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Anthelmintic Resistance in Small Ruminant of Ethiopia: Systematic Review and Meta-analysis

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Abstract

Anthelmintic resistance in small ruminants becomes an emerging problem worldwide including Ethiopia. A systematic review and meta-analysis was conducted to identify, evaluate and synthesize primary literature reporting anthelmintic resistance of GIN in small ruminants in Ethiopia. Based on the predefined criteria, 13 articles published between 2005 and 2017 were included and used for the review. Data on geographic region, adopted animal management, animal spy, number of animals involved, study approach, type of anthelmintic drugs, pre-treatment and post-treatment egg count, route of drug administration and dosage were collected. The final data base was composed of 13 articles with 76 studies using a total of 1,958 animals. Pooled average reduction percentage showed Roomie and Southern regional state showed high resistance. Studies on intensive farm and goats were superior in anthelmintic resistance compared to extensive farm and sheep. There was no significant (p>0.05) difference observed on resistance among anthelmintic drugs used. Tetramizole/levamizole, Albendazole and Ivermectin showed anthelmintic resistance with the prevalence of 37.9% (11/29), 29.2% (7/24) and 26.1% (6/23) respectively. Pooled average value of reduction percentage indicated that more resistance recorded in intensive farm and goats to all three anthelmintic analyzed. The forest plot did not show a difference (P>0.05) between interventions (resistance and efficacy) but indicated differences in proportion of effect sizes and dispersion of true effect size using I_2 and T_2 output, correspondingly. Significant publication bias observed with both Bag's and Egger's which could be due to exclusion criteria and high heterogeneity. The results of this systematic review and meta-analysis suggests anthelmintic resistance in small ruminants can't be overlooked at least in four region reported. Therefore there is a need to bring attention of stakeholders to use strategic anthelmintic treatment.

Keywords: Anthelmintic; Nematodes; Resistance; Small ruminants; Ethiopia

Abbreviations: EPG: Egg Per Gram; FECRT: Feacal Egg Count Reduction Test; MDR: Multidrug Resistance; BZ: Benzimidazoles; MA: Meta–Analysis; ML: Macrocyclic Lactones; AR/AHR: Anthelmintics Resistance; GIN: Gastro Intestinal Nematode; MOX: Moxidectin

Introduction

Gastrointestinal parasites of livestock are economically important diseases that affect productivity, even death if animals are left untreated. Despite the presence of different control strategies the problem of parasitism and the associated negative impact remains a bottleneck in farm practice worldwide. In addition, global warming, climate change, intensive livestock management and regular deworming have given more opportunities to the development of anthelmintic resistance. Anthelmintic Resistance (AR) is becoming an emerging problem worldwide. This is mainly associated due to frequent treatment of anthelmintic drugs and poor farm management practices that provide inadequate refugee. The problem has also been exacerbated due to the presence of counterfeit anthelmintic products throughout the global world the market. Thus the issue of anthelmintic resistance has been documented in most sheep-rearing countries, including Australia, North, Central and South America, Africa, Netherland, Asia and Europe. The problem of AR worsened more due to lack of new drug invention in recent years. Besides, repeated use of

similar drugs for long period has contributed to the development of multidrug resistance. Moreover Multidrug Resistance (MDR) to the most commonly used Anthelmintic Such as Benzimidazoles (BZ), Macro cyclic Lactones (ML), including Moxidectin (MOX) in sheep, cattle, and horses have been reported. Imidazothiazoles in sheep and the tetrahydropyrimidone pirate (PYR) in horses is also causing concern. MDR has been described in sheep flocks. Considering different factors for the emergence of resistance, preventing further development requires a better understanding of management practices associated with anthelmintic resistance. Several studies were conducted to understand the putative factor for the cause of anthelmintic resistance, but still not yet reached a conclusive result though there are different factors incriminated. In Ethiopia, the prevailing weak working regulation and poor understanding of the risk thougt to have created conducive platfo rm for antihelmintic resiatnce developement. Consequent to this assumption, several studies on anthelmintic resistance were conducted on small and large ruminants in different farming systems. However, as t he findings of these reports are in

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consistent there is a need for summarizing the overall status of anthelmintic resistance in Ethiopia for better understanding. One way to evaluate such findings is through a Systematic Review (SR) and Meta-Analysis (MA) approach which gives better in sight in to the context. This type of approach combines the findings of several studies to make a reproducible summary of their data, providing the most substantive clinical evidence based on defined methods that guide the search and inclusion criteria [1-5].

With this point in mind, the review was planned to pool the effect size, *i.e.* pooled mean difference for anthelmintic sensitivity evaluation trials conducted using fecal egg count reduction test in different context [6-10].

Materials and Methods

Literature search

Literature searches were conducted using the PubMed, web science, and Google scholar search engines. Additional studies were identified by scanning the African Journal Online (AJOL) that includes the Ethiopian veterinary journal and bulletin of animal health and production in Africa. All searches were performed from January to April 2018. Search was repeated ones again in November 2021. Peer reviewed primary reports on anthelmintic drug efficacy of gastrointestinal nematodes of sheep and goats included. All search terms are indicated in Table 1. Searches were restricted to peer-reviewed articles published nationally or internationally in English language from 2005 to 2017 GC. Articles published before 2005 GC and those focusing on livestock other than small ruminants were not included [11-15].

Spp of animals	Search string
Sheep, Goats, cattle and horse	(anthelmintic or “macrocyclic lactone*” or Ivermectin or Moxidectin or Doramectin or Levamisole or Fenbendazole) and (gastrointestinal or internal) and (parasite or nematode or worms or worming) and (resistance or resistant) and (efficacy or effectiveness) and (faecal egg count reduction test or FECRT) and (route of administration” or “injectable formulation” or oral) and (“natural infections”)

Table 1: Search string used to identify articles related to anthelmintic resistance in Ethiopian livestock.

Study inclusion criteria and relevance screening

Search and selection of studies are presented in Figure 1. In the course of online search, one hundred eighty titles and abstracts were obtained. Research outside Ethiopia and species other than small ruminants were excluded. A total of nineteen reports and one duplicate were identified based on title and abstract. All of them were primary research works on sheep and goats in Ethiopia.

Almost all studies included in this review were observational study design following selection of animals using minimum egg per gram of faces according to Coles et al. Cohort studies conducted in sheep and goats under a range of field conditions including research stations, university farms or facilities, and individual peasant farms. Papers that investigate other than nematode treatment was not included egg. Fasciolosis treatment. In the process of screening 16 articles with 103 studies selected and for further eligibility, studies with combined treatment, underdo administration and drug with single and other chemical group excluded. Hence 13 papers with 76 studies selected for quantitative meta-analysis [16-20].

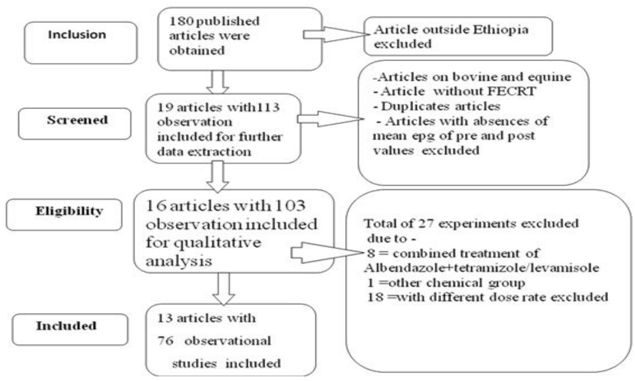

Figure 1: Flow chart of inclusion and exclusion of articles related to anthelmintic resistance studies during search and selection process.

Methodological assessment of the studies

Prior to risk assessment and data extraction, the relevance of papers selected through abstract screening was confirmed using the full articles. Legibility of the papers was undertaken using the following criteria: if the study had an appropriate control group and results were reported in sufficient detail to conduct the data extraction that can be used in MA. At this stage of the review, primary research was restricted to publications written in English languages because the researcher only knew English, and there was no access for translation from another language. Publications reporting more than one study design were duplicated and extracted as separate studies. Many studies reported at least three types of drug treatment comparisons (Tetrazole/Levamisole, Albendazole, Ivermectin), which were extracted as separate treatment (studies) for analytic purposes [21-23].

Study characteristics and variables

Study characteristics and variables that were excuted in each study included: authors, publication years, region of the study, species of animals, sample size, type of management, type of anthelmintics, route of administration, pre- and post-treatment mean EPG value and FECRT. Some of the study characteristics described and categorized in Table 2.

Variable	Descriptions	Categories
Sample size	Number of animals	-
Region	Administrative region of Ethiopia	Ormia, Amhara, SNNPRS, Somali
Species	Animals involved in the study	Sheep, Goats
Management	Study population	Intensive, extensive, semi-intensive
Types of drug	Anthelmintics	Tetramizole/levamizole, Albendazole, Ivermectin
Drug adminstration	Route	Oral or injectable form
Method of evaluation	Egg count per gram	Fecal egg count reduction percentage (FECRT)

Table 2: Study characteristic variables selected for systematic review and meta-analysis of anthelmintics resistance in small ruminants in Ethiopia.

The risk each study bias was assessed using the following criteria:

- Methods of treatment group allocation (randomization);
- Assessment of confounders;
- Blinding of personnel administering the intervention;
- Blinding the laboratory personnel involved;
- Whether artificial challenge or natural infection and
- Laboratory protocols were sufficiently reported (or referenced)

to be replicated (Table 3).

Criteria	Assessment	No. publications (studies)
Was sample size used justified?	Yes	0 (0)
	No	13 (76)
Was type of sampling procedure explained well to be reproducible?	Random	0 (0)
	Reported random[1]	13 (76)
	Systematic	0 (0)
	Convenience or	0 (0)
	unreported	0 (0)
Was the dose rate and route of administration explained?	Yes	13 (76)
	No	0 (0)
Was laboratory methods described well to be reproducible?	Yes	13 (76)
	No	0 (0)
Was AHR evaluation methods described well?	FECRT[2]	13 (76)
	WC	0 (0)
	PME	0 (0)
Did the author report blind treatment was used?	Yes	0 (0)
	No	13 (76)

Based on the study design, was clustering accounted for appropriately in the analysis	Yes	0 (0)
	No	0 (0)
	No applicable	13 (76)
8.Were identified confounders Controlled for or tested	Yes	0 (0)
	No3	13 (76)
9.Was the statistical analysis for AHR determination described according to Coles et al (1992)	Yes	13 (76)
	No	0

* These were the remaining publications and studies subjected for analysis followingthe assessment based on the criteria set.

1=Author indicated random, but randomization process was not described.

2=Anthelmintics resistance in all selected articles evaluated by faecal egg countreduction percentage.

3=Combined drug treatment, other chemical groups and different dose rateexcluded to reduce confounders.

Table 3: Summary of assessment for methodological soundness and/or reporting of 13 publications reporting 76 studies included in this review.

Data extraction

Information on study methods, study animals, and relevant study level factors were retrieved using prepared standard form. The form was designed after examining relevant papers to identify the most consistent information to obtain for the analysis. Studies were systematically evaluated and the information contained in each study was analyzed with regards to study design, treatment and output and then data were extracted. The main criteria for the inclusion of an article in the extraction process were based on pre and post treatment egg count in both control and treatment group, andfaecal egg count reduction percentage. Selection of studies conducted regardless of the effect of anthelmintic results (*i.e.* whether positive or negative effect of drugs on gastrointestinal nematode. The data then compiled in Microsoft® Excel (Microsoft Corporation, Redmond, WA, USA) and subsequently imported into Stata (2012) (SE/12 for Windows, Stata Corporation, College Station, TX 778445, USA) which was used for all statistical analyses [24].

Publication bias

Publication bias was assessed by the Begg's adjusted rank correlation and Egger's regression asymmetry tests in combination with funnel plots for study design and outcome type (FECRT) including all groups of treatment. Bias was considered to be present if at least one of the statistical methods was significant ($P<0.10$).

Statistical analysis

The mean Fecal Egg Counts (FEC) of pre-treatment and post treatment for both control and treatment group recorded. Pooled average value of FECRT in relation to each drug with region, species and management analyzed. Standard Deviation (SD) of pre-treatment and post treatment generated. Mean difference between pre-treatment and post treatment of both control and treatment group generated. Standard error of the mean difference calculated. Pooled standard deviation and pooled mean difference of treatment group used in the analysis. Since control group didn't show any epg difference between pre and post treatment. The pooled effect size was computed from the pooled mean difference of treatment groups. All the analyses were performed in the statistical package Stata V 12.

A forest plot was made in Stata software to analyze the efficacy of anthelmintic against GIN for each study based on the number of events and sample size. The forest plot represents all selected studies (n=76) with confidence intervals of effect size at 95% illustrated by horizontal lines. The central line represents studies with no difference between interventions and separates the graph in studies with resistance (right side) and susceptible (left side). Horizontal lines crossing the central tendency line indicate no difference between interventions ($P>0.05$). In the last line of the graph, the summarized value is shown. Statistical heterogeneity was made using I^2, which describes the proportion of total variation across studies attributed to heterogeneity. Subgroup analysis was conducted to identify the cause of high heterogeneity in intensive farm and goats studies; where analyzed separately because these two risk factors showed high anthelmintic resistance in pooled average analysis.

Results

Literature search findings

In the initial screening, primary literature was composed of 113 studies in 19 publications, which were published between 2005 and 2017 were retained for further selection process. 13 peer reviewed primary research reporting 76 studies were eligible for quantitative meta-analysis. Out of the publications, 57% were from Oromia regional state, 31% of studies were from the Southern nation, nationality people regional state(SNNPR) 11% were from the Amhara region and 3% studies were from Somali regional state. Major modes of drug administration in these studies were oral (74%) and subcutaneous injection (26%). Types of drugs used in these studies were Levamisole or Tetramisole which were group as one drug because of similar chemical compound, Albendazole, Ivermectin. The dosage ranged from 7.5 to 15 mg/kg for Levamisole, 7.5 to 22.5 mg/kg for Tetramisole, 7.5 mg/kg for Albendazole, 0.2 mg/kg for Ivermectin.

The studies were assessed methodologically as shown in Tables 3 and 4. which included four regions mainly in Oromia and SNNPR regions followed by Amhara and Somali regional states; 1958 sheep and goats were included in 13 publications reporting 76 studies. In each publication at least three treatment groups were involved to assess anthelmintics.

Among the anthelmintics group analyzed shown in Table 5-7 the greatest efficacy rate was observed in Ivermectin, Albendazole and Tetrazole/Levamisole with 73.9%, 70.8% and 62.3%, respectively; which was not significantly (p>0.05) different.

Twenty-nine studies were conducted to evaluate tetramizole/levamisole drugs in different study sites, management and species of small ruminants. A total of 728 small ruminants were involved during these studies. Drug administration was oral and the dose rate ranges from 7.5 to 22.5 mg/kg according to the recommendation of the manufacturer. Eleven study groups (37.9%) showed anthelmintics resistance and the rest were susceptible to Tetramizole/Levamisole based on the standard set by Coles, et al., of these 10 of them were recorded in the intensive farm and one group was in the extensive farming system as shown in Table 5.

Efficacy of Albendazole studied using 630 small ruminants in twenty-four study groups. In different region with extensive, intensive and semi-intensive farm management. All experiments were administered orally using the balling gun and the dose rate across the experiment was similar (*i.e.* 7.5 mg/kg of body weight). This descriptive summary showed 7 study groups (29.2%) anthelmintics resistance observed out of 24 studies based on criteria set by Coles, et.al, 1992 as shown in Table 6. Resistant results were more recorded in intensive and semi-intensive than an extensive farm.

Studies on ivermectin anthelmintics resistance were conducted using 600 small ruminants in twenty-three groups of four regions: Amhara, Oromia, SNNPR and Somali under a different management system. Drug administration for this particular drug type was injection with the dose rate 0.2 mg/kg body weight. Among these studies 6 of them showed anthelmintics resistance 26.1% observed as indicated in Table 7.

Pooled average values of anthelmintics resistance of Tetramizole/Levamisole in the Oromia and SNNPR region showed an average value of 91.0 FECRT. Similarly, AHR of Albendazole and Ivermectin in Oromia and SNNPR region also showed an average value of less than 95%. The pooled average value of AHR of Tetramizole/Levamisole, Albendazole and Ivermectin was showed in goats with pooled average value of 87.1, 77.5 and 85.1, respectively. It was observed in the pooled estimate of AHR of Tetramizole/Levamisole, Albendazole and Ivermectin were also showed in intensive farm management with an average value of 84.3, 68.6 and 79.9, respectively; resistance of albendazole was also found in semi-intensive farm management as shown in Table 8.

The forest plot shown in Figure 2 highlights the variation on anthelmintics resistance among the selected studies. Twenty-six studies showed anthelmintics resistance out of seventy-six studies selected. Whereas forty-seven study groups were susceptible to the treatment given and three of them didn't show susceptibility or resistance.

The last line in the graph shows the summarized value of the studies suggesting that there was no significant (p>0.05) difference between susceptible and resistant groups. High proportion of heterogeneity observed among studies showing the real differences in effect size. Accordingly subgroup analysis made on intensive farm and goats showed in Figure 3 and 4, the same high proportion of heterogeneity shown, despite high record of anthelmintics resistance reported in this two risk factors during pooled average value of anthelmentics efficacy analysis. Tau-squared value was also high in all forest plot analysis, indicating the wide dispersion of true effect sizes.

Publication bias analysis using Begge's test and egger's test more likely shows there is publication bias with significantly (p<0.05). Figure 5 funnel plot of mean difference versus standard error of indicating wide dispersion from the regression line.

Authors	Studies	No. animals	region/zone	Animals used	Management type
Melaku, et al., 2013	4	32	Amhara/N.Gondor	sheep	Extensive farm
Niguse, et al., 2014	3	36	Somali/Jigjiga	sheep	Extensive farm
Asmare, et al., 2005	3	90	SNNP/Sidama	sheep	Extensive farm
Asmare, et al., 2005	3	90	SNNP/Hawassa	Goat	Intensive farm
Asmare, et al., 2005	3	90	SNNP/konso	Goat	Semi-intensive
Kumsa and Abebe, 2009	9	270	SNNP/Hawassa	Goat	Intensive farm
Lidetu, 2009	4	90	Oromia/east shewa	Goat	Intensive farm
Sheferaw, et al., 2010	3	60	Wolayta	sheep	Extensive farm
Sheferaw, et al., 2015	3	120	Oromia/Yabello	Goat	Extensive farm
Regassa, et al., 2013	3	60	Oromia/Bishoftu	sheep	Extensive farm
Regassa, et al., 2013	3	60	Oromia/Bishoftu	Goat	Extensive farm
Terefe, et al. 2013	3	270	Oromia/Bedelle	sheep	Extensive farm

Ahmed. et al., 2017	3	90	Oromia/haromaya	sheep	Extensive farm
Sibhatu et al., 2011	2	60	Oromia/west shewa	sheep	Extensive farm
Menkir, et al., 2006	9	180	Oromia/haromaya	sheep	Semi-intensive
Menkir, et al., 2006	9	180	Oromia/haromaya	Goat	Intensive farm
Seyoum, et al., 2017b	9	180	Amhara/N.Gondor	sheep	Extensive farm
Total	76	1958			

Table 4: Data base description of the selected studies based on the region, number of animals and type of management used.

S. no.	Author	region	management	spp	type of drug	dose and route	#animals	FECRT	95% CI of FECRT	Remark
1	Terefe, et al. 2013	Oromia	extensive	sheep	tetramizole	15 mg/kg oral	90	98.5	(98.3, 99.6)	Susceptible
2	Seyoum, et al.,2017	Amhara	extensive	sheep	tetramizole	15 mg/kg oral	20	98.9	(95.3, 99.7)	Susceptible
3	Seyoum, et al.,2017	Amhara	extensive	sheep	tetramizole	15 mg/kg oral	20	98.9	(95.3, 99.7)	Susceptible
4	Seyoum, et al.,2017	Amhara	extensive	sheep	tetramizole	15 mg/kg oral	20	98.9	(95.3, 99.7)	Susceptible
5	Sheferaw, et al., 2015	Oromia	extensive	goat	tetramizole	15 mg/kg oral	40	96.8	(90.7,98.9)	Susceptible
6	Ahmed, et al., 2017	Oromia	extensive	sheep	tetramizole	7.5 mg/kg oral	30	98.8	(95.6,99.8)	Susceptible
7	Melaku et al., 2013	Amhara	extensive	sheep	tetramizole	15 mg/kg oral	8	89.5	(73.9, 98.0)	Resistance
8	Sheferaw, et al., 2010	SNNP	extensive	sheep	tetramizole	15 mg/kg oral	20	97.8	(96.2, 99.8)	Susceptible
9	Regassa, et al., 2013	Oromia	extensive	sheep	tetramizole	22.5 mg/kg oral	20	97	(95.3, 99.5)	Susceptible
10	Regassa, et al., 2013	Oromia	extensive	goat	tetramizole	22.5 mg/kg oral	20	96.6	(95.1, 98.7)	Susceptible
11	Niguse, et al., 2014	Somali	extensive	sheep	tetramizole	22.5 mg/kg oral	12	100	(96.5, 100)	Susceptible
12	Kumsa & Abebe, 2009	SNNP	intensive	goat	tetramizole	22.5 mg/kg oral	30	80	(44, 93)	Resistance
13	Kumsa and Abebe,2009	SNNP	intensive	goat	tetramizole	22.5 mg/kg oral	30	84	(68,92)	Resistance
14	Kumsa and Abebe, 2009	SNNP	intensive	goat	tetramizole	22.5 mg/kg oral	30	81	(45,93)	Resistance
15	Sibhatu et al., 2011	Oromia	extensive	sheep	tetramizole	15 mg/kg oral	30	100	-98,100	Susceptible
16	Melaku, et al., 2013	Amhara	extensive	sheep	levamisole	15 mg/kg oral	8	90.1	(86.3, 94.8)	Resistance
17	Lidetu, 2009	Oromia	intensive	Goat	Levamisole	7.5 mg/kg oral	30	92	(78, 97)	Resistance
18	Lidetu, 2009	Oromia	intensive	Goat	Levamisole	7.5 mg/kg oral	20	96	(88,99)	Resistance
19	Lidetu, 2009	Oromia	intensive	Goat	Levamisole	7.5 mg/kg oral	20	89	(77,94)	Resistance

20	Lidetu, 2009	Oromia	intensive	Goat	Levamisole	7.5 mg/kg oral	20	93	(80,98)	Resistance
21	Menkir. et al., 2006	Oromia	semintensive	sheep	tetramizole	15 mg/kg oral	20	94	(92,96)	Susceptible
22	Menkir. et al., 2006	Oromia	semintensive	sheep	tetramizole	15 mg/kg oral	20	95	(98, 89)	Susceptible
23	Menkir.et al., 2006	Oromia	semintensive	sheep	tetramizole	15 mg/kg oral	20	96	(95,97)	Susceptible
24	Menkir. et al., 2006	Oromia	intensive	Goat	tetramizole	15 mg/kg oral	20	57	(48,68)	Resistance
25	Menkir. et al., 2006	Oromia	intensive	Goat	tetramizole	15 mg/kg oral	20	62	(54, 69)	Resistance
26	Menkir.et al., 2006	Oromia	intensive	Goat	tetramizole	15 mg/kg oral	20	95	(94,96)	Susceptible
27	Asmare, et al., 2006	SNNP	extensive	sheep	tetramizole	15 mg/kg oral	30	97.7	(93, 99.5)	Susceptible
28	Asmare, et al., 2006	SNNP	intensive	goat	tetramizole	15 mg/kg oral	30	98.6	(96,99.1)	Susceptible
29	Asmare, et al., 2006	SNNP	extensive	goat	tetramizole	15 mg/kg oral	30	98.2	(95,99.2)	Susceptible
	Total						728			R=11/29

Table 5: Description of selected studies in the systematic review and meta–analysis of small ruminants infected with nematodes and effect of Tetramizole/Levamizole according to Coles, et al**.**

S. no.	Author	region	management	spp	type of drug	dose and route	#animals	FECRT	95% CI of FECRT	Remark
1	Terefe, et al. 2013	Oromia	Extensive	Sheep	ABDZL	7.5 mg/kg oral	90	95.6	(93.6,97.6)	Susceptible
2	Seyoum, et al.,2017	Amhara	Extensive	Sheep	ABDZL	7.5 mg/kg oral	20	97.2	(93.3, 98.8)	Susceptible
3	Sheferaw, et al., 2015	Oromia	Extensive	Goat	ABDZL	7.5 mg/kg oral	40	95.9	(89.3,98.4)	Resistance
4	Ahmed, et al., 2017	Oromia	Extensive	Sheep	ABDZL	7.5 mg/kg oral	30	97.59	(95.5, 99.9)	Susceptible
5	Melaku et al., 2013	Amhara	Extensive	Sheep	ABDZL	7.5 mg/kg oral	8	99.1	97.9, 100.	Susceptible
6	Sheferaw et al., 2010	SNNP	Extensive	Sheep	ABDZL	7.5 mg/kg oral	20	99.3	96.0,100	Susceptible
7	Regassa, et al., 2013	Oromia	Extensive	Sheep	ABDZL	7.5 mg/kg oral	20	100	98,100	Susceptible
8	Regassa, et al., 2013	Oromia	Extensive	Goat	ABDZL	7.5 mg/kg oral	20	100	98,100	Susceptible
9	Niguse et al., 2014	Somali	Extensive	Sheep	ABDZL	7.5 mg/kg oral	12	97.8	94.9, 100	Susceptible
10	Kumsa and Abebe, 2009	SNNP	Intensive	Goat	ABDZL	7.5 mg/kg oral	30	48	0,74	Resistance

11	Kumsa and Abebe, 2009	SNNP	Intensive	Goat	ABDZL	7.5 mg/kg oral	30	52	0,77	Resistance
12	Kumsa and Abebe 2009	SNNP	Intensive	Goat	ABDZL	7.5 mg/kg oral	30	67	27,85	Resistance
13	Sibhatu et al., 2011	Oromia	Extensive	Sheep	ABDZL	7.5 mg/kg oral	30	100	100	Susceptible
14	Seyoum,et al.,2017	Amhara	Extensive	Sheep	ABDZL	7.5 mg/kg oral	20	97.2	93.3, 98.8	Susceptible
15	Seyoum,. et al.,2017	Amhara	Extensive	Sheep	ABDZL	7.5 mg/kg oral	20	97.2	93.3, 98.8	Susceptible
16	Menkir, et al., 2006	Oromia	Semintensive	Sheep	ABDZL	7.5 mg/kg oral	20	94	91,95	Susceptible
17	Menkir, et al., 2006	Oromia	Semintensive	Sheep	ABDZL	7.5 mg/kg oral	20	94	89,96	Resistance
18	Menkir, et al., 2006	Oromia	Semintensive	Sheep	ABDZL	7.5 mg/kg oral	20	96	95,97	Susceptible
19	Menkir, et al., 2006	Oromia	Intensive	Goat	ABDZL	7.5 mg/kg oral	20	57	49,63	Resistance
20	Menkir, et al., 2006	Oromia	Intensive	Goat	ABDZL	7.5 mg/kg oral	20	61	52,68	Resistance
21	Menkir, et al., 2006	Oromia	Intensive	Goat	ABDZL	7.5 mg/kg oral	20	95	94,96	Susceptible
22	Asmare, et al., 2006	SNNP	Extensive	Sheep	ABDZL	7.5 mg/kg oral	30	100	100	Susceptible
23	Asmare et al., 2006	SNNP	Intensive	Goat	ABDZL	7.5 mg/kg oral	30	99.96	98.9,100	Susceptible
24	Asmare et al., 2006	SNNP	Extensive	Goat	ABDZL	7.5 mg/kg oral	30	99.4	97.9,99.9	Susceptible
	Total						630			R=7/24

Table 6: Description of selected studies in the systematic review and meta–analysis of small ruminants infected with gastro intestinal nematodes and the effect of Albendazole (ABDZL) according to Coles, et al.

S. no.	Author	region	management	spp	type of drug	dose and route	# animals	FECRT	95% CI of FECRT	Remark
1	Terefe, et al. 2013	Oromia	Extensive	sheep	Ivermectin	0.2 mg/kg inject	90	96.7	(94.5,98.8)	Susceptible
2	Seyoum, et al.,2017	Amhara	Extensive	sheep	Ivermectin	0.2 mg/kg inject	20	97.7	(94.0,99.1)	Susceptible
3	Sheferaw et al., 2015	Oromia	Extensive	goat	Ivermectin	0.2 mg/kg inject	40	91.8	(83.3,96.0)	Resistance
4	Ahmed, et al., 2017	Oromia	EXtensive	sheep	Ivermectin	0.2 mg/kg inject	30	99.6	(96.7, 100)	Susceptible
5	Melaku et al., 2013	Amhara	Extensive	sheep	Ivermectin	0.2 mg/kg inject	8	96.7	(93.4,99.5)	Susceptible
6	Sheferaw et al., 2010	SNNP	Extensive	sheep	Ivermectin	0.2 mg/kg inject	20	98.3	(97.5,99.6)	Susceptible
7	Regassa, et al., 2013	Oromia	Extensive	sheep	Ivermectin	0.2 mg/kg inject	20	95.7	(91.5,97.6)	Susceptible
8	Regassa, et al., 2013	Oromia	Extensive	goat	Ivermectin	0.2 mg/kg inject	20	100	-98,100	Susceptible
9	Niguse, et al., 2014	Somali	Extensive	sheep	Ivermectin	0.2 mg/kg inject	12	100	(96.5, 100)	Susceptible

10	Kumsa and Abebe, 2009	SNNP	Intensive	goat	Ivermectin	0.2 mg/kg inject	30	71	(0,94)	Resistance
11	Kumsa and Abebe,2009	SNNP	Intensive	goat	Ivermectin	0.2 mg/kg oral	30	76	(63,85)	Resistance
12	Kumsa and Abebe,2009	SNNP	Intensive	goat	Ivermectin	0.2 mg/kg oral	30	78	(6,86)	Resistance
13	Menkir, et al., 2006	Oromia	Semintensive	sheep	Ivermectin	0.2 mg/kg inject	20	95	(93,96)	Susceptible
14	Menkir, et al., 2006	Oromia	Semintensive	sheep	Ivermectin	0.2 mg/kg inject	20	96	(91,98)	Susceptible
15	Menkir, et al., 2006	Oromia	Semintensive	sheep	Ivermectin	0.2 mg/kg inject	20	98	(95,99)	Susceptible
16	Menkir, et al., 2006	Oromia	Intensive	Goat	Ivermectin	0.2 mg/kg inject	20	67	(60,73)	Resistance
17	Menkir, et al., 2006	Oromia	Intensive	Goat	Ivermectin	0.2 mg/kg inject	20	70	(64,75)	Resistance
18	Menkir, et al., 2006	Oromia	Intensive	Goat	Ivermectin	0.2 mg/kg inject	20	98	(97,98)	Susceptible
19	Asmare, et al., 2006	SNNP	Extensive	sheep	Ivermectin	0.2 mg/kg oral	30	100	100	Susceptible
20	Asmare, et al., 2006	SNNP	Intensive	goat	Ivermectin	0.2 mg/kg inject	30	99.9	(98.7,100)	Susceptible
21	Asmare, et al., 2006	SNNP	Extensive	goat	Ivermectin	0.2 mg/kg inject	30	99.5	(97.5,100)	Susceptible
22	Seyoum, et al.,2017	Amhara	Extensive	sheep	Ivermectin	0.2 mg/kg inject	20	97.7	(94.0,99.1)	Susceptible
23	Seyoum, et al.,2017	Amhara	Extensive	sheep	Ivermectin	0.2 mg/kg inject	20	97.7	94.0, 99.1	Susceptible
	Total						600		R= 6/23	

Table 7: Description of selected studies in the systematic review and meta–analysis of small ruminants infected with gastro intestinal nematodes and the effect of Ivermectin according to Coles, et al.

Type of observation	N*	No. animals	FECRT*	AR	± SD	mini	maxi
Tetra/levamizole							
Region Amhara	5	76	95.2	N	4.98	89.5	98.9
Oromia	16	440	91	Y	21.8	57	100
SNNPR	7	200	91	Y	8.9	80.1	98.8
Somali	1	12	100	N	-	96.5	100
Species Sheep	15	368	96.7	N	3.41	90.1	100
Goat	14	360	87.1	Y	13.31	57	98.6
Mgmt. Extensive	15	398	97.2	N	3.17	90.1	100
Intensive	11	270	84.3	Y	14.6	57	98.6
Semi-intensive	3	60	95	N	1	94	96
Albendazole							
Region Amhara	4	68	97.7	N	0.95	97.2	99.1
Oromia	12	350	90.5	Y	14.91	57	100
SNNPR	7	200	80.8	Y	24.2	48	99.9

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Somali	1	12	97.8	N	-	94.9	100
Species Sheep	14	360	97.5	N	2	94	100
Goat	10	270	77.5	Y	22.3	48	100
Mgmnt. Extensive	14	390	98.3	N	1.6	95.6	100
Intensive	7	180	68.6	Y	16.9	48	99.9
Semi-intensive	3	60	94.7	Y	1.15	94	96.8
Ivermectin							
Region. Amhara	4	68	97.5	N	0.5	96.7	97.7
Oromia	11	320	91.2	Y	11.7	67	100
SNNPR	7	200	88.9	Y	13.2	71	100
Somali	1	12	100	N	-	100	100
Species Sheep	13	330	97.6	N	10.9	95	100
Goat	10	270	85.12	Y	11.9	67	100
Mgmnt. Extensive	13	360	97.8	N	10.9	95.7	100
Intensive	7	180	79.9	N	13.7	67	99.9
Semi-intensive	3	60	96.3	N	1.53	95	98
N*=number of studies, FECRT*=average value of the respective group; AR=Anthemintics resistance, No (N) or Yes (Y), Mgmnt=management.							

Table 8: Pooled average value of anthelmintic efficacy per region, species and farm management of Tetramizole/Levamizole, Albendazole and Ivermectin against gastrointestinal nematodes in small ruminants.

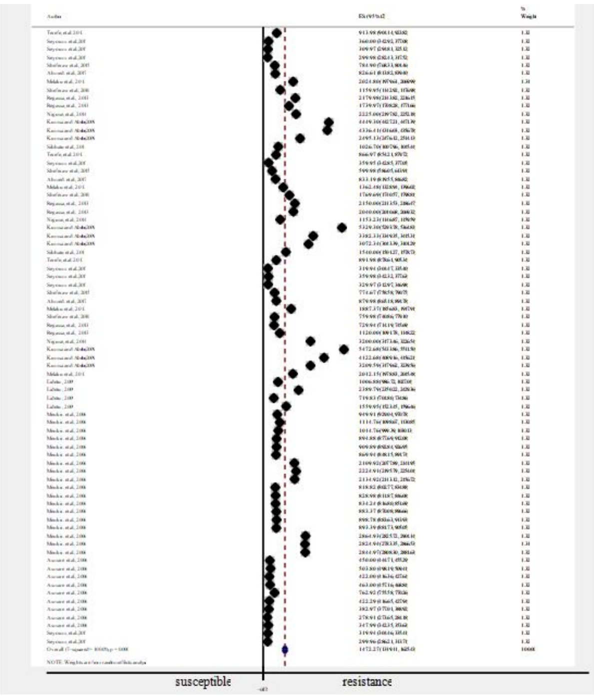

Figure 2: Forest plot about the seventy six studies included in the meta-analysis of anthelmintic resistance of small ruminants infected by gastrointestinal nematodes.

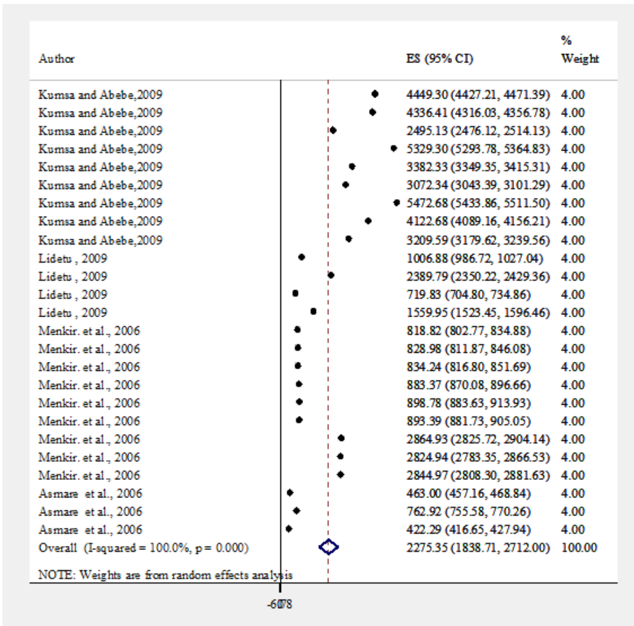

Figure 3: Forest plot of sub group analysis in intensive farm with 25 studies included in the meta-analysis of anthelmintic resistance of small ruminants infected by gastrointestinal nematodes.

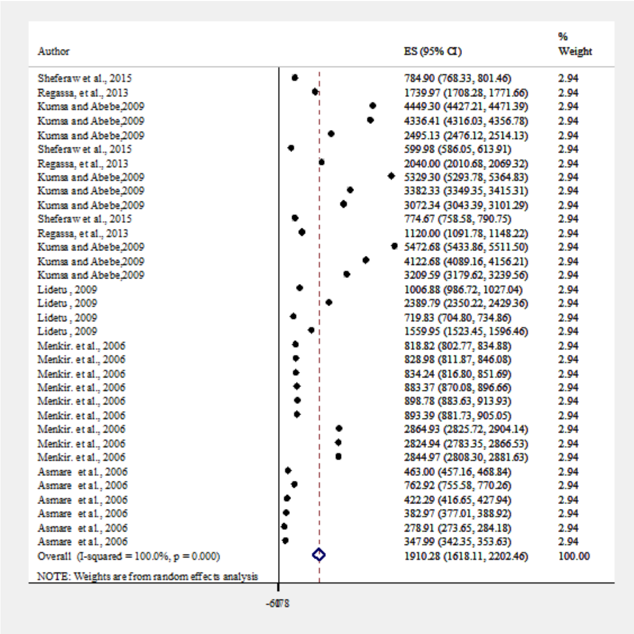

Figure 4: Forest plot of sub group analysis with 34 studies included in the meta-analysis of anthelmintic resistance of goats infected by gastrointestinal nematodes.

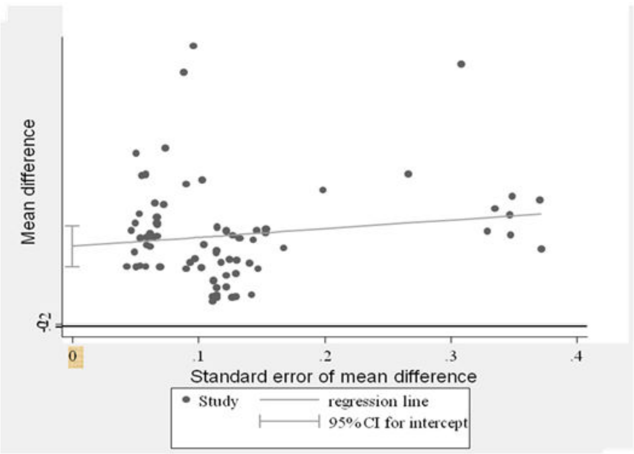

Figure 5: Funnel plot obtained with linear random effect model for 76 studies measuring mean difference and showing the dispersion from regression line.

Discussion

Livestock production was severely hampered due to diseases including parasitism, despite its significant contribution to gross domestic products. The present study contributes to understanding the epidemiological aspect of parasitism about anthelmintics resistance in small ruminants of Ethiopia. Furthermore, it was also assessed the research design used by different scholars, their limitations and their strength. On top of these, based on the information extracted from the selected article, the status of anthelmintics efficacy or resistance were summarized. The search engine indicated that the majority of research work was on small ruminants and few in horse and cattle. Therefore, data related to small ruminants anthelmintics resistance studies were used for this systematic review.

Small ruminant production is an economically important sub-sector of agriculture worldwide in general, in Ethiopia in particular. However, gastrointestinal nematode infection remained one of the health constraints to increase productivity. Anthelmintics treatment is the only means of gastrointestinal nematode control for the last 60 years, which resulted in the emergence of drug resistance. This systematic review summarized the level of anthelmintics resistance in the country and associated risk factors such as species of animals, management type and region assessed. Among other risk factors route of administration that lower the bioavailability of drug has been suggested as a risk factor. However, in this review route of administration was not considered as a risk factor because there was no studies that compare between the route of administration. All studies selected in this review were used one route of administration applied in each type of drugs (either oral administration or injectable). Research finding suggests that oral administration of anthelmintics is more effective than another route. Though it has been proven that orally administered anthelmintics are more effective than injectable or pour-on application of the same type of drug. The physiological status of the host, fasting, lactation, body condition affects absorption and bioavailability of drugs administered.

Studies of anthelmintics resistance were reported in four region of the country where the study conducted. Which is inaggreement with systematic review of Falcon, et al. who reported anthelmintics resistance distributed throughout the world, regardless of variation in the study protocol? All articles selected in this study were based on FECRT criteria. The use of faecal egg count reduction percentage test is more accessible and less costly than necropsy findings. Moreover, the EPG test has a high correlation between the actual presence of nematodes and the predicted values obtained through this test. The diagnostic method for AHR determination is important as it allows quantifying the values to implement the proper disease control management. The faeces test using the McMaster technique, and the coculture test are more accessible tests than the necropsy test; most studies were in-line with faecal egg count reduction percentage.

Underdosing may cause increased AHR. However, studies used below the prescribed dose were excluded from the systematic review and only studies with recommended doses were subjected to meta-analysis to avoid ambugiety.

Despite the exclusion of underdosed experiment, AHR was recorded in three drugs used (Tetramizole/Levamisole, Albendazole, Ivermectin), but which species of strongyle resitance to anthelmintics were not recorded because all the primary studies were selected based on FECRT and there was no further worm count or species identification. A recent study by Leathwick and Luo evaluated the change in gene frequency at different dosing rates and concluded that AHR was increased at a lower and more variable dose. None of the articles among selected have shown a study on dose rate comparison against gastrointestinal nematode in small ruminants and hence difficult to discuss here with other findings.

This analysis shows a high level of significant heterogeneity was observed in pooled estimates. This might be associated with the type of studies included in the MA, where all study designs were observational studies (cohort studies). Such studies could be affected by multiple factors that may include biological (helminths species, host species, age and sex), environmental (agro-ecology, livestock composition, sample size and farming system), types and frequent use of anthelmintic drugs and interaction of factors, which could lead to the selection and confounding biases. Similar high heterogeneity was observed in observational studies. It was suggested to conduct further sub-group analysis and meta-regression, which assists to clarify the elucidation of underlying causes of heterogeneity between studies can provide valuable information for future research (Higgins). In this studies subgroup analysis on intensive farm and goats indicated high heterogeneity which reflects the differences in effect size. Tau-squard value also was high in both subgroup analysis showed the dispersion of true effect sizes between studies.

The presence of publication bias observed in this review. False positive results can be reported in the process of publication bias evaluation in the presence of heterogeneity. The heterogeneity obtained in most of the MA could be contributing to the discordant publication bias results presented in result section. The bias could be also partly due to exclusion and inclusion criteria of articles. Articles with combined drug treatment and those under dosed were excluded.

Anthelmintics resistance of GIN was observed in all regions, farm management and in both sheep and goats, which is in agreement with (Sutherland and Leathwick), AHR become a worldwide concern. This study showed anthelmintics resistance more consistently observed in all three drugs (Tetramisole/Levamisole, Albendazole and Ivermectin) used in goats and intensive farming system; which is in agreement with a systematic review and MA where 83.3% (95% CI=73.5% to 93.1%) of the studied farms presented resistance to macrocyclic lactones; 47.0% (95% CI=27.6% to 66.4%) to the Benzimidazole and 45.1% (95% CI=19.1% to 71.2%) to Imidazothiazole. This findings draw attention that the existing anthelmintics efficacy, for how long does it serve.

This might be associated with regular treatment in the intensive farm, where there is less contamination of susceptible larvae as compared to extensive farms. In which regular treatment increases the selection pressure of resistant parasites. In line with this goats are browsing animals that have low exposition to susceptible refugia larvae and coupled with regular treatment will increase selection pressure of resistant parasites in goats. In addition, goats have a higher metabolic activity than sheep and thus require higher dose rates for effective treatment. The use of sheep dose for both species leads to the selection of resistant parasites in goats so that resistance can then be transferred to sheep. All studies selected didn’t consider dose differences for goats. Hence equal dose with sheep coupled with frequent treatment in less contaminated intensive farms might be the reason to observe more AHR in goats. The finding was in agreement with Falzona et al., where frequent treatment included as a risk factor in MA showed a significant difference ($p<0.05$). Frequent treatment increases the selective advantage for resistant parasites, as they survive the treatment and can reproduce, allowing for an increase in the proportion of resistant parasites over time showed in pooled estimate in the MA indicated that flocks that were treated more frequently had higher odds of having resistance, compared to those farms that treated less often.

The role of refugia in managing resistance parasites has paramount importance in reducing AHR. In addition, the use of anthelmintics in suboptimal doses, prophylactic mass treatment of domestic animals, and frequent and continuous use of a single drug have a significant contribution to the widespread of anthelmintic resistance parasite. Such unwanted practice in the control of parasitism needs to be improved to overcome anthelmintics resistance.

Extensive management has a positive impact in reducing or diluting resistant parasites, when animals are left to graze in an uncontrolled pasture, there is a possibility of ingesting susceptible L3 larvae. This will cross-bred with the resistance group and resulting in susceptibility, consequently increasing susceptibility within resistant parasite groups. A continuous exercise of such uncontrolled grazing ultimately dilutes resistant parasites. In this review also possible to appreciate that the average value of the faecal egg counts reduction test in extensive farming shown above 95%, which is an indication of susceptibility according to Coles et al. The role of refugia is an important factor behind the management system to maintain susceptible parasite populations in grazing areas. A rotational grazing system considering the parasite life cycle and the use of annual alternative drugs helps to reduce anthelmintic resistance which gives the effective result to use chemoprophylaxis without developing drug resistance for long periods.

Though the detailed analysis based on region, species of animal and management showed a difference in anthelmintics resistance, the forest plot of this study showed the summarized result with the centre of dot line, indicating the average value of effect size have no significant variation between resistance and susceptibility. In other studies, forest plot has also demonstrated efficiently the differences. This different finding might be due to data differences in the two studies, but finding related to reisitance should not be overlooked in the country based on statistical values which is not plausible in this regard.

Limitation of the study

The present study showed heterogeneity and tau-squared, indicating difference in effect size and wide dispersion of effect size. The study was not evenly distributed throughout the region, only four regions out of eleven regions have reported; of these two regions namely, Oromia and SNNPR took the leading share. All studies were observational studies, there was no artificially challenged closed experimental work, hence highly prone to confounding bias. Anthelmintics resistance reported was based only on FECRT, which didn’t have information about which species of strongyle is resistant to anthelmintics drugs. Absences of egg hatch assay, post-moreteum finding and worm count were among the limitations or information gap in primary literature.

Conclusion

Anthelmintics resistance reported in four region is an indication of the spread of the problem in Ethiopia. Risk factors like intensive farm and goats were showed the highest AHR according to pooled analysis of anthelmintics efficacy, whereas extensive farming served as protective risk factor. The problem of resistance were observed across all anthelmintics drugs used. Despite high heterogeneity and limitation of research reports in this systematic review the problem of anthelmintics resistance shown as emerging constraint in livestock production and productivity. Therefore, maintaining the refugia are paramount important to conserve drug-susceptible parasite, and hence selected and balanced treatment application based on the severity of infection should be practiced. Mass treatment should not be applied, as this approach encourages the selection of resistant parasite. Continuous and regular treatment using single drug also encourage resistance parasite; therefore programmed treatment using alternative drug will have a great contribution in reducing resistance.

Authors' Contributions

Solomon M. searched published articles, data extraction, data analysis, and write-up the manuscript.

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