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Testing for Albendazole Resistance in Rural Southern Kyrgyzstan

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Abstract

Background

The Kyrgyz people are traditionally pastoral nomads. After the collapse of the Soviet Union, infrastructure to remote pastures fell into disrepair resulting in overgrazing of pastures closer to villages and higher parasite burdens. Most farmers are reliant on Albendazole; a group 1, broad spectrum anthelmintic. However, resistance to Albendazole has been widely documented in other countries.

Objective

To determine whether resistance to Albendazole is present in Southern Kyrgyzstan. Method

From January to AprilMay 2018, households with sheep in the Osh oblast were interviewed about husbandry practices, anthelmintic dosing strategy and pasture management. Fresh faecal samples were collected and gastrointestinal nematodes and Fasciola hepatica eggs were counted using the McMaster's technique. If faecal egg count was >300 nematode eggs per gram or >100 *F. hepatica* eggs per gram, the sheep were treated with Albendazole in accordance with the datasheet. The gastrointestinal nematode and *F. hepatica* faecal egg counts were repeated with fresh faecal samples 2 and 3 weeks respectively after the initial test. If there was <95% reduction in the faecal egg count, the sheep were retreated with either oral Ivermectin for gastrointestinal nematodes or Oxyclozanide for F. hepatica. Following retreatment, a third faecal sample was collected and eggs counted using the McMasters technique 2 or 3 weeks later respectively.

Results

Of the 43 households tested, 1 had <95% reduction in gastrointestinal nematode eggs and 4 had <95% reduction in *F. hepatica* eggs. Retreatment with Ivermectin and Oxyclozanide respectively resulted in zero eggs per gram of faeces.

Conclusion

This study provides evidence of Albendazole resistance in Southern Kyrgyzstan. Programs designed to increase awareness of anthelmintic resistance, provide training in good parasite management to farmers and resource veterinarians with parasite laboratories would be a valuable contribution to improving animal health and productivity. In addition, importing a wider range of veterinary medicines so households where anthelmintic resistance is already present have alternative drug choices is essential.

Keywords Kyrgyzstan; Ovine; Ruminant; Livestock; Albendazole; Benzimidazoles; Resistance; Anthelmintic resistance

Introduction

The Kyrgyz people are traditionally pastoral nomads [1]. Since the dissolution of the Soviet Union, there have been significant changes in animal husbandry. Physical and social infrastructure to remote summer pastures has fallen into disrepair resulting in remote pastures becoming under-grazed whilst those closer to villages and towns are overgrazed [2]. Despite an initial reduction in livestock numbers in the first few years of independence, since 1996, the number of cattle has steadily increase due to their cultural importance. However, the number of sheep and goats has remained constant. In addition, there has been a shift in public to private ownership with smallholders predominating [2]. Under the former Soviet Union, skills were highly specialised and retained within the collective and state farms. Therefore, the disintegration of these systems has left a knowledge gap in veterinary services, pasture management and animal husbandry [2].

In 2017, agriculture contributed 12% of GDP in Kyrgyzstan [3] and was responsible for employing 26% of the national workforce [4]. Economic growth in Kyrgyzstan has increased food purchasing power resulting in an increased consumption of meat and dairy products [2]. Consumption of livestock products in neighbouring China is also increasing [5] and the One Belt, One Road initiative [6] should make future sales into neighbouring countries more accessible for Kyrgyz farmers. Poor production and a lack of veterinary public health

services make capitalising on these opportunities difficult. Therefore, the Kyrgyz government strategic development plan for 2013-2017 highlights the need for improved productivity and veterinary services [7].

Intestinal parasites are ubiquitous and impact on growth rates, milk production and fleece quality [8-10]. Internal parasites are considering a major constraint to improved productivity in Kyrgyz livestock [2]. Reduced access to pasture makes rotational grazing difficult, dosing guns and faecal egg counting (FEC) services are unavailable in most regions, animal weights are usually estimated and knowledge of resistance and availability of veterinary medicines are limited.

Group 1 anthelmintics are a broad spectrum drug effective against gastrointestinal nematodes and adult Fasciola hepatica. However, widespread usage in the UK, New Zealand and the USA has led to resistance, decline in usage and replacement with alternative anthelmintics [11-15]. Development of new anthelmintics can be slow; with a 20 year gap between group 3 and group 4 reaching the market [16]. Therefore, preserving the efficacy of anthelmintics through FEC monitoring, pasture management, appropriate dosing and breeding programs is essential.

Despite the importance of agriculture and reliance on Albendazole, a group 1 anthelmintic, in Kyrgyzstan, little is known about the presence or prevalence of anthelmintic resistance in Kyrgyzstan. The objective of this study was to determine the level of awareness regarding anthelmintic resistance and whether it is already developing in Kyrgyzstan.

Material and Methods

From January to May 2018, households with sheep in two villages, Kenesh and Gulbar, in southern Kyrgyzstan were interviewed about husbandry practises and fresh faecal samples from the sheep were collected and tested for gastrointestinal helminths and Fasciola hepatica.

Semi-structured questionnaires in Kyrgyz language were used to elicit information about who the primary decision maker was with regards to animal health, the involvement of local veterinarians, the timing of anthelmintic treatments, anthelmintics used, and prior awareness of anthelmintic resistance, location of grazing and timing of grazing season.

A quantitative assessment of gastrointestinal helminths was completed using the McMaster's technique [17] with saturated sodium chloride as the flotation fluid. Flocks with a mean faecal egg count over 300 eggs per gram (epg) were treated with oral Albendazole. All sheep were dosed based on an estimated weight of the heaviest sheep at 0.5 ml per 10 kg live body weight. Feed was not withheld from flocks prior to treatment as most were pregnant ewes. Two weeks after treatment with Albendazole, further fresh faecal samples were collected and tested using the McMaster's technique. The pre and post drench egg counts were compared to determine the percentage reduction. If evidence of resistance to Albendazole was present, the drench test was repeated using oral Ivermectin.

A similar technique was used for Fasciola hepatica. The sedimentation technique was used to detect Fasciola hepatica. Flocks with over 100 eggs were treated orally with 0.75 ml per 10 kg live body weight of Albendazole. Three weeks after treatment with Albendazole, further fresh faecal samples were collected, tested and compared with the pre-drench FEC. If evidence of resistance to Albendazole was present, the drench test was repeated using oral Oxyclozanide.

In order to identify potential risk factors for developing anthelmintic resistance, animal husbandry practices, especially those related to parasite control and anthelmintic treatment, were compared between smallholdings with and without anthelmintic resistance using the chi squared test and odds ratios.

Results

A total of 43 households were recruited. The average flock size was 14 adult sheep (minimum=3, maximum=103).

The majority of shepherds (n=38) were breeding ewes, a small number (n=4) exclusively fattening rams and one farmer did a mixture. Most farmers aimed for a single lambing season, which started from October to January and was finished by March/April.

The majority of households (45%) treated their sheep for gastrointestinal nematodes and Fasciola hepatica in spring and autumn, approximately 25% treated in either spring or autumn and almost a third used an alternative strategy (Table 1). Other strategies included treating in autumn and again in January, treating every 3 months and treating only when there were clinical signs. Over 85% of household treated their flock themselves, 10% involved a vet and 3% involved a professional shepherd. Whilst Albendazole (88%) and Ivermectin (12%) were the most commonly used anthelmintic, one household reported using oxytetracycline suggesting a lack of understanding regarding anthelmintics, and another didn't know as the sheep had been received as part of a marriage arrangement (Table 1). Only one farmer was aware of anthelmintic resistance. He felt that Albendzole was less effective than previously with less milky ewes and poorer growth rates in lambs. The remainder of farmers had not heard of anthelmintic resistance and, once it had been explained, felt that it was not an issue.

The majority of flocks (80%) were sent to the jailoos (mountain pastures for grazing during the summer months) and 56% also grazed fields near the village in the Spring and/or Autumn before going to the jailoo (Table 1). Whilst in the jailoo, sheep were managed by a shepherd who, for a fee, manages sheep from multiple households in different villages.

Husbandry Practice	Number of farmers (%)
Timing of anthelmintic treatment	
Spring & Autumn	19 (45)
Autumn only	9 (20)
Spring only	2 (5)
Other	13 (30)
Choice of anthelmintic	
Albendazole	37 (88)
Ivermectin	5 (12)
Other	1 (2)
Grazing practices	
Jailoo (mountain pastures)	34 (80)

Village pastures	24 (56)
Prior awareness of anthelmintic resistance	
Yes	1 (2)
No	42 (98)

Table 1: Summary of husbandry practices relating to anthelmintic resistance amongst 43 households with sheep in Kyrgyzstan.

Only 1 household had a FEC over 300 gastrointestinal helminths epg. This household only drenched with anthelmintics in the Spring. The pre and post drenching FEC were 1550 and 250 respectively (84% reduction rate), which is suggestive of anthelmintic resistance. Interestingly, the initial FEC found a variety of Strongyle, Nematodirus and Trichuris eggs. The post drenching sample exclusively found Trichuris eggs.

Six households had faecal samples with over 100 *F. hepatica* epg. Of these households, 2 had no *F. hepatica* eggs in the post-drench faecal sample. The remaining 4 households had reduction rates ranging from 60 to 85% (Table 2) which is suggestive of *F. hepatica* resistance to Albendazole. At the time of the post drench faecal sampling, one household's sheep had clinical signs of chronic liver fluke, including diarrhoea and sub-mandibular oedema, despite being treated with Albendazole in October and January by the farmer and again in the beginning of March by the author. The family had also slaughtered a sheep on Nooruz, a national holiday, which was the day before the post treatment retest, and had been rather disturbed to find large numbers of adult *F. hepatica* in the sheep's liver. After treatment with Oxyclozanide, the post treatment FEC was zero for all four flocks.

Household	Initial number of *F. hepatica* eggs per gram of faeces	Number of *F. hepatica* eggs per gram of faeces post drenching with Albendazole	Percentage reduction in *F. hepatica* eggs
1	194	0	100%
2	450	0	100%
3	256	46	82%
4	166	25	85%
5	126	42	67%
6	260	156	60%

Table 2: Summary of faecal egg count reductions for *F. hepatica*.

Statistical analysis of risk factors for the development anthelmintic resistance among gastrointestinal nematodes and *F. hepatica* was not possible due to only 1 household having evidence of gastrointestinal nematode resistance and only 4 households having evidence of *F. hepatica* (a chi squared test would require a minimum of 5 household) (Table 2).

Discussion

In order for Kyrgyzstan to take advantage of growing meat consumption at home and in neighbouring countries, it is vital that productivity increases. Many factors are needed to attain efficient production from selective breeding for genetics potential to consistent good quality nutrition to disease prevention. High stocking density in the jailoos has increased internal parasite burdens which in turn reduces growth rates, milk production, fleece quality and partial carcass condemnation. Controlling internal parasites is complex but requires the use of effective anthelmintics at the right time. Unnecessary use of anthelmintics, when FEC are low, wastes money and promotes anthelmintic resistance. Once anthelmintic resistance is developed, there is no evidence that reversion to susceptibility occurs [18,19]. In the Southern hemisphere, multidrug resistant gastrointestinal nematodes have made sheep farming unsustainable [18]. Therefore, training and resourcing veterinarians to provide a FEC service will help preserve anthelmintic efficiency and help farmers improve productivity.

Most livestock return from the jailoos, treated with anthelmintics and housed in autumn. Therefore, the ideal time to test for gastrointestinal nematodes would be September and October as they return from the jailoo. This would provide an indication of the gastrointestinal nematode species present and their prevalence; as well as worm burdens in individual sheep and flocks. However, due to the availability of equipment and personnel, this investigation couldn't be started until January. As most flocks were treated with Albendazole at housing in autumn, any attempts to estimate parasite prevalence and burden would be inaccurate. This also means that estimates of anthelmintic resistance prevalence cannot be calculated using data obtained in this study.

The faecal egg count reduction test is the most widely used field test for anthelmintic resistance among gastrointestinal nematode species [20]. However, due to small flock size and ethical implications of not treating sheep with clinical symptoms of parasitism, a faecal egg count reduction test was not considered advisable in this study. Hence the drench test was used followed by treatment with an oral Ivermectin in flocks were resistance was suspected. Reduction rates of <95% after treatment with Albendazole followed by 100% reduction rates when treated with Ivermectin provide strong evidence of gastrointestinal nematode resistance to Albendazole.

Detecting anthelmintic resistance *F. hepatica* is more complex. An agreed upon standardised approach has yet to be determined [21]. Egg hatch assays or faecal egg counts with Copro-antigen have been suggested as definitive tests for anthelmintic resistant F. hepatica [21,22]. In this study, limited laboratory facilities meant that a thorough history and drench test were used as an indicator of resistance. At the time of the study sheep had been housed for 3 months which means re-infection or maturation of immature fluke are not possible explanations for the treatment failure. In addition, the dosing was done by a veterinarian to ensure appropriate dosing and equipment were used and, when treating with Oxyclozanide, there was a 100% reduction in FEC suggesting that the dosing method was correct and equipment in good working order. Therefore, it would seem reasonable to conclude that *F. hepatica* resistance to Albendazole is present in Southern Kyrgyzstan.

Whilst the samples were collected from a small geographical area, the majority of livestock were sent to jailoos to graze in the summer. Flocks with evidence of anthelmintic resistance were sent to jailoos in the Alai, Kichi Alai and Chugun valleys, which are approximately 100-150 km from Kenesh and Gulbar village. It is possible that the sheep became infected with anthelmintic resistant nematodes whilst grazing in the jailoos and are spreading the resistant genes in the villages, or vice versa. The nomadic nature of pastoral farming in Kyrgyzstan means that the results of this study can be extrapolated

beyond the small study region of Kenesh and Gulbar village to the Osh Oblast and Southern Kyrgyzstan. However, distinct geographical boundaries and cultural differences could limit the spread of anthelmintic resistance into other Oblasts particularly those in Northern Kyrgyzstan.

As resistance to Albendazole is present in Southern Kyrgyzstan, repeating similar studies in the Northern Oblasts (Talas, Chui, Issyk Kul and Naryn) would provide valuable information on the extent of resistance to Albendazole in Kyrgyzstan. Conducting the study in autumn when livestock return from the jailoo would be a simple adjustment that would increase the value of the data and the information it provides.

Faecal egg counting is a simple technique which shepherds themselves can be trained to implement and interpret. The equipment is inexpensive and the consumables, such as Sodium Chloride, are easily and cheaply obtained in Kyrgyzstan. Setting up a series of small parasite laboratories run by local shepherds would provide new business opportunities in the local community, improve animal health and productivity and prolong the effectiveness of anthelmintics. These laboratories could be provided in conjunction with training in pasture management, good practice for anthelmintic usage and anthelmintic resistance awareness. In addition, the presence of resistance to Albendazole alongside limited alternative veterinary medicines means that government approval for importing new anthelmintics is essential so that farmer's already experiencing treatment failure have an alternative drug available.

Conclusion

This study shows that gastrointestinal nematode and F. hepatic resistance to Albendazole is present in Southern Kyrgyzstan. Due to limited drug availability, this could have a huge impact on productivity and individual households' income. Therefore, provision of kits for and training in FEC, pasture management and anthelmintic usage is increasingly necessary. As the prevalence of anthelmintic resistance grows, importing new groups of anthelmintics will also become necessary.

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