(Original article)

Creation and implementation of the modern treatment in eimeria and esophagostomiasis invasion: Case report in the farms "Ulan", "Erlan", and "Balke"

Running title: Cure in associational infestation

Zhanat Nurzhumanova,*[1] Assel Zhexenayeva,[1] Altyn Zhubantaeva,[2] Shyngys Suleimenov,[3] Nurlygul Yessengulova,[1] Leila Kassymbekova[4]

[1]Shakarim University of Semey, Veterinary and Agricultural Management Faculty, Veterinary Medicine Department, Semey, 071400, Abai region, the Republic of Kazakhstan

[2]West Kazakhstan University of Innovation and Technology, Institute of Industrial Technologies, Veterinary Medicine and Technosphere Safety Department, Uralsk, 090000, the Republic of Kazakhstan

[3]Shakarim University of Semey, Agrotechnopark, Semey, 071400, Abai region, the Republic of Kazakhstan

[4]Innovative University of Eurasia, Faculty Economics and Enqineerinq, Veterinary Medicine and industrial Technoloqies Department, Pavlodar, 140000, the Republic of Kazakhstan

***Corresponding Author:** Zhanat Nurzhumanova (https://orcid.org/0000-0001-7576-3545), Ph.D. in Veterianary; 20, Glinka St., Semey, 071400, Abai region, the Republic of Kazakhstan; tel. 8-(701)-129-75-55; e-mail: Nurzhumanova@edursn.com

Abstract

Parasitic diseases in sheep reduce sheep-breeding productivity and decrease the economic efficiency of the industry. Our *research aim* was a study of the dynamics of clinical sings development in manifestation of associated eimeriosis and esophagostomosis invasion, as well as concomitant immunodeficiency state in experimental infested lambs and efficiency of complex treatment approach at associated invasions. A prospective study using helminthoscopic methods with the subsequent calculation of indicators of extensiveness and intensity of infestation, as well as haematological studies with the determination of subpopulations of T- and B-lymphocytes was carried out by the author's team. Due to more active development of protozoa, the main symptoms of associated invasion were those typical for acute eimeriosis. Progression of the disease was accompanied by an increase in the intensity of invasion both in relation to eimeria and esophagostomes. At the same time in animals with the development of invasion there was observed a decrease in the total number of leukocytes (up to 25%), including- T- and B-lymphocytes, which indicates a decrease in humoral defense of the lambs' organism. On the 24th day after infection, an

increase in the level of T-lymphocytes (by 0.8%) was observed due to an increase in T-helpers (by 2.0%). Sulfamonomethoxine in complex with niacid was used for treatment of associated infestation. The use of these drugs in recommended doses and according to the developed scheme allowed to reduce the intensity of eimeriosis invasion by 97-98% and esophagostomosis by 100 %. In the work data on eimerioses and eimeriosis-esophagostomosis infestation of sheep are given. At the description of eimerioses and helminthoses of sheep the species composition, distribution and seasonal - age dynamics of infestation were determined. The developed method of treatment showed high therapeutic effect and can be recommended for use in all sheep farms of the Republic of Kazakhstan.

Keywords. associated parasitic disease, complex therapy, immunosuppression, lymphocyte subpopulations.

1. Introduction

Small ruminant's breeding is widespread all over the Kazakhstan due to the presence of large areas of inaccessible mountainous (7.2 million ha) and stony (18.2 million ha) pastures which can be used only for small ruminants (1). But, the main problem in pasture-based livestock production is the significant spread of parasitic diseases (2). It leads to decreased animal's productivity, high lamb losses, and immunodeficiency development which reduce the life-stock manufactory profitability (1).

Abdrazakova et al. (3) give data that the most common parasitic diseases among goats and sheep in Kazakhstan are mixt-invasions by helminthes and protozoa. It has to be noted that coccidiosis (eimeriosis) most frequent in young sheep (2). Hermosilla et al. (4) detected 5 eimeria's species among 214 different aged tested animals with the biggest intensity of *E. ahsata* (64%), *E. infantrisata* - 18.2%, *E. ovinoidalis* - 56.5%, *E. crandallis* - 39.7%, and *E. parva* - 16.6%.

Akmambaeva et al. (2) found 18 species of parasites in sheep: 4 - trematodes, 6 – cestodes, and 8 - nematodes. Amirov *et al.* (5) recorded associated variants of infestations in small ruminants. Win et al. (6) indicated the occurrence of parasitic agents in sheep in Myanmar: *Eimeria spp.* (96%), *Trichostrongyle* (77.1%), *Trichuris spp.* (35%), and *Moniezia expansa* (14%). Mix-invasion accounted for 84.8% (317 of 374 animals) and mono-infestations for 15.2% (57 of 374 animals).

Helminthiasis can be supported by clinical symptoms but in the most cases they are asymptomatic (7, 8). Chronic helminthiasis causes disturbances in defense responses and increases secondary diseases development. Chauhan et al. (9) noted, only a limited number of parasites are not able to provoke effective immune reactions from in animals. And some species of parasites are able to use immune mechanisms for their accelerated reproduction. Most species of invasive agents secrete toxins with immunosuppressive action. Based on a fairly wide area of parasitic agents in the environment, and the danger they carry to livestock in Kazakhstan, the *research aim* of our research was study the dynamics of immunodeficiency state in lambs after the experimental infestation; and the effectiveness of complex treatment methods in associated eimeriosis and nematode infestation. In this way, following study objectives were formulated:

1) the analyzis the changes in the population of immunocompetent cells during the disease development and treatment flowing;

2) study the efficiency of therapeutic drugs on the invasion intensity.

2. Materials and methods

2.1. Study Design

The research was conducted in a number of sheep farms of Beskaragai district, Abay region "Ulan", "Yerlan" and "Balke", the location of which is shown on the map (Fig.1).

Fig. 1. Territorial distribution of farms in which the research was conducted: *1. Farm "Ulan", Zhanasemey district. S. Ernazar; 2. Farm "Erlan", Zhanasemey district, Bokenchi village; 3. Farm "Balke", Beskaragai district, Birlik village. Birlik.*

The research was carried out in 2023 on 20 lambs (born in 2023), experimentally infected by eimeria and esophagostomies.

2.2. Investigation experiment

Healthy lambs were selected for experimental infection: helminthological tests fixed no nematode's eggs or eimeria oocysts.

Infestation was carried out orally with invasive parasite's forms – esophagostome's larvae and eimeria's sporogonium after their cultivating in the thermostat for 4-5 days at 20-22ºC.

Feces were sampled from control animals on days 7, 14, 24, and 30 after infection to detect parasites' pathogenic forms and helmithosis' clinical signs.

2.3. Helminthological study

Helminthological studies to detect eggs and oocysts were carried out by collecting feces in paper bags and preserved with 2.5% potassium bicarbonate solution for further investigation in a core laboratory. Laboratory tests for detection of eggs and oocysts were carried out by the Darling flotation method (10). Visualisation and species identification were performed using an Olympus CX31 microscope with phase contrast at a magnification of 400. Parasite's species identification performed in comparing the materials of the helminth identification and enumeration manual Mifsut

and Ballarin (11). Traditional parasitological indices as infestation intensity (II) and infestation extensiveness (IE) were also determined.

2.4. Hematology study

Blood for haematological (immunological) studies collected from the jugular vein into vacuum tubes with ethylenediaminetetetraacetic acid (EDTA). Studies to determine the quantitative characteristics of lymphocyte subpopulations (T- and B-lymphocytes, T-helpers, and T-suppressors) were carried out using monoclonal antibodies and flow fluorescent cytometer CytoFLEX LX (Beckman Coulte, USA). Blood sampling to determine the dynamics of the number of different lymphocyte subpopulations was performed with the following frequency.

- prior to experimental infection;
- on days 7, 14, 24 and 30 after infection;
- on days 10 and 24 after treatment.

In cases of animal mortality, pathological autopsy performed according to Garcês and Pires (12) gaudiness.

2.5. Treatment Approach

Treatment conducted in separate cages with lattice floors, previously cleaned and disinfected to avoid re-infection of lambs. All drugs were choosed by the State Register of Veterinary Drugs and Feed Additives (13): sulfadimethoxine or sulfamonomethoxine – for eimeriosis treatemt (once a day mixed with dry feed at a dose of 50 mg per a kg for two five-day courses with an interval of 3 days); and niacid (abamectin, avermectin B1) – for esophagostomiasis treatment (subcutaneously once on the 5th day of the first course at a dose of 0.5 ml per a head). After infestation, all lambs received therapeutic treatment (Table 1). Two preparations in equal doses were used in the treatment against eimeriosis infestation.

Table 1. Treatment schemes for experimentally infected lambs with associated eimeriosis and esophagostomosis infestation

Lamb's No.	Eimeriosis' treatment drug	Oesophagostomiasis treatment Drug
1	sulfadimethoxine	niacid
2	sulfadimethoxine	niacid
3	sulfadimethoxine	niacid
4	sulfadimethoxine	- (control)
5	sulphamonomethoxine	niacid
6	sulphamonomethoxine	niacid
7	sulphamonomethoxine	niacid
8	sulphamonomethoxine	niacid
9	sulphamonomethoxine	- (control)

Upon completion of treatment procedures, the effect of antiparasitic action was carried out by determining II and IE individually in each tested animal.

3. Results

3.1. Infestation experiment

The analysis of lambs' infestation was recorded by coprological analysis (Table 2).

Table 2. Dynamics of invasive agents' isolation after the experimental infection

Study period	Intensity of eimeria's infestation	Intensity of esophagostome's invasion
Before invasion	0	0
Seventh day	0	0
14th days	346.2±124.3	0
24th day	894.7±221.6	5.4±2.3
30th days	1248.2 335.1	19.5±5.9

In the first week after experimental infection, no clinical parasitological signs were detected in the experimental lambs. Only in a lamb gastrointestinal disorders in the form of minor diarrhoea (which stopped in 24 h) were fixed. Therefore, this symptom was not associated with the manifestation of post-infection effects and was not considered. Also, no eggs and oocysts were carried out in the feces in this period.

From 14th day, eimeria's oocysts were detected in the fecal of most lambs in the experiment. The II was 80% (8 out of 10 lambs had sporogoniums in feces). Clinical signs of eimeriosis by different intensities were detected in all animals: depression, anemic mucous membranes, decreased appetite; in some lambs, diarrhea and increased temperature up to 40.5-41.0°C. No signs of esophagostomosis infestation were found in the control animals, and the lambs had no characteristic clinical signs or presence of helminth eggs in feces.

From 24th days after infection, the intensity of eimeriosis infestation was 100%, and esophagostome eggs were detected some animals (60%). From clinical signs in lambs were observed general oppression, decreased appetite, immobility, anemia of visible mucous membranes; tachycardia (of 120-140 beats/min.); tachypnoea (40-52 movements/min.); in some animals fixed high temperature (up to 41°C). Intestinal peristalsis was increased, diarrhea was noted. As the sings was the same in all animals, we can assume that it was associated with eimeriosis development. In this period (from 24th to 30th day), one lamb died.

On the 30th day after invasion, the II of eimeriosis and esophagostomosis was 100%. Clinical signs in animals during this period remained at the same level with no noticeable changes.

3.2. Pathological changes study in lambs

Pathological autopsy revealed significant lesions of the small intestine. The mucosa of duodenum and jejunum was thickened with signs of inflammatory infiltration. There were foci of hemorrhages and small grey-white ulcers on the mucosa. In the large intestine there were practically no signs of esophagostomous invasion. Small thickenings in the mucosa were noted. No parasitic nematodes were found. So, the main pathological changes in the lambs in this period are associated with eimerias active reproduction (Fig. 2).

Fig. 2. Pathological changes in study of the died lamb.

So, we observed the active disease flowing in young animals with mortality of 85-100% without treatment.

3.3. Immunological study

On seventh day after invasion, sheep showed a decrease in the level of T- and B-lymphocytes: decrease in T-helper cells (by 2.4% or 74cl/μl), the content of T-suppressors was reduced insignificantly (by 3.5% or 181cl/μl). At 14th day, lambs showed significant shifts in T- and B- immunity systems. At the same time, a decrease in T- and B-cells compared to the initial ones was observed. The number of T-lymphocytes was 59±4.2% or 2461±153 cells/μL ($P<0.001$), B-

lymphocytes 12.7±2.1% or 332±41 cells/μL (P<0.001). The content of T-helper cells and T-suppressors was reduced. Immunosuppression was observed (Table 3).

Table 3. Some immunobiological blood parameters in experimental infested lambs

Period	Total white blood cells number	T-lymphocytes		T-helper cells		T-suppressors		B-lymphocytes	
		%	count	%	count	%	count	%	count
Before infestation	2763±34	37.5 ±0.5	1145 ±21	20.5 ±0.2	536 ±15.0	15.7 ±0.5	511 ±13.0	16.5 ±0.4	513 ±8.0
7th day	2450±33	33.6 ±0.5	820 ±20	16.1 ±0.4	372 ±17	15.5 ±0.5	336 ±11.0	14.4 ±2.1	359 ±11.0
14th day	2225±103	27.3 ±0.5	547 ±33	13.1 ±0.4	315 ±25	14.2 ±0.6	152 ±8.0	6.7 ±0.5	184 ±16.0
24th day	2121±56	21.0 ±1.2	581 ±25.0	13.1 ±0.6	216 ±11	15.7 ±0.6	265 ±13.0	7.4 ±0.6	214 ±17.0
30th day	2570±15	21.4 ±0.3	727 ±2.0	14.0 ±0.2	305 ±9.0	15.2 ±0.3	321 ±9.0	14.6 ±0.6	326 ±22.0

The absolute number of lymphocytes was reduced compared with baseline and was 4595±253 (P<0.001). The II in both parasites was 100%, with EI was from 1-10 to 80 eimeria and 10-15 esophagostome eggs in a microscope view-field.

Since, during the studies, attention was not paid to immune cells like monocytes and granulocytes. We were carried of T- and B-lymphocytes fraction growing after 14th day, further decrease in the total number of leukocytes was observed. This indicates only a deep depression of the cellular immune defense system, compared to the humoral defense.

From 30th day, it was observed a stable increase in all cellular and humoral immune defense factors, which indicates an active struggle of the organism of infected animals with infectious agents.

3.4. Cure Approach in investigated animals

Already on the 10th day of sulfamonomethoxine application (Table 4), a significant reduction in the intensity of invasion compared to the sulfadimethoxine preparation was noticeable, by about 67%. Subsequently, 24 days after the start of treatment, animals administered sulfadimethoxine were unable to rid themselves of eimeriosis infestation, in contrast to the use of sulfamonomethoxine, when used, the animals virtually ceased to release eimeria oocysts into the

environment. Since only one drug was used for the treatment of esophagostomiasis, animals numbered 4 and 9 were control animals that were not treated with the drug.

Table 4. Results of treatment of experimentally infected lambs

Lamb's nubber	Infestation intensity at the 10th day after treatment beginning		Infestation intensity at the 24th day after treatment beginning	
	eimeria	esophagostome	eimeria	esophagostome
1	376	4	57	0
2	527	8	44	0
3	504	6	49	0
4	621	16	51	41
5	-	-	-	-
6	341	5	2	0
7	359	4	1	0
8	284	7	1	0
9	376	19	0	54

During the treatment procedures a positive tendency to decrease the intensity of esophagostomosis infestation was observed already on 10th day. On the 24th treatment-day no esophagostomes eggs were found in experimental animal's feces. While in control group, the EI had tendency to increase, even with using treatment against eimeriosis. The research protocols did not include the results for lamb No. 5, which died on the second treatment day.

Similarly to the previous studies, in parallel with II determination, blood samplings were carried out (Table 5).

Table 5. Immunology cells checking in blood samples treated lambs

Treatment day	Total count of the white blood cells	T-lymphocytes		T-helper cells		T-suppressors		B-lymphocytes	
		%	count	%	count	%	count	%	count
10th	3121±28	35.2 ±0.6	1120 ±17	20.5 ±0.2	565 ±6.5	17 ±0.6	453 ±19	17.2 ±0.2	458 ±11
24th	3242±59	39.5 ±1.2	1226 ±24	22.3 ±0.6	660 ±30	16.3 ±1.0	555 ±23	21.1 ±0.8	445 ±13

So, positive dynamics of leucocyte count was observed up to the level that exceeded their number before the invasion. Although the humoral immunity indices at the end of treatment were slightly higher than before the disease, the main increase in leucocytes was associated with such immune cells as neutrophils and monocytes. So, we can note, the activating both cellular and humoral immune defense.

4. Discussion

The most frequent pathology of parasitic nature, which is widespread in the Republic of Kazakhstan among the population of small ruminants are pathogens of gastrointestinal tract diseases caused by nematodes (50.4-67%) and protozoa (82.1-87%). Adults are less susceptible to the disease because of developed resistance. However, new disease episodes can happen after the animal is transported in case other Eimeriae strains are present. When afignimals are infected with eimeriosis and esophagostomiasis, mass multiplication occurs in the intestine, destroying many intestinal epithelial cells (3, 14, 15).

We have conducted the experimental invasion experiment in lambs. According to gotten data, first disease signs we have detected between 7 and 14 days after invasion. And esophagostome invasion was delayed by 7-14 days compared to the faster eimeriasis development the main symptoms at experimental associative invasion were characterized as acute eimeriosis. These data are not entirely consistent with the development of immunological depression in invazed animals. There is no data about eimeriasis' negative effect on the animals' immune system in the literature. Just only Bouroutzika et al. (16) confirmed a significant immunosuppressive effect of eimeriosis on the humoral and cellular immune defense of the host organism. According this data, both esophagostome and eimeria are capable to suppress immune defense in the host body. However, a complete picture of the effect of associated invasions on the state of the host immune system is not yet available due to the lack of data on the cellular component of the body's defense system (9). Since the main defense mechanism against parasitic organisms, it is the production of specific antibodies (7), this study focused on lymphocytes as the main producers of the humoral defense (antibody) components.

At the first post-invasion stage, we have fixed the decrease in the total number of leukocytes which indirectly indicated suppression in the cellular component of the immune system. However, we have no fixed a tendency: leucocytes' number was different in different animals. White et al. (17) and Perry et al. (18) confirmed that helminths are able to suppress immunity in hosts and can control the induction of regulatory T-cells. At the same time, the degree of suppression of the immune response correlates with the number of helminths in the host organism. This can be associated with the development of immunosuppression due to parasite's toxins action (9). The maximum decrease in lymphocytes was observed up to 14-th day after invasion.

After 14th day, growth of both T- and B-lymphocytes' fractions was observed. Taking into account physiological peculiarities of immune system functioning, that on the 14th day at the majority of diseases antibodies production is observed (7).

At the 20-th day after invasion, there was a slight increase in the level of T-lymphocytes (by 0.8%) due to the increase of T-helpers (by 2.0%).

Between 14th and 24th day, it has been observed small changes humoral defense system due to different life cycles of the parasites. Incubation period of esophagostomies is longer compared to eimeria (19). The main clinical signs and excretion of oocysts from feces in experimentally infected lambs occurred on the 14th day. At that time, the appearance of the first eggs of esophagostomes was recorded on the 24th day. It is this period, within one week, that causes a more smeared picture in the blood of the number of different fractions of immunocompetent cells and the humoral immune response.

The reduction of the associate invasion is faced by the problem of the different nature of the invasive components (20). In the conducted studies at experimental associated invasion both esophagostome and eimeria with invasion intensity of 100%, the clinical signs of esophagostomiasis in the lamb organism were smoothed. However, when eimeriosis was treated, signs of esophagostomosis invasion developed. So, all prophylactic measures need to take into account the physiology of both pathogens, but this is complicated by the fact that the pathogens belong to different classes of parasites (15). However, it is possible that comensal connections can be formed between eimeriae and nematodes. Thus, favor their simultaneous development in infected animals. Eimeriosis is caused by protozoa (an obligate intracellular parasites) and esophagostomiasis is a typical helminthiasis whose life cycle of the adult nematode is associated with development in the intestinal. So, treating approaches in these diseases are somewhat different, as are the drugs used (1, 21). In this way, an-helminthic drugs are not effective against eimeriosis and anti-coccidial cure have practically no effect against helminths.

In the Register of Approved Veterinary Drugs in the Republic of Kazakhstan (13) no drug was found that could give efficiency both against helminths (nematodes) and eimeria (as *Protozoa*). Almost all drugs, even complex action, are focused on a particular class of parasitic organisms. But even drugs that are provided for the treatment of certain types of parasites, could not guarantee 100% effectiveness. Thus, among sulfonamide drugs sulfadimethoxin significantly lost in anti-eimeriosis action to sulfamonomethoxin which practically allowed to stop completely the release of eimeria oocysts from the organism of infected lambs. In addition, both drugs were able to stop the clinical manifestation of the disease after experimental infection. The effectiveness of sulfonamide group drugs against eimeria was confirmed by Filipenko and Soroka (21) and Bawm and Htun (22). However, no effect was detected on the production of esophagostome eggs, which was confirmed by the increasing dynamics of their excretion in control lambs that did not receive anti-helminthic drugs.

Niacid using in esophagostomiasis treatment was not used before our study (we have no found data about this). However, the efficacy of niacid was found to be high. Up to 24 days from the beginning of treatment, esophagostome egg excretion completely stopped in animals.

In the experimental infestation, the intensity invasion was 100 % in both pathogens. This indicates high susceptibility of young sheep to eimeriosis and esophagostomosis. The dynamics of excretion of invasive agents from feces of infected lambs indicates a more rapid and active development of eimeria than esophagostomosis.

In contrast to the increase in the II, total leucopenia of almost 25% was observed in infected sheep. From 24th day after infestation, a gradual activation of the humoral immune defense was observed which is manifested by an increase in the B-lymphocytes fraction.

In the treatment of the associative invasion, no complex but drugs against fixed parasites (monoinvasions) have been used. For this purpose, it is necessary to use a complex treatment approach, taking into account pathogen's synergy and contraindications. So, we have used sulfonamide drug – sulfamonomethoxine – and a drug of the ivermectin group – niacid. This approach by the recommended scheme and doses allowed reducing the intensity of eimeriosis invasion by 97-98% and esophagostomosis by 100%.

The therapeutic procedures allowed revealing positive dynamics of increasing the immune response in animals due to increasing T- and B-lymphocytes number.

4.1. Limitations

Due to the small control and experimental groups, the gotten results have to be vivificated in bigger groups. The research aim was not to study the manifestation of morbidity according to the parasites' number. Still, it was noticeable that in different lambs both the rate of increase of clinical signs and the degree of manifestation of the disease differed significantly. Since the invasive agents obtained from one sick animal were used in the research, it could be assumed that the intensity of the disease manifestation depended only on the number of parasites ingested into the organism. Therefore, the next research stage will be the study of the parasite's number influence on the degree of clinical signs and the influence of the parasite's number on the level of the disease intensity according to the immunosuppressive effect of the parasite agents.

Statements

Acknowledgements

We'd like to gratitude chiefs of the sheep farms of Beskaragai district, Abay region - "Ulan", "Yerlan" and "Balke"- for their assistance in conducting our research.

Authors contribution

Zhanat Nurzhumanova had a part in the research concept and design creation; collected and analyzed research data; and had a part in the manuscript writing. **Assel Zhexenayeva** and **Altyn Zhubantaeva** were responsible for statistical analysis and presenting of statistical data; made previous critical review and editing of the manuscript. **Shyngys Suleimenov** had a part in the research concept and design creation, analyzed collected data and their presentation in the manuscript. **Nurlygul Yessengulova** and **Leila Kassymbekova** had a part in the introduction and discussion manuscript's part creation; analyzed the research data in comparison with the previous published data; had a part in the conclusion section creation.

Ethics

The research was considered by the Ethical Comity of the Shakarim University of Semey and accepted it as the research in the norms and principles of the Declaration of Helsinki Ethical Principles (Protocol no 3, 24 October, 2024).

Conflict of interest

The authors honesty declare there are no conflicts of interest in the presented research in any possible case for each one author.

Data availability

Supplemental or other research data can be obtained from the correspondence author after reasonable request.

REFERENCES

1. Djurinskaya IM, Kenzhebaeva TE, Rakhimova SM, Niyazbekov BJ. Prospects for the development of down goat breeding in the Republic of Kazakhstan. Bul Almaty Tech Univ. 2020; (3): 5-8.

2. Akmambaeva B, Seitkamzina D, Zhanabaev A, Yelemesova B. Control measures against parasitocenoses of small horned cattle of Tselinograd district of Akmola region. Ġylym žáne bìlìm. 2023; 1(3(72)): 19-29.

3. Abdrazakova KJ, Tulindinova GK, Tarasovskaya NE, Bulekbaeva LT, Kakimov MT. Innovative methods in the diagnosis of parasitic infestations of domestic animals. Herald Sci Seifullin Kazakh Agrotech Res Univ. 2020; 3(106): 181-192.

4. Hermosilla C, Elemesova B, Usenbaev AE, Berdikulov MA, Seitkamzina DM, Lider LA. Species composition of eimeriae in the intestinal biocenosis of sheep in farms of Akmola region. Sci Seifullin Kazakh Agrotech Res Univ. 2022; 4(115(2)): 16-26.

5. Amirov OO, Kuchboev AE, Sobirova HG, Karimova RR. Asociative nematode infestations of the digestive system of sheep in Uzbekistan. Ўzbekiston agrar fani habarnomasi. 2019; 1(75): 112-116.

6. Win SY, Win M, Thwin EP, Htun LL, Hmoon MM, Chel HM, Bawm S. Occurrence of gastrointestinal parasites in small ruminants in the central part of Myanmar. J Parasit Res. 2020; 2020: 8826327.

7. Abdoli A, Ardakani HM. Helminth infections and immunosenescence: The friend of my enemy. Exp. Gerontol. 2022; 133: 110852.

8. Hananeh WM, Radhi A, Mukbel RM, Ismail ZZB. Effects of parasites coinfection with other pathogens on animal host. A literature review. Vet World. 2022; 15(10): 2414-2424.

9. Chauhan RS, Malik YS, Saminathan M, Tripathi BN. Essentials of Veterinary Immunology and Immunopathology. Springer: Singapore; 2024.

10. Khurana S, Singh S, Mewara A. Diagnostic Techniques for Soil-Transmitted Helminths. Rec Advances Res Rep Tropical Med. 2021; 12: 181-196.

11. Mifsut CL, Ballarin SP. Helminths: Handbook for Identification and Counting of Parasitic Helminth Eggs in Urban Wastewater. Iwa Publishing; 2015.

12. Garcês A, Pires I. Necropsy Techniques for Examining Wildlife Samples. Bentham Science Publishers; 2020.

13. State Register of Veterinary Drugs and Feed Additives. [Internet]. 2024 Jan 26. [cited 2024 Sept 12]. Available from: https://www.gov.kz/uploads/2024/1/29/53412aa5eb1a191aaf8a1aa2158ca0d6_original.6032813.pdf

14. Khusayynova NT, Nurzhumanova JM. *Eimeriosis and helminth infestations of farm animals*. Semey: Intellect Pub. House; 2017.

15. Akhmetzhanova A, Duyssembaev S, Zhanat N, Koigeldinova A, Tussupov S. Strongyloides and Eimeria Infection and Its Treatment Way in Sheep. Arch Razi Inst. 2022; 77(6): 2359-2363.

16. Bouroutzika E, Ciliberti MG, Caroprese M, Kantzoura V, Theodosiadou EK, Batikas G, Michailidis ML, Stampinas EG, Mimikou Z, Pantsios G. Melatonin Administration to Pregnant Ewes for Coccidiosis Control in Their Offspring. Animals. 2023; 13(14): 2381.

17. White MPJ, McManus CM, Maizels RM. Regulatory T-cells in helminth infection: induction, function and therapeutic potential. Immunology. 2020; 160: 248-260.

18. Perry JA, Shallberg L, Clark JT. PD-L1–PD-1 interactions limit effector regulatory T cell populations at homeostasis and during infection. Nat Immunol. 2022; 23: 743-756.

19. Juszczak M, Sadowska N, Udala J. Parasites of the digestive tract of sheep and goats from organic farms in Western Pomerania, Poland. Annals Parasitol. 2019; 65(3): 245-250.

20. Igbatigbi LO, Olobaniyi DO, Itodo JIO, Itodo JI, Oricha MI, Shettima I. Gastro intestinal protozoa and helminths infestation in goats slaughtered within lokoja metropolis, Kogi state. Intern J Global Affairs Res Dev. 2024; 1(2): 8-15.

21. Jacobson C, Larsen JW, Besier RB, Lloyd JB, Kahn LP. Diarrhoea associated with gastrointestinal parasites in grazing sheep. Vet Parasit. 2020; 282: 109139.

22. Filipenko OV, Soroka NM. Hematological and biochemical indicators of lambs' blood after the use of chemotherapeutic agents for spontaneous eimeriosis. Reg Mech Biosyst. 2023; 14(4): 595-600.

23. Bawm S, Htun LL. Management and control of eimeria infection in goats. In Goat Science-Environment, Health and Economy. IntechOpen; 2021.