Changing Policy and Practice in the Control of Pediatric Schistosomiasis

Title: Changing policy and practice in the control of paediatric schistosomiasis

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Short title: Controlling paediatric schistosomiasis

Abbreviations:

ALB= albendazole

MDA=Mass Drug Administration

MEB = Mebendazole

PC= preventative chemotherapy

POC= Point of care

PZQ=Praziquantel,

SCI- Schistosomiasis Control Initiative

WHO=World Health Organisation,

Key words: schistosomiasis, bilharzia, urogenital schistosomiasis, *Schistosoma haematobium*, *Schistosoma mansoni*, paediatric, praziquantel, mass drug administration, preventative chemotherapy, World Health Organisation.

Funding Sources: None to declare.

Financial Disclosure: Francisca Mutapi has no financial relationships relevant to this article to disclose.

Conflict of Interest: Francisca Mutapi has no conflicts of interest to disclose.

Contributor's Statements: Francisca Mutapi conceptualized and designed the literature review and the review content and wrote the manuscript and agrees to be accountable for all aspects of the work.

ABSTRACT

Schistosomiasis is a chronic disease that affects approximately 200 million people. The extended health impact of the disease has been estimated to exceed that of malaria or tuberculosis, and be nearer to that of HIV/AIDS. Within endemic areas, children carry the heaviest burden of infection. Infection/disease is controlled by treatment of infected people with the antihelminthic drug praziquantel. Global initiatives from Partners of Parasite Control, including the World Health Organization (WHO) advocate regular school-based de-worming strategies in order to reduce development of severe morbidity, promote school-child health and development as well as to improve the cognitive potential of the children. Until recently pre-school 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 pre-school children, i.e. children aged 5 years and under. This was the culmination of several decades of research on schistosome epidemiology, immunology and pathology in this age group. The recent development of a paediatric formulation of PZQ, soon to enter clinical trials should progress the control efforts in pre-school children, with the vision of seeing these children included in preventative chemotherapy as currently occurs for soil transmitted helminths. This review discusses the research work underpinning the WHO revision of recommendations for treating pre-school children as well as current barriers and knowledge gaps in paediatric schistosomiasis control.

INTRODUCTION

Schistosomiasis (commonly known as bilharzia) is the second most important parasitic disease (after malaria) affecting children in Africa, impacting on 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 people with the antihelminthic drug praziquantel (PZQ). Global initiatives from Partners of Parasite Control including the World Health Organization (WHO), Bill and Melinda Gates Foundation, UNICEF, Schistosomiasis Control Initiative (SCI) and the World Bank advocate regular school-based de-worming strategies to prevent the development of severe morbidity, promote child health and development. Until recently (2010), pre-school children (i.e. children aged 5 years and under) were excluded from schistosome treatment creating a health inequity in affected populations. In our studies, the youngest participant we have diagnosed positive for schistosome infection was 6 months old, which is not unusual in high schistosome transmission areas as has been reported in Nigeria [2] . Such observations re-affirm the need for interventions targeting pre-school children who continue to be excluded from current national control programmes. Exclusion of these children from Mass Drug Administration (MDA) programmes is similar to what was the situation for soil transmitted helminths (STH) two decades ago [3]. In the case of STH, following concerted efforts laying the evidence base for the inclusion of pre-school children in MDA programmes using the antihelminthics albendazole (ALB) and mebendazole (MEB) and advocacy (see [3]), pre-school children are now included in STH control programmes[4]. Primary school children in some helminth endemic areas are benefiting from mass drug co-administration of PZQ and ALB or MEB as is happening in Zimbabwe. Inclusion of the pre-school children in these

programmes will be a significant step in improving child health and development in affected areas.

Schistosome control programmes

Over the past decade, there has been a concerted global effort to control schistosomiasis in Africa, galvanised initially by the Millennium Development Goal (MDG) 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-age children at risk of schistosome morbidity by 2010. We conducted a review of publications quantifying the levels of *Schistosoma haematobium* and *S. mansoni* the most prevalent human schistosome species occurring in African children aged 5 years and below. Using this information we generated the first *S. haematobium* and *S. mansoni* maps of paediatric schistosomiasis in Africa for the period (1995-2014) shown in Figure 1. The map represents all the information currently published on the prevalence of paediatric schistosomiasis and highlights the paucity of data available in this age group. Nevertheless, schistosome prevalences among preschool children are closely related to those of the older children/adults in the same countries and this map is consistent with those published for the older population [5]. Of the African countries where schistosomiasis is endemic, 28 countries have or are currently implementing a schistosomiasis control programme in the period 1995 -2013 as listed in the WHO database on PC of neglected tropical diseases (http://www.who.int/neglected_diseases/preventive_chemotherapy/en/)**.** However, none of them have included children aged 5 years and under, despite more that 60% of them reporting significant schistosome infection levels in this age group (Figure 1). For control programmes commenced before 2011 there are several reasons which were given for not treating children aged 5 years and under, the main ones being 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 involvement of the host immune system acting in synergy with PZQ to clear schistosome worms [8] was interpreted to suggest that the immune system of pre-school children would to be immature/un-primed to act synergistically with PZQ [9, 10]. This 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 pre-school children culminating in the revised recommendations from the WHO in 2010.

Praziquantel

Praziquantel was the first antihelminthic drug to fulfil 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. It was developed in the 1970s by Bayer and licensed as Biltricide© for use in adults and children aged 4 years and above. PZQ is cheap, costing around US$ 0.08 [11]. Through a commitment of the pharmaceutical industry to donate 250 million PZQ tablets/year for school-aged children, PZQ is now an accessible tool for schistosome control. In the field, dosage is determined by weight, but typically a PZQ dose pole is used as scales are not always easily accessible and the pole also facilitates large scale MDA programmes [12]. The PZQ pole indicates the dosage by height following the standardised calibration of weight to height.

Structurally, PZQ is a racemic mixture of the *dextro* (right) and *laevo* (left) isomers of 2-(Cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one, of

which only the *laevo* isomer is active against schistosomes [13]. The pharmacokinetics have not been studied in children aged 4 years and below, but studies in adults show that PZQ is rapidly absorbed from the gastrointestinal tract so that maximal levels in human plasma occur within 1to 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 60mg/kg body weight. The mode of action of PZQ is still to be fully described; however, the drug is thought to cause muscle contraction in adult worms as a result of a Ca^{2+} influx and tegumental damage [15]. The tegument 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 above 75% (see review by Stothard and colleagues [3]) and we routinely achieve cure rates and egg reduction rates above 90% in study populations in Zimbabwe[16, 17]. At the individual level, the effects of PZQ include; (1) killing adult worms reducing infection intensity in the host and the immediate health consequences of infection [18], 2) reversal of pathological processes associated with the 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]. From the pre-licencing safety studies and numerous field studies [16, 25], PZQ treatment is considered safe and efficacious. There are a few side 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

People become infected with schistosomes when they come into contact with infective water. Infectivity of fresh water sources is demonstrated by the presence of patent snail intermediate hosts of schistosomiasis (patency demonstrated by shedding the snails which allows the infective cercarie 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 amongst pre-school 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 [2, 6, 28]. Thus, direct observation and questionnaires in exposure studies missed significant amounts of the exposure behaviour in pre-school children. This was confirmed by studies using GPS logging of water contact behaviour of children. [10]. Two decades ago we used serological and quantitative investigations to study exposure to infective and adult stages of schistosome parasites in young children [29]. Our studies indicated that 79% of children aged 4 months to 6 years showed evidence of exposure to schistosome infection [29]. In our recent studies the youngest patient who tested positive for schistosome infection by parasite egg excretion was 6 months old. We and others have 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] and in some areas their infection levels are as high as those in their carers that were eligible for treatment, while the infected children remain untreated for several years (see review [28]). Furthermore, the limited investigations describing and quantifying morbidity in this age group have shown that the infections in the young children are of clinical significance [34, 35]. Apart from the immediate effects of infection and disease

in the young children, childhood infections have long-term effects on host health as untreated schistosome infections are chronic and disease is progressive, meaning that delayed treatment (termed the PZQ gap[10]) can result in more severe forms of disease including bladder cancer, liver damage[26], poor reproductive health and 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 was the first and considerable step towards highlighting the need for intervention in this age group.

Praziquantel in pre-school children: action, safety and efficacy

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

Having established that there was no immunological reason to hinder with the action of PZQ in young children, there still remained the lack of evidence on 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 not been studies on the safety of PZQ treatment of schistosomiasis infection in children under 5 years of age with a view to include them in MDA programmes. In 2008 the World Health Organisation 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 pre-school children in Africa [40]. All studies tested the tablet PZQ formulation and one study tested both the tablet and paediatric liquid formulation. These studies concluded that PZQ treatment of children aged 6 months -5 years was safe and efficacious[40]. Our own study showed that the pre-school children reported significantly fewer side effects than in the primary school children[16, 17]. The fewer side effects were unsurprising as these are related to the intensity of infection [41-43] and infection intensities are lower in this age group than in primary school aged children. We reported cure rates and egg reduction rates above 90% in pre-school children [17].These results and those from the other groups were reviewed at a WHO working group meeting which made the recommendations detailed below. Furthermore, our results informed the formulation of Zimbabwe's national schistosome and soil transmitted helminth control programme drafted in 2012 [44], making it one of the first national helminth control policies to include pre-school children. In terms of morbidity control, there is a paucity of studies in pre-school children demonstrating the effects of PZQ treatment. We have just completed a three-year study in this age group and our results show that treatment of pre-school children with PZQ significantly reduces morbidity attributable to schistosome infection (submitted). Thus, at policy level, the main hurdle to treating pre-school children was crossed by the demonstration of the utility, efficacy and safety of PZQ treatment in pre-school age children in the independent studies.

Operational aspects of Praziquantel administration to pre-school children

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

The *dextro* isomer gives PZQ a bitter taste which makes it unpalatable[46], this 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 paediatric PZQ formulation are currently underway and if , this will overcome a significant operational hurdle in MDA for pre-school children. In the meantime, the tablet form of PZQ can be administered to pre-school children as crushed tablets taken with some squash and food such as bread[40].

Changing policy and practise

In response to concerted efforts by several scientists and health workers to highlight the significant health inequity that was being perpetuated by exclusion of pre-school 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 and below. In 2010, the WHO arranged a meeting of a working group composed of people working in schistosome

endemic areas to review the results from these studies [40]. The findings and recommendations from the WHO working group were a significant step 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 pre-school children aged 5 years and under. Furthermore, we also concluded that PZQ is 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 [40].

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

Additionally, the working group called on the WHO to formally advocate the treatment of this age group in areas where 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 on operational issues. First, the PZQ dose pole for working out the drug dosage used in the field would be a useful operational tool if it could be extended to below 94 cm of height to incorporate the pre-school children. However, the pole had not been evaluated for use in this age group. As detailed above a subsequent investigation lead by

Stothard showed that the PZQ pole could be extended to be applicable in the pre-school aged children [45]. Second, the size of the PZQ tablet and the need to break it into smaller units for the young children made it cumbersome for use in the field. Therefore, there was need for the development of a child friendly formulation. 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

That pre-school children require treatment is now an acknowledged public health fact. However, there are some remaining challenges especially if the visions of the 2012 World Health Assembly resolution WHA65.21 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. While this is a realistic goal in some schistosome endemic areas, there are still considerable challenges to realizing these visions in areas of high transmission.

Reliable quantification of affected pre-school 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 age children and adults, but not for pre-school children. This is an important omission as this information is critical to inform planning for PZQ requirements and resources to implement MDA in this age group. Pre-school children aged 1 year and above are already

involved in PC for STH[4], thus the potential for co-administration of PZQ with STH antihelminthics ALB and MEB through effective pediatric health systems and activities such as Child Health Days and 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 (haematuria)) are less sensitive in pre-school children as we and others have demonstrated [48, 49]. Serological methods which are more sensitive are applicable only before treatment since PZQ alters parasite specific immune responses [50], while molecular methods detecting parasite DNA [51] or microRNAs [52] have yet to be evaluated in this age group. We have recently 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 (POC) 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 programmes to quantify the efficacy of the interventions and justify the required long-term investment in schistosome control programs. POC diagnostic tools with low sensitivity and specificity can underestimate the effectiveness of control programmes, affecting their cost-benefit ratio and thus their prioritisation and sustenance within ministries of health in affected countries (often with small health budgets) and other stakeholders.

Optimal treatment regimen

There is still a need for information on the number, frequency and optimal timing of treatment to control morbidity. Quantitative studies investigating the effects of frequency of treatments on morbidity in primary school children 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 pre-school children. In our recent studies funded by the Thrasher Research Fund, we have demonstrated that infected pre-school children already suffer morbidity attributable to schistosome infection (submitted), thus, it is important that current understanding of the progression of schistosome morbidity is recalibrated to reflect the previously unacknowledged earlier onset of morbidity in pre-school children [54].

Control/intervention methods

To meet the vision of schistosome elimination, it is clear that it will be necessary to make maximal effective use of already existing tools as well as develop additional tools. 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 (WASH) has recently been re-emphasised as pivotal to a sustained intervention for the control of schistosomiasis and soil transmitted helminths [56] while Knowledge, Attitudes and Practise (KAP) 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 hybridise with cattle schistosomes *S. bovis* and *S. currasoni* [59, 60], introduces a zoonotic feature to the transmission dynamics, and 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 are targeted at primary school children (http://clinicaltrials.gov/show/NCT008706490), this raises the potential of future vaccination excluding pre-school children which would continue the neglect of this age group. There is need for continued research 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 down regulate 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 vaccine is not novel, it forms the basis of successful veterinary parasite vaccines (e.g theileria) and proof or principle studies in human malaria (reviewed in [65]) suggest this to be a potential approach to successful parasite vaccine development as we recently highlighted [65]. The immunological aspects of PZQ treatment warrant further investigation for two additional reasons. First, to address any concerns of undesirable long-term effects in terms of human health (as alluded to by the hygiene hypothesis [66]) and second, to understand the long-term effects of PZQ treatment and consequences of 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 that pre-intervention level [67]. Continued monitoring and evaluation of MDA programmes and their effects on the schistosome population structure as is advocated by several stakeholders including the SCI who are funding our group to monitor and evaluate

Zimbabwe's MDA currently underway, is also vital for early detection of the development of drug resistance. This knowledge will allow long-term planning for the sustenance of schistosome MDA programmes.

Conclusion

Significant advances have been made at the policy and practical/operational level in the control of paediatric schistosomiasis. Investigations in pre-school children have laid a solid evidence base on the need, safety and efficacy of treatment with the antihelminthic drug PZQ in this age group. Currently, the inclusion of pre-school children in schistosome control programmes is slow, with most countries still targeting their MDA at primary school children. 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 pre-school children included in their MDA programmes. A child friendly paediatric formulation of PZQ and current scientific developments improving POC 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 have to continue to work towards delivering an integrated, inclusive, sustainable and globally implemented helminth control programme.

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Acknowledgements:
I am grateful to my colleagues and collaborators in the Understanding Bilharzia Project, Takafira Mduluza and Nicholas Midzi with whom we have conducted collaborative fieldwork to address some of the challenges in paediatric schistosomiasis, the participants in the field studies over the past 20 years and members of the National Institute for Health Research (Zimbabwe) and the University of Zimbabwe for technical support. I also thank my research group, the Parasite Immuno Epidemiology group at the University of Edinburgh for their useful comments on a draft of the manuscript. My final thanks go to Welcome Wami and Catriona Waugh at the University of Edinburgh who conducted the literature search and prepared the prevalence maps.

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List of Figures

Figure 1: Schistosome infection prevalence in pre-school children aged 5 years and under from studies published 1995-2014

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