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# A Review of Anthelmintic Resistance in Domestic Animals

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**Abstract:** Anthelmintic resistance is one of the most serious threats to the effective control of gastrointestinal nematodes of ruminants. Further complicating the situation today and for future parasite control program is the fact that all the economically important parasite species of sheep and goats have developed resistance to all groups of anthelmintics. Although, the chief factors involved have long been recognized, it is evident that their importance varies greatly between situation and some are more easily addressed than others. However, the speed with which selection in a population will occur on a number of factors such as improper treatment strategies, proportion of worm population, that in "refugia; parasite genetics, parasite biology and host-parasite relationship are the major factor for the development of anthelmintic resistance. Thus, requires sensitive diagnostic tests like in-vivo and in-vitro test to identify the development of anthelmintic resistance. Therefore, it is important that farmers and veterinarians should find a balance between achieving good parasite control and sustainability of their control strategies. In this way anthelmintic resistance may be delayed and the effectiveness of anthelmintic drugs may be prolonged.

**Key words:** Anti-Helminthes · Efficacy · Resistance · Ruminants

## INTRODUCTION

Globally, agriculture provides a livelihood for more people than any other industry. Livestock contributes over half of the value of global agricultural output and one third in developing countries [1]. Sales of livestock and their products provide direct cash income to farmers. They are closely linked to the social and cultural lives of millions of resource-poor farmers for whom animal ownership ensures varying degrees of sustainable farming and economic stability [2]. Livestock are also the living bank for many farmers and have a critical role in the agricultural intensification process through provision of draught power and manure for fertilizer and fuel. Official statistics often underestimate the overall contribution of livestock and especially their multipurpose contributions to food and agricultural production in developing countries [3].

Nevertheless, several factors exert an influence on the production and productivity of livestock. Recurrent draught, malnutrition, poor veterinary services and diseases are being the most essential [4]. Diseases can be caused by different etiologic agents' mainly viral, bacterial, protozoal or parasitic origin. Among parasitic diseases that are of economic importance to the livestock industry are helminthosis caused by parasites such as *Haemonchus, Trichostrongylus* and *Fasciola* species [5].

The frequent and continuous use of chemical anthelmintic drugs for deworming sheep flocks has resulted in the presence of lateral and multiple anthelmintic resistances in the parasites. This resistance leads to a concerning ineffectiveness of anthelmintics with large economic losses in sheep productivity. For these reasons, the issue of helminthes control is of particular economic value [6].

Treatment of gastrointestinal helminthosis mainly involves commercially available anthelmintics such as the benzimidazole, imidazothiazole and microcycliclactones groups. However, the extensive use of these anthelmintics for the control of helminthes infections on grazing livestock has often resulted in the development of resistance that has become a major practical problem in many countries of Africa [7].

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Resistance to anthelmintic is common among sheep and goats. It is also becoming problematic among horses, while it appears to be less prevalent among cattle. In addition, adopting appropriate control strategies aimed at preventing the development of resistance is essential one for the purpose of effective worm control in livestock and enhances increased well beingness in animals and promotes productivity [8].

Therefore, information on the use of anthelmintics is extremely important; because drugs are the likely mainstay of nematode control in the near future. Increasing numbers of reports on anthelmintic resistance further emphasize the importance of such knowledge in order to extend the effective life span of the existing anthelmintics on the market and to avoid the use of inefficient treatments. Therefore, the objectives of this paper are to review: the current status, the possible causes, the diagnostic techniques used and the strategies for managing the development of anthelmintic resistance in domestic animals [9].

**Anthelmintics 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 helminthes and a broad spectrum of activity [10]. 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) [10]. Many highly effective and selective anthelmintic are available, but such compounds currently are used incorrectly, in judiciously 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 dosing is likely to result in lowered efficacy and possibly increased pressure for selection of resistance and over dosing result in toxicity without necessarily increasing product efficacy [11].

**Anthelmintic Drug Efficacy:** A drug effects can be evaluated in terms of potency, efficacy, or effectiveness. Anthelmintic 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 it. 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 [12].

**Standards for Rating Anthelmintic Efficacy:** Anthelmintic have been developed to achieve over 98% efficacies 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 [13]. The world association for advancement of veterinary parasitological (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* where as levamisole and morantel are inactive at arrested larvae (Hypobiosislarvae). So efficacy of drug is affected by epidemiological and pathological conditions, dose, git transit time, pharmacodynamics activities (pda) and persistence activities (pa) of the drug [10].

**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 [10].

**Essential Features of Drug Resistance and Historical Development of Anthelminthics:** 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 [10]. 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 Anthelminthics [14]. In most regions of Africa, the development of anthelmintic resistance could be expected to be slow, because of limited availability and infrequent use of anthelmintic 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 [15]. 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 [16]. 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 [17]. 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 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 [18]. 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 [19].

**Development of Anthelmintic Resistance:** Infections with parasitic nematodes restrict the welfare and productivity of livestock throughout the world. The control of these parasites relies heavily on the administration of anthelmintic drugs. Between 1960 and 1990, the pharmaceutical industry made major progress in developing deworming compounds with excellent broad-spectrum activity and safety [20]. This led to the discovery of three major drug classes available for ruminants each with distinct modes of action: benzimidazoles (BZs), imidothiazoles, tetrahydropyrimidines (I/Ts) and macrocycliclactones (MLs). However, shortly after their introduction into the market, the development of resistance against all anthelmintic drug classes has been reported throughout the world. Anthelmintic resistance occurs when parasites usually eliminated by a given dose suddenly survive the treatment. Since resistance is inherited, the surviving worms will pass their resistance alleles to their progeny [21]. Today, the problem of anthelmintic resistance is by far the most severe in the major gastrointestinal nematodes of small ruminants [22].

**Status of Anthelmintic Resistance**

**Anthelmintic Resistance in Ruminants:** Anthelmintic resistance is one of the most serious threats to the effective control of gastrointestinal nematodes of ruminants, especially in sheep and goats [23]. The access to efficient drugs and the ease with which they could be

Table 1: The first reports of anthelmintic resistance in nematodes of sheep to drugs with different modes of action [8].

| Year | Country | Drug | Nematode |
|---|---|---|---|
| 1957 | USA | Phenothiazine | *Hemonchus contortus* |
| 1964 | USA | Thiabendazole | *Hemonchus contortus* |
| 1968 | USA | OP-compounds | *T. circumcinctus.* |
| 1976 | Australia | Levamisole/Morantel | *Hemonchus contortus* |
| 1980 | S. Africa | Rafoxanide | *Hemonchus contortus* |
| 1987 | S. Africa | Ivermectin | *Hemonchus contortus* |

applied, combined with the immense progress made in establishing the epidemiology of the gastrointestinal nematodes of ruminants led to a period of relative success in the control of worms, particularly in the livestock production systems of the industrialized countries. However, the false assumption that worm control is easy and can be accomplished by using broad spectrum drugs without an epidemiological database was also being promoted preventing or delaying the epidemiological studies that are a prerequisite for effective control [8]. Further complicating the situation today and for future parasite control program is the fact that all the economically important parasite species of sheep and goats have developed resistance to all groups of anthelmintics [24].

As reports indicate, anthelmintic resistances in nematodes of cattle have been less common and the general belief is that resistance is not yet an important issue in this host. However, no studies have been performed to investigate the prevalence of resistance in nematodes of cattle. So, there are only clinical case reports describing the failure of treatment to control clinical disease [25]. Furthermore, in some of these reports, multi-drug resistant (MDR) worms were detected. In light of these recent findings, anthelmintic resistance in nematodes of cattle might be considerably more common than is currently recognized in places such as Europe and the USA where anthelmintic resistance has not been reported and/or is not currently considered an important problem in cattle [26].

**Anthelmintic Resistance in Equines:** Though less attention has been given to the problem of anthelmintic resistance in other species, several studies have reported a prevalence of resistance to benzimidazole drugs and it is frequently suggested that extremely high prevalence of anthelmintic resistance, about 75%, to cyathostomin nematodes of horses which is now considered the principal parasitic pathogen of adult horses [27]. Resistance to pyrantel (Tetrahydropyrimidine class) appears to be much less common. But a recent study in southern USA found that over 40% of farms demonstrated resistance to this drug [26]. Interestingly, there are still no reports of cyathostomin resistance to ivermectin due to its ability to kill mucosal larval stages of cyathostomins. These mucosal larval stages tend to be much more numerous than the adult worms in the lumen and therefore provide large refugia. By contrast, there have been two recent reports of suspected ivermectin resistance in *Parascaris equorum,* which is the most important parasitic pathogen of foals [28].

Table 2: Major reported resistances to commonly used anthelmintics.

| | | Broad-epectrum anthelmintic | | | | | Group-specific anthelmimtic | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Izs | | Mls | | | Sns | | | | | |
| Host | Helminth parasite | Bzs | M/p | Lev | Ivm | Mxd | Dmt | mbc | Cst | Rxn | Opp | Onq | Ppz |
| Sheep | *Trichostrongylus* spp. | + | + | + | + | | + | + | | + | | | |
| | *Haemonchus contortus* | + | + | + | + | + | | + | + | + | | | |
| | *Teladorsagia* spp. | + | | + | + | + | | + | + | | | | |
| | *Cooperia curticei* | | | | | | | | | | | | |
| | *Nematodirus* sp. | | | | | | | | | | | | |
| | *Fasiola hepatica* | + | | | | | | | + | | | | |
| Goat | *Ttrichostrongyulus* spp. | + | | + | | | | | | | | | |
| | *Haemonchus contortus* | + | + | + | + | | | | + | | + | | |
| | *Ostertagia* spp. | + | | | | | | | | | | | |
| Cattle | *Trichostrongylus* spp. | + | | | | | | | | | | | |
| | *Haemonchus contortus* | + | | + | + | + | + | | | | | | |
| | *Oesophagostomum* spp. | + | | | | | | + | | | | | |
| | *Trichuris* spp. | + | | | + | | | + | | | | | |
| | *Ostertagia ostertagi* | | | | | | | + | | | | | |
| | *Cooperia* spp. | + | | | + | + | + | + | | | | | |
| | *Fasciola hepatica* | + | | | | | | | | | | | |

Bzs = benzimidazoles; izs = imidazothiazoles [m = morantel, p = pyrantel] ;mls = macrocycliclactones [ivm = ivermectin, mxd = moxidectin, drm = doramectin]; sns = salicylanilide [mbc = milbemycin; cst= closantel];rxn=rafoxanide;opp=organophosphate;oxa = oxamniquine;ppz=piperazin [28].

**Factors Favoring the Development and Emergence of Anthelmintic Resistance:** Although the chief factors involved have long been recognized, it is evident that their importance varies greatly between situations and some are more easily addressed than others. The speed with which selection in a population will occur depends on a number of factors that act independently or in combination. Relevant factors that affect the rate with which resistance develops include the biology and epidemiology of the parasite, the dynamics of the host-parasite relationship, the treatment frequency and the treatment strategies that result in various levels of refugia [29].

**Improper Treatment Strategies:** For instance, under dosing selects for resistance because more individuals, including homozygous and heterozygous individuals survive treatment and will propagate resistant genes to the next generation. Inadvertent under dosing can also occur where products containing less than recommended level of active ingredient are sold on the market [9]. High treatments frequency aimed at reducing the egg output to a minimum level strongly selects for anthelmintic resistance, especially when the treatment frequency is close to the prepatent period. This usually practiced in areas of heavy parasite challenge, especially where *H. contortus* is dominant. Also in developing countries in the tropics where intensive treatment is the major factor promoting resistance where worm egg counting services are not always readily available or affordable [30].

**The Level of Refugia:** In a helminthes population, there are "Infra populations", the parasitic population in the host and the pre-parasitic stages on pasture. The importance of refugia depends on the climate and husbandry conditions. Other risk factor is treatment of all animals at the same time on the same farm. Greater proportion of the population is exposed to the anthelmintic and this in turn favors higher selection pressure [29].

**Parasite Genetics:** Resistance is present in a population when there is a greater frequency of individuals within a population able to tolerate doses of a compound than in a normal population of the same species and is heritable. The bigger the effect of each individual change, the faster resistance will tend to develop [15]. The high genetic diversity of parasitic helminthes coupled with their large populations increases the likelihood that resistance alleles will already be present in a population possibly at relatively high frequency. If resistant worms have enhanced fitness compared to susceptible individuals, or if resistance is linked to other fitness genes, then resistance will tend to spread in the population [31].

**Parasite Biology:** Parasites have a short generation time and high fecundity. Therefore, production of many individuals of several generations in a short time increases the spread of resistance alleles through the population. Direct life cycles mean that the fitness associated with resistance alleles is not dissipated by passage through an intermediate host. Parasite populations tend to be mobile, especially if the hosts are moved. Therefore, there might be low levels of untreated parasites in refugia [32].

**Host-Parasite Relationships:** Infection with pathogenic worms requires treatment to control disease, so selection pressure could be higher for these parasites. Reduced hypobiosis (Larval inhibition or arrested larval development) could shorten life cycles and reduce the refugia of arrested larvae inaccessible to the drug [33].

**Diagnosis of Anthelmintic Resistance:** With the development and spread of anthelmintic resistance in nematodes of livestock, the need for methods to detect resistance has evolved simultaneously. Different in vivo and in vitro tests are now available and there is an ongoing effort to refine, standardize and validate these tests. The development of molecular tests is also progressing and is trying to apply DNA probe and polymerase chain reaction (PCR) technology [34].

**In Vivo Test**

**Fecal Egg Count Reduction Test (FECRT):** This is the most common test to study anthelmintic resistance. This test was originally designed for sheep, but can be used also for cattle, swine and horses. Modern broad spectrum anthelmintics are highly efficacious and treatment should normally result in a reduction of fecal egg counts by more than 95 percent. Thus, the FECRT provides an estimation of anthelmintic efficacy by comparing fecal egg counts of animals before and ten days after treatment. For monitoring of normal fluctuation, the treated group is generally compared with non-treated (Controls). The FECRT is particularly suitable for field surveys and it has the advantage that the number of groups can be increased if appropriate to test the efficacy of a range of broad or narrow spectrum anthelmintics at one time [34].

**The Controlled Test:** In this test, the efficacy of an anthelmintic is determined by comparing parasite populations in groups of treated and non-treated animals. Basically, the procedure compares worm burdens of animals artificially infected with susceptible or suspected resistant isolates of nematodes. The parasitized animals are randomly separated into medicated and non-medicated groups and at a suitable interval after treatment (10 to 15 days), a necropsy is carried out and the parasites are recovered, identified and counted. This test is not extensively used except in cases of special interest or when confirmation of resistance is required at species level and for evaluation of the effect on larval stages [35]. In an attempt to reduce the cost and labor required for this test, laboratory animal models have been used and guidelines for evaluating anthelmintic efficacy using the controlled test have been published [36].

***In vitro* Test**

**The Egg Hatch Assay:** It has been developed to differentiate between resistant and susceptible strains of gastrointestinal nematodes for the benzimidazoles and for the levamisoles. It provides an accurate method for assessing the susceptibility of mixed nematode populations and is comparatively more rapid and economic to conduct than the FECRT. It is based on the determination of the proportion of eggs that fail to hatch in solutions 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. To obtain meaningful data, eggs for the egg hatch test must be fresh and should be used within three hours of being shed from the host as sensitivity to some benzimidazoles decreases as embryonation proceeds. The test has only been shown to work on nematode species in which eggs hatch rapidly. Due to difficulties in the interpretation of the results, this assay is not widely used for field surveys [33].

**Larval Paralysis and Motility Assay:** This assay discriminates between resistant and susceptible strains of parasites by estimating the proportion of third stage larvae in tonic paralysis after incubation with a range of levamisole and morantel drug concentrations. It is relatively easy to carry out stocks of infective larvae are readily obtained and it is reported that there is a fairly good reproducibility of the test, any differences in repeatability being attributed to the age of larvae. However, the interpretation is complicated if the anthelmintic is added to the egg suspension too early and the development has not proceeded far enough if it is added too late, hence the drug has no effect [31].

**Tubulin Binding Assay:** This 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 titrated benzimidazole until equilibrium is reached [23]. 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 claimed to be rapid, robust, highly reproducible and sensitive to minor changes in the resistance status of parasite populations. But it requires relatively large numbers of larvae making it unsuitable for routine field assays. Moreover, it requires access to expensive laboratory apparatus for high performance liquid chromatography (HPLC) estimations and a source of radio labeled drugs [37].

**Larval Development Assay (LDA):** This is the only one that allows the detection of resistance against all the drugs irrespective of their mode of action. The LDA is an in vitro assay for the detection of resistance to benzimidazole, levamisole, combinations of benzimidazole and levamisole, avermectin and milbemycin drenches in the major gastrointestinal nematode parasites of sheep, such as *H. contortus, T. colubriformis* and *O. circumcincta*. In this test, nematode eggs isolated from fecal samples submitted by producers are applied to the wells of a micro-titer plate and larvae hatch and develop to the L3 stage in the presence of anthelmintic. The concentration of anthelmintic required to block development is related to an anticipated in vivo efficacy [37].

**Adult Development Assay:** The adult development assay for detecting benzimidazole resistance in trichostrongylid nematodes has advanced significantly and *H. contortus* has been cultured through to the adult egg laying stages, although this test is mainly for research purposes [23].

**Managing the Development and Emergence of Anthelmintic Resistance:** The key to preventing the development of resistance to anthelmintics is to identify the major causal factors for particular environments and

enterprises. The currently available tool for gastrointestinal nematode control consists of both chemical and non-chemical technologies. The chemical technology relies entirely on treatment with different formulations of anthelmintics used in different control strategies according to whether epidemiological knowledge is absent or available. But, resistance against the most commonly used drug classes is an emerging problem in livestock industries. Therefore, the sustainability of chemically based worm control strategies is dependent upon ensuring the implementation of alternative non-chemical worm control interventions [38].

**Organization of Proper Chemical Treatment:** The pharmacokinetics of the drug is generally considered preferable to use short acting drugs to prevent worms being exposed to the sub-therapeutic concentrations that result from an extended half-life of a drug. It is important to avoid under dosing and ensure that treatments are fully efficacious. Drugs should be used in ways that maintain refugia [35].

Treatments should be planned through timing and management to reduce the survival of free-living stages in the environment. The use of persistent anthelmintic products may also contribute to the development of resistance in some situations, but the potential can be reduced if these are used according to recommendations which minimize the selective effect [9]. If practical, the access of free-living stages to the next host should be reduced by measures such as removal of faces and alternate grazing of different hosts. Use of other control methods to complement anthelmintics or the use of alternative chemical classes [23].

**Pasture Management:** A safe pasture is one that has had no sheep or goats grazed on it for 6 months during cool/cold weather or 3 months during hot (dry) weather. Weaning sheep and goats at 2 months of age and rotating them through pastures ahead of the adults will minimize the exposure to large numbers of infective larvae. Pastures should be rotated following any administration of anthelmintics to the animals [38].

It has been advocated to keep dewormed animals in a holding pen for 24 hours following deworming and then move them to a safe pasture. Small ruminants can graze pastures after cattle and this is considered to be a safe pasture (Assuming cattle are under adequate parasite control themselves). Pastures that have a heavy thatch or extensive overgrowth provide a good environment for larval survival. Short duration grazing carries pasture rotation to a level that maximizes forage production and harvesting by controlled animal grazing. Pastures which have become heavily contaminated due to miss-management can be tilled and reseeded. This is an opportunity for pasture improvement and shortens the time that an area needs to remain ungrazed to become a safe pasture. In the future, pastures may be reseeded or over seeded with forages containing condensed tannins to take advantage of their anthelmintic effects [23].

**Selection of Appropriate Weather for Treatment:** Anthelmintic administration should be coordinated with the weather. Many producers religiously deworm their flocks according to a set schedule. During hot (dry) weather, there will be little or no exposure to infective larvae. As soon as there is significant rainfall (0.5-1.0 inches), larvae exposure goes up exponentially as previously inactive larvae become active and new larvae are hatched. The producers should be trained to plan deworming within three weeks of significant rain after a dry spell. Similar strategies can be used during cool weather. Once ambient temperatures drop below $50^{O}$F, the flock can be dewormed and no further treatments are necessary until temperatures become favorable to larval development and activity [39].

**Treatment Strategy:** Recent work in South Africa has developed a patented FAMCHA plan that recommends treating the host categories at risk. It utilizes a chart of mucus membrane color to determine whether an individual should be dewormed or not [37]. The initial research in sheep exposed to heavy contamination with *H. contortus* only dewormed those with PCV below 15% to prevent death. The majority of the flock (69%) required no treatment and 21% required only one treatment, since, the use and expense of anthelmintics was greatly reduced. This approach revolutionizes traditional deworming strategies. The goal is to maintain a susceptible population of nematodes in the environment that controls the population of resistant nematodes. Only animals developing pathological parasite burdens are treated. Indiscriminant selection for resistant parasites by blitz treatment is avoided [40].

**Ethno-Veterinary Preparations:** Ethno-veterinary medicine (EVM) is defined simply as the medicines that livestock keepers are using now other than modern synthetic drugs [33]. Ethno-veterinary medicine covers people's knowledge, skills, methods, practices and beliefs

about the care of their animals. It provides valuable alternatives to and complements western style veterinary medicine. This is increasingly evident in the West where herbal medicine is becoming main stream. Ethno-veterinary medicine is of specific value in developing countries where allopathic veterinary medicines are often beyond the reach of livestock producers. It can play an important role in grassroots development which seeks to empower people by enhancing the use of their own knowledge and resources. Many indigenous veterinary beliefs and practices persist in a wide majority of stock raisers and farmers, particularly in the developing countries [23].

**Plants as a Source of Medicines:** Plants contain many biologically active compounds i.e. alkaloids, flavonoids, triterpenoids, phenols, carotenoids, steroids and ketenes. For example, Neem contains seven isomeric compounds labeled as azadirachtin A-G, salannin, volatile oils, meliantriol and nimbin. Neem leaves were used to cure eczema, ringworm and show anti-inflammatory and anti-hyperglycemic activities. It is used to heal chronic wounds, diabetes and gangrene, remove toxins from the body, neutralize free radicals and purify the blood. It is also used in treatment of malaria filarial, leismaniasis and possesses anti-cancer and hepato-renal protective activity and show hypolipidemic effects. The intake of juice of green neem leaves with milk increases and relieves from headaches and cure eye infections. A boiled neem leaf in water shows an excellent antiseptic activity and used to clean wounds, soothes swellings and eases skin problems [39].

**Condensed Tannins (CT):** There are hydrolysable and condensed tannins but the CT are more common. Condensed tannins can be detrimental to monogastrics. Condensed tannins containing forages increases weight gains, wool growth and milk production while decreasing the effects of GIN in red deer and sheep. The direct parasitic effects include: decreased fecal egg counts and decreased L3 viability. The indirect effect of CT is by binding to dietary protein, which allows it to bypass rumen and thus increases protein availability in the small intestine. The most commonly investigated forages are: *Lotuspedunculatus* (Big or large trefoil*), Lotus corniculatus* (bird's foot trefoil), *Hedysarumcoronarium* (Sulla*)* and *Onobrychusvicifolia* (Sainfoin*). Quebracho* is a cold soluble extract from *Schinopsis sp.* tree bark. It can be used as a drench or incorporated into pelleted feeds [41].

**Nematophagous Fungi (As a Biological Control Agent)** Nematophagous fungi are micro-fungi which utilize nematode larvae as their main source of nutrients. The fungi are ingested by ruminants pass through the digestive tract and colonize fecal material. Three predaceous fungi have been identified but only one is suitable for including in ruminant diets. *Duddingtonia flagrans* has thick-walled spores that can be fed to ruminants and passes safely through to the feces. The spores must be fed daily to maintain the reduction in L3 numbers [41].

**Vaccine Development:** Using the successful development of the irradiated larval vaccine against the bovine lungworm (*Dictyocaulus viviparus),* as a model attempts have been made to produce vaccines against gut parasites in ruminants, but they have all been disappointing. Early attempts to immunize ruminants against gastrointestinal helminthes, either with crude worm homogenate antigen or by ectopic infection met with little or no success [42].

Currently, attempts are being made to direct high titer antibody responses towards potentially susceptible targets on or secreted by the parasite. In the case of blood feeding species, several target molecules have been identified on the surface of the intestine of the parasites. Because molecules on the luminal surface of the parasite's intestinal cells are not normally recognized by the host during infection and these antigens are classified as "Hidden". Several vaccines using "Hidden" antigens were developed for *H. contortus* in sheep and these provided 94 percent protection in relation to egg per gram (EPG) and their efficacy reached 90 percent when worm burdens were studied [33].

Another way to induce protection has been to use "homologous" antigen; that is an antigen first shown to be protective against another helminthes species. An example is the glutathione-Stransferases (GST) of *Fasciola hepatica (F. hepatica)*, which were chosen as candidate vaccine antigens because homologous protein from *S. mansoni and S. japonicum* had been shown to be protective in laboratory animal models of infection. Sheep and cattle immunized with native GSTs isolated from *F. hepatica* have been protected on average by 49 and 29 percent respectively, although the results from individual trials have been quite variable [26].

**Application of Copper Particles:** The interest in copper formulations was renewed when the importance of trace elements and mineral deficiency were identified. It was

shown that there were great benefits from low dose depot delivery of copper to the rumen of sheep and cattle grazing on deficient pastures and also from the equally lengthy protection such boluses gave to sheep against *H. contortus*. This however coincided with the promotion of thiabendazole, the first of the safe broad-spectrum anthelmintics. Hence, the possibilities for control of *H. contortus* using low-dose administration of copper were over looked [43]. Currently the use of copper oxide wire particles (COWP) delivered by way of a capsule not only to treat copper deficiency, but also to ameliorate the effects of abomasal parasites are being tested. The apparently prolonged action of COWP against *H. contortus* could prove to be of enormous benefit in restoring some measure of control in those regions of the world where this parasite predominates and anthelmintic resistance is rampant [44].

**Proper Nutrition:** The strongest link between nutrition and parasitism has been illustrated between protein intake and resistance to gastrointestinal nematode (GIN) infection. The most dramatic has been the abolishment of the peri-parturient egg rise in lambing ewes by providing protein at 130% of requirements. Supplementation with phosphorus has been shown to prevent worm establishment. Adequate copper levels are necessary for development of immunity to GIN. Recent work suggests treatment of lambs with copper oxide wires orally reduces *H. contortus* burdens. However, copper toxicity would be a concern with these treatments. Surprisingly, addition of molybdenum at 6-10 mg Mo/day decreases worm burdens in lambs that were not attributable to the expected copper deficiency. Molybdenum may have a role in increasing jejunal mast cells and blood eosinophil numbers [23].

**Genetics:** Discussions of genetic selection include the terms resistance and resilience. Resistance is the ability of the host to prevent or limit establishment of GIN infection. Resilience is the ability to maintain a reasonable level of production when subjected to parasitic challenge. Resistant animals utilize a larger proportion of their resources to developing their immune responses. On the other hand, high producing animals funnel the majority of their resources to growth and less to immunity, thus becoming more susceptible to parasitism. Resilience was based on drench on demand programs that deworm based on loss of body condition. Genetics of the GIN must also be considered. A free living nematode has been used as model to identify the genes of interest (Embryo development, fecundity and larval development). Biological anthelmintics are also being investigated. These are phages that are carried into the parasite and either block normal protein replication or provide new binding sites for anthelmintics [43].

**Status of Anthelmintic Resistance in Ethiopia:** Recent attempts towards privatization of veterinary services in Ethiopia have resulted in a remarkable increase in veterinary pharmaceutical importers and distributors [45]. This in turn contributed to the importation of different anthelmintic brands, mainly from the benzimidazole and imidazothiazole groups under different trade names from different manufacturers. The geographical location of the country also invites an illegal influx of veterinary drugs. Under such circumstances the possible introduction of products of an inferior pharmaceutical quality is likely. Under dosing may also contribute to the acceleration of selection for resistant worms [46].

Apart from its potential danger for the development of drug resistance, the availability on the market and use of sub-standard products may also lead to a loss of confidence in chemotherapy among animal owners. In spite of the frequent complaints of the livestock producers on the efficacy of anthelmintics sold on Ethiopian markets, no systematic study has been conducted to verify whether the complaints were real or due to miss-application [47]. The problem of such sub-standard products has been reported in Kenya. In spite of long use of albendazole to treat livestock in Ethiopia, no report of resistance against this drug has been made. Two brands of albendazole and tetramisole were 100% effective against Ogaden isolates of *H. contortus* in artificially infected lambs [45]. In contrast, a few reports of resistance exist for goats [48] although both authors used anthelmintics at the dosage level recommended for sheep. Treating goats with benzimidazole and levamisole drugs at the sheep recommended dose has been considered as under-dose due to difference in pharmacokinetic behavior of the drugs in the two species and hence a higher dose was suggested for goats compared to sheep [49].

## CONCLUSION AND RECOMMENDATIONS

Livestock like sheep, cattle, equine and others live with a burden of parasites. Parasitism compromises animal health and productivity and parasite control imposes considerable cost and time burdens on farmers. The main form of parasite control for most farmers is small number of anthelmintic compounds. However; the

inevitable development of anthelmintic resistance is generating an increasing challenge that has made it virtually uneconomic to keep livestock in some regions. Miss uses of drugs to treat helminthes of livestock such as under-dosing, treatment of all animals at the same time on the same farm, continued administration of anthelmintics of bad quality and frequent use of anthelmintics of the same family are the likely cause for the development of resistance. In Ethiopia, Some of these drugs, particularly albendazole and tetramisole have been continuously imported and distributed to every corner of the country through different trade names by different manufacturers. As there is no practice of rotating anthelmintic categories in the country, continuous use of the same drug in a given area is causing the development of resistance. Therefore, based on the above conclusion, the following recommendations are forwarded. Using proper treatment strategy which includes the right dose in the right way at the right time. Reducing dependence on anthelmintic treatment rather, using alternative worm control. Limiting introduction of resistant worms through importation of infected animals should be practiced. Avoid frequent and unnecessary treatment with anthelmintics, opting instead for strategic deworming. Awareness creation of livestock owners should be conducted for the appropriate use of anthelmintics in treating animals. More ever, studies are needed based on a comparative efficacy on from reliable source and drugs used by the owners from unreliable sources.

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