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## Post-treatment assessment of praziquantel efficacy among school-age children infected with schistosomiasis in Ipogun area of Ondo State, Nigeria

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### ABSTRACT

Schistosomiasis, a major public health challenge is caused by trematodes of the genus *Schistosoma* whose intermediate host is snails. Sub-Saharan African (SSA) carried 85% of the global burden of this infection principally amongst school age children. Similarly, Nigeria bears the highest weight of this highly preventable infection in SSA. Preventive chemotherapy (PC) with 40-60 mg/kg praziquantel (PZQ) annually is the focal control strategy in endemic areas. Despite more than two decades of PZQ usage in Nigeria, the disease is still prevalent in affected communities. Thus, the study sought to assess the current post-treatment efficacy of PZQ use for urinary schistosomiasis among primary school age children of Ipogun village. Urine reagent strip (Haemastix)<sup>®</sup> was initially used to screen pupils for haematuria, while Kato-Katz and urine filtration were employed to confirm the presence of schistosome ova in the faeces and urine of the study population pre- and post-treatment. A total of 202 children were screened, out of which 117 (57.9%) were positive for microhaematuria and 91 (45.0%) had ova of *Schistosoma haematobium* in their urine. The 14 and 21 day post-treatment assessment revealed 73.6% and 23.1% of the initially infected children to still be with infection respectively. Additionally, there was a statistical significant ( $P=0.02$ ) in the reduction of egg count twenty-one days post-treatment. Though the efficacy of the drug as observed in the egg reduction rate in the study area can be classified as satisfactory, continuous monitoring of schistosome response should not cease if the global target of eliminating morbidity due to schistosomiasis by year 2020 is to be achieved.

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**Keywords:** preventive chemotherapy, egg reduction rate, elimination, morbidity, microhaematuria.

### INTRODUCTION

Schistosomiasis is caused by infection with trematodes of the genus *Schistosoma* whose intermediate host is snails. African region is burdened with *Schistosoma* (*S.*) *haematobium* which causes urinary schistosomiasis and *S. mansoni* / *S. intercalatum* causing intestinal

schistosomiasis. Schistosomiasis displays a focal distribution within affected countries and hence mapping of the disease distribution is critical for programme success (WHO, 2012). Schistosomiasis is one of the most prevalent neglected tropical diseases (NTDs) (Melman et al., 2009).

Sub-Saharan Africa (SSA) carries a major burden of this disease representing 85% of the global burden which infects 200 million people, most of whom are children. In Africa, Nigeria is saddled with the highest burden of the disease, with 116 million people infected out of the estimated 555 million infected Africans. Schistosomiasis is a disease of significant and growing importance in Nigeria due to poor water supply, waste management and intensified water development (FMoH, 2012).

In Ondo, one of the 36 States in Nigeria, schistosomiasis is of public health importance as prevalence rates reported for the disease in all 18 Local Government Areas were between 41- 95.7%, with Ifedore Local Government having 47.3% (FMoH, 2012). In Ifedore Local Government Area, urinary schistosomiasis is endemic particularly in Ipogun village. The village first came to national focus in 2001 when 'Newslines', a national television documentary program, reported the village as one where "men menstruate", referring to symptom of the disease (presence of blood in the urine). Since then, it has remained endemic with prevalence rates ranging from 59% in 2003 (Odaibo et al., 2004) to 53.1% in 2006 (Oniya and Odaibo, 2006). Oniya and Olofintoye (2009) also reported a prevalence rate of about 18.22% among school pupils in the Local Government area in 2008. Recently, Oniya et al. (2013) recorded a prevalence rate of 18% in five of the primary schools in the village area.

Preventive chemotherapy (PC) is the main strategy for controlling morbidity caused by this disease using single dose drug, praziquantel (PZQ) at a dose of 40-60 mg/kg annually administered to the infected population with special emphasis on school based treatment to capture the most heavily infected segment of the population (school-aged children) due to their close contact with infected body of water (Fenwick and Webster, 2006; Fenwick et al., 2003; Satayathum et al., 2006). Although significant progress has been made in the control of schistosomiasis over the past few decades, the present thrust is that

of the elimination of morbidity due to the disease as a public health problem (WHO, 1993). The Nigeria National schistosomiasis control programme was initiated in 1988 with the ultimate goal of delivering regular anthelmintic to at least 75% of school aged children in endemic areas, in line with the World Health Organization (WHO) roadmap on the implementation of the policies and strategies for schistosomiasis control and elimination as set in the WHO Global Plan to combat NTDs 2008-2015 (WHO, 2007). Now more than ever, there is immense global support and commitment by pharmaceutical companies, government and health organizations for the implementation of this roadmap (The London Declaration on NTDs (January 31<sup>st</sup> 2012) (DFID, 2012). Also the Ministers of Health of Member States in the African Region at the Regional Committee (RC 59, Kigali, Sept 2009) have expressed their commitment to scaling up proven interventions against the major NTDs of which schistosomiasis is among (WHO, 2014).

With its (PZQ) free donation to all needy countries for as long as needed, the National control programme has embarked on a nationwide use of the drug in its control programme with aim that aligns with that of WHO. Hence, there will be considerable increase in the number of individuals receiving treatment through preventive chemotherapy over the coming years, for which the potential risk of resistance development by the parasite to the drug is real, as a consequence of drug pressure.

The guideline released by WHO in 1999 on helminthic efficacy has been replaced by a more recent guideline. This guideline was instigated by recent studies which provided new insight into: pointer of drug efficacy (Montessor, 2011), level for reduced efficacy (Levecke et al., 2012; Vercruysse et al., 2011), Sample size (Levecke et al., 2012b; 2011), number of days of follow-up (Scherrer et al., 2009) amongst other criteria. Thus in line with suggestions put forward by members of the WHO working committee in assessing the efficacy of anthelmintic drugs against

schistosomiasis and soil transmitted helminthiasis, evaluation of drug efficacy is called for when drug performance is suspected to have reduced. This will be depicted in one or a combination of the following scenario; persistency in parasite attributable morbidity (such as haematuria, malnutrition, anaemia) in target population following multiple rounds of treatment, high prevalence of schistosome and/or soil transmitted helminth infections of high intensity in target population, inadequate reduction in prevalence and intensity of infection in the target population- seen as a low egg reduction rate ERR (WHO, 2013).

Consequently, this study was undertaken in line with the proposed protocol in the most recent WHO guideline in assessing treatment efficacy in schistosomiasis.

## **MATERIALS AND METHODS**

### **Study design**

School-aged children attending primary schools within Ipogun village area aged 9 to 12 years old who gave their assent were recruited into the study, following informed consent of the parents through the school authority. Other criteria for inclusion in the study include having received at least two doses of praziquantel within the past five years, not received anthelmintic treatment in the last 6 months, and having no severe medical condition at the time of the survey. These children were requested to provide their urine samples which were screened for haematuria using the reagent strip (Haemastix). Those found positive were further requested to provide both stool and urine samples in clearly labelled containers (serially numbered to tally with their names) for easy identification and the height of the children were collected for proper determination of dosage. All diarrhoeal specimens were not processed and the child (ren) excluded from the study. The remaining specimens were processed using parasitological methods and the names of those found positive were submitted to the State Primary Health Care centre in the village for treatment, in line with the annual treatment

program. Parasitological assessment was repeated in treated children fourteen and twenty-days post treatment following the WHO protocol (WHO, 2013).

### **Study area**

The study was carried out in Ipogun, (7° 19'N; 5° 05'E), a village in Ifedore Local Government Area of Ondo State, south western Nigeria. The two distinct seasons in the area are the wet and dry seasons. The wet season lasts from April to October and is characterised by heavy rains with occasional flooding of the river banks. The dry season lasts from November to March, and is associated with an increased temperature (Oniya and Olofintoye, 2009). The primary source of water for agricultural and most domestic activities is the 'Aponmu' river, flowing through the village; it is this river that serves as the contact site (Oniya et al., 2013). Though there are several bore-hole dug by the state government, most of them however were non-functional, making the people to rely heavily on the river. Furthermore, the inhabitants being mainly farmers depend on and use water from the river in carrying out their daily and recreational activities including bathing and washing.

### **Inclusion/exclusion criteria**

Children between age 9-12 years were included in this study. However, those with severe medical condition, who produced diarrhoeal specimen, had received two or more combination, praziquantel or anthelmintic treatments 6 months prior to the study were all excluded. .

### **Study population**

School-aged children aged 9-12 years in the seven primary schools in Ipogun village were screened for schistosomiasis. The primary schools are Muslim primary school, Morohunkeji Nursery and Primary school, St. Jude primary school, Evangel nursery and primary school, Sancta Trinitas Nursery and primary school, St. Paul CAC primary school and Aseyori International Group of School.

## Sample collection and evaluation

### Urine

Urine samples were collected between October and November 2014 from each of the primary school children between 10 a.m-2:00 p.m in a universal container, transferred to the Ondo State Primary Health Care Laboratory, Oke Eda, Akure and processed using filtration technique pre and post-treatment (WHO, 1991). Briefly, two drops of eosin were added to each sample container and each urine sample was flushed through a 10 ml syringe over a filter paper placed in a Swinnex filter holder held over a sink. Twenty ml of Lugol's iodine was then flushed through each sample. Each filter paper was taken out of the holder with the aid of a forceps and placed over two drops of ninhydrin stain. The filter papers were allowed to air-dry for about 10 minutes and examined at  $\times 40$  magnification. All children found positive were treated with 40 mg/kg of praziquantel through the primary health care Centre using the WHO dose pole for dose determination. Samples were collected 14 and 21 days after treatment from treated school children.

### Stool sample

The stool samples were collected same time with the urine samples and analysed using the Kato-Katz procedure. A small amount of the stool specimen voided in a small container by each child was scooped out with the aid of a spatula, and placed on a newspaper, on top of which a piece of nylon screen was pressed so that small amount of faeces accumulated on the screen which was then collected with the spatula and placed in the hole of the Kato-Katz template already on the microscope slide. Excess faeces was removed from the edge of the template before removing the template. The specimen on the slide was then covered with a pre-soaked cellophane strip and pressed against another slide to spread the faecal sample evenly. The second slide used as a spreader was carefully removed and the sample allowed to air-dry at room temperature before examination (WHO, 1998). All children found positive were treated with 40 mg/kg of praziquantel through the primary health care Centre using the WHO

dose pole for dose determination. Samples were collected 14 and 21 days after treatment from treated school children.

## Ethical Consideration

The ethical clearance for this study was received from the Institutional Review Board of the Nigerian Institute of Medical Research with Project number IRB/13/232. Approval was also sought from Ondo State Ministry of Health, parental consent as well as assent obtained from school pupils.

## Statistical analysis

The prevalence rate was determined as a proportion of the positive individuals in the total population examined as stated below:

$P = (\text{Number of children identified as positive} / \text{Total number of children who provided specimen}) * 100$

The indicator of drug efficacy is the Egg Reduction Rate at 95% Confidence Interval. The intensity of infection was used to estimate the Egg Reduction Rate (ERR) using the baseline and post-treatment data with the formula below:

$ERR = 100 \cdot [1 - (\text{arithmetic mean of EPG at follow-up}) / (\text{arithmetic mean of EPG at baseline})]$

Drug efficacy is reduced when Egg Reduction Rate is under the reference value and 95% CI does not include reference value. Paired student t-test was used to compare the difference between the observed and expected ERR and a P-value of 0.05 was used to evaluate the level of significance in all statistical analyses carried out in this study.

## RESULTS

### Pre-treatment assessment

Of the 202 children screened prior treatment, 117 (57.9%) were positive for microhaematuria while 91 (45.0%) had ova of *Schistosoma haematobium* in their urine, however eggs of *Schistosoma mansoni* was not detected in the stool samples collected. The highest prevalence (66.7%) by the detection of *Schistosoma haematobium* ova was recorded in Sancta Trinitas nursery and primary school, while St. Paul and St. Jude

had equal level of prevalence (50.0%) and the least prevalence (12.5%) was recorded in Aseyori International Group of Schools (Table 1).

Stratification of prevalence by gender showed females (45.1%) to be slightly more infected than males (45.0%) with Sancta having the highest female prevalence of 87.5% while Aseyori had the least female prevalence (14.3%). On the other hand, St. Jude had the highest male prevalence (58.1%) while same level of prevalence was recorded amongst males of both Sancta and St. Paul and no male was found to be infected with eggs of *Schistosoma haematobium* in Aseyori (Table 2). Stratification of microhaematuria according to gender revealed females of Sancta School (8/8; 100%) to be the most infected while those of St. Paul (6/12; 50%) showed the least prevalence (Figure 1).

**Post treatment assessment**

Of the 91 subjects found infected (presence of schistosome ova in urine) at baseline study, 67 and 23 of them were still found infected 14 and 21 days after treatment respectively. Using paired student t-test, there

was a statistical significant difference (P=0.02) in the reduction of prevalence 21 days post-treatment.

In Muslim and Morohunkeji Nursery and Primary school, prevalence of infection did not change 14 days post-treatment, however, during the 21 days follow-up, none of the infected subject in Muslim School was found to still be with infection. However, in Morohunkeji, 45% (10) of those initially infected were found to still carry the infection. St. Jude Nursery and Primary school also recorded high reduction of infection in the follow-up survey with 15 and 5 subjects found to still be with infection 14 and 21 days post-treatment respectively (Figure 2).

**Egg reduction rate (ERR)**

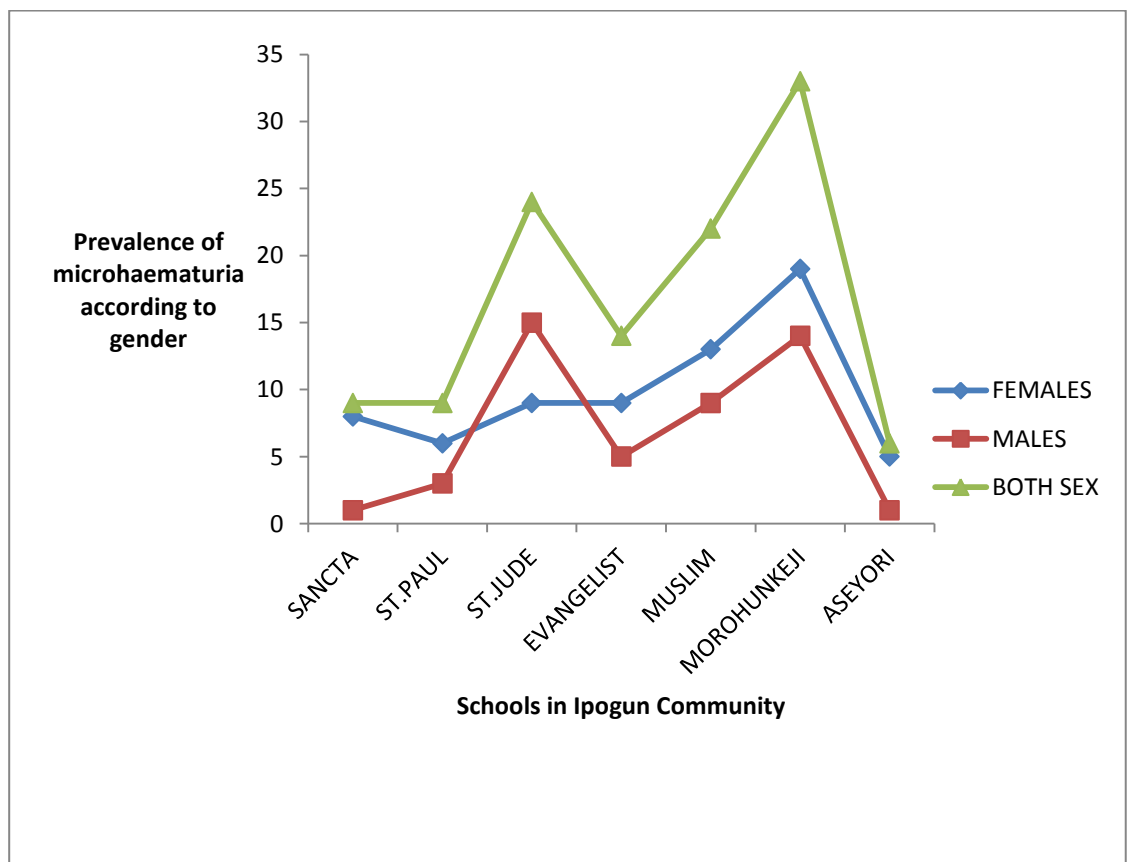
During the 14 days follow-up survey, three schools recorded ERR of 100% and an additional school during the 21 days follow-up making a total of four schools recording 100% ERR. Overall, the egg reduction rate in all schools during the follow-up period indicates that praziquantel is still efficacious (Table 3).

**Table 1:** Prevalence of Schistosomiasis in the different schools before treatment.

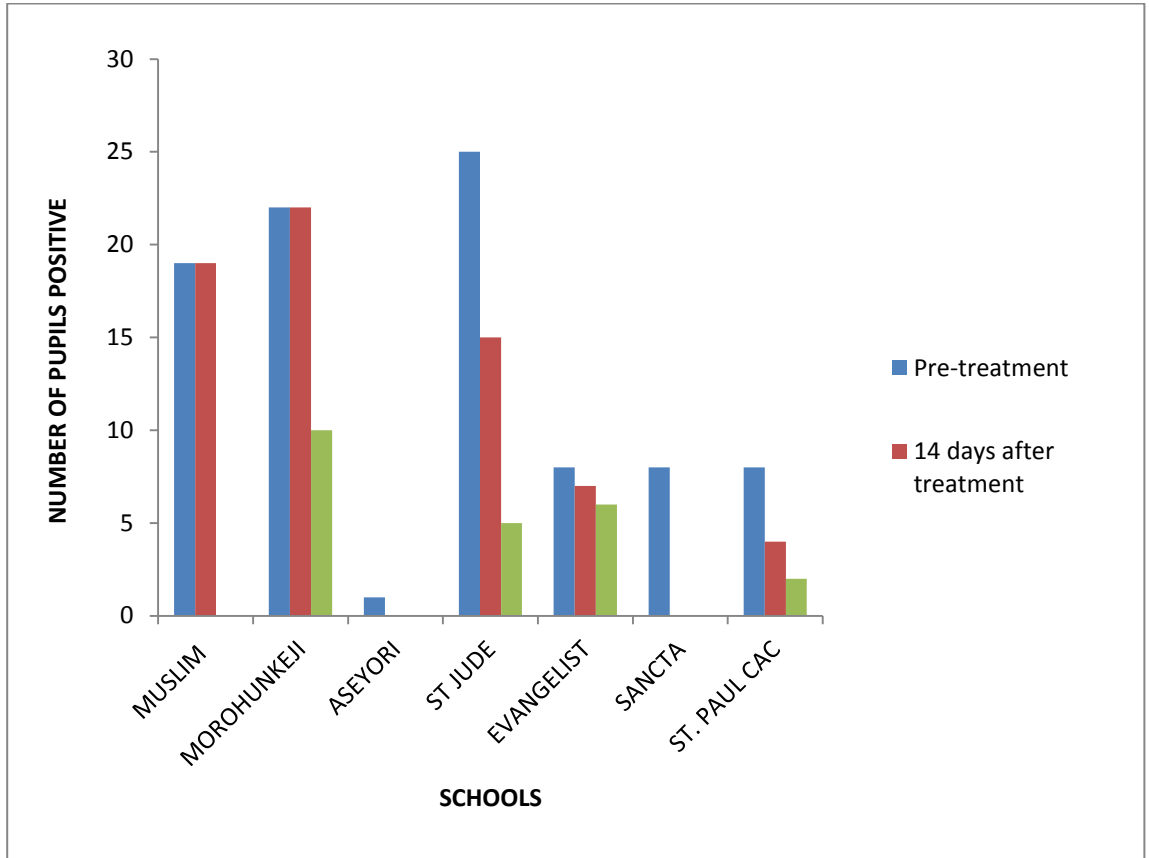
Schools	Ova of <i>Schistosoma haematobium</i>		Haematuria	
	Examined	Positive (%)	Examined	Positive (%)
Sancta Trinitas	12	8(66.7)	12	9(75.0)
St. Paul CAC	16	8(50.0)	16	9(56.3)
St. Jude	50	25(50)	50	24(48.0)
Evangelist	23	8(34.8)	23	14(60.9)
Muslim	41	19(46.3)	41	22(53.7)
Morohunkeji	52	22(42.3)	52	33(63.5)
Aseyori	8	1(12.5)	8	6(75.0)
<b>Total</b>	<b>202</b>	<b>91(45.0)</b>	<b>202</b>	<b>117(57.9)</b>

**Table 2:** Prevalence of schistosomiasis by gender.

Schools	Detection of ova in urine			
	Female		Male	
	Examined	Positive (%)	Examined	Positive (%)
Sancta Trinitas	8	7(87.5)	4	1(25.0)
St. Paul CAC	12	7(58.3)	4	1(25.0)
St. Jude	19	7(36.8)	31	18(58.1)
Evangelist	12	4(33.3)	11	4(36.4)
Muslim	17	8(47.1)	24	11(45.8)
Morounkeji	27	12(44.4)	25	10(40.0)
Aseyori	7	1(14.3)	1	0
<b>Total</b>	<b>102</b>	<b>46(45.1)</b>	<b>100</b>	<b>45(45.0)</b>



**Figure 1:** Prevalence of microhaematuria according to gender.



**Figure 2:** Pre and post-treatment prevalence with a drastic reduction in prevalence St. Jude and Sancta.

**Table 3:** Rate of egg reduction 14 and 21 days post-treatment.

Schools	ERR 14 post-treatment (%)	ERR 21 post-treatment (%)
MUSLIM	100	100
MOROHUNKEJI	99.3	100
ASEYORI	100	100
ST. JUDE	98.4	98.6
EVANGELIST	98	99
SANCTA	100	100
CAC	98.6	98.7

## DISCUSSION

Schistosomiasis is a serious public health challenge for children in poor rural areas such as in this study area where community members lack access to pipe-borne water. Despite the continuous effort by government and WHO to reduce the prevalence of this infection through annual distribution of praziquantel, the prevalence in this study is still a two-digit figure showing no positive impact of control programmes.

The overall prevalence rate of *S. haematobium* was far higher than the prevalence rate recorded in the same Ipogun community the previous year by Oniya et al. (2013), considering the fact that this area receives praziquantel on an annual basis, prevalence would be expected to be lower than what was obtained. This persistent high prevalence could be the result of constant contact with the river which acts as source of infection since most of the bore holes dug by the State government are no longer functional, or perhaps due to reduced sensitivity of the parasite to drug regimen. The latter is yet to be determined as the causal factor, since there is need for comparative genomics of parasite eggs pre- and post-treatment, which is beyond the scope of the present study.

More so, females had a higher rate of prevalence than the males, which is contrary to previous studies in the same community where males were observed to have higher rate of prevalence than the females (Oniya et al., 2013) and in Edo state by Ugbomoiko (2000). This thus shows that it is the frequency of contact with an infected body of water and not their gender that determines the rate of transmission.

The prevalence of microhaematuria in both sexes for most of the schools is far higher than prevalence due to the detection of eggs in urine. This phenomenon could be due to the fact that haematuria could also result from other causes other than from schistosomiasis, hence the use of microscopy as a “gold standard” for diagnosis should be emphasized.

The observed ERR in all schools in this study area during the 14 and 21 days follow-up is superior to the reference value (EER for *S. haematobium* is  $\geq 90$ ) as stipulated in the

WHO new guideline, thus the efficacy of praziquantel in Ipogun is considered satisfactory. Nevertheless, there is need for continuous monitoring of the sensitivity of schistosome to this drug in this study area as well as in other endemic areas partaking in the annual drug distribution, so as to aid early detection of resistant strain. Most of the efficacy studies of PZQ employ the geometric egg mean (as against the arithmetic egg mean) to evaluate the ERR (Oniya et al., 2013), hence data from such study cannot be comparatively used. It is therefore necessary for programme implementers to commence praziquantel assessment using the arithmetic egg mean count or have a common means of assessing the mean egg count.

Given the global target of eliminating morbidity due to schistosomiasis by year 2020, concerted effort by the State government to interrupt transmission through provision of pipe-borne water or bore holes, mollusciciding and health education to promote individual and community hygiene should be put in place to augment the annual treatment strategy, as the most effective solution to eliminate schistosomiasis and soil transmitted helminthiasis is to improve the environmental condition enhanced with positive behavioural display in endemic communities (WHO, 2011). Alternatively, the control programme in Ipogun should consider increasing the dosage from 40 to 60 mg/kg for greater impact or increasing the frequency of treatment to twice yearly if logistic permits as recommended by Lambertson et al. (2010) where children found to be positive after the initial treatment received one or two more subsequent doses.

## Conclusion

Though the efficacy of the drug as seen in the ERR in the study area can be classified as satisfactory, continuous monitoring of schistosome response to PZQ should not cease.

## COMPETING INTERESTS

The authors declared that they have no competing interest.



## AUTHORS' CONTRIBUTIONS

MAM and MAO designed the study, MAO and TEI collected samples. MAO performed experiment, analysed result and wrote first draft of manuscript, MAM critically review first draft. All authors read and made input to final draft.

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