The promise and pitfalls of Mass Drug Administration to control intestinal helminth infections

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Abstract

Purpose of review: Intestinal helminth infections continue to cause significant morbidity in resource limited settings. Recent efforts at global control have centered on Mass Drug Administration (MDA) of praziquantel and benzimidazole anthelminthics to reduce the prevalence and intensity of schistosomiasis and soil transmitted nematode infections, respectively. This review summarizes progress and potential challenges associated with MDA.

Recent findings: Data from studies conducted in endemic areas show that chemotherapeutic interventions can reduce prevalence and intensity of infection with intestinal helminths, and have the potential to reduce transmission within populations. However, consistent benefits in high risk groups, including children and pregnant women, have not been established. The long term benefits of MDA remain to be determined, and the potential for emerging resistance to impact effectiveness have not yet been defined.

Conclusions: While studies evaluating MDA have shown benefit in certain populations, intensive monitoring and evaluation, as well as a commitment of resources for new drug development are essential for long-term control or elimination of intestinal helminth infections.

Key words: Mass Drug Administration; soil transmitted nematodes; schistosomiasis; praziquantel; benzimidazoles;

Introduction

Targeted and/or community based Mass Drug Administration (MDA) of anthelminthic chemotherapy presently serves as a cornerstone of global efforts to reduce morbidity and mortality caused by parasitic worms. The rationale for MDA as a means of control is based on evidence from trials demonstrating individual benefit attributable to reduced intensity of infection, as well as its potential to limit transmission through overall reductions in prevalence and intensity within communities at risk. While MDA has the potential to alleviate disease burden in endemic communities, there are potential hazards in relying so heavily on currently available chemotherapeutic agents for global helminthiasis control. In addition to significant disparities in effectiveness at the community-level, expanded distribution of drugs with limited efficacy will likely hasten the emergence of resistant strains and increase exposure to potential toxicity, which necessitates commitment of additional expenditures to ensure essential monitoring of safety and impact. This review will highlight critical achievements and ongoing uncertainties surrounding the implementation of MDA for the control of soil transmitted nematode (STN) infections and schistosomiasis.

Global epidemiology and burden of parasitic helminths

As many as 4 billion people live in countries endemic for one or more of the major STNs, specifically *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworms (*Ancylostoma duodenale*, *A. ceylanicum*, and *Necator americanus*) [1, 2]. It is estimated that one out of every two people living in a developing country is infected with at least one STN [3], and the cumulative burden of disease, as measured in Disability Adjusted Life Years (DALYs), approximates the impact of major global killers like malaria and tuberculosis [4, 5].

With as many as 740 million people infected worldwide, hookworm is one of the most common parasitic infections associated with the rural poverty [6-9]. The highest prevalence and

intensity of infection occurs in Sub-Saharan Africa (29%), followed by China (16%), South (16%) and East (26%) Asia, and the Americas (10%) [10, 11]. Hookworms infect nearly 200 million people in sub-Saharan Africa, and are responsible for up to 34% of the total disease burden [12]. These parasites are typically acquired through skin contact with soil contaminated with larvae, although *Ancylostoma* are also infectious when ingested orally. Adult worms attach to the small intestine, where they feed on blood and tissue using sharp teeth or cutting plates. The major clinical sequelae of hookworm infection include anemia, malnutrition, and growth delay, although light infections are usually asymptomatic.

Infections with the roundworm *Ascaris lumbricoides* (26.6 million DALYs) and whipworm *Trichuris trichiura* (10.5 million DALYs) are also widespread, affecting more than a billion people in the tropics [4-6]. After ingestion of fertilized eggs through fecal oral contact, *A. lumbricoides* larvae migrate through the lungs before reaching the adult stage in the small intestine. Although light infections are often asymptomatic, high intensity ascariasis is frequently associated with intestinal obstruction due to the size of adult worms, as well as malabsorption and growth delay [4, 5, 13]. In contrast to *A. lumbricoides*, *T. trichura* eggs develop during transit in the gut, with adult worms residing in the large intestine. Infection with *T. trichiura* causes anemia, malnutrition, and cognitive deficits, as well as an uncommon but severe form of colitis (*Trichuris* dysentery). School-aged children living in areas of extreme poverty are at highest risk for infection with *Ascaris* and *Trichuris* and the corresponding clinical consequences [3, 4, 13, 14]. Along with the age-associated peaks in prevalence and intensity of infection, children are often co-infected with all three STNs [4, 11], which can lead to synergistic negative effects on nutritional status, growth, and ultimately productivity [13].

Schistosomiasis is endemic in 74 countries [15*] and affects between 190 – 250 million people, at least 85% of whom live in sub–Saharan Africa [15*-18]. The economic and social

burden of the disease is often underestimated [19] due to the lack of accurate data [20]. Schistosomiasis is associated with two distinct disease manifestations (intestinal and urogenital), which are caused by different parasite species. Intestinal schistosomiasis is caused mainly by *Schistosoma mansoni* and *S. japonicum*, with *S. intercalatum*, *S. mekongi* and *S. malayensis* found in limited geographical areas[18]. Urogenital schistosomiasis is caused by *S. haematobium*, which has been referred to as the "neglected schistosome" despite its significant global impact [21]. In Africa alone, annual *S. haematobium* associated mortality is estimated at 150,000, compared to 130,000 for *S. mansoni* [22].

The complex schistosome life cycle includes a developmental stage within an intermediate snail host. Humans acquire the infection through contact with freshwater contaminated with the infectious cercarial stage, and following tissue migration, adult schistosomes reside within the veins of the intestine (*S. mansoni*, *S. japonicum*) or bladder (*S. hematobium*). Adult female worms release eggs, which lodge in the liver or bladder and elicit a profound host inflammatory response. Disease is attributable primarily to chronic inflammation, which results in liver cirrhosis, cystitis, bladder cancer, and in women, genital lesions that promote susceptibility to sexually transmitted infections, including HIV [21].

Evidence for a positive impact of Mass Drug Administration

The use of MDA has been proposed as an effective means of reducing morbidity from schistosomiasis and STNs by decreasing the intensity of infection and limiting transmission within endemic communities [23-25]. Anthelminthics remain integral in control programs against soil-transmitted helminths due to their low cost and widespread availability [13, 26, 27]. The range of single-dose oral anthelminthics recommended by the World Health Organization (WHO) for treatment of STN infections include the benzimidazoles albendazole (400 mg) and mebendazole (500 mg), as well as levamisole (2.5 mg/kg), and pyrantel pamoate (10 mg/kg)

[13], while praziquantel (40 mg/kg) is currently recommended for treatment of schistosomiasis. Most STN control programs exclusively use benzimidazoles due to the availability of single-dose regimens, safety, and ease of administration in children [28]. Albendazole has become the preferred agent for many MDA programs targeting STNs due to a unique broad spectrum of activity, including efficacy against immature larval stages, and low toxicity in the host, and reduced effectiveness of mebendazole with repeated use [29, 30]. The efficacy of mebendazole varies considerably due to factors such as preexisting diarrhea and gastrointestinal transit time, intensity of infection, and strain diversity in helminth parasites [31, 32].

The recent WHO report on soil transmitted helminthiasis [15*] and a series of reviews [27, 33-39] provide excellent overviews of the last twenty years of global control efforts. The 2001 World Health Assembly Resolution WHA54.19 [40] recommended annual deworming in areas with >20% prevalence of STNs and schistosomiasis, and bi-annual treatment if prevalence is $\geq$50%, with an initial goal of achieving regular administration of chemotherapy for at least 75% of at-risk school age children (SAC) by 2010. Rapid scale up has led to reported coverage of over 170 million pre-SAC, and over 220 million SAC in 2010 [41]. Many endemic countries have adopted a strategy of a school based MDA supplemented by a community component to effectively reach children who are not in school [42, 43].

In a recent study conducted in Uganda, large-scale MDA of praziquantel achieved substantial reductions in *S. mansoni* reinfection and community transmission [44]. Subsequent modeling analyses demonstrated that MDA also reduced the rate of parasite acquisition over the four year study period, providing evidence of an effect on transmission as well as disease. In 2009, the National Neglected Tropical Diseases control program in Sierra Leone conducted a school-based MDA program using praziquantel and mebendazole. Targeting school-age children in schistosomiasis endemic areas with a single-round treatment regimen, the overall

prevalence and intensity of *S. mansoni* and hookworm infections post-MDA was significantly reduced compared to pre-MDA levels (69.0% to 38.2% for schistosomiasis and 41.7% to 14.5% for hookworm, respectively) [45]. Interruption of schistosomiasis transmission has been achieved in selected endemic regions, including Puerto Rico, Iran and Japan through a combination of disease control efforts and broader socioeconomic growth [15*, 35**]. Together, these promising results have enabled the Schistosomiasis Control Initiative (SCI) and other national control programs to galvanize efforts to expand access to praziquantel via MDA initiatives [46].

With regard to STNS, surveys in areas of targeted chemotherapy in school children suggest an overall decrease in intensity and prevalence of *Ascaris*, *Trichuris*, and hookworm over time, even though elimination has not been achieved [47-50]. Improvements in morbidity have also been reported [20], with countries such as Uganda [51], Sierra Leone [45], and Kenya [52] reporting significant reductions in prevalence and intensity of both schistosomiasis and hookworm following implementation of MDA. Hookworm prevalence has decreased in Asia and the Americas over the past few decades, likely through a combination of economic development and institution of control programs [6]. For example, the prevalence of hookworm in Thailand decreased from 40.6% in 1982 to 11.4% in 2001 [53],while the overall prevalence of STNs in China also dropped significantly between 1990 (53.6%) and 2003 (19.6%) [5]. A recent report from Zanzibar, after four years of annual MDA with albendazole and praziquantel, demonstrated reductions in the prevalence of *Trichuris* and hookworm, although a slight increase in *Ascaris* was observed [54]. In all, there is evidence that MDA has the potential to reduce morbidity through reductions in prevalence and intensity of infection with STNs in highly endemic areas, and recent commitments from the donor community should allow for sustained access to low cost benzimidazoles.

Shortcomings and potential risks of MDA

While encouraging reports suggest that in certain communities MDA can reduce prevalence and intensity of infection with geohelminths, measurable benefits of deworming have not been observed in all settings [55*]. For example, early schistosomiasis control programs that utilized praziquantel did not lead to substantive reductions in the prevalence and intensity of infection [56, 57]. Recent reviews have found limited effects of deworming on anemia in pregnant women or on birth outcomes [58*, 59]. A Cochrane review of 34 randomized trials and a subsequent meta-analysis also identified no or only modest differences in weight gain, while no significant effect of deworming was shown for cognitive function or school performance in children compared to placebo [60**, 61]. Part of the explanation may be the heterogeneity in distribution of parasite species across (and within) communities, coupled with the fact that benzimidazoles are not uniformly active against all three STNs [7, 62]. While both mebendazole and albendazole remain highly effective for the treatment of ascariasis, their activity against hookworm is quite variable, and neither drug works particularly well against *Trichuris*. Therefore, currently available drugs may lack the broad clinical efficacy necessary to control STN infections on a worldwide scale.

Our recent field research illustrates another cautionary example, namely the risk of extrapolating data from selective communities to the broader population. In Ghana, the prevalence of STN infections ranges from approximately 40% in the central part of the country, to as high as 87% in the rural north [63, 64]. In 2007, a cross-sectional study of 292 children and adults in the Kintampo North Municipality in central Ghana [65] revealed a 44.9% overall prevalence of hookworm infection (in the absence of other STNs), with 93% of infected individuals having light infections (<2000 eggs per gram feces). Directly observed treatment with single dose albendazole (400mg) resulted in a cure rate of 61% and a fecal egg count reduction (FECR) rate of 82%, which is below the 90% FECR rate threshold proposed for effective

therapy [62]. A second study in 2010 enrolled children ages 6-11 years old (n=286) from 16 schools in Kintampo North, and confirmed a comparable prevalence (39%) of low intensity hookworm infection. Albendazole treatment was again associated with a low cure rate (44%), and also with a sub-optimal FECR rate of 87%. In our most recent field study, we enrolled children ages 6-13 (n=141) in 5 contiguous Kintampo communities, with a specific goal of probing factors associated with treatment response. We observed an overall albendazole cure rate of 40%, but surprisingly found that treatment responses varied widely based on village of residence. For example, while albendazole therapy was associated with cure rates of greater than 70% and 95% FECR rates in one village, in the contiguous community treatment had no measurable effect (0% cure rate; 0% FECR rate). This striking and unexpected difference in response across closely situated villages with comparable prevalence and intensity profiles implies that the projected benefit of MDA to individual communities might also be expected to vary widely. Moreover, in communities like those in Kintampo, which are characterized by moderate prevalence (approximately 40%) of low intensity (<2,000 epg) hookworm infection, it may not be justified on public health or ethical grounds to subject children to repeated MDA in the absence of evidence demonstrating effectiveness and most importantly, clinical benefit at the local level. These data establish the need, if not obligation, to commit necessary resources for thorough monitoring and evaluation of deworming programs, as has been suggested [34, 66]. Furthermore, the wide variation in response to deworming across parasite species and geographic regions raises doubts about the potential to achieve global control of STN infections by scaling up distribution of currently available anthelminthics.

In addition to unproven public health benefits of MDA, recent reports also highlight potentially negative effects of deworming, specifically an increase in the risk of allergies and autoimmune disorders [59, 67]. For example, a randomized trial in Uganda found that albendazole treatment during pregnancy increased the risk of eczema among infants, while

praziquantel during pregnancy also increased the risk of eczema, but only in infants of mothers with schistosomiasis [59]. Individuals with Multiple Sclerosis who were infected with STNs exhibited fewer relapses than those without worms, and that deworming was associated with significant exacerbations of symptoms [67]. These studies lend credence to theories ascribing potentially beneficial roles that low intensity helminth infections might play in modulating host immunity.

Lastly, widespread implementation of mass chemotherapy will eventually result in the development of resistance to currently available anthelminthics, including the benzimidazoles and praziquantel. Although there has been no indication or evidence of resistance of the parasite to praziquantel, cases of individual failures have been reported, and in vitro studies demonstrate the capacity of schistosomes to develop tolerance to praziquantel [68]. With regard to hookworm, there have been reports of reduced efficacy of pyrantel, mebendazole, and albendazole [25, 28, 69-71]. In fact, two recent trials in Vietnam found that only a three dose regimen of albendazole was more effective than placebo against hookworm, while single dose albendazole and a three dose regimen of mebendazole were not [72]. Our data from Ghana (see above) confirm that the response to albendazole is quite variable across local communities, which creates an opportunity, if not a responsibility, to monitor for evidence of emerging resistance. The experience gleaned from programs to control veterinary nematodes clearly demonstrates that it is simply a matter of time before resistance will emerge in populations repeatedly exposed to broad spectrum anthelminthics. These concerns underscore the need for intensive monitoring of control programs for evidence of reduced effectiveness in endemic populations.

Conclusion

It is too soon to know the potential impact of MDA, especially if adopted at a national or global scale, with regard to long term health effects or the emergence of parasite resistance [27**]. Given the recent donor-driven push to scale up MDA, it is imperative that adequate resources be allocated for intensive monitoring and active surveillance to identify changes in disease epidemiology, potential toxicities, and emerging anthelminthic resistance, despite limited Ministry of Health budgets in most endemic areas [27**, 38*, 73]. Changes in prevalence of infections following MDA also necessitate regular revisions to cost-benefit analyses to stay abreast of changing conditions. Some have already recommended altering the thresholds for treatment, and instituting three-tiers of treatment to more effectively and cost-effectively deliver anthelminthics [3]. Simultaneous investments in new drug development will be critical to sustaining any progress made once parasite resistance emerges [36]. Ultimately, new strategies designed to augment treatment efficacy, decrease susceptibility to infection through improved nutritional status, as well as development of new drugs and/or vaccines could significantly improve the likelihood of achieving global control, if not elimination, of intestinal helminth infections.

Key points:

- Mass Drug Administration (MDA) using anthelminthic drugs is being widely implemented to control soil transmitted nematodes and schistosomiasis in endemic populations.
- Evidence suggests that MDA has the potential to reduce morbidity from chronic helminth infections and may also block transmission, although the benefits of currently available deworming therapies are not uniform across communities and risk groups.
- The long term impact of expanded MDA is unknown, and could result in emerging parasite resistance and unexpected health consequences, thereby altering existing cost-benefit analyses.
- Monitoring and evaluation of MDA, especially at the local community level, is necessary to ensure that treatments are safe, effective, and achieve the desired public health benefit.

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