MULTIDRUG RESISTANCE OF SHEEP GASTROINTESTINAL NEMATODES IN BAKRAJO DISTRICT, NORTH IRAQ TO ALBENDAZOLE, IVERMECTIN, AND LEVAMISOLE

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ABSTRACT

A survey including 25 sheep farms in Bakrajo District, Sulaymaniyah, Iraq, was conducted to determine anthelmintic resistance (AR) against albendazole, ivermectin, and levamisole. Fecal Egg Count Reduction Test (FECRT) was used to accomplish this goal. Forty 6–24 month-old sheep of mixed sexes were selected from each farm and randomly divided into four groups. One group served as the untreated control, and the other groups orally administered the recommended doses of the tested drugs. Multidrug resistance against all three drugs was present in 8 of 25 farms (32%). Also, resistance to albendazole and ivermectin was detected on one farm. Albendazole was the most effective anthelmintic agent. Resistance to ivermectin was significantly higher than levamisole and albendazole. Larval cultures revealed that *Trichostrongylus* spp., *Nematodirus* spp., and *Trichuris* spp. were the prevalent gastrointestinal nematodes in the study area. The nematode genera were also detected in the posttreatment larval cultures. It is concluded that AR to albendazole, ivermectin, and levamisole is widespread in sheep in Bakrajo District, north Iraq. This resistance is mainly caused by the emergence of resistant *Trichostrongylus* and *Nematodirus* spp.

Keywords: Albendazole, anthelmintic resistance, gastrointestinal nematodes, ivermectin, levamisole, *Trichostrongylus*

المقاومة المتعددة للديدان الخيطية المعوية في الاغنام في منطقة بكرجو، شمال العراق ضد ألبيندازول، إيفرمكتين وليفاميزول

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المستخلص

تم إجراء مسح شمل 25 مزرعة أغنام في منطقة بكرجو، السليمانية، العراق، لتحديد مقاومة الديدان الخيطية المعوية ضد ألبيندازول، إيفرمكتين وليفاميزول. تم استخدام اختبار تقليل عدد البويضات في البراز (FECRT) لتحقيق هذا الهدف. تم اختيار أربعين من الأغنام بعمر 6–24 شهرًا من الجنسين من كل مزرعة وقسمت عشوائياً إلى أربع مجموعات. عملت إحدى المجموعات كمجموعة تحكم غير معالجة، بينما أعطيت المجموعات الأخرى الجرعات الموصى بها من الأدوية المختبرة عن طريق الفم. كانت المقاومة ضد الأدوية الثلاثة موجودة في 8 مزارع من أصل 25 (32٪). كما تم الكشف عن وجود المقاومة ضد ألبيندازول وإيفرمكتين في مزرعة واحدة. كان ألبيندازول أكثر الادوية المضادة للديدان فعالية، و كانت مقاومة الإيفرمكتين أعلى من الليفاميزول والألبيندازول. أظهرت نتيجة زرع اليرقات أن أنواع *Trichostrongylus* spp و *Nematodirus* spp و *Trichuris* spp كانت الديدان الخيطية المعوية السائدة في منطقة الدراسة. كما تم الكشف عن أجناس الديدان الخيطية في مزارع اليرقات بعد المعالجة. استنتج أن المقاومة ضد ألبيندازول وإيفرمكتين وليفاميزول منتشر في الأغنام في منطقة بكرجو، شمال العراق. هذه المقاومة ناتجة بشكل رئيسي عن ظهورانواع من *Trichostrongylus* و*Nematodirus* المقاومة.

الكلمات الدالة: ألبيندازول، مقاومة الديدان، الديدان الخيطية المعوية، إيفرمكتين، ليفاميزول، *Trichostrongylus*.

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INTRODUCTION

Infection with gastrointestinal nematodes (GIN) is a common worldwide problem in pasturing sheep that directly and indirectly affects infected animals' health and production. Generally, infection with GIN causes lower feed consumption, tissue damage and decreased organ functions, diversion of energy from production towards defense and immunity, and death of severely infected sheep. The cost of anthelmintic therapies and reduced productivity indirectly impact livestock productivity (12, 14, 17). Anthelmintic therapy is the most common GIN control method because it is easy to carry out, and results can be seen within a short time. Different classes of anthelmintics are used internationally to treat nematode infections such as the macrocyclic lactones (e.g., ivermectin and moxidectin), benzimidazoles (e.g., thiabendazole and albendazole), imidazothiazoles (e.g., tetramisole and levamisole), spiroindoles (e.g., derquantel), and amino-acetonitrile derivatives (e.g., monepantel). However, the most common classes used are benzimidazoles, imidazothiazoles, and macrocyclic lactones (6). Dewormers are effective broad-spectrum drugs with a broad safety margin. However, anthelmintic therapy encounters the problem of anthelmintic resistance (AR) development. AR occurs when the therapeutic dose fails to expel all helminths from a treated animal (19). It is mainly caused by the extensive use of drugs to terminate GIN infections. Continuous use of the same anthelmintic drug, or drugs with the same mechanism of action, poses a selective pressure, favoring the development of resistant parasites. Helminths which are carriers of drug resistance genes survive the anthelmintic therapy and, in the absence of competition from drug-susceptible helminths, flourish in the previously occupied niches by susceptible helminths (10). The development of AR is a continuously rising problem for livestock production. The occurrence of AR continues to be reported from different parts of the world. Lately, many reports of AR are emerging from the top sheep-producing countries such as China (20), Australia (15), India (1), Iran (7), and United Kingdom (9). Kurdistan Region of Iraq is home to about 3.4 million sheep and goats, mainly raised by grazing free pasture. Little is known about the most common nematode species affecting small ruminants and AR in this area. Hence, this study was conducted to discover the common species of nematodes affecting sheep in the region. We aimed to determine the extent of resistance development against albendazole, ivermectin, and levamisole, the most commonly used anthelmintics in the Kurdistan Region.

MATERIALS AND METHODS

Study area and selection of sheep farms

This study was conducted in the Bakrajo District, which lies 15 km southwest of Sulaymaniyah, northeast Iraq (Figure 1). The district comprises 65 villages, and the sheep population stands at around 60,000 heads. The majority of the sheep are of the Karadi breed. The sheep are kept in different size flocks, reared by grazing on free pasture for most of the year. Water springs and streams are used as the source of drinking water for livestock, and pasture is shared among different sheep flocks. The farmers do not follow enough quarantine measures; sheep from different villages and herds might be mixed and graze in the same area. Most of the farmers treat their livestock with anthelmintics once or twice a year, in Spring and Fall. The most commonly used dewormers in the region are albendazole, ivermectin, and levamisole. Farmers in Bakrajo District were asked to answer a questionnaire about the breed, age, the number of sheep, time of the last anthelmintic treatment, and type of dewormer used in the therapy. The first part of the sample collection was between March and June 2019, while the second part was in March 2020. Climatic conditions such as temperature, rainfalls, and humidness are appropriate for the survival of nematode larvae in the months from mid-February to May. Hence, the rate of GIN infection increases from March to June in the study area. Farms that included less than 40 sheep between 6 and 24 months of age were not included. Also, farms that have been treated with an anthelmintic drug in the past three months were excluded. The Animal Care and Use Committee (ACUC) at the College of Veterinary Medicine, University of Sulaimani, approved the study protocol.

Anthelmintic treatment and sample collection

The total number of sheep included in this study was 1,000, which belonged to 25 farms. Forty sheep of mixed sexes, and 6–24 months old, were selected from each flock. The sheep were randomly divided into four groups of ten and appropriately numbered. One of the groups was used as the untreated control and administered distilled water. The other groups were treated with 0.2 mg/kg ivermectin (Intermectin Drench), 5.0 mg/kg albendazole (Albenol-100), and 10.0 mg/kg levamisole (Leva-200), respectively. All anthelmintics were manufactured by Interchemie (Venray, Holland). Treatment was through the oral route via a drenching gun. About 5–10 grams of fecal samples were collected twice from each sheep. The first fecal collection was just before administering the anthelmintic agent, while the second sample was taken two weeks after treatment. Fecal samples were taken directly from the rectum and put in separate containers labeled according to the farm number and treatment group. The containers were transported to the laboratory in an icebox, taking less than four hours. The samples were stored in a refrigerator at 4 °C in the laboratory and were tested for nematode eggs no later than three days after delivery.

Fecal egg count reduction test

The Fecal Egg Count Reduction Test (FECRT) is the most frequently advocated anthelmintic resistance detection method *in vivo*. This technique can be implemented to detect resistance with all groups of vermifuges (11). FECRT measures a drug's efficacy by comparing the posttreatment Fecal Egg Count (FEC) to the pretreatment count. The FECRT was conducted following a procedure previously described by Coles and coworkers (4), and the pretreatment and posttreatment FECs were determined using a McMaster technique. In this technique, the total number of nematode eggs is calculated by multiplying the number of observed eggs under a microscope by 50. Hence, the minimal detectable concentration of nematode eggs in this technique is 50 eggs per gram (EPG) of feces.

Calculation of the Fecal Egg Count Reduction (FECR) was conducted using the formula:

$$\boldsymbol{ECR = 100 \times \left(1 - \frac{mean\ FEC\ in\ the\ treatment\ group\ 14\ days\ posttreatment}{mean\ FEC\ in\ the\ control\ group\ 14\ days\ posttreatment}\right).}$$

The confidence interval (95%) was calculated as FECR $\pm\ 1.96\sqrt{variance}$. Flocks were considered sensitive to a particular anthelmintic if the FECR ≥ 95% and the lower CI was ≥ 90%. A flock was considered suspected of resistance development if only one criterion were met. In contrast, if the FECR and lower CI were < 95% and 90%, the flock was considered resistant (8).The FECR of the three anthelmintics were compared statistically to determine the drug against which resistance was highest. The average FECR values for each drug in the resistant farms were calculated and compared using a one-way analysis of variance (ANOVA), followed by Duncan's post hoc test. Probability values < 0.05 were considered statistically significant.

Identification of resistant gastrointestinal nematode genera

The posttreatment fecal samples collected from flocks that scored an FECR < 95.0% were cultured for larval development. This procedure was done to determine the resistant GIN that survived the anthelmintic therapy. About two grams of fecal pellets from each sheep were taken, and samples from the same treatment group were pooled together and put in a glass jar. The fecal pellets were moistened by mixing with distilled water, and the jar was incubated at 25 ± 2 °C for one week. The third-stage larvae (L_3s) were isolated and stained with Lugol's iodine, using the procedure previously described by Coles *et al*. (3). The harvested larvae were examined under 100 × magnification, and the genera of the first 100 detected larvae were morphologically determined using reference keys (18). The genera of GIN that showed resistance to a particular anthelmintic drug were identified in farms where the drug failed to reduce the FEC by 95%. The rate of reduction of each nematode genus was calculated using the formula

$100 \times$ E***rr***or! Bookmark not defined., where pre- indicates samples taken before treatment and post- indicates samples taken two weeks after anthelmintic therapy.

RESULTS AND DISCUSSION

Study area and selection of sheep farms

Anthelmintics are commonly used by sheep farms in the north of Iraq to reduce soil-transmitted nematodes' burden in small ruminants. This study was conducted in the Bakrajo District of Sulaymaniyah Governorate in the northeast of Iraq. The area is located 35.28°N–35.38°N and 45.13°E–45.29°E. Thirty-seven villages in Bakrajo contained one or more sheep flocks at the time of this study, and 122 flocks contained more than 50 sheep between 6 and 24 months. However, only 25 farms fulfilled the selection criteria and were included in this study. The other farms were excluded because they were recently treated with one or more anthelmintics. The total number of sheep in the included farms was about 6,950, making about 11.6% of the region's total sheep population. Flocks' sizes ranged between 135 and 626 heads, averaging 278.0 ± 31.1 (SEM) sheep per farm.

Fecal egg count in the untreated control and pretreatment samples

FECs are used to assess the worm burden in animals and decide on anthelmintics in grazing livestock. A fecal egg density in a well-mixed pooled sample from 10 sheep will provide an adequately accurate FEC representing the extent of GIN infection on a farm. It was suggested that the minimum FEC in a composite of 10 samples that demand the use of anthelmintics would be 500 EPG. However, if samples were examined individually, an average FEC of 200–300 EPG would be sufficient to decide anthelmintics' strategic use (13). In our study, fecal samples from each animal were examined individually, and the mean pretreatment FECs in all groups exceeded 520 EPG. This result indicates that our data were sufficiently accurate to support the conclusions of this study. Before the study, animal groups' homogenous distribution of animal groups is necessary to ensure that the collected data represent a more significant population and avoid bias. The pretreatment FECs of the control and treatment groups were compared statistically to ensure samples' homogeneity before treatment. The results indicated no statistical differences in the mean FECs between the groups, and sheep were equally distributed. The FEC of the control group was measured before treatment and after two weeks of the first sampling. The average pretreatment FEC was 535.0 EPG, while the posttreatment count was 527.4 EPG, which scored a decrease of 1.4%. However, no statistical difference was seen between the groups ($p > 0.05$). The pretreatment FECs of the control and treated groups are illustrated in Figure 1.

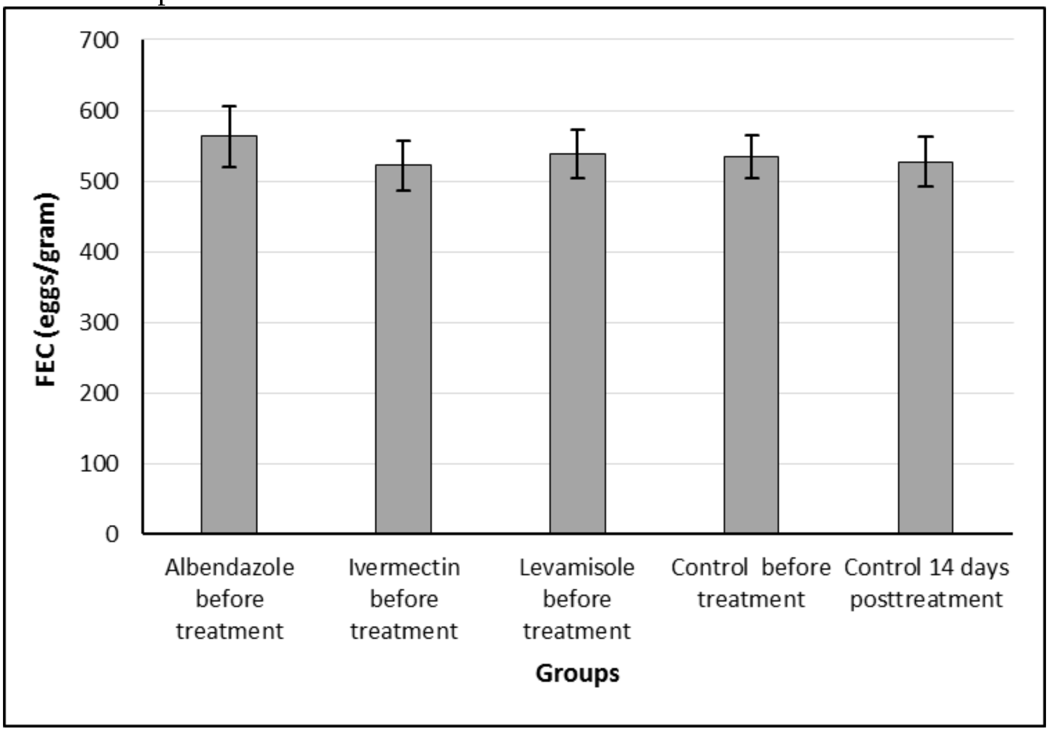

Figure 1. Fecal Egg Count (FEC) of the control and pretreatment samples. Columns represent the mean FEC of 25 farms, and error bars indicate standard errors of means. No statistical differences were observed between the groups (p > 0.05).

Fecal egg count reduction test

The FECR results revealed that GIN resistance against albendazole, ivermectin, and levamisole was present in the studied region. Both albendazole and ivermectin failed to clear sheep from GIN in 36.0% of the examined flocks, while resistance to levamisole was evident in 32.0% of the sheep farms (Table 1). The ivermectin's FECR values were ≤ 60.0% in eight of the 25 farms, which indicated that AR against this drug is widespread. Nine farms showed multidrug resistance against albendazole and ivermectin, and eight farms showed resistance development against all tested dewormers. The results of FECR indicated that multidrug resistance was present in more than one-third of the examined farms. Farmers often use shared pasture and water springs, facilitating the spread of resistant nematodes between different sheep flocks. Although less common, the simultaneous use of two or more anthelmintics at dosage rates below recommendations might lead to the survival of resistant nematodes and the emergence of multidrug-resistant species (16). The tested drugs' efficacies in the resistant farms were compared statistically to determine the most and least effective anthelmintics. The results revealed that ivermectin was the least efficacious drug as the mean FECR of this drug in the resistant farms was 58.7%, while albendazole was the most efficacious (Figure 2). A comparison of the tested drugs' efficacies indicated that the least effective anthelmintic was ivermectin, an endectocide used to treat nematode infections and external arthropod parasites infestations of livestock. Ivermectin is used more frequently than other anthelmintic drugs in the north of Iraq due to its dual purpose, which accelerates AR development. Albendazole was the most effective anthelmintic to treat GIN in the study area. It is a benzimidazole developed in the 1960s to treat nematode, cestode, and trematode infections in domestic animals (6). However, compared to ivermectin, albendazole was less frequently used by farmers in the area, which may justify this drug's higher efficacy against GINs.

Table 1. Fecal Egg Count Reduction of albendazole, ivermectin, and levamisole in sheep in Bakrajo District

Farm	95% confidence interval (mean FECR ± $1.96\sqrt{variance}$)		
	Albendazole	Ivermectin	Levamisole
1	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
2	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
3	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
4	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
5	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
6	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
7	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
8	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
9	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
10	86.0 ± 7.1	48.6 ± 4.6	82.7 ± 7.7
11	89.4 ± 6.3	48.9 ± 5.3	73.6 ± 6.6
12	83.7 ± 6.7	52.3 ± 5.3	66.3 ± 4.1
13	75.7 ± 4.4	61.7 ± 7.3	67.4 ± 5.1
14	82.6 ± 6.3	92.6 ± 8.2	99.5 ± 2.2
15	78.8 ± 6.2	56.6 ± 8.8	71.0 ± 5.0
16	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
17	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
18	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
19	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
20	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
21	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
22	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
23	73.8 ± 5.1	50.5 ± 6.7	64.6 ± 5.2
24	85.4 ± 6.1	57.1 ± 7.1	66.5 ± 3.9
25	83.6 ± 6.3	60.0 ± 8.6	75.2 ± 7.4

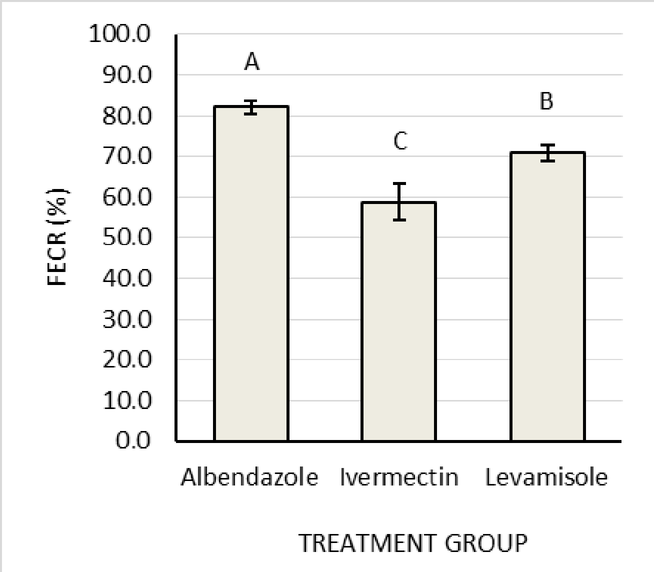

Figure 2. Mean FECR of albendazole, ivermectin, and levamisole in the farms where FECR was < 95.0%. Values represent the mean FECR (columns) ± SEM (error bars). Different letters denote significant differences between groups ($p < 0.05$).

Gastrointestinal nematodes in control and treated animals

Larval cultures provide information about the common nematodes that parasitize animals and discover the genera responsible for resistance development in an area (2). Our results indicated that the common nematodes in the pretreatment fecal samples were *Trichostrongylus* spp., *Nematodirus* spp., and *Trichuris* spp. This study is considered the first large-scale investigation about GINs in sheep in Bakrajo. In a previous study, the prevalent GINs in the nearby subdistrict Piramagroon were *Nematodirus* spp., *Trichostrongylus* spp., *Trichuris* spp., and *Marshallagia* spp. (5). However, samples collected in the previous study were from sheep farms that suffered from severe GIN infections, and the owners voluntarily participated by reporting to the public veterinary services in the area. Samples collected in the current study were from a broader area and included many sheep farms. Moreover, the GIN infection rate of sheep flocks in this study was less extensive, making the data more representative of the north of Iraq's nematode infection status. Fecal samples of the control groups of 25 farms were cultured, and the hatched third-stage larvae of GINs were identified to the genus level. This procedure was conducted to determine the GINs affecting sheep in Bakrajo District. The results revealed that *Trichostrongylus* spp., *Nematodirus* spp., and *Trichuris* spp. were the prevalent helminths affecting small ruminants in the study area. *Trichostrongylus* spp. were the most commonly identified L3s in the untreated groups, as they made about 88.8 ± 1.6% of the detected larvae in 25 farms. *Nematodirus* and *Trichuris* spp. made 8.6 ± 1.0% and 2.6 ± 0.8% of the L3s, respectively (Figure 3A). The posttreatment samples revealed that *Trichostrongylus* mainly caused resistance. This resistance was mostly against albendazole and levamisole. Resistance development by *Nematodirus* was more pronounced against levamisole than the other drugs. Although resistant *Trichuris* spp. were also detected in the posttreatment samples, this genus' impact on the overall FEC was less compared to the other genera. Future research may help determine the relationship between the type of anthelmintic agent used and the nematode's genus that develops resistance faster. The percentage of *Trichostrongylus* in the first 100 larvae of the posttreatment fecal samples of nine albendazole-treated groups was 88.8 ± 2.8%, while *Nematodirus* and *Trichuris* made 6.7 ± 1.7% and 4.5 ± 1.9% of the L3s, respectively (Figure 3B). Nine of the ivermectin-treated groups remained to shed nematode eggs after 14 days of treatment. In the posttreatment samples, 91.9 ± 2.9% of the L3s were *Trichotrongylus,* and 3.1 ± 0.7% were *Nematodirus*. *Trichuris* spp. accounted for 4.6 ± 2.5% of the larvae (Figure 3C).

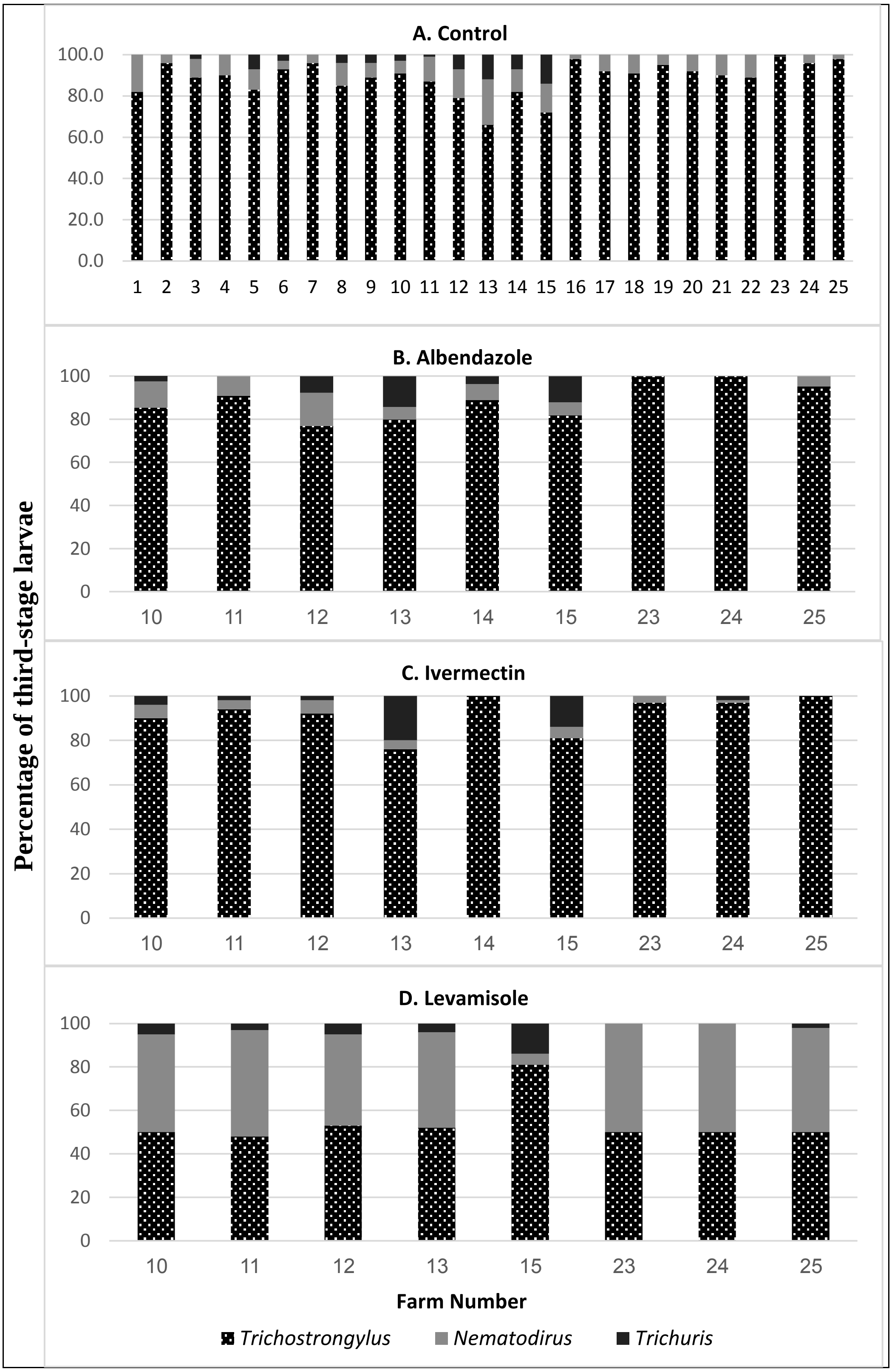

Figure 3. Percentage of third-stage larvae in the first 100 larvae isolated from a pooled posttreatment fecal sample of the control and treated groups

The percentage of reductions for the specific genera are depicted in Table 2. Resistance to albendazole and ivermectin was reported in nine farms. Also, levamisole resistance was evident in eight farms of the study. *Nematodirus* spp. resistance to albendazole was present in 28.0% of the studied flocks. The resistance of *Nematodirus* to ivermectin and levamisole was reported in 28.0% and 32.0% of the studied flocks. About 36.0% of the farms showed resistance of *Trichostrongylus* spp. to both albendazole and ivermectin. Also, eight of the 25 flocks showed *Trichostrongylus* resistance to levamisole. The resistance of *Trichuris* spp. against the studied drugs was evident in this study, as 20.0% of the sheep flocks were still infected with these nematodes after therapy with albendazole and ivermectin. Furthermore, 24.0% of the flocks were infected with *Trichuris* spp. after two weeks of treatment with levamisole. These results imply that multiple species of nematodes cause the occurrence of AR in Bakrajo, but *Trichostrongylus* was the most resistant genus to the administered drugs in the study area.

Table 2. Percentage of reduction of *Nematodirus* spp., *Trichostrongylus* spp., and *Trichuris* spp. after treatment with albendazole, ivermectin, and levamisole in sheep farms in Bakrajo

Farm	Albendazole				Ivermectin				Levamisole			
	FECR	Percentage reduction in			FECR	Percentage reduction in			FECR	Percentage reduction in		
		Nemat.	*Trichos.*	*Trichu.*		*Nemat.*	*Trichos.*	*Trichu.*		*Nemat.*	*Trichos.*	*Trichu.*
10	86.0	84.8	71.8	96.7	48.6	84.0	27.1	83.9	82.7	66.3	75.2	88.2
11	89.4	89.5	82.3	100.0	48.9	88.0	37.1	85.7	73.6	61.5	71.9	90.0
12	83.7	85.2	77.5	81.8	52.3	82.4	44.3	75.0	66.3	61.1	65.1	82.6
13	75.7	87.5	68.5	84.8	61.7	86.7	55.4	61.5	67.4	55.4	64.5	83.3
14	82.6	85.7	75.0	95.2	92.6	100.0	90.6	100.0	99.5	n/d	n/d	n/d
15	78.8	90.5	71.0	82.6	56.6	85.0	40.7	71.0	71.0	95.8	55.3	25.0
23	73.8	100.0	73.1	n/a	50.5	33.3	49.3	n/a	64.6	60.1	63.3	100.0
24	85.4	100.0	82.4	n/a	57.1	50.0	52.2	n/a	66.5	63.0	66.2	100.0
25	83.6	50.0	81.1	n/a	60.0	n/a	54.4	n/a	75.2	70.6	70.5	66.7

Only farms that scored FECR percentages of ≥ 95% were included. *Nemat.* = *Nematodirus* spp., *Trichos.* = *Trichostrongylus* spp., *Trichu.* = *Trichuris* spp., n/a = not available because the pretreatment FEC did not reach 50 EPG. n/d = not determined because the posttreatment FEC did not reach 50 EPG

The results of this study provide information about the extent of resistance development, the GINs that parasitize small ruminants, and the genera that have developed resistance against the common anthelmintic drugs in the north of Iraq. These data would furnish the ground to design and commence a suitable control plan to tackle AR in the region and reduce the economic losses caused by GINs and anthelmintic compounds.

CONCLUSION

Infection with GINs is a significant problem of small ruminant management in Bakrajo District, Sulaymaniyah, Iraq. Multidrug resistance against albendazole, ivermectin, and levamisole was present in many sheep flocks. Resistance to ivermectin was significantly higher than the other drugs, while the lowest resistance development rate was against albendazole. Pretreatment larval development revealed that the prevalent genera of nematodes in the study area were *Trichostrongylus*, *Nematodirus*, and *Trichuris* spp. Moreover, posttreatment larval cultures revealed that the AR was mainly due to the emergence of multidrug-resistant *Trichostrongylus* spp. However, resistant *Nematodirus* and *Trichuris* spp. were also present in the larval cultures after two anthelmintic therapy weeks. This study revealed that a control strategy of nematode infections in small ruminants is necessary to reduce the currently available anthelmintic agents' extensive use. Farmers should avoid complete dependence on anthelmintic therapy. They must be urged to implement other helminth control methods, such as following stricter quarantine measures, using pasture on other seasons, and using other anthelmintics that act via mechanisms of action different from the currently available compounds.

Conflict of interest

The authors declare no conflict of interest

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