Changing Policy and Practice in the Control of Pediatric Schistosomiasis

Francisca Mutapi, BSc, PhD

abstract

Schistosomiasis is a chronic disease that affects ~200 million people. The extended health impact of the disease has been estimated to exceed that of malaria or tuberculosis and to be nearer to that of HIV/AIDS. Within endemic areas, children carry the heaviest burden of infection. Infection/disease is controlled by the treatment of infected subjects with the anthelminthic drug praziquantel. Global initiatives from Partners of Parasite Control, including the World Health Organization (WHO), advocate regular school-based deworming strategies to reduce the development of severe morbidity, promote school–child health and development, and improve the cognitive potential of children. Until recently, preschool-aged children were excluded from schistosome treatment, creating a health inequity in affected populations. In 2010, the WHO updated their recommendations for the treatment of schistosomiasis in preschool-aged children (ie, children aged ≤5 years). This change was the culmination of several decades of research on schistosome epidemiology, immunology, and pathology in this age group. The recent development of a pediatric formulation of praziquantel (soon to enter clinical trials) should advance control efforts in preschool-aged children, with the goal of including these children in preventative chemotherapy (as currently occurs for soil-transmitted helminths). This review discusses the research work supporting the WHO revision of recommendations for treating preschool-aged children, as well as current barriers and knowledge gaps in pediatric schistosomiasis control.

Institute of Immunology and Infection Research, Centre for Immunity, Infection and Evolution, School of Biological Sciences, University of Edinburgh, Edinburgh, United Kingdom

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Address correspondence to Francisca Mutapi, BSc, PhD, Institute of Immunology and Infection Research, Centre for Immunity, Infection and Evolution, School of Biological Sciences, Ashworth Laboratories, University of Edinburgh, Charlotte Auerbach Rd, Edinburgh, EH9 3FL United Kingdom. E-mail f.mutapi@ed.ac.uk

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Schistosomiasis (commonly known as bilharzia) is the second most significant parasitic disease (after malaria) in children in Africa, affecting their general health, growth, cognitive development, and future reproductive health.[1] Sixty percent of African children carry schistosome infections. Infection/disease is controlled by treatment of infected subjects by using the anthelminthic drug praziquantel (PZQ). Global initiatives from Partners of Parasite Control, including the World Health Organization (WHO), the Bill & Melinda Gates Foundation, UNICEF, the Schistosomiasis Control Initiative, and the World Bank, advocate regular school-based deworming strategies to prevent the development of severe morbidity and to promote child health and development. Until recently (2010), preschool-aged children (ie, children aged ≤5 years) were excluded from schistosome treatment, creating a health inequity in affected populations. In our studies, the youngest participant diagnosed positive for schistosome infection was 6 months old, which is not unusual in high schistosome transmission areas, such as in Nigeria.[2] Such observations reaffirm the need for interventions targeting preschool-aged children who continue to be excluded from current national control programs. Exclusion of these children from mass drug administration (MDA) programs is

similar to treatment strategies 2 decades ago for soil-transmitted helminths (STHs).[3] In the case of STHs, because of the concerted attempts to produce an evidence base for the inclusion of preschool-aged children in MDA programs using the anthelminthics albendazole and mebendazole, as well as advocacy efforts (as noted by Stothard et al[3]), these children are now included in STH control programs.[4] Primary schoolchildren in some helminth-endemic areas are benefiting from mass drug coadministration of PZQ and albendazole or mebendazole (eg, Zimbabwe). Inclusion of preschool-aged children in these programs will be a significant step in improving child health and development in affected areas.

SCHISTOSOME CONTROL PROGRAMS

Over the past decade, concerted global efforts have been made to control schistosomiasis in Africa, galvanized initially by the Millennium Development Goal 6 to combat HIV/AIDS, malaria, and other diseases by 2015 and the World Health Assembly resolution 54.19 to treat at least 75% of all school-aged children at risk for schistosome morbidity by 2010. We conducted a review of publications quantifying the levels of *Schistosoma haematobium* and *Schistosoma mansoni*, the most prevalent human schistosome species occurring in African children aged ≤5 years. Using this information, the first *S haematobium* and *S mansoni* maps of pediatric schistosomiasis in Africa were generated for the period shown in Fig 1 (1995–2014). The maps represent all the information currently published on the prevalence of pediatric schistosomiasis and highlights the paucity of data available in this age group. Nevertheless, schistosome prevalence levels among preschool-aged children are closely related to those of older children and adults in the same countries, and this map is consistent with those published for the older populations.[5]

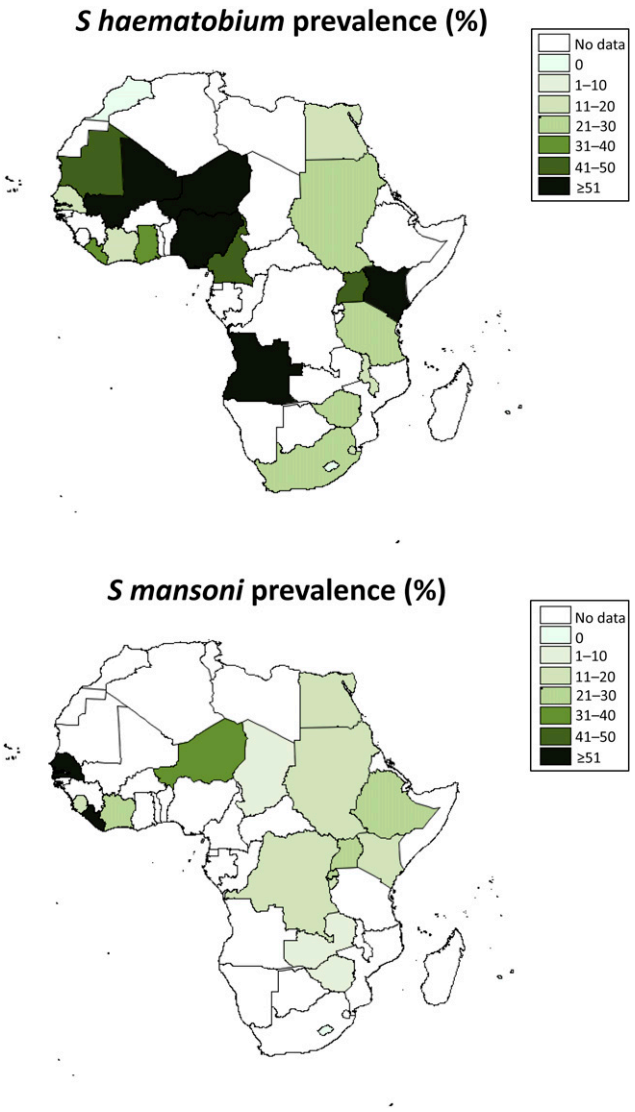

FIGURE 1
Schistosome infection prevalence in preschool-aged children (ie, ≤5 years of age) from studies published in 1995 to 2014.

Of the African countries in which schistosomiasis is endemic, 28 countries have or are currently implementing a schistosomiasis control program (1995–2013) as listed in the WHO database on preventative chemotherapy of neglected tropical diseases (http://www.who.int/neglected_diseases/preventive_chemotherapy/en/). However, none of these countries includes children aged ≤5 years, despite >60% of them reporting significant schistosome infection levels in this age group. For control programs commenced before 2011, there are several reasons given for not treating children aged ≤5 years; the main ones are: (1) uncertainties in levels of exposure of this age group to infective water sources[6]; (2) uncertainties in the levels of infection and morbidity in this age group[7]; (3) unknown safety and efficacy of PZQ; and (4) the belief that involvement of the host immune system acting in synergy with PZQ to clear schistosome worms[8] was insufficient (ie, the immune system of preschool-aged children would be too immature/unprimed to act synergistically with PZQ).[9,10]

The present review discusses, in part, the scientific research conducted by my group and those of others that challenged these misconceptions and barriers to schistosome treatment of preschool-aged children, culminating in the revised recommendations from the WHO in 2010. The preview's methods for generating the pediatric schistosome maps are described in the Supplemental Information.

PRAZIQUANTEL

PZQ was the first anthelminthic drug to fulfill the WHO's requirements for population-based chemotherapy of a broad range of parasitic infections (http://apps.who.int/medicinedocs/en/d/Jwhozip48e/6.html) and is on the WHO List of Essential Medicines, a list of the most important medications needed in a basic health system. PZQ was developed in the 1970s by Bayer and licensed as Biltricide for use in adults and children aged ≥4 years. The drug is inexpensive, costing approximately US $0.08 per tablet.[11] Through a commitment of the pharmaceutical industry to donate 250 million PZQ tablets per year for school-aged children, PZQ is now an accessible tool for schistosome control. In the field, dosage is determined by weight, but a PZQ dose pole is typically used because scales are not always easily accessible and the pole also facilitates large-scale MDA programs.[12] The PZQ pole indicates dosage-by-height by following the standardized calibration of weight to height.

Structurally, PZQ is a racemic mixture of the dextro (right) and levo (left) isomers of 2-(cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino [2,1-a]isoquinolin-4-one, of which only the levo isomer is active against schistosomes.[13] The pharmacokinetics of PZQ have not been studied in children aged ≤4 years, but studies in adults show that the drug is rapidly absorbed from the gastrointestinal tract; thus, maximal levels in human plasma occur within 1 to 2 hours of administration, and the drug has a half-life of ~0.8 to 1.5 hours in adults with normal renal and liver function.[14] It is taken as a single dose of 40 or 60 mg/kg of body weight. Although the mode of action of PZQ has yet to be fully described, it is thought to cause muscle contraction in adult worms as a result of a calcium influx and tegumental damage.[15] The tegumental damage exposes parasite antigens, allowing immune attack of the damaged worms by the already primed host immune system. Thus, PZQ acts synergistically with the host immune system.[9] The drug is not effective against immature worms.[14]

PZQ is efficacious, with schistosome cure rates and egg reduction rates typically >75% (as reviewed by Stothard et al[3]). Cure rates and egg reduction rates >90% are routinely achieved in study populations in Zimbabwe.[16,17] At the individual level, the effects of PZQ include: (1) killing adult worms by reducing infection intensity in the host and the immediate health consequences of infection[18]; (2) reversal of the pathologic processes associated with infection[19]; (3) accelerating the development of schistosome-specific acquired immunity,[20,21] which is protective against re-infection[22,23]; and (4) reducing pathology from subsequent re-infection.[24] At the population level, PZQ treatment reduces transmission of the parasites.[18] PZQ is effective against trematodes (including all schistosome species) and cestodes in humans.[14] Based on the prelicensing safety studies and numerous field studies,[16,25] PZQ treatment is considered safe and efficacious. There are a few adverse effects, including fatigue, urticaria, gastrointestinal and abdominal pains, nausea, vomiting, headache, and dizziness (see Biltricide product sheet on http://www.bayerresources.com.au/resources/uploads/pi/file9318.pdf), which are related to infection intensity.[16]

CHALLENGING THE BARRIERS TO TREATMENT

Demonstrating Exposure to Infective Water, Infection, and Morbidity

Individuals become infected with schistosomes when they come into contact with infective water. Infectivity of freshwater sources is demonstrated by the presence of patent snail intermediate hosts of schistosomiasis (patency demonstrated by shedding the snails, which allows the infective cercariae to emerge from the snails). Exposure to infective water is usually measured by quantifying the type, frequency, and duration of contacts with infective water.[26,27] This active exposure is low among preschool-aged children, which resulted in their exposure levels to infection being assumed to be low. Field studies have demonstrated that young children do experience significant passive exposure to infective water, however.[2,6,28] Thus, direct observation and questionnaires in exposure studies missed significant amounts of the exposure behavior in preschool-aged children. This limitation was confirmed by studies using GPS logging of children's water contact behavior.[10] Two decades ago, serologic and quantitative investigations were used to study exposure to infective and adult stages of schistosome parasites in young children.[29] These studies indicated that 79% of children aged 4 months to 6 years showed evidence of exposure to schistosome infection. In recent studies, the youngest patient who tested positive for schistosome infection on the basis of parasite egg excretion was 6 months old. Other researchers have also demonstrated that young children in several African countries (including Nigeria, Cote d'Ivoire, Kenya, Mali, Uganda, and Zimbabwe) are infected with schistosomes.[2,17,30–33] In addition, in some areas, their infection levels are as high as those in their caregivers; these caregivers,

however, were eligible for treatment, while the infected children remain untreated for several years (as reviewed by Stothard et al[28]). Furthermore, the limited investigations describing and quantifying morbidity in this age group have shown that these infections in young children are clinically significant.[34,35]

Apart from the immediate effects of infection and disease in this age group, childhood infections have long-term effects on host health; untreated schistosome infections are chronic and the disease is progressive, meaning that delayed treatment (termed the PZQ gap[10]) can result in more severe forms of disease (eg, bladder cancer, liver damage,[26] poor reproductive health, increased susceptibility to HIV infection in adulthood).[36] Taken together, these studies corrected the misconceptions that young children were not sufficiently exposed to be infected and that even if infected, their parasite burdens were too low to be of clinical significance.[10] This research was the first (and considerable) step toward highlighting the need for intervention in this age group.

PZQ in Preschool-aged Children: Action, Safety, and Efficacy

A number of studies have demonstrated that the schistosomicidal effect of PZQ depends on the immune status of the host and is mediated through schistosome-specific antibodies.[8,9,37] These observations led to the belief that the childhood immune system may be too immature or not sufficiently primed to synergize effectively with PZQ to kill the parasites. Our earlier studies had shown this scenario was not the case; we demonstrated that children as young as 4 months mounted schistosome-specific antibody responses.[29,38] These studies found that children aged 5 years were already immunologically primed to kill parasites damaged by PZQ and that being immunocompromised did not affect the efficacy of PZQ. Furthermore, research in Kenya found that PZQ was as efficacious in schistosome-infected immunocompromised HIV patients as in non–HIV-positive volunteers.[39]

Having established that there was no immunologic reason to hinder the use of PZQ in young children, there remained a lack of evidence regarding the safety and efficacy of PZQ in this age group. Although PZQ could be prescribed on a case-by-case basis in young children, there had been no studies on the safety of PZQ treatment of schistosomiasis infection in children aged <5 years with a goal of including them in MDA programs.

In 2008, the WHO funded 3 groups (including our own) to formally conduct studies determining the safety, efficacy, and acceptability of PZQ for the treatment of *S haematobium* and *S mansoni* in preschool-aged children in Africa.[40] All studies tested the tablet formulation of PZQ, and 1 study tested both the tablet and the pediatric liquid formulation. These studies concluded that PZQ treatment of children aged 6 months to 5 years was safe and efficacious. Our own study found that preschool-aged children reported significantly fewer adverse effects than primary schoolchildren.[16,17] The fewer adverse effects were unsurprising: these are related to the intensity of infection,[41–43] and infection intensities are lower in this age group than in children of primary school age. We reported cure rates and egg reduction rates >90% in preschool-aged children.[17] These results and those from the other groups were reviewed at a WHO working group meeting that made the recommendations detailed in the following discussion. Furthermore, our results informed the formulation of Zimbabwe's national schistosome and STH control program drafted in 2012,[44] making it 1 of the first national helminth control policies to include preschool-aged children.

In terms of morbidity control, there are few studies in preschool-aged children demonstrating the effects of PZQ treatment. We have just completed a 3-year study in this age group, and our results show that treatment of preschool-aged children with PZQ significantly reduces morbidity attributable to schistosome infection (F.M., unpublished observations). Thus, at the policy level, the main hurdle to treating preschool-aged children was crossed by the demonstration of the utility, efficacy, and safety of PZQ treatment in preschool-aged age children in independent studies.

Operational Aspects of PZQ Administration to Preschool-aged Children

At the practical level, a challenge to treating preschool-aged children was how to determine the dosage in the field. Our own experiences in the field with digital weighing scales demonstrated their limited use: within 1 week of purchase, the scales were no longer functioning. An initiative arising from the WHO working group meeting was to determine the potential for extending the PZQ dose pole to <94 cm to include children aged ≤5 years.[40] A comparative study using anthropometric data from several African countries in which schistosomiasis is endemic demonstrated that height was a good surrogate for weight in pre-school children; thus, the PZQ dose pole could be reliably used to determine dosage in this age group.[45]

The dextro isomer gives PZQ a bitter taste that renders it unpalatable.[46] This feature, combined with the size of the tablet, makes it difficult for young children to swallow. Efforts by the private/public partnership of Merck KGaA, Astellas Pharma Inc, and the Swiss Tropical and Public Health Institute to develop a pediatric PZQ

formulation are underway and if successful, this will overcome a significant operational hurdle in MDA for preschool-aged children. In the meantime, the tablet form of PZQ can be administered to preschool-aged children as crushed tablets taken with some squash and food such as bread.[40]

CHANGING POLICY AND PRACTICE

In response to concerted efforts by several scientists and health workers to highlight the significant health inequity that was being perpetuated by exclusion of preschool-aged children from PZQ treatment (as reviewed by Stothard in 2007),[6] the WHO funded several groups in 2008, including my own group, to investigate the safety and efficacy of PZQ treatment of *S mansoni* and *S haematobium* infections in children aged ≤5 years. In 2010, the WHO arranged a meeting of a working group composed of individuals involved in schistosome-endemic areas to review the results of these studies.[40] The findings and recommendations from the WHO working group were a significant step forward in improving child health and development in affected countries. In summary, the working group concluded that both *S mansoni* and *S haematobium* presented a significant public health problem in preschool-aged children aged ≤5 years. Furthermore, PZQ was also determined to be acceptable, safe, and efficacious in this age group. Based on these considerations, the working group made the following recommendations (published by the WHO in 2010).

1. Preschool-age children should be regarded as a high-risk group in areas endemic for schistosomiasis; treatment should be made available to these children through the regular health services;
2. Administration of PZQ to preschool-aged children should be included in ongoing public health interventions such as the Expanded Program on Immunization activities, Mother and Child Days, and Child Health Days;
3. In the absence of an appropriate pediatric formulation, broken or crushed tablets are recommended for administration of PZQ; development of a water dispersible tablet for this age group is recommended.[40]

In addition, the working group called on the WHO to formally advocate the treatment of this age group in areas in which schistosomiasis is endemic and for the WHO to call for additional research to develop child-friendly formulations of PZQ. Finally, the working group made recommendations regarding operational issues. First, the PZQ dose pole for determining the drug dosage used in the field would be a useful operational tool if it could be extended to <94 cm in height to incorporate preschool-aged children. However, the pole had not been evaluated for use in this age group. As detailed earlier, a subsequent investigation lead by Stothard et al[45] found that the PZQ pole could be extended and was applicable in preschool-aged children. Second, the size of the PZQ tablet and the need to break it into smaller units for young children made it cumbersome for use in the field. Therefore, development of a child-friendly formulation was needed. This need was communicated to the pharmaceutical industry, culminating in Merck KGaA pledging to develop a child-friendly PZQ formulation at the London Declaration on Neglected Tropical Diseases in January 2012. Thus, significant progress has been made at the policy level in addressing the health inequity created by delayed treatment of childhood schistosomiasis.

REMAINING CHALLENGES

It is now an acknowledged public health fact that preschool-aged children require treatment of schistosomiasis. However, there are some challenges remaining, especially if the visions of the 2012 World Health Assembly resolution 65.21 advocating for the elimination of schistosome transmission and the WHO Schistosomiasis Strategic Plan 2012–2020 for a world free from schistosomiasis[47] are to be met. Although this goal is realistic in some schistosome-endemic areas, considerable barriers still exist to realizing these visions in areas of high transmission.

Reliable quantification of affected preschool-aged children and demand for PZQ in this age group has yet to be systematically conducted. The WHO Schistosomiasis Strategic Plan 2012–2020, which advocated the scaling up of schistosomiasis control and elimination activities (as well as ensuring the provision of PZQ in endemic countries), calculated the PZQ requirements for school-aged children and adults but not for preschool-aged children. This omission is significant because the information is critical to inform planning for PZQ requirements and resources to implement MDA in this age group. Preschool-aged children ≥1 year of age are already involved in preventative chemotherapy for STHs.[4] Thus, the potential for coadministration of PZQ with the STH anthelminthics albendazole and mebendazole through effective pediatric health systems and activities such as Child Health Days and the Expanded Program on Immunization represents a realistic objective for improving child health and development in endemic areas.

Point-of-Care Infection and Morbidity Diagnosis

Current infection diagnostic methods used for schistosome control (microscopic enumeration of eggs excreted in urine or stool and reported/observed blood in urine [hematuria]) are less sensitive in preschool-aged children.[48,49]

Serologic methods that are more sensitive are applicable only before treatment because PZQ alters parasite-specific immune responses[50]; molecular methods detecting parasite DNA[51] or microRNAs[52] have yet to be evaluated in this age group. It has recently been reported that egg count methods can result in misclassification of the endemicity of schistosomiasis in an area and consequently lead to fewer treatments than actually required.[53] Furthermore, the point-of-care morbidity diagnostic tools have not fully been evaluated in this age group.[10] These tools are important for the monitoring and evaluation of PZQ treatment programs to quantify the efficacy of the interventions and to justify the required long-term investment in schistosome control programs. Point-of-care diagnostic tools with low sensitivity and specificity can underestimate the effectiveness of control programs, affecting their cost–benefit ratio and thus their prioritization and support within ministries of health in affected countries (often with small health budgets) and other stakeholders.

Optimal Treatment Regimen

Information on the number, frequency, and optimal timing of treatment to control morbidity is still needed. Quantitative studies investigating the effects of frequency of treatments on morbidity in children of primary school age indicated that early and repeated treatment is required to make a significant impact on stunting and malnutrition.[54] There have been no such studies for the additional long-term schistosome-related morbidity such as liver- and bladder-associated pathology, nor have there been any such studies in preschool-aged children. In our recent studies funded by the Thrasher Research Fund, we found that infected preschool-aged children already experience morbidity attributable to schistosome infection (F.M., submitted observations). Thus, it is important that our current understanding of the progression of schistosome morbidity is recalibrated to reflect the previously unacknowledged earlier onset of morbidity in preschool-aged children.

Control/Intervention Methods

To meet the goal of schistosome elimination, maximal effective use of existing tools, as well as the development of additional tools, is needed. Thus, in addition to increasing accessibility to safe water, sanitation, and health education, the 2012 WHO List of Research Priorities for Helminth Infections highlights the need for a concerted effort to develop other interventions, including molluscicides and vaccines.[55] The important role of improved water, sanitation, and hygiene programs has recently been re-emphasized as pivotal to a sustained intervention for the control of schistosomiasis and STHs,[56] whereas knowledge, attitudes, and practice studies[2,57] highlight the importance of education (particularly of caregivers[58] to reduce their passive exposure to infective water).

The demonstration that *S haematobium*, the most prevalent human schistosome species in Africa, can hybridize with the cattle schistosomes *Schistosoma bovis* and *Schistosoma curassoni*[59,60] introduces a zoonotic feature to the transmission dynamics. It also presents the potential for schistosome infection animal reservoirs maintaining transmission and compounding control efforts reliant predominantly on human chemotherapy.

Current Phase III clinical trials of the leading schistosome vaccine candidate targeting primary schoolchildren (http://clinicaltrials.gov/show/NCT008706490) raises the potential of future vaccinations excluding preschool-aged children, which would continue the neglect of this age group. Continued research is needed on the action of PZQ, particularly its ability to induce immune responses protective against re-infection,[20,21,23,61,62] as well as an immune phenotype that can downregulate future pathology.[24] Our studies and those of others continue to investigate the mechanistic pathways underlying the potential "vaccinating" effect of PZQ.[20,61,63,64] The concept of an infection-treatment-vaccination is not novel; it forms the basis of successful veterinary parasite vaccines (eg, *Theileria*), and proof or principle studies in human malaria (as reviewed by Mutapi et al[65]) suggest this method may be a potential approach to successful development of parasite vaccines. The immunologic aspects of PZQ treatment warrant further investigation for 2 additional reasons. First, research is needed to address any concerns of undesirable long-term effects regarding human health (as alluded to by the hygiene hypothesis[66]) and second, to understand the long-term effects of PZQ treatment and consequences on cessation of MDA. Though quantitative studies, we recently illustrated that due to detrimental effects on the development of protective immunity, cessation of MDA under certain conditions could result in infection levels higher than the preintervention level.[67] Continued monitoring and evaluation of MDA programs and their effects on the schistosome population structure, as advocated by several stakeholders (including the Schistosomiasis Control Initiative, who are funding our group to monitor and evaluate Zimbabwe's current MDA program), are also vital for the early detection of drug resistance development. This knowledge will allow long-term planning for the support of schistosome MDA programs.

CONCLUSIONS

Significant advances have been made at the policy and practical/operational levels in the control of

pediatric schistosomiasis. Investigations in preschool-aged children have laid a solid evidence base regarding the need, safety, and efficacy of treatment with the anthelminthic drug PZQ in this age group. Currently, the inclusion of preschool-aged children in schistosome control programs is slow, with most countries still targeting their MDA at primary schoolchildren. Several African countries are currently preparing their schistosome control master plans (see http://www3.imperial.ac.uk/schisto/wherewework). It would be monumental and a significant triumph for African child health to have preschool-aged children included in their MDA programs. A child-friendly pediatric formulation of PZQ and current scientific developments improving point-of-care infection and morbidity diagnosis should remove the remaining operational barriers to delivering a schistosome MDA strategy on par with the inclusive STH control policy and practice. Until then, we must continue to work toward delivering an integrated, inclusive, sustainable, and globally implemented helminth control program.

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