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## Comparative Assessment of Health Benefits of Praziquantel Treatment of Urogenital Schistosomiasis in Preschool and Primary School-Aged Children

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1 **Comparative Assessment of Health Benefits of Praziquantel Treatment of Urogenital**  
2 **Schistosomiasis in Preschool and Primary School-Aged Children**

3 *Welcome M. Wami<sup>1,2\*</sup>, Norman Nausch<sup>1,2#a</sup>, Nicholas Midzi<sup>3</sup>, Reggis Gwisai<sup>4</sup>, Takafira*  
4 *Mduluza<sup>5,6</sup>, Mark E.J. Woolhouse<sup>2</sup>, Francisca Mutapi<sup>1,2</sup>*

5 <sup>1</sup>Institute of Immunology and Infection Research, School of Biological Sciences, University  
6 of Edinburgh, Edinburgh, UK

7 <sup>2</sup>Centre for Immunity, Infection and Evolution, School of Biological Sciences, University of  
8 Edinburgh, Edinburgh, UK

9 <sup>3</sup>Department of Medical Microbiology, College of Health Sciences, University of Zimbabwe,  
10 Harare, Zimbabwe

11 <sup>4</sup>Ministry of Health and Child Care, Murewa District Hospital, Murewa, Zimbabwe

12 <sup>5</sup>Department of Biochemistry, University of Zimbabwe, Harare, Zimbabwe

13 <sup>6</sup>School of Laboratory Medicine and Medical Sciences, University of KwaZulu-Natal,  
14 Durban, South Africa

15 **\*Corresponding author:** Welcome Mkululi Wami, Institute of Immunology & Infection  
16 Research, University of Edinburgh, Ashworth Laboratories, King's Buildings, West Mains  
17 Rd, Edinburgh, EH9 3JT  
18 E-mail: [wwami2002@yahoo.com](mailto:wwami2002@yahoo.com)

19 <sup>#a</sup>**Current address:** Pediatric Pneumology and Infectious Diseases Group, Department of  
20 General Pediatrics, Neonatology and Pediatric Cardiology, University Children's Hospital,  
21 Duesseldorf, Germany

## 22 **Abstract**

23 Schistosomiasis is a major public health problem in Africa. However, it is only recently that  
24 the burden of schistosomiasis has become recognised as a significant component impacting on  
25 the health, wellbeing and development of infants and preschool children (aged  $\leq 5$  years). A  
26 longitudinal study was conducted in Zimbabwean children to determine the effect of single  
27 praziquantel treatment on *Schistosoma haematobium*-related morbidity markers:  
28 microhaematuria, proteinuria, and albuminuria. Changes in these indicators were compared in  
29 1–5 years *versus* 6–10 years old to determine if treatment outcomes differed by age-group.  
30 Praziquantel was efficacious at reducing infection 12 weeks post-treatment: cure rate=94.6%;  
31 (95% CI: 87.9–97.7%). Infection rates remained lower 12 months post-treatment compared to  
32 baseline in both age-groups. Among children who received praziquantel, the odds of presenting  
33 with two markers of morbidity 12 weeks post-treatment were significantly lower compared to  
34 baseline; proteinuria: odds ratio, OR=0.54; (95% CI: 0.31–0.95), and albuminuria: OR=0.05;  
35 (95% CI: 0.02–0.14). Levels of microhaematuria significantly reduced 12 months post-  
36 treatment, and the effect of praziquantel did not differ between the two age-groups: OR=0.97;  
37 (95% CI: 0.50–1.87). Praziquantel treatment has health benefits in preschool-aged children  
38 exposed to *S. haematobium* and the efficacy of praziquantel on infection and morbidity is not  
39 age-dependent.

## 40 **1. Introduction**

41 Urogenital schistosomiasis, caused by the water-borne parasitic helminth *Schistosoma*  
42 *haematobium*, is an important but neglected tropical disease in Africa [1-3]. The disease causes  
43 significant paediatric health problems in endemic regions, with negative impacts on child  
44 health and development. In *S. haematobium* infections, damage caused by the parasite eggs  
45 lodged in tissues or exiting the body via the urine can result in bladder or urinary tract  
46 pathology, often characterized by blood in urine (macro- or microhaematuria), painful urination  
47 (dysuria) and proteinuria [4, 5]. High levels of albumin in urine have also been shown to be  
48 strongly correlated with urinary tract pathology due to *S. haematobium* infection [6]. Chronic  
49 infection with schistosomes in children is associated with complications such as anaemia,  
50 malnutrition, growth retardation, reduced physical fitness, and impaired memory and cognition  
51 [7, 8]. Infection and morbidity are controlled by treatment of infected individuals with the  
52 antihelminthic drug, praziquantel (PZQ) [9, 10]. Delayed or a lack of intervention can result in  
53 more severe and irreversible forms of morbidity including urinary bladder cancer (squamous  
54 cell carcinoma) and chronic kidney disease, which may eventually result in death [11-13].

55 In several countries implementing schistosomiasis control programmes, the control strategies  
56 follow the directive by the World Health Assembly resolutions (WHA 54.19 and WHA 65.21)  
57 in 2001 [9], involving regular school based de-worming using PZQ, aimed at reducing  
58 morbidity and promoting child health. However, a growing number of studies from Africa have  
59 shown that preschool children (aged  $\leq 5$  years old) are also at high risk of schistosomiasis  
60 through passive exposure to infection whilst being bathed with infested water [14-18].  
61 Furthermore, recent studies have also shown that PZQ treatment of schistosome infection is  
62 safe in preschool children [16, 19]. These findings have led to a new major recommendation  
63 by the World Health Organization (WHO) in 2010, stating that preschool-aged children should  
64 be considered for treatment through the regular health services as well as in ongoing public

65 health intervention programmes [20]. This recent development in schistosomiasis control  
66 policy has heightened the need for a clear understanding on the health benefits of PZQ beyond  
67 the immediate reduction in infection levels in preschool-aged children in order to improve the  
68 effectiveness of interventions targeting this age group [21].

69 In a previous study in this population, we showed that, based on attributable fractions,  
70 albuminuria measured as the urine albumin-to-creatinine ratio (UACR) was the most reliable  
71 tool for detecting schistosome-related morbidity, followed by proteinuria and microhaematuria  
72 determined by dipsticks, visual urine inspection, questionnaires, and lastly clinical examination  
73 [22]. Thus, in this current study we focused on albuminuria, proteinuria and microhaematuria.  
74 The aim of this study was to evaluate the immediate health benefits of PZQ in preschool-aged  
75 (1–5 years) children endemically exposed to *S. haematobium* at 12 weeks post-treatment, and  
76 to determine if a single dose of PZQ (40 mg/kg) has sustainable impact on the health status of  
77 these children by assessing changes in infection rates and levels of schistosome-related  
78 morbidity markers (microhaematuria, proteinuria and albuminuria) 12 months after treatment.  
79 Furthermore, we sought to determine whether the impact of PZQ treatment outcome is age-  
80 dependent by comparing these indicators in preschool and primary school-aged (6–10 years)  
81 children in the same population. The findings of our present study provide an operational  
82 recommendation for future studies on the control of paediatric schistosomiasis, whilst also  
83 giving further insights into the health benefits of antihelminthic treatment in preschool-aged  
84 children.

## 85 **2. Materials and Methods**

### 86 **2.1 Ethics Statement and Consent**

87 Prior to commencing the study, ethical clearance was obtained from the Medical Research  
88 Council of Zimbabwe (Approval Reference: MRCZ/A/1615). In addition, the study received  
89 institutional approval from the University of Zimbabwe. Permission to conduct the study was  
90 obtained from the Provincial Medical Director, the District Educational Officer, and heads of  
91 schools in the study area. Study objectives and procedures were fully explained to the  
92 community, parents/guardians, teachers, and primary school-aged children in the local  
93 language, Shona. Samples were collected only after obtaining informed written parental  
94 consent and study participants' oral assent. Participants were permitted to withdraw from the  
95 study at any point without further obligation.

### 96 **2.2 Study Site**

97 The study was undertaken in Murewa district, in the north-east of Zimbabwe (31°90'E;  
98 17°63'S) where *S. haematobium* is endemic. The area has low transmission of *S. mansoni* and  
99 soil-transmitted helminths (STH) as previously reported in other studies [23, 24]. In a nation-  
100 wide survey among school-aged children in 2010 in Zimbabwe, Midzi *et al* [25] reported a  
101 schistosomiasis prevalence of 31.2% in Murewa district based on parasitological diagnostic  
102 methods. To confirm this reported level of schistosome infection in the community in our study  
103 site, we initially conducted a pilot study among primary school-going children (aged 6–10  
104 years old) as per sampling guidelines and recommendations by the WHO [26, 27]. A random  
105 sample of 50 compliant children from the two schools in the study area (25 from each school)  
106 was screened for schistosome infections by parasitology. Children found positive for infection  
107 during the pilot survey were treated with the recommended single dose of PZQ (40 mg/kg), but  
108 were then ineligible for participation in the main study.

### 109 **2.3 Study Design and Population**

110 The longitudinal study was designed to relate changes in the levels of infection and markers of  
111 schistosome-related morbidity to the two age groups of children (1–5 years vs. 6–10 years)  
112 conducted over a period of 12 months. There were two aspects to the longitudinal study design  
113 investigating; (i) the short term effects of PZQ treatment which measured the morbidity  
114 markers and infection levels before treatment/baseline (February–March 2012) and 12 weeks  
115 (May 2012) after treatment ; the workflow for this aspect of the study is shown in Figure 1a  
116 and, (ii) the longer-term effects of PZQ treatment which measured the morbidity markers and  
117 infection levels before treatment and 12 months (March 2013) after treatment; the workflow  
118 for this aspect of the study is shown in Figure 1b. The 388 children who received treatment at  
119 baseline (Figures 1a/b) participated in both aspects of the study, so that the 303 children whose  
120 infection status was confirmed egg negative at the 12 weeks efficacy check survey formed the  
121 treated cohort for follow up at 12 months (Figure 1b). Untreated children (Figure 1a) were not  
122 followed up beyond 12 weeks. Children were recruited from two primary schools (typically for  
123 6–10 years olds) and the early childhood development centres (ECDs) for preschool-aged  
124 children located within each of the primary schools. The schools also served as recruitment  
125 centres for children aged between 1–5 years not enrolled in any of the educational programmes  
126 in the study area who were also invited for enrolment to participate in this study. The villages  
127 within the study sites share the same river systems, therefore the transmission dynamics in the  
128 two schools (and associated ECDs) were similar.

### 129 **2.4 Screening and Follow-up Criteria**

130 In order to be included in this study at baseline, children had to meet the following criteria: (i)  
131 had been life-long (i.e., permanent) residents of the study area, (ii) had no prior history of  
132 antihelminthic treatment (assessed by questionnaires administered to parents/guardians of all  
133 children), and (iii) had provided at least two urine samples collected on consecutive days for

134 the parasitological diagnosis of *S. haematobium* infection. For potential exclusion, children  
135 were assessed to identify: (i) pre-existing medical conditions or clinical symptoms of  
136 tuberculosis, any form of fever, or other signs of being unwell upon examination by study  
137 clinicians, (ii) recent major operation or illness as reported by parents/guardians, and (iii)  
138 infection with any of STHs or *S. mansoni*. No soil transmitted helminth infections were  
139 detected in this study cohort and 27 children positive for *S. mansoni* were offered PZQ treated  
140 but excluded based on this criterion. Participating children that were found egg-positive for *S.*  
141 *haematobium* at the 12 week efficacy check were treated with 40 mg/kg praziquantel but  
142 excluded from further follow-up to ensure that in addition to new infections, only ‘true’ re-  
143 infection was measured. Children who met the eligibility criteria, with informed consent, but  
144 would not accept treatment on religious grounds, or were absent on treatment survey days but  
145 voluntarily remained in our study cohort at 12 weeks effectively became untreated controls for  
146 evaluating the effect of treatment on schistosome-related morbidity markers. At the end of the  
147 study (12 months), PZQ treatment was offered to all children diagnosed egg positive for  
148 infection.

## 149 **2.5 Parasitological Methods**

150 At all survey time points, urine samples were collected on three consecutive days for  
151 parasitological examinations. *S. haematobium* infection was detected by microscopic  
152 examination of the parasite eggs in urine, processed using the standard urine filtration method  
153 [28]. For each child, infection intensity was expressed as the arithmetic mean of egg counts per  
154 10 mL urine of samples collected on consecutive days. At least two stool samples were also  
155 collected over three consecutive days, processed using the Kato-Katz method [29], and  
156 subsequently examined by microscopy for the diagnosis of *S. mansoni*. In a previous study we  
157 also determined the infection status of the children by serology, details of this methodology are  
158 described elsewhere [30].



159 **2.6 Assessment of Morbidity Markers**

160 Three urinary markers; microhaematuria, proteinuria and albuminuria identified in our earlier  
161 published study [22] were chosen for investigating the effect of PZQ treatment on schistosome-  
162 related morbidity in this present study. Urine samples collected between 10:00h and 14:00h  
163 and processed on the first day of each survey time point were examined for microhaematuria  
164 and proteinuria, detected by dipstick reagent strip test (Uripath, Plasmatec, UK). Briefly, the  
165 reagent end of the test strip was dipped into fresh, well-mixed urine for 40 seconds. Upon  
166 removal, the test area was compared with a standard colour chart following the manufacturer's  
167 guidelines and the dipstick test results were calibrated as either positive or negative. To assess  
168 the stability of dipstick urinalysis [31], repeated tests (at least two repetitions) were performed  
169 on a random sample (n=189) of urine specimens, allowing for time delay of up to 5 minutes  
170 between each of the repeated readings. There were no marked differences observed between  
171 repeated tests to suggest potential instabilities of urinalysis due to delays in dipstick testing.  
172 No observer bias was suggested by the urinalysis results when comparing the visually recorded  
173 dipstick readings to those read automatically using Siemens' CLINITEK Status + Analyzer  
174 (Bayer, UK). CLINITEK Microalbumin Reagent Strips (Bayer, UK) were used to determine  
175 the urine albumin-to-creatinine ratio (UACR) threshold levels (normal:  $UACR < 3.4$  mg/mmol,  
176 abnormal:  $UACR \geq 3.4$  mg/mmol, or high abnormal:  $UACR \geq 33.9$  mg/mmol), as read from the  
177 instrument following the manufacturer's guidelines. For each child, albuminuria as a marker  
178 of schistosome-related morbidity associated with urinary tract pathology was defined as a  
179 positive test for high abnormal UACR in each of the fresh urine samples examined [4].

## 180 **2.7 Praziquantel Treatment**

181 After collection of samples at baseline, compliant children were offered treatment with PZQ at  
182 the standard oral dosage of 40 mg/kg body weight. The PZQ drug was procured from  
183 Pharmaceutical and Chemical Distributors (Pvt) Ltd., Harare, Zimbabwe, a company registered  
184 and licensed to sell the antihelminthic drug in Zimbabwe. The tablets were swallowed with  
185 squash juice to reduce their bitter taste and a slice of bread to reduce the side effects of PZQ  
186 [16, 32]. For the very young children, the tablets were crushed according to the current  
187 recommendation by the WHO [20].

## 188 **2.8 Sample Size Calculations**

189 The relationship between schistosomiasis infection levels and indicators of morbidity is still  
190 unclear. We thus based our sample size calculations under the expectations that PZQ treatment  
191 reduces re-infection rates by more than 50% after 12 months. These expected effects are  
192 consistent with data from previous studies [16, 25], and are of sufficient magnitude to be of  
193 practical interest. Allowing for dropouts, our simulation studies using StatXact v.8 (Cytel  
194 Software Corp, Cambridge, MA, USA) indicated that the sample sizes shown in Figures 1a and  
195 1b will give us more than 80% power to detect age-related and treatment-related differences  
196 with significance level,  $\alpha = 0.05$ .

## 197 **2.9 Data Management and Statistical Analysis**

198 Infection intensity was log-transformed:  $\log_{10}(\text{egg count} + 1)$  to meet the distributional  
199 assumptions of parametric test-statistics. Treatment efficacy against *S. haematobium* infection  
200 was assessed by means of cure rates (CR) and egg reduction rates (ERR), defined as: CR=  
201 (number of children *S. haematobium* egg-negative at 12 weeks post-treatment/ number of  
202 children confirmed egg-positive at baseline) X 100; ERR= (arithmetic mean egg count at  
203 baseline –arithmetic mean egg count at 12 weeks post-treatment/ arithmetic mean egg count at  
204 baseline) X 100. The 95% confidence intervals (95% CI) for the ERR were calculated using a

205 bootstrap resampling method with 1000 replicates in R 3.1.2 (R Development Core Team,  
206 Vienna, Austria), package="eggCounts". A Chi-square test ( $\chi^2$ ) or the Fisher's exact test in  
207 the case of small expected frequencies ( $n < 5$ ) was used for comparison of infection prevalence  
208 and cure rates between the two age groups. For infection intensity, a paired *t*-test was used to  
209 compare levels of infection pre- vs. post-treatment. For each of the three urinary markers of  
210 schistosome-related morbidity (microhaematuria, proteinuria, and albuminuria), the outcome  
211 of interest was a dichotomous variable indicating whether the child presented with morbidity  
212 or not at a given time point (morbidity: 0=negative; 1=positive). The main predictor variables  
213 included the host factors sex (male vs. female) and age group (1–5 years vs. 6–10 years),  
214 treatment group (untreated vs. PZQ treated) and time (pre- vs. post-treatment). To assess the  
215 effect of treatment (pre/post) on morbidity markers, we used the method of generalized linear  
216 mixed model (GLMM) with a random effect to account for the correlation between children  
217 recruited from the same primary school/ECD as described earlier. The model-building process  
218 involved backward stepwise inclusion of the main effect covariate terms and their two-way  
219 interactions. All statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary,  
220 NC, USA). The GLMMs were run using "PROC GLIMMIX" with a logit-link function to  
221 model the log odds of the probability of a child presenting with morbidity marker upon  
222 examination, and the parameter estimation was implemented using the method of penalized  
223 quasi-likelihood to account for over-dispersion [33]. Comparisons for the binary morbidity  
224 marker responses between different sub-groups of predictor variables were implemented using  
225 the contrast options within the "GLIMMIX" procedure. In all the analyses, multiple pairwise  
226 comparisons were adjusted for family-wise type I error using the less conservative (i.e. has low  
227 rate of false negatives) simulation-based approach [34]. The level of significance was set at  
228  $P < 0.05$  for all the statistical tests performed. To aid the interpretation of the relative effect of

229 treatment on infection levels and morbidity markers, standard errors (SE), 95% CI and adjusted  
230 odds ratios (OR) were presented along with the significance test statistics.

## 231 **3. Results**

### 232 **3.1 Demographic Characteristics and Pre-treatment Infection Levels**

233 Of the eligible children screened at baseline (see Figure 1a and Figure 1b), a total of 508  
234 children were included in the study, with 388 receiving PZQ treatment and 120 remaining  
235 untreated. Infection prevalence in the 508 children was 24.2% (95% CI: 20.5–28.0%), 6.7%  
236 (95% CI: 3.5–9.9%) in 1–5 year olds (n=239) and 39.8% (95% CI: 33.9–45.7%) in 6–10 year  
237 olds (n=269). In a subgroup of the 508 children, serological analysis showed that 63.0% (95%  
238 CI: 57.7–68.2%) of the children were seropositive for *S. haematobium* egg antigens, 39.8%  
239 (95% CI: 33.9–45.7%) were 1–5 year olds (n=131) and 79.1% (95% CI: 73.4–84.8%) were 6–  
240 10 year olds (n=201). The characteristics of the current study population are shown in Table 1.  
241 When considering the children treated at baseline and followed up at 12 weeks (n=303, Figure  
242 1a), the baseline infection prevalence determined by parasitology was 30.4% (95% CI: 25.2–  
243 35.6%) compared to 18.0% (95% CI: 8.1–28.0%) in the children who were not treated at  
244 baseline (n=61, Figure 1a) but voluntarily remained in the study at 12 weeks.

### 245 **3.2 Treatment Efficacy on Infection Levels at 12 weeks Post-treatment**

246 Twelve weeks after treatment, PZQ was efficacious at reducing *S. haematobium* infection  
247 among treated children in both age groups, as shown by high cure and egg reduction rates in  
248 Table 2. The overall cure and egg reduction rates in our study were 94.6%; (95% CI: 87.9–  
249 97.7%) and 97.9% (90.6–99.5%), respectively. There was no significant difference (Fisher's  
250 exact test,  $P=0.481$ ) in cure rates between the two age groups (1–5 years vs. 6–10 years) 12  
251 weeks after treatment shown in Table 2.

### 252 **3.3 Effect of Treatment on Infection/re-infection rates at 12 months Post-treatment**

253 Following initial treatment at baseline, children who had successful curative treatment were  
254 further followed-up to determine the re-infection rates and proportion of new infections 12

255 months after intervention. Table 3 shows the percentage proportion of treated children who  
256 were infected at baseline and then got re-infected (n=7) and those newly infected (n=11) within  
257 12 months following treatment. The infection prevalence 12 months after treatment was low  
258 (i.e. <10% according to WHO classifications) as shown in Table 3. Furthermore, the proportion  
259 of infected/re-infected children did not significantly differ ( $\chi^2=0.37$ ;  $P=0.542$ ) between the two  
260 age groups: 1–5 years, n=5: 6.3% (95% CI=2.7–13.8%) vs. 6–10 years, n=13: 8.5% (95% CI:  
261 4.8–14.4%). Similarly, the mean infection intensity level 12 months post-treatment  
262 (mean=0.74 egg/10 mL urine; SE=0.27) was significantly lower (paired  $t$ -test=-7.95;  $P<0.001$ )  
263 compared to the baseline level (mean=14.3 egg/10 mL urine; SE=4.63) in this study, with all  
264 egg-positive children carrying light infection intensities only.

### 265 **3.4 Effect of Treatment on Morbidity Markers at 12 weeks Post-treatment**

266 The effect of PZQ on levels of morbidity markers was assessed in those children that had  
267 successfully cleared the infection at 12 weeks. Praziquantel significantly reduced levels of  
268 proteinuria and albuminuria 12 weeks after treatment (Figure 2). In addition, the odds of  
269 children who received praziquantel presenting with each these markers of morbidity 12 weeks  
270 after treatment were lower compared to the odds before treatment, adjusting for sex and age  
271 group; proteinuria: OR=0.54; (95% CI: 0.31–0.95) and albuminuria: OR=0.05; (95% CI: 0.02–  
272 0.14). Furthermore, all the treated children aged 1–5 years successfully cleared albuminuria at  
273 12 weeks and a significant reduction from baseline was observed among the 6–10 year olds  
274 (Figure 2). A mild decrease in the levels of microhaematuria among the treated preschool-aged  
275 children was also observed, however, these changes were not significant. Changes from  
276 baseline in the levels of the three markers of schistosome-related morbidity in untreated  
277 children at 12 weeks were not significant (Figure 2). Furthermore, when evaluating the overall  
278 changes in morbidity markers among the treated group (pre- vs. post-treatment) compared to  
279 the changes in untreated children, it was observed that the odds of albuminuria were lower:

280 OR=0.43 (95% CI: 0.19–0.98;  $P=0.045$ ), adjusting for sex and age group.**3.5 Effect of**

### 281 **Treatment on Morbidity Markers at 12 months Post-treatment**

282 Following curative treatment of infection at 12 weeks, as assessed by parasitology, children  
283 were further followed-up and examined for morbidity at 12 months. Our analyses showed that  
284 when morbidity marker levels were investigated relative to baseline levels, microhaematuria  
285 significantly dropped in both age groups at 12 months after treatment (Figure 3). Furthermore,  
286 the results of GLMMs weighted by age-group sample sizes showed that the odds of treated  
287 children presenting with microhaematuria 12 months post-treatment did not significantly differ  
288 between 1–5 years *vs.* 6–10 years old children: OR=0.97; (95% CI: 0.50–1.87). In the case of  
289 proteinuria and albuminuria at 12 months, there was a significant reduction relative to baseline  
290 in the older age group, but not in 1–5 year olds (Figure 3). This was despite the initial reduction  
291 in albuminuria levels in this age group observed 12 weeks after treatment, as was shown in  
292 Figure 2.

## 293 4. Discussion

294 Praziquantel is currently the recommended antihelminthic drug of choice by the WHO for  
295 treating schistosomiasis, and is effective against all the major schistosome species infecting  
296 humans [9]. As of present, the health benefits of PZQ treatment in children aged 5 years and  
297 below has not yet been extensively evaluated. Thus, in this study we sought to determine if  
298 PZQ treatment improves the current health status of children aged 1–5 years old. The pre-  
299 treatment infection levels reported in this study confirmed that preschool-aged children are  
300 exposed to schistosome infection, in concurrence with findings from other recent studies [16,  
301 30], and further support the premise that if left untreated, these children are at an increased risk  
302 of developing severe morbidity that may cause serious health consequences and negatively  
303 impact their future quality of life [18, 35, 36]. In this study there were few children aged  
304 between 1 and 5 years who were excreting parasite eggs, but the prevalence of 6.7% is typical  
305 in this age group. More importantly, we and others [17, 30], have shown that the widely utilised  
306 egg count diagnostic method greatly underestimates infection prevalence in young children.  
307 Indeed, in a seroprevalence study of a subgroup of the 508 children in this group, the  
308 seropositive rate for *S. haematobium* egg antigen was 39.8% in 1–5 year olds. Thus, it is  
309 important to investigate the effects of treatment on other markers with health implications other  
310 than just the egg counts.

311 Our study results at 12 weeks after chemotherapy showed that a single standard dosage of PZQ  
312 was efficacious against *S. haematobium* infection in both 1–5 year olds and 6–10 year olds.  
313 The ranges of cure and egg reduction rates observed in this study for both age groups are  
314 consistent with data reported in the literature that have also shown high PZQ treatment efficacy  
315 within six weeks after treatment [16, 37, 38]. More interestingly, our study further revealed  
316 that PZQ treatment was effective in reducing *S. haematobium* infection levels in preschool-



317 aged children as was observed in their older counterparts (6–10 year olds), further supporting  
318 their inclusion in current schistosomiasis control programmes [20, 39].

319 Infection prevalence remained lower 12 months after treatment compared to baseline levels,  
320 and the proportion of infected/re-infected children did not significantly differ between the two  
321 age groups. In addition, our study showed significant reductions in mean *S. haematobium* egg  
322 counts 12 months after treatment compared to baseline. These results are in agreement with  
323 those of previous studies from different endemic areas that also reported a lower risk of *S.*  
324 *haematobium* re-infection after annual school-based treatment [40, 41], indicative of the benefit  
325 of treatment in the prevention of infection through reduced parasite transmission at population  
326 level [40]. This combination of findings on the benefits of PZQ chemotherapy against infection  
327 provides some strong support for the need for inclusion of preschool-aged children in ongoing  
328 schistosomiasis control programmes, in order to increase the effectiveness of coverage of those  
329 infected, also recently highlighted in a study by Garba *et al* [1].

330 Since schistosome-related morbidity is cumulative and progressive [42], decrease in current  
331 morbidity can reduce the long-term schistosomiasis sequelae. At 12 weeks after the first  
332 treatment, there was a significant decrease in the levels of the morbidity markers proteinuria  
333 and albuminuria in children successfully treated for infection. Interestingly, the effects of  
334 treatment were found not to be age-related, with microalbuminuria completely reversed in  
335 preschool-aged children at 12 weeks. The study also revealed that the prevalence of morbidity,  
336 diagnosed by presence microhaematuria, declined slowly, with a significant reduction observed  
337 after 12 months post-treatment. Our findings on the immediate health benefits of PZQ  
338 treatment were further reinforced by the results of the untreated group, showing no significant  
339 change in the levels of markers of schistosome-related morbidity at the 12 weeks follow-up.

340 The results showing persistently high levels of microhaematuria 12 weeks after treatment differ  
341 from some published studies that reported a considerable drop in microhaematuria within eight  
342 weeks after PZQ treatment [5, 43, 44]. However, most of these studies focused on older school-  
343 aged children who may have developed chronic infection. The high sensitivity of dipstick  
344 reagent strips in detecting microhaematuria, as previously reported [45], could also be one  
345 possible reason for these findings in our study. Another possible explanation for this delayed  
346 decrease in microhaematuria may be that most of the observed microhaematuria in these  
347 children may have likely been due to other health conditions other than schistosome infection.  
348 In an earlier study of this population we showed that the proportion of microhaematuria  
349 attributable to schistosome infection was less than that of albuminuria and proteinuria [22].  
350 These results therefore need to be interpreted with caution.

351 One of the main objectives of schistosomiasis control programmes in endemic areas is  
352 preventative chemotherapy to combat the development of severe morbidity [20]. Thus, more  
353 efforts are needed to ensure that the immediate health benefits of chemotherapy are sustained  
354 in the targeted populations for effective control [1]. The current study revealed that a single  
355 PZQ treatment had sustained effects on the reduction of schistosome-related morbidity, as  
356 indicated by the levels of urinary markers that remained low 12 months after treatment.  
357 Furthermore, it is interesting to note that both the preschool and primary-school age groups  
358 demonstrated improved health beneficial treatment effect in terms of reduced morbidity burden  
359 measured by microhaematuria 12 months following single treatment with PZQ. In view of the  
360 current observations showing no age-related differences in treatment efficacy, it is thus  
361 practically possible for control programmes in endemic areas targeting preschool-aged children  
362 to be implemented using the existing treatment strategies designated for school-aged children.  
363 Nevertheless, our study has limitations that must be considered when interpreting these results.  
364 Firstly, participation of the controls was on a voluntary basis for ethical reasons, hence leading

365 to a small sample size for this group. This could have introduced additional uncertainties in the  
366 levels of infection and schistosome-related morbidity markers leading to a potential bias in the  
367 effects of treatment reported in this study. To minimise the effects of this potential bias, a  
368 random effect was included in the statistical models to account for some of the uncertainty.  
369 Secondly, since the majority of the children carried light infections, the parasitological cure  
370 rates may have been overestimated. Nonetheless, it is reassuring that efficacy rates reported in  
371 our study were comparable with those observed from other previous epidemiological studies  
372 in the same age range [1, 16].

## 373 **5. Conclusions**

374 In this study, we have demonstrated that praziquantel treatment does not only effectively  
375 reduces *S. haematobium* infection levels, but also the levels of related morbidity in both  
376 preschool and primary school-aged children, with the reduction in some morbidity markers  
377 recorded within 12 weeks of treatment being sustained over a period of one year. In conclusion,  
378 praziquantel treatment has immediate health benefits in preschool-aged children exposed to *S.*  
379 *haematobium*, and the effects of praziquantel on infection and morbidity measures is not age  
380 dependent. These findings are important for practitioners, policy makers and stakeholders  
381 involved in the control of schistosomiasis and timely because of the current global drive to  
382 address the health inequity created by the paucity of information on the impact of praziquantel  
383 treatment on schistosome-related morbidity in children aged 5 years and below.

## 384 **Conflict of Interests Disclosure**

385 The authors declare that they have no competing interests.

## 386 **Authors' Contribution**

387 Conceived and designed the experiments: Francisca Mutapi, Nicholas Midzi, and Takafira  
388 Mduluzza. Performed the experiments, participated in the fieldwork, supported experiments,  
389 and contributed to draft manuscript editing/reviewing: Welcome Mkululi Wami, Norman  
390 Nausch, Nicholas Midzi, Reggis Gwisai, Takafira Mduluzza, Mark Woolhouse, and Francisca  
391 Mutapi. Statistical analyses of the data: Welcome Mkululi Wami, with inputs from Mark  
392 Woolhouse, and Francisca Mutapi. All authors contributed to the revisions and approved the  
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539 **List of Tables**

540 **Table 1: Demographic characteristics of the study cohort followed-up at 12 weeks and 12**  
 541 **months post-treatment with complete parasitology data for *S. haematobium* infection.**

Variable	Characteristic	Treated group		Untreated controls <sup>a</sup>
		Baseline/12 weeks	12 months	Baseline/12 weeks
Sample size	n	303	233	61
Sex	M/F	142/161	108/125	29/32
Age (years)	Mean age (range)	6.6 (1–10)	6.9 (1–10)	4.9 (1–10)
	Median	6	7	5
Age group, n (%)	1–5 years	109 (36%)	80 (34%)	40 (66%)
	6–10 years	194 (64%)	153 (66%)	21 (34%)

542 <sup>a</sup>The data on voluntary untreated controls was only collected at baseline and 12 weeks follow-  
 543 up surveys.

544 **Table 2: Treatment efficacy of a single dose of praziquantel (40 mg/kg) against *S. haematobium* infection by age group at 12 weeks post-**  
 545 **treatment.** SE=standard error; CR=cure rate; ERR=egg reduction rate, with 95% confidence intervals (95% CI).

Age group	Baseline (pre-treatment)			12 weeks post-treatment		Treatment efficacy	
	Number screened and treated	Number diagnosed positive	Mean egg count (SE)	Number of cases cured	Mean egg count (SE)	CR (95% CI)	ERR <sup>a</sup> (95% CI)
1–5 years	109	8	2.7 (1.79)	8	0.0 (–)	100.0% (67.7–100.0%)	100.0% (–)
6–10 years	194	84	28.8 (8.40)	79	0.6 (0.45)	94.0% (86.8–97.4%)	97.9% (89.9–99.5%)

546 <sup>a</sup>The 95% confidence intervals for the ERRs were calculated using a bootstrap resampling method with 1000 replicates.

547 **Table 3: Levels of *S. haematobium* re-infection and new infection rates among treated**  
 548 **children in the study 12 months following treatment with as single dose of 40 mg/kg**  
 549 **praziquantel.** Percentage proportions, with 95% confidence intervals (95% CI) of children  
 550 infected with *S. haematobium* detected by parasitology.

		<b>12 months post-treatment <i>S. haematobium</i> infection/re-infection rate</b>	
<b>Infection group</b>	<b>Sample size (n)</b>	<b>Number egg-positive</b>	<b>Prevalence (95% CI)</b>
Re-infections <sup>a</sup>	76	7	9.2% (4.5–17.8%)
New infections <sup>b</sup>	157	11	7.0% (4.0–12.1%)

551 <sup>a</sup>Egg-positive at baseline and re-infected 12 months after treatment.

552 <sup>b</sup>Uninfected at baseline, and found egg-positive 12 months after treatment.

553 **List of Figure Legends**

554 **Figure 1a: Study design flowchart showing the number of children included for the final**  
555 **analysis to assess the effect of praziquantel treatment efficacy 12 weeks after treatment.**

556 Participants who preferred not to receive treatment but voluntarily remained in the study at 12  
557 weeks were utilised as untreated controls.

558 **Figure 1b: Study design flowchart to assess the effect of praziquantel 12 months after**  
559 **treatment.**

560 **Figure 2: Effect of praziquantel (PZQ) treatment on the levels of urinary markers of**  
561 **schistosome-related morbidity 12 weeks after treatment.** (A) Microhaematuria, (B)  
562 Proteinuria, and (C) Albuminuria. The error bars indicate the 95% confidence intervals. The  
563 *P*-values for pairwise comparisons are from generalized linear mixed models investigating the  
564 probability of a child presenting with morbidity marker pre- vs. post-treatment adjusted for sex  
565 and age group. Significant *P*-values are highlighted in bold. \*Contrast *P*-value determined  
566 using the Binomial exact test.

567 **Figure 3: Effect of praziquantel treatment on levels of urinary markers of schistosome-**  
568 **related morbidity 12 months post-treatment.** (A) Microhaematuria, (B) Proteinuria, and (C)  
569 Albuminuria. Error bars indicate 95% CI and the *P*-values for pairwise comparisons are from  
570 the generalized linear mixed models investigating the probability of a child presenting with  
571 morbidity markers pre- and post-treatment, adjusted for sex and age group. Significant *P*-  
572 values are highlighted in bold.