Ivermectin and albendazole co-administration: opportunities for strongyloidiasis control

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Summary

In 2020, the World Health Organization recognised the importance of strongyloidiasis alongside soil-transmitted helminths (STH) in their 2021-2030 roadmap, which aspires to target *Strongyloides stercoralis* with preventive chemotherapy (PC) using ivermectin. Combination treatment using both albendazole, the primary drug used to treat STH, and ivermectin would improve the efficiency of mass drug administration targeting both STH and *S. stercoralis*. In this Personal View, we discuss the challenges and opportunities towards the development of an efficient control programme for strongyloidiasis, particularly if it is to run concurrently with STH control. We argue the need for defining the prevalence threshold to implement PC for *S. stercoralis*, the target populations and optimal dosing schedules, and discuss the added benefits of a fixed-dose co-formulation of ivermectin and albendazole. Implementation of an efficient control programme will require improvement of current and validation of new diagnostics to target and monitor *S. stercoralis* infections, and consideration of the challenges of multi-species diagnostics for *S. stercoralis/*STH control. Finally, the evolution of ivermectin resistance represents a credible risk to control *S. stercoralis*; we argue that genome-wide approaches together with improved genome resources are needed to characterise and prevent the emergence of resistance. Overcoming these challenges will help to reduce strongyloidiasis burden and enhance the feasibility of controlling it worldwide.

Introduction

Despite affecting over 600 million people worldwide,[1] strongyloidiasis is considered one of the most neglected of the neglected tropical diseases (NTDs).[2] *Strongyloides stercoralis,* the primary parasitic species that causes strongyloidiasis in humans, is responsible for infections that include asymptomatic cases as well as those with symptoms including skin and gastrointestinal conditions, and may be life-threatening if left untreated.[3] Whilst other intestinal nematodes such as *Ascaris lumbricoides, Trichuris trichiura*, and the hookworms (*Necator americanus* and *Ancylostoma duodenale*), collectively termed soil-transmitted helminths (STH), have long been considered important human pathogens of public health interest and warranting action by the World Health Organization (WHO), *S. stercoralis* has not been included in the WHO roadmaps that define global targets and milestones to prevent, control, eliminate, or eradicate NTDs, until recently.[4] As a consequence, there have been no formal public health programmes focused on its control. This situation is, however, slowly changing. Recent works suggest that the real prevalence and burden of this disease have been globally underestimated for decades. Besides, the recent pre-qualification of generic ivermectin (IVM), the preferred drug to treat this parasite, by the WHO will facilitate and expand its use in preventive chemotherapy (PC), particularly in areas where the drug was not available. These two factors together have contributed to highlight the tremendous burden of the disease and enable its control. As a result, in 2020 the WHO incorporated strongyloidiasis alongside STH in their 2021-2030 roadmap for NTDs,[4] which included the aim of targeting 96% of countries endemic for *S. stercoralis* with PC using IVM.

Most mass drug administration (MDA) approaches to target STH species use benzimidazole-class (BZ) anthelmintics such as mebendazole (MBZ) and albendazole (ABZ). Although the widespread use of these drugs is effective at controlling *A. lumbricoides* and hookworms, they are less effective against *T. trichiura* and *S. stercoralis.*[5,6] In addition, there is growing evidence that the efficacy of ABZ against *T. trichiura* is further decreasing, which may reflect the early stages of drug resistance as commonly observed in veterinary parasites frequently targeted with BZ compounds.[7] To address the need for new treatment approaches, co-administration of IVM and ABZ has been evaluated as a potential alternative to ABZ alone for the treatment of *T. trichiura*. This new approach has repeatedly shown improvements in efficacy in trichuriasis treatment compared to the current standard treatment (ABZ 400 mg),[8-11] reaching

cure rates closed to 100% when IVM was administrated at higher doses (600 µg/kg)[12] Similarly, the combination of the two drugs was more efficacious than the combination of ABZ and MBZ.[13] Recent meta-analyses also confirmed increased efficacy of IVM plus ABZ for trichuriasis treatment,[14] without compromising the treatment of hookworms or *A. lumbricoides.*[15]

Considering the evidence of improved efficacy when combining IVM with ABZ, it seems reasonable that future PC programmes targeting STH could also include IVM.[16,17] If this is implemented, it will almost certainly have the added benefit of targeting *S. stercoralis*, especially given that IVM is broadly considered to be the preferred drug used to this parasite. Importantly, a combination treatment approach would mean that strongyloidiasis could be directly controlled alongside STH within a single MDA programme. To begin to address the 2021-2030 WHO aim for strongyloidiasis control, an adequate design and implementation of monitoring and evaluation programs are of utmost importance for the future assessment of the effectiveness of PC against *S. stercoralis*.

Implementation of IVM and ABZ combination for strongyloidiasis control

The 2021-2030 WHO roadmap for STH advocates for the distribution of IVM together with ABZ or MBZ to school-aged children (SAC) in areas of high endemicity of *S. stercoralis.*[4] To implement this, several challenges and questions must be addressed so that a control program for strongyloidiasis can be undertaken. For instance, an understanding of the global transmission limits and national endemicity, together with reliable measurements of prevalence at the level of programmatic implementation units, is needed to assess where control programs should be prioritised. Moreover, the implementation of IVM and ABZ combination shares the challenges of implementing IVM programmes in areas endemic for *Loa loa*.

A key feature of ABZ-based MDA for STH control is that its implementation and frequency of administration is based on the pre-intervention prevalence -currently set at a minimum threshold of 20% of all species within the "target group" - *A. lumbricoides*, *T. trichiura*, and hookworms.[4] The equivalent baseline prevalence for implementing specific MDAs for strongyloidiasis has not yet been defined, this must be considered as the most urgent action to implement PC for this parasite. A recent work assessed the factors influencing the different

approaches for PC in strongyloidiasis. Establishing a prevalence threshold for the implementation of MDA with IVM must consider the reduction in the number of infections (which is higher with higher prevalence thresholds) and the cost per recovered person (which decreases with higher prevalence threshold). In addition, additional factors must be locally taken into account, such as the national health resources and infrastructures, or the overall funds. In that work, authors concluded a prevalence threshold of 15-20% as the most adequate for strongyloidiasis in consideration of a balance between costs and effectiveness of the intervention, although this estimation has not been yet evaluated under field conditions.

However, in the context of a new regime of IVM and ABZ co-administration for both STH and strongyloidiasis control, new challenges of PC implementation must also be considered; further research is needed to determine how best to integrate a minimum prevalence threshold for *S. stercoralis* to warrant PC along with other STH prevalence. For example, should strongyloidiasis prevalence be considered independently to other STHs?, or should *S. stercoralis* be included in the "target group" of STHs and its prevalence added to the overall prevalence threshold? Furthermore, it will need to be determined how to approach PC and MDA in areas where *S. stercoralis* infections are sufficiently high to warrant intervention, but the minimum threshold of 20% STH prevalence is not met; and *viceversa*.[4]

WHO guidelines for STH control have primarily focused on pre-SAC and SAC, however, pregnant women and women of reproductive age have also been recently included.[16] Thus, the larger adult population within an endemic region is not typically considered a target for control. *S. stercoralis* infections can persist for long periods of time and be maintained within a single host into adulthood, given their ability to reproduce and cause autoinfections.[18-20] Current (ABZ) and future (ABZ and/or ABZ+IVM) PC strategies focused predominantly on children will, therefore, exclude a highly relevant population of adults acting as a reservoir for this parasites, which will ultimately limit the long-term impact of PC due to reinfection of treated groups. This is particularly relevant in *S. stercoralis*-hookworm co-endemic areas, where there is often a higher prevalence of hookworms in the adult population.[21] This reservoir of untreated parasites, together with evidence from modelling studies comparing school-based versus community-wide MDA for the other STH species,[22] makes a strong argument for treating adult populations. Although empirical cost-effective evidence is still

lacking, health economics and outcome research (HEOR) studies are likely to be an important source of supporting data to guide future IVM-ABZ MDA strategies.

The optimal dose and schedule of IVM in PC against *S. stercoralis* has not been established. IVM at 200 µg/kg for one or two days is considered the most appropriate treatment for uncomplicated strongyloidiasis,[23,24] although this has not been yet widely determined in the context of MDA. Considering that the most frequent regimen of IVM and ABZ co-administration in trichuriasis treatment is a single dose of 200 µg/kg IVM and 400 mg ABZ, it is reasonable to expect that this dosage will also be effective in PC for both strongyloidiasis and trichuriasis. The optimal dosing regimen for IVM and ABZ in strongyloidiasis should be one that is easy to implement and produces the greatest probability of "individual cure" while maintaining efficacy against STH.

Considerations for a fixed-dose co-formulation of IVM and ABZ

At present, IVM is usually administered on a weight-based, height-based or age-based dosing schedule. A variable dosing strategy potentially makes MDA more complicated due to the need to measure individual-based parameters before administration and may result in inaccurate dosing.[25,26] A fixed-dose co-formulation (FDC) of IVM and ABZ has the potential to simplify drug administration during MDA and prevent underdosing of IVM. Both drugs possess complementing pharmacokinetic properties that make them ideal for co-formulation. For example, they have a similar Tmax (the time taken to reach maximum concentration) of 4 to 6 hours, [27,28] such that after an oral dose, both drugs achieve peak blood levels almost simultaneously, potentially enhancing their anthelminthic action. Furthermore, IVM has the additional advantages of a longer elimination half-life,[28] potentially producing a longer therapeutic effect and a wider therapeutic index, and that high doses of IVM (above 400 µg/kg) are safe to use in both adults,[27-29] and children.[28]

A FDC will likely have additional, immediate benefits over conventional treatment strategies. The shipping and distribution of FDC in integrated control programmes are likely to be significantly more cost effective compared with the delivery of two individual drugs for MDA.[30] Previous use of FDC to treat other diseases like tuberculosis, HIV, or malaria, have resulted in an increased therapeutic efficacy, reduced pill burden, improved adherence, and

prevented the emergence of drug resistance.[31] Together, these factors will contribute to achieving greater community-wide coverage and, therefore, improved control using a FDC.

A multicentre phase II/III adaptive randomised trial to assess the safety and efficacy of different dosing regimens of both IVM and ABZ as a FDC for STH and *S. stercoralis* is now being conducted. The data from this trial are expected to provide valuable evidence to guide implementation of this strategy.

Diagnostics to target and monitor control programs

Accurate diagnostics are necessary for an effective control programme for strongyloidiasis. Sensitive diagnostics are first needed to assess the baseline prevalence of parasites in an area, and second, diagnostics with high specificity are needed to monitor the prevalence after the commencement of a control strategy and to assess the effectiveness of one or even several rounds of MDA.[32] A range of parasitological, serological, and molecular techniques have been developed and applied, each with strengths and limitations that must be overcome for the implementation of effective diagnostics.[33] The choice of diagnostic approach should also take into account the need for simultaneous or concurrent detection of both *S. stercoralis* and one or more STH species.

Unlike other STHs which deposit eggs in faeces, *S. stercoralis* develops and matures into larvae before being excreted. As such, standard microscopy techniques based on the examination of stool, for example Kato-Katz, that are widely used to diagnose STHs are unsuitable for diagnosing strongyloidiasis. Although some coprological techniques, for example the Baermann technique,[34,35] are considered more sensitive to detect *S. stercoralis*, the fact that most chronic cases are characterised by low and infrequent larval outputs increases the likelihood of a false negative test result. As a result, such approaches may misclassify as either not requiring intervention prior to control, or reaching intervention targets too soon, particularly when the infection intensity is low. Considering that microscopy methods to detect *S. stercoralis* in stool are time-consuming and require laboratory expertise, they are not an ideal diagnostic for an efficient control programme, particularly if STHs must be monitored simultaneously. Modifications to the standard Baermann technique, such as charcoal preincubation have been shown to offer some promise, increasing the prevalence estimation from 9.6% to 31.3% when compared with conventional Baermann,[36] while

requiring less space and material. Although this is an important step forward in the standardisation of parasitological diagnosis of strongyloidiasis, it still falls short of being programmatically applicable.

Serological methods that detect antibodies in response to infection are significantly more sensitive than microscopy-based diagnostics. Serology may be useful for monitoring active infections, as some studies have identified patients that have become antibody negative within six to twelve months after successful treatment.[37] Also, the use of dried blood samples has proved to be a simple and affordable method for sample collection and storage in serodiagnosis,[38,39] which together with the use of point-of care devices may facilitate its implementation at scale.[40,41] However, the applicability of this to endemic settings where repeated exposure is common is yet to be determined. A promising study using NIE antigen-based serological analysis before and after IVM MDA for scabies reported a decrease in strongyloidiasis prevalence from 9·3% to 5·1%.[42] However, the specificity of serological methods can be limited due to cross-reactivity with other helminths,[33] and the diagnostic accuracy can vary significantly depending on the test format used as well as the source of the targeted antigen material. Recent WHO recommendations suggested serology in combination with a fecal test (microscopy or a molecular test) to evaluate *S. stercoralis* prevalence in post-intervention settings.[43] However, the need for two distinct diagnostic methods will increase the laboratory work and its cost when monitoring deworming programs, which will hamper its implementation at scale, particularly if STH must be monitored simultaneously.

Recent investigations in diagnostics for strongyloidiasis have focused on molecular techniques and in particular, real-time quantitative PCR (qPCR). Several studies have showed qPCR is more sensitive than microscopy, although microscopy-positive cases were still occasionally missed, likely due to low parasite levels and the low input volume used by qPCR.[35,44,45] Other studies have reported low qPCR sensitivity (range between 63·3% and 90%) when compared with serology.[46] The variation in diagnostic performance could be due to the lack of harmonisation of protocols for sample collection, processing, DNA extraction, and amplification.[47] As a consequence, there is not a consensus regarding the use of qPCR as a "gold" standard in *S. stercoralis* diagnostic, reflected in recent WHO recommendations that have mainly focused on serodiagnosis.[43] Despite the clear need for further improvement, qPCR has the unique benefit (compared to available parasitological or immunological

methods to diagnose strongyloidiasis) in that it can facilitate simultaneous detection of *S. stercoralis* and STHs from the same biological sample using a single multiplex assay. There is increasing interest in using qPCR in epidemiological or clinical studies, and large-scale deworming programs targeting STH,[48,49] which may elevate qPCR towards becoming a universal standard in the near future for STH detection in low prevalence settings. In the context of using IVM and ABZ to simultaneously control STH infections and strongyloidiasis, multiplex qPCR targeting all STH species and *S. stercoralis* has the potential to be used as a sole diagnostic tool to monitor overall MDA effectiveness and as a sensitive and specific alternative to serology and microscopy.

Monitoring the emergence of anthelmintic resistance

IVM is already used at scale to control onchocerciasis and lymphatic filariasis and is now being also evaluated for malaria,[50,51] and scabies control.[52] The implementation of co-administered IVM and ABZ for STH control might dramatically increase the exposure of *S. stercoralis* to IVM. One consequence of such pressure is the evolution of and selection for resistant strains that can survive in the presence of the drug. Therefore, MDA programmes must also begin to coordinate efforts toward monitoring for resistance, to ensure these drugs remain effective so that sustainable control can be achieved.

Although IVM resistance has been widely reported in veterinary medicine, the impact of MDA on the development of anthelmintic resistance in *S. stercoralis* is still unknown. Recently, genetic variation associated with IVM resistance in the ruminant gastrointestinal nematode *Haemonchus contortus* has been mapped to a single discrete region in the genome,[56(preprint)] a genetic signal found in parasites collected on multiple continents.[57] This is in contrast to the genetic signature associated with sub-optimal response to IVM in *O. volvulus*, which was clearly multigenic and distinct in different countries examined.[58] Hence, monitoring resistance emergence in strongyloidiasis should not be restricted to a small number of genes and will likely benefit, at least in the short term, by using broad-scale “genome-wide” rather than candidate gene approaches.

Genome-wide approaches provide an unbiased method whereby genetic change throughout the genome is monitored to identify signatures of selection consistent with the emergence of resistance.[59] To do so, genome-wide genetic variation is determined before and after MDA

interventions and together with drug response information (either from the host or parasite), aims to identify species-specific variants and genes associated with survival after treatment. Such genetic data could also inform more broadly about genetically defined populations or "transmission zones",[60] be used to monitor parasite population decline over time and distinguish between resistance emergence and transmission of parasites from outside of the treatment zones; with the potential benefit of detecting zoonotic sources of infection.[61] In this way, resistance emergence can be monitored, prevented.

We acknowledge that genome-wide techniques are less accessible particularly in endemic countries, require significant costs in terms of infrastructure and expertise, and may rely on coordinated efforts and centralised diagnostics laboratories. However, it is clear from the veterinary field that significant advances have recently been made in understanding the genetic basis of resistance using genome-wide approaches, and that similar investment to understand resistance in human-infective helminths will likely provide equivalent advances towards more targeted, cost-effective molecular diagnostics for monitoring resistance.[63] Key to genome-wide analyses is the availability of a genome assembly; a draft genome assembly already exists for *S. stercoralis*,[64] however, it remains in a fragmented state, which will limit the interpretation of genome-wide analyses of drug response.[57] Recent development of long-read genome sequencing, for example, PacBio or Oxford Nanopore sequencing, offers the best opportunity to improve this reference genome. Nevertheless, genome-wide analyses should be the cornerstone for the study of anthelmintic resistance in the near future.[59]

Conclusion

There is growing evidence supporting the combined use of IVM and ABZ in MDA campaigns for STH. In doing so, it will provide an opportunity to completely integrate *S. stercoralis* control into such programs, and in turn, renew efforts to alleviate strongyloidiasis as a prevalent but neglected disease. Several challenges need to be addressed in order to effectively implement and monitor the massive use of IVM and ABZ for strongyloidiasis (see Box 1). However, overcoming these challenges will help to understand the real burden of strongyloidiasis, reducing its impact on the communities and individuals that currently suffer *S. stercoralis* infections, and enhance the feasibility of controlling (and perhaps even eliminating) the disease worldwide.

Author Contributions

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Box 1. Checklist towards improved *Strongyloides stercoralis* and soil-transmitted helminths (STH) control using a co-administration of ivermectin (IVM) and albendazole (ABZ)

A. Implementation of IVM-ABZ combination regimen:

- Establishment of an optimal *S. stercoralis* prevalence threshold to implement preventive chemotherapy and its integration with STH prevalence in co-endemic areas.
- Identification of the target population to maximise impact (mass drug administration vs age-targeted preventive chemotherapy).
- Impact evaluation and cost-effectiveness assessment needed to provide evidence to guide policy change.
- Evaluation of appropriate dosing schedule for preventive chemotherapy using IVM and ABZ, preferably as a single dose.

B. Fixed dose IVM and ABZ co-formulation:

- Clinical evaluation of a IVM fixed-dose coformulation with ABZ.
- Regulatory approval of IVM-ABZ fixed dose combination based on robust safety and efficacy data on higher dose IVM in children.

C. Diagnostics to target and monitor control programs:

- Pilot studies that evaluate different diagnostic schemes in MDA interventions, including combinations of different available methods and the cost-effectiveness of each scheme.
- Evaluation and harmonisation of protocols for DNA-based detection of *S. stercoralis* to improve its diagnostic performance.
- Evaluation and harmonisation of multiplexing *S. stercoralis* along other STH species using qPCR, particularly in low-prevalence settings.

D. Monitoring anthelmintic resistance:

- Funding and capacity building for genomics approaches in endemic countries relying on coordinated efforts and centralised diagnostics laboratories.

- Validation and standardisation of protocols for samples processing, DNA extraction, whole-genome sequencing, and bioinformatics for assessing drug resistance in *S. stercoralis.*
- Improvement of *S. stercoralis* reference genome, preferably using long-read sequencing technologies.

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