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Resistance of gastrointestinal nematoids of goats and sheep to the antihelmintics levamisol, ivermectin and albendazole

Resistência de nematoides gastrintestinais de caprinos e ovinos aos anti-helmínticos levamisol, ivermectina e albendazol

Swênia Christina Pinheiro Soares[1], Arnon Cunha Reis[1], Rogério Lean Pereira Castro[1], Pedro Celestino Serejo Pires Filho[2], Celecina Saraiva Martins Cabral[1], Durval Oliveira Diniz Júnior[1], Camila Barros Costa[1], Dara Maria da Costa Pinheiro[1], Yasmin Suelen Alves Pinheiro[1], Nayla Helena Silva Buna[1], Livio Martins Costa Júnior[2], Danilo Rodrigues Barros Brito[1*]

[1]Instituto Federal do Maranhão (IFMA), São Luiz, Maranhão, Brazil
[2]Universidade Federal do Maranhão (UFMA), São Luiz, Maranhão, Brazil
[*]Corresponding author: danilobrito@ifma.edu.br

Abstract
The aim of this study was to determine the resistance of gastrointestinal nematodes in goats and sheep to the anthelmintic drugs levamisole, ivermectin, and albendazole in the metropolitan region of São Luís Island, Maranhão, Brazil. Fecal samples were collected from 150 animals across four different farms; two farms had goats, and the other two had sheep. The samples were then randomly divided into three to four groups of 10 animals: Group I: control, without treatment; Group II: ivermectin treatment; Group III: levamisole treatment; and Group IV: albendazole treatment. Stool samples were collected from the rectal ampulla one day before treatment and 10 days after anthelmintic treatment. Individual coproparasitological examinations were performed using the modified McMaster technique at the Animal Health Laboratory of the Federal Institute of Maranhão, Campus São Luís-Maracanã. The efficacies of the anthelmintic drugs against gastrointestinal nematodes in goats and sheep were: 14.28%, and 13.6% for ivermectin; 0% and 79.4% for levamisole; and 59.8% and 3.43% for albendazole, respectively Gastrointestinal nematodes demonstrated multiple anthelmintic resistance, as the percentage reduction in egg count was less than 95% and the lower limit of the confidence interval was less than 90%.
Keywords: antiparasitic drugs; anthelmintic resistance; small ruminants

Resumo
Objetivou-se determinar a resistência de nematoides gastrintestinais aos anti-helmínticos levamisol, ivermectina e albendazol em caprinos e ovinos da região metropolitana da Ilha de São Luís, Maranhão, Brasil. Foram coletadas amostras de fezes de 150 animais de quatro propriedades diferentes, sendo 2 com caprinos e 2 com ovinos, e aleatoriamente distribuídos de três a quatro grupos de 10 animais: Grupo I: grupo controle, sem tratamento. Grupo II: tratado com anti-helmíntico à base de ivermectina, administrado oralmente na dose de 200 mcg/kg; Grupo III: tratado com anti-helmíntico à base de levamisol, administrado oralmente na dose de 7,5mg/kg e Grupo IV: tratado com anti-helmíntico à base de albendazol administrado oralmente na dose de 3mg/kg. Amostras de fezes foram colhidas da ampola retal um dia antes do tratamento e 10 dias após o tratamento anti-helmíntico. Foram feitos exames coproparasitológicos individuais, pela técnica de McMaster modificada, no Laboratório de Sanidade Animal, do Instituto Federal do Maranhão (IFMA), Campus São Luís-Maracanã. A ivermectina, na espécie caprina, mostrou eficácia de 14,28%, enquanto para ovina, 13,6 e 52,2%. Considerando o levamisol na espécie caprina, não apresentou eficácia contra os nematoides gastrintestinais, enquanto para ovinos, apresentou eficácia de 79,4%. Já o albendazol, apresentou eficácia de 59,8% para caprinos, e 3,43% para ovinos. Os nematoides gastrintestinais demonstraram resistência múltipla (RAM), visto que a percentagem de redução da contagem de ovos foi inferior a 95% e o limite inferior do intervalo de confiança menor do que 90%.
Palavras-chave: antiparasitários; resistência anti-helmíntica; pequenos ruminantes

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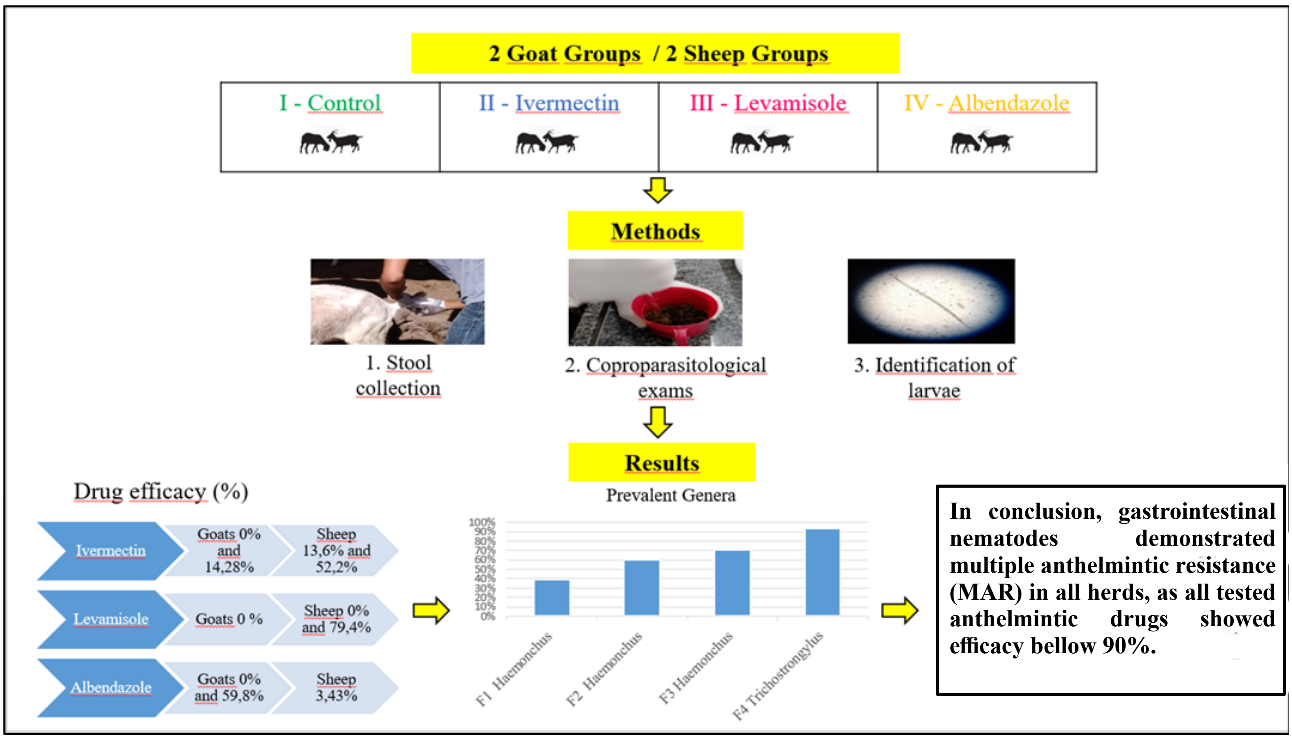

Graphical abstract - Resistance of gastrointestinal nematoids of goats and sheep to the antihelmintics levamisol, ivermectin and albendazole

1. Introduction

The Brazilian Institute of Geography and Statistics [14], through the Municipal Livestock Survey – PPM 2020, recorded a significant increase in the number of medium-sized animals; a 4.0% and 3.3% increase in the goat and sheep herd, respectively, totaling 12.1 and 20.6 million goats and sheep, respectively. The Northeast region continues as the national leader in goat and sheep farming with around 95.0% of goats and 70.6% of sheep of the entire herd in the country, and the only region that recorded growth in both.

Several factors have been favorable to the growth of goat and sheep farming. However, aspects of animal husbandry, such as precarious sanitary conditions, inadequate management, low investment capacity on the part of breeders, and lack of specialized technical assistance, the indiscriminate use of medicines, among other factors, have hampered this growth. Gastrointestinal parasites in goats and sheep are a major problem faced in the breeding of these animals. The acute form of these infection can lead to the death of the infected animal, while the chronic form can lead to damages such as a decrease in productive performance and reproduction, weight loss, reduced immunity, and low body development in the infected animals.[22]

Considering the nematodes of greatest economic burden for the infection of small ruminants, the endoparasites with the highest prevalence and intensity of infection in Northeast Brazil are *Haemonchus contortus, Trichostrongylus colubriformis, Strongyloides papillosus,* and *Oesophagostomum colubianum*, with *Haemonchus contortus* causing the greatest economic loss in sheep farming worldwide[1-31].

The indiscriminate use of anthelmintics has been one of the main causes for the resistance of gastrointestinal endoparasites in small ruminants; besides, the drugs are easily available in the market. Some habits can cause or accelerate the occurrence of parasitic resistance. Among the predisposing factors, the following are noteworthy: treating the herd at short intervals, especially when they are shorter than the pre-patent period of the helminths; rotating different families of drugs at intervals of less than one year; making use of long-acting products frequently in a year (in this case, more than three times); getting animals infected with resistant parasites; and treating the entire herd, known as mass treatment, thus preventing the survival of parasites in refuge[32]. The search for alternative methods of parasite control is continuously pursued with the aim of make production systems more efficient and sustainable by reducing anthelmintic resistance and developing animal-derived products free of chemical substances.

The Famacha method is a selective treatment, as a control option, since the use of anthelmintic drugs is recommended only for animals exhibiting clinical anemia. The objective of this method is to clinically identify animals that are resilient or resistant and sensitive to infections caused by parasites. In addition to reducing the number of applications, it selectively optimizes treatment, generates savings in production, and prolongs the effectiveness of anthelmintic drugs[5-13].

The indiscriminate use of anthelmintic drugs has considerably increased the resistance of these parasites, bringing economic losses to the breeder and directly affecting the effectiveness of the drugs. Therefore, research is needed to assess this anthelmintic resistance and study the main drugs used for these animals. The results present choices for the most appropriate bases that can be used in each farm.

2. Material and methods

The study was conducted in the municipalities of São Luís and São José de Ribamar, which are part of the Metropolitan Region of São Luís Island, Maranhão, Brazil. This region is bounded in the north by the Atlantic Ocean, in the south by the bay of São José and the Mosquito Strait, in the east by São José Bay, and in the west by São Marcos Bay. All procedures were approved by the Committee on Ethics in the Use of Animals in Teaching and Research – CEUA, of the Federal Institute of Maranhão – IFMA, under number 001/2021.

Four farms located on São Luís Island were selected for this study. Questionnaires related to animal husbandry were distributed to the breeders. Two of the farms had predominantly goats; they also had some sheep and used a semi-extensive organic system. The other two farms focused on sheep farming, with one of them also having some goats, and used a semi-extensive farming system. On each farm, 30–40 goats or sheep were selected, aged between -1 and +4 years old, and were left without anthelmintic treatment for a minimum period of eight weeks. The selected animals were marked individually and randomly distributed into three to four groups of 10 animals: Group I: control, no treatment; Group II: treated with ivermectin administered orally at a dose of 200 mcg/kg; Group III: treated with levamisole administered orally at a dose of 7.5 mg/kg; and Group IV: albendazole administered orally at a dose of 3 mg/kg.

Stool samples were collected directly from the rectal ampoule one day before treatment and 10 days after treatment with the anthelmintic[15-19]. Individual coproparasitological examinations were conducted with these samples at the Animal Health Laboratory of the Federal Institute of Maranhão (IFMA), Campus São Luís-Maracanã, using the modified McMaster technique, as described by Ueno & Gonçalves[36], with the results given in number of eggs per gram of feces (EPG).

Stool cultures were performed by pooling fecal samples from the animals in each experimental group and mixing them using the Roberts & O'Sullivan technique[28]. A minimum of 100 third-stage larvae were identified in the cultures of each group, according to Georgi & Georgi[12]. The arithmetic mean of the number of eggs in the stool for each treated group (EPGt) was calculated and compared with the mean of the control group (EPGc). The results obtained were calculated according to the reduction in fecal egg count (RFEC) determined using the formula: RFEC = [1- (EPGt / EPGc)] ×100. The animals were also subjected to the Famacha method.

The data obtained were analyzed using the statistical program RESO (1989) which follows the instructions of the *World Association for the Advancement of Veterinary Parasitology* (WAAVP)[7]. The conditions for a farm to be classified as resistant were: the percentage reduction in egg count was <95%, and the lower limit of the 95% confidence interval was <90%. If both conditions were not met, resistance was suspected.

3. Results

3.1 Characterization of the herd

Two goat farms had animals younger and/or older than 12 months, with no defined breeding pattern. According to a questionnaire answered by the breeders, the animals in one farm received closantel sodium in July 2020 and those in the other farm received albendazole in December 2020. In the two sheep farms, samples were collected from animals with no defined breeding pattern and younger and/or older than 12 months. The animals in one farm received ivermectin in February 2021 and those in the other received moxidectin in December 2020.

On day 0, the EPG (Eggs Per Gram) results for farm 1 (goat) ranged from 50 to 13,950, with an average of 1,538.46; for farm 2 (goat), the counts ranged from 100 to 12,000, with an average of 790; for farm 3 (sheep), the counts ranged from 50 to 16,050, with an average of 2,830.26; and for farm 4 (sheep), the counts ranged from 50 to 2,850, with an average of 541.66.

3.2 Mean EPG and efficacy of anthelmintic drugs ivermectin, levamisole, and albendazole

In 100% of the herds, the animals were weighed for the correct administration of the dosage according to the medicine leaflet. Multiple anthelmintic resistance (MAR) was observed in the herd of all farms. In farm 1, the EPG values ranged from 100 to 2650 for the control group, with an average of 980. Based on the results of the egg count reduction test to evaluate the effectiveness of anthelmintic drugs, it was observed that ivermectin achieved 14.28% efficacy, albendazole achieved 59.8% efficacy, and levamisole was found to be ineffective. The genera *Haemonchus* (39%), *Trichostrongylus* (36%), and *Oesophagostomum* (25%) were identified in stool culture. In farm 2, the EPG values in the control group ranged from 100 to 1,050, with a mean of 475. The results of the EPG indicated that levamisole, ivermectin, and albendazole were all ineffective (Table 1). The genera *Haemonchus* (60%) and *Trichostrongylus* (40%) were identified in the stool culture. In farm 3, the control group's EPG values ranged from 0 to 12,500, with a mean value of 4,621.4. The results of the EPG showed that albendazole had a 3.43% efficacy, while ivermectin and levamisole were found to be ineffective. In stool culture, larvae of *Haemonchus* (71%), *Trichostrongylus* (28%), and *Oesophagostomum* (1%) were identified. In farm 4, the EPG values in the control group ranged from 50 to 3750, with a mean of 1215. The results of the EPG showed that levamisole and ivermectin had 79.4% and 13.6% efficacy, respectively (Table 2). There were not enough animals in farm 4 to form the albendazole group. In stool culture, the genera *Haemonchus* (6%) and *Trichostrongylus* (94%) were identified.

Table 1. Means of egg count per gram of feces (EPG) of gastrointestinal nematodes in feces of goats from São Luís Island and efficacy of anthelmintic drugs ivermectin, levamisole, and albendazole

Farm	**Group Control**	**Ivermectin**		**Levamisole**		**Albendazole**	
		EPG	Efficacy %	EPG	Efficacy %	EPG	Efficacy %
1	980	840	14.3	1042	0	393.8	59.8
2	475	925	0	705	0	885	0
Mean	727.5	882.5	7.1	873.5	0	639.4	29.9
Confidence interval limits at 95%		**Ivermectin**		**Levamisole**		**Albendazole**	
		Inferior	Higher	Inferior	Higher	Inferior	Higher
Farm 1		0	66	0	82	28	86
Farm 2		0	34	0	21	0	19

Table 2- Mean EPG of gastrointestinal nematodes in feces of sheep from São Luís Island and efficacy of anthelmintic drugs ivermectin, levamisole, and albendazole

Farm	**Group Control**	**Ivermectin**		**Levamisole**		**Albendazole**	
		EPG	Efficacy %	EPG	Efficacy %	EPG	Efficacy %
3	4621.4	7033.3	0	6100	0	4462.5	3.4
4	1215	1050	13.6	250	79.4	-	-
Mean	2918	4041.6	6.8	3175	39.7	2231.2	1.7
Confidence interval limits at 95%		**Ivermectin**		**Levamisole**		**Albendazole**	
		Inferior	Higher	Inferior	Higher	Inferior	Higher
Farm 3		0	45	0	85	0	77
Farm 4		0	80	48	97	-	-

3.3 Famacha Method

The results of the Famacha method indicated that out of a total of 70 sampled sheep: 1.43% (1) had color grade 1; 12.86% (9) had color grade 2; 57,14% (40) had color grade 3; 28.57% (20) had color grade 4; and 0% (0) had color grade 5. Among the 80 goats sampled, the results showed that: 1 goat (1.25%) had color grade 1; 25 goats (31.25%) had color grade 2; 22 goats (27.5%) had color grade 3; 23 goats (28.75%) had color grade 4, and 9 goats (11.25%) had color grade 5 (Figure 1).

3.4 Prevalence of nematode genera

In the stool cultures, the genus *Haemonchus* was the most prevalent on farms 1 (39%), 2 (60%), and 3 (71%), followed by the genera *Trichostrongylus* and *Oesophagostomum*. However, on farm 4, the most prevalent genus was *Trichostrongylus* (94%), followed by *Haemonchus* (6%), as shown in Figure 2.

4. Discussion

The results obtained showed MAR to ivermectin, levamisole, and albendazole in all farms of the study; all tested drugs showed efficacy below 95% and lower limit below 90%. Similarly, Castro et al.[8] studied goats in the municipality of Petrolina, *São Francisco Valley region, Northeastern Brazil and observed MAR to levamisole, albendazole, and ivermectin in 10 farms, with means lower than 80%.*

Silva et al.[32] studied sheep in the semi-arid region of Paraíba, in northeastern Brazil, and also observed

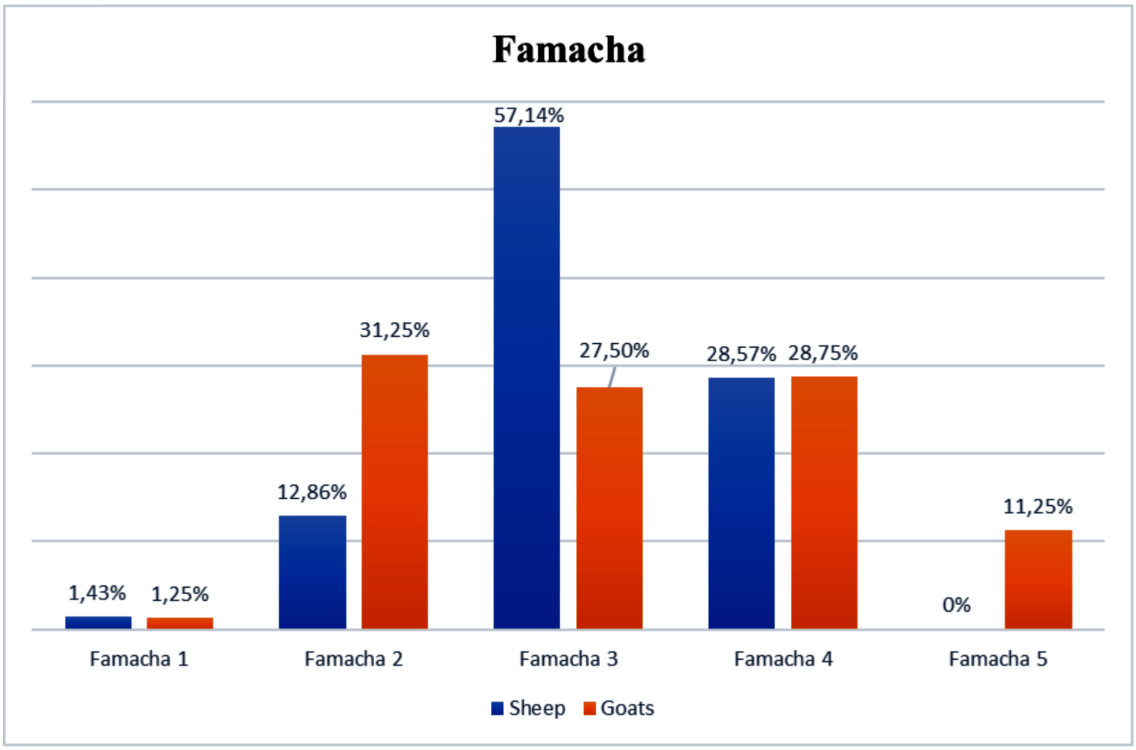

Figure 1. Percentage of the Famacha method in goats and sheep from farms in the metropolitan region of São Luís, Maranhão, Brazil.

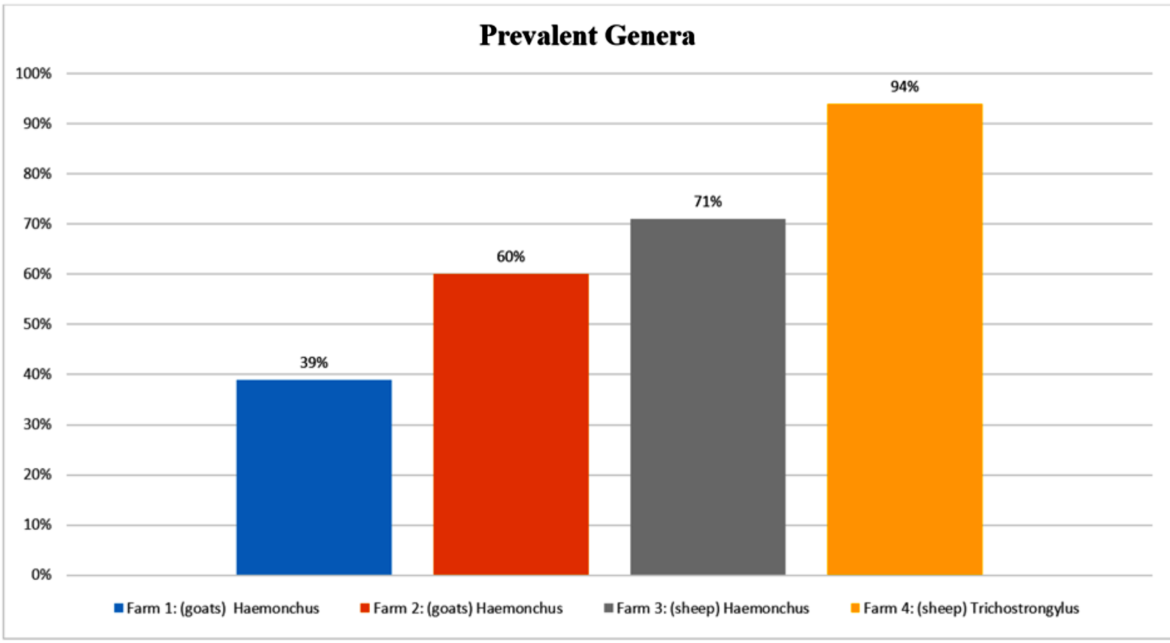

Figure 2. Identification of the most prevalent genera in the four farms (Farms 1 and 2: goats and Farms 3 and 4: sheep) in the metropolitan region of São Luís, state of Maranhão.

MAR in the studied farms, where approximately 85% of the farms showed resistance to the ivermectin group, 95% to albendazole, and 40% to levamisole. MAR was also diagnosed in the southeastern region in a study conducted by Veríssimo et al.[41] in São Paulo. Thirty sheep farms underwent a fecal egg count test, and after the use of anthelmintic drugs, widespread MAR was observed, with 100% of the farms having helminths resistant to albendazole, ivermectin, and levamisole, in addition to other administered drugs. In southern Brazil, Oliveira et al.[24], evaluated the efficacy of six commercially available drugs, abamectin, albendazole, closantel, levamisole, monepantel, and trichlorfon in 22 sheep herds and observed resistance to at least three anthelmintic drugs, abamectin, levamisole, and trichlorfon in all farms.

Borges et al.[4] conducted a study in the state of Bahia with 18 goat herds from the Caatinga biome and obtained efficacy results below 90% for the use of ivermectin, ranging from 0% to 75%, while levamisole and albendazole demonstrated efficiency with values ranging from 0% to 91% and 0% to 92%, respectively. This problem is spread across the country and has been constantly reported. According to Salgado and Santos[30], Brazil has stood out as one of the world leaders in publications on anthelmintic resistance, having several reports of cases in small ruminants in the Americas. Egg count reduction test per gram of feces and its correlation with management practices in the field has been studied from north to south of the country.

The MAR can be explained by the frequency with which deworming is performed, in addition to the usual practice of deworming all animals systematically and with different drugs. The use of long-acting products more than three times a year and the acquisition of animals already infected with resistant parasites, under or high dosage of medications, are factors that also contribute directly to anthelmintic resistance[23-27].

It is important to emphasize that anthelmintic drugs must be considered valuable resources and should be used strategically; their indiscriminate use, without any guidelines, may render them ineffective. The search for new anthelmintic molecules that may collaborate with the rotation of current drugs is an increasingly difficult process for the pharmaceutical industry[11]. Case reports of resistance to monepantel, which was launched in the global market in 2010, were reported three years after its launch in New Zealand[33], Uruguay[18], and Holland[37]. There are also reports from Brazil, where the drug was launched in 2012, including those from 18% of the sheep herds tested by Oliveira et al.[24].

One attempt at containing the advancement of anthelmintic resistance is the adoption of selective treatments by breeders, where only part of the herd is treated, since the highest parasitic loads are generally present in a small number of animals. Coproparasitological exams can be performed to identify parasitized animals with high EPG (>500–1000 EPG) for treatment. Additionally, the Famacha method can be used to identify animals with anemia caused due to parasite infection. This method involves observing the ocular mucosa and using a card to determine the degree of anemia, indicating which animals require treatment[9, 26-27].

In this study, there was a prevalence of the genus *Haemonchus* in three of the four farms, where drugs from three different chemical groups albendazole, ivermectin, and lavamisol were used. Two farms bred goats and one bred sheep. However, the second sheep farm showed a prevalence of the genus *Trichostrongylus,* with the use of ivermectin and levamisole, since the number of animals was not enough to create an albendazole group. This distinct result can be explained by the fact that different nematode species are more prone to the development of resistance to a certain class of anthelmintic drugs. In a study conducted by Mickiewicz et al.[20] on drug resistance in gastrointestinal nematodes in the goat population in Poland, they found that *T. colubriformis* was the most persistent gastrointestinal nematode after treatment with levamisole. Levamisole is one of the anthelmintic drugs used on the farm that was studied.

The Famacha method can be used to identify animals that are resilient or resistant and sensitive to infections caused by these parasites. This helps to reduce the number of unnecessary dewormings and optimize treatment selectively, leading to cost savings in breeding and prolonging the effectiveness of anthelmintic drugs, without compromising the productivity of the animals[13]. Fernandes et al.[10] evaluated the productivity and carcass traits of non-weaned Suffolk lambs subjected to three endoparasite control strategies: prophylactic treatment of all animals every 28 days, treatment of animals with EPG ≥700, and treatment of animals with Famacha ≥3. They found that the parasite control strategies did not affect the productivity of lambs on pasture or their carcass traits. The researchers concluded that selective treatments could be considered advantageous due to the decrease in selection pressure on populations of resistant parasites and the less use of drugs.

Molento et al.[21] in a study conducted with Ile de France and Texel sheep, compared two methods of parasitic control, the suppressive and the partial selective based on the Famacha evaluations. They noted that the Famacha method allowed a large amount of sheep that were naturally infected to be treated sparingly with anthelmintic drugs without any negative effect on their reproductive indices. The species *H. contortus, T. colubriformis, S. papillosus, and O. colubianum* are the endoparasites with the highest prevalence and intensity of infection and are the most important nematodes for the economy and for the exploitation of small ruminants, with *H. contortus* being the one that causes greater economic damage than the others[1], which was also found in the central region of the south of the state of Maranhão[6].

The Famacha method is one of the most indicated treatments for herds infected with *H. contortus*[3]. The method is relatively less cost, requiring only the card with five different colors to which the ocular mucosa of the animals will be compared[2 - 38]. As a result of this method, there is a reduction in the use of anthelmintic drugs, which conserves the refuge population. These parasites are not exposed to anthelmintic treatment, which helps maintain genes that are susceptible to vermifuge[39]. The Famacha method was initially developed for use in sheep but was later adjusted for goats, which have different characteristics compared to that of sheep. For goats classified as color grade 3, administration of medicine is recommended. The same applies to color grades 4 and 5. While it has been proven to be effective for diagnosing anemia caused by *H contortus*, success with this method is only guaranteed with a proper understanding of its use. Appropriate training is essential for the correct application of the methodology[40 , 16, 17-35].

Other treatments such as the use of medicinal plants as an economical alternative for the control and treatment of gastrointestinal parasites have been studied. Some plants have demonstrated anthelmintic potential in small ruminants, regardless of the preparation process. They have the ability to inhibit parasites at some stage of their life cycle[23]. Another alternative to combat anthelmintic resistance is the breeding of animals resistant to the parasites, a sustainable alternative within a parasite control program[29].

5. Conclusion

Gastrointestinal nematodes of sheep and goats from rural farms located on the island of São Luís, Maranhão, showed resistance to all tested drugs, ivermectin, levamisole, and albendazole, with *Haemonchus and Trichostrongylus* being the most prevalent genera in these herds. Strategies should be implemented in the region to address the issue of multiresistant nematodes. These strategies should focus on reducing the use of chemical products and rely on alternatives, such as the Famacha method. The Famacha method involves identifying animals that are resilient or resistant to infections caused by these parasites, which can reduce the number of deworming treatments needed and selectively optimize the treatment, leading to reduction in the cost of production and prolonging the effectiveness of anthelmintic drugs without compromising animal productivity.

Conflict of interest statement

The authors declare no conflict of interest.

Author contributions

Conceptualization: D.R.B. Brito and L.M. Costa Júnior. *Data curation*: S.C.P. Soares. *Formal Analysis*: S.C.P. Soares. *Funding acquisition*: D.R.B Brito and L.M. Costa Júnior. *Investigation*: S.C.P. Soares., A.C. Reis., R.L.P. Castro., P.C.S. Pires Filho., C.S.M. Cabral., D.O. Diniz Júnior., C.B. Costa., D.M.C. Pinheiro., Y.S.A. Pinheiro and N.H.S. Buna. *Methodology*: A.C. Reis and D.R.B. Brito. *Project administration*: S.C.P. Soares and D.R.B. Brito. *Supervision*: D.R.B. Brito. *Visualization*: S.C.P. Soares. *Validation*: S.C.P. Soares., A.C. Reis., R.L.P. Castro., P.C.S. Pires Filho., C.S.M. Cabral., D.O. Diniz Júnior., C.B. Costa., D.M.C. Pinheiro., Y.S.A. Pinheiro and N.H.S. Buna. *Writing (original draft, review & editing)*: S.C.P. Soares and D.R.B. Brito.

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