Journal of Helminthology

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Efficacy of levamisole, ivermectin and moxidectin against *Capillaria* spp. in European hedgehogs (*Erinaceus europaeus*)*

Y. Van de Weyer[1,3], M.C. Santos[1], N. Williams[1], A.M. Gonçalves[1], W. Hawley[1], K. McVay and S. Bexton[2]

[1]RSPCA Stapeley Grange Wildlife Centre, CW5 7JW Nantwich, UK; [2]RSPCA East Winch Wildlife Centre, PE32 1LG King's Lynn, UK and [3]Institute of Infection, Veterinary and Ecological Sciences, Department of Veterinary Anatomy, Physiology and Pathology, University of Liverpool, Leahurst Campus, Neston, United Kingdom

Research Paper

Cite this article: Van de Weyer Y, Santos MC, Williams N, Gonçalves AM, Hawley W, McVay K and Bexton S (2023). Efficacy of levamisole, ivermectin and moxidectin against *Capillaria* spp. in European hedgehogs (*Erinaceus europaeus*). *Journal of Helminthology*, **97**, e99, 1–9
https://doi.org/10.1017/S0022149X23000718

Received: 17 July 2023
Revised: 08 October 2023
Accepted: 09 October 2023

Keywords:
European hedgehog; *Capillaria*; *Crenosoma*; levamisole; ivermectin

Corresponding author:
Y. Van de Weyer;
Email: yvandeweyer20@rvc.ac.uk

*The article has since been updated on the 21/02/2024.

Abstract

This randomised study aimed to assess and compare the efficacy of treatment protocols containing levamisole, ivermectin, or moxidectin against *Capillaria spp.* in naturally infected European hedgehogs (*Erinaceus europaeus*) presented to a British wildlife rehabilitation centre. Faecal analysis, consisting of wet mount and flotation, was performed for 229 hedgehogs weighing ≥200g. Animals testing positive for *Capillaria spp.* (81%), excluding pregnant females, were randomly allocated a treatment protocol. Initially, hedgehogs (n = 50) received one of six 'pilot' protocols, whereas the remaining animals (n = 97) received one of three 'main' protocols. Faecal analysis was repeated on day 8 and day 12 after treatment initiation. Efficacy of each treatment was assessed based on *Capillaria* reduction rate (CRR), weight gain, presence of respiratory clinical signs, and outcome. Pilot protocols containing only moxidectin had a significantly lower CRR (≥28.1%) compared to those with levamisole or ivermectin (≥86.6%), whereas the main protocols containing levamisole had a significantly higher CRR (≥93.0%) compared to those containing only ivermectin (≥69.3%). Clinical parameters did not differ significantly between treatments, but animals with respiratory clinical signs at the end of the trial were significantly more likely to have lower CRR and test positive for *Crenosoma striatum*. *C. striatum* often appeared refractory to treatment, and managing these infections requires additional anthelmintic therapy. Based on the formulations and dosages trialled, moxidectin is not recommended for treating capillariosis in European hedgehogs, whereas levamisole given orally for two consecutive days at 25–35 mg/kg is suggested as the treatment of choice.

Introduction

The European hedgehog (*Erinaceus europaeus*) is a frequently presented species for wildlife rehabilitation in Europe (Gaglio *et al.* 2010; Bexton 2016). Despite currently being listed as 'Least Concern' by the IUCN (Amori 2016), populations have been facing significant declines in Great Britain (GB), thought to be caused predominantly by habitat fragmentation, predation, and road traffic accidents (Hof 2009; *Pettett et al.* 2018). Therefore, hedgehogs have been classified as 'vulnerable to extinction' in GB since 2020 (Matthews and Harrower 2020; Wembridge *et al.* 2022). Endoparasites are relatively common in all age groups of free-living European hedgehogs (Rasmussen *et al.* 2021), with high prevalences of *Capillaria* spp. and *Crenosoma striatum* reported (Majeed *et al.* 1989; Gaglio *et al.* 2010; Mariacher *et al.* 2021). Three *Capillaria* species have been described in European hedgehogs: *C. erinacei*, *C. ovoreticulata*, and *C. aerophila (Syn. Eucoleus aerophilus)*. Coprological examination is a useful indicator of endoparasite burden in hedgehogs, although *Capillaria* eggs of different species are often morphologically similar and can be difficult to differentiate (Gaglio *et al.* 2010). Moreover, false negative results are common when attempting to detect *Crenosoma* by wet mount examination.

Intestinal capillariosis is caused by *C. erinacei* and *C. ovoreticulata*, whereas the predilection sites for *C. aerophila* are the tracheal and bronchial lumina, as well as the epithelium (Bexton 2016; Lehmann *et al.* 2023). Together with *Crenosoma striatum*, a lungworm found in the bronchi and bronchioles, *C. aerophila* is associated with respiratory disease (Majeed *et al.* 1989; Bexton and Couper 2019; Lehmann *et al.* 2023). Lungworms are considered the most common cause of respiratory disease in European hedgehogs, and clinical signs of infection can include anorexia, weight loss, lethargy, nasal discharge, coughing, sneezing, wheezing, and dyspnoea (Bexton 2016; Lehmann *et al.* 2023). Furthermore, it is generally presumed that lungworm infection can predispose to secondary bacterial pneumonia (Bexton 2016). Intestinal capillariosis has been associated with lethargy, anorexia, weight loss, and green mucoid diarrhoea (Bexton 2016). When left unattended, these nematodes can contribute to morbidity and mortality,

thereby compromising the rehabilitation process. This is especially pertinent for so called 'autumn juveniles', which often present in poor body condition with mixed nematode infections and an immune system that may largely be naive to these endoparasites (Bexton 2016; Bexton and Couper 2019).

Anthelmintics are widely used in hedgehog rehabilitation centres to control endoparasites, but there are concerns that inappropriate therapy could result in drug resistance (Sangster *et al.* 2018). Therefore, it is important to ensure anthelmintics are effective and only used when parasites are contributing to morbidity or debility (Rasmussen *et al.* 2021). Furthermore, *C. aerophila* has zoonotic potential which would justify treatment (Lalosevic *et al.* 2008).

Macrocyclic lactones (ML) such as ivermectin and moxidectin are popular antiparasitic agents in veterinary medicine (Prichard *et al.* 2012; Laing *et al.* 2017). Both compounds work by binding with glutamate and GABA chloride channels, resulting in paralysis of the parasite. Whereas ivermectin is classified as a first-generation ML, moxidectin is considered a second-generation drug, resulting in a different spectrum (Prichard *et al.* 2012). Except for certain dog breeds with MDR1 mutations, ML are considered relatively safe for use in most mammalian species due to their inability to penetrate the central nervous system (Prichard *et al.* 2012; Laing *et al.* 2017). Macrocyclic lactones are highly lipophilic compounds with a long duration of activity and excretion, because of redistribution from adipose tissues (Laing *et al.* 2017). Subcutaneous injection of ivermectin is well tolerated in the hedgehog, and good activity against nematodes has been reported when used at a dose of 3 mg/kg (Barutzki *et al.* 1987).

Levamisole is an imidazothiazole that induces spastic paralysis in endoparasites by activating nicotine acetylcholine receptors. This broad spectrum anthelmintic is predominantly used to treat or prevent gastrointestinal nematode and lungworm infections in production animals (Galtier *et al.* 1983). Levamisole generally has a short half-life, low efficacy against ova, and a relatively narrow safety margin, especially when administered parenterally (Galtier *et al.* 1983; Garcia *et al.* 1994). Levamisole given subcutaneously at a dose of 27 mg/kg has been described as the treatment of choice for parasitic bronchopneumonia in hedgehogs, although refractory lungworm burdens have been reported (Bexton 2016; Bexton and Couper 2019).

The main aim of this study was to compare the efficacy of different anthelmintic protocols for the treatment of *Capillaria* spp., whilst also establishing the prevalence of capillariosis in European hedgehogs admitted to a British wildlife rehabilitation centre.

Materials and methods

Study population

The study gathered data from European hedgehogs admitted to the RSPCA Stapeley Grange wildlife centre between 31 January 2022 and 1 February 2023. The initial study population included all hedgehogs weighing at least 200 grams on admission, excluding animals that required immediate euthanasia and animals that already received anthelmintics from a veterinary practice prior to arrival at the wildlife centre. Animals below 200g were excluded because faecal parasitology often is unrewarding in this group, questioning the justification for anthelmintic therapy at relatively high doses. Pregnant females had a faecal sample taken but were excluded from the trial based on the potentially teratogenic effect of levamisole and the fact that they are ideally released as soon as possible, allowing them to give birth in nature rather than in captivity. Animals suspected of trauma, usually caused by predator attacks or road traffic incidents, were radiographed on admission. If pneumothorax, diaphragmatic rupture, or rib fractures were diagnosed, affected animals were euthanised, thereby excluding them from the study population.

Sampling and faecal analysis

From each hedgehog weighing ≥200 g, excluding animals that received prior anthelmintics and those that required immediate euthanasia, a faecal sample was taken within 48 hours of admission and processed within 24 hours of collection. Faecal analysis included wet mount preparation and flotation. Flotation was used as the golden standard for the detection of *Capillaria* spp. (Figure 1)

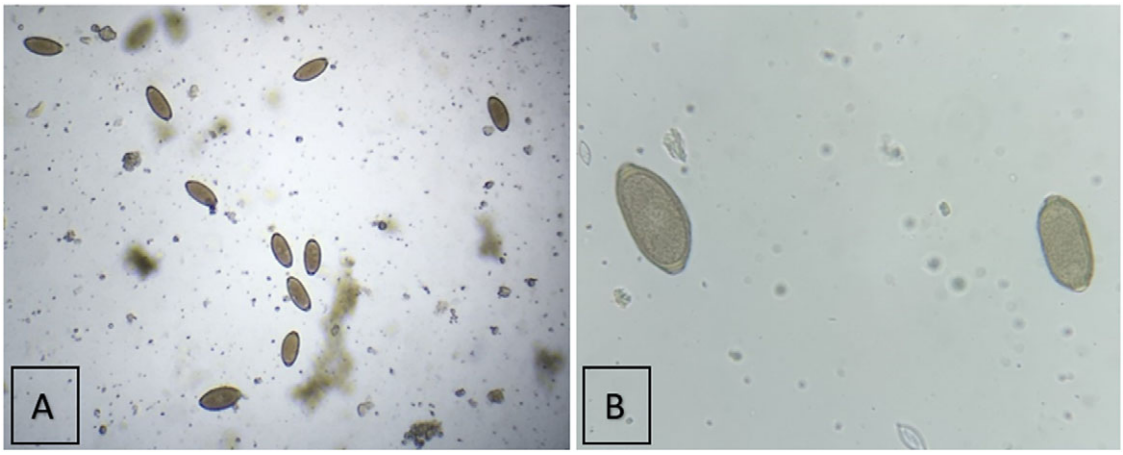

Figure 1. A. Capillaria species in the European hedgehog observed via microscopy (100x) after faecal flotation. B. *Capillaria* in the European hedgehog observed via microscopy (400x) after faecal flotation.

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and this was applied according to the following protocol: one gram of faeces (± 10%) was dissolved in 8 ml of NaCl solution (SG 1.20) until a homogenous mixture was obtained. This solution was sieved and transferred into a tube, after which a square 18 mm cover slip was applied over the meniscus. After 10 to 20 minutes, the cover slip was transferred onto a microscope slide, while ensuring that a homogenous layer of flotation solution covered the entire surface between the cover slip and adjacent slide. In the absence of counting chambers, all *Capillaria* ova underneath the cover slip were manually recorded at a magnification of 100–400x, with a maximum count of 250 due to staff time limitations. Faecal samples with a higher number of ova were recorded as 250+. Wet mount preparation was used to assess the presence of live *C. striatum* larvae. This was accomplished by mixing a small amount of faeces and three drops of water with a spatula. This solution was then mounted onto a glass slide with a clean dropper for immediate microscopic examination of the entire wet surface area at 100x magnification.

Treatment protocols

Animals that tested positive for *Capillaria* spp. were randomly assigned a treatment protocol in two studies (pilot and main). During the first half of the study period (January–June 2022), six different treatment protocols (A–F) were trialled in a pilot study. For the second half of the study (July–January 2023), three 'main' protocols (1–3) were selected based on preliminary results from the pilot study. For each protocol, anthelmintic therapy was started on 'day 0' and faecal analysis was repeated on 'day 8' and 'day 12' (Table 1). A twenty-four-hour deviation from these days was accepted to mitigate the uncertainty regarding faecal sample collection. Randomisation was achieved by drawing a letter (pilot) or number (main) from an enclosed bag, each of which corresponded with a treatment protocol.

All anthelmintic drugs used in this study are commercially available in GB. There are no licensed products for hedgehogs, and therefore, all were used off-label under the cascade. Accounting for bioavailability, a dose of 35 mg/kg was chosen for oral levamisole (Levacide© 7.5% oral solution, Norbrook) treatments, based on anecdotal recommendations for injectable levamisole in hedgehogs and pharmacokinetic data in rabbits (Garcia *et al.* 1994; Bexton and Couper 2019). Considering the relatively short half-life of levamisole and the possibility of administration failure, especially if given by untrained volunteers commonly relied upon in wildlife rehabilitation, it was decided to provide a minimum of two administrations by feeding tube (Figure 2). All treatments in this study were given by experienced staff members.

Figure 2. Administration of oral levamisole by feeding tube. The hedgehog is restrained below the chin and at the back of the head, whilst a rigid rubber tube is gently inserted between the maxillary incisors. The tube should reach all the way into the distal oesophagus before pushing the plunger. Note the use of personal protective equipment. Credit: Nicola Williams.

Table 1. Overview of the different treatment protocols used for the treatment of endoparasites in European hedgehogs admitted for rehabilitation between January 2022 and February 2023. Day 0 corresponds to the day on which treatment was instigated. 'FA' stands for faecal analysis, 'po' for *per os*, 'sc' for subcutaneous injection, and 's-o' for spot-on anthelmintic formulations and administration.

Pilot study						
Protocol	First 48 hrs	Day 0	Day 2	Day 4	Day 8	Day 12
A	FA	Levamisole po	Levamisole po		FA	FA
B	FA	Levamisole po	Levamisole po	Levamisole po	FA	FA
C	FA	Levamisole po	Levamisole po	Moxidectin s-o	FA	FA
D	FA	Moxidectin s-o			FA	FA
E	FA	Moxidectin sc			FA	FA
F	FA	Ivermectin sc			FA	FA

Main study					
Protocol	First 48 hrs	Day 0	Day 1	Day 8	Day 12
1	FA	Levamisole po	Levamisole po	FA	FA
2	FA	Levamisole po	Ivermectin sc	FA	FA
3	FA	Ivermectin sc		FA	FA

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Moxidectin-imidacloprid spot-on is a popular antiparasitic product in veterinary practice which is licensed for the treatment of *C. aerophila* in dogs and cats. A dose of 0.2 ml/kg (Prinovox©Cat 1% moxidectin and 10% imidacloprid Spot-on, Virbac) was used for hedgehogs in this study, which equates to 2 mg/kg moxidectin. Doses as high as 16 mg/kg of topical moxidectin have been trialled for the treatment of mites in African pygmy hedgehogs (*Atelerix albiventris*), with no adverse effects reported (Kim *et al.* 2012). Given the relatively high cost of these spot-ons compared to alternative formulations, however, doses above 2 mg/kg were considered financially unviable for use in wildlife rehabilitation centres.

Although good results were reported when using ivermectin at a dose of 3 mg/kg (Barutzki *et al.* 1987), it was decided to use a slightly increased dose of 5 mg/kg (Panomec© 1%, Boehringer Ingelheim Animal Health UK Ltd) based on unsatisfactory results of lower doses (0.4–4 mg/kg) when treating hedgehogs at the wildlife centre during previous years. The same 5 mg/kg dose was used for injectable moxidectin (Cydectin© 2%, Zoetis). Considering the relatively long half-life and high doses of the ML used, one single subcutaneous injection or topical application was deemed sufficient for the study. The goal was to effectively reduce the parasite burden to acceptable levels allowing hedgehogs to recover and gain weight, while also reducing both stress on the animals as well as staff resources by minimizing the number of administrations required.

Treatment efficacy

Efficacy of treatment was predominantly assessed through *Capillaria* reduction rate (CRR). This was calculated by the following formula: $CRR = 1 - \frac{Mean\ day\ 8\ and\ day\ 12\ egg\ counts}{day\ 0\ egg\ count}$. Additionally, three other parameters consisting of weight gain (WG), presence of respiratory clinical signs, and outcome were assessed to establish whether significant differences between treatment protocols could be observed.

For each animal in the study, the number of *Capillaria* ova was recorded on days 0, 8, and 12, after which a comparison was made before (day 0) and after (mean of days 8 and 12) treatment to obtain the CRR. Weight gain during the study was calculated by subtracting the weight at the start of treatment (day 0) from the weight at the end (day 12), and then dividing the result by the day 0 weight. The presence of respiratory clinical signs (RESPD0/12), defined as coughing, sneezing, audible breathing, or moderate to severe nasal discharge, was recorded on days 0 and 12 in a binomial format (0/1). This was assessed retrospectively based on notes from staff responsible for husbandry (blinded) and veterinarians, which were written within a 24-hour window of days 0 and 12. Outcome was classified as 'release', 'euthanasia', or 'death', with 'release' considered as the only positive outcome. Finally, the presence of *Crenosoma striatum* was also recorded on days 0, 8, and 12 in a binomial format (0/1).

Statistics

Statistical analyses were conducted in R (R-4.1.0, RStudio, Boston, MA 02210, USA) using a significance level of $p < 0.05$. Pilot data trialling six treatments (A, B, C, D, E, F) were analysed separately from the final study (treatments 1, 2, 3). Continuous dependent variables, CRR and WG, were assessed for normality by means of Shapiro wilk test, alongside visualisation of data in histograms. The efficacy of treatments was determined by either Kruskal-Wallis rank sum test (for non-parametric) or an analysis of variance (ANOVA) model. Categorical dependent variables, Outcome and RESPD0/12 were evaluated for any significant effect of treatments using either Fisher's exact test for low count data or Pearson's chi-squared test. To assess whether RESPD12 was associated with a lower CRR, both data sets were combined and a Wilcoxon rank sum test with continuity correction was performed. Additionally, Pearson's chi-squared test with Yate's continuity correction was performed to assess whether there was a relationship between RESPD12 and presence of *Crenosoma striatum* on day 12.

Results

During the 1-year study period, a total of 229 hedgehogs weighing ≥200 grams were subjected to faecal analysis, from which 186 animals (81%) tested positive for *Capillaria* spp., 95 animals (41%) tested positive for *Crenosoma striatum*, and 84 (37%) had a mixed infection on admission. After exclusion of animals with a negative *Capillaria* result (n = 43), pregnant females (n = 9) and animals that died before receiving anthelmintics (n = 23), 154 hedgehogs divided across two studies (pilot and main) were randomly assigned a treatment protocol. From these 154 animals, 7 were lost to follow up or received additional anthelmintics during the trial, thereby excluding them and leaving a final study population of 147 hedgehogs. Out of these animals, 50 presented during the first half of the year and received a protocol from the 'pilot' study, whereas the remaining 97 hedgehogs received one of three 'main' anthelmintic protocols (Figure 3).

Pilot study

In total, 70 hedgehogs had a faecal sample taken during the pilot study period, from which 68 (97.1%) tested positive for *Capillaria*, 27 (38.6%) for *Crenosoma*, and 24 (34.3%) had a mixed infection on admission. Fifty of these animals could be enrolled in the pilot study, 30 of which were male, 13 were female, whilst sex was unknown for the remaining seven hedgehogs. Eight animals (16%) had a *Capillaria* burden between 1–10, 23 (46%) between 11–100, six (12%) between 101–250, 13 (26%) greater than 250 ova per 3.24 cm^2 field and respiratory clinical signs were observed in 12 (24%) animals. Thirteen animals received protocol A, nine received protocol B, five received protocol C, seven received protocol D, nine received protocol E, and seven received protocol F. Thirty-nine animals (78%) survived for the duration of the study and were released, whereas eight (16%) were euthanised and three (6%) died during rehabilitation. The most common reasons for euthanasia during the study were severe, persistent lethargy and dyspnoea. The total number of animals (n) in each group that completed the full trial can be found in Table 2.

The CRR ranged from 28.1% (Protocol D) to 99.6% (Protocol C) (Table 2, Figure 4) and differed significantly among treatments (Kruskal-Wallis $\chi2=19.4$, $df=5$, $p=0.00161$). Dunn's multiple comparisons test and post-hoc analysis determined a significant difference in CRR between treatments A – D (p = 0.0181), C – D (p = 0.0207), A – E (p = 0.0409), C – E (p = 0.0227), D – F (p = 0.0154) and E – F (p = 0.0205). Mean weight gain during the 12-day period varied between groups from 20% (Protocol F) to 64% (Protocol C) but this did not differ significantly across treatments (Kruskal-Wallis $\chi2=7.77$, $df=5$, $p=0.1695$). Respiratory clinical signs were observed in 10/39 (25.6%) animals on day 0, and they were still

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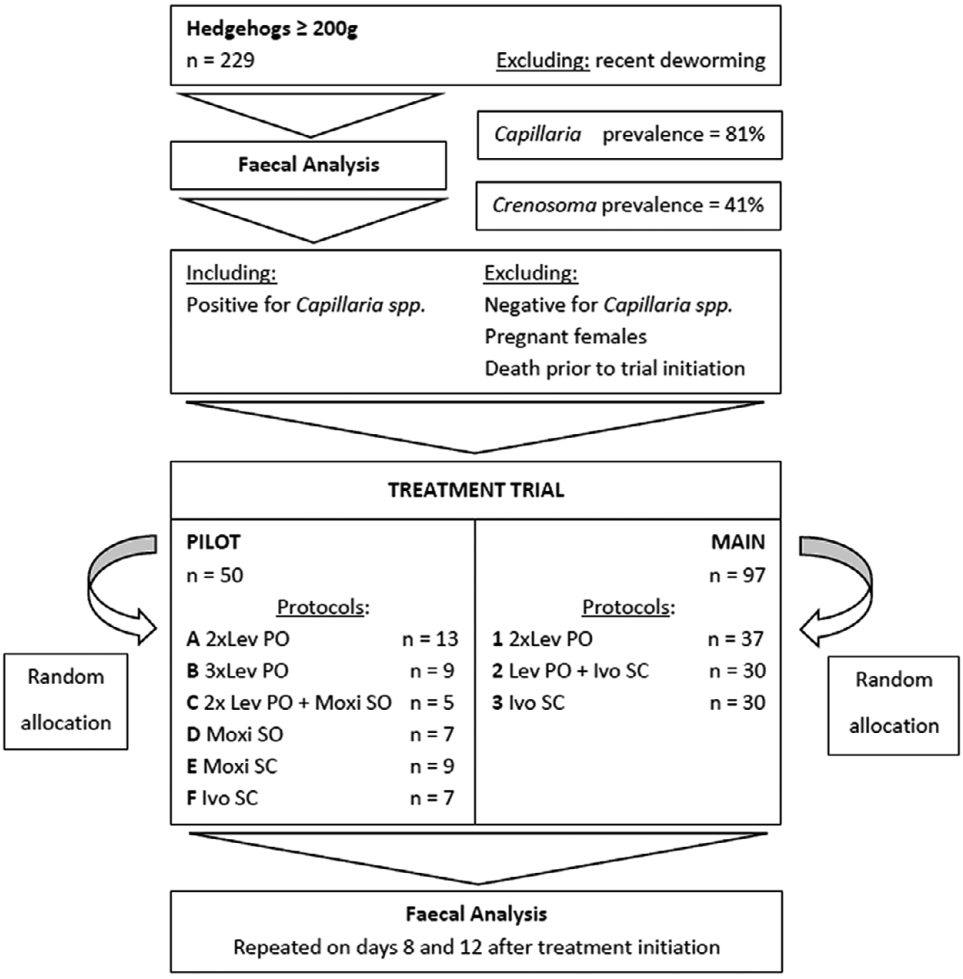

Figure 3. Flowchart providing an overview of the study methodology, as well as results on obtained sample sizes and prevalence of *Capillaria spp.* and *Crenosoma striatum.*

Table 2. Descriptive data regarding the parameters used for treatment efficacy across different anthelmintic protocols in the study. WG = Weight gain, RESPD0 = Presence of respiratory clinical signs at the start of treatment, RESPD12 = Presence of respiratory clinical signs at the end of treatment, CRR = *Capillaria* reduction rate. Sample size (n) refers to the number of animals for which a full data set was obtained. The total number of animals that received treatment can be found in the 'outcome' column.

Protocol	Sample size (n)	WG (%)	RESPD0 (%)	RESPD12 (%)	CRR (%)	Positive outcome (%)
Pilot						
A	10	27.1	20.0 (2/10)	20.0 (2/10)	86.6	76.9 (10/13)
B	6	45.0	33.3 (2/6)	33.3 (2/6)	92.1	66.7 (6/9)
C	5	64.0	00.0 (0/5)	00.0 (0/5)	99.6	100.0 (5/5)
D	5	29.1	60.0 (3/5)	40.0 (2/5)	28.1	71.4 (5/7)
E	7	30.9	14.3 (1/7)	00.0 (0/7)	56.4	77.8 (7/9)
F	6	20.0	33.3 (2/6)	00.0 (0/6)	99.4	85.7 (6/7)
Main						
1	31	41.1	9.7 (3/31)	32.2 (10/31)	93.2	83.8 (31/37)
2	26	37.0	11.5 (3/26)	19.2 (5/26)	93.0	76.7 (23/30)
3	25	33.3	16.0 (4/25)	8.0 (2/25)	69.3	80.0 (24/30)

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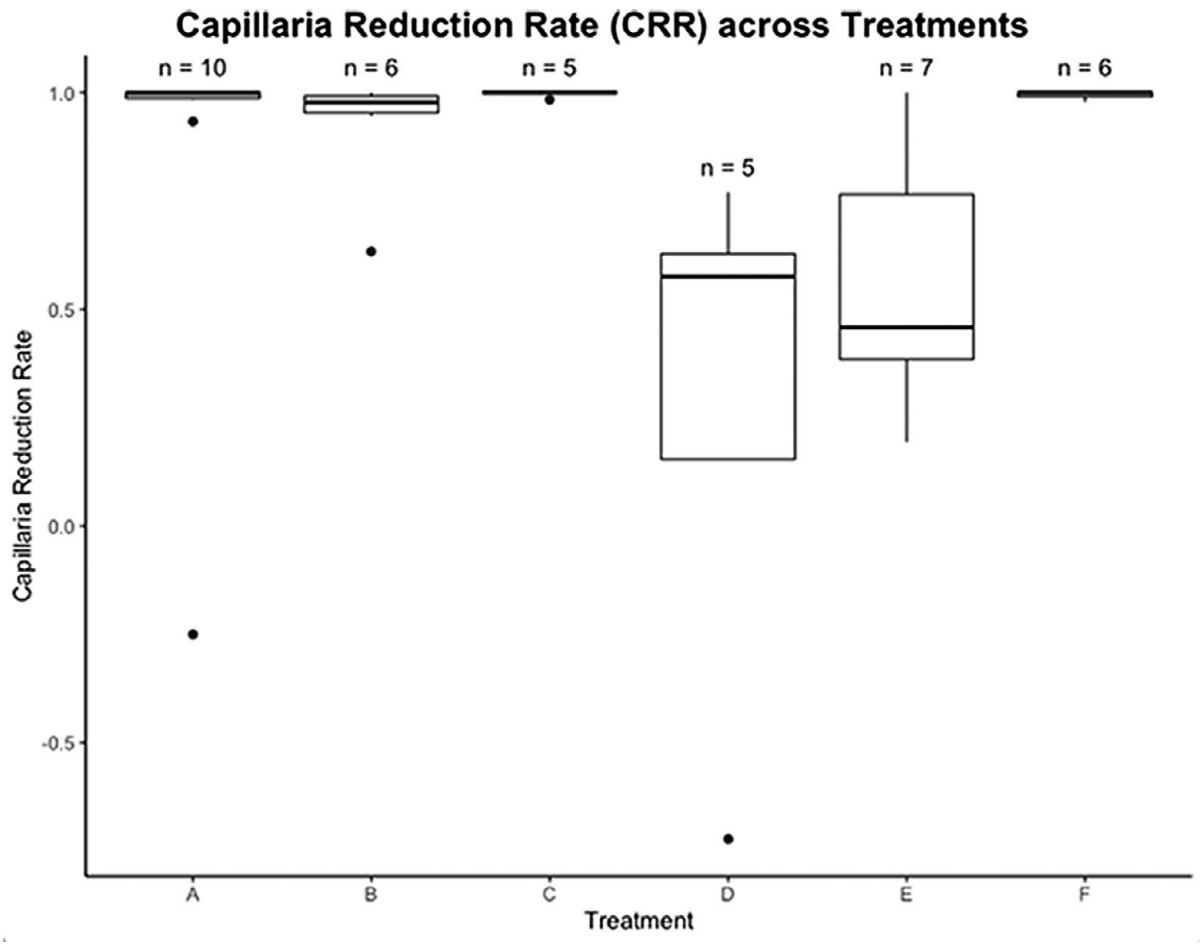

Figure 4. Box plot comparing the *Capillaria* reduction rate (CRR) across the six different anthelmintic treatments given to European hedgehogs in the pilot study. 'n' refers to the number of animals in each group that completed the trial and for which a full dataset was available.

present in 6/39 (15.4%) at the end of the trial. When instigating treatment, 14/39 (35.9%) hedgehogs were positive for *Crenosoma*, whereas this was reduced to 2/39 (5.1%) at the end of the trial.

Main study

In total, 159 hedgehogs had a faecal sample taken during the main study period, from which 118 (74.2%) tested positive for *Capillaria,* 68 (42.8%) for *Crenosoma*, and 60 (37.7%) had a mixed infection on admission. Ninety-seven of these animals could be enrolled in the main study, out of which 46 were male, 44 were female, and for seven the sex was unknown. Thirteen (13.4%) animals had a *Capillaria* burden between 1 and 10, 28 (28.9%) between 11 and 100, 22 (22.7%) between 101 and 250, 34 (35.1%) greater than 250 ova per 3.24 cm^2 field and respiratory clinical signs were observed in 14 (14.4%) animals. Thirty-seven hedgehogs received Protocol 1, 30 received Protocol 2, and another 30 animals received Protocol 3. Seventy-nine hedgehogs (81.4%) were released, whereas 16 were euthanised and two died during rehabilitation. The most common reasons for euthanasia during the study were severe, persistent lethargy and dyspnoea. Neurological signs were observed in two euthanised animals, one of which was diagnosed with a skull fracture.

The CRR ranged from 93.2% for Protocol 1, 93.0% for Protocol 2, and 69.3% for Protocol 3 (Table 2, Figure 5). CRR across treatments varied significantly (Kruskal-Wallis $\chi 2=7.75$, $df=2$, $p=0.0208$) with pairwise post-hoc analysis, Dunn's multiple comparisons test, indicating a significant difference between Treatment 1 – Treatment 3 (p = 0.0212) and Treatment 2 – Treatment 3 (p = 0.0109). Average WG during the 12-day period was 41.1% in Protocol 1, 36.9% for Protocol 2, and 33.3% for Protocol 3, but this did not differ significantly among treatments (F-value = 0.646, p = 0.527). Respiratory clinical signs were observed in 10/82 (12.2%) animals at the start of treatment (day 0), whilst they were noted in 17/82 (20.7%) hedgehogs on day 12. When instigating treatment, 51/82 (62.2%) hedgehogs were positive for *Crenosoma*, whereas this was reduced to 28/82 (34.1%) at the end of the trial.

CRR differed significantly between hedgehogs with respiratory clinical signs on day 12 and those without ($p = 0.003497$). Additionally, a significant relationship between RESPD12 and presence of *Crenosoma* on day 12 ($p = 0.005143$) was observed.

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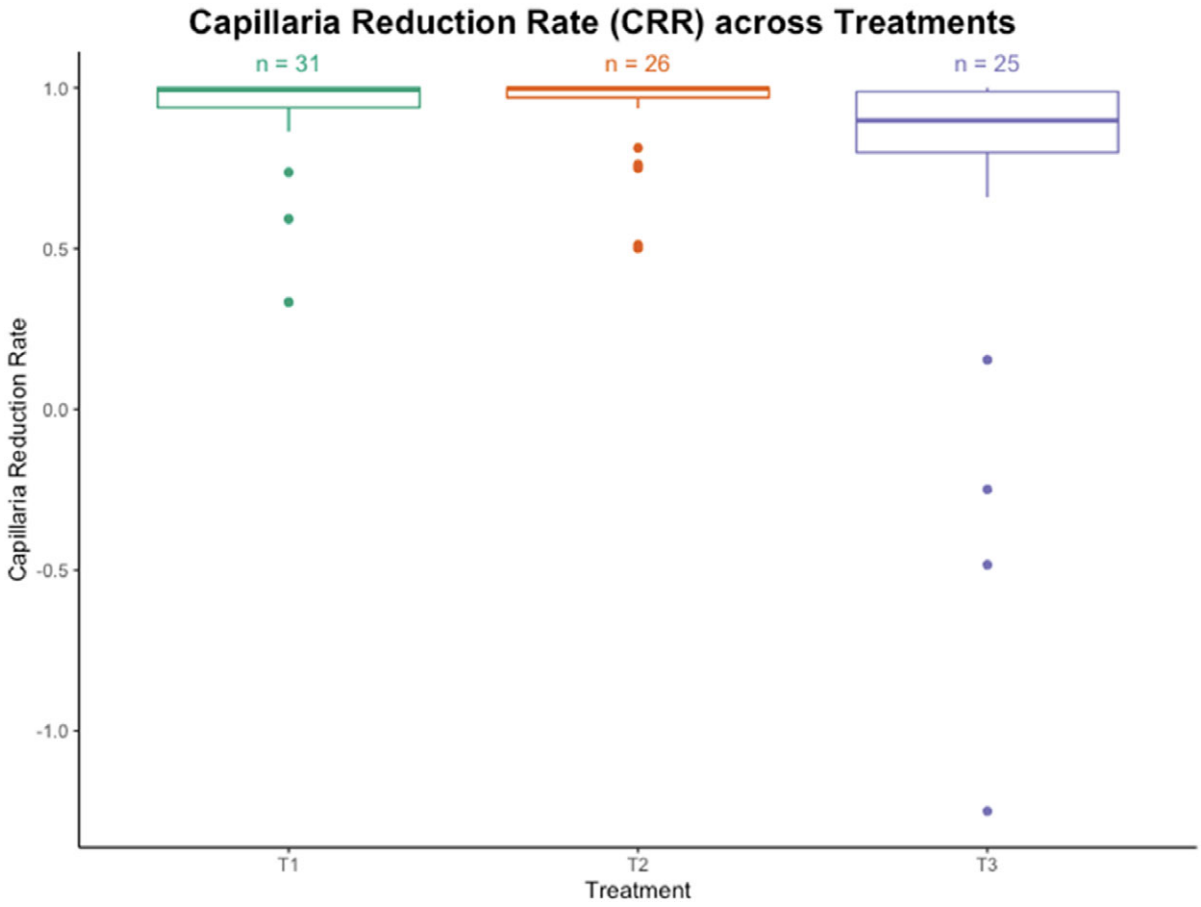

Figure 5. Box plot comparing the *Capillaria* reduction rate (CRR) across the three different anthelmintic treatments (T1-T2-T3) given to European hedgehogs in the main study. 'n' refers to the number of animals in each group that completed the trial and for which a full dataset was available.

Discussion

This study assessed the efficacy of levamisole, ivermectin, and moxidectin given in different treatment regimens for the treatment of naturally acquired *Capillaria spp.* infection in European hedgehogs weighing ≥200g. A *Capillaria* prevalence of 81% and *Crenosoma* prevalence of 41% indicates that endoparasite infections are common in European hedgehogs admitted for wildlife rehabilitation, a finding comparable with those from other studies (Majeed *et al.* 1989; Gaglio *et al.* 2010; Mariacher *et al.* 2021). Moreover, these data are likely an underestimation, because of intermittent faecal shedding and the methods used for detection (e.g., analysis of a single initial faecal sample and the relatively low sensitivity of wet mount for *Crenosoma*).

Spot-on moxidectin has been used to successfully treat pulmonary capillariosis caused by *C. aerophila* in cats (Traversa *et al.* 2012), and it is occasionally administered to hedgehogs suffering from similar infections in first-opinion veterinary practices. One aim of the current study was, therefore, to investigate the efficacy of moxidectin as a treatment of capillariosis in hedgehogs. Spot-on medication, if found to be effective, would overcome the difficulties of oral administration in hedgehogs and the discomfort associated with injectable products. Based on data from the pilot study, however, moxidectin/imidacloprid spot-on alone demonstrated significantly poorer efficacy at reducing *Capillaria* egg counts in hedgehogs compared to other protocols. One could argue this to be a result of different bioavailability and dose-dependent effects when administering a ML via topical rather than parenteral route. Nonetheless, the protocol with injectable moxidectin at a high dose also yielded unsatisfactory results, and moxidectin was consequently abandoned for the main study.

A presumed CRR of 100% has previously been reported for injectable ivermectin when used at a dose of 3 mg/kg (Barutzki *et al.* 1987). More recently, injectable levamisole has been recommended as the treatment of choice for parasitic bronchopneumonia in hedgehogs (Bexton and Couper 2019). Injectable levamisole is no longer marketed in GB. Therefore, the current study investigated the use of an oral formulation as an alternative. Results from the main study indicated that protocols containing levamisole had a significantly better CRR than those containing only ivermectin. The CRR of ivermectin in this study was much lower than observed by Barutzki *et al.* (1987). This could be attributable to different drug formulations or methods used for ova detection, but it may also indicate reduced susceptibility of *Capillaria* spp. against ivermectin.

The combination of levamisole with ivermectin yielded no additional benefits when compared to the protocol containing only levamisole. Considering this, combined with the presumed longer half-life and associated ecotoxicity of ivermectin (Lumaret *et al.* 2012), levamisole may be the anthelmintic of choice for the treatment of capillariosis in European hedgehogs. The levamisole protocol used in this study entailed administering oral levamisole for two consecutive days at a dose of 35 mg/kg. Despite treatment, *Crenosoma* could still be detected at the end of the trial for approximately half of positive cases in the main study. Several of these positive

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animals were showing respiratory clinical signs or failure to thrive, thereby requiring repeated administration of anthelmintics on day 12. In the author's experience, it appears that *Crenosoma*, or rather, mixed lungworm infections, are more detrimental to the health of hedgehogs compared to infections consisting exclusively of *C. aerophila*. This observation is further supported by pathological findings (Lehmann *et al.* 2023). The fact that treatment against *Crenosoma* appeared more successful in the pilot compared to the main study trials may be because of the small pilot sample size, higher parasite burdens, and higher representation of subadults in autumn. Although *Crenosoma* could not be quantified in this study, results indicate that more hedgehogs presented with higher *Capillaria* egg counts in autumn compared to spring. This fact, combined with the small sample size of pilot protocols, may also account for seemingly better CRR of ivermectin as observed in the pilot study compared to the main study.

Notably, more animals on average ended the trials from the main study with respiratory clinical signs than those observed with respiratory clinical signs at the start of treatment. A possible explanation for this may be inflammation and bacterial involvement secondary to dying nematodes in the respiratory system or, alternatively, persistent lungworm burdens. Although both hypotheses are likely, the fact that animals with respiratory clinical signs at the end of the trial were significantly more likely to have a lower CRR and test positive for *Crenosoma* is in support of the latter. Therefore, it is recommended to not blindly rely on anthelmintic treatment but to repeat faecal analysis in hedgehogs with persistent (≥7 days) respiratory clinical signs or ill thrift. Animals with clinical signs that still test positive for *Capillaria* and/or *Crenosoma* may require additional anthelmintic therapy, rather than additional antibiotic therapy. The authors recommend repeating levamisole (protocol 1) between days 10 and 12 for such animals. It should be noted that animals from this study presenting in very poor body condition score, with respiratory clinical signs, or with lethargy often received supportive care including fluid therapy, antibiotics, bronchodilators, and mucolytics. These animals should, however, be spread equally across different anthelmintic groups because of randomisation.

The percentage of animals with a positive outcome was similar across treatments, with an average release rate of 80% in the main study. Despite anecdotal reports of fipronil toxicity in hedgehogs and subsequent concerns of potential increased GABA sensitivity and ML toxicity, no obvious adverse effects attributable to anthelmintic treatment were observed. Only one animal in the entire study had unexplained neurological signs, and most animals that were found dead or euthanised because of severe lethargy were already lethargic prior to initiation of anthelmintic therapy. As such, the treatment protocols used in the main study may be considered relatively safe, albeit that certain side effects such as agranulocytosis sometimes associated with levamisole are difficult to pick up on. A larger sample size and control group are required before definitive conclusions can be drawn.

Hedgehogs that received a course of levamisole showed better average WG compared to those receiving an injection of ivermectin, though this was not significant. One could argue if it matters whether levamisole or ivermectin is given for treating capillariosis, considering the lack of significant differences in WG, respiratory clinical signs, and outcome. This study did not assess the number of days in rehabilitation required before release, however, and animals with high parasite burdens at the end of treatment may require additional anthelmintic therapy, thereby delaying release. Nonetheless, anthelmintic therapy could potentially also delay release for some hedgehogs because dying parasites may temporarily induce more pronounced inflammation and obstruction of the airways. The latter is why animals should be monitored closely after deworming. It is recommended that, ideally, only 1) animals with clinical signs attributable to endoparasite burdens and 2) those with insufficient weight for release as well as a concurrent high endoparasite burden (usually autumn juveniles requiring many weeks in rehabilitation) are treated with anthelmintics. Although lungworm is widely regarded as a cause for respiratory clinical signs, failure to gain weight, and death (Bexton and Couper 2019; Lehmann *et al.* 2023), this study did not aim to make such association as this would require a control group.

The results of this study need to be interpreted within the context of multiple limitations associated with a wildlife rehabilitation setting within an animal welfare charity. Ideally, this randomised study would have had a control group. However, considering the morbidity and mortality associated with endoparasites in European hedgehogs presented for wildlife rehabilitation, not providing anthelmintic therapy to animals diagnosed with these nematodes was considered a welfare concern and consequently abandoned. The flotation method used in this study is suboptimal because of the lack of counting chambers and a relatively broad interval (10 minutes) before interpretation. However, these were necessary compromises to enable the study. Given that all faecal *Capillaria* burdens above 250 ova were recorded equally as 250+, the CRR obtained in this study amounts to the minimum percentage by which the parasite burden was reduced, and the actual efficacy of the treatments is likely to be higher. Nonetheless, the flotation method was standardised and consistently applied, from a wildlife perspective, in a relatively large number of animals. Therefore, the authors consider these results to be valid. Wet mount is a less sensitive method for the detection of *Crenosoma striatum*, and the true prevalence of this parasite is likely to be higher. As such, it proved difficult to make any robust conclusions regarding treatment efficacy against *Crenosoma*, and no comparison between protocols was made.

Additional studies, applying the Baermann technique, are required to accurately diagnose and quantify *Crenosoma* in hedgehogs, enabling further investigation of treatment efficacy against this nematode. It should be noted that exotic animal formularies (Doss and Carpenter 2023), despite being mostly focused on African pygmy hedgehogs, describe lower doses of both levamisole and ivermectin compared to those used in this study. It may be possible that, especially for ivermectin, lower doses are equally (in)effective at reducing *Capillaria* burdens, and poor results from previous years can be attributed to reduced parasite susceptibility rather than suboptimal dosing. Therefore, it is not recommended to further increase ivermectin doses in hedgehogs without first elucidating its pharmacokinetics and pharmacodynamics. In their absence, 35 mg/kg levamisole should be considered the upper end of the dose range. Although this dose appeared to work well for this study and no adverse effects were reported, the efficacy of lower doses was not explored with similarly standardised methods. Especially when attempting to treat intestinal capillariosis, a lower dose of oral levamisole may be sufficient. Therefore, a more cautious dose range of 25–35 mg/kg levamisole is suggested till more data becomes available.

Conclusions

Treatment protocols containing only moxidectin had poor efficacy at reducing *Capillaria* egg counts and moxidectin, whether

https://doi.org/10.1017/S0022149X23000718 Published online by Cambridge University Press

administered as a spot-on (Advocate©, Prinovox©) or injectable (Cydectin©) formulation, may therefore not be recommended for the treatment of capillariosis in European hedgehogs. Oral levamisole given for two consecutive days at a dose of 35 mg/kg appeared more effective at reducing *Capillaria* burdens compared to a single subcutaneous injection of ivermectin at 5 mg/kg. No significant differences in weight gain, respiratory clinical signs, and outcome were observed between treatments. Lower CRR and refractory *Crenosoma* infections were associated with animals that showed respiratory clinical signs at the end of the trial. Therefore, it is recommended to repeat coprological examination in animals with persistent clinical signs and to subsequently provide additional levamisole on days 10–12 when indicated. It should be noted that complete elimination of endoparasites is unnecessary in European hedgehogs, as reinfection in the wild is almost inevitable. The goal should be reducing parasite burdens to an acceptable level, which does not result in clinical signs or failure to thrive.

Acknowledgements. The authors would like to thank all staff members at RSPCA Stapeley Grange for enabling this study, especially those who collected countless faecal samples and carried out treatments. Special thanks to Lee Stewart and Bev Panto for their support.

Author contribution. Yannick Van de Weyer, Mariana Santos, Nicola Williams, Alda Goncalves, and Wendy Hawley contributed to the study conception and design, material preparation, and data collection. Data analysis was performed by Kate McVay. The first draft of the manuscript was written by Yannick Van de Weyer, whilst Steve Bexton, Mariana Santos, and Nicola Williams commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Competing interest. The authors have no competing interests to declare that are relevant to the content of this article.

Ethical standard. Not applicable as all animals in this study were given treatments that are routinely being used for the deworming of European hedgehogs.

Financial support. No funding was received to assist with the preparation of this manuscript.

Consent to participate and publish. All authors consent to publish this work.

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