Original Article

Treatment of pre-school children under 6 years of age for schistosomiasis: safety, efficacy and acceptability of praziquantel

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Abstract

Background

The World Health Organization (WHO) recommends praziquantel for the control and treatment of schistosomiasis, with no real alternative. Pre-school children are excluded from population treatment programs mainly due to paucity of safety data on this age group.

Objectives: This study investigated safety, efficacy and acceptability of praziquantel for the treatment of *S. haematobium* and *S. mansoni* infections among pre-school children aged <6years. The study also investigated the burden of schistosomiasis in this age group.

Methods: Pre-school children (n=188) from Sudan were included in the study. The children were treated with praziquantel tablets at a single dose of 40 mg/kg body weight. Adverse events were assessed at 24 hours and 7 days later, via questionnaire administration to parents and guardians. Efficacy of treatment was assessed at 1, 3 and 6 months by examining stool and urine samples for schistosome eggs. Acceptability was determined by the number of children spitting or vomiting during administration of the drug.

Results: The burden of schistosomiasis among pre-school children aged <6 years was high (31.1%), and this was comparable to that observed among school children-aged ≥6 years (32%). Praziquantel treatment achieved high cure rates (egg negative) for both *S. haematobium* and *S. mansoni* infections when assessed at 1 month after treatment (89.6-92.1%) and remained high for *S. haematobium* (89.6-100%) up to 6 months. However, cure rate dropped from 90.5% at one month to 58.8% and 69.2% at 3 and 6 months among *S. mansoni*-treated children. Praziquantel treatment decreased egg counts considerably with post-treatment geometric mean egg reductions rates ranging from 96.4% to 99.4% at 1 month. Acceptability of praziquantel treatment was high, only for one child the dose had to be repeated after initial spitting. Treatment resolved haematuria and improved weight of the children. There were no drug-related adverse events in all the treated children during follow-up at 24 hours and 7 days.

Conclusions: Praziquantel is safe, effective and acceptable among children aged <6 years. Pre-school children represent a high risk group for schistosomiasis and should be included in population treatment programs.

Keywords: Schistosomiasis,Praziquantel, Safety,Young Children.

Schistosomiasis can lead to significant ill-health and economic burden[1,2] .Two main species, *Schistosoma mansoni* (causing intestinal schistosomiasis) and *S. haematobium* (causing urogenital schistosomiasis) are endemic in Africa and

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account for about 85% of the global burden of the disease[1, 2, 3]. In most African countries, there is an overlap of the two schistosome species resulting in mixed infections[4]. Continuous exposure to contaminated water causes repeated infections during childhood but severe-chronic disease appears later in life. Other, more subtle, effects of the infection in school children include short-term memory loss, slower reaction time, lower scores in some tests of cognitive ability, and poor growth[5,4]. Anaemia and other nutritional deficiencies have also been linked with the infection[6].

The disease can be prevented or the underlying pathology reversed by treatment with praziquantel, the anti-schistosomal drug of choice[7,-13] . With the high price of praziquantel following its discovery in the late 1970s, experts suggested that selective treatment i.e. identification of high prevalence communities, screening the people and treating those identified to have the infection would be more cost-effective[14]. Also, intensity of infection is highest in children and adolescents, hence treatment should be targeted to school-aged children[15,4,10]. Within this approach the standard single dose of 40 mg/kg of praziquantel is recommended [14, 4]. In parts of sub-Saharan Africa, population-based treatment campaign programs remain the only option for most individuals suffering from schistosomiasis to receive treatment[9].

Since the early millennium, however, praziquantel use has increased considerably mainly due to the sharp fall in price[16, 17]. The finding of a meta-analysis that first suggested that although emergence of clinical resistance could not be ruled completely out, there was no eminent threat to praziquantel, contributed to the adoption of the policy for mass distribution of this drug to endemic countries[18]. A recent study also concluded that there is no evidence to suggest that resistance against praziquantel has emerged, or is emerging[17]. The 54th World Health Assembly endorsed mass drug distribution and treatment of at least 75% of school-aged children and other high-risk groups with praziquantel by 2010[4]. The Schistosomiasis Control Initiative (SCI), started in 2003 and supported by Bill and Melinda Gates, has been in the forefront of these large-scale control programs across selected countries in sub-Saharan Africa[16, 19].However,

pre-school children under 5 five years have been excluded from population treatment programmes[20] There is emerging evidence that the burden of schistosomiasis is high in pre-school children and the World Health Organization (WHO) is considering a recommendation that will include pre-school children and infants in population treatment programs. However, there is paucity of safety and efficacy data on praziquantel in pre-school children aged <5 years[21]. In order to contribute evidence to inform treatment policies, this study was sponsored by WHO to assess safety, efficacy and acceptability of praziquantel among pre-school children in schistosomiasis endemic area along the Gezira Irrigation Scheme in Sudan. The study was also to document the extent of schistosomiasis burden in pre-school children by determining prevalence and intensity of *S. haematobium* and *S. mansoni*; to describe morbidity related to schistosomiasis from micro and macro haematuria. With most population treatment administered without prior diagnosis in the approach termed 'preventive chemotherapy' - the control strategy currently recommended by the WHO and applied in many endemic countries[4,22], this study also assessed age-specific prevalence rates within this age group to inform on the age at which treatment should best be initiated.

Materials and Methods

Ethical clearance

Ethical clearance for the study was obtained from WHO's Research Ethics Review Committee,

National Ministry of Health and Ahfad University for Women in Sudan. Parents and guardians were adequately informed about the treatment and possible treatment-related side-effects and what they should do in the event of side effects. Written consent of a child to

participate in the study was obtained from household heads, parents or guardians.

Study area and population

This study was conducted in Hassahesa and Kamlin localities in the Gezira Irrigation Scheme, Gezira State, Sudan. The Irrigation Scheme was initiated in 1924 and located between the Blue and White Niles, South Khartoum. The scheme provides over 800,000 hectares of farm land intended to boost agricultural production, but this in turn has favoured breeding of the intermediate host snails responsible for transmission of schistosomiasis. The inhabitants in this area are mainly Arab tenants who live with their families, but there are also non-tenant Arabs. Outside of Arab villages there is scattered population of workers from west Sudan and migrants from neighboring countries who live either in camps or in unregistered villages without health services, electricity clean piped water supply or schools. The children can attend the nearest primary school and some immigrants make use of the nearby dispensary or dressing station. In 1985 the total permanent and migrant population was estimated to be 2 million[23].The estimate of the population of the Gezira State in 2009 was over 3.6 million[24]. A detailed description of the Gezira Irrigation Scheme has been reported elsewhere[25].

School surveys

Surveys were conducted in primary schools to identify villages with schistosomiasis prevalence rates greater than 40%. On the basis of the prevalence in the school surveys, 10 villages were further surveyed for schistosomiasis in pre-school children aged <6 years. Three villages namely, Hilat Daoud, Branco and Hamad Alla were then selected. *S. haematobium* is the predominant species in Hilat Daoud and Branco whilst Hamad Alla is mainly endemic for *S. mansoni*.

Parasitological diagnosis of the infection

The Kato-Katz method [26] was used for parasitological diagnosis of the infection and egg count was expressed as eggs per gram (epg) of stool. Three slides were examined from a single stool sample. *S. haematobium* was diagnosed by the urine filtration technique and egg count expressed as eggs per 10 ml of urine[27].The intensity of infection was categorized according to the WHO classification as light infection (1 to 99 epg) moderate (100 to 399 epg) and heavy *(*≥400 epg) for *S. mansoni* and *for S. haematobium*, light infection was (≤50 eggs/10ml urine) and heavy was (≥50 eggs/10 ml).

Clinical examination

All the children underwent clinical examination before treatment was given. Urine samples of participating children were examined and 103 (74.6%) had abnormal urine color, mainly blood in urine (haematuria). Abdominal pain was also prevalent among these children and infants (n=78; 56.5%). Only three children (2.2%) reported general fatigue. General physical examinations and anthropometric measurements revealed that 11 patients (8%) had stunted growth (Height-for-age <3rd percentile); 9 patients (6.5%) were under weight according to Welcome classification of malnutrition. Hepatosplenomegaly was not common among these children but in case it was detected the affected child was referred to the district hospital for further evaluation and management. Children with umbilical hernias were also referred. The children with vitamin A deficiency were given therapeutic doses of vitamin A. Children with other minor infections were treated with the appropriate medication.

Treatment

Praziquantel tablets (Distocide, Batch No. DISTT 4010) made in Korea, and provided by the WHO was used for treating the pre-school children in this study. Each child was weighed using a calibrated weighing scale and a single dose of 40 mg/kg praziquantel was administered. For children aged 1-3 years, their weight ranged from 6-20 kg (mean, 13 kg), and the corresponding mean dose administered was 518 mg with the number of tablets a child received ranging from ⅓ -1⅓ (mean, 1 tablet). Children aged 3-5 years had weight ranging from 12-28 kg (mean, 18.6 kg) and the mean dose was 740 mg, with the number of tablets ranging from

1-2 (mean 1¼ tablet). The 5-6 year old children had weight ranging from 17.5-33 kg (mean, 24.5kg), mean dose (977 mg) and the corresponding number of tablets ranging from ¼-2¼ (mean, 1⅔ tablet). The praziquantel tablets were broken into pieces before administration. For children who could not swallow, the tablets were crushed and administered with honey to decrease the bitter taste. The drug administration was supervised using a modified Direct Observation Therapy (DOT). All the children included in the study received a snack before the drug was administered. The mothers or guardians of the treated children were interviewed 24 hours and 7 days post treatment by the clinician using structured questionnaire for episodes of treatment-related side effects. The children were followed (less actively) until 6 months to record adverse events. At each of the visits, specific signs and symptoms (abdominal pain, nausea, vomiting, diarrhoea, anorexia, fever, headache, dizziness and fever) were evaluated. Other symptoms reported by parents or guardians were also recorded. Each symptom was classified according to severity as mild, moderate, severe or life-threatening; seriousness was assessed using a grading scale. The symptoms were graded as not related, unlikely, possible, probable, most probable or insufficient data to enable adequate assessment. The efficacy of praziquantel was assessed at one, three and six months using the same diagnostic criteria as baseline. Any treated child presenting stool sample from which three slides were free for schistosome eggs or no eggs found in 10 ml of urine was considered to be cured. In this study treatment acceptability was defined as the number of children spitting or vomiting during administration of the drug, and it was assessed by direct observation therapy (DOT). The weight of children was measured using a calibrated weighing scale; heights were measured using a stadiometer with a flat wooden base.

Inclusion and exclusion criteria

Pre-school children under six years of age with confirmed schistosomiasis by microscopy were eligible for inclusion in the study. Seriously ill children; or children reporting a history of epilepsy, other signs of potential central nervous system involvement such as subcutaneous nodules suggestive of cystercosis; or have previously suffered one of the rare serious adverse events such as Stevens-Johnson syndrome, were excluded. These criteria were based on the World Health Organization (WHO) Manual of Preventive Chemotherapy[22]. Over all, one hundred and eighty-eight pre-school children were included in the study.

Results

Overall, prevalence of schistosomiasis among pre-school children in the three selected study villages (n=604) was high (31.1%). Urine examination revealed that in Branco a high number of pre-school children were infected with *S. haematobium* (43%); this was 22% in Hilat Daoud. The prevalence of *S. mansoni* in Hamad Alla was also high (44%). Age-specific prevalence rates in the three villages have been reported in (Table 1). There was no significant difference across age-specific categories in this group in Hilat Daoud and Branco, but differences were observed in Hamad Alla ($p \leq 0.005$). Strikingly, the rates of infection with schistosomiasis in pre-school children aged <6 years was comparable to that observed among school children aged ≥6 years in the 26 primary schools surveyed (n=1,427): 31.1% versus 32%, respectively.

In this study praziquantel treatment achieved high cure rates (egg negative rates) for both *S. haematobium* and *S. mansoni* infections at 1 month and remained high for *S. haematobium* at 3 and 6 months (Table 2). Fifty-nine of 77 (76.6%) children assessed at baseline who were found with *S. haematobium* were available for treatment in Hilat Daoud with a respondent rate of 76.6%. Of these 48 (81%) children were available at one month's follow-up, 36 (61%) at three months and 29 (49%) at six months. The overall cure rate was 89.6%, 91.6% and 100% at one month, and three and six months, respectively. In Branco, 50 of 64 (70.1%) children were available for treatment and 38 (76%) children were available at one month's follow- up, 35

(70%) at three months and 36 (72%) at six months follow-up. The cure rates were 92.1%% at one month, 91.4% at three months and 91.7% at six months. In Hamad Alla 29 of 47 (61.8%) children found to have S. mansoni infection were available for treatment. Of these 21 (72%) children attended for follow-up assessment at one month, 17 (59%) children at three months and 13 (45%) children at six months. The cure rate was 90.5% at one month, but this dropped to 58.8% at 1 month and 69.2% at 6 months. Instability and lack of cooperation of the inhabitants contributed to the low turn out rate at follow-up in this village.

For the two villages investigated for S. haematobium infections, the geometric mean egg count was higher for children in Hilat Dauod (166.1 eggs/10ml) than in Branco (28.2 eggs/10ml). Egg reduction rates were very high one month after treatment: in the children from Hilat Dauod egg count reduced to 1.5 eggs/10ml (a reduction of 99.4%) and in Branco to 1.3 eggs/10ml (a reduction of 96.4%). The pretreatment geometric mean egg count for S. mansoni infection in the children from Hamad Alla was 97.8 epg and reduced to 1.5 epg after one month after treatment leading to a reduction rate of 99.0% (Figure1).

All children accepted the drug without spitting or vomiting except for one child aged 1½ years for whom the dose was repeated. However, dose determination, preparation and administration of the medication in this study were cumbersome. During post-treatment follow-up visits and contacts after 24 hours and 7 days, when the children and their parents or guardians were asked about drug related side effects including gastro intestinal symptoms, skin manifestations, bleeding episodes, dizziness, general fatigue or change in gait or behaviour, no side effects were reported in all the treated children. Also, during the less active follow-up at 3 and 6 months, no events were recorded.

For anthropometry measurements, a significant increase in weight in children from Hilat Daoud ($P \leq 0.005$) was observed one month after treatment (Figure 2).

Table 1. Prevalence of schistosomiasis among pre- school children in the three study villages.

Village	Species	Age-group			Total
		1-3	>3-5	>5-6	
Hilat Daoud	*S. haematobium*				
No. Examined		94	176	80	350
No. positive		21	32	24	77
Prevalence		22.3%	18.2%	30%	22%
Branco	*S. haematobium*				
No. Examined		43	82	23	148
No. positive		14	36	14	64
Prevalence		32.6%	43.9%	60.9%	43.2%
Hamad Alla	*S. mansoni*				
No. Examined		33	54	19	106
No. positive		6	29	12	47
Prevalence		18.2%	53.7%	63.2%	44.3%
Total positive		41	97	50	188
Prevalence		24.1%	31%	41%	31.1%

Table2. Results of follow-up urine and stool examinations.

Village	No. treated	Follow-up examinations								
		One month			Three months			Six months		
		No followed	No. cured	% cured	No followed	No. cured	% cured	No followed	No. Cured	% cured
Hilat Daoud	59	48	43	89.6	36	33	91.6	29	29	100
Branco	50	38	35	92.1	35	32	91.4	36	33	91.7
Hamad Alla	29	21	19	90.5	17	10	58.8	13	9	69.2

Discussion

This study revealed that the prevalence of schistosomiasis in pre-school children from the three selected villages was high (31.1%), comparable to that observed among school children aged ≥6 years (32%) in the 26 primary schools surveyed (n=1,427). The findings are consistent with emerging evidence that the burden of schistosomiasis is high in pre-school children [21]. In Ghana, a study investigating the extent of schistosomiasis in pre-school children and infants found prevalence of 11.2% for *S. haematobium*, with the highest egg count detected in a 4-month old infant [28]. In a rural endemic area in Nigeria, prevalence of 58.1% was reported for *S. haematobium* in children aged 1-6 years [29], whereas in Niger, rates of the infection among infants and their mothers were 61% and 72%, respectively [30]. Similar findings have emerged from Mali where prevalence of *S. haematobium* among pre-school children aged 1-4 years was found to be 51.2% [31]. In Uganda nearly 50% of children less than three years of age living along the northern shoreline of Lake Victoria had *S. mansoni* infections [32]. A recent study from the shoreline villages of Lakes Albert and Victoria in Uganda found even higher prevalence of *S. mansoni* (62.3%) in pre-school children [33]. In Sudan, an earlier study found high prevalence of schistosome infection (40%) among pre-school children in the Gezira Irrigation Scheme [34]. The common feature associated with infection in these children from the various settings is that the children and their caregivers (parents or guardians) have high levels of water contact and thus intense exposure to the infective parasite.

The implications of these findings are serious in the sense that since the advent of safe and efficacious drugs that shifted the focus of schistosomiasis control to individual or population-based chemotherapy, pre-school children have been excluded from such interventions mainly due to paucity of data to document the safety of praziquantel in this age group[4]. Other reasons for excluding pre-school children from population chemotherapy programs include the following: these children cannot swallow praziquantel tablets and when the tablets are broken or crushed they reject it mainly because of the bitter taste; syrup formulations are not readily available; and the WHO recommended dose-pole for determining dose of praziquantel applied in control programs only works for children of height >94cm[20]. Therefore, the suggestion was that pre-school children and infants should seek treatment in the regular health service or clinics. These facilities on the other hand deal with symptomatic cases and only the children presenting with symptoms would obtain treatment, which also is dependent on whether their parents or guardians would send them to health facilities at all. It means that even if a child has heavy worm burden but does not show symptoms, he/she is unlikely to receive treatment. However, without early treatment, schistosomiasis in children often leads to serious health consequences including nutritional deficiencies,

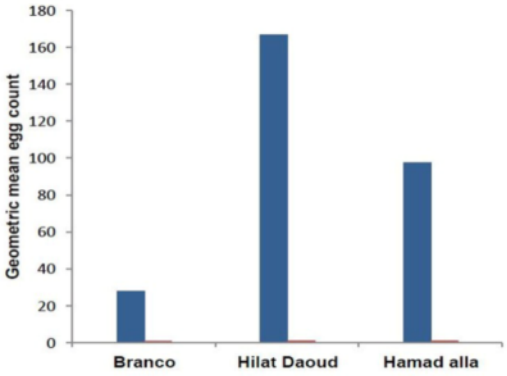

Fig.1. Geometric means of egg counts in Hilat Daoud, Branco and Hamad Alla before and one month after treatment

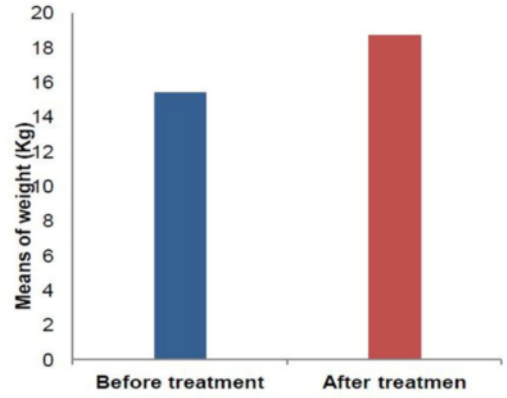

Fig.2. Means of weight in Hilat Daoud before and one month after treatment.

retarded growth, reduced physical activity, and impaired cognitive function[35,4]. Another concern is that schistosomiasis is associated with rural dwelling[36,37] and in such settings the peripheral health facilities where parents would send their children for treatment for schistosomiasis are mostly not available or nonfunctional. Even if available, these peripheral health facilities are faced with difficulties from lack diagnostic capacity and availability of praziquantel making it less likely for infected children to obtain the much needed intervention[38,39]. Also, whereas population-based schistosomiasis chemotherapy interventions delivered through vertical programs are free of charge[40], visiting regular health care facilities is not free and the money charged may deter parents and guardians from seeking treatment from these facilities. Perceived seriousness of schistosomiasis-related symptoms which is usually underestimated at the community level may decrease the tendency for obtaining treatment for these vulnerable children[41]. Therefore, for some who are unable to seek health care from the regular health facilities, their disease-related morbidity has not been averted raising serious public health concern for leaving pre-school children out of population-based chemotherapy campaign programmes[42]. Results of recent Cochrane systematic review showed that treatment with the standard dose of praziquantel (40 mg/kg) generally results in cure rates of ≥80% 1-3 months after treatment[43]. In this study praziquantel achieved high cure rates of 89.6–91.4% against *S. haematobium* and 90.5% against *S. mansoni* infections 1 month after treatment. Strikingly, cure rate from *S. haematobium* treatment rose to 100% at 6 months but that of *S. mansoni* dropped to 58.8% at 3 months and 69.2% at 6 months. This observation, particularly the former, calls for caution when interpreting these findings as high losses to follow-up were experienced in the study mainly as a consequent of civil disturbances in the study setting at the time of the trial. The drop in cure rate over time for *S. mansoni* infection may be explained by factors such as rapid re-infection rate after treatment, high pretreatment worm load that could not be completely cleared by the treatment that remained in the treated children and started producing eggs, and the presence of high numbers of immature worms less sensitive to praziquantel that escaped drug action and matured to egg producing worms during subsequent follow-ups[18]; praziquantel is refractory against immature worms[43]. The effect of treatment in terms of egg reduction rates ranging from 96.4–99.4% was high and supported by evidence of Cochrane systematic review[44].

No drug-related adverse events were recorded or reported for the treatment of pre-school children with praziquantel during follow-up visits at 24 hours and 7 days. Possible bias could not be ruled as parents or guardians

reported side-effects on behalf of their preschool children who could not speak for themselves. However, in other studies involving pre-school children, minor and transient side-effects 24 hours after treatment were reported in Uganda [33], in Zimbabwe [45] and in Mali [31] in accordance with established evidence that praziquantel is associated with minor and transient adverse events[46,47].

Conclusions and recommendations

The results of this study shows that chemotherapy with praziquantel against *S. haematobium* and *S. mansoni* in pre-school children aged <6 years is safe, effective and acceptable. Therefore, these young children should be included in the national treatment control programs in order to prevent long-term chronic ill-health or schistosomiasis-related complications later in life. Given the cumbersome nature of dose determination, preparation and administration, it is important for manufacturers to come with smaller or easy to break tablets.

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The authors declare that they have no competing interests.

References:

1. Savioli L, Renganathan E, Montresor A et al. Control of schistosomiasis-a global picture. Parasitol Today. 1997;13:444-8.
2. Chitsulo L, Engels D, Montresor A et al. The global status of schistosomiasis and its control. Acta Tropica. 2000;77(1):41-51.
3. Hotez PJ, Kamath A. Neglected tropical diseases in sub-Saharan Africa: review of their prevalence, distribution, and disease burden. PLoS neglected tropical diseases. 2009;3(8):e412.
4. World Health Organization. Prevention and control of schistosomiasis and soil-transmitted helminthiasis: report. WHO Techenical Report Series No912, Geneva; 2002 Contract No.: Document Number|.
5. Partnership for Child Development. The cost of large-scale school health programmes which deliver anthelmintics to children in Ghana and Tanzania. Acta Tropica. 1999;73(2):183-204.
6. Awasthi S, Bundy DAP, Savioli L. Helminthic infections. Bmj. 2003;327(7412):431.
7. Zhang Y, Koukounari A, Kabatereine N et al. Parasitological impact of 2-year preventive chemotherapy on schistosomiasis and soil-transmitted helminthiasis in Uganda. BMC medicine. 2007;5(1):27.
8. Webster JP, Koukounari A, Lamberton PHL et al. Evaluation and application of potential schistosome-associated morbidity markers within large-scale mass chemotherapy programmes. Parasitology. 2009;136(13):1789-99.
9. Utzinger J, Raso G, Brooker S et al. Schistosomiasis and neglected tropical diseases: towards integrated and sustainable control and a word of caution. Parasitology. 2009;136(13):1859-74.
10. Savioli L, Albonico M, Engels D et al. Progress in the prevention and control of schistosomiasis and soil-transmitted helminthiasis. Parasitology International. 2004;53(2):103-13.
11. Koukounari A, Donnelly C, Sacko M et al. The impact of single versus mixed schistosome species infections on liver, spleen and bladder morbidity within Malian children pre-and post-praziquantel treatment. BMC infectious diseases. 2010;10(1):227.
12. Hatz CFR. The use of ultrasound in schistosomiasis. Advances in parasitology. 2001;48:225-84.
13. Doehring-Schwerdtfeger E, Abdel-Rahim IM, Kardorff R et al. Ultrasonographical investigation of periportal fibrosis in children with Schistosoma mansoni infection: reversibility of morbidity twenty-three months after treatment with praziquantel. The American journal of tropical medicine and hygiene. 1992;46(4):409.
14. World Health Organization. The control of schistosomiasis and soil-transmitted helminthiasis: report. WHO Techenical Report series No728, Geneva. World Health Organization; 1985.
15. Magnussen P, Ndawi B, Sheshe AK et al. The impact of a school health programme on the prevalence and morbidity of urinary schistosomiasis in Mwera Division, Pangani District, Tanzania. Transactions of the Royal

Society of Tropical Medicine and Hygiene. 2001;95(1):58-64.
16. Fenwick A, Savioli L, Engels D et al. Drugs for the control of parasitic diseases: current status and development in schistosomiasis. Trends in parasitology. 2003;19(11):509-15.
17. Doenhoff MJ, Cioli D, Utzinger J. Praziquantel: mechanisms of action, resistance and new derivatives for schistosomiasis. Current opinion in infectious diseases. 2008;21(6):659-67.
18. Danso-Appiah A, De Vlas SJ. Interpreting low praziquantel cure rates of Schistosoma mansoni infections in Senegal. Trends in parasitology. 2002;18(3):125-9.
19. Fenwick A. Waterborne infectious diseases—could they be consigned to history? Science. 2006;313(5790):1077-81.
20. Stothard JR, Gabrielli AF. Schistosomiasis in African infants and preschool children: to treat or not to treat? Trends in parasitology. 2007;23(3):83-6.
21. Keiser J, Ingram K, Utzinger J. Antiparasitic drugs for paediatrics: systematic review, formulations, pharmacokinetics, safety, efficacy and implications for control. Parasitology. 2011;138:1620-32.
22. World Health Organization. Preventive chemotherpy in Human Helmenthiasis Coordinated use of Anthelmenthic Drugs in Human Intervention: a Mannual for Health Professionals and Programme Managers. Geneva, World Health Organization; 2006 Contract No.: Document Number|.
23. El Gadal AA. The Blue Nile Health Project: a comprehensive approach to the prevention and control of water associated diseases in irrigated schemes of the Sudan. Journal of Tropical Medicine and Hygiene. 1985;88:57-63.
24. National Ministry of Health. Annual Health Statistical Report. Sudan: National Health Information Centre; 2009 Contract No.: Document Number|.
25. Fenwick A, Cheesmond AK, Amin MA. The role of field irrigation canals in the transmission of Schistosoma mansoni in the Gezira Scheme, Sudan. Bulletin of the World Health Organization. 1981;59(5):777-86.
26. Katz N, Chaves A, Pellegrino J. A simple device for quantitative stool thick-smear technique in schistosomiasis mansoni. Rev Inst Med Trop Sao Paulo. 1972;14(6):397-400.
27. Ageel ARM, Amin MA. Integration of schistosomiasis control activities into the primary health care system in the Gizan region, Saudi Arabia. Annals of tropical medicine and parasitology. 1997;91(8):907-16.
28. Bosompem KM, Bentum IA, Otchere J et al. Infant schistosomiasis in Ghana: a survey in an irrigation community. Tropical Medicine & International Health. 2004;9(8):917-22.
29. Ekpo UF, Laja-Deile A, Oluwole AS et al. Urinary schistosomiasis among preschool children in a rural community near Abeokuta, Nigeria. Parasites & Vectors. 2010;3(1):58-62.
30. Garba A, Barkiré N, Djibo A et al. Schistosomiasis in infants and preschool-aged children: Infection in a single Schistosoma haematobium and a mixed S. haematobium-S. mansoni foci of Niger. Acta Tropica. 2010;115(3):212-9.
31. Dabo A, Badawi HM, Bary B et al. Urinary schistosomiasis among preschool-aged children in Sahelian rural communities in Mali. Parasites & Vectors. 2011;4:21.
32. Odogwu SE, Ramamurthy NK, Kabatereine NB et al. Schistosoma mansoni in infants (aged< 3 years) along the Ugandan shoreline of Lake Victoria. Annals of tropical medicine and parasitology. 2006;100(4):315-26.
33. Sousa-Figueiredo JC, Pleasant J, Day M et al. Treatment of intestinal schistosomiasis in Ugandan preschool children: best diagnosis, treatment efficacy and side-effects, and an extended praziquantel dosing pole. International Health. 2010;2(2):103-13.
34. Amin MA, Fenwick A, Teesdale CH et al. The assessment of a large snail control programme over three-year period in the Gezira Irrigated Area of the Sudan. Annals of tropical medicine and parasitology. 1982;76(4):415.
35. Jukes MC, Nokes CA, Alcock KJ et al. Heavy schistosomiasis associated with poor short-term memory and slower reaction times in Tanzanian schoolchildren. Trop Med Int Health. 2002;7(2):104-17.
36. Hotez PJ, Brindley PJ, Bethony JM et al. Helminth infections: the great neglected tropical diseases. The Journal of clinical investigation. 2008;118(4):1311-21.
37. Wang L, Utzinger Jr, Zhou X-N. Schistosomiasis control: experiences and lessons from China. The Lancet. 2008;372(9652):1793-5.
38. Danso Appiah A, De Vlas SJ, Bosompem KM et al. Determinants of health seeking behaviour for schistosomiasis related symptoms in the context of integrating schistosomiasis control within the regular health services in Ghana. Tropical Medicine & International Health. 2004;9(7):784-94.
39. van der Werf MJ, Bosompem KM, de Vlas SJ. Schistosomiasis control in Ghana: case management and means for diagnosis and treatment within the health system. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2003;97(2):146-52.
40. Fenwick A, Webster JP, Bosque-Oliva E et al. The Schistosomiasis Control Initiative (SCI): rationale, development and implementation from 2002–2008. Parasitology. 2009;136(13):1719-30.
41. Danso-Appiah A, Stolk WA, Bosompem KM et al. Health Seeking Behaviour and Utilization of

42. Health Facilities for Schistosomiasis-Related Symptoms in Ghana. PLoS neglected tropical diseases. 2010;4(11):e867.
43. Stothard JR, Sousa-Figueiredo JC, Betson M et al. Closing the praziquantel treatment gap: new steps in epidemiological monitoring and control of schistosomiasis in African infants and preschool-aged children. Parasitology. 2011;138(12):1593-606.
44. Sabah AA, Fletcher C, Webbe G et al. Schistosoma mansoni: chemotherapy of infections of different ages. Experimental parasitology. 1986;61(3):294-303.
45. Danso-Appiah A, Utzinger J, Liu J et al. Drugs for treating urinary schistosomiasis. Cochrane Database Syst Rev. 2008;16(3):CD000053.
46. Mutapi F, Rujeni N, Bourke C et al. Schistosoma haematobium Treatment in 1–5 Year Old Children: Safety and Efficacy of the Antihelminthic Drug Praziquantel. PLoS neglected tropical diseases. 2011;5(5):e1143.
47. Cioli D, Pica-Mattoccia L, Archer S. Antischistosomal drugs: past, present... and future? Pharmacology & therapeutics. 1995;68(1):35-85.
48. Utzinger J, Keiser J. Schistosomiasis and soil-transmitted helminthiasis: common drugs for treatment and control. Expert opinion on pharmacotherapy. 2004;5(2):263-85.