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Research Article

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Posted Date: November 4th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11342091/v1

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Additional Declarations: No competing interests reported.

Comparative efficacy of levamisole, ivermectin and moxidectin against the lungworm *Crenosoma striatum* in rehabilitating Western European hedgehogs (*Erinaceus europaeus*)

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Background Anthelmintics are frequently used to treat verminous pneumonia in European hedgehogs (*Erinaceus europaeus*), but recommendations remain anecdotal due to limited scientific evidence regarding efficacy and safety. This randomized clinical trial compared the efficacy of a single subcutaneous injection of levamisole (27 mg/kg) versus ivermectin (3 mg/kg) against *Crenosoma striatum* by assessing larval shedding and clinical parameters. Hedgehogs (*n=51*) from two wildlife rehabilitation centres each received either treatment during autumn. *Crenosoma striatum* larval count per gram faeces (LPG) was measured via Mini-FLOTAC before, 12 and 24 days after treatment followed by a faecal larva count reduction test. Relative weight gain, respiratory clinical signs and mortality were obtained at similar time points. In a follow-up trial the next autumns, hedgehogs (*n=12*) received a single subcutaneous injection of moxidectin (3mg/kg) with similar LPG determination.

Results Neither ivermectin nor levamisole resulted in significant LPG reduction 12 days after treatment with both scoring below 90%. Hedgehogs that received levamisole had significantly higher relative weight gain (*p=0.041*) compared to hedgehogs receiving ivermectin. Survival or clinical signs did not differ significantly. For moxidectin, all animals initially positive for lungworm and surviving became negative for *C. striatum* on day 12.

Conclusions This and other studies suggest that moxidectin is effective at reducing *C. striatum* LPG in European hedgehogs. Contrary, a single injection of levamisole or ivermectin failed to significantly reduce LPG, suggesting treatment failure due to resistance or other factors. We provisionally recommend a single subcutaneous moxidectin injection at 1 mg/kg for crenosomosis but encourage further studies to optimize the dosage regimen.

Keywords

Treatment, anthelmintics, endoparasites, rehabilitation, verminous pneumonia, hedgehog, deworming

Introduction

Respiratory disease is a common cause for morbidity and mortality in rehabilitating Western European hedgehogs (*Erinaceus europaeus*) whereby verminous pneumonia and bacterial rhinitis are considered the main aetiologies [1, 2, 3]. Hence, anthelmintics and antibiotics are often administered to hedgehogs with respiratory clinical signs. Despite their frequent usage, few studies explored efficacy, safety and pharmacological parameters, resulting in recommendations based mostly on anecdotal evidence, sometimes with contradicting results [4, 5, 6].

Verminous pneumonia in European hedgehogs is caused by *Crenosoma striatum*, *Eucoleus aerophilus* (Syn. *Capillaria aerophila*) or both [2]. The species specific metastrongyloid nematode *C. striatum* has an indirect life cycle comprising an intermediate gastropod host and the European hedgehog as the definitive host [7, 8]. Adult *C. striatum* live in the bronchi and bronchioles whereas larvae migrate through the lung parenchyma causing bronchopneumonia, epithelial hyperplasia and airway obstruction resulting in clinical signs such as respiratory distress, coughing, wheezing, weight loss, poor growth and death [2, 9]. With a prevalence ranging from 51-95%, *C. striatum* is highly prevalent in European hedgehogs [7, 10, 11] and infection has been associated with increased mortality during rehabilitation [12]. Moreover, *E. aerophilus* infection is negatively correlated with body weight [10]. Nevertheless, only a proportion of infected animals develops clinical signs and require treatment. Therefore, it is important to corroborate faecal microscopy results with clinical signs and other diagnostic investigations when making therapeutic decisions.

Levamisole is an imidazothiazole derivative that acts as a nicotinic acetylcholine receptor agonist, producing spastic paralysis in susceptible nematodes [13, 14]. It is highly water-soluble and rapidly distributed throughout the body including the respiratory tract with a relatively short half-life and negligible residual activity but with a narrow therapeutic index [15, 16, 17, 18]. Levamisole has good activity against adult worms and later larval stages especially when in open luminal spaces such as the gastrointestinal tract, bronchi or cardiovascular system [14, 19], Its larvicidal activity is variable and depends on the parasite species and larval location, with reduced activity reported against tissue-migrating or encysted stages [13, 19]. Apart from its antiparasitic action, levamisole is known for its immunomodulating effects [20, 21). Levamisole has been suggested as the treatment of choice for *C. striatum* associated verminous pneumonia in hedgehogs at a dose of 27 mg/kg administered subcutaneously [1, 2, 4, 5]. A previous

study demonstrated that levamisole given orally for two consecutive days at 35 mg/kg resulted in significantly better reduction of *Capillariid* spp. egg counts by 8-12 days post-treatment when compared to injectable ivermectin or moxidectin protocols, whereas *C. striatum* infections were often refractory to both levamisole and ivermectin [22]. All animals that received moxidectin in the latter study tested negative for *C. striatum* after treatment but the number of initially positive animals from this group was small (n=5).

Macrocyclic lactones (ML) such as ivermectin and moxidectin are popular anthelmintics in domestic animals and have a relatively long half-life due to redistribution in adipose tissues [23, 24]. These adipose-dependent pharmacokinetics mean that ML have reduced persistence and elimination half-life when used in patients with poor body condition [25, 26], which could negatively impact clinical efficacy. This may especially apply to ivermectin because of its lower volume of distribution (Vd), a shorter mean residence time in host tissues and reduced persistence compared to moxidectin [23, 27, 28]. Generally, ML are considered safe in mammalian species, but prolonged excretion and excessive use have caused concerns regarding parasite resistance and highly detrimental non-target effects in aquatic and invertebrate organisms [29, 30]. Overall, moxidectin is considered less toxic than ivermectin [23, 28]. An older study on European hedgehogs from Germany recorded a treatment efficacy against *C. striatum* of nearly 96% with parenteral ivermectin at 3 mg/kg [31], but a more recent study from Portugal observed frequent refractory nematode infections with the same dose [32]. Adam and Eshar (2024) reported a 96 to 100% clearance of *C. striatum* infections in southern white-breasted hedgehogs (*Erinaceus concolor*) 1-2 weeks after administration of oral moxidectin at 1.2 mg/kg [33], which is promising. However, most of these studies didn't quantify larval reduction or used wet mount to detect *C. striatum*, which lacks in diagnostic sensitivity and can result in approximately one in three infections being missed [11].

Another study in *E. concolor* (n=14) which used esafoxolaner and eprinomectin (NexGard® Combo) at 0.2 ml/kg resulted in faecal samples negative for *C. striatum* 10 and 14 days post-treatment as determined by Baermann's technique and flotation [34]. Nevertheless, injectable formulations are generally preferred in hedgehogs given their ease and reliability of administration compared to oral equivalents [5, 22].

This study aims to compare short-term efficacy against *C. striatum* of two commonly used anthelmintics: injectable levamisole or ivermectin as a single subcutaneous dose by assessing shedding of first stage larvae (L1) and clinical parameters via a randomized clinical trial. In a smaller non-randomized follow-up trial, the effectiveness of moxidectin was explored as well by measuring LPG reduction.

Materials and methods

Study design and inclusion criteria

A randomized clinical trial was carried out in 2024 for 7 weeks from early November till end of December to compare the efficacy of two anthelmintic treatments against *C. striatum* in rehabilitating Western European hedgehogs. Veterinary teams at East Winch (EW) and Stapeley Grange (SG) Royal Society for the Prevention of Cruelty against Animals (RSPCA) wildlife hospitals performed faecal collection, treatments and clinical assessments. Hedgehogs recently admitted (<48h) to the centres weighing >200 g, testing positive for *C. striatum* on wet mount and/or MiniFlotac with ZnSO4 were allocated one of the two treatments depending on their admission number. Individuals with even admission numbers were allocated to group A (levamisole) while odd numbers were in group B (ivermectin). Admission numbers are routinely assigned to hospitalized animals in chronological order based on time of admission, which was considered suitable for randomisation. Hedgehogs were kept indoors in parasite-free conditions with no access to natural prey. Animals with a history of previous anthelmintic therapy or unable to produce >1 g of faeces within 48 hrs were excluded. Due to abnormally low weights for the time of year of the animals admitted during the trial, the weight criterion was lowered after 3 weeks to >175 g. A control group was not utilized due to ethical concerns within RSPCA regarding withholding treatment.

During October and November of 2025 and 2026, a small number of hedgehogs at the same RSPCA centres were selected based on similar criteria as above for a separate moxidectin trial.

Treatment protocols

During the main trial (2024), hedgehogs in group A received a single subcutaneous injection of levamisole (Quadrosol 10%, Prodivet) at 27 mg/kg [1] diluted in saline 1:4, whilst those in group B received a single subcutaneous injection of ivermectin (Panomec 1%, Boehringer Ingelheim) at 3 mg/kg [31]. Although 2-3 doses of levamisole are recommended in literature [1, 5], we decided on a single administration to achieve similar handling frequency as in the ivermectin group, because the datasheet of Quadrosol recommends a single administration in cattle or pigs and because there is currently little evidence to suggest that multiple doses are necessary to achieve acceptable efficacy. The day of treatment was considered ‘day 0’ (D0). Hedgehogs from the moxidectin trial received a single subcutaneous injection of moxidectin (Cydectin 1%, Zoetis) at 3 mg/kg which was allocated according to veterinary discretion under the cascade rather than randomized.

Faecal analyses

Faecal samples were routinely obtained from hedgehogs at both wildlife centres before treatment (D0) and 12 (±1) days after (D12). Twelve days is considered an appropriate interval to assess the efficacy of levamisole in production animals [37] and although slightly longer intervals of 14-20 days are recommended for ML, the higher metabolism in hedgehogs is expected to enable a shorter period of action. Day 24 (D24) faecal

samples were encouraged as well but this was not a requirement for the trial to avoid delaying the release of animals that were deemed healthy enough to return to the wild. The presence or absence of *C. striatum* was initially assessed via wet mount at the wildlife centres, after which the faecal samples were sent to Leahurst campus, University of Liverpool. Here, quantitative assessment took place by the primary investigators within 7 days of sample collection via Mini-FLOTAC with a ZnSO4 based solution: a technique with high sensitivity for detection of *C. striatum* that only requires 0.5 g of faeces and does not require live larvae [11]. All *C. striatum* L1 larvae across both grids were counted, after which the sum was multiplied by 5 to obtain the LPG. Further details on storage, transportation and analysis can be found in Wu et al. (2026).

Clinical assessments and mortality

Clinical examinations assessing respiratory clinical signs (dyspnoea, tachypnoea, coughing, sneezing, wheezing and other abnormal respiratory noises) and weighing were performed on D0 and D12, ideally by veterinary nurses blinded to the allocated treatments but due to human resource limitations, this was also done by veterinarians. Additionally, D12 mortality data (dead/alive) were collected retrospectively from wildlife centre records.

Rescue protocol

Animals from the study could receive supportive care such as antibiotics or anti-inflammatory drugs at the discretion of the veterinarians in charge of their care, whereas additional anthelmintic therapy was not permitted. However, if clinical deterioration was suspected to be associated with treatment failure, then a rescue protocol could be started if there were reasonable grounds to believe that the cause for this was indeed verminous pneumonia. 'Reasonable grounds' was based on exclusion of other causes for decline which included all of the following investigations and treatments: 1) Radiographs 2) Antibiotic therapy for ≥ 48 hours and 3) A follow-up faecal sample positive for *C. striatum* or *E. aerophilus*.

Postmortem examinations

Veterinarians were encouraged to submit fresh carcases from animals that died during the trial to the University of Liverpool for a holistic postmortem examination. Alternatively, if logistics hampered timely carcass transport, veterinarians could perform the autopsy themselves and submit tissues from all major organs in formalin for histology and swabs for bacteriology instead.

Ethical approval and animal test certificate

The University of Liverpool granted ethical approval to this project under the reference numbers VREC1533 (levamisole and ivermectin) and VREC1623 (moxidectin). An animal test certificate type S with application number 02233/2024 was received from the

Veterinary Medicine Directorate (VMD) for the use of Panomec and Quadrosol as described. Cydectin was administered under the cascade based on veterinary discretion, after consulting with the VMD.

Sample size

A power analysis calculation suggested data from a minimum of 40 animals was required to obtain statistical significance when comparing the efficacy of ivermectin versus levamisole. In accordance with the VMD type S animal test certificate, we anticipated a maximum of 50 animals thereby determining our sample size.

Statistical analysis

Statistical analyses were performed using IBM SPSS statistics 29.0.1.0. Normality plots were carried out to assess the distribution of the data. Mann-Whitney U, McNemar and Chi-square statistical tests were performed to assess significance.

Relative LPG reduction and weight gain were calculated for each individual by comparing the D12 results to the D0 results then multiplying them by 100 to obtain a percentage (Figure 1) [35]. Due to expected non-normal data distribution and outliers, medians were provided for both LPG and weight gain, but because of the preference of mean in LPG reduction, arithmetic means were calculated as well for this parameter. Log transformation was attempted but did not result in normal data distribution and given its many limitations in interpretation [36], it was not included.

$$Relative\ LPG\ reduction = \left[1 - \left(\frac{D12LPG}{D0LPG}\right)\right].100$$

$$Relative\ weight\ gain = \left[\frac{D12\ weight(g) - D0weight(g)}{D0weight(g)}\right].100$$

Fig. 1 Formulae and calculations used to obtain relative *Crenosoma striatum* larvae per grams of faeces (LPG) reduction and relative weight gain on day 12 (D12) after deworming of hedgehogs on day 0 (D0) in the trial.

Faecal larval count reduction test (FLCRT) analyses, based on the current gold standard faecal egg count reduction test to assess resistance in production animals [37], were performed via an online webtool application [38]. Here, an expected efficacy of 95% and lower efficacy threshold of 80% were used based on limited available quantitative data regarding efficacy of ivermectin and levamisole against *C. striatum* in hedgehogs [22, 31]. Results from the Delta method according to a recommended 90% confidence interval were selected [39].

Results

Animals

A total of 51 hedgehog met the study criteria and were enrolled in the clinical trial, 26 of which received treatment A (Levamisole) and 25 received treatment B (Ivermectin). Suboptimal communication during the final stage of the trial accidentally resulted in the enrolment of one animal above the maximum sample size (n=50). Ten animals died during the trial (e.g. euthanised for trauma or other issues) precluding collection of D12 data. Hence, a complete D0-D12 dataset was obtained from 41 animals, 19 of which from the levamisole group and 22 from the ivermectin group. A D24 sample was available from seven animals, five from the levamisole group and two from the ivermectin group.

Twelve hedgehogs were enrolled in the moxidectin trial. Here, a complete D0-D12 dataset was obtained from seven animals.

Larvae per grams faeces

Overall, 24 out of 41 hedgehogs (11 from group A and 13 from group B) had a lower LPG on D12 compared to D0. The median D0 LPG (n=51) was 395, the median D12 LPG (n=41) was 225, and the median D24 LPG (n=7) was 50. The mean D0 LPG was 1229, the mean D12 LPG was 572, and the mean D24 LPG was 335 (Figure 2), substantially higher than the median values because of several outliers. The mean D0 LPG of the animals that died before D12 (n=10) was 1102, which did not differ significantly from the mean D0 LPG of those that survived till D12.

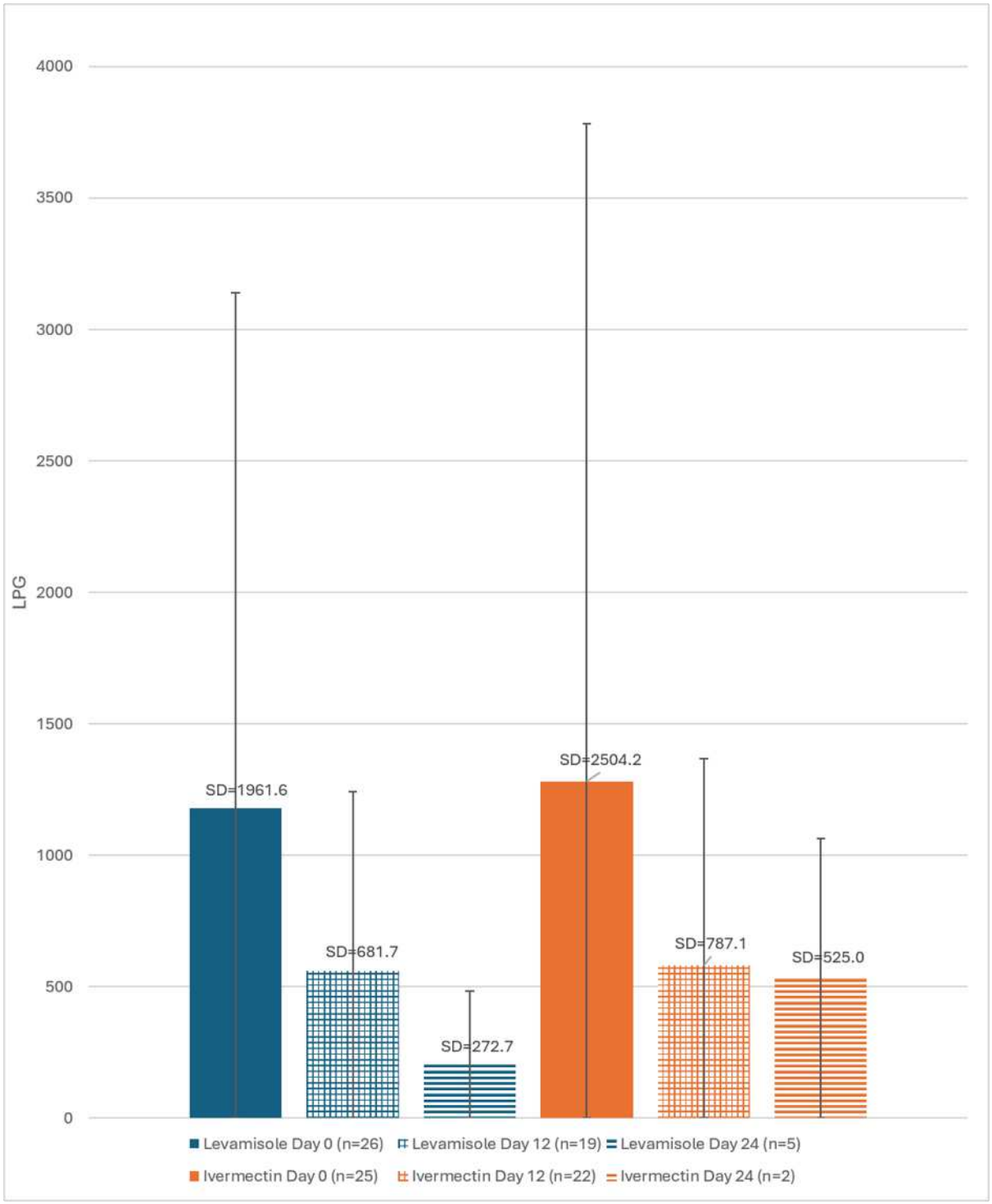


Fig. 2 Change over time in mean *Crenosoma striatum* L1 larval count per gram faeces (LPG) with error bars in European hedgehogs treated with a single subcutaneous injection of either levamisole (blue) or ivermectin (orange). Treatment was administered on day 0, after faecal sample collection.

There was no significant difference between the median D0 and D12 LPG for the levamisole group (p=0.615), nor for the ivermectin group (p=0.101) based on Wilcoxon signed ranks test. The median LPG changes from D0 to D12 were -45 for levamisole and

-250 for ivermectin, whereas the mean LPG changes from D0 to D12 were lower at -550 for levamisole and -807 for ivermectin. The median relative LPG reduction for levamisole was 0.62 (62% reduction), whereas ivermectin scored slightly lower at 0.53 (53% reduction) (Figure 3). The difference between both treatment groups were not statistically significant with the Mann Whitney U test (p=0.958). Mean relative LPG reduction scores were negative for both groups with -2.62 (262% increase) for levamisole and -0.75 (75% increase) for ivermectin.

Hedgehogs from the moxidectin trial had a median D0 LPG of 333 (n=12), whereas all animals surviving till D12 (n=7) were negative for *C. striatum* after treatment. This corresponds to a median and mean relative LPG reduction score of 1.00 (100% reduction).

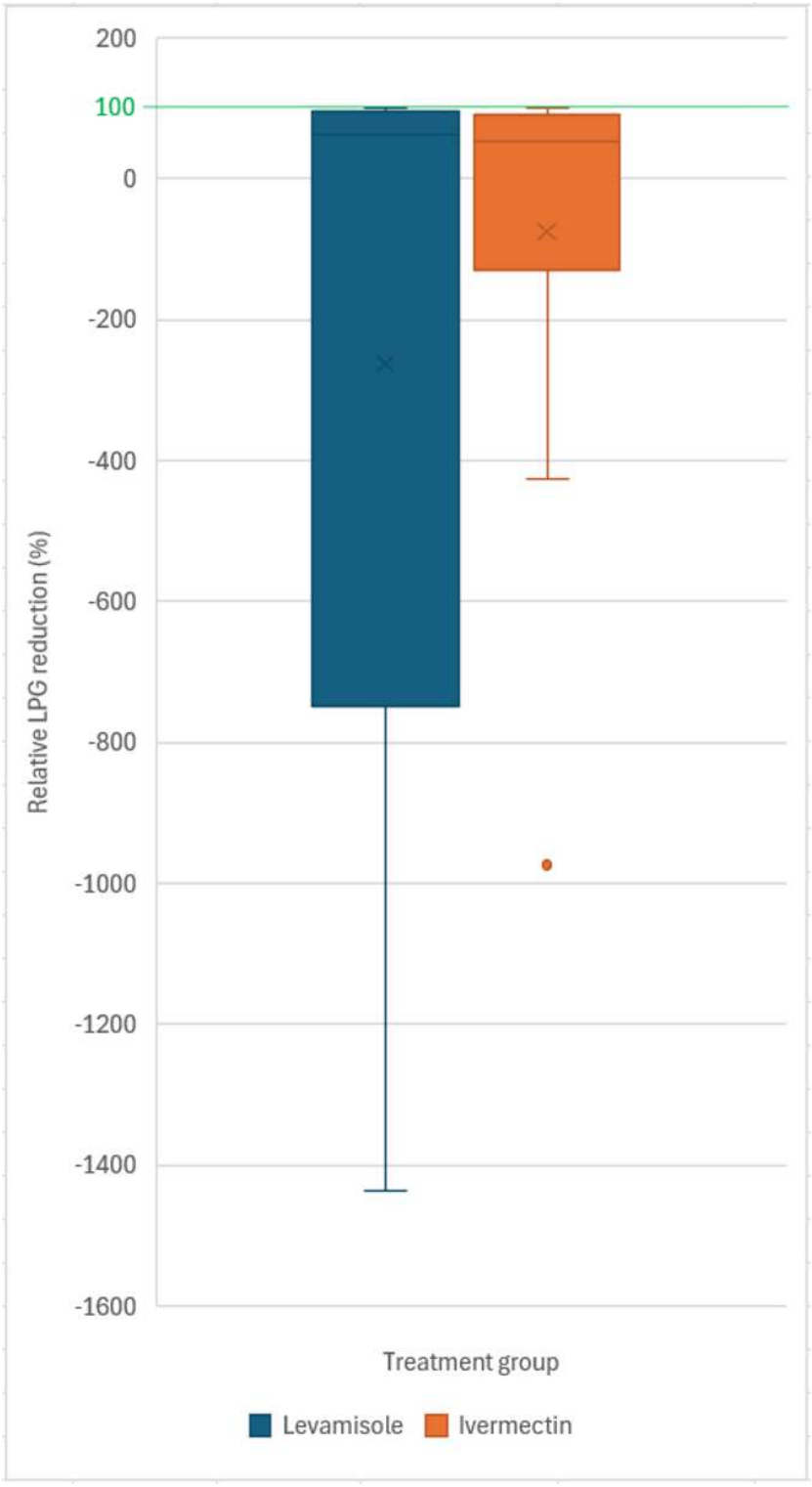


Fig. 3 Box plots comparing the relative reduction in larval count per gram of faeces (LPG) 12 days after anthelmintic therapy with either levamisole or ivermectin in European hedgehogs with *Crenosoma striatum* lungworm infection. Positive values reflect a reduction in LPG, whereas negative values correspond with an increase. For example, a value of 100% means that all parasites were eliminated after treatment, whereas a value of -100% means that the parasite burden doubled after treatment.

Faecal larvae count reduction test (FLCRT)

The FLCRT suggested that *C. striatum* was resistant to both ivermectin and levamisole. According to the delta method, the 90% confidence interval was 0-83.8% for levamisole and 17.9-86.2% for ivermectin.

Clinical parameters and mortality

Weight data was non-normally distributed with a mean absolute weight of 272.4±75.5 g on D0 and 402.9±88.8 g on D12 for the levamisole group, whereas the mean absolute weight of hedgehogs in the ivermectin group was 292.5±94.0 g on D0 and 395.3±140.3 g on D12. The median weight gain on D12 after treatment was 112 g for levamisole (n=19) and 119 g for ivermectin (n=22). Levamisole ranked higher than ivermectin for weight gain with the Mann-Whitney U test, but this was not statistically significant (p=0.174). The median relative weight gain was 0.547 (54.7% increase) for levamisole (n=19) and 0.373 (37.3% increase) for ivermectin (n=22) (Figure 4). Levamisole ranked significantly higher than ivermectin for relative weight gain (p=0.041) with the Mann-Whitney U test.

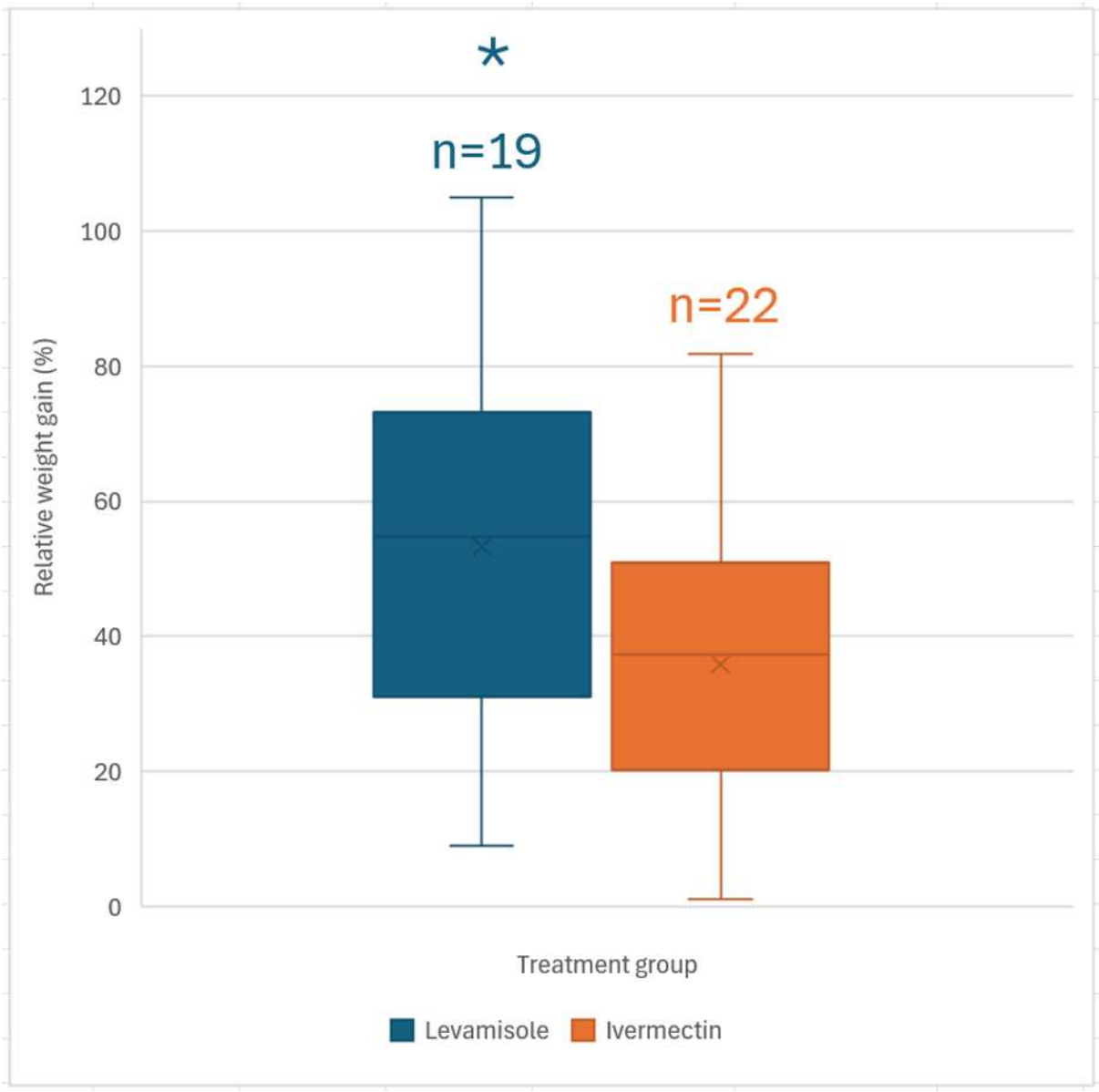


Fig. 4 Box plots comparing the relative increase in median weight gain on day 12 after anthelmintic therapy with either levamisole or ivermectin in European hedgehogs with *Crenosoma striatum* lungworm infection. A value of 50% means that the animal gained half of its initial body weight during the 12-day randomized trial. The levamisole group (asterisk) scored significantly higher ($P < 0.05$) compared to the ivermectin group.

For the levamisole group, five out of 26 animals had respiratory clinical signs on D0 and four out of 19 on D12. None of the five animals with clinical signs on D0 had clinical signs on D12 (100% resolved), meaning that the four animals from D12 developed clinical signs after therapy. For the ivermectin group, eight out of 25 animals had respiratory clinical signs before treatment and four out of 22 animals had clinical signs on D12. Six from the eight animals with respiratory clinical signs on D0 no longer had clinical signs on D12 (75% resolved). Two out of four animals with clinical signs on D12 presumably developed these after ivermectin therapy. There was no significant difference in the presence of

clinical signs before and after treatment for either treatment group (p=1.000 for levamisole and p=0.289 for ivermectin).

Three out of 25 (12%) animals from the ivermectin group and seven out of 26 (27%) animals from the levamisole group died during the 12-day trial. No statistically significant difference was observed with Chi squared test (p=0.144) for mortality between groups. For the moxidectin group, five out of twelve (42%) hedgehogs died during the trial.

Postmortem and safety data

No adverse drug reactions were reported during the trial and the rescue protocol was not invoked by the participating wildlife veterinarians. Ten deceased animals were presented for further examinations, four from the initial trial and five from the follow-up moxidectin trial. Available samples included four whole carcases for postmortem examination and formalin-fixed tissues from the major organs with or without lung swabs for the remaining five hedgehogs. The main causes of death were verminous pneumonia and/or tracheitis with partial obstruction of the airways by exudate (4/9), bacterial pneumonia associated with *Bordetella bronchiseptica* (1/9) and systemic salmonellosis (3/9 confirmed, 1/9 suspected), whereas two out of three animals with available nasal cavity histology also had rhinitis. At least three out of five deceased animals submitted from the moxidectin trial were infected with *Salmonella enteritidis ST 183*, accounting for ≥60% of total deaths in this group and thereby confounding the mortality number.

Discussion

This study explored the efficacy of the treatment regimen using either a single subcutaneous administration of levamisole or ivermectin on the shedding of *C. striatum* L1. Despite both being widely recommended for treatment of lungworm in hedgehogs [1, 2, 5, 6], neither drug resulted in a significant LPG reduction 12 days post-treatment. Combined with anecdotal reports and other studies reporting frequent refractory *C. striatum* infections following ivermectin or levamisole therapy [2, 22, 32], this suggests treatment failure for which there could be various explanations. A first option is that neither anthelmintic work sufficiently against *C. striatum*, possibly due to resistance of the nematode, a hypothesis supported by the FLCRT results of <90% [37]. Secondly, it could be that the dosages were insufficient, but this is considered unlikely given the relatively high doses used in hedgehogs (3 mg/kg) compared to other mammalian species (0.2-0.5 mg/kg) and long residual effects of ML [24, 26, 28]. Other variables such as body condition score and injection site can affect the pharmacokinetics and efficacy of anthelmintics [27, 40]. For example, the mantle, a popular site for subcutaneous injection in hedgehogs and used for most animals in this study, is considered poorly vascularized but it is unknown to which extent this affects drug efficacy and such variables were not explored here [41]. For levamisole, three doses with 48hr intervals have been recommended [1] whereas only a single dose was used in this study. Although studies in human medicine suggest that multiple doses can be beneficial in some

circumstances [14], in domestic animals there is currently limited literature to support this. Moreover, a double dose in another randomized hedgehog trial also resulted in refractory *C. striatum* infections [22], but ultimately more research is required to establish the benefit of additional levamisole doses. A third argument could be that 12 days between the drug administration and second faecal sample was insufficient to see an effect on LPG. Both anthelmintics are considered to have a reasonably rapid onset of action [18, 24], but they may not affect all parasite stages equally. Nevertheless, one study in dogs exploring the efficacy of milbemycin oxime (Milbemax, Novartis) against experimental infection with *Crenosoma vulpis* noted a significant LPG reduction in the treatment compared to the control group both at 7 and 14 days post-treatment [42] and another using moxidectin for treatment of *C. striatum* recorded equally impressive LPG declines over a similar period [33], suggesting that LPG reduction following anthelmintic therapy can be rapid for this parasite genus. Hedgehogs from our study did exhibit a clear LPG reduction over time, moving from a median LPG of approximately 400 to just 50 after 24 days. This change may only partially be related to anthelmintic therapy because *C. striatum* presumably has a lifespan of several months and requires an intermediate host to complete its life cycle, which is not available to captive hedgehogs kept indoors, precluding re-infection. Hence, one could expect *C. striatum* burdens to decline with time in captivity, but Conboy et al. (2013) demonstrated that larval shedding of *C. vulpis* can continue for at least 7 weeks post infection. Although a control group would be ideal for conclusive evidence, before and after treatment samples are currently preferred in faecal egg count reduction testing [37] and the use of control groups is controversial in wildlife medicine.

Hedgehogs in the levamisole group had significantly better relative weight gain compared to those from the ivermectin group. Albeit marginally statistically significant, this could imply that levamisole is more beneficial for rehabilitating hedgehogs than ivermectin at the provided doses. A similar trend was observed during a previous hedgehog study [22] and a study in pigs also observed significantly better weight gain in piglets receiving levamisole [43]. There are various hypotheses for this finding. Firstly, oral levamisole appears more effective at eliminating *Capillariid* spp. [22] and Shütte et al. (2025) found a negative association between *E. aerophilus* infection and body weight. Hence, successful treatment of *E. aerophilus* may facilitate weight gain in hedgehogs. Another hypothesis could be related to an unexpected positive effect of levamisole or alternatively, because of side-effects associated with ivermectin at the administered dosage. Levamisole has immunomodulatory properties and an experimental rat pleuritis study observed reduction in pulmonary inflammation whereas a study in weaned pigs recorded improved gut health and immunity following levamisole therapy [20, 21]. An example supporting the latter theory is illustrated by a study in rats whereby ivermectin at a dose of ≥10 mg/kg resulted in sleepiness, staggering and central nervous system suppression [44]. Although ivermectin doses of 3 mg/kg are commonly recommended for use in hedgehogs [1, 31, 32], they approach the toxic threshold from the above study in

rats, especially when injections are repeated weekly, which some rehabilitators advocate for. Despite that no reduction in appetite or other adverse reactions were reported during the trial, side effects such as reduced appetite are easily overlooked or attributed to other circumstances in wildlife rehabilitation.

The presence of respiratory clinical signs before and after treatment did not differ significantly for either group. Interestingly, most animals with clinical signs on D12 did not have clinical signs on D0, suggesting that they developed them after treatment. However, an important limitation of the study design is that a single clinical assessment before treatment is prone to error, because animals may have had clinical disease but not express it at the time of assessment. Hence, it would have been better to perform daily assessment throughout the 12-day trial, which was deemed too time consuming for the staff members and stressful for wild patients. Moreover, respiratory clinical signs do not always indicate verminous pneumonia in hedgehogs as upper respiratory disease is an important differential diagnosis [3], in which case anthelmintic therapy alone is unlikely to result in clinical improvement.

Mortality was not significantly different between animals in the levamisole versus the ivermectin groups. Although the mortality during the moxidectin trial was unusually high (42%), most of it can be explained by a concurrent salmonellosis outbreak. In the absence of thorough postmortem examinations, many would falsely conclude that treatment failure of moxidectin was the cause for the excessive mortality, illustrating how easy it is for other diseases and environmental conditions to affect outcomes of rehabilitation and subsequently confound results. Moreover, given that there was no significant difference in mortality between the levamisole and ivermectin groups in this and another study [22], one could argue whether it makes a difference which of either anthelmintic is administered. Nevertheless, the reality is complex, and several limitations should be considered before interpreting outcome results. Firstly, animals were selected for treatment based on the presence of *C. striatum* in their faeces. *C. striatum* infections are often subclinical and although this could still contribute to morbidity and ill-thrift, presumably only a minority of animals in this study had clinically relevant verminous pneumonia and would have directly benefited from successful anthelmintic therapy. Secondly, verminous pneumonia is a multifactorial condition with at least two major contributors: *C. striatum* and *E. aerophilus*. For some hedgehogs in the study, *C. striatum* could have been the main clinical problem, whereas for others it may have been *E. aerophilus* or both. Hence, even if one anthelmintic works better against *C. striatum*, another may work better against *E. aerophilus*, thereby cancelling each other's benefits out on a population level. For the individual animal there may nevertheless be a difference in outcome, yet it remains difficult to establish antemortem which of both parasites is the main pathogen and subsequently decide on the most appropriate anthelmintic therapy. On the other hand, the superior relative weight gain (54.7% in 12 days) for animals receiving levamisole is a positive indicator. Combined with the better

efficacy of levamisole against *Capillariid* spp., presumably including *E. aerophilus* [22], this anthelmintic appears to be more beneficial for treatment of verminous pneumonia when compared to ivermectin.

Notably, the doses of ML, especially for ivermectin (3-5 mg/kg), used in this and a previous clinical trial are likely unnecessarily high and should not be considered the gold standard [22]. There were multiple reasons for using these doses in both studies, most of which related to empirical evidence and strong beliefs of experienced rehabilitators within the participating hospitals. Although ivermectin doses as high as 3 mg/kg were reported from Germany since the 1980s [31], doses for treatment of lungworm in UK hedgehogs have been increased progressively over the last decade (personal observation), likely because of a perceived reduction in efficacy. However, if the underlying cause for this is resistance or reduced susceptibility of *C. striatum*, then further increasing the dose is not a solution as it would only increase the risk of adverse effects [30]. Therefore, the authors urge caution and although ivermectin at lower doses (e.g. 0.5 mg/kg) could still be useful against ectoparasites in hedgehogs, the results from this study do not support the use of ivermectin for treatment of crenosomosis. Regarding moxidectin, another study reported good efficacy against *C. striatum* in southern white-breasted hedgehogs with an oral dose of 1.2 mg/kg [33]. Hence, one could presume that a 1 mg/kg dose of injectable moxidectin may be equally effective in European hedgehogs. However, if the long-acting formulation (Cydectin 2% LA, Zoetis) is to be used, then a higher dose (e.g. 2-3 mg/kg) may be recommended for European hedgehogs based on their higher metabolic rate and the manufacturer's recommendation of a 1 mg/kg dose for use in sheep. Nevertheless, further studies exploring pharmacokinetics, pharmacodynamics and establishing efficacy of lower doses via Mini-FLOTAC or Baermann's technique, ideally including a control group, are warranted.

Importantly, the FLCRT applied to explore resistance in this study is based on guidelines developed for nematodes with mostly simple life cycles in production animals [37], as similar guidelines are unavailable for wildlife and resistance in the genus *Crenosoma* is understudied. Hence, the obtained results should be considered an estimate only. Although our results indicate poor efficacy of ivermectin and levamisole against *C. striatum*, excretion of L1 larvae can be inconsistent and conclusive evidence of resistance would require additional studies such as larval motility assays and exploration of genetic markers. Twelve days was considered an appropriate interval to assess the efficacy of the anthelmintics tested based on data from production animals [37] and the higher metabolic rate of hedgehogs. However, because efficacy was evaluated solely by faecal larvae excretion, without recovery of adult worms at necropsy or longer-term follow-up, the results reflect suppression or cessation of larval shedding rather than confirmed elimination of all adult parasites.

Longer follow-up periods could have been useful to monitor LPG changes over time. However, mortality associated with verminous pneumonia usually occurs during the first

week of rehabilitation (personal observation), and *C. striatum* burdens are expected to decline over time in most captive environments unless animals have direct access to the gastropod intermediate host [32]. Wild hedgehogs are also ideally released as soon as their condition allows, whereby lungworm reinfection is likely. Therefore, the success of anthelmintic therapy against *C. striatum* should focus on short-term efficacy, clinical improvement and outcome, rather than on obtaining sterility with absolute negative faecal samples in the long-term. Anthelmintic susceptibility of parasites can vary between geographical regions, and parasite burdens may differ between seasons and age groups. The latter was not recorded in this study, but presumably a substantial proportion of treated animals were juveniles given that sampling occurred during late autumn. Further studies investigating the pharmacokinetics and pharmacodynamics of ML and levamisole in hedgehogs would be useful, especially those exploring the suitability of the mantle as an injection site and the effect of variables such as body condition score and season. Although no obvious adverse drug reactions were reported in this study, some side effects can be difficult to recognize especially when it concerns vague clinical signs like mild lethargy and reduced appetite rather than conspicuous biochemical or histological changes. Hence, caution and continued monitoring remain warranted.

Conclusions

For the randomized clinical trial evaluating the efficacy of the two injectable anthelmintics in European hedgehogs, neither levamisole nor ivermectin significantly reduced *C. striatum* larval counts 12 days post-treatment with expected larval reduction scores well below 90%, thereby suggesting treatment failure and questioning the efficacy of a single dose of levamisole or ivermectin in eliminating *C. striatum*. Levamisole produced marginally greater but statistically significant weight gain during the 12-day period, and a previous study suggests that it is more effective against *Capillariid* spp. than the ML tested [22]. Hence, levamisole may be more beneficial than ivermectin for treatment of verminous pneumonia in European hedgehogs. Based on our pilot trial and several other small studies, moxidectin appears highly effective at reducing *C. striatum* LPG, but it may be less effective when attempting to treat *Capillariid* spp. [22].

Following veterinary principles, anthelmintic therapy can be useful for the treatment of verminous pneumonia in European hedgehogs when a presumptive diagnosis is made based on faecal analyses combined with clinical signs and, where possible, medical imaging such as radiography and ultrasound (personal observation). Regardless of the underlying aetiology of the verminous pneumonia and choice of anthelmintic, supportive care such as bronchodilators, mucolytics, anti-inflammatory drugs and for some cases antibiotics, currently remain an integral part of the treatment [1, 5]. Further research, ideally including a control group and larger sample size for moxidectin, is necessary to provide conclusive evidence on the efficacy of anthelmintic therapy, to identify those

individuals that would benefit the most and to establish the most appropriate administration regimens.

Competing interests and Funding

This research was funded by the budget allocated for the intercalated BSc in Veterinary Conservation Medicine (XW) at the University of Liverpool. There was no external funding. The authors have no competing interests to declare.

Acknowledgements

We sincerely thank Beverley Panto and other staff members at RSPCA Stapeley Grange and East Winch wildlife centres for their collaboration and/or aid in sample collection.

Author contributions

Yannick Van de Weyer: Conceptualization, Writing – original draft, Methodology, Investigation, Project administration. Xiaoran Wu: Formal analysis, Data curation, Writing, Investigation. Mariana Santos: Investigation, Review and editing. Paul Gilmore: Methodology, Writing – review & editing, Resources. Anna Sturaro: Investigation, Review. Steve Bexton: Investigation, Writing – review & editing. Julian Chantrey: Supervision, Methodology, Investigation, Project administration.

Availability of data and materials

All data generated or analysed during this study are included in this published article, and the raw datasets are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The University of Liverpool granted ethical approval to this project under the reference numbers VREC1533 (levamisole and ivermectin) and VREC1623 (moxidectin).

Animal test certificate

An animal test certificate type S with application number 02233/2024 was received from the Veterinary Medicine Directorate (VMD) for the use of Panomec and Quadrosol as described. Cydectin was administered under the cascade based on veterinary discretion, after consulting with the VMD. All methods were carried out in accordance with relevant guidelines and regulations. All protocols were approved by the VMD, RSPCA and the University of Liverpool.

Consent to publish and participate

Consent was requested and received from all participating wildlife veterinary staff members. All authors consent to publish this work.

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