CATS

In dogs with *T. callipaeda* infection, it is possible to perform mechanical removal of nematodes with the use of general or local anesthesia (Figure 4), depending on the severity of the infection and on the resulting complications in the form of inflammation (keratitis, ulcer).



Figure 4. Adult form of *T. callipaeda* axially positioned on the cornea of a dog after application of 1% tetracaine eye drops (original image supplied by Petar Krivokuća)

The procedure is carried out using microsurgical ophthalmic instruments (atraumatic tweezers). The use of only local anesthetic (e.g., tetracaine 1% eye drops) can be practiced exclusively in dogs that cooperate and are infected with a small number of nematodes (Figure 5). For the purpose of a detailed inspection of the eye, an eye swab is taken at this stage, the analysis of which determines the presence of bacterial or fungal co-infections (Čabanová et al., 2017; Dimitrijević and Ilić 2011).



Figure 5. Removal of adult form of *T. callipaeda* from the conjunctival sac (original image supplied by Milan Hadži-Milić)

One of the therapy protocols is oral administration of imidazothiazoles: tetramizole 15 mg/kg of body weight and levamisole 5-7.5 mg/kg of body weight. These drugs are effective because a high concentration of them is achieved in the lacrimal secretion. Macrolide antihelminitics can also be administered: subcutaneous ivermectin 0.2 mg/kg body weight; doramectin 0.5 mg/kg body weight applied by the pour-on method; milbemycin oxime used twice in 7 days. The treatment is repeated 2-3 times over 7 days (Dimitrijević and Ilić, 2011).

Milbemycin oxime (minimum dose 0.5 mg/kg), praziquantel tablets and spot-on preparations of imidacloprid (10%) and moxidectin (2.5%) have been shown to be effective in the treatment and prevention of thelaziosis in dogs. For prophylactic purposes, a spot-on ectoantiparasitic preparation (combined imidacloprid and moxidectin) is useful. Eye drops to treat thelaziosis are not recommended in veterinary

practice because the treatment can lead to irritation of the conjunctiva and cornea (Bianciardi and Otranto, 2005; Motta et al., 2012; Lechat et al., 2015).

For the treatment of thelaziosis in dogs, Otranto et al. (2016) reported that a rapid effect was achieved with a spot-on preparation (imidacloprid 10% and moxidectin 2.5%), which proved to be effective within five (90.47%) to nine (95.23%) days after application. A milbemycin oxime/praziquantel tablet formulation required two administrations to completely cure *T. callipaeda* infection in dogs (Otranto et al., 2016). Another of the protocols for the treatment of thelaziosis in dogs recommends single doses of ivermectin of 0.2 mg/kg (Maia et al., 2016).

To treat cats with thelaziosis, the use of ivermectin in the form of eye drops has shown success, although it is not recommended because it can cause unwanted reactions such as itching, irritation and redness of the eye. Local moxidectin at 1.0 mg/kg of body weight has also been used (Maia et al., 2016). The combination of esafoxolaner, eprionmectin and praziquantel in the treatment of cats naturally infected with *T. callipaeda* showed a good result (Di Cesare et al., 2024). Moxidectin is registered for use against *T. callipaeda* in cats, and preventive treatment with a spot-on formulation of 100 mg/ml imidacloprid and 10 mg/ml moxidectin once a month throughout the year prevents recurrence of infection. In order to detect subclinical cases, especially in cats that live in endemic areas or have traveled to endemic areas, in addition to adequate prophylaxis against thelaziosis, an ophthalmological examination should be performed (Marino et al., 2021).

Prevention of thelaziosis in dogs and cats is crucial to prevent the spread of the disease from endemic areas (where its prevalence is up to 60%) to non-endemic areas. Treatment of animals is necessary for infection control, primarily because of the risk that *T. callipaeda* poses to humans and because of its tendency to spread among the human population in non-endemic areas (Otranto et al., 2003; Otranto et al., 2006). Application of milbemycin oxime monthly (Ferroglio et al., 2008) and imidacloprid 10% and moxidectin 2.5% spot-on (Lechat et al., 2015), reduced the frequency in dogs of Thelazia infection by 90% and 100%, respectively. In the endemic regions of France, collars with slow release active substances (10% imidacloprid and 4.5% flumethrin) were tested in the prevention of thelaziosis in dogs, but did not show a sufficient or expected level of protection (Lechat et al., 2015). The dogs in that study were regularly ophthalmologically monitored, and in the group of dogs that were protected with a slow-release collar, 33% still had persistent *T. callipaeda* at the end of treatment (Lechat et al., 2015).

EPIDEMIOLOGICAL IMPORTANCE OF THELAZIA CALLIPAEDA

The wide distribution of this nematode in different climatic areas indicates the parasite's ability to adapt. In the European and American continents, the intermediate host for humans is the fruit fly, *P. variegata*, and in Asia, it is *P. okadai*. The first case of thelaziosis

in humans was recorded in China in 1917, but in Europe was in 2008, in northwestern Italy and southeastern France (Jin et al., 2021). During 2016, the zoonotic potential of this parasite was confirmed in the form of individual cases, in Serbia in a 36-year-old man (Tasić-Otaševići et al., 2016) and in neighboring Croatia in an 82-year-old man (Paradžik et al., 2016). In Romania, in 2019, findings of thelaziosis in the European badger and mink were described, which expanded the number of species that can be susceptible hosts for *T. callipaeda* (Ionica et al., 2019). Extensive animal husbandry is considered to be one of the risk factors for the occurrence, maintenance and spread of the disease, given that dogs are outside throughout the day and are continuously exposed to contact with the intermediate host populations (Maia et al., 2016).

According to Ruytoor et al. (2010) most of the recorded cases of ocular thelaziosis were registered in animals that lived in areas where strawberries are grown. Research results show that in summer and autumn, dogs with a history of traveling in rural and mountainous areas should be treated with antihelmintics as a preventive measure (Liu et al., 2024). The lack of prophylactic measures in all carnivores could be a key factor explaining the increase in the number of dogs infected with this nematode (Motta et al., 2012).

CONCLUSION

In order to prevent the spread of thelaziosis from endemic regions to non-endemic areas, prophylaxis for dogs and cats is of key importance. Treatment of animals with anthelmintics, antibiotics and surgery in the case of high-intensity infections is necessary to control the infection. Treatment of animals will also reduce its tendency to spread among the human population in non-endemic regions, so reducing the risk that *T. callipaeda* presents to public health.

Authors' contributions

All authors contributed equally to the preparation of this manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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KLINIČKO-PARAZITOLOŠKI ZNAČAJ TELAZIOZE PASA I MAČAKA

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Kratak sadržaj

Telazioza predstavlja oboljenje očiju parazitske etiologije, koje prouzrokuju nematode iz roda Thelazia (Spirurida, Thelaziidae). Pored domaćih životinja (goveda, konji, psi i mačke), oboljenje se javlja i kod divljih životinja, sisara i ptica. Nematode iz roda Thelazia poseduju zoonozni potencijal i mogu se sa životinja (najčešće pasa) preneti na čoveka, putem populacije prelaznih domaćina - voćne mušice iz familije Drosophilidae. Infekcija vrstom T. callipaeda ima endemski karakter, a oboljenje se uglavnom javlja u periodu od maja do oktobra kada je najveća aktivnost prelaznih domaćina ove nematode. Prisustvo parazita kod pasa i mačaka u Republici Srbiji je očekivano, s obzirom da su klimatski uslovi na ovom epizootiološkom području identični kao i u zemljama u kojima su prijavljeni autohtoni slučajevi telazioze. Oboljenje je praćeno pojačanim suzenjem, crvenilom oka i konjunktivitisom, a u težim slučajevima se može javiti keratitis. Dijagnostika telazioze može biti veoma jednostavna, u slučajevima infekcija visokog intenziteta, kada se paraziti makroskopski primećuju u oku psa. U pojedinim slučajevima, problem u dijagnostici ove parazitoze mogu napraviti alergijski ili bakterijski konjunktivitis, od kojih se telazioza teško razlikuje. U cilju sprečavanja širenja oboljenja iz endemskih regiona u neendemska područja, od ključnog značaja je profilaksa telazioze pasa i mačaka. Tretman životinja antihelminticima, antibioticima i hirurški kod infekcija visokog intenziteta, neophodan je za kontrolu infekcije i smanjenje tendencije njenog širenja među humanom populacijom u neendemskim krajevima, kao i smanjenje rizika koji T. callipaeda predstavlja za javno zdravlje.

Ključne reči: telazioza, pas, mačka, oftalmološke promene, zoonoza