

Short Report: The Sensitivity of *Schistosoma japonicum* to Praziquantel: A Field Evaluation in Areas with Low Endemicity of China

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Abstract. The purpose of the current study was to investigate the susceptibility of *Schistosoma japonicum* to praziquantel in low endemic foci of China. During the non-transmission period of schistosomiasis, a total of 43 of 1,242 subjects were identified as being infected with the parasite using parasitological stool examinations in two low-endemicity areas of China, with a prevalence rate of 3.46%. All stool-egg-positive subjects were treated with praziquantel in a single oral dose of 40 mg/kg or 30 mg/kg for two successive days. Six weeks post-treatment, no *S. japonicum* eggs were detected in the 43 treated villagers. The results indicate that the current efficacy of praziquantel against *S. japonicum* seems satisfactory and has not changed over the past three decades in the low endemic areas of China. It is also suggested that no evidence of tolerance or resistance to praziquantel in *S. japonicum* is detected in areas with low endemicity in China.

Human infection by the blood-fluke *Schistosoma japonicum* remains a major public health concern in the People's Republic of China, the Philippines, and parts of Indonesia.¹ In China, concerted control efforts since the 1950s have dramatically reduced the number of the areas endemic for the parasite and the burden of disease among humans.^{2,3} Nevertheless, in the remaining core endemic regions, mainly located along the middle and lower reaches of the Yangtze River and some mountainous areas of provinces of Yunnan and Sichuan, over 0.7 million people are estimated to be infected, with a further 30 million at risk of infection.⁴

Because of high efficacy, excellent tolerance, few and transient side effects, simple administration, and competitive cost, praziquantel is currently the drug of choice for treatment of human schistosomiasis.⁵ Treatment of schistosomiasis japonica has shown great advances with the introduction of the drug into the therapeutic arsenal in China,⁶ and praziquantel-based chemotherapy was considered as a priority control strategy for the national schistosomiasis control program.⁷ Under laboratory conditions it is possible to induce resistance of *Schistosoma mansoni* and *S. japonicum* to praziquantel in mice following treatment with multiple subcurative doses of the drug,^{8,9} and a decreased sensitivity to praziquantel in field isolates of *S. mansoni* has also been found in many endemic foci.^{10–13} In addition, there are several schistosomiasis cases caused by infections with *S. haematobium* in which repeated standard treatment failed to clear the infection.^{14,15} Extensive, long-term, repeated praziquantel chemotherapy has been used to control the morbidity and reduce the prevalence and intensity of *S. japonicum* infection for about 30 years⁷; it is, therefore, of great importance to monitor the current efficacy of praziquantel in areas where the drug is widely used because there is concern that continued use of praziquantel may result in drug resistance in schistosomes, and there are currently few other drugs being developed that are likely to be alternatives to praziquantel. Previously, there were several studies reporting the sensitivity of praziquantel in areas with

moderate or high endemicity.^{16–18} However, the majority of schistosome-endemic areas in China are currently characterized by a low endemicity, which is mainly caused by praziquantel-based comprehensive control.^{19,20} Given that many populations in these areas received praziquantel for treatment or prevention of *S. japonicum* infection many times, it is essential to investigate the susceptibility of *S. japonicum* to praziquantel in low endemic areas. Here, a field investigation was carried out in two foci with low endemicity in China, to evaluate the current efficacy of praziquantel against *S. japonicum*.

Two villages that are endemic for *S. japonicum*, namely Xuguang and Sanshan villages located in Dantu District of Zhenjiang City and Jiangpu District of Nanjing City, Jiangsu Province, were involved in this study, with populations of 1,045 and 1,152, and 2.7% and 1.9% of the people infected, respectively (local epidemiological data in 2006). The praziquantel-based integrated control program, including mass synchronous chemotherapy for both humans and domestic animals (mainly bovine) with praziquantel, control of the snail host of *S. japonicum*, health education, etc., has been successively implemented in both villages for more than 10 years with the World Bank Loan Project for Schistosomiasis Control.²¹ During the period of schistosomiasis non-transmission (from November 2007 to February, 2008), a random sample of 1,242 volunteers 6–70 years of age from the two study villages was included in this study, however pregnant women were excluded. *Schistosoma japonicum* infection was detected by parasitological stool examinations using the miracidium hatching test,²² and the total number of eggs detected in each stool specimen (about 30 g) was counted and recorded, and the intensity of infection was expressed as the number of eggs per gram of feces. Epidemiological case surveys were conducted in those subjects with positive stool examinations, to obtain information including name, age, sex, history of treatment of schistosomiasis, etc. Praziquantel tablets (Nanjing Pharmaceutical Factory Co. Ltd, Nanjing, China; batch no. 20070607) were given to those subjects whose fecal examinations were positive at a single oral dose of 40 mg/kg or 30 mg/kg for two successive days recommended by the Ministry of Health, China. Fecal samples were collected for parasitological stool examinations 6 weeks post-treatment.

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TABLE 1

Demographical features of the detected schistosomiasis patients in the two study villages

| Characteristic | Xuguang Village | Sanshan Village |
|---|-----------------|-----------------|
| Infection rate (%) | 3.12 | 3.64 |
| No. villagers examined | 417 | 825 |
| No. cases infected with <i>S. japonicum</i> | 13 | 30 |
| Age range (years) | 10–61 | 9–60 |
| Sex | | |
| Male | 7 | 17 |
| Female | 6 | 13 |
| Intensity of infection | | |
| EPG 24–96 | 10 | 23 |
| EPG 216–312 | 3 | 7 |
| No. cases with history of infection | 9 | 21 |
| No. cases with history of treatment with praziquantel | 12 | 28 |
| Treatment interval | | |
| < 1 year | 4 | 12 |
| 1–3 years | 4 | 10 |
| > 4 years | 5 | 8 |

This study was approved by the Ethics Review Committees of Jiangsu Provincial Department of Health and Jiangsu Institute of Parasitic Diseases. Informed consents were obtained from all participants following a detailed description of the purpose and potential benefits of the current study. Praziquantel (oral dose of 40 mg/kg or 30 mg/kg) was offered to those cases with stool eggs for free, and all subjects accepted the treatment protocol.

Of the 1,242 residents examined in both villages, 43 had *S. japonicum* eggs in the first stool examination, with a prevalence rate of 3.46%. The infection rate, age range, sex ratio, intensity of infection, history of infection, history of treatment with praziquantel, and treatment interval of the infected patients are shown in Table 1. Among the 43 infected subjects, 13 received praziquantel treatment at a single dose of 40 mg/kg, and 30 were treated with praziquantel at a dose of 30 mg/kg for two successive days. Six weeks after treatment, all of the treated villagers were re-examined and no *S. japonicum* eggs were detected.

Since praziquantel, a highly effective and safe anti-schistosomal drug, was developed,²³ it has replaced all other schistosomicidal agents to become the only anti-schistosomal drug of choice for treatment against all the major species of schistosome.⁵ Praziquantel makes mass chemotherapy possible as a priority control strategy in almost all countries worldwide where schistosomiasis is endemic.⁵

Diagnosis is central to schistosomiasis control.²⁴ Currently, definitive diagnosis of *S. japonicum* infection still requires the demonstration of eggs or miracidia in feces,^{25,26} either by means of the Kato-Katz technique²⁷ or the miracidium hatching method.²¹ It has been shown that the routine Kato-Katz technique underestimates the real prevalence of *S. japonicum* in areas with low endemicity.²⁸ Therefore, the miracidium hatching test was used for detection of *S. japonicum* infection in this study. However, considering the result of the hatching test depends on environmental factors such as temperature and water quality,²⁹ a failure to detect *S. japonicum*-infected residents cannot be excluded.

Our findings indicate that the current efficacy of praziquantel against *S. japonicum* seems satisfactory and has not changed after about three decades of repeated, long-term extensive use in the low endemic areas of China. Together with our previous findings,¹⁷ it seems that the susceptibility of *S. japonicum* to praziquantel remains high in China. Therefore, periodical

monitoring of the efficacy of the drug against schistosomes and systematic survey of praziquantel sensitivity in different geographical isolates of *S. japonicum* in China are required, and development of tools that can be used for field surveillance of drug resistance in *S. japonicum* in China seems justified.

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