



# Human soil-transmitted helminths: implications of mass drug administration

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## Purpose of review

With the London Declaration on neglected tropical disease (NTD), we are entering a new era of combating NTDs. However, the worldwide prospects of increased mass drug administration (MDA) treatments warrant caution on the development of anthelmintic resistance. In this review, we discuss the practical implications of MDA programs on the development of anthelmintic resistance in human soil-transmitted helminths (STH).

## Recent findings

There is poor evidence of anthelmintic resistance in human STH. Moreover, there is presumptive evidence that the refugia in MDA programs to control human STH is currently large, suggesting that the development of anthelmintic resistance in STH will be slow or may not occur. It remains unclear whether the current MDA strategy to control STH will sufficiently delay or prevent the development of anthelmintic resistance. First, differences in efficacy across and within STH species, and seasonal transmission of STH have not yet been considered. Second, any surveillance system to monitor drug efficacy is lacking. Finally, there is still no agreed strategy on how to deal with anthelmintic resistance once it emerges.

## Summary

Although anthelmintic resistance in human STH is currently of limited concern, various actions should be put in place for its delay and monitoring, and strategies should be developed in case anthelmintic resistance occurs.

## Keywords

anthelmintic resistance, mass drug administration, soil-transmitted helminths

## INTRODUCTION

Currently, we are entering a new era of combating neglected tropical diseases (NTDs): the WHO has made a roadmap [1] to guide the implementation of the policies and strategies set out in the Global Plan to combat NTD 2008–2015; and more than 70 pharmaceutical companies, governments, and global health organizations have committed to support the implementation of this roadmap in the London Declaration on NTD (31 January 2012) by sustaining or expanding the existing drug donation programs, with the support of the Bill & Melinda Gates Foundation and under the leadership and coordination of the WHO [2<sup>\*\*</sup>].

For the soil-transmitted helminths (STH) – *Ascaris lumbricoides* (roundworm), *Necator americanus*/*Ancylostoma duodenale* (hookworms), and *Trichuris trichiura* (whipworm) – the goal is to reduce the morbidity due to this cluster of NTDs by 2020, predominantly by targeted mass administration of one of the two benzimidazole drugs, albendazole or

mebendazole. Specific guidelines to control STH were recently updated by the WHO [3<sup>\*\*</sup>].

However, to control and eventually eliminate helminthiasis will require technically and scientifically sound research to improve current tools and strategies, as summarized in the six comprehensive reviews by the Disease Reference Group on Helminth Infections (DRG4) [4<sup>\*\*</sup>–9<sup>\*\*</sup>]. Most important, however, may be the fact that the arsenal of

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## KEY POINTS

- Anthelmintic resistance in human STH is currently of limited importance.
- Choice of drug and period of treatment need to be considered in mass drug administration programs to control STH.
- It is recommended that an international platform or network to guarantee the monitoring of drug efficacy and to map the emergence of anthelmintic resistance in all neglected tropical disease areas where MDA programs are being implemented.
- New anthelmintics against STH are needed.
- An agreed strategy on how to deal with anthelmintic resistance, once it emerges, needs to be developed.

available drugs with good spectrum and efficacy to treat STH, and which are available as donations, is limited to two benzimidazole anthelmintics, with very little development of new drugs specifically targeted to human helminthiasis. This makes mass drug administration (MDA) highly vulnerable should anthelmintic resistance develop and spread [9].

In this opinion article, we discuss briefly why anthelmintic resistance against STH is currently of limited importance, how we can delay anthelmintic resistance in the coming decade(s), how we should monitor for the emergence of anthelmintic resistance, and what we can do once anthelmintic resistance appears.

### WHY IS ANTHELMINTIC RESISTANCE CURRENTLY OF LIMITED IMPORTANCE?

Anthelmintic resistance in humans has received far less attention than resistance to antibacterial or other anti-infective agents, which is surprising and worrying because of the relatively small number of anthelmintics available and the various anthelmintic resistance reports in veterinary medicine. For instance, entering key words 'antibiotic' and 'resistance' in PubMed resulted in  $\pm 130\,000$  hits, whereas 'anthelmintic' and 'resistance' only resulted in  $\pm 4000$  hits. Moreover, adding 'humans' to these keywords reduced the scientific output by 25% for antibiotic resistance, but by 75% for anthelmintic resistance.

Recently, Vercruyse *et al.* [10] have critically evaluated the evidence of anthelmintic resistance in STH and concluded that anthelmintic resistance against human STH is currently of limited importance. Studies reporting anthelmintic resistance were

few in numbers; moreover, this suffered from a number of flaws, for example, ignoring the quality of the drugs as an important confounder of drug efficacy and being significantly underpowered. In addition to this poor evidence of anthelmintic resistance, it should be acknowledged that refugia, that is, the proportion of the parasite population that is not exposed to drugs and thus escapes selection for resistance, in MDA programs to control human STH, is currently large. The size of refugia is mainly determined by the fraction of the population treated, the frequency of treatment, and the proportion of the worm population present in the environment where it is not subject to drug action. MDA programs to control STH are mostly directed at specific target groups (often school-aged children), and this effect of low coverage is further magnified by low compliance [11]. Moreover, it has recently been demonstrated that animals such as dogs are a potential reservoir for STH infections [12,13,14]. These animals are often abundant in countries endemic to STH, but rarely treated, and therefore contribute to the fraction of the parasite population that is not exposed to drugs. Finally, the low frequency of treatments (once or twice a year) and the long survival of eggs (but less for hookworm larvae) all suggest that in the case of *Ascaris* and *Trichuris*, refugia should still be high after MDA programs, suggesting that the development of anthelmintic resistance in STH will be slow or may not occur.

This of course is in sharp contrast to the problems veterinarians are currently facing to control parasite infections in livestock. Yet, this discrepancy can be explained by the differences both in strategies to control infections and parasite specific features. First, animals are more frequently treated (up to 8 times per year), covering the entire herd. In fact, targeted treatment as implemented to control human STH is now also advocated to control parasite infections in livestock, as it slows down the development of anthelmintic resistance [15,16]. Second, the daily egg production of female worms is relatively small for parasite species displaying anthelmintic resistance in livestock (*Ostertagia*: 100–200; *Cooperia*: 1000–3000; *Haemonchus*: 5000–15000 vs. *Trichuris*: 3000–5000; hookworms: 9000–30000; *Ascaris*: 200000), and hence there may be fewer life stages that remain untreated in the environment. In addition to this, these life stages can survive no longer than 1 year in the environment, whereas embryonated eggs of *Ascaris* and *Trichuris* can survive up to 10 years. It should also be noted that *Ascaris* and *Trichuris* come from nematode clades 1 and 3, respectively, whereas the ruminant trichostrongyles that have developed

anthelmintic resistance belong to clade 5 (as do the hookworms), and thus *Ascaris* and *Trichuris* are evolutionarily and genetically far removed from the clade 5 nematodes in which anthelmintic resistance has become a problem in livestock. Because of this genetic distance, they may not have the same genetic capacity to develop anthelmintic resistance as the trichostrongyles.

However, this absence of evidence of anthelmintic resistance should be interpreted with caution, as the absence of evidence does not imply the absence of anthelmintic resistance. This is particularly possible when there is a lack of any surveillance system to monitor the efficacy of drugs used in control programs, appropriate tools to diagnose anthelmintic resistance in STH [17,18,19], and adequate guidelines to evaluate drug efficacy. These limitations may bias the perception that anthelmintic resistance is currently of limited importance.

### HOW CAN WE DELAY ANTHELMINTIC RESISTANCE IN THE NEXT DECADE(S)?

Updated guidelines to control STH recommend MDA once a year when the STH prevalence is 20% or more but less than 50%, and twice a year when the prevalence is 50% or more, followed by a stepwise drop in the frequency according to the infection rate [3]. However, it remains unclear whether this strategy is sufficient to delay or prevent the development of anthelmintic resistance.

First, this strategy ignores the differences in efficacy between the two benzimidazole drugs. Both albendazole and mebendazole are highly efficacious against *A. lumbricoides* (>98%), but albendazole has low efficacy against *T. trichiura*, whereas mebendazole is less efficacious against hookworms. Moreover, Levecke *et al.* [20] have recently demonstrated that the efficacy of albendazole against *T. trichiura* is also affected by the infection intensity, being highly efficacious when fecal egg counts (FEC) are low, but being less efficacious when FEC are high. Resultant suboptimal dosing, between and within STH, needs careful consideration. In veterinary nematodes, benzimidazole resistance is usually recessive, meaning that at recommended dose rates, worms (which are diploid) that are homozygous for the susceptible wild-type alleles and heterozygotes will be removed by the treatment and only worms that are homozygous for the resistance genotype will survive the treatment. Initially, such homozygous resistant worms will be extremely rare and resistance will not be apparent. However, if the dose rate is decreased and resistance is not fully recessive, at suboptimal dose rates heterozygotes may survive treatment and this will increase the frequency of

resistance alleles in the population and the selection for resistance. At this stage, there is almost no information on the frequency of putative resistance alleles in human STH [9], although Diawara *et al.* [17] have reported the presence of a mutation associated with benzimidazole resistance in *T. trichiura*. Moreover, the frequency of resistance alleles and the effect of recommended dose rates on heterozygous STH need to be assessed in order to better predict the potential for anthelmintic resistance development in human STH.

Second, seasonality of transmission, and hence the proportion of STH stages in the environment (refugia) and in the host are the important factors that need to be considered when planning MDA, both for maximizing the efficacy and reducing the risk of emergence of anthelmintic resistance. In the wet season, STH stages are spread in the environment (large refugia) and the drug pressure for selecting resistant strains is moderate to low. However, MDA is less effective in reducing transmission, as it only hits worms that are in the host. In contrast, free-living stages may be less abundant in the environment in the dry season, and the total parasite population will be mainly in the host (small refugia). Consequently, MDA is more effective, but the drug selection pressure for anthelmintic resistance will be higher. However, the relevance of the timing of treatment on the refugia for the human STH has yet to be thoroughly studied, and the purposeful timing of control programs may present logistic problems and be less effective in controlling the overall community morbidity. Villagers are usually more easily accessible in the dry season, so that entire communities can be treated simultaneously, whereas in the wet season people may leave villages early to work on their agricultural plots and thus be more difficult to reach for treatment, so a compromise has to be reached.

### HOW SHOULD WE MONITOR THE EMERGENCE OF ANTHELMINTIC RESISTANCE?

For STH, the egg reduction rate (ERR) remains the primary parameter to monitor the efficacy of drugs against STH. Guidelines on how to perform such an ERR assessment were provided by the World Health Organization [21]. Since the publication of these guidelines, an increasing number of novel insights have arisen, including choice of indicator of drug efficacy [22,23], the validity of the thresholds defining reduced efficacy [20,23], the development of novel diagnostic methods [24], the role of sensitivity of diagnostic methods to assess ERR [25,26], and their cost-effectiveness under field

conditions [27<sup>11</sup>]. New WHO guidelines on how to monitor drug efficacy against STH are, therefore, being developed and they will provide specific recommendations on required sample size, laboratory methods, statistical analysis, and final interpretation of the ERR based on novel thresholds defining reduced efficacy. In addition to this, a list of the most important confounders of drug efficacy will be provided (see also [10<sup>11</sup>]). It is expected that the new guidelines will be published soon (2012).

It is important, however, that these guidelines not only are introduced, but also that they should result in robust drug monitoring programs systematically verifying the efficacy of the drugs administered. In fact, given the paucity of suitable alternative anthelmintics for STH, it can even be argued that this monitoring should be a required component of MDA programs based on drug donations. To increase the efficiency, it could be initiated according to the frequency of MDA, assessing the efficacy of drug administered every 5 years when MDA is irregularly implemented, every 3 years when MDA is implemented once a year, and every year when MDA is implemented twice a year or more often.

Finally, there is an urgent need for an international platform or network to guarantee 'good monitoring practice' and to map the emergence of anthelmintic resistance in all NTDs for which MDA programs are being implemented. This would require the establishment of reference or collaborating centers, which are well equipped and staffed, allowing the support of local program managers. By analogy with the global database for NTDs [28,29], the NTD community could benefit from an open-access database on the use of anthelmintics (e.g. manufacturer and treatment regimen) and drug efficacy data that is constantly updated and can be utilized by researchers and disease control managers. However, it is clear that all of this will demand an increasing awareness of the importance of monitoring drug efficacy by pharmaceutical companies, governments, and global health organizations, highlighting the reality that providing drugs for free will not be enough to combat NTDs.

### WHAT CAN WE DO ONCE ANTHELMINTIC RESISTANCE EMERGES?

To date, there is still no agreed strategy on how to deal with anthelmintic resistance once it emerges, and this requires urgent consideration and agreement. It is pertinent that only a limited number of anthelmintic classes are available for the treatment of human STH. Therefore, there is an urgent need to develop new anthelmintics that work through novel modes of action. Already in the veterinary field, a

limited number of such candidates, meeting some of the criteria for selection, have been developed in recent years, but none are ideal for the treatment of STH [30<sup>11</sup>,31<sup>11</sup>]. Screening of anthelmintic activity in medicinal plants holds promise [32<sup>11</sup>] and should be encouraged. Should anthelmintic resistance arise and spread, at a time when our anthelmintic armory is still so limited, we may have to put more emphasis on nonchemical means of control, such as improvements in sanitation and education to change human behavior, and to ensure that footwear is worn in hookworm endemic areas [5<sup>11</sup>,33]. A recent meta-analysis [34<sup>11</sup>] showed that sanitation is associated with a reduction in the prevalence of STH infections. However, for a durable impact, the process of implementing improved sanitation requires community involvement and setting-specific public education and communication strategies to change human behavior. The worrying aspect of this, of course, is that we have known about the relevance of these latter control measures for well over a century, but STH have persisted nevertheless.

### CONCLUSION

To date, anthelmintic resistance in human helminthiasis has not received the attention it deserves. It has been assumed that anthelmintic resistance does not present a significant threat to the sustainability of the current STH control practices, as mainly specific groups are targeted, the treatment of MDA is low, and free-living life stages survive in the environment. To delay the development of anthelmintic resistance in the coming decades, control strategies might consider choosing the benzimidazole drug according to the epidemiological setting or to treat at specific periods of the year. Given the paucity of suitable anthelmintics, it is imperative that programs monitoring the drug efficacy are introduced and systematically implemented. The establishment of an international platform or network based on reference or collaborating laboratories and a global database on drug use and drug efficacy results is recommended. Finally, there is no agreed strategy on what to do if anthelmintic resistance emerges. Therefore, it is hoped that in the coming decade anthelmintic resistance, despite a major increase in MDA programs, will not become a major problem, allowing time for us to better understand the factors relevant to anthelmintic resistance and to develop new anthelmintics.

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## Conflicts of interest

There are no conflicts of interest.

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 725).

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2. Uniting to combat neglected tropical diseases. Ending the neglect and reaching 2020 goals. <http://www.unitingtocombatntds.org/>. 2012

This website provides details on the London Declaration on Neglected Tropical Diseases (30 January 2012) and highlights the worldwide commitment to combat NTD by 2020.

3. World Health Organization. In: Helminth control in school-age children: a guide for managers of control programmes. 2nd ed. Geneva: World Health Organization Press; 2011. p. 76.

This booklet provides updated guidelines to help managers plan, implement, and monitor programs for deworming school-aged children using methods based on the best current evidence and experience.

4. Basañez MG, McCarthy JS, French MD, *et al.* A research agenda for helminth diseases of humans: modelling for control and elimination. *PLoS Negl Trop Dis* 2012; 6:e1548.

This review article summarizes the historical developments in helminth infection modeling, the current frameworks and their main features, and key modeling priorities to aid the implementation, monitoring and evaluation, and surveillance of programs for the control and elimination of the human helminth infections.

5. Gazzinelli A, Correa-Oliveira R, Yang GJ, *et al.* A research agenda for helminth diseases of humans: social ecology, environmental determinants, and health systems. *PLoS Negl Trop Dis* 2012; 6:e1603.

This review article provides an overview of the relations and interactions of these various factors with health resources in the control of the STHs, schistosomiasis, lymphatic filariasis, onchocerciasis, foodborne trematodiasis, and taeniasis using the strategic social ecological framework developed by Stokols and identifies some research priorities.

6. Lustigman S, Geldhof P, Grant WN, *et al.* A research agenda for helminth diseases of humans: basic research and enabling technologies to support control and elimination of helminthiasis. *PLoS Negl Trop Dis* 2012; 6:e1445.

This review article summarizes the recent advances and identifies the challenges in the investigation of the fundamental biology of helminth parasites of humans according to parasite genetics, genomics, and functional genomics; parasite immunology; host–parasite interaction and pathogenesis in vertebrates; and host–parasite interactions and transmission biology in invertebrates.

7. McCarthy JS, Lustigman S, Yang GJ, *et al.* A research agenda for helminth diseases of humans: diagnostics for control and elimination programmes. *PLoS Negl Trop Dis* 2012; 6:e1601.

This review article summarizes the available diagnostic tests for soil-transmitted helminthiasis, schistosomiasis, lymphatic filariasis, onchocerciasis, and considers, in the context of the specific technical requirements, diagnostic tests needed for control of these parasites, and identifies critical gaps in diagnostic technology.

8. Osei-Atweneboana MY, Lustigman S, Prichard RK, *et al.* A research agenda for helminth diseases of humans: health research and capacity building in disease-endemic countries for helminthiasis control. *PLoS Negl Trop Dis* 2012; 6:e1602.

This review article focuses on the research and development needs for the establishment and strengthening of research capacity in disease-endemic countries.

9. Prichard RK, Basañez MG, Boatman BA, *et al.* A research agenda for helminth diseases of humans: intervention for control and elimination. *PLoS Negl Trop Dis* 2012; 6:e1549.

This review article summarizes the current strategies and available tools for the control of single helminth infections and discusses the challenges posed by integrated control in the face of coendemicity and polyparasitism with more than one infection.

10. Vercruyse J, Albonico M, Behnke JM, *et al.* Is anthelmintic resistance a concern for the control of human soil-transmitted helminths? *Int J Parasitol* 2011; 1:14–27.

This review article evaluates the evidence of anthelmintic resistance in human soil-transmitted helminths and summarizes the possible confounding factors of reduced efficacy. The study highlights that there is currently poor evidence of anthelmintic resistance in soil-transmitted helminths.

11. Parker M, Allen T. Does mass drug administration for the integrated treatment of neglected tropical diseases really work? Assessing evidence for the control of schistosomiasis and soil-transmitted helminths in Uganda. *Health Res Pol Systems* 2011; 9:3.

This study assessed the compliance to drug uptake for soil-transmitted helminthiasis and schistosomiasis in Uganda over a 4-year period 2005–2009 and highlights that compliance to donated drugs may be unsatisfactory.

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13. Ngui R, Lim YAL, Traub R, *et al.* Epidemiological and genetic data supporting the transmission of *Ancylostoma ceylanicum* among human and domestic animals. *PLoS Negl Trop Dis* 2012; 6:e1522.

This study provides some of the first epidemiological and genetic data supporting the transmission of a dog hookworm (*Ancylostoma ceylanicum*) to humans, and that mass drug programs targeting humans only will be sufficient to control hookworm infections.

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This study assessed the change in drug efficacy measured as egg reduction rate of a single-dose albendazole against different levels of *Trichuris trichiura* infections. The results indicate that the efficacy dropped as a function of the infection intensity and highlights that single-dose albendazole may still be recommended in areas where level of infection is low, and that the current threshold used as a guide to assess anthelmintic efficacy in *T. trichiura* (FECR <50%) may lead to wrong conclusions regarding anthelmintic resistance, particularly when the level of infection intensity is high.

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22. Montresor A. Cure rate is not a valid indicator for assessing drug efficacy and impact of preventive chemotherapy interventions against schistosomiasis and soil-transmitted helminthiasis. *Trans R Soc Trop Med Hyg* 2011; 105:361–363.

This study assessed the validity of cure rate as a measure of drug efficacy. The results highlight that cure rate outcomes are thwarted by infection intensity at baseline (mainly because of the lack of sensitive diagnostic methods), and hence underscore that cure rate is not the indicator of choice to monitor drug efficacy.

23. Vercruyse J, Behnke JM, Albonico M, *et al.* Assessment of the anthelmintic efficacy of albendazole in school children in seven countries where soil-transmitted helminths are endemic. *PLoS Negl Trop Dis* 2011; 29:e948.

This is the first multinational study assessing the efficacy of single-dose albendazole against soil-transmitted helminths based on a standardized protocol. The study provides new thresholds defining reduced efficacy for *Ascaris lumbricoides* and hookworms, and underscores that fecal egg count reduction is the recommended indicator for the assessment of drug efficacy.

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27. Levecke B, Speybroeck N, Dobson R, *et al.* Novel insights in the fecal egg count reduction test for monitoring drug efficacy against soil-transmitted helminths in large-scale treatment programs. *PLoS Negl Trop Dis* 2011; 5:e1427.

This study is the first to identify important factors affecting the interpretation of the fecal egg count reduction test for monitoring drug efficacy. The study showed that the interpretation of this test is affected by a complex interplay of factors inherent to both study design and host–parasite interactions.

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This study is the first to assess both in-vitro and in-vivo efficacy of monepantel against laboratory models for human soil-transmitted helminths. Monepantel reveals low or no activities, hence does not qualify as a drug development candidate for human soil-transmitted helminthiasis.

32. Koné WM, Vargas M, Keiser J. Anthelmintic activity of medicinal plants used in Côte d'Ivoire for treating parasitic diseases. *Parasitol Res* 2012; 110:2351–2362.

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34. Ziegelbauer K, Speich B, Mäusezahl D, *et al.* Effect of sanitation on soil-transmitted helminth infection: systematic review and meta-analysis. *PLoS Med* 2012; 9:e1001162.

This systematic review and meta-analysis assessed the effect of sanitation on soil-transmitted helminth infections. The results revealed that sanitation is associated with a reduced risk of transmission of helminthiasis to humans. Access to improved sanitation should therefore be prioritized alongside preventive chemotherapy and health education to achieve a durable reduction of the burden of helminthiasis.