



Review Article

One Health Bulletin

johb.info



Emerging antihelminthic drug resistance: Implications for mass drug administration program

Agarwal Harshita, Rajkumari Nonika✉

Department of Microbiology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry 605006, India

ABSTRACT

Soil transmitted helminth infections and lymphatic diseases are significant neglected tropical diseases that pose public health challenges in both low and middle economic populations. These parasites live in the human intestine, consuming nutrients intended for the human body. Research findings suggest that the development of resistance to antihelminthic drugs is notably delayed when a combination of medications is used. Antihelminthic tablets are excellent candidates for mass drug administration (MDA) because they are highly effective and safe. Their reliability and safety make them well-suited for widespread distribution among populations at risk of parasitic worm infections. School-based deworming programs have proven successful in providing access to large numbers of children, offering them antihelminthic treatments in various settings. MDA is a key strategy in the global effort to eliminate lymphatic filariasis, with school-based deworming being an integral part of this approach. However, the longer the program lasts, the higher the risk of treatment failure is due to potential parasite resistance. Therefore, there is an urgent call for new methods to monitor and combat the emergence of drug resistance. While MDA has shown significant impact on various helminth infections, the threat of resistance remains a concern. Although there is currently no concrete evidence of resistance to common antihelminthics in humans, experiences from other infectious diseases, particularly in livestock, serve as a cautionary tale against over-reliance on these drugs for controlling lymphatic filariasis.

KEYWORDS: Antihelminthics; Mass drug administration; Drug resistance

1. Introduction

Soil-transmitted helminth (STH) infections and lymphatic diseases are major public health concerns, particularly in low and middle-income regions. These diseases significantly impact the health of populations in these areas, posing considerable challenges to healthcare systems[1]. STHs live in the human intestine and consume nutrients meant for the human body. STH include mainly hookworm, whipworm and roundworm, affecting children living in poverty where there is inadequate sanitation. Although *Strongyloides stercoralis* is usually considered alongside the STHs, it does not come under the definition of STHs.

The highest prevalence of STH infections is found in tropical and subtropical regions, particularly in Asia, including countries like India, China, Southeast Asia, and in sub-Saharan Africa[2]. Studies have shown that the development of resistance to antihelminthic drugs is notably slowed down when a combination of drugs is used for treatment. Eleven different drug combinations were evaluated to their effect against STH infection[1–3].

Therefore, it's crucial to enhance the availability of antihelminthic drugs with diverse mechanisms of action. Additionally, establishing a comprehensive surveillance system is essential to monitor any

✉To whom correspondence may be addressed. E-mail: nonika.raj@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-Non Commercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

©2024 One Health Bulletin Produced by Wolters Kluwer- Medknow.

How to cite this article: Harshita A, Nonika R. Emerging antihelminthic drug resistance: Implications for mass drug administration program. One Health Bull 2024; 4(4): 157-163. doi: 10.4103/ohbl.ohbl_19_24

Article history: Received 4 April 2024
Accepted 26 June 2024

Revision 10 June 2024
Available online 5 July 2024

alterations in the effectiveness of these drugs due to the emergence of antihelminthic resistance. Also, a need for concerted efforts to discover and develop the next generation of antihelminthic drugs cannot be overlooked.

2. Mass drug administration and chemotherapeutic agents

Lymphatic filariasis (LF) is a disease caused by three types of parasitic worms: *Wuchereria (W.) bancrofti*, *Brugia (B.) malayi*, and *B. timori*. In India, *W. bancrofti* is spread by the common mosquito, *Culex quinquefasciatus*, while *B. malayi* is transmitted by *Mansonia* mosquitoes. Recognized as a significant global health concern, LF affects around 120 million individuals across more than 80 nations, according to the World Health Organization (WHO)[4–5]. Given the absence of a vaccine and the limited success of vector control efforts, the eradication of lymphatic filariasis hinges on MDA[6].

Schistosome resistance to certain drugs, like oxamniquine and hycanthone, is primarily observed in the absence of a drug-activating enzyme found in susceptible schistosomes and mammalian hosts. This phenomenon has been extensively studied through genetic and biochemical analyses facilitated by the availability of *Schistosoma (S.) mansoni* strains resistant to these drugs. Notably, praziquantel, a widely used drug, has not shown any documented cases of resistance[7].

The effectiveness and safety of anthelmintic tablets make them well-suited for MDA, especially in early intervention programs targeting large numbers of children, often implemented through school-based deworming initiatives[8]. Various combinations of anthelmintic drugs are utilized, such as albendazole in conjunction with ivermectin and diethylcarbamazine, to combat the transmission of *W. bancrofti*, the primary causative agent of lymphatic filariasis. In MDA campaigns, different combinations of drugs are administered depending on the endemicity of other diseases like onchocerciasis or loiasis. Despite their effectiveness in reducing the number of cases, the prolonged treatment duration, particularly the five-year regimen for lymphatic filariasis, remains a significant drawback[9]. Recently, a triple drug regimen incorporating ivermectin, diethylcarbamazine (DEC), and albendazole has been introduced to enhance efficacy[10]. The objective of this review is to assess the magnitude of antihelminthic resistance in STHs and lymphatic filariasis, and its implications for MDA. Both STHs and LF control programs are implemented by preventive chemotherapy in the form of MDA.

WHO advises assessing the decrease in the number of STH eggs expelled in stool post-treatment, employing methods such as the Kato-Katz technique, McMaster method, or thick smear. The objective is to ensure that at least 75% of school-aged children who require treatment are reached. Research has demonstrated that mass administration of a single dose of ivermectin, diethylcarbamazine, albendazole, or a combination of these drugs results in a significant reduction in microfilariae intensity[11].

A community or subpopulation can receive treatment without individual diagnosis using MDA, which distributes affordable, safe medications based on preventative chemotherapy principles[12]. The main problem with the existing drug regimen is that substantial treatment coverage is necessary to accomplish elimination and suspend transmission. However, after prolonged mass treatment with the current treatments, drug resistance may become a serious problem[13].

While MDA for lymphatic filariasis brings about health benefits by reducing the prevalence of intestinal nematode infections like whipworm, ascaris, and hookworm, it also comes with its own set of advantages and disadvantages. One significant advantage is the simultaneous reduction in the burden of these intestinal nematodes alongside filariasis treatment. However, a notable concern is the potential emergence of drug resistance among intestinal nematodes due to MDA for filariasis. The three main drugs used in MDA programs are albendazole, DEC, and ivermectin. The increase in MDA coverage from 2004 to 2019 is depicted in Figure 1.

2.1. Drugs used in lymphatic filariasis treatment

2.1.1. Albendazole

Albendazole is a benzimidazole carbamate which exhibits larvicidal, vermicide and ovicide. It exerts its antihelminthic activity by inhibiting tubulin polymerisation and disrupting the worm's metabolism[14]. Reports indicate the emergence of albendazole resistance in various nematode parasites, primarily attributed to single nucleotide polymorphisms (SNPs). Interestingly, studies have shown that similar SNPs exist in untreated populations of *W. bancrofti*, suggesting the potential for resistance development in this context as well. Various studies have also reported that use of drug combinations (albendazole, DEC, and ivermectin) in filariasis elimination programmes might help to prevent the development of resistance[3–5].

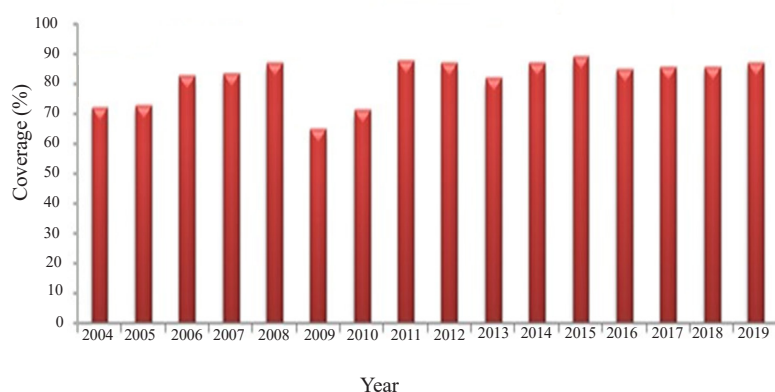


Figure 1. Mass drug administration (MDA) coverage among eligible population (2004-2019).

2.1.2. Diethylcarbamazine

For many years, DEC has been used to treat lymphatic filariasis. Although its exact mode of action is still unknown, several investigations have revealed that DEC blocks the cyclooxygenase pathway in parasites, causing microfilariae to die[15]. As a derivative of piperazine, DEC has been a mainstay of the chemotherapeutic arsenal for treating lymphatic filariasis for the past 15 years. Variations in the observed microfilaricidal effects across different studies are likely attributable to the varying levels of transmission prevalent in the areas where the studies were conducted.

Chronic administration of low dose diethylcarbamazine, such as in medicated salt, can effectively control filariasis[16]. However, due to *in-vivo* effect, there is not much researches on resistance to DEC.

2.1.3. Ivermectin

Ivermectin was identified in the mid-1970s and introduced as an antiparasitic agent in 1981. It marked the debut of macrocyclic lactone endectocides in the market and remains the sole macrocyclic lactone employed against parasites affecting humans[15]. Ivermectin interacts with a range of acetylcholine-gated chloride channels, ligand-gated ion channels, histamine gated-chloride channels is correlated with its antihelminthic activity mediating the paralytic actions in the motor neurons system[17]. Ivermectin increases the sensitivity the host immune system by acting *in-vivo* on microfilaria, although the mechanism is still unknown.

2.2. Challenges of drug resistance in helminth treatment

There is an ongoing debate about defining resistance versus tolerance in the context of drug treatment. Tolerance signifies the stage between treatment success and failure[18]. According to WHO, resistance denotes the development of an organism's ability to withstand doses of a toxic substance that would typically be lethal to most individuals of the same species[19]. Helminths in humans suspected or confirmed of exhibiting drug resistance include *Necator americanus* (to mebendazole) in Mali, *Ancylostoma duodenale* (to pyrantel) in Australia, *S. mansoni* (to oxamiquine in Brazil and praziquantel in Senegal and Egypt), and *Onchocerca volvulus* (to ivermectin) in West Africa[20]. The first reported case of parasite resistance to antihelminthics dates back to 1957 with phenothiazine, and often, *Haemonchus contortus* is the initial nematode to develop resistance to various antihelminthic drugs[21]. Helminthic diseases are treated with various drugs, including macrocyclic lactones, benzimidazoles, imidazothiazoles, and praziquantel. Resistance has emerged across all major families of broad-spectrum antihelminthics[18]. With their widespread use in both animals and humans, the emergence or potential emergence of drug resistance is a significant concern[22].

Unlike livestock, where nearly all animals in a herd or flock receive

treatment, community-based mass treatment of humans typically achieves a compliance rate of less than 80%. Factors such as absenteeism and lack of interest contribute to this lower compliance. There is substantial evidence indicating that when a parasite develops resistance to one antihelminthic within a specific group, it often becomes resistant to other agents within the same group (known as side resistance). For instance, resistance to albendazole can confer side resistance to other members of the benzimidazole family due to their shared mode of action[19].

Drug resistance can arise through mechanism such as a change in the drug receptor, which can render it ineffective at low concentrations because it no longer binds tightly or with high affinity and a modification in the way the drug is distributed within the target organism, which can hinder its access to the intended site of action[19].

Antihelminthic resistance poses a significant threat to agricultural incomes, with reports emerging from various regions worldwide and involving all classes of helminths and available drugs[18]. There is ongoing debate regarding the authenticity of reported cases of drug resistance. However, there is solid documentation of *S. mansoni* exhibiting resistance to oxamiquine in Brazil, and evidence also supports instances of resistance to praziquantel in Egypt.

It has not yet been confirmed that ivermectin developed resistance to *Onchocerca volvulus* but reduced susceptibility of microfilaria has been observed in some regions of West African onchocercosis control programme[20]. Several authors have given the alarming sign to the development of resistance to ivermectin against onchocerciasis in large scale programmes which uses the same drug continuously over years.

Various factors have been considered to mitigate against drug resistance in lymphatic filariasis which includes the combined use of drugs with different modes of action & the long and complex life cycle. Albendazole, a member of the benzimidazole class of drug, has little effect on microfilariae but when it is combined with either ivermectin or DEC, synergistic activity is observed, but along with it widespread resistance to benzimidazoles is observed in number of nematodes[6].

3. Factors contributing to drug resistance

Several factors contribute to the development of drug resistance, including frequent treatment, reliance on single drug regimens, the specific targeting and timing of mass treatment efforts, and inadequate dosing.

3.1. High treatment frequency

Well-controlled experiments conducted by Bernardo Pereira

Moreira *et al.* have demonstrated that a high treatment frequency more strongly favors the selection of resistance compared to less frequent dosing schedules[23]. Furthermore, compelling evidence suggests that resistance develops more rapidly in areas where deworming of animals occurs frequently. For instance, in humid tropical regions where parasite control in small ruminants involves 10 to 15 treatments per year, significant issues with antihelminthic resistance in *Haemonchus contortus* have been reported[24]. However, even with lower treatment frequencies, drug resistance can still develop when the same medication is used repeatedly over an extended period. Several studies have documented the emergence of resistance even with only two or three treatments given annually[25].

3.2. Single drug regimens

It's a common occurrence that a medication initially effective gradually loses its efficacy with consistent use until it eventually fails[26]. Geerts *et al.* conducted a survey of sheep producers in the United States and found that one out of every two flocks were treated with a single antihelminthic until it ceased to work. Even with a low annual treatment frequency and a perception that bovine helminths develop resistance less readily than those in small ruminants, long-term administration of levamisole in cattle led to resistance development[27]. In South Africa and New Zealand, the frequent use of ivermectin without alternation with other medications has been linked to the rapid emergence of resistance in *Haemonchus contortus* in sheep and goats[28].

S Geerts and B Gryseels have cautioned about the potential for antihelminthic resistance problems in onchocerciasis control programs in western Africa, particularly as these programs increasingly rely on periodic community-based treatment with ivermectin. While the initial goal of drug-based control techniques for schistosomiasis and helminthiasis was solely to reduce and prevent disease in humans, they are now also recommended for controlling and even interrupting transmission[27].

3.3. Targeting and timing of mass treatment

The widespread evolution of antihelminthic resistance (AR) in helminths has undoubtedly been aided by mass preventative therapies given to domestic animals. Although there are no data from experimental research, computer models show that when 20% of the flock is not treated, resistance development is postponed. This strategy would guarantee that the offspring of the worms that survive the treatment will not only be resistant worms. Given the well-known over-distributed distribution of helminths, not treating some members of the group, particularly those with the lowest worm burdens, shouldn't necessarily lessen the treatment's overall effectiveness[29].

To prevent rapid reinfection in livestock, common practices include moving flocks frequently to clean pastures after bulk treatment or scheduling treatment during dry seasons. However, these practices can inadvertently lead to the next generation of helminths being primarily composed of worms that survived the therapy, potentially contributing to the development of AR[27]. For instance, Roose *et al.*[30] found issues with AR in sheep and goat helminths on some small Greek islands experiencing prolonged drought, while the mainland, under similar management and deworming procedures, did not exhibit AR.

In contrast to livestock, where nearly all animals receive treatment, population compliance in community-based mass treatment of humans is typically below 80% due to various reasons like absences, lack of interest, illness, or pregnancy. Compliance often further declines after initial treatments, particularly as morbidity decreases[27]. Timing therapy during dry, low-transmission periods has been suggested. In certain regions of China, synchronized treatment for humans and cattle is employed to curb disease spread, although logistical and organizational challenges hinder implementation[31]. The development and spread of AR in humans may be delayed by various factors, but not guaranteed. However, if routine treatments primarily target school-age children for intestinal worms or isolated communities for onchocerciasis, where participation is well controlled and transmission occurs within a relatively closed ecological system, the situation and risks may not differ significantly from those in livestock[27].

3.4. Under-dosing

Under-dosing is widely recognized as a significant contributor to the development of drug resistance because sub-therapeutic doses can prolong the lifespan of heterozygous resistant worms. Laboratory studies have demonstrated that under-dosing influences the selection of resistant or tolerant strains, and this notion is supported by some indirect field data[32]. Recent research has revealed that goats require larger doses (1.5 to 2 times) of anthelmintics compared to sheep due to differences in drug bioavailability. However, for many years, both sheep and goats were administered the same doses, potentially contributing to the relatively frequent and widespread occurrence of antihelminthic resistance in goats.

The field scenario of antihelminthic resistance may not always be straightforward, as indicated by recent modeling experiments[33]. Depending on the original frequency of resistance alleles, there may be a range of dose levels where under-dosing impedes resistance and another range where it promotes resistance. Despite the need for further research on the impact of under-dosing on resistance formation, sub-curative doses should be avoided. Under-dosing has been encouraged in some cases to reduce the costs of anthelmintic treatment campaigns in underdeveloped nations, but this practice is not

advisable due to its potential to exacerbate resistance issues[34].

In many impoverished nations, under-dosing among people happens frequently. Poor families sometimes share or consume drugs at half the usual doses or less. Additionally, subpar generic goods, products that have been repackaged or modified, and outdated medications are widely available in pharmacies and general markets. Additionally, both human and veterinary medicine have been shown to contain low-quality medications. Numerous unlicensed businesses worldwide generate human medications, particularly antibiotics and anthelmintics. These medications typically don't have enough quality control[35].

4. Detection of drug resistance

4.1. *In-vivo methods*

One of the most commonly used tests to assess anthelmintic resistance is the fecal egg count reduction test. It's particularly useful for field surveys as it provides an estimate of anthelmintic efficacy by comparing the number of parasite eggs in fecal samples before and ten days after treatment. This test is straightforward and doesn't require highly trained personnel. The procedure involves using the modified McMaster technique to determine the pre- and post-treatment fecal egg counts. It can be applied across various animal species including sheep, goats, cattle, horses, and pigs[27].

4.2. *In-vitro methods*

The larval development assay is a widely used method for detecting resistance to anthelmintic drugs such as benzimidazoles, levamisole, and macrocyclic lactones. It's highly sensitive and quantitative, making it the method of choice for assessing resistance to these drugs *in vitro*[21].

4.3. *Molecular methods*

4.3.1. *Polymerase chain reaction techniques*

Conventional and real-time polymerase chain reaction techniques are now established for identifying AR in various populations of small and large ruminants, as well as equine gastrointestinal nematodes. Through polymerase chain reaction, researchers can detect resistant (homozygous resistant) or susceptible (heterozygous and homozygous susceptible) adult worms or larvae. Using four primers in a single reaction mixture, worms can be genotyped for the mutation on the β -tubulin residue 200, which is linked to benzimidazole resistance[36].

4.3.2. *Pyrosequencing*

Pyrosequencing, a novel sequencing strategy, offers accurate and high-throughput SNP quantification. This method relies on detecting light signals generated during a multi-enzyme reaction, with pyrophosphate released in proportion to the number of incorporated nucleotides. By systematically adding nucleotides one at a time in a predetermined sequence, pyrosequencing determines the nucleotide sequence of the template DNA[37].

5. Conclusions

MDA has become a primary strategy for achieving the elimination goals of global programs targeting parasites like soil-transmitted helminths and lymphatic filariasis. However, numerous challenges impede its successful implementation. While the elimination goal for LF is attainable, it requires addressing issues related to drug distribution, health systems, and implementation. Prolonged program durations increase the risk of treatment failure and contribute to parasite resistance. There is an urgent need for developing new methods to monitor drug resistance emergence and investigating alternative antiparasitic drugs for future control measures. Despite the significant impact of MDA on various helminths, the emergence of resistance remains a pressing issue. Further research is essential to determine the most effective strategies for addressing this problem.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

This study received no extramural funding.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon request.

Authors' contributions

Nonika R conceptualized and designed the study. Harshita A collected the data, analysed it and wrote the initial draft of the manuscript. Nonika R then critically reviewed the manuscript and refined it. All authors have read and agreed to the published version of the manuscript.

References

- [1] Mascarini-Serra L. Prevention of soil-transmitted helminth infection. *J Glob Infect Dis* 2011; **3**(2): 175-182.
- [2] Tefera E, Belay T, Mekonnen SK, Zeynudin A, Belachew T. Prevalence and intensity of soil transmitted helminths among school children of Mendera Elementary School, Jimma, Southwest Ethiopia. *Pan Afr Med J* 2017; **27**: 88
- [3] Tripathi B, Roy N, Dhingra N. Introduction of triple-drug therapy for accelerating lymphatic filariasis elimination in India: Lessons learned. *Am J Trop Med Hyg* 2022; **106**(5 Suppl): 29-38.
- [4] International Conference on Multimedia Retrieval. Prospects of elimination of lymphatic filariasis in India. *ICMR Bull* 2002; **32**(5&6): 1-14.
- [5] Fernando SD, Rodrigo C, Rajapakse S. Current evidence on the use of antifilarial agents in the management of bancroftian filariasis. *J Trop Med* 2011; **4**. doi:10.1155/2011/175941
- [6] McCarthy J. Is antihelminthic resistance a threat to the program to eliminate lymphatic filariasis? *Am J Trop Med* 2005; **73**(2): 232-233.
- [7] Nascimento IJDS, Albino SL, da Silva Menezes KJ, Cavalcanti MAT, de Oliveira MS, et al. Targeting SmCB1: Perspectives and Insights to Design Antischistosomal Drugs. *Curr Med Chem* 2024; **31**(16): 2264-2284
- [8] Schwab AE, Boakye DA, Kyelem D, Prichard RK. Detection of benzimidazole resistance-associated mutations in the filarial nematode *Wuchereria bancrofti* and evidence for selection by albendazole and ivermectin combination treatment. *Am J Trop Med Hyg* 2005; **73**(2): 234-238.
- [9] Gyapong JO, Owusu IO, da-Costa Vroom FB, Mensah EO, Gyapong M. Elimination of lymphatic filariasis: Current perspectives on mass drug administration. *Res Rep Trop Med* 2018; **9**: 25-33.
- [10] Sulaiman WA, Kamtchum-Tatuene J, Mohamed MH, Ramachandran V, Ching SM, Lim et al. Anti-Wolbachia therapy for onchocerciasis & lymphatic filariasis: Current perspectives. *Indian J Med Res* 2019; **149**(6): 706-714.
- [11] Stolk WA, Swaminathan S, Oortmarssen GJ, Das PK, Habbema JD. Prospects for elimination of bancroftian filariasis by mass drug treatment in Pondicherry, India: A simulation study. *J Infect Dis* 2003; **188**(9): 1371-1381.
- [12] Webster JP, Molyneux DH, Hotez PJ, Fenwick A. The contribution of mass drug administration to global health: Past, present and future. *Philos Trans R Soc Lond B Biol Sci* 2014; **369**(1645): 20130434.
- [13] Agrawal VK, Sashindran VK. Lymphatic filariasis in India: Problems, challenges and new initiatives. *Med J Armed Forces India* 2006; **62**(4): 359-362.
- [14] Gyapong JO, Kumaraswami V, Biswas G, Ottesen EA. Treatment strategies underpinning the global programme to eliminate lymphatic filariasis. *Expert opin Pharmacother* 2005; **6**(2): 179-200.
- [15] Cobo F. Determinants of parasite drug resistance in human lymphatic filariasis. *Rev Esp Quimioter* 2016; **29**(6): 288-295.
- [16] Townson S, Hutton D, Siemieniska J, Hollick L, Scanlon T, Tagboto et al. Antibiotics and *Wolbachia* in filarial nematodes: Antifilarial activity of rifampicin, oxytetracycline and chloramphenicol against *Onchocerca gutturosa*, *Onchocerca lienalis* and *Brugia pahangi*. *Ann Trop Med Parasitol* 2000; **94**(8): 801-816.
- [17] Yadav P, Singh R. A review on antihelminthic drugs and their future scope. *Int J Pharm Pharm Sci* 2011; **3**(3): 17-21.
- [18] Shalaby HA. Antihelminthics resistance; How to overcome it? *Iran J Parasitol* 2013; **8**(1): 18-32.
- [19] Kebede A. Review on antihelminthic drug resistance nematodes and its methods of detection in Ethiopia. *J Vet Med Animal Sci* 2019; **2**(1): 1013.
- [20] Geerts S, Gryseels B. Antihelminthic resistance in human helminths: A review *Trop Med Int Health* 2001; **6**(11): 915-921.
- [21] Food and Agriculture Organisation of the United Nations. *Module 2. Helminths: antihelminthic resistance: diagnosis, management and prevention*. [Online] Available from: <https://www.semanticscholar.org/paper/MODULE-2.-HELMINTHS%3A-ANTHELMINTIC-RESISTANCE%3A-AND/928fc8dade25b688731fb3d3eedbc5e731a6b415>. [Assessed on 4 June 2024].
- [22] Várady M, Papadopoulos E, Dolinská M, Königová A. Anthelmintic resistance in parasites of small ruminants: Sheep versus goats. *Helminthologia* 2011; **48**: 137-144.
- [23] Moreira BP, Weber MHW, Haeberlein S, Mokosch AS, Spengler B, Greveling CG, et al. Drug repurposing and de novo drug discovery of protein kinase inhibitors as new drugs against schistosomiasis. *Molecules* 2022; **27**(4): 1414.
- [24] Charlier J, Bartley DJ, Sotiraki S, Martinez-Valladares M, Claerebout E, Samson-Himmelstjerna, et al. Anthelmintic resistance in ruminants: Challenges and solutions. *Adv Parasitol* 2022; **115**: 171-227.
- [25] Montresor A, Mupfasoni D. Achievements of the deworming programme in Sri Lanka. *Lancet Glob Health* 2019; **7**(9): e1156-e1157.
- [26] Perera DJ, Koger-Pease C, Paulini K, Daoudi M, Ndao M. Beyond schistosomiasis: Unraveling co-infections and altered immunity. *Clin Microbiol Rev* 2024; **37**(1): e0009823.
- [27] Geerts S, Gryseels B. Drug resistance in human helminths: current situation and lessons from livestock. *Clin Microbiol Rev* 2000; **13**(2): 207-222.
- [28] Ng'etich AI, Amoah ID, Bux F, Kumari S. Anthelmintic resistance in soil-transmitted helminths: One-Health considerations. *Parasitol Res* 2023; **123**(1): 62.
- [29] Schneeberger PHH, Gueuning M, Welsche S, Hürlimann E, Dommann J, Cécile Häberli, et al. Different gut microbial communities correlate with efficacy of albendazole-ivermectin against soil-transmitted helminthiasis. *Nat Commun* 2022; **13**(1): 1063.
- [30] Roose S, Avramenko RW, Pollo SM, Wasmuth JD, Ame S, Ayana M, et al. Characterization of the β -tubulin gene family in *Ascaris lumbricoides* and *Ascaris suum* and its implication for the molecular detection of benzimidazole resistance. *PLoS Negl Trop Dis* 2021; **15**(9): e0009777.
- [31] Moser W, Schindler C, Keiser J. Drug combinations against soil-

- transmitted helminth infections. *Adv Parasitol* 2019; **103**: 91-115.
- [32]Dolinská M, Königová A, Letková V, Molnár L, Várady M. Detection of ivermectin resistance by a larval development test-back to the past or a step forward? *Vet Parasitol* 2013; **198**(1-2): 154-158.
- [33]Hennessey M, Whatford L, Payne-Gifford S, Johnson KF, Van Winden S, Barling D, et al. Antimicrobial & antiparasitic use and resistance in British sheep and cattle: A systematic review. *Prev Vet Med* 2020; **185**: 105174.
- [34]Agrawal R, Pattnaik S, Kshatri JS, Kanungo S, Mandal N, Palo SK, et al. Prevalence and correlates of soil-transmitted helminths in schoolchildren aged 5 to 18 years in low- and middle-income countries: A systematic review and meta-analysis. *Front Public Health* 2024; **12**: 1283054.
- [35]Neto AFR, Di Christine Oliveira YL, de Oliveira LM, La Corte R, Jain S, de Lyra Junior DP, et al. Why are we still a worm world in the 2020s? An overview of risk factors and endemicity for soil-transmitted helminthiasis. *Acta Parasitol* 2023; **68**(3): 481-495.
- [36]Fissiha W, Kinde MZ. Antihelminthic resistance and its mechanism: A review. *Infect Drug Resist* 2021; **14**: 5403-5410.
- [37]von Samson-Himmelstjerna G. Molecular diagnosis of antihelminthic resistance *Vet Parasitol* 2006; **136**(2): 99-107.

Publisher's note

The Publisher of the *Journal* remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Edited by Qi Y, Liang TC