



## 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.<sup>1,2</sup> The World Health Organization (WHO) has recommended and encouraged preventive chemotherapy as the chief strategy to combat this tropical disease worldwide.<sup>3</sup> 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.<sup>3</sup> 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.<sup>3</sup>

In the Philippines, over 865 000 people are estimated to have schistosomiasis, with another 12 million exposed to the disease.<sup>4,5</sup> 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.<sup>5,6</sup> 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.<sup>4–6</sup> Moreover, recently published data reported a very high prevalence of the disease in both humans and bovines throughout the country.<sup>4–6</sup> Advanced schistosomiasis cases and related deaths are currently being reported by the National Department of Health for Mindanao, Samar, Leyte, and Oriental Mindoro.<sup>6</sup>

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.<sup>7</sup> Oesophageal and gastric variceal rupture are the lethal outcomes of severe disease.<sup>8,9</sup> The evaluation of schistosomiasis-induced liver fibrosis in the field setting is best made with a portable ultrasound (US).<sup>8</sup> 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.<sup>8</sup> Several studies over the past three decades have confirmed its usefulness in evaluating hepatosplenic schistosomiasis in the field.<sup>8,10–13</sup>

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.<sup>6</sup> 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

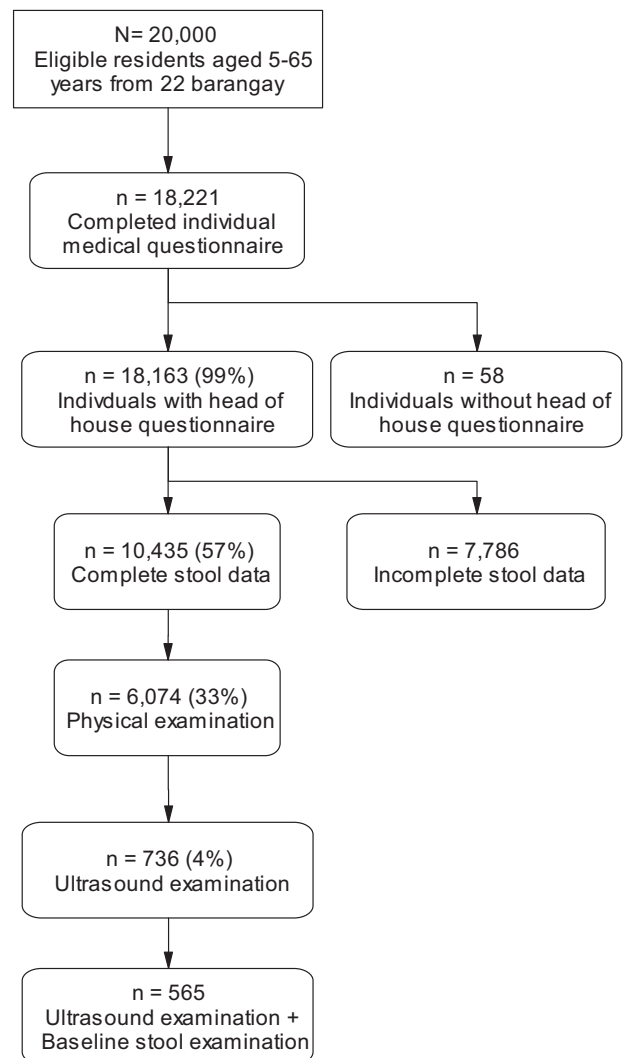
### 2.1. Study area

Subjects from 18 endemic barangays in the municipalities of Laoang and Palapag, Northern Samar, the Philippines, participated in the study.<sup>7</sup> 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).<sup>7</sup> 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.<sup>14</sup> 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.<sup>14</sup> The intensity of infection was graded according to WHO criteria: light infection (1–99 epg), moderate infection (100–399 epg), and heavy infection ( $\geq 400$  epg).<sup>15</sup>

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.

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