

Can Mass Drug Administration Lead to the Sustainable Control of Schistosomiasis?

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Background. In the Philippines, the current national control strategy for schistosomiasis is annual mass drug administration (MDA) with 40 mg/kg of praziquantel in all schistosomiasis-endemic villages with a prevalence $\geq 10\%$.

Methods. A cross-sectional survey of schistosomiasis was conducted in 2012 on 18 221 individuals residing in 22 schistosomiasis-endemic villages in the province of Northern Samar. The prevalence of schistosomiasis, intensity of *Schistosoma* infection, and morbidity of disease were assessed.

Results. Despite an active schistosomiasis-control program in Northern Samar for >30 years, which included a MDA campaign in the last 5 years, the mean prevalence of schistosomiasis among 10 435 evaluated subjects was 27.1% (95% confidence interval [CI], 26.3%–28.0%), and the geometric mean intensity of infection among 2832 evaluated subjects was 17.2 eggs per gram of feces (95% CI, 16.4–18.1). Ultrasonography revealed high levels of schistosomiasis-induced morbidity in the schistosomiasis-endemic communities. Left lobe liver enlargement (≥ 70 mm) was evident in 89.3% of subjects. Twenty-five percent of the study population had grade II/III liver parenchyma fibrosis, and 13.3% had splenomegaly (≥ 100 mm).

Conclusions. MDA on its own was insufficient to control the prevalence of schistosomiasis, intensity of *Schistosoma* infection, or morbidity of the disease. Alternative control measures will be needed to complement the existing national MDA program.

Keywords. schistosomiasis; mass drug administration (MDA); control; elimination.

Schistosomiasis, caused by blood flukes of the genus *Schistosoma* (phylum Platyhelminthes), is a neglected tropical disease of poverty prioritized by the World Health Organization (WHO) for control and, by 2020, for possible elimination [1]. Globally, an estimated 240 million people are infected, and >700 million are at risk of infection in 78 countries of the developing world [1–3]. The estimated global burden of schistosomiasis accounts for up to 70 million disability-adjusted

life years (DALYs) lost annually [4]. This estimate exceeds that of malaria or tuberculosis and is almost equivalent to the DALYs lost due to human immunodeficiency virus infection [4, 5]. The majority of human infections and morbidity are due to 3 schistosome species: *Schistosoma mansoni*, *Schistosoma haematobium*, and *Schistosoma japonicum* [6]. In cases of infection with *S. mansoni* and *S. japonicum*, a T-cell-mediated granulomatous reaction to schistosome eggs leads to fibrosis and chronic disease of the human liver, resulting in the development of severe hepatosplenic schistosomiasis. In cases of *S. haematobium* infection, this reaction leads to fibrosis and calcification of the bladder and ureters, which can result in bladder cancer [7–9].

Schistosomiasis was first reported in 1906 in the Philippines, where approximately 865 000 people are currently infected and another 7 million are at risk of infection [10]. Major endemic foci (80%) are in the

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poorest regions of the Visayas (Samar and Leyte) and Mindanao [10–12]. This includes 28 provinces, 190 municipalities, and 2230 barangays (villages) [10–12]. The current (as of 2000) national control program comprises annual free mass drug administration (MDA) with 40 mg/kg of praziquantel (PZQ) in all schistosomiasis-endemic communities with a prevalence of >10% [10–12]. However, the program is failing because of poor drug compliance rates (<50%), poor drug coverage, infrequent monitoring and evaluation, and rapid reinfection rates [10, 13]. There are now advanced schistosomiasis cases and deaths being reported by the National Department of Health for Mindanao, Samar, Leyte, and Oriental Mindoro [11]. The current (from 2012) national funding for schistosomiasis control in the Philippines is PHP\$47 684 000 (US\$1 126 477.54) [11], an amount representing only a tiny fraction (<1%) of what is currently budgeted in China, where the manpower and infrastructure (20 000 full-time staff) far surpasses that of the Philippines (200 part-time staff) [11]. To evaluate the success of the current national schistosomiasis-control program, we conducted a cross-sectional survey to determine the prevalence of schistosomiasis, intensity of *Schistosoma* infection, and level of disease morbidity in 22 schistosomiasis-endemic villages participating in the national MDA program.

METHODS

Study Design and Population

We conducted a cross-sectional parasitological survey of schistosomiasis and soil-transmitted helminths in 2012 among 22 barangays in the municipalities of Laoang and Palapag, Northern Samar, the Philippines (Figure 1). The region is known to have a high level of schistosomiasis endemicity, but no medical research projects had been conducted there previously. People residing within the schistosomiasis-endemic area are typically very poor rice farmers with family incomes far below the national average; >50% of the population lives below the poverty line, with rudimentary water sources, sanitation, and hygiene [11]. The rates of parasitic diseases, acute respiratory infections, diarrheal diseases, and other communicable diseases are, likewise, high. Most of those living in the barangays are Catholic by faith, with usually 6–10 children per family [11].

Study Procedures

Individuals were asked, over the course of a week, to provide 2 stool specimens from which 6 Kato-Katz thick smears were prepared on microscope slides. Slides were examined under a light microscope by experienced laboratory technicians, who counted the number of *S. japonicum* and soil-transmitted helminth eggs per slide. Infection intensity was expressed as the number of eggs per gram of feces (epg). For quality control, 10% of slides were randomly selected and reexamined by a senior microscopist at the Research Institute for Tropical Medicine, Manila.



Figure 1. Location of the study villages, Palapag and Laoang, in Northern Samar, the Philippines.

Clinical examinations, involving liver and spleen palpations, were performed by physicians involved in the study. A portable ultrasonographic device (Sonolayer-L SAL-33B; Toshiba) was used for assessment of size, texture, and fibrosis and other abnormalities of the liver; portal vein diameter; interior portal vein diameter; spleen size; and biliary duct abnormalities. Standard positions, views, measurements, and classification protocols were followed [14].

Data Management and Statistical Analysis

FoxPro (version 6.0) was used for double entry of data, and data were cross-checked and analyzed with SAS, version 9.4. *S. japonicum* infection intensities were categorized as light (1–100 epg), moderate (101–400 epg), or heavy (>400 epg). All variables, including sex, age group, and schistosomiasis-endemic setting, were explored individually by χ^2 statistics. Infection intensity was evaluated by the Student *t* test and Kruskal–Wallis test. The standard error (SE) of each estimate was converted to a variance; all variances were summed to provide an overall variance, SE, and 95% confidence interval (CI). Logistic and negative binomial regression models were fitted for *S. japonicum* infection status and intensity, respectively, to assess for significant associations with morbidity indicators.

Study Oversight

Ethical consent for the study was obtained from the ethical review boards of the Department of Health in the Philippines

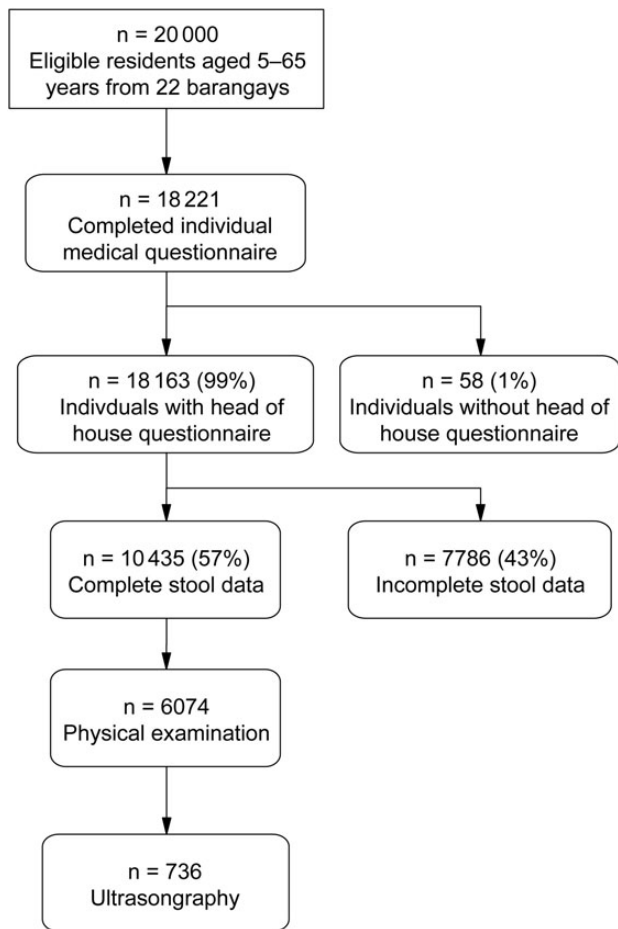


Figure 2. Study profile and compliance among 18 221 residents from 22 schistosomiasis-endemic barangays in Palapag and Laoang, Northern Samar, the Philippines. All inhabitants aged 5–65 years were invited to participate in the questionnaire and provide 2 stool samples for parasitological examination.

(institutional review board number 2012-13-0) and Griffith University, Australia. Written informed consent was obtained from each individual or, for those aged <15 years, from their parents/legal guardians. All questionnaires were translated to the local dialect, and responses were translated to English.

Individuals found to be positive for schistosomiasis, apart from pregnant women, were treated (by directly observed therapy [DOT]) with 60 mg/kg of PZQ, following the Department of Health guideline.

RESULTS

Study Compliance and Demographic Characteristics of Participants

The cross-sectional survey was conducted on approximately 20 000 eligible residents (age range, 5–65 years; Figure 2). A total of 18 221 completed an individual medical questionnaire that comprised information on their demographic characteristics (name, age, sex, level of education, and occupation), schistosome exposure (place, frequency, and duration), treatment history (diagnosis, number of times treated, and participation in the MDA program in the past 2 years), and level of morbidity (fever, diarrhea, abdominal pain, malaise, hepatitis status, and alcohol intake). In addition, 18 163 individuals had a head-of-household questionnaire completed for them that included information on home and land ownerships, number of animals owned and raising practices, animal waste-disposal practices, pasturing of animals, sanitation, and housing characteristics (roof, wall, and floor materials). Approximately 500 individuals per barangay ($n = 22$ barangays) were asked to participate in the stool survey. A total of 10 435 individuals provided stool specimens for fecal examination. Ultrasonography was conducted on 736 individuals who either reported symptoms of gastrointestinal illness or were believed to have clinical morbidity, based on physical examination. One schistosomiasis-endemic barangay was randomly selected to assess a representative sample (age and sex stratified) of the entire village for ultrasonography.

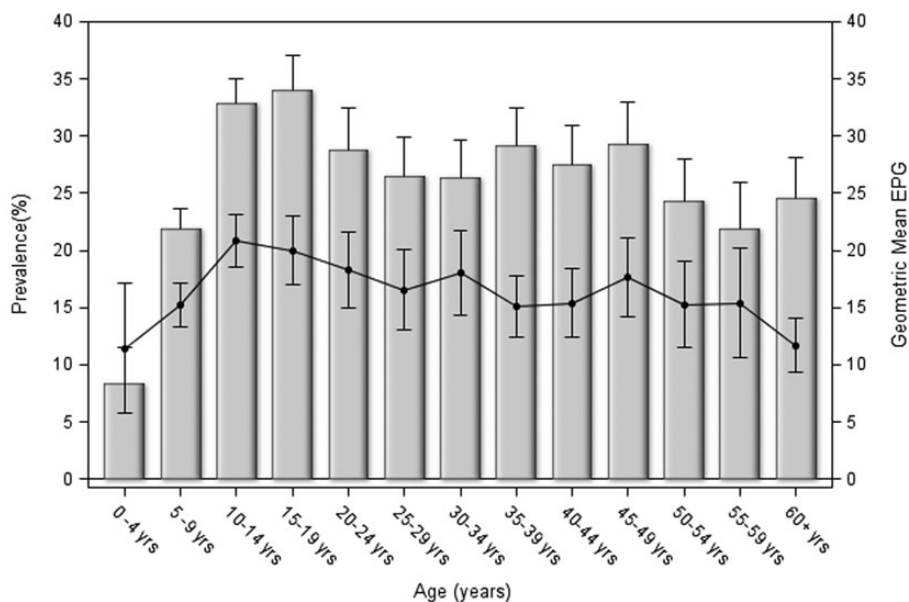
Fifty-one percent of the study sample ($n = 18 221$) was male, with a mean age of 28.5 years (95% CI, 25.9–27.1). Most were rice farmers by occupation with a primary school level of education (48.6%). The majority (89.2%) stated they owned their own home, but few (31.9%) owned their own farmland. For 63.7%, wells were the primary source of drinking water and for washing clothes. The majority of residents (69.9%) claimed

Table 1. Prevalence and Intensity of Parasitic Helminth Infections in Northern Samar, the Philippines

Parasite	Prevalence		Geometric Mean Intensity	
	Specimens Evaluated, No.	Positive, % (95% CI)	Specimens Evaluated, No.	Eggs/g (95% CI)
<i>Schistosoma japonicum</i>	10 435	27.1 (26.3–28.0)	2832	17.2 (16.4–18.1)
<i>Ascaris lumbricoides</i>	10 434	40.3 (39.3–41.2)	1655	530.5 (460.4–611.3)
<i>Trichuris trichiura</i>	10 434	62.4 (61.5–63.3)	2204	104.3 (96.3–113.0)
Hookworm	10 434	31.3 (30.4–32.2)	1289	25.3 (23.3–27.4)
Any STH	10 434	77.2 (76.4–78.0)

Abbreviations: CI, confidence interval; STH, soil transmitted helminth.

A Prevalence and intensity of *Schistosoma japonicum* infection in humans



B Prevalence and intensity of *Schistosoma japonicum* infection in humans

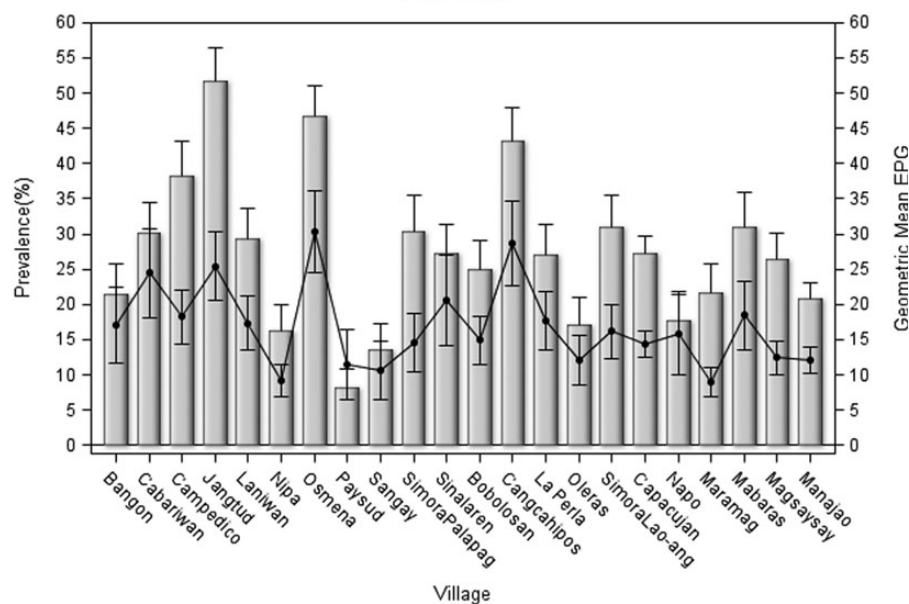


Figure 3. Prevalence (line) and intensity (bar) of *Schistosoma japonicum* infection, by age (A) and village (B). Abbreviation: EPG, eggs per gram of feces.

to have their own water-sealed toilet. Most homes had roofs (56.8%) and walls (35.5%) made of Nipa or palm leaves and cement floors (53.6%). Few of the farmers owned their own cows (17.8%), carabao (water buffalo; 24.5%), or pigs (32.3%). The prevalence of childhood malnutrition was high in a subset of 693 children, with stunting, thinness, and wasting observed in 49.2%, 27.9%, and 59.7%, respectively. Only 1.0% of the population reported having been diagnosed with hepatitis; however,

38.4% drank alcohol on a regular basis. Most of the residents (68.8%) claimed to have had frequent freshwater exposure.

Prevalence and Intensity of Infection

The prevalence of human schistosomiasis among 10 435 participants was 27.1% (95% CI, 26.3%–28.0%), and the prevalence of any soil-transmitted helminth (*Ascaris*, *Trichuris*, and hookworm) among 10 434 participants was 77.2% (95% CI,



Figure 4. A male child aged 12 years with advanced schistosomiasis in Northern Samar, the Philippines. Ultrasonograms of the boy illustrate severe portal vein thickening of the right lobe of the liver (left) and a markedly enlarged spleen and splenic vein (right).

76.4%–78.0%; Table 1). The geometric mean intensity of *S. japonicum* infection among 2832 evaluated individuals was 17.2 epg (95% CI, 16.4–18.1). Figure 3 depicts the prevalence and intensity of *S. japonicum* infection by age and village. Overall, infection was homogeneous across the age categories except for those very young (aged <5 years). This was probably due to limited schistosome exposure. The peak prevalence and geometric mean intensity infection occurred in individuals aged 10–19 and 35–39 years, respectively. The drop observed in those aged 20–34 years may be due to acquired immunity and/or a change in health-seeking behavior. The decline in the older age category reflects reduced occupational exposure to *S. japonicum* cercariae. Examination of prevalence and intensity by village revealed a more heterogeneous distribution, with a small number of villages either heavily or lightly infected.

MDA Participation and Morbidity Outcomes

Laoang and Palapag have had an active schistosomiasis-control program since 1980. From 1980 to 1990, the program consisted of active case finding and DOT of all positive cases with 60 mg/kg of PZQ. Approximately 10%–20% of the target population aged 5–65 years was sampled. The overall schistosomiasis prevalence ranged from 1% to 30% among the schistosomiasis-endemic barangays. From 1990 to 2007, case finding was intensified to include approximately 30%–50% of the entire schistosomiasis-endemic population. All stool-positive individuals again received DOT with 60 mg/kg of PZQ. The schistosomiasis prevalence during this time ranged from 1% to 33% in the schistosomiasis-endemic barangays. The MDA DOT program for schistosomiasis control commenced in 2008 in the study area and used 40 mg/kg of PZQ, based on the recommendations from both the National Department of Health and WHO. All individuals aged 5–65 years were offered annually 40 mg/kg PZQ free of charge in accordance with Department of Health Administrative Order 2007–0015. In the initial year (2008), the drug compliance rate was high (70%–85%), but it has dropped substantially (to 25%–65%) in the succeeding years (2009 to the present). The schistosomiasis prevalence rates

ranged from 1% to 46% in the schistosomiasis-endemic barangays over this period. It is noteworthy that an individual can be examined and, if found positive for schistosomiasis, treated at any time of the year at the local health center. Medication is provided free of charge by the National Department of Health.

Ninety-seven percent of the study population reported having been treated for schistosomiasis previously, and 75.6% reported having been treated in the past 2 years through the MDA DOT program. Levels of morbidity in the study population during the 2 weeks before questionnaire completion were low for bloody diarrhea (4.3%), weakness (3.7%), fever (5.8%), and headache (7.1%). However, follow-up ultrasonography of a subset of 736 individuals revealed high levels of schistosomiasis-induced morbidity (Figure 4). Left lobe liver enlargement (≥ 70 mm) was seen in 89.3% of subjects sampled. Twenty-five percent (24.6%) had grade II/III liver parenchyma fibrosis, but only 2.8% had stage 2 (>5 to 7 mm) or 3 (>7 mm) periportal thickening. A total of 13.3% of the population sample had splenomegaly (≥ 100 mm). A comparison of morbidity measures (reported or observed by ultrasonography) for those who were treated through the MDA DOT program in the previous 2 years and those who were not revealed no statistically significant differences for any of the morbidity indicators between the 2 groups (Figure 5).

DISCUSSION

This cross-sectional survey of schistosomiasis in the Philippines is one of the largest of its kind to have been undertaken. Despite >30 years of active control, including study subjects participating in an MDA program over the past 5 years, the prevalence and intensity of *S. japonicum* infection and the morbidity of the disease remains high in Northern Samar. Fundamental to the problem is, we believe, the use of a suboptimal dose (40 mg/kg) of PZQ, poor drug compliance (<50%), and the lack of other control measures to interrupt the schistosome life cycle. Given the zoonotic nature of the disease caused by

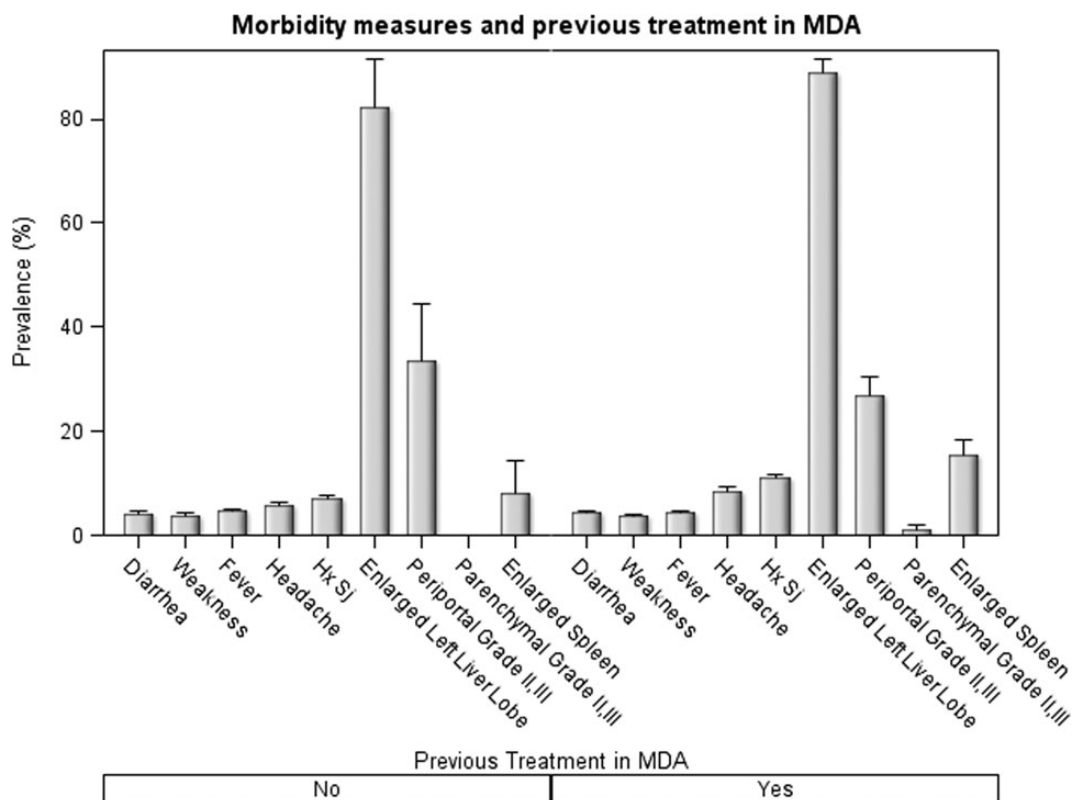


Figure 5. Measures of morbidity for individuals who were (right) or were not (left) treated in the past 2 years through the mass drug administration (MDA) program for schistosomiasis. Abbreviation: Hx Sj, history of *S. japonicum* infection.

S. japonicum (bovines have been identified as major contributors to transmission) [15], a multifaceted integrated approach targeting transmission pathways for the disease should involve PZQ treatment, vaccination of bovines (cattle and carabao), snail control, health education, and improved sanitation for sustainable control and future elimination [11, 16, 17]. Like China, we believe an integrated national control program is needed in the Philippines to control the disease in the long term.

A recent systematic review and meta-analysis of 52 clinical trials showed that, compared with placebo, a PZQ dose of 30–60 mg/kg produced a cure rate of around 76% (range, 67%–83%) for human schistosomiasis [18]. No significant differences in cure rates were found among subjects infected with *S. haematobium*, *S. japonicum*, or *S. mansoni*. The cure rate of the drug at a 40-mg/kg dose (which is the current dose recommended by the WHO) was 52% (range, 49%–55%), compared with 91% (range, 88%–92%) when the total dose was increased to 60, 80, 100 mg/kg, divided into ≥ 2 individual doses [18]. In the Philippines, residents of schistosomiasis-endemic areas are treated empirically with a 40-mg/kg dose of PZQ during MDA campaigns. However, if residents are found to be positive via case detection (eg, by Kato-Katz thick smear stool examination), they are treated with a 60-mg/kg dose. The rationale for this discrepancy remains unclear, but given the rapid

reinfection rates in areas of high schistosomiasis endemicity (as in this study), we recommend implementation of a 60-mg/kg dose in the national control program.

Despite the commitment to MDA programs, it is becoming increasingly clear that the sustainable control of schistosomiasis will require an integrated, intersectorial approach that goes beyond deworming. While the global use of PZQ is being scaled up, there are also growing concerns about inadequate drug coverage, low cure rates, poor drug compliance, lack of baseline information prior to the commencement of MDA programs, and their inadequate monitoring and evaluation once commenced. The results presented here have global implications for schistosomiasis control where MDA is used as the primary strategy.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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