Mass drug administration for the control of Strongyloides stercoralis infection: progress and challenges

Valdir Sabbaga Amato, Felipe Francisco Tuon

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Valdir Sabbaga Amato [1,2], Felipe Francisco Tuon [3]

[1] Laboratório de Parasitologia, Instituto de Medicina Tropical, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR.

[2] Departamento de Molestias Infecciosas e Parasitarias da Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR.

[3] Laboratory of Emerging Infectious Diseases, School of Medicine, Pontifícia Universidade Católica do Paraná, Curitiba, Paraná, Brazil

CORRESPONDING AUTHOR:

Valdir Sabbaga Amato

Adjunct Professor of Infectious Diseases

Departamento de Moléstia Infecciosas e Parasitárias da Faculdade de Medicina da Universidade de São Paulo

Av. Dr. Enéas de Carvalho Aguiar, 470 - andar térreo sala 06 - Cerqueira Cesar - São Paulo - Brazil. Zip Code: 05403000

valdiramato@usp.br

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Soil-transmitted helminths (STHs) are recognized causative agents of Neglected Tropical Diseases (NTDs), common chronic conditions that primarily afflict the world's poorest [1]. Among these STHs, the roundworm *Strongyloides stercoralis* causes systemic infections that can lead to different clinical manifestations. Although infected individuals are often asymptomatic, nonspecific gastrointestinal symptoms, such as diarrhea and abdominal pain, and even dermatological disorders, such as urticarial, have been reported in patients infected with *S. stercoralis* [2]. Infection can also lead to more severe disease states, particularly in immunosuppressed individuals, such as hyperinfection syndromes and disseminated strongyloidiasis, which can be fatal [2].

Strongyloidiasis prevalence rates have been reported by several global/regional studies and systematic reviews to range from 0 to 99% [2-4]. Worryingly, some determined national/sub-national prevalence levels are extremely high (up to 70%) and/or consistent year over year. For instance, in the Caribbean islands, in the last 40 years, strongyloidiasis prevalence rates have not decreased, remaining at approximately 20% [4]. However, we must keep in mind that prevalence estimates are highly affected by survey methods.

Mass drug administration (MDA) approaches have been considered and/or used for the control of several NTDs, supported by the results obtained in a pioneer MDA campaign implemented in China for the elimination of lymphatic filariasis (using diethylcarbamazine) [8]. MDA comprises the use of safe and single-dose drugs highly effective against specific pathogenic agents on a large scale to control particular diseases. Such approaches are extremely important for the control of NTDs. They have demonstrated success in the control (but not elimination) of *Loa loa* microfilaremia with

ivermectin or albendazole [9, 10], STH with albendazole or ivermectin [11, 12], *Schistosoma* spp. with praziquantel [13], and trachoma with azithromycin [14]. However, some recognized barriers may impact their consideration/outcomes, such as the time needed to conduct epidemiological studies required for the determination of NTD prevalence and effectiveness of the MDA campaign, the significant initial monetary investment, and the need for complete involvement of health systems that sometimes dictate establishment of mutual agreements with neighboring countries [15].

Although robust MDA data have been reported for some STH-induced NTDs, such as filariasis and trachoma, mass drug administration studies for *S. stercoralis* infection are scarce (Table 1). There has been no systematic review on the issue. Furthermore, even published studies present evident limitations, discussed below, related to their diagnostic methods, administered drugs, evaluated populations, and selected interventions.

Most MDA studies have used stool samples for diagnosis [16-19]. In such studies, the prevalence of *S. stercoralis* infection before intervention varied from 12 to 41%, with decreases of 17 to 69% after MDA. However, the diagnosis of *S. stercoralis* infection using stool examination has a known low sensitivity. Fecal examination methods, including observation of direct or concentrated stool smears, effectively detect eggs in medium- to high-intensity infections, but often fail to detect the larvae used for diagnosis of *S. stercoralis* infection [5]. Furthermore, molecular techniques (qPCR) usually have low sensitivity, although their specificity is frequently high [7]. On the other hand, serological tests are important strongyloidiasis diagnosis tools, with typically high sensitivity (70 to 95%) and variable specificity, which increase with the use of recombinant antigens, such as a 31-kDa candidate protein (NIE) [6].

In strongyloidiasis therapy, ivermectin is widely recognized as the best treatment option for *S. stercoralis* infections, particularly in the context of MDA. Nevertheless, most MDA approaches have used other drugs, including mebendazole and albendazole, mainly because they target STH genera (*Trichuris*, *Ancylostoma*, and *Necator*), in addition to *S. stercoralis*. Despite use of these less effective drugs, the prevalence of strongyloidiasis decreased, probably because these studies used multimodal interventions.

Marks *et al.* performed an MDA trial in the Solomon Islands using NIE antigen-based serological analysis to detect and ivermectin to treat *S. stercoralis* infection (THE REFERENCE OF THE MANUSCRIPT ACCEPTED BY CID FOR THIS EDITORIAL). The survey approach consisted of before-and-after analysis to determine the effect of MDA on the prevalence of *S. stercoralis* antibodies in 448 children. The average prevalence was 9.3% in six communities, ranging from 2.2% to 14.3%. These values for this particular population were low compared to those reported in other studies. Consequently, the global impact of MDA was low, although still relevant: prevalence significantly decreased after intervention. Although the diagnostic test used in this study had high sensitivity, the number of false-positives was not negligible. Antibodies against the recombinant NIE antigen were detected in 6.5% of healthy controls [21]. *S. stercoralis* seroprevalence was 5.1% after MDA; this prevalence is low enough that it is difficult to determine the number of false-positives in the population. Two additional factors may have influenced the outcome of this MDA study. The first is related to the interventions selected. When an MDA program is implemented, it can include multi-disciplinary approaches, such as educational intervention that highlight the importance of hygiene, food washing, shoes, and boiling water. The success of STH infection control should be based on socio-educational approaches and improvement of economic conditions, not only on MDA. The second factor is related to the notion that a single therapeutic dose may not be enough to control

parasites. To achieve better control of parasitic agents and diseases, we must consider that the most effective STH control programs implemented two to three years of MDA, not a single drug administration.

Multidisciplinary MDA approaches should consider expanding the elimination of possible animal reservoirs; to control human strongyloidiasis, concomitant treatment of dogs should be considered [20]. Furthermore, access to proper sanitation and safe water supplies may have the highest impact on disease control and survival. However, implementation of such measures is hindered by emphasis on HIV, malaria, tuberculosis, other neglected diseases, and war.

Since the 2000s, several ambitious targets have been suggested by the Millennium Development Goals, including the elimination of hunger and poverty in the world, as well the control of HIV infection, malaria, and other diseases [15]. Such goals may suggest that eradicating poverty is easier than eliminating NTDs. However, one cannot be accomplished without the other, since NTDs promote and re-enforce poverty, and poverty is itself a risk factor for the development of NTDs. MDA is a useful approach to fighting STHs, including *S. stercoralis* and other NTD etiologic agents. However, MDA must be considered in the frame of multiple interventions, which can lead to improvements in socio-economic conditions.

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CONFLICT OF INTEREST DISCLOSURE

The authors declare that they have no conflicts of interest to disclose.

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Table 1. Published MDA interventions targeting *S. stercoralis* infection.

Author	Year	Country	Drug	Test	N	%	%	% Decrease
Longfils	2005	Cambodja	mebendazole	Stool direct exam	2412	12%	6%	50%
Anselmi	2015	Ecuador	ivermectin	Stool direct exam and serum test	200	24%	16%	69%
Kearns	2017	Australia	Ivermectin	Serum test	818	21%	5%	24%
Steinmann	2015	China	albendazole	Stool direct exam	320	13%	9%	67%
Barda	2017	Tanzania	Ivermectin	Stool direct exam	1034	41%	7%	17%