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Biennial versus annual treatment for schistosomiasis and its impact on liver morbidity



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SUMMARY

Objective: This study assessed the impact of annual versus biennial praziquantel treatment regimens on the prevalence, intensity of infection, and liver fibrosis dynamics of Asiatic schistosomiasis (caused by *Schistosoma japonicum*) among individuals residing in 18 endemic barangays in Northern Samar, Philippines.

Methods: Five hundred and sixty-five subjects who reported symptoms of gastrointestinal illness and/or were believed to have clinical morbidity based on physical examination were selected for cohort follow-up.

Results: The mean prevalence of schistosomiasis was 34% and the mean intensity of infection was 123.1 eggs per gram. Moderate to severe hepatic fibrosis (grade II/III) was demonstrated in approximately 25% of the study population. As expected, a greater reduction in both the prevalence and intensity of infection was documented with two treatment rounds versus one. Overall, hepatic fibrosis (grades I–III) regressed in only 24.3% of those who received a single treatment and in only 19.3% of those who received two doses. The prevalence of grade II–III fibrosis at baseline (25.2%) remained unchanged 2 years after treatment.

Conclusions: These findings suggest that in order to reverse moderate to severe liver fibrosis due to schistosomiasis and improve clinical outcomes, a higher clinical dosage of praziquantel (i.e., 60–80 mg/kg) may be required over an extended duration.

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1. Introduction

Schistosomiasis, a water-borne trematode disease, remains a significant public health problem. It affects over 240 million people worldwide, causing up to 70 million disability-adjusted life years lost.^{1,2} The World Health Organization (WHO) has recommended and encouraged preventive chemotherapy as the chief strategy to combat this tropical disease worldwide.³ Since the release of the anti-schistosomal drug praziquantel (PZQ) for global use in 1979,

mass drug administration (MDA) has been relied on for the control of schistosomiasis. Furthermore, the WHO decided to optimize the PZQ dose by reducing it from 60 mg/kg given in two equal doses 3–4 h apart to a single oral dose of 40 mg/kg, based on the results of a series of multi-country clinical trials.³ Several studies have claimed that preventive chemotherapy (i.e., 40 mg/kg PZQ), given once or twice annually, can significantly reduce the prevalence and intensity of infection, and ensure the long-term control of morbidity.³

In the Philippines, over 865 000 people are estimated to have schistosomiasis, with another 12 million exposed to the disease.^{4,5} The poverty-stricken regions of the Visayas (Samar and Leyte) and Mindanao are the main endemic foci (80%) in the country. These

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include 28 provinces, 190 municipalities, and 2230 barangays (villages). The existing national control programme involves annual free MDA (40 mg/kg PZQ) in all schistosomiasis-endemic communities with a prevalence of >10%. According to the Philippines National Schistosomiasis Control Programme, the recent human prevalence has dropped to less than 3% nationwide.^{5,6} However, contradictory reports have stated that the programme is failing due to poor drug compliance, poor drug coverage, irregular monitoring and evaluation, and rapid reinfection rates.^{4–6} Moreover, recently published data reported a very high prevalence of the disease in both humans and bovines throughout the country.^{4–6} Advanced schistosomiasis cases and related deaths are currently being reported by the National Department of Health for Mindanao, Samar, Leyte, and Oriental Mindoro.⁶

Hepatic fibrosis is the major cause of morbidity and mortality among people with chronic schistosomiasis. Morbidity associated with schistosomiasis includes variceal formation, splenomegaly, and thrombocytopenia.⁷ Oesophageal and gastric variceal rupture are the lethal outcomes of severe disease.^{8,9} The evaluation of schistosomiasis-induced liver fibrosis in the field setting is best made with a portable ultrasound (US).⁸ The device is reportedly reliable and practical for detecting and assessing the degree of schistosome-induced liver abnormalities, and for monitoring pathological changes following chemotherapy.⁸ Several studies over the past three decades have confirmed its usefulness in evaluating hepatosplenic schistosomiasis in the field.^{8,10–13}

In an earlier cross-sectional survey (2012) in the Philippines involving 18 schistosomiasis-endemic barangays in Northern Samar, an overall human prevalence of 27% was found.⁶ Furthermore, the morbidity assessment in the area using US showed that liver fibrosis occurred among 50% of the population. In this study, the impact of annual versus biennial treatment on reversing the prevalence and intensity of *Schistosoma japonicum* infection was evaluated, as well as the schistosomiasis-induced morbidity.

2. Methods

2.1. Study area

Subjects from 18 endemic barangays in the municipalities of Laoang and Palapag, Northern Samar, the Philippines, participated in the study.⁷ Laoang and Palapag have had an active schistosomiasis control programme dating back to 1980. From 1980 to 1990, the programme involved active case finding and directly observed therapy (DOT) with 60 mg/kg PZQ given to all positive cases; approximately 10–20% of the target population aged 5–65 years was treated. The overall schistosomiasis prevalence ranged from 1% to 30% among the schistosomiasis-endemic barangays. From 1990 to 2007, case finding was strengthened to cover approximately 30–50% of the entire schistosomiasis-endemic population. All egg-positive individuals again received DOT (60 mg/kg PZQ). The schistosomiasis prevalence during this time ranged from 1% to 33% in the schistosomiasis-endemic barangays. In 2008, the MDA DOT programme for schistosomiasis control commenced in the study area and used 40 mg/kg PZQ, based on the recommendations of both the National Department of Health and the WHO. All individuals aged 5–65 years were offered 40 mg/kg PZQ annually, free of charge, as per the Philippines Department of Health Administrative Order 2007–0015. In the same year, the drug compliance rate was high (70–85%), but it has declined significantly (25–65%) from 2009 to the present. The schistosomiasis prevalence ranged from 1% to 46% in the schistosomiasis-endemic barangays over this period. It is noteworthy that an individual can be examined and, if found positive for schistosomiasis, treated for free at any time of the year at a local health centre.

2.2. Study procedures

The subjects who reported symptoms of gastrointestinal illness and/or were believed to have clinical morbidity based on physical examination were selected for cohort follow-up upon completion of the cross-sectional survey in 2012 (Fig. 1).⁷ At baseline, the prevalence and intensity of infection were determined by Kato–Katz (KK) thick smear stool examination. Individuals were asked, over the course of a week, to provide two stool specimens from which six 50-g KK thick smears were prepared on microscope slides according to established methods.¹⁴ Slides were examined under a light microscope in a designated barangay laboratory by experienced technicians, who counted the number of *S. japonicum* eggs per slide. For quality control, 10% of slides were randomly selected and re-examined by a senior microscopist at the Research Institute for Tropical Medicine, Manila. *S. japonicum* egg counts were expressed as eggs per gram (epg) of stool.¹⁴ The intensity of infection was graded according to WHO criteria: light infection (1–99 epg), moderate infection (100–399 epg), and heavy infection (≥ 400 epg).¹⁵

The degree of hepatic fibrosis was assessed using a portable gray-scale ultrasonogram equipped with a 3-MHz curve array

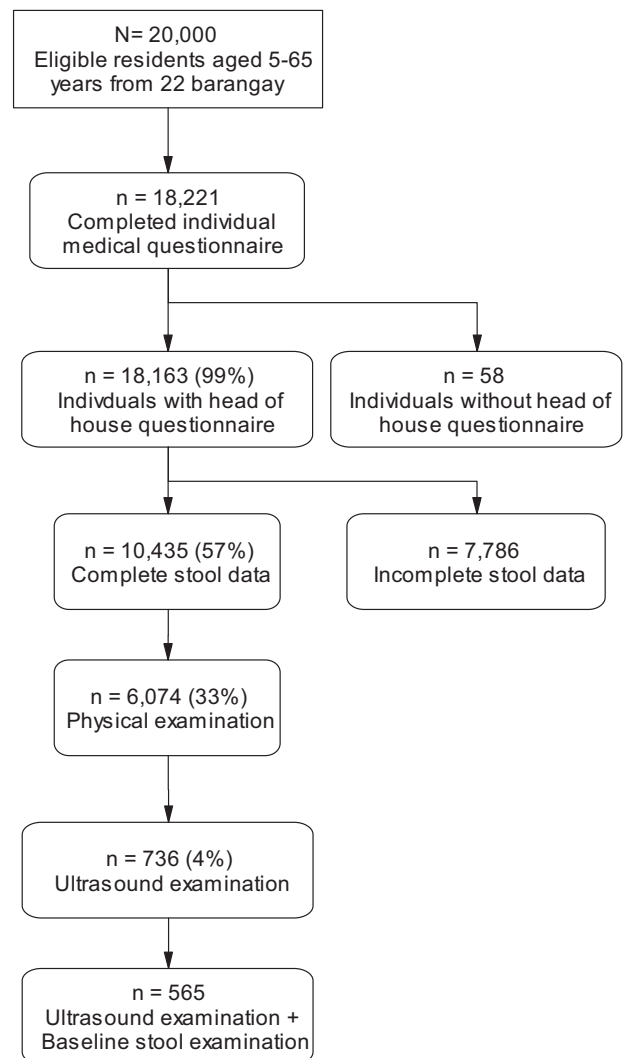


Fig. 1. Study profile and compliance among 18 221 residents from 22 schistosomiasis-endemic barangays in Palapag and Laoang, Northern Samar, the Philippines. All inhabitants aged 5–65 years were invited to participate in the study and provide two stool samples for parasitological examination. A subset of patients ($n = 736$) were selected for ultrasound investigations.

transducer (SONOACE X1; Madison Co., Ltd, Seoul, South Korea). Liver size was measured in millimetres along the Mid-sternal line (MSL) and Mid-clavicular line (MCL) for the left lobe and right lobe, respectively. Spleen size was also measured in millimetres, along the left mid-axillary line (MAL). The hepatic fibrosis grading was adopted from the practical guidelines established for ultrasonography by the WHO/Tropical Disease Research (TDR) (1990).¹⁶ US findings were arrived at by consensus agreement of two experienced sonographers. Ten per cent of the US images were independently validated by a radiologist.

Individuals found to be positive for schistosomiasis, apart from pregnant women, were treated with oral DOT comprising 60 mg/kg PZQ, following the Department of Health guidelines. More specifically, egg-positive subjects were treated orally with 60 mg/kg PZQ in two divided doses, followed by another treatment of the same dose 2 weeks later. Stool-negative individuals were treated with a single oral dose of 40 mg/kg. Following baseline assessment, treatment follow-up was as follows: the first cohort (group A; $n = 278$) comprised subjects from 12 endemic barangays who were treated once after baseline assessment and followed-up 2 years later (biennial treatment). The second cohort (group B; $n = 159$) comprised individuals from six endemic barangays who were treated twice, the first time at baseline and then 1 year later, before final follow-up 2 years later (annual treatment).

All questionnaires were translated into the local dialect; responses were back-translated into English. Ethical consent for the study was obtained from the ethics review boards of the Department of Health in the Philippines (Institutional Review Board Number 2012-13-0) and Griffith University, Australia. Written informed consent was obtained from each individual, or from the parents/legal guardians of those aged < 15 years.

2.3. Statistical analysis

Data were double-entered into FoxPro (version 6.0), cross-checked, and subsequently analysed with STATA SE version 13.0 software (StataCorp LP, College Station, TX, USA). Data were summarized as frequencies or as the mean \pm standard deviation (SD), as appropriate. All categorical variables were evaluated using the Chi-square test. The Wilcoxon signed rank test and McNemar test were used for paired analysis of the intensity of infection and prevalence, respectively, across different age groups. With regards to treatment impact on the intensity of infection, *S. japonicum* egg count + 1 was \log_{10} -transformed to bring observed distributions closer to normality. A significance level of 5% was used for statistical inference.

3. Results

3.1. Study descriptors

Five hundred and sixty-five subjects were initially enrolled in the study. Fifty-three percent of the study population was male, and the mean age of the subjects was 39.4 years (95% confidence interval (CI) 38–41 years). Most were poor rice farmers with a primary level of education and a high degree of water exposure. There was no statistical difference in the sex profile. However, most of the study participants belonged to the age groups 36–45 years (24%) and 46–55 (27%) years. Only 1.0% of the population reported having been diagnosed with hepatitis B; however, 38.4% drank alcohol moderately (consumed 1–2 drinks per day).

3.2. Annual versus biennial PZQ treatment: impact on prevalence and intensity of infection

The impact of treatment on the prevalence and intensity of *S. japonicum* infection in group A ($n = 278$) and group B ($n = 159$) was evaluated at baseline and at follow-up 2 years later (Figs. 2 and 3). The initial prevalence of *S. japonicum* infection in group A was 34.5% ($n = 96/278$; 95% CI 31.8–43.2%), and intensity was 152.2 epg (95% CI 79.3–224.8). Two years after treatment, the prevalence was reduced to 28.1% ($n = 78/278$; 95% CI 23.3–33.9%) and intensity to 121.0 epg (95% CI 52.1–189.9). With regard to group B, the pre-treatment prevalence was 32.1% ($n = 51/159$; 95% CI 24.8–39.3%) and intensity of infection was 89.1 epg (95% CI 51.4–126.8). The prevalence was reduced to 18.3% ($n = 29/159$; 95% CI 12.3–24.3%) and the intensity of infection to 29.2 epg (95% CI 8.6–49.8) at 2 years of follow-up. It is noteworthy that the initial prevalence of infection of 40.0% among group B individuals aged 16–25 years ($n = 10$) dropped to zero ($p = 0.046$). Significant drops in the intensity of infection were also observed only among group B subjects aged 16–25 years ($p = 0.047$) and 46–55 years ($p = 0.004$). Overall, significant drops in prevalence in both cohort groups were observed among individuals aged 16–25 years ($p = 0.008$) and 46–55 years ($p = 0.001$). On the other hand, the overall intensity of infection across all age categories decreased in both cohorts compared with pre-treatment levels. Furthermore, only subjects aged 46–55 years from both cohort groups showed significant decreases in intensity of infection compared with the baseline results ($p = 0.0028$).

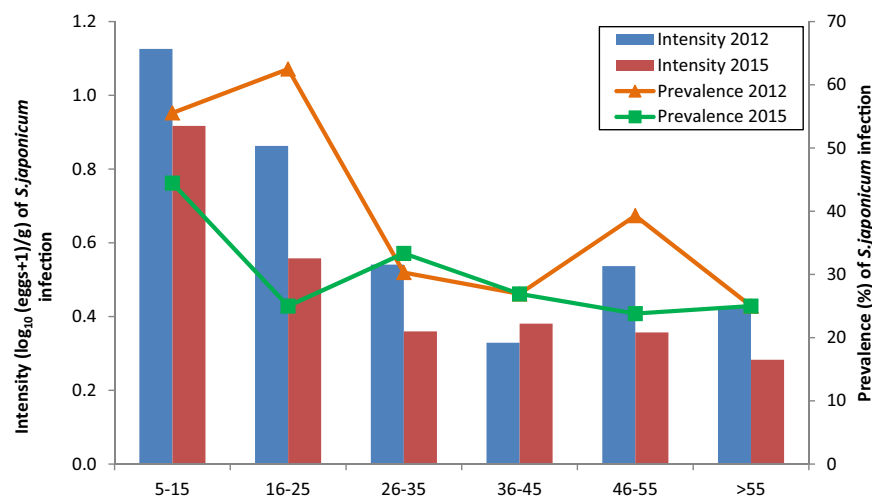


Fig. 2. Cohort prevalence and intensity of infection with *Schistosoma japonicum* by age, before (2012) and after (2015) one treatment of praziquantel (group A).

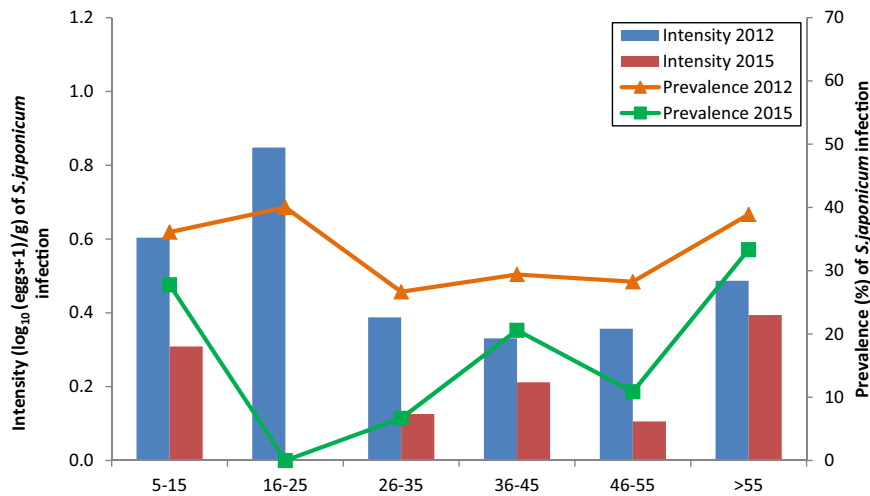


Fig. 3. Cohort prevalence and intensity of infection with *Schistosoma japonicum* by age, before (2012) and after (2015) two treatments of praziquantel (group B).

Table 1

Dynamics of liver parenchyma grading before and after one dose (group A) or two doses (group B) of praziquantel treatment in Northern Samar, Philippines.

Parenchyma grading 2012	Liver parenchyma grading 2015				Total (n)	Progressed	Regressed
	Normal	Grade I	Grade II	Grade III			
One dose of praziquantel							
Normal	99	28	1	0	128	29	0
Grade I	30	24	7	5	66	12	30
Grade II	4	11	20	13	48	13	15
Grade III	2	1	13	6	22	0	16
Total (n)	135	64	41	24	264	54	61
Two doses of praziquantel							
Normal	57	26	2	0	85	28	0
Grade I	10	16	10	2	38	12	10
Grade II	4	6	13	9	32	9	10
Grade III	0	0	1	4	5	0	1
Total (n)	71	48	26	15	160	49	21

3.3. Annual versus biennial PZQ treatment: impact on hepatic fibrosis

The impact of treatment on liver fibrosis dynamics was assessed in both cohort groups (Tables 1 and 2). Compared with baseline, 20.5% (54/264) of group A subjects had progression of parenchymal fibrosis, while 23.1% (49/264) had fibrosis regression at follow-up. With regard to group B, 30.6% (49/160) of the subjects progressed, while only 13.3% (21/160) regressed at follow-up. The initial grade II–III fibrosis prevalence in group A was 26.5% ($n = 70$), but decreased to 24.6% ($n = 65$) at follow-up. In contrast, the initial grade II–III fibrosis prevalence in group B was 23.1% ($n = 37$), but increased to 25.6% ($n = 41$) at follow-up. Overall, the prevalence of grade II–III fibrosis among the 424 subjects at baseline was 25.2%

Table 2

Liver parenchyma (grade II–III) dynamics by age at baseline and after treatment (one versus two doses) with praziquantel.

Age, years	With one treatment		With two treatments			
	Number	Liver parenchyma grade (II–III)	Number	Liver parenchyma grade (II–III)		
		2012		2015	2012	2015
5–15	25	1	0	39	0	0
16–25	8	4	4	10	1	0
26–35	37	8	9	18	2	7
36–45	72	20	19	30	10	11
46–55	79	20	20	46	18	17
>55	43	17	13	17	6	6
Total	264	70	65	160	37	41

($n = 107$), but remained largely unchanged at 25.0% ($n = 106$) at follow-up. As a whole, the prevalence of grade II–III fibrosis increased steadily with age.

4. Discussion

Although PZQ has proven to be safe and effective for the treatment of schistosomiasis, it has certain limitations. PZQ is not 100% curative and does not prevent reinfection.¹⁷ It has no effect on immature schistosomes, which may lower cure rates in areas with very high levels of transmission.^{18,19}

Based on the drug's limitation in killing only adult worms, Tukahebwa et al. performed a study to determine whether giving a second dose increased the efficacy against *Schistosoma mansoni* infection in a highly endemic community in Mayuge District, Uganda.²⁰ This study, which compared one versus two PZQ doses on cure rates for *S. mansoni* infection and reinfection, involved 395 subjects randomized to two groups: one received a single standard dose of 40 mg/kg, while the other received a second dose 2 weeks later. The cure rate and intensity of infection were evaluated 9 weeks after the first treatment, while reinfection levels were monitored 8 and 24 months after treatment. The results showed that those who were given the double dose of treatment were more likely to be cured (69.7%) compared with those who received only a single dose of PZQ (47.9%) ($p < 0.001$). However, at endpoint, the difference in geometric mean intensity of reinfection for those in the single-dose arm versus the two-dose arm was insignificant. Hence it was suggested that two doses of PZQ provided no added benefit in terms of reduced reinfection rates.²⁰

In contrast, King et al.²¹ reviewed the benefits of repeated PZQ dosing administered 2–8 weeks apart in Schistosoma-endemic areas in Africa, and the results of this systematic review demonstrated that treating children or communities with two sequential doses of PZQ could be a cost-effective treatment plan for areas with a high prevalence of *S. mansoni* or *Schistosoma haematobium*, even in the face of ongoing transmission risk. Another seeming advantage of the two-dose administration was that more community subjects would be covered by giving them a second chance of treatment.²¹

An earlier investigation (2012) by the present investigators in the study area revealed that the baseline prevalence and intensity of *S. japonicum* infection were high at 34% and 123.1 epg (95% CI 78.9–167.3), respectively.^{6,22} Furthermore, baseline US indicated an alarmingly high level of schistosomiasis-induced liver morbidity: 88% of subjects had left lobe enlargement (≥ 70 mm) and 25% had moderate to high (grade II–III) fibrosis. These findings suggested that the prevalence, intensity of infection, and morbidity had persisted in the endemic communities despite three decades of human treatment and control carried out by the Municipal Department of Health. These results were attributed to low drug coverage (<36%), low drug compliance (<40%), and zoonotic transmission (e.g., water buffalos and cattle acting as reservoir hosts).²³

In the current study, the impact of two treatment schedules (one versus two rounds) on schistosomiasis prevalence, intensity of infection, and hepatosplenic disease was assessed 2 years after baseline curative treatment (i.e., a dose of 40–60 mg/kg PZQ). As expected, the results showed greater reductions in both the prevalence and intensity of infection with two treatment rounds compared with one, especially among those aged 16–25 years and 46–55 years. However, treatment had less of an impact on lowering schistosomiasis-induced morbidity. Overall, severe hepatic fibrosis (grades II–III) regressed in only 24.3% of those who received a single treatment and in only 19.3% of those who received two doses of PZQ. This outcome is similar to that reported for *S. japonicum* morbidity in China.¹⁰

The present results also suggest that in order to reverse fibrosis and improve clinical outcomes among individuals with significant morbidity, a higher clinical dosage (i.e., 60–80 mg/kg) and longer treatment duration may be required. The progression of fibrosis in a subset of individuals with hepatosplenic disease, despite treatment, was also demonstrated. Some of these subjects might belong to a small percentage of the population whose fibrotic lesions will eventually progress, regardless of treatment. Genetic factors that regulate disease development may possibly account for this outcome.^{24–26} Since not all of the population is subjected to annual mass treatment, as evidenced by low drug coverage and compliance,^{5,6,22} timely identification of genetically susceptible individuals may lead to improved clinical outcomes.

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