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Perspective

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A multifaceted approach to combatting the emergence of drug−resistant helminths

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The emergence of drug-resistant helminths poses a significant threat to public health and animal welfare. Currently, multidrug resistance among human parasites is particularly concerning in protozoans, such as *Plasmodium* and *Giardia*. However, in veterinary medicine, the emergence of multidrug-resistant helminths is a rising concern both in companion animals and livestock. A growing number of evidence of dog hookworms (*Ancylostoma caninum*) being resistant to benzimidazoles, ivermectin, and pyrantel in the United States and Canada is reported[1−3]. Similarly, multidrug-resistant *Haemonchus contortus*, which exhibits refractory responses to benzimidazole, ivermectin, and levamisole treatments, has already been documented in the United States, the United Kingdom, Europe, Asia and certain African regions[4−7]. The emergence of multidrug resistance in veterinary helminths is attributed to the prolonged use of combination treatments[8]. Hence, the rising trend of combination treatments (*e.g.*, benzimidazoles combined with ivermectin) for the control and elimination of soil-transmitted helminths may bring about multidrug-resistant pathogens in the field[9]. These issues threaten to undermine current drug-based control and elimination programs, which can result in prevalence rebounds and more pathologic consequences among affected populations.

1. Research advances against drug−resistant helminths

Repurposing existing anthelmintics with demonstrated efficacy against other parasites or pathogens has been identified as a potential strategy to combat resistant isolates. A recent study assessed the possibility of using ivermectin as a potential alternative to artemisone in the treatment of schistosomiasis[10]. Similarly, antibiotics such as tetracyclines and rifampicin have been advocated as treatment options for lymphatic filariasis; however, a longer treatment course to eliminate infection may be a drawback[11]. The discovery of novel resistance pathways has opened avenues for exploiting them to regain the efficacy of frontline drugs. Regarding benzimidazole resistance, the role of helminths' capacity to biotransform drugs has been investigated. UDP-glycosyltransferases have been shown to participate in drug metabolism through glycosylation causing the inactivation of xenobiotics and elimination due to enhanced solubility[12]. It has been proposed that drug compounds that can inhibit benzimidazole glycosylation by serving as a competitive substrate can be used in combination to limit drug metabolism before it can take effect[13].

Advances in the diagnostics of resistant parasites have also been on the rise. In the case of benzimidazole resistance, commercially available services that offer multiplex quantitative polymerase chain reaction (qPCR) panels have been developed to identify gastrointestinal parasites and detect markers of benzimidazole resistance (*i.e.*, F167Y mutation) in *Ancylostoma caninum*[14]. Moreover, point-of-care tests through isothermal amplification assays have also been developed to detect resistance markers. The F167Y, E198A, and F200Y mutations can be detected in *Necator americanus* using the SmartAmp2 platform[15].

Several advancements in biomedical research and technology may potentially be useful in addressing the emergence of resistant parasitic infections. Of these, deciphering the exact mechanisms of resistance is moving beyond single gene analysis toward whole genome, transcriptomics, and metabolomics, similar to research conducted in *Haemonchus* (*H.*) *contortus* and *Eimeria tenella*[4,16]. Among these, metabolomics is particularly significant as it provides insights into resistance that extend beyond the genome and transcriptome levels. For instance, in *H. contortus* resistant to ivermectin, metabolomics found that the refractory response to treatment is linked with the upregulation of metabolic pathways involved in key amino acid uptake and biosynthesis[17]. The authors

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surmise that amino acid metabolism may provide resistant strains with specific adaptive traits to counteract the ivermectin treatment. Currently, metabolomics has yet to be applied in the study of drug resistance in soil-transmitted helminths. A better understanding of resistance mechanisms will enable the development of drugs that can achieve parasite killing despite the occurrence of resistance.

Vaccine development against helminths offers a glimmer of hope in the ongoing battle against these resistant parasites. Research on human hookworm vaccines has yielded positive results. *Necator americanus* glutathione-S-transferase and aspartic protease have been used to create recombinant vaccines[18]. The vaccine targets are enzymes that facilitate hookworm blood-feeding. These vaccines are currently undergoing phase 1 and 2 clinical trials[19]. A clinical trial evaluating a recombinant aspartic protease vaccine with Alhydrogel adjuvant demonstrated a favorable immune response, including high IgG levels, and had few adverse events[20]. Recently, a multiepitope vaccine against *Opisthorchis viverrini* paramyosin was designed using computational methods[21]. The development of vaccines for helminths of public and veterinary health concern via *in vitro*, *in vivo,* and *in silico* approaches can help prevent infections without relying on pharmacological interventions, thereby mitigating the risk of drug resistance.

2. Consequences of drug–resistance of helminths

The introduction and proliferation of these resistance-associated mutations in parasitic helminth populations has several consequences for the development of novel therapies and other interventions. One of the consequences is the reduced efficacy of current and in-development drugs. As in the case of benzimidazoles, drug classes often share similar core structures and modes of action. Hence, resistance to one drug may also lead to resistance to others that belong to the same family. We see a clear indication of this in our preliminary *in silico* docking studies, despite testing four types of benzimidazole drugs with relatively different structures (*i.e.*, Fenbendazole, Mebendazole, Oxfendazole, and Albendazole), the trend of binding alterations is similar regardless of hookworm species indicating similar effects[22]. If novel benzimidazole anthelmintics are to be developed, there is a possibility that confirmed resistance-associated mutations may also undermine its parasite-killing performance.

The more we know about these resistance-associated mutations, the better our future interventions will be. Research that elucidates the mechanisms of resistance, including studies on mutations, should be used in developing novel therapeutic interventions against helminth infections. The design of these new drugs should take into consideration new research results. Moreover, alternative mechanisms of resistance, like helminth metabolic enzymes and efflux proteins, may be targeted by novel drug developers as an alternative to the mutated target receptors.

The emergence of resistance-associated mutations in the field can hinder efforts to control and eliminate parasitic helminths of public health concern. Therefore, drug discovery pipelines should not only focus on developing parasite-killing drugs for clinical use, but also consider how these new interventions can be applied within control and elimination programs. Consequently, investigating the occurrence of these mutations in endemic areas is crucial for informing drug development and providing insights into their epidemiological impact. Although the option of combination drug therapy to broaden the spectrum of efficacy against resistant helminths has been considered, it may not be amenable to control program participants due to concerns of adverse effects or MDA fatigue[23]. Drug development for controlling and eliminating these helminths of public health concern should consider how new drug candidates can be sustainably applied across diverse populations.

3. The role of policy and international cooperation

Policy and international cooperation play an important role in addressing parasitic infections of public health concerns. Crafting and promulgating policy regarding the control and elimination of parasitic infections ensure that funding can be appropriated for such efforts. For example, the Philippines has been implementing the Integrated Helminth Control and Elimination Program since its inception and adoption in 2006[24]. Since then, the yearly implementation of control efforts centered on mass drug administration has resulted in the reduction of soil-transmitted helminth infections from nearly 50% prevalence before the program to about 28% according to the latest survey[25]. This relative success is a testament to the positive effect of institutionalizing control programs against parasitic infections that threaten public health.

Policy interventions against the emergence of drug resistance in public health parasites are currently needed as a supplement to existing control programs. Several provisions can be included in this policy: 1) Limiting the access of the general public to anthelmintic drugs by making them prescription-only; 2) Evaluating the efficacy of Mass Drug Adminisitration every five years; 3) Clinical and public health guidelines on the prudent use of anthelmintics in veterinary and human health fields should be promulgated; 4) Public awareness of the harms and risks of drug resistant parasites and pathogens should be raised through community health education campaigns; 5) Research on drug development and discovery, as well as re-evaluation of other drugs for use in control and elimination efforts, should be prioritized and given attention.

International cooperation has played a significant role in global efforts to control and eliminate neglected tropical diseases. Through donations from affluent countries and individuals, drugs for control programs have been provided to resource-limited endemic areas, such as those in Africa and Southeast Asia[26]. Similarly, research funding from affluent countries and institutions for tropical diseases prevalent in poverty-ridden areas has provided novel insights that can be utilized to improve control and elimination efforts. These contributions include a better understanding of pathogen biology, improvement of point-of-care diagnostics, vaccine development, and drug discovery[26]. These collaborative contributions may have a positive effect on the battle against resistant parasitic infections.

Lastly, internationalization of health issues, including drug resistance in parasites, can lead to harmonization and standardization of control efforts, surveillance, reporting of resistant isolates, and resource sharing which benefit initiatives aimed at mitigating infections and abating the threat of resistance development.

4. Conclusions

In conclusion, the rise of multidrug-resistant helminths poses a significant threat to public health and veterinary medicine. Although recent advancements in diagnostics and therapeutic strategies provide optimism, addressing this challenge requires a multifaceted approach. Continued research on resistance mechanisms, development of novel drugs and vaccines, and strengthened international cooperation are essential to combat the growing prevalence of drug-resistant parasites and ensure sustainable disease control.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Data availability statement

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

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