

A Review on Anthelmintic Resistance and Potential Risk Factors in Domestic Ruminants

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Abstract: Chemotherapy remains the main control method of helminth infections, optimized anthelmintic usage is important to preserve anthelmintic efficacy and prevent resistance. Studies of drug efficacy and resistance can help to increase the efficacy or the shelf life of the few drugs available and to reduce its effect on economy. Ability to detect resistance is useful to determine the prevalence of resistance in specific geographical regions or can also prevent the use of useless and toxic drugs for patients infected with resistant parasites. The understanding of resistance mechanisms help to develop or, to propose new strategies for chemotherapeutic interventions. Preventing seasonal buildup of parasite contamination is important to minimizing parasite resistance from developing within the animals. Diagnosis of the level of parasite infection is essential in order to decide the appropriate treatment and control measures. The resistance detection methods such as *in-vivo* faecal egg count reduction tests and *in-vitro* egg hatch assays, larval paralysis and motility tests, larval development assay and adult development test, have been developed for the detection of resistance to the main anthelmintic groups. Parasite biology, parasite genetics, managemental factors and operational factors are major potential risk factor for resistance. The mutation of gene receptor in macrocyclic lactone, b-tubulin gene-isotypes mutation in benzimidazole group, the change/or reduction in receptor as in levamisole group and as well as overexpression of g-protein in avermectins group are the main mechanisms of anthelmintic drug resistant. Therefore, correct dose supply, rotation anthelmintics, quarantine newly coming stocks and alternative management strategies including, breeding resistance breed and biological control of parasites (*Duddingtonia flagrant*) are good management strategies to overcome the resistance development.

Key words: Anthelmintics • Anthelmintic Efficacy And Potency • Anthelmintic Resistance • Helminthes • Ruminants

INTRODUCTION

Ethiopian livestock production systems are broadly characterized as low input, mixed crop-livestock, agro-pastoral and pastoral systems; as well as medium input, peri-urban and urban enterprises however, they make a critical contribution to food self-sufficiency for rural households by providing milk, meat, skin, manure and traction, as well as generating direct cash income. In addition, livestock are a source of risk mitigation against crop failures [1]. Despite the large livestock population of Ethiopia, the economic benefits remain marginal due to prevailing diseases, poor nutrition, poor animal production systems, reproductive inefficiency, management constraints and general lack of veterinary care. Among the most prevalent animal diseases, helminth parasitism is the one, which is responsible for the death of

one third of calves, lambs and kids and considerable losses of parts of carcasses condemned during meat inspection [2]. Helminthiasis caused by nematodes, trematode and cestodes is the most important cause of production loss in small and large ruminants in many parts of the world. In addition, it has been estimated that helminths infect a quarter of the world's population and are a major cause of morbidity, anemia, malnutrition and immunosuppression in the tropics and some temperate regions [3]. Irreparable physical and physiological damages, sometimes exacerbated by cognitive retardation, loss of productivity among the workforce and maintenance of poverty are often the indubitable consequences [4].

Small-holders or pastoralists may not easily detect the effects of internal parasites on their animals, because of the generally sub-clinical or chronic nature of the

helminth infections [5]. Thus, the sub-clinical parasite infections are responsible for significant economic loss, because once clinical disease is noticed in a group of animals much economic loss in terms of animal productivity has already occurred [6]. Therefore, it is important to assess the type and level of parasitism in ruminant livestock, in order to be able to determine the significance of parasite infections and to recommend the most beneficial and economically acceptable control measures.

The causes of helminth parasitism in ruminants are multiple and often interactive, the vast majority of cases are due to any of the following basic reasons an increase in the number of infective stages on pasture, an alteration in host susceptibility, the introduction of susceptible stock into an infected environment [5]. Infections with gastro-intestinal nematodes can have a detrimental effect on animal health leading to clinical and sub-clinical diseases that may result in financial loss and overall decreased productivity [7]. The compulsory and often excessive use of chemo-therapeutics, often in combination with poor management practices has resulted in endoparasite nematodes starting to develop resistance to treatment drugs.

Anthelmintic resistance is the phenomenon of change in gene frequency of a worm's population, produced by drug selection, which renders the minimal effective dosage-previously used to kill a defined portion of the population, or the ability of individual worms to survive the lethal effect of a compound known to have anthelmintic efficacy [8]. The consequence of inappropriate anthelmintic treatment procedures (poor quality drugs, poor dosing procedures, intensive use), has been considered as the main factors for the development resistance against the three classes of broad-spectrum anthelmintic drugs (benzimidazoles, imidothiazoles and macrocyclic lactones) in countries that have significant effect on small and large ruminant populations [9]. Therefore, the objectives of the paper are:

- To review current reports on the status of anthelmintic resistance in domestic ruminants in the world.
- To review the mechanisms of anthelmintic drug resistance.
- To highlight the possible potential risk factors of anthelmintic resistance.
- To review the resistance management strategies in domestic ruminants.

Overview of Anthelmintic and Their Efficacy: Resistance development occurs, 'when greater numbers of individuals in a parasite population, usually affected by a dose or concentration of compound, are no longer affected (or a greater concentration of drug is required to reach a certain level of efficacy). Most anthelmintic generally have a wide margin of safety, considerable activity against immature (larval) and mature stages of helminths and a broad spectrum of activity [8]. Nonetheless, the usefulness of any anthelmintic is limited by the intrinsic efficacy of the drug itself, its mechanism of action, its characteristics of the host animal (e.g. Operation of the esophageal groove reflex) and characteristics of the parasite (e.g. Its location in the body, its degree of hypobiosis) [8]. Many highly effective and selective anthelmintics are available, but such compounds currently are used Incorrectly, injudiciously and without consideration of the parasite/host interaction that fail to obtain a favorable clinical response. Under dosing is likely to result in lowered efficacy and possibly increased pressure for selection of resistance and overdosing result in toxicity without necessarily increasing product efficacy [10].

Anthelmintic Drug Efficacy: A drug effects can be evaluated in terms of potency, efficacy, or effectiveness. Ahs drug efficacy, or intrinsic activity: is the maximal effect of the drug can produce. In pharmacodynamics, efficacy refers to the capacity of a drug to produce an alteration in a target cell/organ after binding to its. Potency is a comparative measure, refers to the different doses of two drugs needed to produce the same effect. Effectiveness: refers "how the drug works in a real world situation, " and is "often lower than efficacy because of interactions with other medications or health conditions of the patient, receptor [11].

Standards for Rating Anthelmintic Efficacy: Anthelmintics have been developed to achieve over 98% efficacy against the common parasitic nematodes when used at their effective dose (ed). In general, to be economically successful, a new product should have broad spectrum, high activity against all major nematodes, both adult and larval stages, or fulfill a specific niche against parasites such as trematodes or cestodes or nematodes not controlled by present products [12]. The world association for advancement of veterinary parasitology (waavp) recommends the followings: the claims for efficacy of a product should be expressed

against each genus, or species (larvae, or adults) as highly effective (over 98%), effective (90-98%), moderately effective (80-89%) or insufficiently active (less than 80%). This classification should be used for the rating of products for nematodes, trematodes and cestodes. Dose rates on the product label should be based on body weight. Knowledge of the mode of action of a product should not be a requirement for registration. However, it may be useful to establish whether the product will be effective against resistant strains of parasites. For example, bzl and avermectin/milbemycins are usually active products against arrested larvae of bovine and ovine *Ostertagia* whereas levamisole and morantel are inactive at arrested larvae (hypobiosis larvae). So efficacy of drug is affected by epidemiological and pathological conditions, dose, gut transit time, pharmacodynamic activities (pda) and persistence activities (pa) of the drug [8].

Potential Factors Contributing to Antiphrostatic

Resistance Parasite Factors: Genetics (mutation: point, or multiple gene), biology, cystation, hypobiosis [13]. Hypobiosis and cystation are the behaviours of the parasites that exhibited by undergoing avoidance mechanism from host immune attack while they are not metabolically fit with the host in case anthelmintic drugs fail to inhibit the parasite activities and there after these parasites become re-activated later and will be exposed to residual drugs either in the host, or in the environment that increases their resistance capacity time to time. Biology and genetic factors are described below.

Parasite Biology: Parasites have short generation time as well as high prolificacy. So there is high increase in generation with spread of resistance alleles in the population. Therefore, their life cycle contributes to resistance. For example, in indirect life cycle parasite populations tend to be mobile as hosts are moved there by leaving low levels of untreated parasites in refugia [13].

Parasite Genetics: Many parasites of veterinary importance have genetic features that favor the development of anthelmintic resistance. Among the most important of these are rapid rates of nucleotide sequence evolution and extremely large effective population sizes that give these worms an exceptionally high level of genetic diversity [14]. It appears, however, that several environmental factors affect how quickly or how often resistant parasites flourish. In addition, most nematode

species that have been studied demonstrate a population structure consistent with high levels of gene flow, suggesting that host movement is an important determinant of nematode population genetic structure. Thus, these worms possess not only the genetic potential to respond successfully to chemical attack, but also the means to assure dissemination of their resistant genes through host movement [15]. Resistance alleles might be dominant, as suggested for resistance to the avermectins and/or milbemycins [16]. If heterozygotes are resistant, then clinical resistance will be apparent at much lower allele frequencies than if resistance is recessive. There might be few genes, or only one, involved in resistance. The bigger the effect of each individual change, the faster resistance will tend to develop. The high genetic diversity of parasitic helminths coupled with their large populations, increases the likelihood that resistance alleles will already be present in a population, possibly at relatively high frequency [17].

Treatment Factors: Treatment factors such as underdosing, which is a common problem, are likely to favor the survival of heterozygous individuals, possibly enhancing the selection pressure for resistance. And frequency of dosing, frequent and repeated use of the same drug class of anthelmintic was determined to be a considerable risk factor for development of resistance. The consequence of inappropriate anthelmintic treatment procedures (e.g. Poor quality drugs, poor dosing procedures, intensive use, etc.), has been the development of resistance to the three classes of broad-spectrum anthelmintic drugs (benzimidazoles, imidothiazoles and macrocyclic lactones) in countries that have significant effect on small and large ruminant populations [9].

Host-Parasite Relationship: The epidemiology of nematode parasites of ruminants is also strongly influenced by aspects of host-parasite biology after infection occurs and larvae of important GI nematodes are able to undergo a period of arrested development (hypobiosis) in the host (in the abomasal or intestinal mucosae). Following infection, larvae may become metabolically inactive for several months [18]. Although the immune status of the host also has an influence on rates of hypobiosis, the greatest proportion of larvae usually becomes arrested at times when conditions in the external environment are least favorable for development and survival of eggs and larvae that reduces the refugia to drug of arrested larvae inaccessible [19].

Managemental Factors: Relying solely on antiparasitic drugs to control parasites, rather than changing management practices using only drugs instead of incorporating methods to preserve refugia and better manage the pasture can speed up antiparasitic resistance. In certain livestock management practices, when a producer administers a parasite-control product and fails to see a result, the efficacy of that product is in question. The question becomes, why was the product not efficacious? Was it excessive parasite burden? Was the proper dose given for the animal's body weight? Was the timing wrong, allowing for re-infection through grazing? Or had the resistant parasites in the herd reached damaging levels? How producers handle the cattle, their stocking rate and age of cattle, pasture contamination level at the start of grazing and weather conditions all help determine parasite challenges more than location. The intensive use of antiparasitic drugs also increases the risk of drug residues in animal products [20].

Operational Factors: The chemical nature of the drug used (mechanism of action and rotation of chemicals): no rotation and very frequent rotation equally contribute the spread of resistance. Frequency and timing of dosing's: frequent and continuous uses of ahs from one family, as well as from one or two treatments only contribute for high refugia. Dose rates: under dosing, high dose promotes dangerous condition of resistance, grazing management and weather, movement of stock between farms [8]. Treating every animal in the herd or treating the entire herd eliminates susceptible parasites from all animals at once. This may increase the proportion of resistant parasites in the population. Frequent routine deworming without performing diagnostic tests or determining if treatment is necessary, herd variation, this stands to reason because no two cattle operations are managed the same or is their history of deformer use the same, deworming when environmental refugia is low, treating animals when there are few eggs on the pasture, such as after a harsh winter or hot, dry summer, increases the proportion of resistant eggs in the environment. Using antiparasitic drugs for unapproved uses, such as to increase weight gain in the short-term, increases the opportunities to eliminate susceptible parasites, leaving only resistant parasites behind [21] and based on scops principles, there are five key factors which define the rate resistance develops which includes: proportion of resistant worms on a farm, frequency of anthelmintic use, efficacy of each treatment, proportion of the total worm population in the animal and dilution of any worms that survive treatment with unselected worms [22].

Resistance and Resistance Development

Types of Resistance: There are the different types of resistance that are side-resistance, cross-resistance and multiple resistances. The side and cross resistances are condition in which a drug-selected population has a gene coding for a mechanism that defeats the toxicity of the drugs within a mode of action families and from different mode of action families, respectively whereas multiple drug resistance (mdr) is a state in which a population has been selected independently by drug from different mode of action families to produce different but concurrent mechanism of evasion [8].

Essential Features of Drug Resistance and Historical Development of Anthelmintics:

The effect of drug resistance includes inheritable physiological property, resistance development is evolutionary, is based on genetic variability/due to holding alleles of a resistance [8]. Resistance is probably an inevitable consequence of the use of anthelmintic and the history of parasite resistance to anthelmintic starts with the first report on phenothiazine resistance approved in 1957. *Haemonchus contortus* was the first nematode to develop resistance against the different anthelmintics [23]. In most regions of africa, the development of anthelmintic resistance could be expected to be slow, because of limited availability and infrequent use of anthelmintics by most small-scale farmers. The exception is south africa, where on large-scale commercial sheep farms the intensive use of anthelmintics for several decades has led to very high levels of multiple anthelmintic resistances [24]. However, the overall prevalence of anthelmintic resistance has not been extensively investigated throughout the african continent, anthelmintic resistance in sheep and goat parasites has been reported from at least 14 countries [25]. There are several phases in the process of resistance development. Firstly, there is an initial phase of susceptibility where the number of resistant individuals within the parasite population is low with continued exposure to the same drug group. An intermediate phase then follows in which the frequency of heterozygous resistant individuals within the population increases. Finally, sustained selection pressure results in a resistant phase where homozygous resistant individuals predominate within the population [26]. The speed of this process will depend on how severe the selection pressure is on the parasite population. It is known that this is linked to the frequency of treatment and the fact that widespread and excessive use (8 to 12 times per year) of the drugs without considering the epidemiology and ecology of the parasites, has led to the

Table 1: Major reported resistances to commonly used anthelmintics

Host	Helminth parasite	Broad-spectrum anthelmintic					Group-specific anthelmintic						
		Izs			Mls		Sns						
		Bzs	M/p	Lev	Ivm	Mxd	dmt	mbc	Cst	Rxn	Opp	Onq	Ppz
Sheep	<i>Trichostrongylus</i> spp.	+		+	+	+		+	+		+		
	<i>Haemonchus contortus</i>	+	+	+	+	+			+	+			
	<i>Teladorsagia</i> spp.	+		+	+	+		+	+				
	<i>Cooperia curticei</i>												
	<i>Nematodirus</i> sp.												
	<i>Fasciola hepatica</i>	+								+			
Goat	<i>Trichostrongylus</i> spp.	+		+									
	<i>Haemonchus contortus</i>	+	+	+	+				+		+		
	<i>Ostertagia</i> spp.	+											
Cattle	<i>Trichostrongylus</i> spp.	+											
	<i>Haemonchus contortus</i>	+		+	+	+	+						
	<i>Oesophagostomum</i> spp.								+				
	<i>Trichuris</i> spp.	+			+				+				
	<i>Ostertagia ostertagi</i>	+							+				
	<i>Cooperia</i> spp.	+			+	+	+	+					
	<i>Fasciola hepatica</i>												

bzs = benzimidazoles; iza = imidazothiazoles [m = morantel, p = pyrantel]; mls = macrocyclic lactones

[ivm = ivermectin, mxd = moxidectin, drm = doramectin]; sns = salicylanilide [mbc = milbemycin; cst = closantel]; rxn = rafoxanide; opp = organophosphate; oxa = oxamniquine; ppz = piperazin.

source: [31]

development of resistance of the parasites to drugs. There is also evidence that strategic treatments have contributed to resistance development, particularly at times when the free-living component of the parasite population has been small (low level of refugia) the size of the unselected proportion of the parasite populations (refugia) is one of the most important factor affecting the rate of selection of anthelmintic resistance [27]. This unselected parasite populations (including unexposed eggs and larvae on pastures and worms inside the host that are left untreated with anthelmintic) provided a pool of drug-sensitive genes, thus diluting the frequency of resistant genes in a populations of worms [28].

Anthelmintic Resistance in Common Worms in Domestic Ruminants: The real drug resistance in common worm infections is not yet widespread in human medicine, but as it is in veterinary medicine [29]. There are mainly three broad-spectrum anthelmintics available for the control of helminths. The earliest reports of anthelmintic resistance in sheep involved bzs, followed by resistance to lev and finally resistance to mls [30]. Reports on the prevalence of anthelmintic resistances are summarized in Tebla 1.

Mechanism of Anthelmintic Resistance: Anthelmintic drug resistance can arise in a limited number of ways: 1) a change in the molecular target, so that the drug no longer recognizes the target and is thus ineffective; a change in metabolism that inactivates or removes the drug, or that prevents its activation; 2) a change in the distribution of the drug in the target organism that prevents the drug from accessing its site of action; or amplification of target genes to overcome drug action [32]. Those mechanisms implicated in anthelmintic resistance are summarized in Table 2.

Benzimidazoles: Benzimidazoles act by inhibiting polymerization of b-tubulin to form microtubules and it is clear that resistance is associated with point mutations in β -tubulin genes that prevent drug binding. However, several different polymorphisms of the β -tubulin genes have been correlated with benzimidazole resistance [34].

Ivermectin: Ivermectine opens worms 'chloride channels which lead to starvation or paralysis. These drugs act on ligand-gated channels, including glutamate (glucl) and gaba-gated (gabacl) chloride channels, a family

Table 2: Anthelmintic family and mechanism of resistance

Anthelmintic family	Mechanisms of resistance	Comments
Benzimidazoles	B-tubulin isotype 1 mutations: f200y, f167y B-tubulin isotype 2 mutations: f200y, f167y, deletion. Altered metabolism and or uptake	The best studied mutations and probably the most important. F200y seems to be the most important mutation in <i>haemonchus contortus</i> , but this might not be true for all species. Also present in <i>h. Contortus</i> , field importance unknown. Might be important in triclabendazole-resistant flukes: importance in nematodes unknown, but probably minor.
Avermectins and milbemycins	Mutations in gluel and/or gaba-r genes Overexpression of p-glycoproteins	Molecular evidence from <i>cooperia oncophora</i> : population genetic evidence from <i>h. Contortus</i> . Population genetic and some pharmacological evidence. The relative importance of these two mechanisms is yet to be determined.
Levamisole	Changes in nicotinic	Physiological and pharmacological evidence: no molecular data to date.

Source: [33]

of receptors widely distributed in nematodes that regulate locomotion, feeding and reproduction [35]. A p-glycoprotein homologue may be responsible for ivermectin resistance in a number of worm genus [36]. In the nematode, simultaneous mutation of genes encoding glutamate-gated chloride channel α -type subunits confers high-level resistance to ivermectin suggesting that both target mutation and transport alteration can lead to ivermectin resistance in worm. Genetic studies have found that ivermectin resistance is dominant in *Haemonchus contortus*, perhaps reflecting a gain-of-function mutation, although it could be that true resistance results from polymorphisms in several closely linked genes. Multiple mutations are required for high-level am resistance in *C. elegans* [37].

Levamisole: Levamisole is the most widely used cholinergic anthelmintic, acting as an agonist at nicotinic acetylcholine receptors (nachr) at the nematode neuromuscular junction (nmj) and causing a spastic paralysis but the resistance mechanism to this class of drugs is yet unknown. A reduction in the number of receptors has nonetheless been proposed as one possible mechanism for resistance [29]. Nematodes resistant to levamisole are also resistant to other nicotinic agonists such as morantel and pyrantel. Membrane preparations from resistant nematodes have reduced binding affinity at a low affinity site for a levamisole analogue [38].

Anthelmintic Resistance and its Detection Methods: Despite success in the development of anthelmintics in the later part of the last century, helminth infections continue to play a significant role in limiting livestock productivity, particularly that of small ruminants

worldwide [39]. The appearance over the last decades of populations of parasitic worms that have developed resistance to one or more of the available anthelmintic groups has threatened livestock productivity globally [40]. The growing importance of anthelmintic resistance has led to an increased need for reliable and standardized detection methods. A variety of in vivo faecal egg count reduction tests and controlled test [13] and *in vitro* (egg hatch assays, larval paralysis, migration and motility tests, larval development assay), adult development test, bio-chemical tests [41] and molecular techniques [42] have been developed for the detection of resistance to the main anthelmintic groups. However, each test has some shortcomings, which may include high cost, poor reliability, reproducibility, sensitivity and ease of interpretation [43].

The Faecal Egg Count Reduction Test: The faecal egg count reduction test provides an estimation of anthelmintic efficacy by comparing faecal egg counts before treatment with those taken 10–14 days after treatment [44]. The arithmetic mean faecal egg counts are used for the interpretation of data and resistance is considered to be present if the percentage of reduction is less than 95% and the 95% lower confidence limit is less than 90%. If only one of the two criteria is met, resistance is suspected. To conduct a fenct, a minimum of 10-15 animals should be randomly selected for the untreated control group, as well as for each drug to be tested [45] according to scops technical journal of (2012) fecs can be used to determine the need to treat, test the efficacy of a treatment and give information on the amount of contamination going onto the pasture.

Table 3: Bioassays for the diagnosis of anthelmintic resistance

Egg hatch	Assay benzimidazoles-levamisole/morantel
Larval paralysis	Levamisole/morantel
Tubulin binding	Benzimidazoles
Larval development	All drugs
Adult development	Benzimidazoles

Source: [47].

In vitro Test: Several different in vitro tests are available but the majority is almost exclusively used for research purposes. These tests can be used to quantify the level of resistance but they require considerable technical expertise and in some cases, expensive laboratory equipment. Ideally, these tests require mono-specific infections. The maintenance of standard laboratory strains, both drug susceptible and resistant is necessary for comparative purposes [46]. The main bioassays are listed in Table 3.

Egg Hatch Assay: Egg hatch assay was developed to differentiate between of the susceptible strain of gastrointestinal tract nematodes for benzimidazole and for levamisole is comparatively more rapid and economic to conduct than fecal egg count reduction test. The principle is based on determination of the proportion of the eggs that fail to hatch in solution of increasing drug concentration in relation to the control wells enabling the user of the test to develop a dose response line plotted against the drug concentration [48].

Larval Paralysis and Motility Assay: The principle is in that it estimates the proportion of the third stage larvae in tonic paralysis after incubation with a range of levamisole and drug concentration to differentiate between resistance and susceptible strain of parasites. It is relatively easy to carry out, fairly good reproducibility of test [48].

Larval Development Assay: This test allows the detection of resistance against all drugs the irrespective of their mode of action for detection of resistance to bzl, levamisole, combination of both, avermectin and milbemycin drenches in git nematodes parasites of sheep, like *H. contortus* and *T. colubriformis*. The test isolate nematode eggs from fecal samples and submitted by producers are applied to the wells of a micro-titer plate and larvae hatch and develop to the 3rd larval stage in the presence of anthelmintics. The concentration of the drug required to block development is related to anticipate *in vivo* efficacy [49].

Tubulin Binding Assay: This test is based on the mode of action of the drugs. The mechanism of benzimidazole resistance appears to be associated with a reduced affinity of tubulin for the anthelmintics. The test is based on the differential binding of benzimidazoles to tubulin, an intracellular structural protein from susceptible and resistant nematodes. The test involves the incubation of a crude tubulin extract from adult parasites, infective larvae or eggs, with a tritiated benzimidazole until equilibrium is reached. The free, unbound drug in test suspension after incubation is removed using charcoal and the tubulin-bound label is sampled and counted by liquid scintillation spectrophotometry. Tubulin extracts from resistant parasites bind substantially less strongly than do those from susceptible parasites. The test is considered to be rapid, highly reproducible and sensitive to minor changes in the resistance status of parasite populations, but it is unsuitable for routine field assays [50].

Adult Development Assay: Adult development assay is used for detecting benzimidazole resistance in trichostrongylid nematodes and *Haemonchus contortus* has been cultured through to the adult egg-laying stages, although this test is mainly for research purposes [15].

Measures Has to Be Taken to Control Drug Resistance
Principal Measures of Resistance (Chemical Controls): Whatever the right time to combat drug resistance is before it becomes apparent and wide spread, the following method and principles has to be applied to reduce resistance risk, or levels and to prevent existing from getting worse. These are use effective anthelmintics, the correct dose, rotate anthelmintic categories on an annual basis, quarantine newly coming stocks (to avoid introducing resistance worm), use minimal number Treatments, treatment frequency, use epidemiological principles of nematode control and integrate dosing with stock management, encouraging farmers to monitor on an annual basis to follow intensive and constant deworming programs [8].

Alternative Control of Resistance: Because of drug resistance a non-chemical control options are considered to be the major approaches to reduce resistance development including management strategies, breeding resistance breed, vaccine development and biological control of parasites before they infect the host (*Duddingtonia flagrant*). Management strategies includes animal targeted methods such as supplement

feeding, herd managements includes herd movements. Alteration of different host species, mixed grazing, tethered husbandry and night housing, exploiting breed resistance and pasture/grazing management which includes stocking rate, provision of safe pasture, rotational grazing or pasture spelling, integrated crop/pasture management, prolonged pasture destocking, clean pasture approach, integrated control strategies for production animals at pasture grouped as preventive strategies, invasive strategies and diluting strategies [8].

CONCLUSION AND RECOMMENDATIONS

The provision of information to farmers and their advisors is crucial in resistance minimization. Optimized anthelmintic usage is important to preserve anthelmintic efficacy and prevent resistance to occur in anthelmintics. Education of the small-holder communities regarding correct ways to improve animal management systems that reduce resistance development is mandatory. Studies of drug resistance can help to reduce its effect and strategies to increase the efficacy or the life span of a few drugs available. Ability to detect resistance can be useful to determine the prevalence of resistance in specific geographical regions or can also prevent the use of useless and toxic drugs for patients infected with resistant parasites. The understanding of resistance mechanisms can also lead to new strategies for chemotherapeutic interventions. The genomic and proteomic approaches will lead to more detailed understanding of resistance. Preventing seasonal buildup of parasite contamination is important to preventing parasite resistance from developing within the animals. Therefore, based on the above conclusion, the following recommendations are forwarded as follow:

- Treatment schedule should be strategic to prevent seasonal buildup of parasite contamination.
- It is important to avoid under-dosing and ensure that treatments are fully efficacious.
- Practical education and trainings should be offered to farmers about proper livestock management and risk of resistance.
- Veterinarians should be allocated in every veterinary clinics for proper anthelmintic implementation.
- Molecular based researches should be done for better determination of resistance level now and fore (genomic; proteomic).
- Restrict illegal importation of drugs and movement of cattle; preventing the importation of problems to your farm and choosing the right produc.

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