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Review article

Thelaziosis due to *Thelazia callipaeda* in Europe in the 21st century—A review

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ABSTRACT

Thelazia callipaeda was first described at the beginning of the 20th century in Asia, but this eyeworm is now frequently reported in Europe in the 21st century. To date, thelaziosis has been described in the following European countries (in order of appearance): Italy, France, Germany, Switzerland, Spain, Portugal, Belgium, Bosnia and Herzegovina, Croatia, Serbia, Romania, Greece, Bulgaria, Hungary, Slovakia, the United Kingdom, Turkey and Austria. The infected vertebrate host species include domestic carnivores (dogs and cats), wild carnivores (red foxes, wolves, beech martens, wildcats and golden jackals), lagomorphs (brown hares and wild European rabbits) and humans. In Europe, 11 cases of human thelaziosis have been reported, the majority of which are autochthonous. However, some of them have been imported, a fact which highlights the importance of surveillance policies to restrict cross-border spread of the parasite. The objectives of this article are to review key aspects of the epidemiology of *T. callipaeda*, summarise animal and human cases in Europe and emphasise the importance of education and awareness among veterinarians, physicians (particularly ophthalmologists) and animal, in order to owners to tackle this zoonosis.

1. Introduction

Members of the genus *Thelazia* (Spirurida, Thelaziidae) are parasites of the eyes of mammals and birds (Anderson, 2000). Adult worms can be found under the lids, on the conjunctiva and nictitating membrane, in nasolachrymal ducts, conjunctival sacs or excretory ducts of the lachrymal glands, according to the species of *Thelazia* (Anderson, 2000; Otranto and Traversa, 2005). At least 16 species of the genus *Thelazia* (*T. brevispiculata*, *T. bubalis*, *T. californiensis*, *T. callipaeda*, *T. depressa*, *T. erschowi*, *T. ferulata*, *T. gulosa*, *T. hsüi*, *T. iheringi*, *T. kansuensis*, *T. lacrymalis*, *T. leesei*, *T. petrowi*, *T. rhodesii* and *T. skrjabini*) have been identified in different mammalian hosts (Otranto and Traversa, 2005; Seixas et al., 2018). Besides being frequently reported in cattle (*T. rhodesii*, *T. skrjabini* and *T. gulosa*) and horses (*T. lacrymalis*), eyeworms can also be found in carnivores, particularly dogs and red foxes (*Vulpes vulpes*) (Beugnet et al., 2018). Cats are not a typical host because of their intensive cleaning habits and small body mass index (Farkas et al., 2018). However, several feline cases have been reported in enzootic areas of Europe (Beugnet et al., 2018).

Thelazia callipaeda Railliet & Henry, 1910 (Faust, 1928) is responsible for canine thelaziosis in Europe and Asia, while *T. californiensis* Price, 1930 (Burnett et al., 1957) is confined to the western part of the USA, but both species can infect humans (Beugnet et al., 2018). Moreover, the first case of human thelaziosis caused by *T. gulosa* Railliet & Henry, 1910 was recently described in the USA (Bradbury et al., 2018). *Thelazia callipaeda* is also known as "the oriental eyeworm" because of its distribution through the former Soviet Union, other countries of Asia, including China, India, Indonesia, Japan, South Korea and Thailand (Anderson, 2000; Shen et al., 2006; Otranto and Dutto, 2008; Colwell et al., 2011; Sharma et al., 2019), and also Bangladesh (Hossain et al., 2011; Akhanda et al., 2013), Nepal (Sah et al., 2018) and Vietnam (De et al., 2012). Nevertheless, recent decades have witnessed its increasing presence in some European countries both in animals and humans (Motta et al., 2014), such as in Italy (Lia et al., 2000; Otranto et al., 2003, 2007, 2009; Otranto and Dutto, 2008), France (Chermette et al., 2004; Dorchies et al., 2007; Otranto and Dutto, 2008; Ruytoor et al., 2010), Germany (Hermosilla et al., 2004; Magnis et al., 2010), Switzerland (Malacrida et al., 2008; Motta et al., 2014), Spain (Miró et al., 2011; Fuentes et al., 2012; Calero-Bernal et al., 2013; López Medrano et al., 2015; Marino et al., 2018; Deltell

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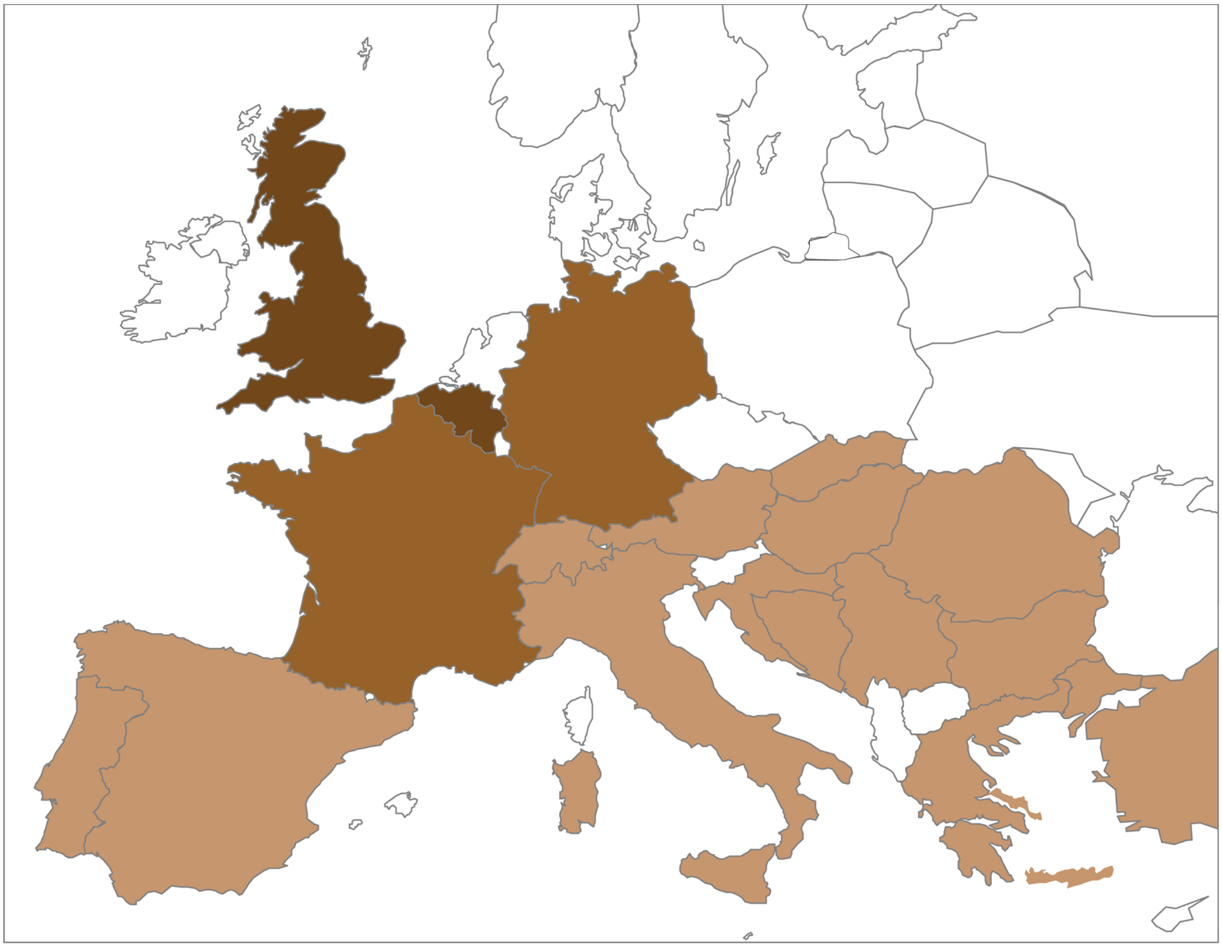

Imported cases (Belgium and the UK)

Imported and autochthonous cases (France and Germany)

Autochthonous cases (Austria, Bosnia and Herzegovina, Bulgaria, Croatia, Greece, Hungary, Italy, Portugal, Romania, Serbia, Slovakia, Spain, Switzerland and Turkey)

Fig. 1. Thelaziosis in Europe. Belgium and the UK have only reported imported cases of canine thelaziosis. France and Germany have identified one imported case of canine thelaziosis each. The other reported cases have been autochthonous and occurred in dogs, cats and in one human. Austria, Bosnia and Herzegovina, Bulgaria, Croatia, Greece, Hungary, Italy, Portugal, Romania, Serbia, Slovakia, Spain, Switzerland and Turkey have just reported autochthonous cases in several species, such as dogs, cats, red foxes, wolves, beech martens, wildcats, golden jackals, hares, wild rabbits and humans.

et al., 2019), Portugal (Rodrigues et al., 2012; Vieira et al., 2012; Pimenta et al., 2013; Soares et al., 2013; Sargo et al., 2014; Gama et al., 2016; Maia et al., 2016; Seixas et al., 2018), Belgium (Caron et al., 2013), Bosnia and Herzegovina (Hodžić et al., 2014), Croatia (Hodžić et al., 2014; Paradžik et al., 2016), Serbia (Gajić et al., 2014; Tasić-Otašević et al., 2016; Pavlović et al., 2017), Romania (Mihalca et al., 2015; Ioniţă et al., 2016; Mihalca et al., 2016; Tudor et al., 2016; Dumitrache et al., 2018; Ionică et al., 2018, 2019), Greece (Diakou et al., 2015; Papadopoulos et al., 2018), Bulgaria (Colella et al., 2016), Hungary (Colella et al., 2016; Farkas et al., 2018), Slovakia (Čabanová et al., 2017, 2018), the United Kingdom (UK) (Graham-Brown et al., 2017; Hammond, 2018), Turkey (Eser et al., 2018) and Austria (Hodžić et al., 2019) (Fig. 1).

The present article reviews the eyeworm itself and reported European ocular thelaziosis cases, underlining the importance of prevention based on the One Health paradigm. Cases of infection and disease by the eyeworm *T. callipaeda* in Europe are reviewed by primarily sourcing MEDLINE bibliographic database through PubMed. Based on a combination of keywords "Europe AND (*Thelazia callipaeda* OR *Phortica variegata* OR eyeworm OR eye worm OR thelaziosis OR thelaziasis)", references published between January 1st 2001 and July 31st 2019 were retrieved and analysed. Listed publications were screened by title and abstract, with selected articles then undergoing full-text analysis and data extraction. References lists of the available articles were also searched for additional publications deemed as relevant to this review.

2. Morphology

Thelazia callipaeda is a whitish filiform nematode (Fig. 2). In European countries adult males and females typically measure 7.5–13 mm and 12–18.5 mm in length and 340–430 μm and 370–510 μm in width, respectively (Otranto and Traversa, 2005; Otranto and Eberhard, 2011; Beugnet et al., 2018).

Adult females are identified by the position of the vulva, located anteriorly to the oesophageal-intestinal junction and in the anterior half of the body (Fig. 3). Male worms have a ventral curved caudal end, five pairs of papillae on the ventral surface and two spicules, which significantly differ from each other in both shape and size (Otranto and Eberhard, 2011) (Figs. 4 and 5).

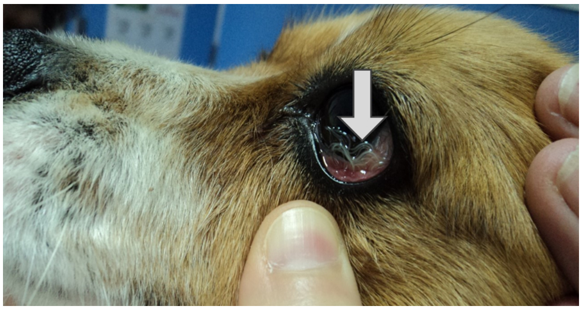

Fig. 2. Left eye of a dog with *Thelazia callipaeda* adult worm (arrow).

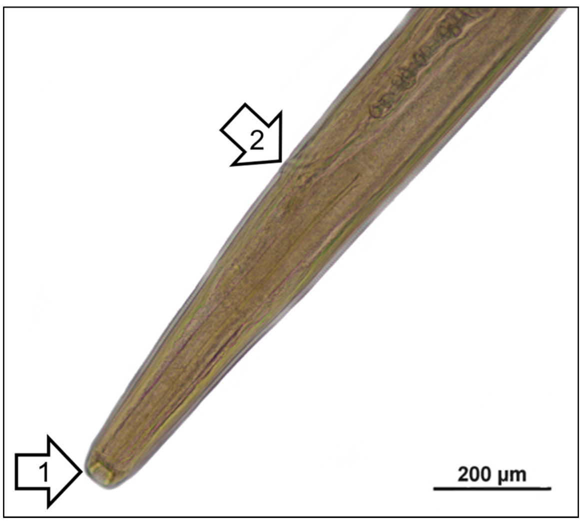

Fig. 3. Adult female of *Thelazia callipaeda*. Anterior extremity with buccal capsule (arrow 1) vulva (arrow 2).

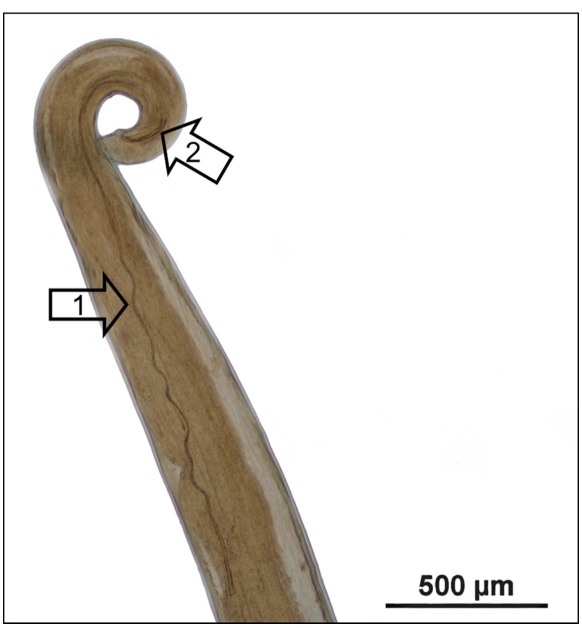

Fig. 4. Adult male of *Thelazia callipaeda*. Posterior end with long spicule (arrow 1) and short spicule (arrow 2).

3. Molecular characterisation

Studies on the molecular characterisation of partial cytochrome c oxidase subunit 1 (cox1) gene sequences have demonstrated the circulation in animals (i. e., dogs, cats and red foxes) and humans of a single haplotype of *T. callipaeda* in Europe (Otranto et al., 2005b, 2005c; Otranto and Dutto, 2008; Hodžić et al., 2014). This contrasts with the situation in Asia, where seven haplotypes have already been isolated (Otranto et al., 2005a; Shen et al., 2006; Hodžić et al., 2014). However, based on the *cox*1 gene, 20 haplotypes have recently been identified in Korea, Japan and China, which reveals a high genetic diversity of *T. callipaeda* isolates in East Asia (Zhang et al., 2018). These results throughout Europe indicate significant specificity of *T. callipaeda* for its vector *P. variegata*. Thus, the distribution of the parasite is believed to coincide with that of the vector (Otranto et al., 2005b, 2008; Hodžić et al., 2014). The low genetic variability of *T. callipaeda* in Europe supports the hypothesis that the infection could have been introduced into non-endemic regions by wildlife migration and by dogs travelling from countries or regions where thelaziosis is endemic (Otranto et al., 2007; Ruytoor et al., 2010; Miró et al., 2011; Hodžić et al., 2014; Ioniţă et al., 2016; Palfreyman et al., 2018). However, one study conducted in Germany reported the existence of a novel haplotype which differs 1.3% from haplotype 1. This identification supports the view of autochthonous transmission (Magnis et al., 2010).

4. Life cycle

First-stage larvae (L1) are produced by female eyeworms and released in the lachrymal secretions (under the eyelids and nictitating membrane, at the conjunctival surfaces, in the conjunctival sac or the nasolacrimal ducts) of the definitive hosts, after mating with the adult males. Transmission occurs when secretophagous nonbiting male flies feed on lachrymal secretions and ingest L1, becoming infected. First-stage larvae undergo two moults to the infective third-stage larvae (L3) into the drosophilids' testes. Thereafter, L3 migrate to their proboscis, and when the flies again feed on lachrymal secretions of animals or humans, L3 are released into the conjunctival sac of the hosts. In the eye socket of the hosts, L3 develop into the adult stage over ~35 days (Bianciardi and Otranto, 2005; Otranto and Traversa, 2005; Otranto et al., 2004, 2006a; Ioniţă et al., 2016) (Fig. 6).

5. Sylvatic cycle

The geographical dispersion of *T. callipaeda* in previously non-endemic European countries has been attributed to several wildlife species such as wild carnivores (i.e. red foxes, beech martens, wolves and a badger) and lagomorphs (hares and wild rabbits) (Otranto et al., 2007, 2009; Otranto and Dantas-Torres, 2015; Gama et al., 2016; Mihalca et al., 2016; Dumitrache et al., 2018; Ionică et al., 2019). The role of wild carnivores in introducing, maintaining and spreading this eyeworm in areas where there are no reports of infected domestic animals should be underlined (Otranto and Dantas-Torres, 2015).

Among wild carnivores, red foxes (*Vulpes vulpes*) have played a particularly important role in spreading thelaziosis given their high population density in areas with well-established infection in dogs and cats (Hodžić et al., 2014; Otranto and Dantas-Torres, 2015). Moreover, the fact that adult foxes of the same sex are separated from each other within their territory (which can range from 10 to 30 km) may facilitate expansion of the infection to neighbouring regions (Hodžić et al., 2014).

Red foxes are known to be more active during dusk and dawn. On the other side, the vector also has seasonal patterns and a predominant crepuscular activity. This coincidence between the seasonality and crepuscular activity of *P. variegata* and fox behaviour may favour transmission of the parasite, therefore potentially making foxes the primary wildlife reservoir host (Hodžić et al., 2014; Otranto and Dantas-Torres, 2015; Ionică et al., 2018).

Wild fauna is responsible for maintaining and spreading thelaziosis among humans and domestic animals in rural areas (Ruytoor et al., 2010; Caron et al., 2013). Furthermore, canine thelaziosis in Europe

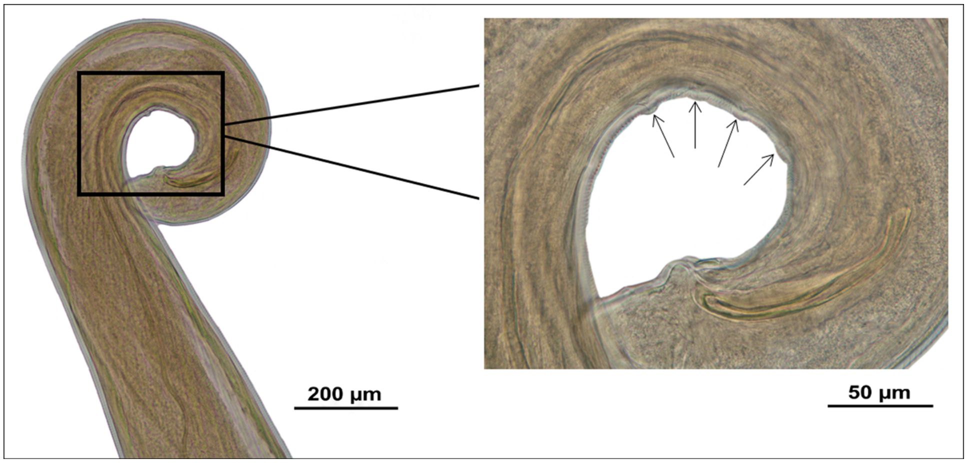

Fig. 5. Adult male of *Thelazia callipaeda*. Posterior end with evident papillae (arrows).

may occur due to the increased mobility of dogs (due to hunting, international tourism and trade), allied to the presence and distribution of the vector and nematode. It is of interest to note a breed-size predisposition for dogs with lower prevalence values in both small-sized breeds and younger dogs (Malacrida et al., 2008; Miró et al., 2011). On the other hand, the less commonly diagnosed feline thelaziosis may be due to the cats' intensive hygiene habits, which eliminate eye discharges, and to their small body index but also because of the difficulties experienced by veterinarians inspecting their eyes (Otranto et al., 2003; Miró et al., 2011; Hodžić et al., 2014; Farkas et al., 2018).

6. Vector – Phortica variegata

In Europe, *T. callipaeda* is mainly transmitted by the fruit fly *P. variegata* (Otranto et al., 2005c, 2006b, 2012). Under experimental conditions, both males and females of *P. variegata* can act as *T. callipaeda* vectors (Otranto et al., 2005a, 2012). However, only males typically feed on animal and human ocular secretions. Thus, only male *P. variegata* have contact with the first stage *T. callipaeda* larvae (L1) and act as their intermediate host, transmitting the infective stage larvae (L3) to domestic and wild carnivores, lagomorphs and humans (Otranto et al., 2012; Máca and Otranto, 2014; Colella et al., 2016; Marino et al., 2018).

While this zoophilic attitude, also termed lachryphagous behaviour or lachryphagy, is exclusive to *P. variegata* males, females feed on fruit and other vegetable matter (Dorchies et al., 2007; Máca and Otranto, 2014). This behaviour contrasts with that observed in mosquitoes, of which only adult females are haematophagous (Máca and Otranto, 2014). The predominance of males around the eye of the animal and human hosts can be justified by their dietary habits and needs, given that male *P. variegata* drosophilids require high-protein supplementation for gonadotrophic development (Otranto et al., 2006a, 2006b; Roggero et al., 2010; Soares et al., 2013; Marino et al., 2018).

According to several studies, *T. callipaeda* emerge in those areas suited for development of the *Phortica* fruit flies (Otranto et al., 2006a, 2012). Thelaziosis cases have been described in regions with slime, decaying fruits and fruit plantations such as strawberry fields and orchards comprising apple and plum trees (Otranto et al., 2006a, 2012;

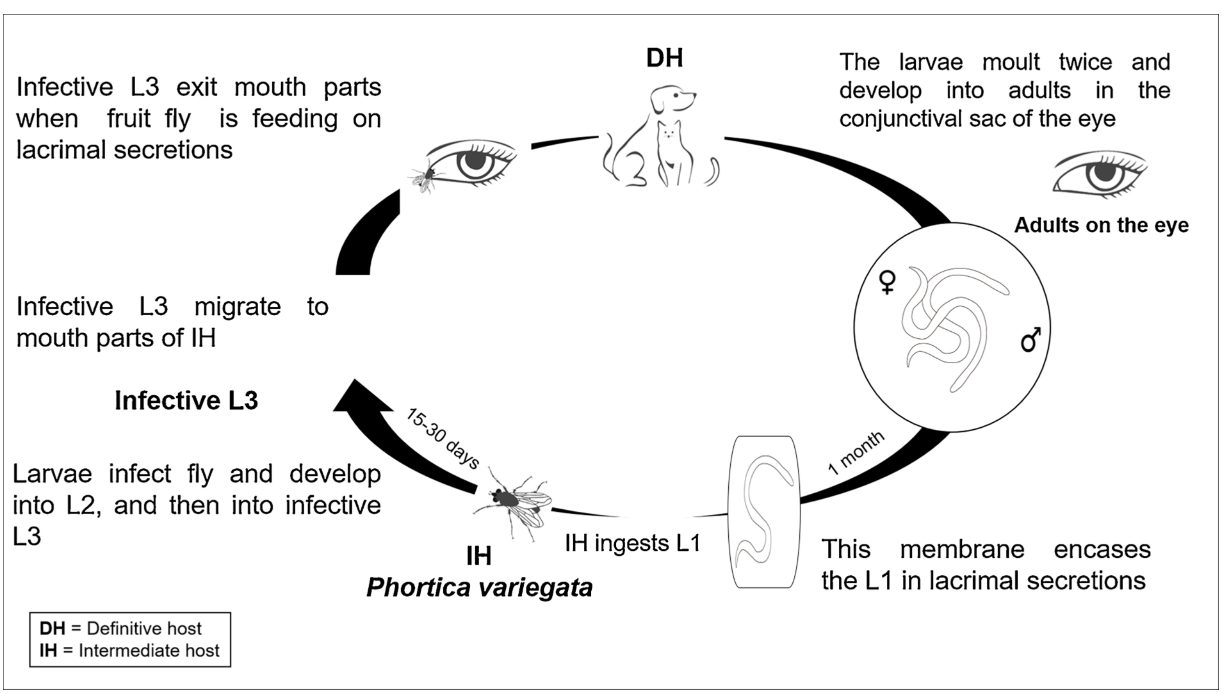

Fig. 6. Lyfe cycle of *Thelazia callipaeda*.

Dorchies et al., 2007; Magnis et al., 2010; Ruytoor et al., 2010; Tudor et al., 2016).

It appears that the biological activity of *P. variegata* is greater when the temperature ranges between 20 °C and 25 °C and relative humidity is about 50–75%. Ocular thelaziosis may have a seasonal pattern due to the presence, density and activity of the vector (Shen et al., 2006; Otranto and Dutto, 2008; Diakou et al., 2015). Adult parasites may survive for more than one year in the conjunctival sacs, a situation which may explain the occurrence of two peaks of infection, one in early summer and the other in late summer (Otranto et al., 2004, 2006a), predominantly in forest and hilly regions and in areas surrounded by rivers (Otranto et al., 2006a; Máca and Otranto, 2014; Čabanová et al., 2017; Marino et al., 2018; Palfreyman et al., 2018). However, the apparent absence of seasonality in the detection of adult nematodes of *T. callipaeda* and of the vector in endemic areas has also been described (Ruytoor et al., 2010; Maia et al., 2016).

Based on this information and the natural niche model of this insect, it was suggested that several European regions (mainly in Central Europe) are likely to be an ideal habitat for *P. variegata*, a circumstance which could lead to the expansion of thelaziosis (Otranto et al., 2006a). The case reports about thelaziosis that have been described in several European countries prove the model's prediction accuracy.

7. Clinical signs

Infections with *Thelazia* may be asymptomatic or subclinical, but detectable clinical signs are sometimes reported due to the lateral serration of the *Thelazia* cuticle which irritates and damages the conjunctival and corneal epithelium (Otranto and Traversa, 2005; Beugnet et al., 2018).

When this nematode lodges in the eye socket and associated tissues of its hosts, it can induce mild (i. e. blepharospasm, conjunctivitis, epiphora, itching and ocular discharge) to severe (i. e. keratitis and corneal ulceration) ocular signs (Otranto and Traversa, 2005; Shen et al., 2006; Fuentes et al., 2012; Hodžić et al., 2014). According to several case reports, the severity of clinical signs does not appear to correlate with worm burden (Miró et al., 2011; Vieira et al., 2012; Hodžić et al., 2014).

8. Diagnosis

Thelaziosis should be included in the differential diagnosis of all cases in which the eye is affected, for exemple allergic conjunctivitis (Otranto and Dutto, 2008; Miró et al., 2011; López Medrano et al., 2015; Diakou, 2017). The detection of a whitish nematode on the conjunctiva and conjunctival sacs is pathognomonic of thelaziosis (Beugnet et al., 2018; Mérindol et al., 2018). Identification of the species of *Thelazia* can be efficiently performed by microscopic examination and molecular analysis (Otranto et al., 2003, 2005c; Malacrida et al., 2008; Miró et al., 2011; Calero-Bernal et al., 2013; Caron et al., 2013; Hodžić et al., 2014; Farkas et al., 2018). Diagnosis can be challenging when most parasites are at an immature stage, when few adult nematodes are present or in cases that *Thelazia* specimens are located within the excretory ducts of the lacrimal glands (Caron et al., 2013). Ocular inspection is essential during routine clinical examination to correctly detect subclinical infections, even if there are no apparent ocular signs (Diakou, 2017).

9. Treatment

Treatment can be based on mechanical removal of worms directly from the eyes of affected animals (after local or general anaesthesia). However, given the eyeworm's habitat, thelaziosis can equally be treated by direct instillation of antiparasitic drugs into the eyes (Bianciardi and Otranto, 2005; Otranto and Traversa, 2005; Beugnet et al., 2018). Nonetheless, mechanical removal of parasites does not guarantee complete extraction of all nematodes from the eye, given that they can be hidden under the third eyelid. Moreover, it is challenging to remove the immature stages of *T. callipaeda* (Caron et al., 2013). For this reason, the antiparasitic treatment appears to be more appropriate. Drug administration should be local instead of systemic, since it is more direct and requires a reasonable quantity of the product (Lia et al., 2004). To date the only antiparasitic drugs licended for treatment of ocular thelaziosis have been moxidectin and milbemycin oxime (Motta et al., 2012; Otranto et al., 2016; Diakou, 2017; Graham-Brown et al., 2017). The use of ivermectin in subcutaneous injections has also been reported. However, this appears to be less feasible since it is painful and can cause tissue damage due to the presence of propylene glycol (Lia et al., 2004).

A spot-on formulation containing moxidectin 2.5% and imidacloprid 10% (Advocate®; Bayer Animal Health), administered for dermal absorption, has been shown to be highly effective in the treatment of thelaziosis in dogs (Bianciardi and Otranto, 2005; Lechat et al., 2015; Otranto et al., 2016). Another study proved the high efficacy of moxidectin 1% (Cydectin®; Fort Dodge) ocular instillation, administered as a single dose to dogs infected by *T. callipaeda* (Lia et al., 2004). The spot-on formulation for cats containing moxidectin 1% and imidacloprid 10% (Advocate®; Bayer Animal Health) has been reported as highly effective and safe in the treatment of feline thelaziosis (Otranto et al., 2019).

Ferroglio et al. (2008) showed that treatment efficacy by the administration of milbemycin oxime (Interceptor®; Novartis) appears to be dose-dependent. Their data suggested that two doses (1 week apart) of 0.86 mg/kg were 100% effective, since they ensured optimal blood concentration of milbemycin oxime to supply the required concentrations of the product in the conjunctiva of infected dogs. Another scientific study reported high efficacy in ocular thelaziosis treatment through the commercial formulation of milbemycin oxime (Milbemax®; Novartis) at the minimal dose of 0.5 mg/kg and 2 mg/kg in dogs and cats, respectively (Motta et al., 2012). A study with dogs treated with milbemycin oxime on days 0, 7, 14, 28 and 35 found maximal efficacy from day 18. The group of animals treated with imidacloprid 10% and moxidectin 2.5% showed 100% of efficacy shortly after the first treatment (Otranto et al., 2016).

Oral treatment of Border Collies (a dog breed sensitive to macrocyclic lactones due to a mutation of the MDR-1 gene) using mebendazole 20 mg/kg (Telmin®; Esteve) proved to be effective (Calero-Bernal et al., 2014).

10. Animal thelaziosis

Since the first reported case of canine thelaziosis (Rossi and Bertaglia, 1989), other cases have surfaced in dogs and other vertebrate species including humans. The absence of efficiently implemented prophylactic measures in carnivores may represent a crucial factor for increased thelaziosis cases (Motta et al., 2012). It is equally noteworthy that increasing awareness between veterinarians, parasitologists and ophthalmologists on thelaziosis has contributed to an increased number of reports in Europe (Otranto et al., 2013). An ecological niche model for Europe suggests vast areas as suitable for *P. variegata* and therefore conducive to the expansion of thelaziosis (Otranto et al., 2006a). In fact, *T. callipaeda* has been found in many regions across western and central Europe (Otranto et al., 2013; Hodžić et al., 2014; Mihalca et al., 2015) (Fig. 1). Moreover, recent years have seen frequent reports of cases emerging in Eastern Europe (Čabanová et al., 2018). This highlights the increased risk of this emerging vector-borne zoonosis (Colwell et al., 2011; Ioniţă et al., 2016; Dumitrache et al., 2018) (Fig. 1).

Thelazia callipaeda is considered endemic in Italy, France and Switzerland. However, thelaziosis has also been expanding to previously non-endemic countries such as Portugal, Bosnia and Herzegovina, Croatia, Serbia, Greece and Slovakia, among others (Diakou, 2017). In addition, the same haplotype (i.e. h-1) circulates

Table 1
Cases of thelaziosis reported in Italy of presumable autochthonous origin, by region/area, year of reporting and vertebrate host species.

Area	Year	Species (no. infected/total)	References
Basilicata	NA	Dog (1)	Lia et al. (2000)
Piedmont	1995–2002	Dog (21/91) Cat (4) Red fox[b] (46/903)	Otranto et al. (2003)
Basilicata	1999–2003	Dog (185/443)	
Basilicata	2006	Wolf[c] (3)	Otranto et al. (2007)
Roja Valley (Liguria)[a]	2005	Human (1)	Otranto and Dutto (2008)
Canelli (Piedmont)	2006	Human (1)	
Cuneo (Piedmont)	2006	Human (1)	
Basilicata	2009	Red fox (37/75) Wolf (1/2) Beech marten[d] (3/22) Hare[e] (3/13) Wildcat[f] (3/8)	Otranto et al. (2009)

NA: not available.
[a] This patient from Liguria had gone trekking in the woods in Tenda (Piedmont region, Italy), approximately 3 weeks before the onset of clinical signs.
[b] *Vulpes vulpes*.
[c] *Canis lupus*.
[d] *Martes foina*.
[e] *Lepus europaeus*.
[f] *Felis silvestris*.

throughout Europe, which suggests the spread of this parasite from a common origin to all areas where it has already been reported (Otranto et al., 2005c, 2008, 2013; Ioniţă et al., 2016; Palfreyman et al., 2018).

The presence of thelaziosis in domestic carnivores in Europe is likely derived from increased international trade and travel, which favour mass movement of people and domestic animals, as well as vectors, and their associated pathogens (Hermosilla et al., 2004; Hodžić et al., 2014).

10.1. Italy

Thelaziosis is widespread throughout Italy (Table 1). In the Basilicata region (southern Italy), the prevalence of infection in dogs was about 60% (Otranto et al., 2003).

10.2. Belgium, France and the United Kingdom

The French department of Dordogne is an endemic area of ocular thelaziosis (Dorchies et al., 2007). Most local canine thelaziosis cases originated from the communes of Vergt, Saint Pierre-de-Chignac and Villamblard, in the Dordogne department (Table 2). This department is at the same latitude as Piedmont (northern Italy), where canine thelaziosis has also been reported (Dorchies et al., 2007). It has been suggested that the autochthonous population of red foxes presumably contributed to the introduction of canine thelaziosis in this region (Dorchies et al., 2007). Of interest is that the three communes previously referred to have several strawberry farms, as well as other types of fruit production, where *P. variegata*, can develop (Otranto et al., 2006a; Dorchies et al., 2007).

According to the ecological niche model (Otranto et al., 2006a), the Landes department, not far from the Dordogne department, is also a potential area for thelaziosis. Most of its surphace is covered by a forest of pines, and the introduction of *T. callipaeda* may occur by importation or dispersal of vectors and/or through migration of infected wild animals, such as red foxes and wolves (Otranto and Dantas-Torres, 2015; Mérindol et al., 2018).

Apart from autochthonous cases, there are also some reports of imported cases in non-endemic areas of Europe, such as Belgium and more recently the UK (Fig. 1; Table 2). All such cases were related to animals that had travelled to or lived in endemic European countries just before clinical signs appeared (Graham-Brown et al., 2017).

In the UK, the government's Pet Travel Scheme facilitates the movement of dogs to and from European Union (EU) contries without the need for quarantine. Consequently, many pathogens, including *T. callipaeda*, constitute a considerable threat to the UK canine population (Graham-Brown et al., 2017).

10.3. Austria, Germany and Switzerland

Bühl town, in southern Germany, from where a case of canine thelaziosis was reported, also incorporates fruit fields, including strawberry fields as in Dordogne department (Table 3). An imported case has also been reported in Germany (Hermosilla et al., 2004). The Ticino canton, in Southern Switzerland (Table 3), is located at similar latitudes to Piedmont region (Italy) and to the Dordogne department (France). The first autochthonous case of feline ocular thelaziosis was recently reported in Austria (Table 3).

Table 2
Cases of thelaziosis in Belgium, France and the United Kingdom (UK) by region/area, year of reporting and vertebrate host species.

Country	Area	Year	Species (no. infected/total)	References
Belgium	Liège[a]	2012	Dog (2)	Caron et al. (2013)
France	Paris[b]	1993	Dog (1)	Chermette et al. (2004)
	Nice	2005	Human (2)	Otranto and Dutto (2008)
	Dordogne	2007	Dog (4) Cat (1)	Dorchies et al. (2007)
	Ariège, Dordogne[c], Gironde, Haute-Garonne, Lot-et-Garonne, Puy-de-Dôme, Pyrénées-Atlantiques, Tarn and Tarn-et-Garonne	2010	Dog (115) Cat (2)	Ruytoor et al. (2010)
United Kingdom	NA[d]	2016	Dog (3)	Graham-Brown et al. (2017)
	Hampshire[e]	2018	Dog (1)	Hammond (2018)

NA: not available.
[a] The infections had been acquired in south western France and southern Italy.
[b] The dog had travelled to Piedmont region (Italy) 4 months before clinical signs developed.
[c] Most cases (104/117) were diagnosed in the Dordogne department. Furthermore, most of the infected animals in the other regions had spent time in Dordogne a few months before clinical signs developed.
[d] One dog had been imported to the UK from Hateg, Hunedoara county (western Romania) 6 weeks before. Other dog had returned from travel to Lombardia region (northern Italy). The third dog had spent 1 month in Saint Avit Loisirs camping, Dordogne department (France).
[e] The dog presented a unilateral conjunctivitis 1 month after returning from a 2-week stay in the Dordogne department (France).

Table 3
Cases of thelaziosis in Austria, Germany and Switzerland by region/area, year of reporting and vertebrate host species.

Country	Area	Year	Species (no. infected/total)	References
Austria	Deutschandberg	2018	Cat (1)	Hodžić et al. (2019)
Germany	NA[a]	2004	Dog (1)	Hermosilla et al. (2004)
	Bühl	2010	Dog (1)	Magnis et al. (2010)
Switzerland	Grisons and Ticino[b]	2008	Dog (106; 28/529)[c]	Malacrida et al. (2008)
			Cat (5)	
			Red fox[d] (7/126)	
	Ticino	2014	Cat (17/2171)	Motta et al. (2014)

NA: not available.
[a] The dog had visited several parts of Italy for a few weeks before clinical signs developed.
[b] Out of 95 *Thelazia*-positive dogs with known data about travel history, 40 had previously been to Italy (1 year before diagnosis).
[c] Partial of 106 *Thelazia*-positive dogs from a retrospective analysis and from ongoing cases between 2005 and 2007; 28 dogs were found positive out of 529 randomly selected dogs.
[d] *Vulpes vulpes*.

10.4. Portugal and Spain

In Portugal, thelaziosis has been reported in domestic carnivores (Rodrigues et al., 2012; Vieira et al., 2012; Pimenta et al., 2013; Soares et al., 2013; Maia et al., 2016), lagomorphs (Gama et al., 2016) and wild carnivores such as red foxes and beech martens (Sargo et al., 2014; Seixas et al., 2018). Cases have been described in the North (municipalities of Bragança, Chaves, Macedo de Cavaleiros, Vila Real, Vinhais, Montalegre) and in the Centre regions of Portugal (municipalities of Coimbra, Sabugal, Fundão, Covilhã) (Table 4). Thelaziosis has been expanding to the south, perhaps due to the southerly dissemination of *P. variegata* or because of the introduction of infected hosts in areas where the vector had already been present (Maia et al., 2016). The majority of reported cases have occurred in rural areas where agriculture and livestock represent the main economic activities. Shepherd, hunting and feral dogs roam in these regions in close contact with wildlife such as red foxes and wolves. This situation may favour the connection with the insect vector and, consequently, parasite transmission (Sargo et al., 2014; Maia et al., 2016).

The introduction of the eyeworm in Portugal could be due to the arrival of hunting dogs from endemic regions during the hunting season and to the movement of Portuguese emigrants (who live abroad and come to Portugal for vacations) and tourists with their pets from countries where endemic areas of *T. callipaeda* have been identified, such as France and Switzerland (Sargo et al., 2014).

The province of Cáceres (Spain), and particularly in La Vera, is a destination for hunters from Italy, who travel with their dogs during the hunting season. It is also a region chosen by French holidaymakers, who often bring their pets (Miró et al., 2011). This area falls within the range of the geoclimatic provisional model for *P. variegata* distribution (Otranto et al., 2006a; Miró et al., 2011; Calero-Bernal et al., 2013) and also holds fruit production fields (apples, pears, figs, blueberries and raspberries) and vineyards, which represents an ideal habitat for the vector (Marino et al., 2018). The sylvatic life cycle of *T. callipaeda* in red foxes in Cáceres suggests that this species may act as potential reservoirs of the eyeworm for domestic carnivores and humans (Miró et al., 2011; Calero-Bernal et al., 2013). According to Marino et al. (2018), in addition to the La Vera (Cáceres province), which is endemic for canine thelaziosis, there are at least two other risk areas for *T. callipaeda* infection: the El Escorial and the Miraflores de la Sierra municipalities (Madrid community) (Marino et al., 2018). The prevalence of canine thelaziosis in the Cáceres province as well as in the provinces of Salamanca, Ávila and Toledo has been estimated at around 40% (Table 4).

Table 4
Cases of thelaziosis reported in Portugal and Spain of presumable autochthonous origin, by region/area, year of reporting and vertebrate host species.

Country	Area	Year	Species (no. infected/total)	References
Portugal	Bragança	2011	Dog (3)	Vieira et al. (2012)
	Chaves		Dog (6)	
	Macedo de Cavaleiros	2011	Cat (1)	Rodrigues et al. (2012)
	Vila Real[a]	2012	Dog (1)	Pimenta et al. (2013)
	Coimbra	2013	Cat (1)	Soares et al. (2013)
	Belmonte, Covilhã, Fundão, Gouveia, Guarda, Penamacor and Sabugal	2013–2014	Dog (22/586)	Maia et al. (2016)
			Cat (4/22)	
	Montalegre	2014	Red fox[b] (1)	Sargo et al. (2014)
	Sabugal		Red fox (2)	
	Vilar de Ossos (Vinhais)	2016	Wild rabbit[c] (2)	Gama et al. (2016)
	Vila Real	2018	Beech marten[d] (1)	Seixas et al. (2018)
Spain	La Vera (Cáceres)	2010	Dog (182/456)	Miró et al. (2011)
	Cáceres	2011	Human (1)	Fuentes et al. (2012)
	Cáceres	2011	Red fox (2)	Calero-Bernal et al. (2013)
	El Bierzo	2015	Human (1)	López Medrano et al. (2015)
	La Vera (Cáceres)	2016–2017	Dog (51/75)	Marino et al. (2018)
	El Escorial (Madrid)		Dog (23/88)	
	Miraflores de la Sierra (Madrid)		Dog (41/124)	
	Ourense	NA	Human (2)	Deltell et al. (2019)

[a] The dog frequently traveled to the near city of Macedo de Cavaleiros, from where the case of ocular thelaziosis in a cat was reported (Rodrigues et al., 2012).
[b] *Vulpes vulpes*.
[c] *Oryctolagus cuniculus*.
[d] *Martes foina*.

Table 5
Cases of thelaziosis reported in Bosnia and Herzegovina, Croatia, Hungary, Serbia and Slovakia of presumable autochthnous origin, by region/area, year of reporting and vertebrate host species.

Country	Area	Year	Species (no. infected/ total)	References
Bosnia and Herzegovina	Eastern, northeastern, northern, central and northwestern	2011–2014	Red fox[a] (51/184)	Hodžić et al. (2014)
	Sarajevo	2012–2014	Dog (2)	
	Rudo		Dog (2)	
			Cat (1)	
Croatia	Slovanski Brod	2013–2014	Dog (1)	Hodžić et al. (2014)
	Našice		Dog (1)	
	NA	2014	Human (1)	Paradžik et al. (2016)
Hungary	NA	2016	Dog (1)	Colella et al. (2016)
	Budapest, Kazincbarcika, Miskolc, Mohács, Sajógalgóc, Sajómercse and Sajószentpéter	2015–2017	Dog (10)	Farkas et al. (2018)
			Cat (1)	
Serbia	Brvenik, Kladurovo, Kruševac, Požega, Umka and Užice	2012–2013	Dog (4)	Gajić et al. (2014)
			Cat (2)	
	Belgrade	2014	Red fox (2)	Pavlović et al. (2017)
	Požarevac		Red fox (1)	
	Medveđa	2016	Human (1)	Tasić-Otašević et al. (2016)
	Niš		Dog (2)	
Slovakia	Koromľa (Sobrance)	2016	Dog (1)	Čabanová et al. (2017)
	Hlivištia (Sobrance)		Dog (1)	
	Michalovce (Košice)		Dog (1)	
	Vinné (Michalovce)		Dog (1)	
	Košice	2016–2017	Red fox (6/523)	Čabanová et al. (2018)
	Trenčín		Red fox (1/523)	
	Košice	2017	Dog (1)	

NA: not available.
[a] *Vulpes vulpes*.

10.5. Bosnia and Herzegovina, Croatia, Hungary, Serbia and Slovakia

Regarding Bosnia and Herzegovina, the highest prevalence (50%) of thelaziosis occurred in Eastern Bosnia, characterised by mountains with river streams, orchards and forests, and by a rural environment with hunting and stray dogs (Table 5). The sylvatic cycle plays a vital role in maintaining the infection in these countries, whose latitude is similar to that of north-western Italy and France, both areas in Europe recognised as endemic for thelaziosis (Hodžić et al., 2014).

In Serbia, the origin of *T. callipaeda* in domestic carnivores may relate to the establishment of infection in wildlife on affected areas (Table 5). Cases of animal or human thelaziosis have also been reported from Croatia, Hungary and Slovakia (Table 5).

10.6. Bulgaria, Greece, Romania and Turkey

In Romania, thelaziosis has been reported in many species (dogs, cats, red foxes, wolves, wildcats, golden jackals, a badger and a beech marten) in a relatively broad distribution range (Table 6). The infection was probably introduced into this country by dogs travelling with their emigrant owners from southern and western Europe, mainly Italy and Spain, where thelaziosis is endemic (Ioniţă et al., 2016). Cases of animal thelaziosis have also been reported from Bulgaria, Greece and the European part of Turkey (Table 6).

11. Human thelaziosis

Since the case reports of human thelaziosis in Italy and France, other cases have been described in patients from Spain, Serbia and Croatia (Tables 1, 2, 4 and 5). All together, these suggest that the eyeworm is moving from West to East, potentially via the migratory behaviour of red foxes (McGarry et al., 2017).

Human thelaziosis is considered a neglected disease. This could be due to its association with poor rural communities having inadequate living conditions and low socioeconomic standards (Shen et al., 2006; Otranto and Dutto, 2008), where the infection is highly prevalent in domestic and wild carnivores (Shen et al., 2006; Fuentes et al., 2012; Hodžić et al., 2014; Colella et al., 2016). Under such conditions, the elderly and children are those most affected people. The lack of awareness amongst physicians across Europe concerning the zoonotic potential of *T. callipaeda* can lead to incorrect diagnosis and, consequently, to inadequate treatment and prolongation of the parasite's survival and related effects (Shen et al., 2006; Otranto and Dutto, 2008; Caron et al., 2013; Colella et al., 2016).

12. Prevention and one health concept

The term “One Health” refers to distinct relationships between animals, humans and the environment. This concept arises as a global strategy adopted by the World Organisation for Animal Health (OIE) aimed at interdisciplinary collaboration between national authorities and organizations involved in animal and human health. This concept is based on the application of practices related to prevention, monitoring and detection of animal diseases (including zoonoses), food safety and security, and further applications in the field of resistance to antimicrobial agents (Ryu et al., 2017).

Vector-borne parasitic zoonoses have a considerable impact on animal and human health, but they also represent a major threat for any country's economy. However, developing countries are always among those most disadvantaged (Colwell et al., 2011). Ecological and climatic changes, drastic variations in human demographics and behaviour, enhancement of international trade and travel, dramatic alterations in land use (e.g. deforestation and development of irrigation) and the increased resistance to drugs by vector arthropods create opportunities for them to spread and establish (Colwell et al., 2011; Otranto and Eberhard, 2011; Baneth et al., 2012).

As previously mentioned, poor living conditions and low socioeconomic standards seem to be risk factors involved in acquiring infection (Shen et al., 2006; Otranto and Dutto, 2008; Otranto and Eberhard, 2011). Moreover, the increased close contact between pets and their owners, some of them suffering from particular conditions (immunological and oncological diseases and transplants) may increase the odds of transmission (Stull et al., 2014, 2015). Thus, some practical measures must be implemented to prevent the occurrence of infection

Table 6
Cases of thelaziosis reported in Bulgaria, Greece, Romania and Turkey of presumable autochthonous origin, by region/area, year of reporting and vertebrate host species.

Country	Area	Year	Species (no. infected/ total)	References
Bulgaria	NA	2016	Dog (9)	Colella et al. (2016)
Greece	Thessaloniki	2015	Dog (1)	Diakou et al. (2015)
	Athens, Chalkidiki, Drama, Edessa, Giannitsa, Grevena, Kalambaka, Kilkis, Larisa, Serres, Thessaloniki and Veroia	2014–2016	Dog (46) Cat (3) Rabbit[a] (1)	Papadopoulos et al. (2018)
Romania	Oradea	2014	Dog (1)	Mihalca et al. (2015)
	Lugoj	2013–2015	Dog (1)	Ioniţă et al. (2016)
	Râmnicu Vâlcea		Dog (1)	
	Târgovişt	2015	Dog (1)	Tudor et al. (2016)
	Snagov		Dog (1)	
	Ostrovu Mare (Mehedinţi)	2014–2016	Golden jackal[b](1/64)	Mihalca et al. (2016)
	Pianu de Sus (Alba)		Wolf[c] (1/13)	
	Mesteacanu (Sălaj)		Wildcat[d] (1/9)	
	Arad, Bihor, Cluj, Gorj, Hunedoara, Maramureş, Mureş, Sălaj, Satu-Mare and Timiş	2016–2017	Red fox[e] (151/514)	Ionică et al. (2018)
	Baia Mare (Maramureş)	2016–2018	Dog (3) Cat (1)	Dumitrache et al. (2018)
	Cluj-Napoca		Dog (1)	
	Tauţii Măgherăuş		Dog (1)	
	Central, northwestern and western	2015-2019	Europea badger[f] (1/55)	Ionică et al. (2019)
	Eastern, northern, central, southern and northwestern		Beech marten[g] (1/13)	
Turkey	Thrace	2017	Dog (1)	Eser et al. (2018)

NA: not available.
[a] *Oryctolagus cuniculus*.
[b] *Canis aureus*.
[c] *Canis lupus*.
[d] *Felis silvestris*.
[e] *Vulpes vulpes*.
[f] *Meles meles*.
[g] *Martes foina*.

and disease.

Better sanitation and hygiene conditions will probably contribute to prevention (Otranto and Eberhard, 2011). The use of bed nets would allow vector control, avoiding contact while children sleep (Otranto and Dutto, 2008).

Monthly oral administration of milbemycin oxime (Interceptor®; Milbemax®) or milbemycin oxime/afoxolaner (NexGard Spectra®; Boehringer Ingelheim) or monthly application of a spot-on containing 10% imidacloprid and 2.5% moxidectin (Advocate®) are highly effective in preventing *T. callipaeda* infection in dogs (Ferroglio et al., 2008; Lechat et al., 2015; Diakou, 2017; Lebon et al., 2019).

Education and disease awareness among veterinarians, physicians (particularly ophthalmologists) and animal owners represent the first step to tackle the disease (Colwell et al., 2011; Fuentes et al., 2012; Gajić et al., 2014; Farkas et al., 2018). Early diagnosis and efficient treatment prevent complications associated with the parasitosis, such as pain and discomfort (Gajić et al., 2014). In addition, it also avoids the unnecessary use of antibiotics where there is no bacterial activity (Fuentes et al., 2012). Furthermore, it is essential to develop surveillance policies for travelling animals, in order to restrict distribution of the parasite across borders (Graham-Brown et al., 2017). National public health services are recommended to carry out disease surveillance and vector control programs and perform systematic entomological surveys in vector-free areas that are at risk of the introduction of vectors through animal or human population activities (Colwell et al., 2011).

13. Conclusions

Thelaziosis is far from control and its expansion in Europe has shown a spread to new geographical areas. Given the zoonotic character of *T. callipaeda*, knowledge improvement and awareness about this disease are crucial to ensure correct diagnosis and appropriate treatment and prevention. Closer cooperation between veterinary and medical services and animal owners is necessary to control this zoonosis.

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CRediT authorship contribution statement

Beatriz do Vale: Conceptualization, Investigation, Methodology, Writing - original draft, Writing - review & editing. **Ana Patrícia Lopes:** Writing - review & editing. **Maria da Conceição Fontes:** Writing - review & editing. **Mário Silvestre:** Writing - review & editing. **Luís Cardoso:** Supervision, Writing - review & editing. **Ana Cláudia Coelho:** Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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