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Mass drug administration and the global control of schistosomiasis: successes, limitations and clinical outcomes

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Abstract

Purpose of review: Preventive chemotherapy is advocated for the global control and elimination of schistosomiasis. Despite the well-known short-term benefits of treating patients for schistosomiasis, the impact of mass drug administration (MDA) campaigns to control the disease in the long-term remains unresolved.

Recent findings: Many studies have advocated the success of MDA programs in order to attract donor funds for elimination efforts but such successes are often short-lived given the drug does not alter the life cycle of the organism or prevent reinfection. Within a matter of months to years after halting treatment, the prevalence, intensity of infection and morbidity of disease returns to baseline levels. Other mitigating factors contribute to the failings of MDA campaigns namely: poverty, poor drug coverage, poor drug compliance, and, in the case of Asiatic schistosomiasis, zoonotic transmission. Genetic and innate and acquired immunologic mechanisms complicate the epidemiologic picture of schistosomiasis globally, and may contribute indirectly to MDA shortcomings. The possibility of drug resistance is an ever present concern due to the sole reliance on one drug, praziquantel.

Summary: Preventive chemotherapy is advocated for the global control and elimination of schistosomiasis. The short-term benefits of MDA campaigns are well documented but the long term benefits are questionable.

Key words: Schistosomiasis, Mass Drug Administration (MDA), Control, Clinical Morbidity

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Introduction

Schistosomiasis is a major public health problem in the tropics affecting more than 240 million individuals globally and causing an estimated loss of 3-70 disability-adjusted life years (DALY's)[1, 2]. More than 78 countries are affected, and nearly 800 million people are at risk of infection [2]. Preventive chemotherapy, using the drug praziquantel (PZQ), has been the mainstay of global control [3]. Mass Drug Administration (MDA) has been successful in reducing the prevalence, intensity of infection, and schistosome-induced end-organ morbidities in the short-term [4-6] but the long term impact of this strategy on its own is questionable given disease transmission in many localities remains uninterrupted [7, 8]. Studies have shown that when MDA programs were discontinued, the prevalence, intensity of infection, and end organ pathology rebounded to pre-baseline levels; moreover, despite continuous MDA, the prevalence, and clinical indicators of schistosome-induced morbidities remained high [2, 9]. This article reviews studies wherein MDA faltered. We also consider some of the factors and mechanisms that may have contributed to this limitation.

Pathogenesis and clinical morbidity

Chronic schistosomiasis pathology in the host is mainly caused by the eggs released by adult schistosome worms [10]. Morbidities due to the disease are mainly due to granulomatous reactions and the subsequent fibrosis formed around the eggs trapped in the host tissues or, due to inflammatory cytokines induced by egg or worm products [10]. End-organ complications include hepatosplenomegaly, hepatic fibrosis, portal hypertension, and colonic polyposis induced by infection with *Schistosoma mansoni, S. japonicum, S. intercalatum* and *S. mekongi* and bladder thickening, ulceration, and polyposis, along with hydronephrosis and renal dysfunction, during *S. haematobium* infection. Lumbosacral myelopathy is most commonly noted with *S. mansoni* and *S. haematobium*, while encephalic disease is mostly seen with *S. japonicum* infection [11]. Subtle morbidities include anaemia, growth retardation, malnutrition and impaired cognitive functions in children, and poor pregnancy outcomes [12].

MDA and evidence of rebound infection and morbidity

Despite the reported positive effects of MDA in many endemic zones worldwide, the long term effects of continuous community-based PZQ-based chemotherapy remain largely unknown. Several studies have documented MDA failure with the prevalence and intensity of schistosome infection quickly returning to baseline levels when the drug programme was relaxed or suddenly stopped. Moreover, there is evidence of rebound morbidity in those who become re-infected due to the loss of protective immunity. Table 1 summarizes different studies from around the world that examined the impact of MDA on the reduction of prevalence, intensity of infection and morbidity.

African Studies

Several African studies have evaluated the impact of PZQ-based MDA on schistosomiasis control. Despite treatment over several years, rapid reinfection rates have been observed in Kenya, Tanzania, Egypt, Senegal, and Mali once treatment was halted [9, 13-24]. More specifically, many communities reported that the human prevalence and intensity of infection returned to pre-treatment, baseline levels once MDA programmes ceased. For instance, a study compared the spatial distribution of schistosomiasis (utilizing Bayesian geostatistical models) in two time periods (1984-1989 and 2004-2006) in Mali, West Africa, wherein a 10-year (1982-1992) GTZ donor-funded control programme was implemented. Their results showed no significant difference in the national prevalence and spatial distribution pattern of schistosomiasis (*S. haematobium* and *S. mansoni*) in both time periods. It was implied that the impact of donor-funded mass distribution of PZQ on the burden of schistosomiasis was not evident in the subsequent Malian generations, probably due to rapid reinfection. The study concluded that, after the cessation of the control programme in 1992, in Mali, the national prevalence of both schistosome species had rebounded to pre-intervention levels [20].

Aside from rapid reinfection rates following the cessation of MDA, rebound schistosome-induced morbidity has also been described in Africa. Gross haematuria is thought to be considered a major morbidity indicator [22-24]. A retrospective study [22] from Pemba Island, Tanzania assessed the efficacy of PZQ treatment against *S. haematobium* infection and gross haematuria. Pemba had a ten-year history of intermittent mass drug administration. Shortly after the interruption of PZQ treatment, owing to a lapse of donor funding, infection prevalence rebounded to 66% which was noted to be higher than the pre-treatment, baseline level (55%). On the other hand, gross haematuria (morbidity) levels decreased from pre-

treatment level of 15.8% to a post-treatment level of 0.9%, but returned at a much slower rate, at approximately 5%, in the absence of therapy. Despite the second treatment, the morbidity level steadily increased to around 10%; and would eventually return to pre-treatment levels over time [22].

Asian Studies

MDA has been widely deployed against zoonotic schistosomiasis in China, the Philippines, Laos, and Cambodia for several decades [25-33]. Unlike Africa, these countries [34] have utilised integrated control strategies to supplement MDA in order to achieve sustainable, long-term control. For instance in China, rapid reinfection rates were observed in the country following the cessation of chemotherapy, particularly in areas with uninterrupted transmission, such as the highly endemic provinces of Hunan, Hubei, Anhui, Sichuan and Jiangxi [25, 28]. Thus, integrated control strategies, including health education, improved irrigation, snail control, sanitation, environmental modification and treatment of bovine reservoir hosts, were adopted by the national Ministry of Health to complement MDA [3]. This has led to a dramatic decrease in the prevalence and intensity of human and animal schistosomiasis in all endemic provinces in China [3, 35].

Concerning the Philippines, the long term impact of annual case-finding and chemotherapy on schistosomiasis japonica was examined in an eight year study (1981-1989) conducted in Leyte province; abrupt discontinuation of PZQ treatment resulted in rapid rebound of liver morbidity [30]. The development of liver fibrosis and pathology due to *S. japonicum* has also been reported in other highly endemic locations throughout Philippines where follow-up treatment was delayed [2, 12, 30-32].

Factors contributing to rebound prevalence, intensity and morbidity

As earlier indicated, despite tangible decreases in the prevalence and intensity of schistosome infection, and reduced clinical morbidity when MDA is continued, transmission has remained uninterrupted in many endemic areas of Sub-Saharan Africa, the Eastern Mediterranean, the Western Pacific, Latin American, and the Caribbean [15, 36, 37]. This is due to several factors (Table 2) including: 1. Socio-cultural, economic and political barriers to MDA implementation; 2. the inability of PZQ to provide 100% cure rate and to prevent reinfection [38]; 3. Significant zoonotic transmission in Asia especially in the case of *S. japonicum*; 4. Low treatment coverage (<25% globally); 5. Low drug compliance for free MDA (<50%); and 6. Immunological factors possibly complicating MDA.

Socio-cultural, economic and political barriers

Social-cultural factors can delay the diagnosis and treatment of a neglected tropical disease such as schistosomiasis. For example, a cross-sectional qualitative survey was conducted in eight *S. mansoni* endemic districts in rural Nyanza Province, Kenya, used focus group discussions to assess knowledge, awareness, beliefs, attitudes, and practices of villagers with regards to schistosomiasis treatment [39]. Social stigmatism due to disease represented a barrier to some of the Nyanza subjects from disclosing clinical information out of fear of being discriminated in the community which in turn hindered people from seeking appropriate treatment for schistosomiasis [39]. A similar study was undertaken in four districts in the province of Napula, Mozambique which revealed a low level of knowledge regarding how schistosomiasis was acquired, transmitted, and prevented [40]. One apparently common misconception was that schistosomiasis is sexually transmitted. Overall, the study concluded that poor knowledge of the causes of schistosomiasis and its prevention, along

with persisting misconceptions, continued to impede effective disease prevention and control [40].

Political factors can also cause problems in controlling schistosomiasis through MDA. For instance, in 1990, the Philippines received external funding from the World Bank through the Philippine Health Development Program (PHDP) which resulted in the examination and treatment of 75% of the target population annually, compared with the previous treatment coverage of 25% [7]. However, in 1995, funding ceased and the treatment coverage reverted to previous levels because the government did not provide matching funds to maintain the drug coverage [12]. Like many African countries, which have depended on external funding, the MDA program in the Philippines could not be sustained without the appropriate political will. The Chinese government was also a recipient of a 10-year World Bank Loan Project (1992-2001), which resulted in the acceleration of MDA for schistosomiasis control [41-44]. This led to a significant decline in human infection prevalence and intensity. When the loan ended, the government maintained the appropriate funds not only for MDA but also for integrated control measures that disrupted disease transmission [41-43]. 'Political will' is clearly critical for the sustainability of MDA programs [45, 46].

Limitations of the drug praziquantel

Reliance on one drug to treat all schistosome species is another drawback of MDA. PZQ is not 100% curative and it is not protective against reinfection [45]. It has no effect on immature parasites which may lower cure rates in areas with intense transmission [47, 48]. The drug's limitation was further enhanced by WHO's decision to optimize the PZQ dose (from 60 mg/kg given in two equal doses 3-4 hours apart to a single oral 40mg/kg dose) based on the results of a multi-country clinical trial [49]. However, a recent meta-analysis of 52 studies comparing the efficacy of different PZQ doses, demonstrated that the level of

protection of the 40 mg/kg dose was only 52% compared with >90% when the dosage was increased to 60, 80, and 100 mg/kg given in two to three equally divided doses [50]. A recent study further emphasised the low levels efficacy with the 40 mg/kg PZQ dose by examining the drug's pharmacokinetics/pharmacodynamics profile in children with intestinal *S. mansoni* infection given either the 40 mg/kg or 60 mg/kg dosage. The results showed significantly greater egg reduction rates at 24 days in older children (> 5 years old) and in those with moderate intensity *S. mansoni* infection in those receiving the 60mg/kg dose [51, 52].

In addition to these limitations, several investigators have raised the possibility that relying on a single drug to combat schistosomiasis can lead to drug resistance. There is evidence, albeit controversial, for this possible scenario [29, 48, 53-56], although these are mainly laboratory reports, with some less drug-responsive isolates found in the field and hospital setting.

Low drug coverage

Inadequate treatment coverage is another obstacle for MDA implementation. In 2001, the 54th World Health Assembly officially endorsed chemotherapy as the key public health strategy to combat schistosomiasis with the goal of achieving target drug coverage of 75- 100% among school-age children at risk of morbidity by 2010 [57, 58]. However, that target coverage was not attained according to the 65th World Health Assembly [58]. In 2014 the global coverage was reported to be 20.74% [59].

Low drug coverage was further demonstrated in an African cross-sectional study in which the impediments to mass treatment campaigns in schools were examined [60].The PZQ treatment coverage rate in 43 primary and high schools was 44.3%. One reason for the low coverage rate was the policy that MDA should only be administered by health professionals;

thus, it was suggested that teachers might contribute more to MDA implementation efforts because of their personal knowledge of the students. Other administrative hurdles were also noted including the reluctance of schools to give more than one day of treatment to minimise class disturbances. Student identification in the class room was also a problem [60], as was the lack of a continuous supply of PZQ [61].

Low drug compliance

Low patient compliance in taking PZQ is another MDA impediment. In the year 2000, the Philippines' Department of Health decided to adopt mass chemotherapy to eliminate schistosomiasis based on the reported cost-effectiveness of the treatment strategy in high endemic areas. In 2004, mass treatment was given to an eligible population of residents in fifty Western Samar villages [62]. MDA was offered free of charge to all residents aged five years and above in villages with an infection prevalence of >15%. A subsequent survey examining participation and coverage rates among the subjects found an overall participation and drug coverage of 48.6% (14,678/30,187) and 44% (13,416/30,187), respectively [62]. The investigators concluded that much more extensive community-based engagement, education, and incentives would be required to increase drug coverage and compliance.

A qualitative study undertaken in Jinja District, Uganda assessed the reasons for the low uptake of mass treatment for intestinal schistosomiasis in school children [63]. The authors noted insufficient disease knowledge both in students and teachers. Moreover, inadequate incentives or compensation for the teachers may have influenced the treatment. Additionally, the drug's large tablet size, bitter taste, and side effects were unappealing to students [63]. In contrast, MDA was generally well accepted among the participants in a *S. mekongi* study conducted in Laos [64]. Their awareness of the health consequences of infection and the community's desire to avoid severe schistosomiasis appeared to motivate compliance.

Zoonotic transmission of schistosomiasis in Asia

Studies from China and Philippines have reported very high infection rates (>80%) in bovines and their substantial role in human schistosomiasis transmission [12, 44, 65-69]. Irrefutable evidence indicates bovines, particularly water buffaloes (*Bubalus bubalis*), play a major role in human transmission. The daily faecal output from a water buffalo (~25 kg) has been estimated to be at least 100 times that produced by a human individual (0.25 kg) [44]. A recent study showed that the environmental contamination attributable to infected bovines was 28.7 million eggs/day, emphasising the major contribution of bovines to the release of *S. japonicum* eggs into the external environment [44]. While dogs, rats and pigs can indeed be infected with *S. japonicum* in the Philippines they are considered to be minor contributors to transmission, because rats only produce ~1g of faeces per day compared to ~250 g produced by humans and dogs and 25 kg produced by carabao [69]. Furthermore, studies have shown that the eggs produced by rats are not viable [69].

Loss of acquired immunity following MDA

The complex immunologic issues associated with schistosomiasis infection may potentially complicate treatment. Host genetics [70-75], concomitant immunity [76-79], innate immunity [80, 81] and adaptive mechanisms [82-90] may influence the clinical course and/or infection status of individuals living in endemic areas. Host genetic studies have identified certain genes that increase an individual's chance of getting re-infected or acquiring severe forms of the disease. Recently, it has been suggested that some components of the innate immune system (e.g., Toll-like receptors) may be responsible for immunity against *S. mansoni* infection among elderly residents in endemic areas in Brazil [81]. Whether or not one an individual can be re-infected may also depend on the balance of some components of the adaptive immune system, such as Th1/Th2 arms [84] and IgE/IgG4 immunoglobulin balance

[85-89]. Schistosome antigens may generate some level of immunity against reinfection [85, 90, 91], and a sufficient amount of parasite antigens may be needed by the host immune system to develop resistance [91, 92]. There have been several studies that have suggested that one of the benefits of mass chemotherapy is to induce a protective immune response against reinfection [85, 93, 94]. However, in contrast, other authors believe that constant MDA may result in disruption of immunity against schistosomiasis among subjects treated long term due to declining antibodies [95].

Conclusions

Numerous studies from around the world have shown a rebound in the prevalence, intensity of infection, and morbidity associated with schistosomiasis when MDA campaigns have been interrupted. These findings indicate that chemotherapy-based programs on their own will not lead to sustainable control or disease elimination in the long term. There are a number of factors involved in the persistence or rebound of infection and morbidity. Uninterrupted transmission of infection is a major factor, and host immunologic mechanisms also play a significant role. However, the relationship between man and parasite cannot be overlooked regardless of the status and degree of acquired immunity among populations [96]. Hence, time, energy, and resources must be spent on integrated control strategies if we are to ultimately eliminate this neglected tropical disease.

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Table 1: Studies from Africa and Asia that show evidence of persistent infection and/or morbidity in known schistosomiasis-endemic areas despite mass drug administration campaigns.

Continent	Study	Results	Conclusions	Reference
Africa	A cross-sectional study was carried out on 387 primary school children (aged 8-16 years) in Mwea Kenya (subject to 4 years of MDA) to assess the *S. mansoni* infection prevalence after drug withdrawal of two years.	The overall *S mansoni* infection prevalence among children was 53.7%, with males having a higher prevalence than females.	*S. mansoni* infection prevalence was high in the study site, two years after withdrawing the MDA programme.	Masaku et al., 2015[97]
	Sixty-seven children subjected to the MDA program were followed up for 4 years. Microsatellite genotype was obtained from faecal samples from 15 re-infected children.	No evidence of decrease in transmission or schistosome population decline over the course of the MDA program as shown by the high reinfection in 67 children. Egg counts and estimated worm burdens did not decline in 15 children (between 1-4 years) studied in detail.	The school based control programs have no effect in reducing transmission and significantly impacting schistosome transmission in endemic areas.	Lelo et al., 2014[14]
	Four KK slides were taken from 2382 subjects (both sex and all ages) in five high-risk Nile Delta villages in Egypt were included the study to assess the impact of MDA in this site	The overall *S mansoni* infection prevalence in the study area was 29% while the mean geometric mean egg count (GMEC) was low (66.78+/-4.4) indicating low intensity of infection	The *S. mansoni* transmission in the high-risk Delta villages hasn't stopped, which calls for the need for more improved, comprehensive control strategies	Elmorshedy et al., 2015[8]
	The transmission and re-infection dynamics of both schistosome species (*S. mansoni* and *haematobium*), single, and mixed infection foci at three villages were investigated. In each village, infected children were identified and selected for a one year study involving two treatments three weeks apart at the start of the study and again after 6 months.	Before treatment in all three villages, the prevalence was noted to be 79-100% and 81-97% for *S. mansoni* and *S. haematobium* respectively. The first round of drug treatment resulted to cure rates for both species ranging from 38-96% with egg reduction rates of 97-99%. However, high and rapid re-infection followed, especially for the S. mansoni, within the 6 month period. The infection intensity of *S. mansoni* remained high in one village after four rounds of chemotherapy.	The general annual treatment protocol of one dose of 40 mg/kg of PZQ is not sufficient to gain control of intestinal schistosomiasis in the study area. The treatment regimens along the Senegal River Basin need to be reviewed.	Webster et al., 2013[18]
	A repeated cross-sectional study was done in five schools (all with a *S haematobium* prevalence > 50% at baseline) in Matuga Distrinct, Kwale County, Kenya to evaluate school-based co-administration of praziquantel and albendazole against urogenital schistosomiasis and soil-transmitted helminth infections. Subsequently, two of the five schools were selected for final survey at the end 5-year study period.	The prevalence and intensity of *S. haematobium* infection decreased significantly after treatment, but varying levels of rebound were noted in between treatment periods, especially in the Mlafyeni school. On the other hand, the school-based treatment did not have any significant effect on both the prevalence and intensity of hookworm infection.	Once a year deworming programmes may not be enough to control hookworm infection and urogenital schistosomiasis in the rural areas of Kwale County. Consideration of including adults in the control was recommended.	Njenga et al., 2014[19]
	The spatial distribution of schistosomiasis, using Bayesian geostatistical model, was conducted in Mali following a decade of chemotherapy-based donor-funded control program and 12 years later after discontinuation of the control program.	*S. haematobium* prevalence was 25.7% in 1984 - 1989 and 38.3% in 2004-2006; S. mansoni prevalence was 7.4% in 1984 - 1989 and 6.7% in 2004-2006. There was no difference in the spatial distribution schistosomiasis pattern in both periods.	Planning for sustainability of continuing interventions, including strengthening endemic country healthy systems, are requisite to achieve long-term control.	Clements et al., 2009[20]

	A cohort of school children in an endemic area in Mali, Niger was included in a study that examined the dynamics between reinfection and repeated treatment. Urine from 214 subjects and stool samples from 220 subjects were collected. Treatment was initiated at the start of the study, and follow-up was done at three time points. Subjects that were found to be infected received repeated treatment.	The prevalence rate for *S. haematobium* was reported to be 55.1% at baseline, decreased to 3.7% at first follow-up, and rose to 35% at the second follow-up. The prevalence rate for *S. mansoni* was 62.7% at baseline, initially decreased to 46.3% at first follow-up, but subsequently rebounded to 73.1% at the second follow-up. Within this study period, the reinfection rates for *S. haematobium* and *S. mansoni* was 84.5% and 57.8%, respectively.	This finding demonstrates that additional measures such as proper sanitation and vector control are needed to control human schistosomiasis in irrigated rice paddies.	Dabo et al., 2000[21]
	A study was conducted in Pemba island, Tanzania, a site with a 20-year MDA history, in order to assess the effectiveness of PZQ treatment, and the performance of the schistosomiasis control programs implemented in this area. A total of 1531 schoolchildren were included in the study.	Despite egg passage in 5% of the children treated, no eggs were found to be viable after PZQ treatment.However, soon after treatment was stopped, the prevalence returned rapidly to pre-interventional levels	There was no evidence of PZQ resistance, and MDA was effective in reducing prevalence in the area. However, soon after treatment was stopped, the prevalence returned rapidly to pre-interventional levels	Guidi et al 2010[22]
Asia	Two longitudinal cohorts in Sichuan, China were followed up at two time points to determine whether there are persistent human reservoirs for *S. japonicum* present in areas where treatment was on going. One cohort (N=424) was derived from areas with a history of high infection prevalence and intensity. The other cohort (N=400) was obtained from areas where schistosomiasis re-emerged following the reduction of human infection prevalence below 1%. Treatment was administered upon identification of infection among the participants at two follow-up points.	Two models were used to estimate the ratio of observed to expected proportion of the population with two consecutive infections at follow-up: a prevalence-based model, and a host exposure model. A ratio of more than 1 in both models suggests that there are people who are repeatedly infected, and there are people infected unaccounted by exposure. Using the first model, there were 1.5 and 5.8 more individuals with two consecutive infections than expected in cohorts 1 and 2, respectively. Using the second model, the ratio was 1.3 and 2.1 in cohort 1 and 2, respectively.	There were some groups of people whose infections are not fully accounted by host exposure. It was suggested that some hosts may be particularly susceptible to *S. japonicum* infection, or that uncured infections persists despite treatment.	Carlton et al., 2013[29]
	A total of 10,435 subjects living in endemic villages, in Northern Samar, the Philippines, which has been the subject to MDA for more than 20 years, were examined for the presence and intensity of *S. japonicum* infection by KK techniques.	Prevalence of infection was 27.1% (range: 26.3%–28.0%), and the geometric mean intensity of infection among 2832 evaluated subjects was 17.2 eggs per gram of faeces.	The prevalence of infection remained high despite of more than 20 years of MDA.	Ross et al., 2015[2]
	One hundred seventy one subjects (171) in Cabariwan village, Northern Samar, the Philippines, which has been the subject of MDA, were examined my ultrasound to determine prevalence of significant hepatic fibrosis.	Eighteen per cent of the subject examined were found to have moderate to severe fibrosis	High prevalence of moderate to severe hepatic fibrosis determined by ultrasound, persisted despite of more than 20 years of MDA.	Olveda et al., 2014[12]

Table 2: Factors contributing to schistosomiasis transmission within endemic areas.

Factor(s)	Study	Results	Conclusions	Reference
Socio-cultural, Economic, and Political Barriers	A cross-sectional study was conducted on 237 participants in eight *S. mansoni* high prevalence districts in rural Nyanza Province, Kenya. Focused group discussions were utilized in each district to evaluate knowledge, awareness, attitudes, and practices among subjects regarding schistosomiasis treatment	Most participants learn about schistosomiasis from schools, posters, radio broadcasts, and community meetings. Various views regarding schistosomiasis were noted which include associating it with unclean food and water. Treatment was sought thru various avenues mostly thru health centres. Other avenues include spiritual intervention, herbalism, and medical shops. Treatment obstacles include attitudes of community members toward infection, particularly fallacies that lead to stigma and the perception that diagnosis and treatment are expensive.	Although the participants exhibited fair knowledge regarding schistosomiasis, some beliefs on the mode of transmission and pathology may impede control efforts. Socio-cultural studies on schistosomiasis to gauge the social burden of disease were encouraged.	Musuva et al. 2014[39]
	A cross-sectional survey was done in four districts of Nampula Province, Mozambique. A total of 791 households were interviewed using a structured questionnaire.	Despite high awareness for schistosomiasis (91%), correct knowledge of how it is acquired (18%), transmitted (26%) and prevented (13%) was low among those who had heard of the disease. Misconceptions, such as the belief that schistosomiasis is transmitted through sexual contact (27%), were common. Only about a third of those who were aware of the disease stated that they practiced a protective behaviour and only a minority of those (39%) reported an effective behaviour. Despite several MDA rounds for schistosomiasis in the recent past, only a small minority of households with children reported that at least one of them had received a drug to treat the disease (9%).	Inadequate knowledge of the causes of schistosomiasis and its prevention, together with persisting misconceptions, continues to hinder effective disease prevention and control. To attain high levels of MDA uptake and adoption of protection behaviours, it will be important to engage individuals and communities, improving their understanding of the causes and symptoms of schistosomiasis, recommended prevention methods and the basis behind MDA.	Rassi et al. 2016[40]
	In the Philippines, schistosomiasis infection prevalence has been reported to be maintained at a low level (<5%) thru MDA control efforts despite cessation of external funding in 1995. In 2011, we conducted a cross-sectional epidemiological survey to determine the current schistosomiasis burden across six villages in Northern, Samar. We expanded our assessment to 12 more villages in 2012.	Our results of the 2011 survey revealed an overall human prevalence of 26.4% (n = 1,955; 95% CI 24.5-28.4%), while in water buffaloes it was found to be 65.4% (n = 211; 95% CI 24.5-28.4%). The results of our expanded study revealed human schistosomiasis prevalence ranging from 5% to 48%.	The MDA results were unsatisfactory for our study, and like the chemotherapy-based programs in the African endemic regions, the treatment strategy may not be sustainable in the long term unless multi-component integrated control strategies (such as ones enforced in China thru political will) are implemented.	Olveda et al. 2014[12], Changsong et al. 2002[41]
Limitations of Praziquantel (ie. PZQ is not 100% curative and does not prevent reinfection)	The anti-schistosomal efficacy of different medication strategies involving three drugs (praziquantel, artemether, and artesunate) was evaluated thru meta-analysis (52 trials, 38 articles). The treatment strategies assessed included monotherapy and combination therapy of the three drugs.	Compared with placebo, the 30-60 mg/kg PZQ dose generated a 76% cure rate (95 CI, 67-83%) for treating human schistosomiasis; no significance difference was noted among *S. haematobium*, *S. japonicum*, and *S. mansoni* species. The 52% cure rate with 40mg/kg increased to 91% (95% CI 88-92%) with 60/80/100 mg/kg divided into two or more doses. Combining PZQ with artemisinin derivatives produced a higher cure rate (84%; 95% CI 64-91%) compared with PZQ monotherapy. PZQ and artesunate combination resulted in 96% protection rate for preventing infection.	PZQ is still effective in schistosomiasis treatment, but efficacy may be improved with multiple 30-60 mg dosage. Combination treatment of PZQ with artemisinin derivatives may be appropriate for repeatedly exposed subjects.	Liu et al. 2011[50]
	PZQ pharmacokinetics / pharmacodynamics were studied among sixty Ugandan children (aged 3-8 years) with intestinal *S. mansoni* infection treated with either 40 mg/kg or 60 mg/kg dosage.	Significant egg reduction rates at 24 days were noted in older children (>5 years) and in those with medium intensity *S. mansoni* infection in those receiving the 60 mg/kg doses.	Result favoured higher dosing in school-age children, especially in those with moderate and heavy egg-intensity infections	Bustinduy 2014[51]

Low Treatment Coverage	A cross-sectional study was conducted to investigate implementation, the coverage, challenges and limitations of a mass treatment campaign implemented Ugu District in south-eastern KwaZulu-Natal, South Africa.	Treatment coverage of 44.3% was achieved among 10,632 out of 24,005 students in 43 primary and high schools. A median of two schools per day were visited over the course of 39 days. Older students, being male and attending a large school were noted to be independent significant predictors for low treatment coverage.	Result was far below recommended treatment coverage (75%) by WHO and South African National Department of Health. Coverage may improve with better consent procedures and more school visits. Compliance among older male students in large schools may increase with further information.	Randjelovic 2015[60]
Low drug compliance	Mass treatment activities were described and secondary analysis was done in 50 villages in Western Samar Province, the Philippines, involving 30,187 subjects previously treated with MDA in 2004. Advocacy, information dissemination and social mobilization activities were conducted prior to mass chemotherapy. Census-based participation proportion was estimated.	The estimated overall participation and drug coverage were 48.6% (14,678/30,187) and 44% (13,416/30,187), respectively. Using an adjusted eligible population of 28,268 people, the adjusted coverage was estimated to be 47.5%. At the village level, the participation proportion ranged from 21.1% to 83.5% (mean of 53.1%), while the coverage ranged from 15.8% to 80.7% (mean of 48.3%).	The conduct of mass treatment in the 50 villages resulted in far lower participation than expected. Concern is raised for the ongoing mass-treatment initiatives now taking place in developing countries.	Tallo et al. 2008[62]
Zoonotic Transmission	The level and extent of schistosomiasis was verified in Donting Lake region (including schistosome-induced morbidity estimates) based on data from the 2004 national schistosomiasis periodic epidemiological survey (PES). The data included 47,144 human serological and 7,205 stool exams, 3,893 clinical exams and questionnaires, 874 buffalo stool exams in 47 Hunan province villages. The results were compared with the 1995 PES for observed changes.	Sero-prevalence was 11.9% (range: 1.3–34.9% at the village level), and estimated egg-positive stool rate was 1.9% (0–10.9%) for the same population. The infection prevalence in buffaloes was 9.5% (0–66.7%). Extrapolating to the entire population of the Dongting Lake region, an estimated 73,225 people and 13,973 buffaloes were infected. Abdominal pain (6.2%) and bloody stools (2.7%) were the most frequently reported symptoms. More than half of the clinically examined people reported having had at least one prior antischistosomal treatment.	The number of *S. japonicum* infected humans was significantly reduced since the 1995 PES due to comprehensive chemotherapy campaigns. Yet, near-stable number of infected buffaloes suggests continuing human re-infection which may lead to future rise in human prevalence.	Balen et al. 2007[65]
	A cross-sectional survey was conducted in 2010 in Samar Province (specifically Cantaguic, Diaz, and Hinugacuan villages and one dairy farm), the Philippines, to determine the *S. japonicum* infection status in carabao and humans using several diagnostic techniques (ie. FEA-SD, real time PCR, conventional PCR, Kato-Katz, and miracidial hatching test). Primary endpoints were carabao and human prevalence and intensity of infection; secondary end points were sensitivity and specificity of the diagnostic techniques employed.	The FEA-SD and qPCR results showed high prevalence of *S. japonicum* infection among the carabao from the study areas. Bovine infection prevalences of 100%, 87.5%, 85.71%, and 85.71% by FEA-SD were reported in the dairy farm, Hinugacan, Diaz, and Cantaquic village, respectively. The bovine infection prevalence by qPCR revealed 100%, 95.4%, 87.5% and 71.43% in Diaz village, the dairy farm, Hinugacuan, and Cantaguic villages, respectively. The qPCR showed a human infection prevalence of 92.31%. With the carabao samples, the most sensitive of the tools used were qPCR (95.25%) and FEA-SD (97.62%). The qPCR was also the most sensitive in detecting eggs in the human samples (94.0%).	The overall *S. japonicum* infection prevalence was high, suggesting the major role that bovines play in human transmission in the Philippines.	Gordon et al. 2012[68]

Loss of acquired immunity	Previous studies have suggested that immunity against *S. haematobium* mainly develops from antigens released from dying worms. Using a model with protective immunity stimulated by antigens released from dying *S. haematobium* worms, the expected impact of MDA on the development of acquired immunity, and on measured egg output, both during and after a mass treatment campaign was assessed.	Antibody levels were initially enhanced by MDA, but declined below pre-intervention levels during or after MDA if protective immunity was short-lived. Following cessation of MDA, it was predicted that measured egg counts could sometimes overshoot pre-intervention levels, even if MDA had had no effect on transmission. With no reduction in transmission, this overshoot occurred if protective immunity was short-lived. This suggests that disease burden may momentarily increase following discontinuation of treatment, even in the absence of any reduction in the overall transmission rate. If MDA was additionally assumed to reduce transmission, a larger overshoot was seen across a wide range of parameter combinations, including those with longer-lived protective immunity. MDA may reduce population levels of immunity to urogenital schistosomiasis in the long-term (3–10 years), particularly if transmission is reduced. If MDA is stopped while *S. haematobium* is still being transmitted, large rebounds (up to a doubling) in egg counts could occur.	The model predicted that, with protective immune responses stimulated by dying S. haematobium worms, repeated MDA may boost protective immunity initially, but eventually, the antibody levels would decline below pre-treatment levels during or after MDA. In some circumstances, it was predicted that the post-MDA egg output could exceed pre-interventional levels.	Mitchell et al. 2014[95]