Capillaria boehmi (syn. Eucoleus boehmi): challenging treatment of a rarely diagnosed nasal nematode in dogs and high prevalence in Swiss foxes

Gillis-Germitsch, Nina ; Müller, Stefan ; Gori, Francesca ; Schnyder, Manuela

Abstract: Despite morphological differences of eggs and adults, Capillaria boehmi infections have been occasionally misdiagnosed as C. aerophila infections in the past. Capillaria boehmi is found in the nasal and paranasal sinuses of wild canids and dogs, which may suffer from nasal discharge, sneezing, epistaxis and, importantly, their scent can be impaired. In this study we present three challenging cases of nasal capillariosis in dogs, report and review the variable success of anthelmintic treatments and investigate C. boehmi prevalence in Swiss red foxes, considered as potential wild life reservoir. Out of two females and one male dog (all scent hounds, aged 3-9 years and weighing 19-31 kg), two dogs were previously coproscopically misdiagnosed with Trichuris infections. Two dogs showed clinical signs such as sneezing, coughing and impaired scent. From one dog adult living C. boehmi were obtained by nasal lavage. The identity of worms and eggs of all three dogs were genetically confirmed (18S rRNA, 100 % identity in 578 base pairs). Dogs 1-3 were followed-up for overall 54, 8, and 67 months, respectively. All dogs repeatedly excreted C. boehmi eggs in faecal samples despite treatments with the following compounds, in various dosage and retreatment protocols: fenbendazole, milbemycin oxime (orally), moxidectin/imidacloprid/ (spot-on) and levamisole (intramuscularly). The different anthelmintic compounds showed variable success regarding their effect on clinical outcome and on stopping egg excretion. Reinfections due to a contaminated environment could not be fully excluded. In winter 2016 and 2017, 218 foxes from the canton of Zurich, Switzerland, were examined. Tissues of nasal and paranasal sinuses were investigated for adult Capillaria specimens and eggs. We describe for the first time C. boehmi infections in Switzerland, observing a high prevalence (190/218, 87.2 %). Overall, 107 of 126 adults (84.9 %, 95 % Confidence Interval, CI: 77.5-90.7 %) and 83 of 92 youngsters (90.2 %, CI: 82.2-95.4 %) were infected. The presence of C. boehmi did not correlate with age (P = 0.209), but correlated significantly with sex: male foxes (102 of 107, 95.3 %, CI: 89.4-98.5 %) were significantly (P = 0.001) more often infected than females (88 of 111, 79.3 %, CI: 70.5-86.4 %). Worm burden ranged from 1 to 72 adult specimens (geometric mean: 5.7). In conclusion, C. boehmi infections can be mis- and/or underdiagnosed in dogs. Appropriate anthelmintic treatments, preventing coprophagia and egg contamination of the surroundings and performing coproscopic controls after treatments are fundamental aspects. Potentially, nasal washing may represent an auxiliary alternative. However, the successful elimination of C. boehmi infections in dogs remains challenging.

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Capillaria boehmi (syn. *Eucoleus boehmi*): Challenging treatment of a rarely diagnosed nasal nematode in dogs and high prevalence in Swiss foxes

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ABSTRACT

Despite morphological differences of eggs and adults, *Capillaria boehmi* infections have been occasionally misdiagnosed as *C. aerophila* infections in the past. *Capillaria boehmi* is found in the nasal and paranasal sinuses of wild canids and dogs, which may suffer from nasal discharge, sneezing, epistaxis and, importantly, their scent can be impaired. In this study we present three challenging cases of nasal capillariosis in dogs, report and review the variable success of anthelmintic treatments and investigate *C. boehmi* prevalence in Swiss red foxes, considered as potential wild life reservoir. Out of two females and one male dog (all scent hounds, aged 3–9 years and weighing 19−31 kg), two dogs were previously coproscopically misdiagnosed with *Trichuris* infections. Two dogs showed clinical signs such as sneezing, coughing and impaired scent. From one dog adult living *C. boehmi* were obtained by nasal lavage. The identity of worms and eggs of all three dogs were genetically confirmed (18S rRNA, 100 % identity in 578 base pairs). Dogs 1–3 were followed-up for overall 54, 8, and 67 months, respectively. All dogs repeatedly excreted *C. boehmi* eggs in faecal samples despite treatments with the following compounds, in various dosage and retreatment protocols: fenbendazole, milbemycin oxime (orally), moxidectin/imidacloprid/ (spot-on) and levamisole (intramuscularly). The different anthelmintic compounds showed variable success regarding their effect on clinical outcome and on stopping egg excretion. Reinfections due to a contaminated environment could not be fully excluded. In winter 2016 and 2017, 218 foxes from the canton of Zurich, Switzerland, were examined. Tissues of nasal and paranasal sinuses were investigated for adult *Capillaria* specimens and eggs. We describe for the first time *C. boehmi* infections in Switzerland, observing a high prevalence (190/218, 87.2 %). Overall, 107 of 126 adults (84.9 %, 95 % Confidence Interval, CI: 77.5–90.7 %) and 83 of 92 youngsters (90.2 %, CI: 82.2–95.4 %) were infected. The presence of *C. boehmi* did not correlate with age ($P = 0.209$), but correlated significantly with sex: male foxes (102 of 107, 95.3 %, CI: 89.4–98.5 %) were significantly ($P = 0.001$) more often infected than females (88 of 111, 79.3 %, CI: 70.5–86.4 %). Worm burden ranged from 1 to 72 adult specimens (geometric mean: 5.7). In conclusion, *C. boehmi* infections can be mis- and/or underdiagnosed in dogs. Appropriate anthelmintic treatments, preventing coprophagia and egg contamination of the surroundings and performing coproscopic controls after treatments are fundamental aspects. Potentially, nasal washing may represent an auxiliary alternative. However, the successful elimination of *C. boehmi* infections in dogs remains challenging.

1. Introduction

Capillarid nematodes are part of a large and taxonomically complex group that infect carnivores and small mammals (Guardone et al., 2013). *Capillaria aerophila* (syn. *Eucoleus aerophilus*) is the first described and most widely distributed capillarid of the respiratory airways of carnivores (Creplin, 1839; Deplazes et al., 2016). In subsequent studies capillarid specimens recovered from the trachea and from nasal sinuses were observed to have different sizes; nevertheless, they all were defined as *C. aerophila* (Christenson, 1935).

In 1953 Supperer described capillarid eggs isolated from fox faeces and attributed them to an unknown capillarid species. In his investigations he mentioned findings of Prof. Böhm from Vienna, who had observed and recorded pictures with comparable eggs from faeces originating from silver foxes in 1929. Supperer then isolated nematodes from the sinuses frontales of three foxes, described adult specimens and

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eggs and defined them, in honour of Prof. Böhm, as a new species of *Capillaria*, *Capillaria boehmi*. These nematodes were differing from the more frequently reported *C. aerophila* (Supperer, 1953). Despite morphological differences between *C. aerophila* and *C. boehmi* eggs and adults, infections with *C. boehmi* have been presumably misdiagnosed as *C. aerophila* infections (Christenson, 1935; Evinger et al., 1985; Muchmore, 1998). *Capillaria boehmi* eggs characteristically show a pitted surface; usually they have a space between the egg cells and the egg wall. Also, they frequently are shorter than *C. aerophila* eggs, which in addition display interconnecting lattice-work or ridges on their surface (Al-Sabi and Kapel, 2013; Conboy, 2009; Di Cesare et al., 2012; Supperer, 1953). Adult females of *C. boehmi* are slightly larger than *C. aerophila* females, and were described to have a lower number of stichocytes (Christenson, 1935; Supperer, 1953). However, due to overlapping findings, these cannot be considered absolute criteria (Lalosevic et al., 2013). More reliable is the localisation of adult stages. *Capillaria boehmi* is found in the nasal and paranasal sinuses of wild canids such as wolves, jackals and foxes in Europe (Al-Sabi et al., 2018; Cabrilo et al., 2018; Sreter et al., 2003), and in foxes, marten and captive wolves in North America (Balinsky et al., 2019; Lopez et al., 2016; Spriggs et al., 2016), reviewed in Table 1. In contrast, *C. aerophila* is a worldwide occurring parasite residing in trachea, bronchi and bronchioles in various animal species (Muchmore, 1998).

Table 1
Occurrence of *Capillaria boehmi* in wild animals.

Animal species	Country	Positive/ tested animals (%)	Detection method	Reference
Foxes				
Vulpes vulpes	Austria	3/4 (75.0)	Dissection	(Supperer, 1953)
Vulpes vulpes	Poland	29/31 (93.5)	Dissection	(Zarnowski and Patyk, 1960)
Vulpes vulpes	Austria	14/190 (7.4)	Dissection	(Hinaidy, 1976)
Vulpes vulpes	Germany	13/100 (13.0)	Dissection	(Schöffel et al., 1991)
Vulpes Vulpes	Hungary	8/100 (8.0)	Dissection and faecal analysis	(Sreter et al., 2003)
Vulpes vulpes	Norway	88/174 (51.6)	Dissection and faecal analysis	(Davidson et al., 2006)
Vulpes vulpes	Denmark	22/31 (71.0)	Faecal analysis	(Al-Sabi and Kapel, 2013)
Vulpes vulpes	Serbia	9/10 (90.0) 45/118 (38.1)	Dissection Faecal analysis	(Lalosevic et al., 2013)
Vulpes vulpes	Italy	55/179 (30.7)	Dissection	(Veronesi et al., 2014a)
Vulpes vulpes	Italy	1/2 (50.0)	Dissection	(Magi et al., 2015)
Vulpes vulpes	Bosnia and Herzegovina	51/79 (64.6)	Dissection	(Hodzic et al., 2016a)
Vulpes vulpes	Austria	39/47 (83.0)	Dissection	(Hodzic et al., 2016b)
Vulpes vulpes	Canada	28/36 (77.8) 26/36 (72.2)	Dissection Faecal analysis	(Lopez et al., 2016)
Vulpes vulpes	Serbia	33/184 (17.9)	Dissection	(Cabrilo et al., 2018)
Wolves				
Canis lupus lupus	Sweden	12/20 (60.0)	Faecal analysis	(Al-Sabi et al., 2018)
Canis lupus lupus, captive	USA	13/38 (34.2)	Faecal analysis	(Balinsky et al., 2019)
Jackals				
Canis aureus	Serbia	3/30 (10.0)	Dissection	(Cabrilo et al., 2018)
Marten				
Marten americana	USA	3/31 (9.7)	Faecal analysis	(Spriggs et al., 2016)

In dogs, single cases of *C. boehmi* are described from different countries (summarised in Table 2a, b). The route(s) of transmission are poorly known: earthworms are suggested as intermediate and/or paratenic hosts, but direct ingestion of infective third stage larvae in eggs or other ways of transmission cannot be excluded (Conboy, 2009; Muchmore, 1998; Veronesi et al., 2013). Infected dogs may suffer from nasal discharge, sneezing, reverse sneezing, epistaxis, gagging, and, importantly, they can be affected by impaired scent. Rarely, dogs also were affected by tachypnoea and convulsive seizures, (Clark et al., 2013; Piperisova et al., 2010; Veronesi et al., 2013, 2014b). Some dogs may not show clinical signs at all (De Liberato et al., 2009; Di Cesare et al., 2012; Veronesi et al., 2014b). Occasionally, *C. boehmi* infections were observed to persist for up to 8 years in dogs, causing tissue damages and inflammation in the nasal passages, accompanied by massive mucous or purulent secretion (Muchmore, 1998; Piperisova et al., 2010). Therefore, *C. boehmi* infections were determined economically relevant for racing dogs (Muchmore, 1998), and represent a substantial threat for the performance of hunting and working dogs (Veronesi et al., 2013). In fact, the impact of infection on the olfactory sense has been rarely assessed, but in a pilot treatment trial five out of twenty infected dogs suffered from anosmia or hyposmia (Veronesi et al., 2014b). Additional clinical and economic relevance is given by repeated veterinary visits and treatment attempts. Due to misdiagnosis and limited knowledge, the occurrence of this parasite is likely underestimated. Moreover, contradicting reports of efficacy of anthelmintics contribute to uncertainty of the most suitable procedures.

In this study we present three hard to treat cases of nasal capillariosis in dogs from Switzerland, report and review the variable success of anthelmintic treatments and investigate *C. boehmi* prevalence in Swiss red foxes, considered as potential wildlife reservoir Tables 2a and 2b.

2. Materials and methods

2.1. Dogs

Faecal samples received from infected dogs were examined by the combined sedimentation-flotation technique using zinc chloride salt solution (specific gravity: 1.3) (Deplazes et al., 2016). In order to confirm the morphological identification, isolated eggs were genetically analysed. For this, the eggs were subjected to 3 repeated steps of freezing in liquid nitrogen and thawing (at 56 °C) and to alkaline lysis as previously described (Stefanic et al., 2004). DNA was isolated using the Qiagen® stool Minikit following the instructions, and the PCR performed using primers as previously described (Guardone et al., 2013), targeting parts of the small subunit rRNA (18S rRNA) gene. Adult specimens obtained from one dog (case 2) were also analysed. The amplicons were purified and submitted for DNA sequencing (Microsynth®). Sequencing results were then compared with entries in the GenBank nucleotide database, using BLAST search (http://www.blast.ncbi.nlm.nih.gov).

2.2. Foxes

Overall 218 foxes from the canton of Zurich, Switzerland, were shot by hunters during the regular hunting season in winter 2016 and 2017, and dissected at the Institute of Parasitology. Sex and approximate age (young animals below one year and older animals) defined according to tooth wear and morphology (Wood, 1958) were determined for each animal. Foxes were examined for intestinal and pulmonary endoparasites for other purposes and decapitated. Fox heads were frozen at -80 °C for at least three days to ensure that potential *Echinococcus multilocularis* eggs contaminating the carcasses were inactivated (Eckert and Deplazes, 2004). The heads were cut sagittal with a band saw and stored at −20 °C until examination. The examination of the nasal cavities was performed as previously described (Veronesi et al., 2014a), with modifications.

Table 2a
Occurrence of *Capillaria boehmi* (syn. *Eucoleus boehmi*) in dogs: clinical presentation, anthelmintic treatments as well as parasitological and clinical outcomes (in chronological order of publication).

Number of dogs, age, breed	Country (area)	Symptoms	Anthelmintic treatments[a]	Outcome[b]	Reference
1-year-old, male Dalmatian	USA (Indiana)	4-month history of nasal discharge; sneezing	Ivermectin 0.2 mg/kg BW p.o.	Clinical recovery within 7 days. Egg shedding neg. after 14, 28, 60, 90 and 120 days	(Evinger et al., 1985)
Two 7.5-years-old greyhounds	USA (Kansas)	not reported	Ivermectin 0.2 mg/kg BW p.o.	Egg shedding pos., although numbers reduced for one week	(Muchmore, 1998)
Adult intact, female Bluetick Hound	USA (Oklahoma)	not reported	Numerous oral anthelmintic treatments with pyrantel, disophenol, oxantel (dosages not specified)	Egg shedding pos. throughout the stay (8 years)	(Muchmore, 1998)
5-year-old, female Bluetick Hound	USA (Florida)	2-month history of intermittent nasal discharge, epistaxis	Fenbendazole 50 mg/kg BW for 10 days	Clinical recovery, egg shedding neg. 1 month later. Egg shedding pos. four months later	(King et al., 1990)
		Nasal discharge	Ivermectin 0.2 mg/kg BW p.o.	Clinical recovery. Egg shedding pos. for next three months	
6 kennel dogs (no further details)	Italy	No specific clinical signs	Treatments with one or more of the following: febantel, pyrantel, praziquantel, oxantel) p.o., dosages according to leaflet instructions (no more details)	Egg shedding pos.	(De Liberato et al., 2009)
8-year-old, neutered male, mixed-breed dog	USA (North Carolina)	17-month history of sneezing, gagging, and unilateral nasal discharge	Fenbendazole (dosage not reported)	Clinical recovery within two weeks; no further information	(Piperisova et al., 2010)
3.5 year-old male castrated American Foxhound dog	USA (Wisconsin)	chronic purulent nasal discharge, nasal worms in situ	Fenbendazole 50 mg/kg BW daily for 14 days	Initial clinical recovery, recurrent after a few weeks (reinfection)	(Baan et al., 2011)
			Fenbendazole 50 mg/kg BW daily for 14 days	Clinical recovery; egg shedding neg. in follow-ups	
4-year-old, spayed Great Dane	USA (Texas)	General convulsive seizures	Fenbendazole 110 mg/kg BW p.o. twice daily for 14 days	Clinical recovery within the following 2 months	(Clark et al., 2013)
		Chronic sneezing, intermittent post-exercise nasal discharge	Monthly ivermectin 0.006 mg/kg and pyrantel pamoate 5 mg/kg BW	Heartworm prevention before diagnosis of *C. boehmi* infection	
			Milbemycin oxime 0.5 mg/kg BW p. o.	Egg detection pos. after 14 days	
2 year-old castrated male Boxer x Chinese Shar Pei	Canada (PEI) (originally from USA (Ohio))		Milbemycin oxime 1 mg/kg BW p.o.	Egg shedding neg. after 7 days, pos. after 14 days	(Conboy et al., 2013)
			Milbemycin oxime 1 mg/kg BW p.o.	Egg shedding neg. after 7 and 14 days, pos. after 21 days	
			Milbemycin oxime 2 mg/kg BW p.o.	Egg shedding neg. after 7, 14, 21 and 28 days and 5 months later. Clinical improvement, no complete recovery	
4-year-old, male crossbred dog	Italy (Tuscany)	chronic, year-old history of muco-purulent nasal discharge, sneezing and reverse sneezing, tachypnea, bilateral nasal discharge and discomfort on nose inspection	10 % imidacloprid/2.5 % moxidectin spot-on according to BW	Clinical recovery within one week. Egg shedding neg. after one and four weeks. Recurrence of clinical signs 10 weeks after treatment (reinfection)	(Veronesi et al., 2013)
			10 % imidacloprid/2.5 % moxidectin spot-on according to BW	Clinical recovery. Egg shedding neg. in the following 4 months.	
Twenty dogs (of which 10 dogs acted as untreated controls)	Italy (Centre)	Sneezing, reverse sneezing, nasal discharge, hypo/anosmia, cough	10 dogs: 10 % imidacloprid/2.5 % moxidectin spot-on according to BW	Clinical recovery in all treated dogs 28 and 42 days after treatment. Egg shedding neg. in 8/10 dogs after 28 days, pos. in 2 dogs.	(Veronesi et al., 2014b)
			2 dogs: 10 % imidacloprid/2.5 % moxidectin spot-on according to BW	Egg shedding neg. after 12 days	
6-year-old mixed breed male dog	Portugal (near Lisbon)	Reverse sneezing of 2 months' duration and bilateral nasal serous discharge	Milbemycin oxime 2.0 mg/kg BW p. o.	Egg shedding pos.	(Alho et al., 2016)
			Fenbendazole 100 mg/kg BW p.o, daily for 14 days	Egg shedding pos.	
			10 % imidacloprid/2.5 % moxidectin spot-on according to BW	Clinical recovery. Egg shedding neg. in 3 follow-up examinations	
12-month-old female Italian pointing dog	Italy (Centre)	3-month history of bilateral mucous and haemorrhagic nasal discharge, sneezing and excessive pawing at the nose.	Fenbendazole 50 mg/kg BW p.o. for 14 days	Improvement in clinical signs. Egg shedding neg. in three monthly follow-ups. At the 4th follow-up: absence of clinical signs, but egg shedding pos.	(Cervone et al., 2017)
			Ivermectin 0.2 mg/kg BW s.c. weekly for 3 weeks	Egg shedding pos. four months later	
			Fenbendazole 50 mg/kg BW p.o. for 14 days	Egg shedding pos. six weeks later	
			Milbemycin oxime 2.0 mg/kg BW p. o. once a month (for six months)	Egg shedding neg. during monthly examinations	
		chronic sneezing			

(*continued on next page*)

Table 2a (*continued*)

Number of dogs, age, breed	Country (area)	Symptoms	Anthelmintic treatments[a]	Outcome[b]	Reference
3-year-old mixed-breed male dog			10 % imidacloprid/2.5 % moxidectin spot-on according to BW Milbemycin oxime 2 mg/kg BW p.o.	Clinical signs present two weeks and two months later. Egg shedding pos. Clinical recovery after one month. Egg shedding neg. during monthly examinations (six months)	

[a] BW: body weight; p.o.: per os; s.c.: subcutaneously.
[b] pos.: positive; neg.: negative.

Briefly, the tissue of the whole nasal cavity, including dorsal, ventral and ethmoidal conchae as well as frontal nasal and paranasal sinuses were removed with a sharp spoon and collected in a petri dish until only the maxilla bone was left (Fig. 1a, b). The maxilla bone was rinsed with water into the petri dish to remove any potential eggs or worm pieces. The removed tissue was inspected under a stereomicroscope: if capillarids were visible they were removed and placed in PBS solution. Adult specimens were counted and their sex was determined before storage in PBS at −20 °C. A few adult specimens (<20) from different foxes were stained with a carmine staining solution according to Meyer and Olsen (1971) and examined in detail. All stained and examined adult specimens were identified as *C. boehmi* according to their length (females: 29−36 mm) and the number of stichocytes (31) (Fig. 2a, b) (Lalosevic et al., 2013; Supperer, 1953).

After investigation for adult specimens the nasal tissue and water was filtered through a tea strainer and rinsed with water. The water was collected in a beaker and left to sediment for at least 30 min. The supernatant was then removed and the sediment centrifuged and microscopically examined for eggs. If eggs were present, the sediment was passed through a 100 µm filter, centrifuged and collected. Capillarid eggs were identified according to their shape, size and the bipolar plugs. *Capillaria boehmi* eggs were differentiated from *C. aerophila* eggs based on the characteristic porous shell wall surface (Fig. 3b, c) (Al-Sabi and Kapel, 2013).

2.3. Statistical analysis

Microsoft Windows Excel 2007 and IBM SPSS Statistics 22 were used for statistical analysis. Binary logistic regression was performed to determine correlation of sex or age and *C. boehmi* infection in foxes. P values of $P \leq 0.05$ were considered statistically significant.

3. Results

3.1. Cases in dogs

Demographics of dogs, clinical signs at first *C. boehmi* diagnosis, anthelmintic treatments and results of coproscopic analyses are summarised in Table 3. Dogs 1–3 were followed-up for overall 54, 8, and 67 months, respectively. Anthelmintic treatments were selected by the treating veterinarians, relying on limited knowledge about the occurrence and suitable treatment protocols against *C. boehmi* infections, and were based on their experience treating other endoparasitic infections. The reported clinical signs originated from observations annotated by the treating veterinarians in the patient history and/or on information furnished by the animal owners.

3.1.1. Case 1

In June 2015 we were contacted by a veterinarian because a 6-year-old female hunting dog (Beagle mix, 19 kg body weight (BW), originating from Romania) was supposedly infected with therapy resistant trichurids, diagnosed by faecal analysis at the beginning of 2014 in a private laboratory; eggs were defined as *Trichuris vulpis*. During that time the dog was repeatedly treated (exact number of treatments and dates not available) with 50 mg/kg BW fenbendazole per os (p.o.) for 10 days and with praziquantel / pyrantel / febantel (Drontal Plus®, Bayer Health Care). However, egg excretion persisted. In a faecal sample analysis of this dog performed at the Institute of Parasitology in Zurich (IPZ) *C. boehmi* eggs were morphologically identified based on their shape and the bipolar plugs, the characteristic porous shell wall surface

Table 2b
Prevalence data and findings of *Capillaria boehmi* based on faecal examinations and/or necropsies in dogs, in chronological order of publication (n.a.: not applied).

Country (area)	Analysed dogs (n)	Positive dogs (n)	Prevalence (%)	Pathological findings, clinical signs	Reference
Poland (Lublin)	6	3	50.0	Not reported	(Zarnowski and Patyk, 1960)
USA (Kansas)	75 from a single kennel	36	48.0	Positive necropsied dogs had adult *C. boehmi* in the nasal passages and sinuses, increased amount of mucus and damages and inflammation in the corresponding tissues	(Muchmore, 1998)
USA (Louisiana)	2	2	n.a.	No clinical signs observed. Abundant mucus and hyperaemia around the worms at necropsy	(Campbell and Little, 1991)
USA (Kansas)	230 dogs from 3 greyhound breeding farms	4	1.7	No clinical signs observed in one necropsied dog, despite presence of adult worms	(Schoning et al., 1993)
Italy (Rome)	619	42	6.9	No clinical signs observed in infected dogs	(De Liberato et al., 2009)
Italy (Liguria)	270	6	2.1	One of the infected dogs showed nasal discharge and exercise induced cough	(Magi et al., 2012)
Italy (Lazio)	1	1	n.a.	No clinical signs	(Di Cesare et al., 2012)
Italy (North)	1	1	n.a.	Chronic sneezing, reverse sneezing, nasal discharge; erythematous mucosa, adults and eggs observed by rhinoscopy	(Manzocchi et al., 2016)
Argentina (Mar del Plata)	306 samples from 108 households	2	0.7	Not reported	(Lavallen et al., 2018)
Italy (centre)	639	5	0.8	Not reported	(Sauda et al., 2018)

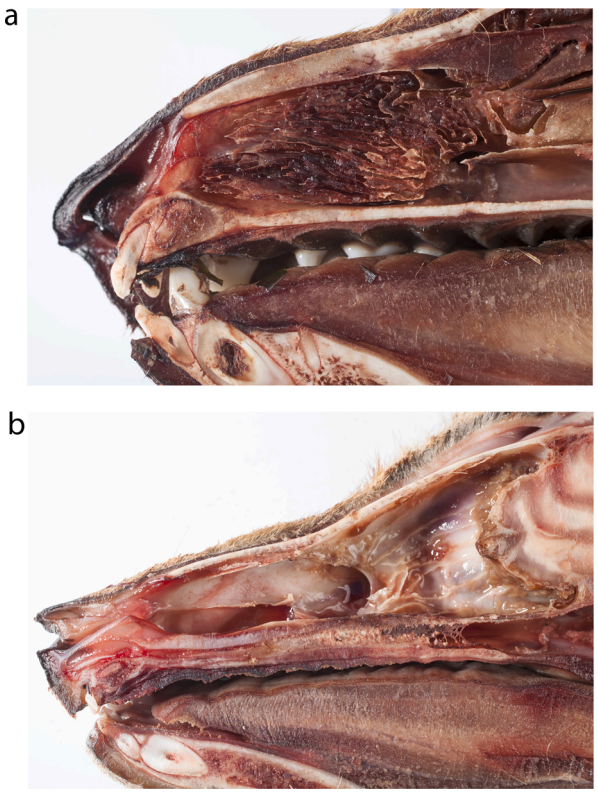

Fig. 1. a, b: Sagittal cut of fox heads before (a) and after (b) scraping nasal conchae and frontal paranasal sinuses for recovery of adult specimens and eggs of *Capillaria boehmi*.

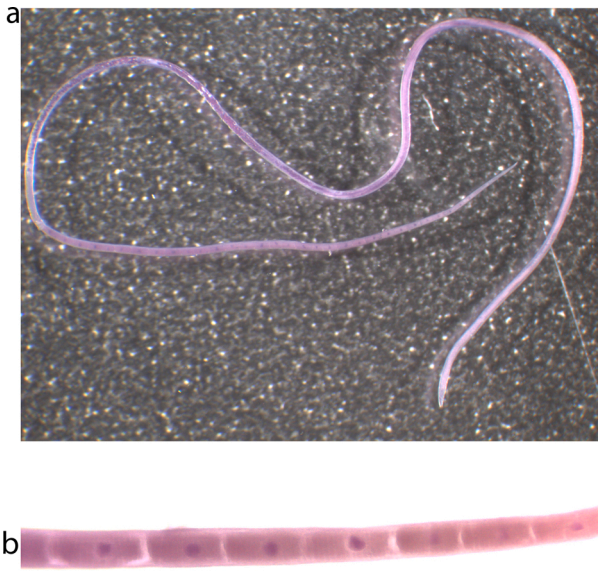

Fig. 2. Adult female carmine stained *Capillaria boehmi* specimen (a) and partial section evidencing stichocytes (b).

and the multicellular embryo leaving empty space between the embryo and the inner egg shell (Fig. 3a). At the same time, no *Trichuris* eggs were observed. Genetic analyses of 18S rRNA confirmed the presence of *C. boehmi* by a 100 % identity of 578 base pairs with gene sequence JX456628 in GenBank.

Deeper enquiries revealed the dog was showing clinical signs such as frequent sneezing and occasional coughing (Table 3). The dog was in good general health and no further clinical signs were observed. After *C. boehmi* diagnosis, the dog was treated topically with a minimal dosage of 2.5 mg/kg moxidectin and 10 mg/kg BW (Advocate® 250, Bayer Health Care), but was still positive four weeks after treatment. The treatment with moxidectin/imidacloprid was repeated, but two weeks after treatment *C. boehmi* eggs were still present in faecal samples. The owner was informed about the relevance of preventive hygiene measures to prevent reinfections and was asked to exclude coprophagia in order to exclude intestinal passages leading to false positive results. Coprophagia was not reported for this dog at no time. A third treatment with moxidectin/imidacloprid was again unsuccessful as 4 weeks after the latter treatment *C. boehmi* eggs were still recovered from faeces. Five months after initial diagnosis of *C. boehmi* infection, the dog was orally treated with 25 mg/kg BW fenbendazole twice daily for 15 days, but was still positive six weeks after this treatment. One month later the dog was treated again with moxidectin/imidacloprid, but was still positive for *C. boehmi* four weeks later. Next, a treatment with orally 100 mg/kg BW fenbendazole daily for 3 days was attempted. Faecal samples collected one week after treatment were negative and the dog had stopped sneezing. In a follow-up faecal examination six weeks later, all three samples were positive again for *C. boehmi* eggs. The dog was sneezing again. Six weeks later the dog was once more treated with moxidectin/imidacloprid, followed by another fenbendazole treatment (dosage unknown) one week after. However, one, four and 12 weeks after this treatment the dog was still positive and sneezing increased. After this last faecal examination, based on a positive experience with a therapy-resistant urinary *Capillaria plica* infection (Basso et al., 2014), the dog was treated with 7.5 mg/kg BW levamisole (Citarin-L® 10 %, registered for hedgehogs) twice on two consecutive days applied intramuscularly. Also this treatment was unsuccessful, because faecal samples were still positive for *C. boehmi* eggs two and four weeks after levamisole treatment. However, the owner claimed that the dog's scent had increased since the levamisole treatment.

3.1.2. Case 2

In October 2015 a 9 year-old female Poitevin (BW: 31 kg) with history of acute diarrhoea and intermittent phases of sneezing was diagnosed positive for *C. boehmi* egg excretion, also confirmed by genetic analysis performed at the IPZ. Before the coproscopic examination the dog had been treated with selamectin (Stronghold® 240 spot-on, Zoetis, exact number of treatments and dates not available) because of suspected infection with nasal mites. After diagnosis, the dog was topically treated with moxidectin/imidacloprid (Advocate® 400 spot-on, Bayer Health Care) at the recommended dosage. One week after treatment the diarrhoea had stopped but the dog was still shedding *C. boehmi* eggs. The owner was also informed about potential environmental contamination by eggs. However, possible reinfections from the surroundings could not be excluded, while coprophagia was excluded also for this dog. A second moxidectin/imidacloprid treatment was given, but also two days after this second treatment egg shedding was proven. The dog was then

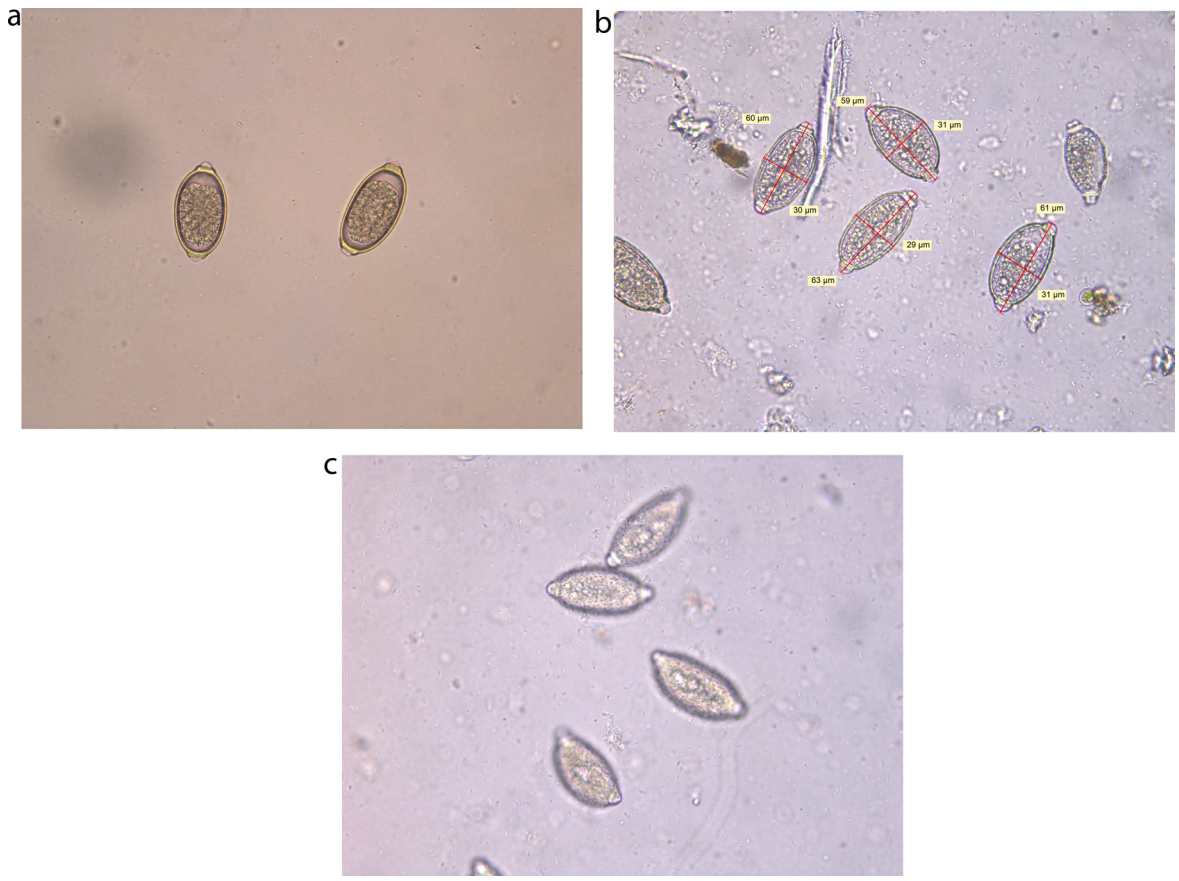

Fig. 3. *Capillaria boehmi* eggs isolated from fresh faeces of an infected dog (case 3) (a) and from nasal tissue of an infected fox (b). All eggs display an asymmetric barrel shape and two polar plugs. The eggs from the dog also display the characteristic multicellular embryo leaving an empty space between the embryo and the inner egg shell. This is not visible in the fox eggs, most probably a consequence of freezing the heads before analysis. In both fox and dog eggs the pitted surface characteristic for *C. boehmi* eggs is visible (c).

treated with 100 mg/kg BW fenbendazole daily for 3 days, but after 2 weeks the dog was still shedding *C. boehmi* eggs. Fenbendazole treatment was repeated with the same protocol. At this stage also a nasal lavage with physiological saline solution was performed under anaesthesia. Moving nematodes were recovered, which were morphologically identified as adult *C. boehmi* specimens; a contemporaneously analysed faecal sample was still positive for *C. boehmi* eggs. Six and eight months later, instead, faecal examination was negative for *C. boehmi* eggs; no information about clinical signs were obtained.

3.1.3. Case 3

In spring 2016 a 3-years-old male Bracco Italiano (BW: 21 kg) was diagnosed with a therapy resistant *Trichuris vulpis* infection in a private laboratory from February 2014 to March 2016 in overall 10 faecal examinations. The dog turned out to be infected with *C. boehmi,* diagnosed at the IPZ. During this period the dog had been treated overall ten times with praziquantel / pyrantel / febantel (Drontal Plus®, Bayer Health Care), milbemycin oxime (Milbemax®, Elanco Animal Health) or fenbendazole (Panacur®, MSD Animal Health) by the attending veterinarian, in dosages according to leaflet instructions. The dog did not show any clinical signs but was shedding *C. boehmi* eggs. Three treatment attempts were performed with moxidectin/imidacloprid (Advocate® 250, according to BW), but parasitological controls performed in the following weeks were regularly positive (for details, see Table 3). With fenbendazole given at 100 mg/kg BW split in two daily doses of 50 mg/kg BW for 6 days, repeated after one week of interruption, egg shedding discontinued at the end of treatment and after one month. However, in the following two months the dog was excreting *C. boehmi* eggs again, despite monthly treatments with milbemycin-oxime/praziquantel. Therefore, the above mentioned fenbendazole treatment was repeated obtaining again successful egg shedding interruption at the end of treatment and 4 weeks later. However, approximately 6 months later and in the following months, the dog was positive again, despite monthly treatments with moxidectin/imidacloprid. A third treatment with fenbendazole adopting the same protocol stopped the egg excretion as determined at the end of treatment and two months later.

3.2. Examination of wild Swiss foxes (Vulpes vulpes)

In 2016 and 2017 85 and 133 foxes were examined, respectively. Of the 218 hunted foxes 107 were males and 111 females; 126 were adults (> one year of age) and 92 were youngsters (< one year of age), respectively. In 2016 and in 2017 83.5 % (71/85) and 89.5 % (119/133) of foxes were positive for *C. boehmi* adults (Fig. 4) and/or eggs, respectively. The overall prevalence was 87.2 % (190/218). Worm burden ranged from 1 to 72 adult specimens (arithmetic mean: 10.2; geometric mean: 5.7).

The presence of *C. boehmi* in foxes did not correlate with age ($P = 0.209$). Overall, 107 of 126 adults (84.9 %, 95 % Confidence Interval, CI: 77.5–90.7 %) and 83 of 92 youngsters (90.2 %, CI: 82.2–95.4 %) were infected. Infection correlated significantly with sex: male foxes (102 of 107, 95.3 %, CI: 89.4–98.5 %) were significantly ($P = 0.001$) more often

Table 3
Clinical signs before treatments, anthelmintic treatments and parasitological outcomes in three Swiss dogs diagnosed with *Capillaria boehmi*.

Clinical signs	Anthelmintic treatments[a]	Parasitological outcome[b]
Case 1 : 6-year-old female Beagle mix, 19 kg		
Sneezing, coughing, impaired scent	Repeated treatments with fenbendazole (50 mg/kg BW, p.o. for 10 days) and praziquantel/ pyrantel/febantel before diagnosis	Egg shedding pos.
	Moxidectin/imidacloprid spot-on (Advocate® 250) according to BW	Egg shedding pos. 4 weeks later
	Moxidectin/imidacloprid spot-on according to BW	Egg shedding pos. 2 weeks later
	Moxidectin/imidacloprid spot-on according to BW	Egg shedding pos. 4 weeks later
	Fenbendazole 25 mg/kg BW twice daily for 15 days	Egg shedding pos. 6 weeks later
	Moxidectin/imidacloprid spot-on according to BW	Egg shedding pos. 4 weeks later
	Fenbendazole 100 mg/kg BW for 3 days	Egg shedding neg. 1 week later Egg shedding pos. 6 weeks later
	Moxidectin/imidacloprid spot-on according to BW, followed one week later by oral fenbendazole treatment (dosage unknown)	Egg shedding pos. 1, 4 and 12 weeks later
	Levamisole, 7.5 mg/kg BW i.m. on two consecutive days	Egg shedding pos. 2 and 4 weeks later
Case 2 : 9-year old female Poitevin, 31 kg		
Intermittent sneezing	Repeated treatments with selamectin (Stronghold® 240) spot-on according to BW before diagnosis	Egg shedding pos.
	Moxidectin/imidacloprid spot-on (Advocate® 400) according to BW	Egg shedding pos. 1 week later
	Moxidectin/imidacloprid spot-on according to BW two weeks after the first treatment	Egg shedding pos. 2 days later
	Fenbendazole 100 mg/kg BW for 3 days	Egg shedding pos. 2 weeks later
	Fenbendazole 100 mg/kg BW for 3 days	
	Nasal rinsing under anesthesia one day after the last fenbendazole treatment	Living adult specimens were recovered, egg shedding pos. Egg shedding negative 6 and 8 months later
Case 3: 3-year-old male Bracco italiano, 21 kg		
No related clinical signs	Repeated (overall 10) treatments with praziquantel / pyrantel / febantel, milbemycin oxime or fenbendazole in the two years before diagnosis	Egg shedding pos. (10 faecal examinations)
	Moxidectin/imidacloprid spot-on (Advocate® 250) according to BW	Egg shedding pos. 2 weeks later
	Moxidectin/imidacloprid spot-on according to BW	Egg shedding pos. 1 week later
	Moxidectin/imidacloprid spot-on according to BW	Egg shedding pos. 1, 14 and 18 weeks later
	Fenbendazole 50 mg/kg BW twice daily for 6 days, repeated after one week of interruption	Egg shedding neg. at the end of treatment and 4 weeks later Egg shedding pos. 10.5 weeks later Egg shedding pos. 8 months later
	0.5 mg/kg milbemycin-oxime/ praziquantel 5 mg/kg BW p.o., monthly administration	Egg shedding pos. approx. 5 months after last treatment
	Fenbendazole 50 mg/kg BW twice daily for 6 days, repeated after one week of interruption	Egg shedding neg. at the end of treatment and 4 weeks later Egg shedding pos. approx. 6 months later
	Moxidectin/imidacloprid spot-on according to BW monthly for 3 months	Egg shedding pos. at the end of the last treatment
	Fenbendazole 50 mg/kg BW twice daily for 6 days, repeated after one week of interruption	Egg shedding neg. at the end of treatment and two months later

[a] BW: body weight; p.o.: per os; s.c.: subcutaneously; i.m.: intramuscularly.
[b] pos.: positive; neg.: negative.

Fig. 4. One adult *Capillaria boehmi* specimen coiled up in a nasal concha.

infected with *C. boehmi* than female foxes (88 of 111, 79.3 %, CI: 70.5–86.4 %).

4. Discussion

In the here presented study, based on the description of three exemplary cases and a review of the literature, we evidence the challenges posed by little knowledge leading to misdiagnosis of *C. boehmi* infections and the difficulties in the anthelmintic elimination of nasal *C. boehmi* infections. In addition, we illustrate the first description of *C. boehmi* infections in foxes from Switzerland. For these, we observed a high prevalence (87.2 %) in the canton and city of Zurich. In this area, also fox population density is high, and simultaneously the human and dog population is among the highest in the country. There are overlapping areas of contact between dogs and foxes especially in the urban periphery and in recreational areas, where dogs are mostly walked (Deplazes et al., 2004). Although different dissection techniques and the number of analysed animals may influence the results, similar high prevalences (see Table 1 for details) have been recently observed in

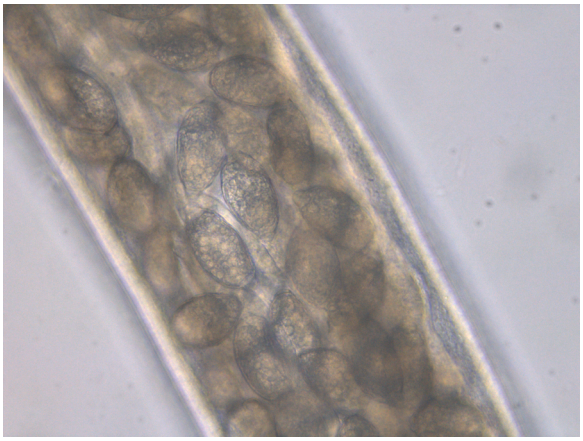

Fig. 5. Section of a female adult specimen of *Capillaria boehmi*, illustrating a high number of already shaped eggs.

foxes from Austria (83.0 %) (Hodzic et al., 2016), Denmark (71.0 %%) (Al-Sabi and Kapel, 2013), Serbia (90.0 %) (Lalosevic et al., 2013), in the sixties in Poland (93.5 %) (Zarnowski and Patyk, 1960) and also in Canada (77.8 %) (Lopez et al., 2016). In other wild animal species, the prevalence was lower (Swedish wolves: 60 % (Al-Sabi et al., 2018); U.S. wolves: 34.2 % (Balinsky et al., 2019); jackals in Serbia: 10 % (Cabrilo et al., 2018), and martens in the U.S.: 9.7 % (Spriggs et al., 2016)), supporting the important role of foxes as wild life reservoir.

Interestingly, we observed a higher prevalence in male foxes compared to female animals, while prevalence in older animals did not differ from the one in youngsters. This may indicate that foxes are exposed to infectious stages at all ages without development of protective immunity. Higher parasite prevalence in males (humans and different animal species) has been repeatedly observed and was attributed to different reasons, such as steroid hormones influencing the immune function, but also genetic and behavioural differences (Klein, 2004).

The life cycle of *C. boehmi* is still not fully explored; based on analogies with *C. aerophila*, it is assumed that infections are directly transmitted by the faeco-oral route by ingestion of larvated eggs and, potentially, through paratenic hosts (Campbell and Little, 1991; Muchmore, 1998). Studying the survival of *C. boehmi* eggs under different environmental conditions revealed that, depending on temperature and relative humidity, eggs may fully develop within 7–30 days (Perrucci et al., 2014). Together with the observed very high fecundity of female worms (Fig. 5), these findings support the hypothesis that, once infected, foxes and dogs as well may be continuously re-infected by eggs from their immediate surroundings. This also could partially explain the repeated positive faecal examinations summarised in this study despite prevention of coprophagia.

Importantly, as observed in two out of the three presented cases in dogs, the capillarid eggs detected in the faeces were repeatedly misdiagnosed as *Trichuris* eggs by different laboratories. Both *Trichuris* and *Capillaria* sp. eggs have pole plugs, allowing easy differentiation from other helminth eggs. However, they consistently differ concerning their form (more 'lemon'- or more 'barrel'-like, respectively) and their plugs. *Trichuris* poles are symmetrical and with rings at the bases, in contrast *C. aerophila* and *C. boehmi* eggs often present with asymmetric placed plugs and no rings at their basis. Admittedly, the differentiation between these latter two parasites is more challenging, especially when knowledge about the occurrence of *C. boehmi* is limited, even in areas where *C. boehmi* infections have been identified in foxes.

In this study we present the first dog cases together with the confirmation that the parasite is present in the wild life reservoir. We assume that the number of cases in dogs is underestimated: after these first three cases, we were involved in the identification of at least further three cases in dogs (M. Schnyder, personal communication). Due to the relevant clinical consequences such as chronic sneezing and nasal discharge with impact on the sense of smell and dog performance, it is fundamental to include *C. boehmi* infection in the differential diagnoses of corresponding clinical signs. Accordingly, it is relevant to be aware of the morphological differences of these helminth eggs. Actually, differentiation between *C. boehmi* and *C. aerophila* is possible even without egg measurements, which may overlap (Al-Sabi and Kapel, 2013; Di Cesare et al., 2012). The most characteristic differences are the space present between the embryo and the internal egg wall in *C. boehmi* eggs, together with the pits visible when focusing on the egg wall (Fig. 3c). Interestingly, the space between embryo and egg wall mostly disappears when observing eggs obtained from fox samples (Al-Sabi and Kapel, 2013), as also observed in our study (Fig. 3a, b). This is most probably due to an artefact, i.e. preserving fox faeces frozen at – 80 °C for biosafety reasons (Eckert and Deplazes, 2004).

Once correctly diagnosed, the next challenges are represented by the anthelmintic treatment(s) combined with appropriate management, especially in multi-dog households. Successful treatments (clinical recovery and interruption of egg shedding) with moxidectin spot-on were described (summarised in Tab. 2a) in dogs from Italy (Veronesi et al., 2013) and Portugal (Alho et al., 2016), but was unfortunately not successful in our three cases, despite repeated treatments. Further effective outcomes (concerning clinical recovery and egg shedding, see Tab. 2a) are described with fenbendazole at oral dosages of 50 mg/kg BW for 14 days (Baan et al., 2011) or 110 mg/kg BW for 14 days (Clark et al., 2013), but was unsuccessful in other dogs (Alho et al., 2016; Cervone et al., 2017; King et al., 1990). In all dogs of the presented study fenbendazole treatments were attempted, in dosages from 50 to 100 mg/kg BW for 3–15 days. Hundred mg/kg BW for three days, and the same dosage for 6 days with repetition after one week of interruption were successful in case 2 and 3, respectively.

A further compound that is registered for dogs and has been repeatedly employed is milbemycin oxime: with single oral dosages of 0.5 and 1 mg/kg BW egg shedding persisted, while 2 mg/kg BW were proven successful for stopping egg excretion in controls performed 1, 2, 3, 4 weeks and 5 months later in a dog, while clinical recovery was incomplete (Conboy et al., 2013). The same dosage stopped egg excretion and induced clinical recovery in two dogs from Italy (Cervone et al., 2017), but not in another dog from Portugal (Alho et al., 2016).

Among not registered compounds for dogs, ivermectin was described effective (clinical recovery and stopping of egg excretion) once (Evinger et al., 1985), but was unsuccessful in other dogs (Cervone et al., 2017; King et al., 1990; Muchmore, 1998). As advanced, successful treatment of *C. plica* infection in a dog with chronic pollakiuria (Basso et al., 2014) has prompted us to use injectable levamisole (applied intramuscularly, being this the only available formulation in Switzerland, registered for hedgehogs) in case one: a clinical recovery was observed, while egg shedding was still positive.

In summary, different anthelmintic compounds showed variable success regarding their effect on clinical outcome and on stopping egg excretion. This may be related to the possibilities of reinfections in a contaminated environment (Baan et al., 2011; Muchmore, 1998; Veronesi et al., 2013). An alternative explanation is that biological availability of anthelmintic compounds may be low in nasal and paranasal cavities, independently of the way of administration. However, it also needs to be considered that absent egg excretion after anthelmintic treatment cannot be directly correlated with a successful therapy. In fact, little is known about dynamics in egg excretion. In absence of deeper knowledge about the life cycle of *C. boehmi* and of specific experimental data, the prepatent period is unknown. Similarly, the persistence of egg excretion after successful anthelmintic treatment is unacquainted. As an example of a nematode that lives in the respiratory system and also produces stages that are excreted in faeces, *Angiostrongylus vasorum* infected dogs may excrete first stage larvae for up to three weeks despite successful elimination of adult stages (Schnyder

et al., 2015). This may also occur in *C. boehmi* infected dogs. Furthermore, anthelmintic treatments may not kill the parasites but only provisionally affect egg excretion by influencing the fertility of adult stages or by killing larval stages, as observed i.e. in *Dirofilaria immitis* infected dogs that are treated with macrocyclic lactones (Bowman and Mannella, 2011). Based on little information about the life cycle and pattern of egg excretion of *C. boehmi* before and after anthelmintic treatments, this is highly speculative. Altogether, the discrimination between therapy resistance, reinfections and provisional suspension of egg excretion is not straightforward.

In conclusion, *C. boehmi* infections can be misdiagnosed and/or underdiagnosed in dogs. Once diagnosed, appropriate anthelmintic treatments, preventing coprophagia and egg contamination of the surroundings and performing coproscopic controls after treatments are fundamental aspects. Potentially, nasal washing of infected dogs may represent an auxiliary alternative. However, the successful elimination of *C. boehmi* infections in dogs remains challenging.

Credit author statement

NGG: data and picture acquisition, laboratory analyses, statistics, writing parts of the manuscript; editing.

SM: laboratory analyses, pictures.

FG: genetic analyses

MS: conceptualisation, methodology, data acquisition, writing original draft, review and editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.vetpar.2020.109103.

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