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

Author: Francisca Mutapi, University of Edinburgh

Affiliations: Institute of Immunology and Infection, Research Centre for Immunity, Infection and Evolution, School of Biological Sciences, University of Edinburgh.

Address correspondence to: Francisca Mutapi (BSc, PhD), Institute of Immunology and Infection Research, Centre for Immunity, Infection and Evolution, School of Biological Sciences, Ashworth Laboratories, University of Edinburgh, Charlotte Auerbach Road, Edinburgh, EH9 3FL, United Kingdom. Email f.mutapi@ed.ac.uk, tel +441316508662.

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.

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1

2 **ABSTRACT**

3 Schistosomiasis is a chronic disease that affects approximately 200 million people. The
4 extended health impact of the disease has been estimated to exceed that of malaria or
5 tuberculosis, and be nearer to that of HIV/AIDS. Within endemic areas, children carry the
6 heaviest burden of infection. Infection/disease is controlled by treatment of infected people
7 with the antihelminthic drug praziquantel. Global initiatives from Partners of Parasite
8 Control, including the World Health Organization (WHO) advocate regular school-based de-
9 worming strategies in order to reduce development of severe morbidity, promote school-child
10 health and development as well as to improve the cognitive potential of the children. Until
11 recently pre-school children were excluded from schistosome treatment creating a health
12 inequity in affected populations. In 2010 the WHO updated their recommendations for the
13 treatment of schistosomiasis in pre-school children, i.e. children aged 5 years and under. This
14 was the culmination of several decades of research on schistosome epidemiology,
15 immunology and pathology in this age group. The recent development of a paediatric
16 formulation of PZQ, soon to enter clinical trials should progress the control efforts in pre-
17 school children, with the vision of seeing these children included in preventative
18 chemotherapy as currently occurs for soil transmitted helminths. This review discusses the
19 research work underpinning the WHO revision of recommendations for treating pre-school
20 children as well as current barriers and knowledge gaps in paediatric schistosomiasis control.

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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 than 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

1 which only the *laevo* isomer is active against schistosomes [13]. The pharmacokinetics have
2 not been studied in children aged 4 years and below, but studies in adults show that PZQ is
3 rapidly absorbed from the gastrointestinal tract so that maximal levels in human plasma occur
4 within 1 to 2 hours of administration and the drug has a half-life of ~ 0.8 to 1.5 hours in adults
5 with normal renal and liver function [14]. It is taken as a single dose of 40 or 60mg/kg body
6 weight. The mode of action of PZQ is still to be fully described; however, the drug is thought
7 to cause muscle contraction in adult worms as a result of a Ca^{2+} influx and tegumental
8 damage [15]. The tegument damage exposes parasite antigens allowing immune attack of the
9 damaged worms by the already primed host immune system. Thus, PZQ acts synergistically
10 with the host immune system [9]. The drug is not effective against immature worms [14].
11 PZQ is efficacious with schistosome cure rates and egg reduction rates typically above 75%
12 (see review by Stothard and colleagues [3]) and we routinely achieve cure rates and egg
13 reduction rates above 90% in study populations in Zimbabwe [16, 17]. At the individual
14 level, the effects of PZQ include; (1) killing adult worms reducing infection intensity in the
15 host and the immediate health consequences of infection [18], 2) reversal of pathological
16 processes associated with the infection [19], 3) accelerating the development of schistosome-
17 specific acquired immunity [20, 21] which is protective against re-infection [22, 23] and, 4)
18 reducing pathology from subsequent re-infection [24]. At the population level, PZQ
19 treatment reduces transmission of the parasites [18]. PZQ is effective against trematodes
20 (including all schistosome species) and cestodes in humans [14]. From the pre-licencing
21 safety studies and numerous field studies [16, 25], PZQ treatment is considered safe and
22 efficacious. There are a few side effects including fatigue, urticaria, gastrointestinal and
23 abdominal pains, nausea, vomiting, headache and dizziness (see Biltricide© product sheet on
24 <http://www.bayerresources.com.au/resources/uploads/pi/file9318.pdf>) which are related to
25 infection intensity [16].

1

2 **Challenging the barriers to treatment.**

3 *Demonstrating exposure to infective water, infection and morbidity*

4 People become infected with schistosomes when they come into contact with infective water.

5 Infectivity of fresh water sources is demonstrated by the presence of patent snail intermediate

6 hosts of schistosomiasis (patency demonstrated by shedding the snails which allows the

7 infective cercariae to emerge from the snails). Exposure to infective water is usually measured

8 by quantifying the type, frequency and duration of contacts with infective water [26, 27].

9 This active exposure is low amongst pre-school children which resulted in their exposure

10 levels to infection being assumed to be low. Field studies have demonstrated that young

11 children do experience significant passive exposure to infective water [2, 6, 28]. Thus, direct

12 observation and questionnaires in exposure studies missed significant amounts of the

13 exposure behaviour in pre-school children. This was confirmed by studies using GPS logging

14 of water contact behaviour of children. [10]. Two decades ago we used serological and

15 quantitative investigations to study exposure to infective and adult stages of schistosome

16 parasites in young children [29]. Our studies indicated that 79% of children aged 4 months to

17 6 years showed evidence of exposure to schistosome infection [29]. In our recent studies the

18 youngest patient who tested positive for schistosome infection by parasite egg excretion was

19 6 months old. We and others have demonstrated that young children in several African

20 countries including Nigeria, Cote d'Ivoire, Kenya, Mali, Uganda and Zimbabwe are infected

21 with schistosomes [2, 17, 30-33] and in some areas their infection levels are as high as those

22 in their carers that were eligible for treatment, while the infected children remain untreated

23 for several years (see review [28]). Furthermore, the limited investigations describing and

24 quantifying morbidity in this age group have shown that the infections in the young children

25 are of clinical significance [34, 35]. Apart from the immediate effects of infection and disease

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

9 10 *Praziquantel in pre-school children: action, safety and efficacy*

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

21
22 Having established that there was no immunological reason to hinder with the action of PZQ
23 in young children, there still remained the lack of evidence on the safety and efficacy of PZQ
24 in this age group. Although PZQ could be prescribed on a case-by-case basis in young

1 children, there had not been studies on the safety of PZQ treatment of schistosomiasis
2 infection in children under 5 years of age with a view to include them in MDA programmes.
3 In 2008 the World Health Organisation funded 3 groups, including our own, to formally
4 conduct studies determining the safety, efficacy and acceptability of PZQ for the treatment of
5 *S. haematobium* and *S. mansoni* in pre-school children in Africa [40]. All studies tested the
6 tablet PZQ formulation and one study tested both the tablet and paediatric liquid formulation.
7 These studies concluded that PZQ treatment of children aged 6 months -5 years was safe and
8 efficacious[40]. Our own study showed that the pre-school children reported significantly
9 fewer side effects than in the primary school children[16, 17]. The fewer side effects were
10 unsurprising as these are related to the intensity of infection [41-43] and infection intensities
11 are lower in this age group than in primary school aged children. We reported cure rates and
12 egg reduction rates above 90% in pre-school children [17]. These results and those from the
13 other groups were reviewed at a WHO working group meeting which made the
14 recommendations detailed below. Furthermore, our results informed the formulation of
15 Zimbabwe's national schistosome and soil transmitted helminth control programme drafted
16 in 2012 [44], making it one of the first national helminth control policies to include pre-
17 school children. In terms of morbidity control, there is a paucity of studies in pre-school
18 children demonstrating the effects of PZQ treatment. We have just completed a three-year
19 study in this age group and our results show that treatment of pre-school children with PZQ
20 significantly reduces morbidity attributable to schistosome infection (submitted). Thus, at
21 policy level, the main hurdle to treating pre-school children was crossed by the demonstration
22 of the utility, efficacy and safety of PZQ treatment in pre-school age children in the
23 independent studies.

24
25 *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

1 endemic areas to review the results from these studies [40]. The findings and
2 recommendations from the WHO working group were a significant step in improving child
3 health and development in affected countries. In summary, the working group concluded that
4 both *S. mansoni* and *S. haematobium* presented a significant public health problem in pre-
5 school children aged 5 years and under. Furthermore, we also concluded that PZQ is
6 acceptable, safe and efficacious in this age group. Based on these considerations the working
7 group made the following recommendations published by the WHO in 2010 [40].

- 8
9 1. Pre-school-age children should be regarded as a high-risk group in areas endemic for
10 schistosomiasis; treatment should be made available to them through the regular
11 health services;
- 12 2. Administration of praziquantel to pre-school-age children should be included in
13 ongoing public health interventions such as the Expanded Programme on
14 Immunization (EPI) activities, Mother and Child Days, and Child Health Days;
- 15 3. In the absence of an appropriate paediatric formulation, broken or crushed tablets are
16 recommended for administration of praziquantel; development of a water dispersible
17 tablet for this age group is recommended[40].

18
19 Additionally, the working group called on the WHO to formally advocate the treatment of
20 this age group in areas where schistosomiasis is endemic, and for the WHO to call for
21 additional research to develop child friendly formulations of PZQ. Finally, the working group
22 made recommendations on operational issues. First, the PZQ dose pole for working out the
23 drug dosage used in the field would be a useful operational tool if it could be extended to
24 below 94 cm of height to incorporate the pre-school children. However, the pole had not been
25 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

1 There is still a need for information on the number, frequency and optimal timing of
2 treatment to control morbidity. Quantitative studies investigating the effects of frequency of
3 treatments on morbidity in primary school children indicated that early, and repeated
4 treatment is required to make a significant impact on stunting and malnutrition[54]. There
5 have been no such studies for the additional long-term schistosome –related morbidity such
6 as liver and bladder associated pathology, nor have there been any such studies in pre-school
7 children. In our recent studies funded by the Thrasher Research Fund, we have demonstrated
8 that infected pre-school children already suffer morbidity attributable to schistosome
9 infection (submitted), thus, it is important that current understanding of the progression of
10 schistosome morbidity is recalibrated to reflect the previously unacknowledged earlier onset
11 of morbidity in pre-school children [54].

13 *Control/intervention methods*

14 To meet the vision of schistosome elimination, it is clear that it will be necessary to make
15 maximal effective use of already existing tools as well as develop additional tools. Thus, in
16 addition to increasing accessibility to safe water, sanitation and health education, the 2012
17 WHO List of Research Priorities for Helminth Infections highlights the need for a concerted
18 effort to develop other interventions including molluscicides and vaccines [55]. The
19 important role of improved Water, Sanitation and Hygiene (WASH) has recently been re-
20 emphasised as pivotal to a sustained intervention for the control of schistosomiasis and soil
21 transmitted helminths [56] while Knowledge, Attitudes and Practise (KAP) studies[2, 57]
22 highlight the importance of education particularly of caregivers [58] to reduce their passive
23 exposure to infective water.

1 The demonstration that *S. haematobium*, the most prevalent human schistosome species in
2 Africa can hybridise with cattle schistosomes *S. bovis* and *S. curraioni* [59, 60], introduces a
3 zoonotic feature to the transmission dynamics, and presents the potential for schistosome
4 infection animal reservoirs maintaining transmission and compounding control efforts reliant
5 predominantly on human chemotherapy.

6 Current Phase III clinical trials of the leading schistosome vaccine candidate are targeted at
7 primary school children (<http://clinicaltrials.gov/show/NCT008706490>), this raises the
8 potential of future vaccination excluding pre-school children which would continue the
9 neglect of this age group. There is need for continued research on the action of PZQ,
10 particularly its ability to induce immune responses protective against re-infection [20, 21, 23,
11 61, 62] as well as an immune phenotype that can down regulate future pathology [24]. Our
12 studies and those of others continue to investigate the mechanistic pathways underlying the
13 potential ‘vaccinating’ effect of PZQ [20, 61, 63, 64]. The concept of an infection-treatment
14 vaccine is not novel, it forms the basis of successful veterinary parasite vaccines (e.g
15 theileria) and proof of principle studies in human malaria (reviewed in [65]) suggest this to be
16 a potential approach to successful parasite vaccine development as we recently highlighted
17 [65]. The immunological aspects of PZQ treatment warrant further investigation for two
18 additional reasons. First, to address any concerns of undesirable long-term effects in terms of
19 human health (as alluded to by the hygiene hypothesis [66]) and second, to understand the
20 long-term effects of PZQ treatment and consequences of cessation of MDA. Though
21 quantitative studies, we recently illustrated that due to detrimental effects on the development
22 of protective immunity, cessation of MDA under certain conditions, could result in infection
23 levels higher than pre-intervention level [67]. Continued monitoring and evaluation of MDA
24 programmes and their effects on the schistosome population structure as is advocated by
25 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.

1

2

1

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12

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2 **List of Figures**

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

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

***S. haematobium* prevalence (%)**

***S. mansoni* prevalence (%)**