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Efficacy of Praziquantel and Schistosomiasis Reinfection Rate among School-Aged Children in Ondo State, Nigeria; How Feasible is the WHO 2030 Elimination Roadmap?

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A B S T R A C T

Background: Schistosomiasis, caused by blood flukes of the genus Schistosoma that depend on snail intermediate hosts for their life cycle, is a neglected tropical parasitic disease of great public health and socioeconomic significance. Most studies on Schistosomiasis are only prevalence data and not purposefully conducted for interventional programmes. There is a need to access the possible intervention impact as the Nation moves towards the elimination of Schistosomiasis. This study was designed to assess the prevalence and efficacy of PZQ and post-treatment reinfection among SAC and adolescent population in an endemic Community (Ayadi, Irele Local Government Area, Ondo State, Nigeria).

Methods: A cross-sectional study was conducted among 140 School Aged Children (SAC) and adolescents at Ayadi, Irele 3 Local Government Area of Ondo State, Nigeria.

Results: The prevalence of Schistosomiasis at baseline was 65% which dropped to 12.01% following 4 weeks post-treatment and unfortunately out of the participants that tested positive at baseline and negative at 4 weeks post-treatment with PZQ, 13.75% of them already got infected 6 months post PZQ single use. A significant Egg Reduction Rate (86.49%) and Cure Rate (87.91%) were obtained in this study.

Conclusion: Treatment with a single dose of 40 mg/kg of PZQ produced a significant result against Schistosomiasis. However, there was a high reinfection rate due to the lack of safe water.

Recommendations: The Schistosomiasis elimination program should be redesigned to accommodate double dose treatment with PZQ and also ensure treatment across all endemic wards without having to sectionalize treatment across moderately and lowly endemic wards. .

INTRODUCTION

Schistosomiasis, caused by blood flukes of the genus Schistosoma that depend on snail intermediate hosts for their life cycle, is a neglected tropical parasitic disease of great public health and socioeconomic significance [1]. It is endemic in the poorest regions of sub-Saharan African countries [2] and caused by five major species of Schistosome. *Schistosoma mansoni, S. intercalatum, S. japonicum,* and *S. mekongi* cause intestinal schistosomiasis while *S. haematobium* causes urogenital morbidities. *S. mansoni* and *S. haematobium* are majorly found in Africa. Transmission occurs when an infected person passes urine or faeces into water bodies [3]. Globally, about 239 million people are infected with Schistosomiasis while in Africa, approximately 171 million people are infected with schistosomiasis [4]. Nigeria appears to be the epicentre of Schistosomiasis in sub-Saharan Africa where we have an estimated 103.9 million at risk of infection and over 29 million people already infected [5]. According to the Global Burden of Disease Study 2016, the global burden of schistosomiasis is estimated at 1.9 million disability-adjusted life years (DALYs) [6]. According to the World Health Organization on disease burden, not fewer than 200,000 people die of Schistosomiasis per year in sub-Saharan Africa. In 2014, 91.4% of people estimated to require treatment for schistosomiasis lived in the African region [7]. The World Health Organization (WHO) developed five (5) strategies to be adopted towards the elimination or eradication of NTDs. These strategies are: Preventive Chemotherapy, Innovative or Intensified Diseases Management (IDMs), Water and Sanitation, Veterinary Public Health Measures and Integrated Vector control.

However, Ondo state among several others in Nigeria had always utilized preventive chemotherapy (use of drugs) and water and sanitation while little has been done about veterinary public Health Measures, Innovative or Intensified Dies Management (IDMs) and vector control.

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The core of the public health approach towards the control and elimination of Schistosomiasis has been the Mass Administration of medicines (Preventive Chemotherapy). This was adopted and officially endorsed as the best method of improving the health of infected Community members, especially school-age children in 2001 by the Fifty-fourth World Health Assembly resolution WHA54.19. However, the assembly equally elucidated the need to complement Preventive chemotherapy with health promotion interventions like the provision of basic sanitation and adequate safe water supplies [7]. The goal of this activity was to achieve a minimum target of regular administration of preventive chemotherapy to at least 75%, and of up to 100% of all SAC at risk of morbidity by 2010.

The World health organization for over 30 years recommended Schistosomiasis control through the annual Mass Administration of Praziquantel [8]. This approach has led to a notable decrease in the prevalence of the disease [9]. Nevertheless, the WHO 2030 target for the elimination of Schistosomiasis in all endemic Countries remains a big challenge [1], especially in African Countries which carry the highest burden of the disease. A major reason for this is that the current strategy for schistosomiasis control and or elimination programme, regardless of the success mentioned above, does not prevent reinfection [1]. Also, there is still the insufficient provision of praziquantel tablets, which are donated by international pharmaceutical companies [10].

According to Oyetunde *et al*., 2020, epidemiological studies about Schistosomiasis in Nigeria are mostly towards acquiring prevalence data and not aimed at influencing interventional programmes and policies [2]. There is a need to access the possible intervention impact as the Nation moves from implementing the Schistosomiasis elimination programme at the Local Government level to the Ward level where interventions may be zoned across the Wards thereby leading to staggered administration of Praziquantel.

Schistosomiasis control programmes had been held consistently in Ondo state across 10 Local Government Areas till the year 2020. In 2021, the WHO developed an elimination strategy in line with the WHO 2030 target which focuses on Ward level disaggregated implementation. As a result, 14 Local Government Areas now have endemic wards in Ondo State.

The Ondo State Government plans to achieve the elimination of schistosomiasis-related morbidity by 2030 in line with the World Health Organization (WHO) target. Therefore, in line with the WHO recommendations, assessing treatment efficacy, reinfection rates, and the effect of MDA campaigns on infection prevalence is crucial. This may inform the policymakers of the State about the possible need to redesign the Schistosomiasis elimination program in order to achieve the WHO 2030 target.

Hence, this study assessed the prevalence, efficacy of PZQ and the occurrence of post-treatment reinfection among SAC and adolescent population in an endemic Community (Ayadi, Irele Local Government Area, Ondo State, Nigeria).

METHODS

Study Area and Subjects

This study was carried out at Ayadi Community in Irele Ward 3, Irele Local Government Area, Ondo State, Nigeria. Ayadi has 2022 WHO projected population of 2887 from the 2006 national census in Nigeria.

The major occupation of the villagers is farming with cocoa and oil palm being the major cash crops. Ayadi is a high-risk Community for Schistosomiasis infection due to the lack of safe water. Though there were reported efforts to sink boreholes in this Community, there exists no functional borehole in the entire Community except a hand pump borehole at the Basic Health Centre which is only functional during the rainy season. The inability to construct boreholes has been attributed to the high density of bitumen in the soil. As a result, members of the community rely absolutely on river Ohin which flows all year round. This river serves as the major source of water supply for domestic and occupational and recreational purposes such as drinking, bathing, washing, swimming (especially the younger ones), farming etc. The inclusion criterion was school enrolled Children from the SAC age to the adolescent age range (5-19 years).

Sample Size

Leslie Fischer's formula for sample size determination in Health studies was used to calculate the sample size given the prevalence of urinary schistosomiasis in a similar study in Ondo state to be 19.9% [4], 95% confidence level, relative precision of 6%. The final sample size was 140 after adjustment for 13% non-respondent or loss to follow-up rate. The participants were determined through simple random selection with the assistance of their Teachers.

Community Engagement: Before commencing the Study, Community Dialogue was held with the Community leader and members of the Community, sensitizing them about the purpose of the study and obtaining their consent.

Baseline Survey: Each participant was given a unique survey code which was the same on the specimen containers for urine samples. Other demographic data such as the sex and age of each child was recorded during the enrollment for the survey. Urine samples were collected from all the participants that consented to participate in the study between 11:00 am and 2:00 pm. The samples were analyzed using the filtration technique. The intensity of *S. haematobium* eggs was recorded as egg output per 10 ml of urine [11]. The infection intensity of the positive sample was classified, as defined by the World Health Organization [12] either a low (1–49 eggs/10 mL of urine) or high (>50 eggs/10 mL of urine) parasite burden [13].

Administration of Medicine: All the recruited participants were treated with a single oral dose of praziquantel (600 mg) at a dose of 40 mg/kg body weight immediately after submitting urine samples by Directly Observed Treatment (DOT).

Follow-up Survey: Children who had a baseline positive urine specimen and were treated with PZQ at baseline were requested to produce a four-week post-treatment urine sample. The same laboratory method used in the baseline survey was used in the follow-up survey.

Reinfection Assessment*:* Children that tested positive at the baseline survey and negative at the 4 weeks post-treatment follow-up survey were tested again after 6 months post-treatment to assess the occurrence of reinfection among them.

Data Analysis

The relationships between characteristics of *S. haematobium* infection (prevalence, intensity and reinfection) and other variables, such as the sex and age of children, were tested at baseline. Prevalence comparisons were performed using the chi-squared test and Fisher's exact modification of the 2 × 2 chi-squared test. For infection intensity values, the Geometric Means of Williams was used to calculate the Geometric Eggs Mean Count (GEMC) in only positive individuals. PZQ efficacy was measured by determining both cure rate (CR) and Egg Reduction Rate (ERR) [13].

The CR is the percentage of children positive for egg-patent infection becoming negative after treatment.

$$CR = \frac{No\ of\ positive\ children\ at\ baseline\ that\ became\ negative\ after\ treatment\ with\ PZQ}{No\ of\ positive\ children\ before\ treatment} * 100$$

The **ERR** is the percentage reduction in GEMC, as measured by *S. haematobium* eggs, after drug treatment of children with egg-patent infections at baseline.

$$ERR = \left[1 - \frac{GEMC\ after\ treatment}{GEMC\ before\ treatment}\right] * 100$$

Reinfection rate

$$RI = \frac{No\ of + ve\ @\ 6\ months\ post\ treatment\ with\ PZQ\ who\ were - ve\ @\ 4\ weeks\ post\ PZQ\ treatment}{No\ of - ve\ @4\ wks\ post\ PZQ\ treatment\ who\ were + ve\ @\ baseline} * 100$$

RESULTS

A total of 140 children were examined for S. haematobium egg (Figure 1) infection at baseline in the community with ages ranging

from 5 to 19 years and a mean age of 10.27 (Table 1). The sample size was made up of 81 females (57.9%) as well as 59 males (42.1%) (Table 2). At the end of 6 months of final analysis, all the children that tested negative after 4 months Post PZQ administration and positive at baseline were still available for reinfection rate analysis (N=80).

The prevalence of infection at baseline was 65% (Males 27.1%; Females 37.9%) though there was no statistically significant difference (P >0.05) in infection rate between males and females at baseline, 4 weeks Post PZQ treatment and reinfection assessment after 6 months of PZQ administration.

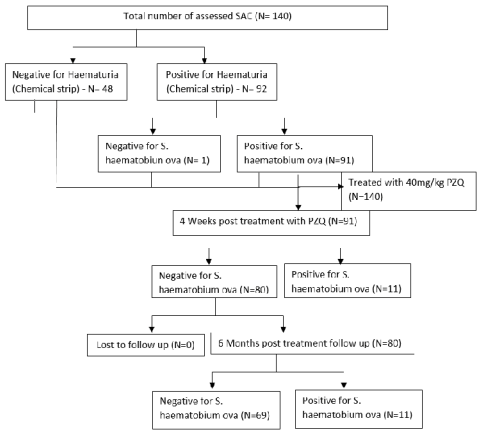

Figure 1: Diagram of study design showing the number of infected children at baseline, follow-up at 4 weeks and 6 months post-treatment for Schistosoma haematobium infections in Ondo State, Nigeria (N = 140) [13].

AGE DISTRIBUTION OF PARTICIPANTS					
		Frequency	**Percent**	**Valid Percent**	**Cumulative Percent**
Valid	**5-7 years**	32	22.9	22.9	22.9
	8-10 years	42	30.0	30.0	52.9
	11-14 years	51	36.4	36.4	89.3
	15 years and above	15	10.7	10.7	100.0
	Total	140	100.0	100.0	

Table 1: Age distribution of respondents at baseline investigation.

SEX DISTRIBUTION OF PARTICIPANTS					
		Frequency	**Percent**	**Valid Percent**	**Cumulative Percent**
Valid	**male**	59	42.1	42.1	42.1
	female	81	57.9	57.9	100.0
	Total	140	100.0	100.0	

Table 2: Sex distribution of respondents at baseline investigation.

Geometric Eggs Mean Count (GEMC)

- **At** baseline

GEMC = 18.5 Eggs/10mL of urine (male = 18.9 Eggs/10mL of urine; Female = 18.2 Eggs/10mL of urine).

- **Infection intensity of positive sample (Baseline Parasite burden)**

High parasitic burden= 5.5%

Low parasitic burden = 94.5%

- **At 4 weeks post treatment with PZQ**

GEMC = 2.9 Eggs/10mL of urine (male = 2.0 Eggs/10mL of urine; Female = 2.9 Eggs/10mL of urine).

- **At 6 months' post treatment with PZQ**

GEMC = 1.36 Eggs/10mL of urine (Male = 1.0 Eggs/10mL of urine; Female = 1.4 Eggs/10mL of urine).

Egg Reduction Rate (ERR) = 86.49%.

Cure Rate = 87.91%

Rate of Reinfection = 13.75% (Male = 5.9%; Female = 19.56%).

There was no significant difference in the intensity of infection using the Geometric Egg Mean Count (GEMC) between males and females across the three levels of assessment (baseline, 4 weeks post PZQ administration and 6 months post PZQ administration). P = 0.499 at baseline, 0.324 at 4 weeks post-treatment and 0.165 at 3 months post-treatment with PZQ.

There was no statistically significant difference in the reinfection rate between male and female participants as well as among the age groups (χ^2 = 3.658; P= 0.161) and (χ^2 = 2.790; P= 0.835).

There was a significant difference in *Schistosoma haematobium* egg count at baseline investigation and four weeks post-treatment with PZQ (P<0.05; CI = 14.899 -21.475).

From Figure *2*, the infection prevalence at baseline was 65% which was reduced to 12.01% after treatment with a single dose of praziquantel. However, there was a reinfection rate of 13.75% after 6 months post-treatment with praziquantel among participants that tested negative at 4 weeks post-treatment with praziquantel.

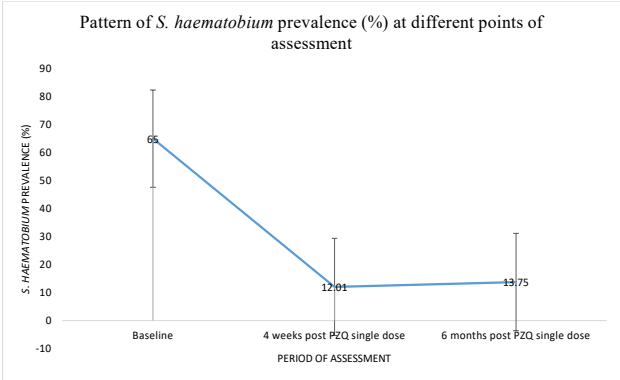

Figure 2: Pattern of *S. haematobium* prevalence at baseline, 4 weeks post-treatment with a single dose of praziquantel and 6 month post-treatment with a single dose of praziquantel.

DISCUSSIONS

Inadequate treatment coverage is a serious obstacle to MDA implementation. In 2001, the 54th World Health Assembly officially endorsed chemotherapy as the key public health strategy to combat schistosomiasis with the goal of achieving a drug coverage rate of 75-100% among school-aged children at risk of morbidity by 2010. However, the target coverage was not attained according to the 65th World Health Assembly. In 2014, the global coverage was reported to be 20.74%. Thus, in reality, only about 5% of the reservoir human population is actually receiving intermittent chemotherapy [14]. Despite claims that more of the drug will soon be made available the current strategy is inherently flawed and will not lead to disease elimination [15].

In order to get PZQ to a majority of the target population in Nigeria, The National Schistosomiasis Elimination Programme (NSCHEP) in November 2020, approved the disaggregation of Schistosomiasis Local Government Areas data implementation to ward level as recommended by the World Health Organization (WHO) as a strategy aimed at eliminating Schistosomiasis in the year 2030. Table *3* presents the implementation strategy across endemic wards in the state. Considering the reinfection rate in this study, the implementation strategy in Table *3* may not yield the desired WHO 2030 elimination target due to staggered intervention.

The prevalence of Schistosomiasis in this study (65%) was higher than the 45% reported by Oboh *et al*., 2018 [16] in Ipogun, Ifedore Local Government Area of Ondo State and the 24.9% reported by Adewale *et al.,* 2018 [17]. This showed that the Ward was highly endemic for Schistosomiasis. Hence, treatment covers both the SAC population and the adult population in the Ward.

At baseline, a low parasite burden was significantly more frequent in comparison to a heavy parasite burden (94.5% versus 5.5%; *P* <0.05).

By gender and age distribution, there was no significant difference in parasite burden (p>0.05). The Geometric Egg mean of this study (GEMC = 18.5 ± 1.355 Eggs/10mL of urine; male = 18.9 Eggs/10mL of urine; Female = 18.2 Eggs/10mL of urine) was lower than the 58.8 Eggs/10mLof urine reported by Homsou *et al.,* 2018 [13].

We obtained a high parasitological cure of 87.91% in this study. This was higher than the cure rate of 82% reported by N'Goran *et al.,* 2001 [18]. However, in the study by Houmsou *et al* [13], the cure rate (98.1%) after 4 weeks post-treatment with PZQ was higher than what we obtained in this study. This could be due to the fact that none of the participants has had previous exposure to PZQ use in the reported study as against our study which represents the 13th round of PZQ administration.

This indicated that the efficacy of a single dose of PZQ may not be absolutely dependent on the parasite load but other factors like previous use of PZQ and possible resistance of the parasite after several years of administration. In the opinion of Montresor, 2011, CR is an efficient indicator of drug efficacy against bacterial diseases. However, this indicator is less efficient for helminth infections [19]. With the understanding that Schistosomes do not replicate in the human host if few parasites survive treatment, they remain few unlike other communicable diseases, in which, if few infectious agents survive treatment, they replicate, restoring the initial pathology. In this study, we incorporated the Egg Reduction rate to facilitate a more efficient measurement of PZQ efficacy.

The observed ERR (86.49%) in this study at the 4 weeks post PZQ treatment was lower than the reference value (ERR for *S. haematobium* is ≥90) as stipulated in the WHO new guideline, thus the efficacy of a single dose of praziquantel in this highly endemic ward was considered non-satisfactory. There was no statistically significant difference (P>0.005) in the Egg Reduction Rate among participants with high parasite burden and low parasite burden at baseline, 88.20% and 84.78% respectively. However, there was a significant difference (P<0.005) in the CR between participants having heavy and low disease burden at baseline. None of the participants with heavy parasite burden at baseline attained 100% CR after 4 weeks post-treatment with single dose PZQ while 94.18% of the participants with low parasite burden at baseline attained 100% CR after 4 weeks post-treatment with single dose PZQ.

It is worthy of note that there was a significant reduction in the GEMC at baseline, 4 weeks post-treatment with PZQ and 6 months post-treatment with PZQ at 18.5, Eggs/10mL of urine, 2.9 Eggs/10mL of urine and 1.36 Eggs/10mL of urine respectively. Though, this difference was not significant across the stages of assessment.

The prevalence of *Schistosoma haematobium* at baseline was 65% which dropped to 12.01% following 4 weeks post-treatment and unfortunately out of the participants that tested positive at baseline and negative at 4 weeks post-treatment with PZQ, 13.75% of them already got infected 6 months post PZQ single use.

The present study revealed the difficulty in relying on a single dose of PZQ to cure totally some children in whom the intensity of the infection was very high at baseline. This finding was in agreement with the report by Adewale *et al,* 2018 [17]. Hence, a supplementary dose of PZQ could be necessary to achieve a 100% cure rate in this category of infected individuals, especially in highly endemic locations [20].

From this assessment, it can be deduced that there is an active infection ongoing in this study population chiefly due to the absence of a safe water supply, making residents depend absolutely on the stream which flows through the Community. As a result, there is a need to incorporate other methods of implementation like Water, Sanitation and Hygiene for the provision of safe water as well as vector control and malacological analysis.

Also, the Cure Rate could be due to the possible resistance to PZQ after several years of implementation with residual parasites causing reinfection.

CONCLUSION

The baseline prevalence confirms that urinary schistosomiasis still remains a public health problem in Irele among other Local Government Areas in Ondo State and Nigeria at large. Treatment with a single dose of 40 mg/kg of PZQ produced a significant result against Schistosomiasis though children with heavy parasite burden and in highly endemic regions may require a second dose to achieve a 100% cure rate. Also, due to the lack of safe water, there was a high reinfection rate (11 out of the initially cured 80 participants were already re-infected after 4 months of PZQ administration). This paper showed that regardless of the significant effect of PZQ on *Schistosoma haematobium*, in the absence of other elimination strategies like Water, Sanitation and hygiene (WASH) and vector control among others, the elimination of urinary schistosomiasis will be close to impossible and the annual effect may only be momentary. It is anticipated that these results will provide a basis for future implementation of the urinary schistosomiasis elimination program in Ondo State and Nigeria as a whole.

Recommendations

There is a need to redesign the schistosomiasis elimination program whereby it is possible to have double dose treatment with PZQ and also ensure treatment across endemic wards without having to sectionalize treatment across moderately and lowly endemic wards. Also, there is an urgent need to prioritize the construction of boreholes in communities or wards endemic to schistosomiasis across the state.

DECLARATIONS

Ethics Approval and Consent to Participate:

Ethical approval was obtained from the University of Medical Sciences Research Ethics Committee

Consent for Publication: Not applicable

Availability of Data and Material: All the data and material used in this research is available upon request from the corresponding Author

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Authors' Contributions:

OIO

Conceptualization, Methodology, Supervision, Writing – original draft

AOF

Resources, Writing – review & editing

OO

Data curation

OTM

Project administration, Writing – review & editing

OA

Investigation, Software

RHM

Formal analysis, Visualization,

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Ethical Approval

Ethical approval was obtained from the University of Medical Sciences Research Ethics Committee.The objectives of the study were explained to the children and to their parents during Community Engagement, from whom informed consent was obtained.

Competing Interests:

The authors declare that they have no competing interests

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