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Schistosoma haematobium Treatment in 1–5 Year Old Children: Safety and Efficacy of the Antihelminthic Drug Praziquantel

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Abstract

Background: Morbidity due to schistosomiasis is currently controlled by treatment of schistosome infected people with the antihelminthic drug praziquantel (PZQ). Children aged up to 5 years are currently excluded from schistosome control programmes largely due to the lack of PZQ safety data in this age group. This study investigated the safety and efficacy of PZQ treatment in such children.

Methods: Zimbabwean children aged 1–5 years (n = 104) were treated with PZQ tablets and side effects were assessed by questionnaire administered to their caregivers within 24 hours of taking PZQ. Treatment efficacy was determined 6 weeks after PZQ administration through schistosome egg counts in urine. The change in infection levels in the children 1–5 years old (n = 100) was compared to that in 6–10 year old children (n = 435).

Principal Findings: Pre-treatment S. haematobium infection intensity in 1–5 year olds was 14.6 eggs/10 ml urine and prevalence was 21%. Of the 104 children, 3.8% reported side effects within 24 hours of taking PZQ treatment. These were stomach ache, loss of appetite, lethargy and inflammation of the face and body. PZQ treatment significantly reduced schistosome infection levels in 1–5 year olds with an egg reduction rate (ERR) of 99% and cure rate (CR) of 92%. This was comparable to the efficacy of praziquantel in 6–10 year olds where ERR was 96% and CR was 67%.

Interpretation/Significance: PZQ treatment is as safe and efficacious in children aged 1–5 years as it is in older children aged 6–10 years in whom PZQ is the drug of choice for control of schistosome infections.

Introduction

Classified among the neglected tropical diseases, urogenital schistosomiasis (bilharzia), remains one of the most prevalent parasitic diseases in the tropical and subtropical countries, constituting a major public health problem. The disease is caused by the helminth parasite Schistosoma haematobium and is the most prevalent form of schistosomiasis in Africa and the Middle East affecting approximately 107 million people. In affected populations, children carry the heaviest burden of infection [1,2] and in young children, urogenital schistosomiasis causes haematuria, dysuria, nutritional deficiencies, anaemia, growth retardation, decreased physical performance and impaired memory and cognition [3,4,5,6,7].

Control of schistosome infections is through treatment of infected people with a single dose of the anti-helminthic drug praziquantel which is safe, highly efficacious, cheap (costing less than US$0.50/dose) and can reverse schistosome-related morbidity particularly in the early stages of disease progression [8]. Current schistosome control programmes advocated by the World Health Assembly in 2001 through resolution 54/19's recommend regular de-worming of school aged children at risk of infection (http://www.who.int/infpr-2001/en/pr2001WHA-6.html), but exclude pre-school children i.e. children aged 5 years and below due to the belief that these children are not sufficiently exposed to infective water to experience high infection rates [9] which would lead to the clinical manifestation of disease and the lack of safety data on praziquantel in this age group [10]. However, several studies have now shown prevalent schistosome infection (as much as 100% in some areas) and morbidity of African children below the age of 5 [11,12,13,14]. Thus these children are both at risk of infection and a potential reservoir for the parasite in communities successfully targeted by...
mass anti-helminthic treatment. These findings have led to a growing number of calls to include pre-school children and infants in schistosome-control programmes [9,11,13,15]. We have previously assessed the side effects reported following PZQ treatment of Zimbabwean school children exposed to S. haematobium aged 6 years and above [16]. However, there have not been any studies on the safety of PZQ treatment of S. haematobium infections in children aged below 5 years of age. Furthermore, given that PZQ works synergistically with the host immune system to kill the worms, the efficacy of the drug in young children whose immune system might differ from older children may be lower. Therefore the present study assesses the safety of PZQ treatment in preschool children (aged 1–5 years) and to subsequently assess the safety and efficacy of the drug praziquantel in this age group. This study confirmed that preschool children carry significant levels of schistosome infection, exceeding those carried by their parents/guardians, highlighting the urgent need for their immediate inclusion in schistosome control programmes. The study also showed that praziquantel treatment is as safe and efficacious in children aged 1–5 years as it is in older children aged 6–10 years who are currently the target for mass drug administration.

Ethical statement

Permission to conduct the study in the region was obtained from the Provincial Medical Director. Institutional and ethical approval was received from the University of Zimbabwe and the Medical Research Council of Zimbabwe respectively. In addition, the study received ethical approval from the World Health Organization’s Research Ethics Review Committee. At the beginning of the study, parents and guardians of participating children had the aims and procedures of the project explained fully in the local language, Shona, and written consent was obtained from participants’ parents/guardians before enrolment into the study. After collection of all samples, all compliant participants (children under 5 years of age, older children (6 years and above) and all parents/guardians) were offered anti-helminthic treatment with the recommended dose of praziquantel (40 mg/kg of body weight).

Case-history questionnaires

At enrolment into the study, the parents/guardians of the children (1–3 years old) were asked 30 questions on behalf of the child recording demographic information, general socio-economic indicators, access to health care, general self-reported health conditions, water contact behaviours and general awareness and knowledge on schistosome infection. Questionnaires were administered in Shona by a trained team member. The questionnaire responses on the current health status of the child and the clinical assessment of the nursing staff informed on the suitability of the child to partake in the study.

Sample collection, PZQ treatment and assessment of side effects

Stool and urine specimens were collected from each participant on 3 consecutive days and processed using microscopic examination of urine samples for S. haematobium following urine filtration [19], and microscopic examination of stool samples for S. mansoni and geo-helmints following the Kato Katz technique [20]. The formol-ether concentration method was performed as previously described [2;21] on a random sample of 25% of the stool samples to confirm results obtained by the Kato-Katz technique. For infants, samples were collected overnight if it was not possible to collect a sample on the spot. After collection of the parasitology samples, participants (children and their guardians/parents) were offered treatment with the standard dose of praziquantel, i.e. 40 mg/kg body weight. Dose was determined for all children by weighing and the weight measure was rounded off to the nearest kg to determine the dose for each child and where necessary, tablets were broken in half or quarters to make up the appropriate dose. Irrespective of infection status, all compliant participants (parents/guardians and children) were treated with praziquantel tablets obtained from the IDA Foundation (http://www.idafoundation.org/, catalogue number 13200; 6600 mg/tablet). This was in keeping with mass drug administration practices during the investigative epidemiological surveys. For children aged 5 years and below, tablets were crushed using spoons and administered by the parent/guardian under supervision of one of the research teams. The tablets were taken with juice. Acceptability of the tablet was assessed directly during PZQ drug administration. A child would be recorded as not accepting drug administration if he/she spat, choked or vomited the drug. All treated people were given bread to eat after antihelminthic treatment. Parents/guardians were encouraged to remain at the treatment centre for 1 hour after administering the medication to assess if the PZQ treatment had immediate side effects and to determine whether the medication was lost through vomiting by the
participants. Parents/guardians reported back 24 hours after PZQ
treatment (preferably with the child) to answer a questionnaire with
9 questions on side effects following PZQ administration (i.e. not
present when PZQ was initially administered). Participants who
would not accept treatment on religious grounds or were absent
from school on treatment days but wished to remain part of the
study cohort effectively became untreated controls.

Inclusion and exclusion criteria
In order to be included in the PZQ safety study, participants
had to meet all the following criteria: 1) be aged 1–5 years at
recruitment, 2) had been resident in the study area since birth, 3)
had provided at least two urine and two stool samples on
consecutive days, 4) be negative for intestinal helminths and S.
mansoni (no one was excluded on this criteria as everyone was
negative for these infections as is reported in other parts of
Zimbabwe [22]), 5) have successfully taken the PZQ tablets
prescribed to them and, 6) parents/guardians had provided
answers to the 24 hour post-treatment side effects questionnaire.
104 participants met these criteria and were included in the PZQ
safety study. To be included in the treatment efficacy study, the
children had to meet criteria 2–4 above. In addition they had to
have been offered PZQ treatment if present on treatment days and
had provided at least 2 urine and 2 stool samples on
consecutive days, 6 weeks after treatment with PZQ. For both studies, children
were excluded if the parents/guardians/child themselves (in
the case of older children) reported a pre-existing illness or if they
were suffering from a fever as assessed by clinical examination by
the nursing staff. 100 children aged 1–5 years of age met this
criteria (72 treated with PZQ, 28 untreated) and 435 children aged
6–10 years old (355 treated with PZQ and 80 untreated). The
larger sample size of 6–10 year olds reflects the school-based
recruitment design of the study.

Statistical analysis
Statistical tests using the statistical package in PASW (formerly
SPSS) were used to test two hypotheses (1) PZQ treatment
significantly reduces infection levels and (2) PZQ efficacy rates in
1–5 year olds are similar to those in 6–10 year olds. The effect of
treatment on infection prevalence levels for the whole study
group was tested using a logistic regression approach with
variables selected using the forward stepwise conditional method
[23]. The dependent variable was infection status 6 weeks after
(treatment (infected vs. uninfected) while the independent
variables were pre-treatment infection intensity (log 10(x
+1) transformed), sex (male vs. female), age group (group 1 (1–5
years old) vs. group 2 (6–10 years old)), treatment status (PZQ
treated vs. untreated) and the interaction between age group and
treatment status. The model passed the Hosmer and Lemeshaw
goodness of fit test [23]. Infection prevalences between age
groups and infection status were compared using a one-tailed chi-
squared test with 95% CI calculated using a Binomial
distribution.

Infection intensity was compared using repeated measures
ANOVA. For this analysis, the dependent variable infection
intensity was log10(x+1) transformed, the independent variables
which were all categorical were sex (male, female) age group (two
groups, group 1 = 1–5 years, group 2 = 6–10 years), treatment
(1 = untreated, 2 = PZQ treated). Potential confounding effects of
sex and village were allowed for by using sequential sums of
squares with these two variables entered first and second in the
model. The interaction between age-group and treatment was also
tested to determine if the effect of treatment varied depending on
age group. Test statistics were taken as significant at p≤0.05. Post-
hoc paired T-tests were conducted to determine differences in
infection levels between the time points (pre-treatment vs. 6 weeks
post-treatment).

Results
Study area infection intensity
The children came from 3 villages endemic for S. haematobium
infection; an initial survey of 1980 permanent residents of the
study villages aged 1–80 years showed an overall infection
prevalence of 30.5% and arithmetic mean infection intensity of
21.1 eggs/10 ml urine (SEM = 1.9 and range 0–1000 eggs/10 ml
urine). Infection prevalence and intensity followed a convex age-
infection profile with infection levels rising to peak in people aged
11 to 20 years old and infection intensity declining faster than
infection prevalence thereafter (Figures 1 and 2). Schistosome
infection levels in 1–5 year olds in the population were higher than
infection in adults aged 21 years and above.

Safety of PZQ in 1–5 year olds
PZQ drug dose was determined by weight which ranged from
8 kg to 24 kg in the 1–5 year olds (mean 16.7 kg, standard error of
the mean = 0.46). During PZQ administration, there was only one
record of failure to accept the drug, where the child vomited
the tablets. There were no other side-effects directly related to tablet
administration. 104 children were treated with PZQ and their
parents completed side effects questionnaires 24 hours after
the successful administration of PZQ tablets. S. haematobium eggs were
detected in urine samples from 15 of these children. Side effects
arising within 24 hours of treatment were reported in 4 children
aged 3–5 years old, none egg positive for S. haematobium infection.
The side effects reported were diarrhoea (3 children), lethargy (2
children), inflammation of the body and face (1 child, this has
subsided by bedtime and was confirmed resolved by the nursing
staff at the 24 hour examination), and loss of appetite (1 child).

Treatment efficacy
353 children were followed-up at the two time points to
determine the efficacy of PZQ treatment 6 weeks post treatment
and test whether PZQ efficacy was age-dependent. Pre-treatment
schistosome infection levels are shown in Table 1 by age group
and by treatment status. A more detailed breakdown of
pre-treatment infection distribution in the 100 children aged 1–5 years
is given in Table 2. There was a significant reduction in S.
haematobium infection intensity in children receiving PZQ treatment
compared to untreated children in both age groups (F = 15.165,
df = 1.528, p = 0.001) as shown in Figure 3. In treated 1–5 year
olds, infection intensity declined from a mean of 9.9 to 0.1 eggs/
10 ml urine, giving an egg reduction rate of 99%. In untreated
children, mean infection intensity increased from 26.8 to 32.0
eggs/10 ml urine, with an egg reduction rate of 19%. In treated
6–10 year olds, infection intensity declined from 27.0 to 1.1 eggs/
10 ml urine (egg reduction rate = 96%) compared to the change in
infection intensity in untreated children from 14.1 to 11.6 eggs/
10 ml urine (egg reduction rate = 19%). The statistical analyses
also showed that there was no significant interaction between
treatment and age group (F = 0.563, df = 1.528, p = 0.45) indicating
that there was no significant difference in the efficacy of PZQ
treatment in 1–5 year olds compared to 6–10 year olds.

Infection prevalence followed similar patterns with prevalences
in treated children in both age groups declining significantly
compared to untreated children in both age groups (Wald = 5.68,
df = 1, p = 0.017) (Figure 4). In untreated children prevalence
declined from 28.5% to 17.9% in 1–5 year olds (χ² = 0.90, df = 1,
p = 0.34) and 17.5% to 16.5% in 6–10 year olds ($\chi^2 = 0.05, \text{df} = 1, p = 0.83$), giving cure rates of 38% and 7% respectively. In treated children prevalences fell from 18.0% to 1.4% in 1–5 year olds ($\chi^2 = 11.4, \text{df} = 1, p = 0.001$) and 38.0% to 11.8% in 6–10 year olds ($\chi^2 = 65.1, \text{df} = 1, p < 0.001$) giving cure rates of 92% and 67% respectively. This difference in cure rates in treated children was not statistically significantly different between the age groups as the interaction between treatment and age-group was not significant.

**Discussion**

Despite the public health prominence of schistosomiasis in Africa and the availability of a cheap and efficacious drug to treat infected people, fewer than 5% of the infected population is receiving treatment [10]. Included in the group of affected people currently not receiving treatment, are children aged 5 years and below. Current mass drug administration (MDA) schistosome control programmes exclude children aged 5 years and below for
several reasons including (1) practicality; mass helminth control programmes in Africa are largely school based so as to take advantage of existing infrastructure serving an accessible population. These children tend to be aged 6 years and above which means non-enrolled children below the age of 6 are excluded from such programmes; (2) misconceptions about the levels of infection in this age group and (3) lack of safety data in this age group. This study showed that children aged 5 years and below carry infection levels higher than those of their parents/guardians i.e. people aged 21 and above, who are currently eligible for inclusion in MDA programmes. Furthermore, whilst it is known that schistosome infection intensity and morbidity are aggregated in school children, current estimates predict that pre-school children, who are relatively under-represented in field studies, also bear a significant urogenital disease burden in sub-Saharan Africa [24]

Therefore, based on infection levels in these children the present study adds field data to support the growing calls for inclusion of children under 5 in schistosome control programmes [9,11,13,15]. Although PZQ can be prescribed on a case-by-case basis in young children, there have not been studies on the safety of PZQ treatment of S. haematobium infection in children under 5 years of age with a view to include them in MDA programmes. In this study four out of 104 children (3.8%) reported mild side effects (headache, loss of appetite, stomach ache and general weakness) occurring within 24 hours after taking praziquantel tablets which is less than what we have reported in older (primary school) children [16] and that reported in S. mansoni studies in endemic [25] and epidemic [26] areas. There are likely to be biases in parent/guardian reporting side effects on behalf of the child, but this approach has recently been used successfully in studies of the safety of PZQ treatment in 0–5 year olds exposed to S. mansoni infections which reported higher percentages of side effects than those reported in the present study. The low percentage of children suffering side effects in the present study may be related to the low levels of infection they were carrying since previous studies show that the frequency and severity of side effects is proportional to the intensity of schistosome infection [25,26].

### Table 1. Distribution of infection intensity and prevalence in both age groups (1–5 years old) and (6–10 years old) in the study population.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>PZQ infection status</th>
<th>Sample size</th>
<th>Mean infection intensity*</th>
<th>SEM**</th>
<th>Min infection intensity</th>
<th>Max infection intensity</th>
<th>Infection prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–5</td>
<td>Untreated</td>
<td>28</td>
<td>26.8</td>
<td>16.1</td>
<td>0</td>
<td>380</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>PZQ–treated</td>
<td>72</td>
<td>9.9</td>
<td>6.4</td>
<td>0</td>
<td>458</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>100</td>
<td>14.6</td>
<td>6.5</td>
<td>0</td>
<td>458</td>
<td>21</td>
</tr>
<tr>
<td>6–10</td>
<td>Untreated</td>
<td>80</td>
<td>14.4</td>
<td>7.1</td>
<td>0</td>
<td>502</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>PZQ–treated</td>
<td>355</td>
<td>27.0</td>
<td>4.8</td>
<td>0</td>
<td>878</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>435</td>
<td>24.7</td>
<td>4.1</td>
<td>0</td>
<td>878</td>
<td>34</td>
</tr>
<tr>
<td>Total</td>
<td>Untreated</td>
<td>108</td>
<td>17.6</td>
<td>6.7</td>
<td>0</td>
<td>502</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>PZQ–treated</td>
<td>427</td>
<td>24.1</td>
<td>4.1</td>
<td>0</td>
<td>878</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>535</td>
<td>22.8</td>
<td>3.6</td>
<td>0</td>
<td>878</td>
<td>32</td>
</tr>
</tbody>
</table>

*Arithmetic mean, units = eggs/10 ml urine;  
**Standard Error of the Mean.

doi:10.1371/journal.pntd.0001143.t001

### Table 2. Distribution of infection intensity and prevalence in 1–5 year old children in the study population.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sample size</th>
<th>Mean infection intensity*</th>
<th>SEM**</th>
<th>Infection prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0–3</td>
<td>13</td>
<td>0.2</td>
<td>0.2</td>
<td>8</td>
</tr>
<tr>
<td>3.1–4</td>
<td>24</td>
<td>22.4</td>
<td>19.1</td>
<td>17</td>
</tr>
<tr>
<td>4.1–5</td>
<td>63</td>
<td>14.7</td>
<td>7.3</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>14.6</td>
<td>6.5</td>
<td>21</td>
</tr>
</tbody>
</table>

*Arithmetic mean, units = eggs/10 ml urine;  
**Standard Error of the Mean.

doi:10.1371/journal.pntd.0001143.t002
Figure 3. Praziquantel efficacy in reducing infection intensity in different age groups. Comparison of treatment efficacy in 1–5 year old children vs. 6–10 year old children. Infection intensity before treatment is shown in black and those 6 weeks after treatment are shown in white. Bars represent standard error of the mean. Test-statistic values are from paired T tests.
doi:10.1371/journal.pntd.0001143.g003

Figure 4. Praziquantel efficacy in reducing infection prevalence in different age groups. Comparison of PZQ treatment between 1–5 year old children vs. 6–10 year old children. Infection prevalence before treatment is shown in black and those 6 weeks after treatment are shown in white. Bars represent 95% CI. Test-statistic values are from χ2 tests.
doi:10.1371/journal.pntd.0001143.g004
References


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Author Contributions

Conceived and designed the experiments: FM TM NM. Performed the experiments: FM NN NM KM CB LA NM TM. Analyzed the data: FM. Wrote the paper: FM. Contributed to the fieldwork and the final version of the manuscript: FM NN KM CB LA NM TM.


