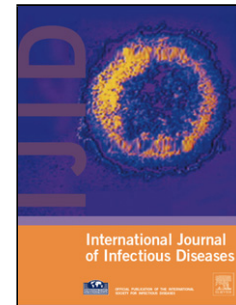


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[ARTICLE TYPE – REVIEW ARTICLE]

Bilharzia in the Philippines: past, present, and future

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Summary

Schistosomiasis japonica has a long history in the Philippines. In 1975, 24 endemic provinces were identified in the northern, central, and southern islands of the Philippines. More than five million people were at risk, with approximately one million infected. In 2003, new foci of infection were found in two provinces in the north and central areas. For the past 30 years, human mass drug administration (MDA), utilizing the drug praziquantel, has been the mainstay of control in the country. Recent studies have shown that the schistosomiasis prevalence ranges from 1% to 50% within different endemic zones. Severe end-organ morbidity is still present in many endemic areas, particularly in remote villages with poor treatment coverage. Moreover, subtle morbidities such as growth retardation, malnutrition, anemia, and

poor cognitive function in infected children persist. There is now strong evidence that large mammals (e.g. water buffaloes, cattle) contribute significantly to disease transmission, complicating control efforts. Given the zoonotic nature of schistosomiasis in the Philippines, it is evident that the incidence, prevalence, and morbidity of the disease will not be controlled by MDA alone. There is a need for innovative cost-effective strategies to control schistosomiasis there in the long term.

Introduction

[Au?3]

Schistosomiasis or bilharzia currently infects over 200 million people worldwide and results in approximately 25 million disability-adjusted life years lost.^{1,3} The disease is caused predominantly by five blood fluke species of the genus *Schistosoma*: *S. mansoni*, *S. japonicum*, *S. mekongi*, *S. intercalatum*, and *S. haematobium*. Zoonotic transmission is a unique factor with *S. japonicum* (and *S. mekongi*) infection, making control measures more complicated (Figure 1). Over the last two decades schistosomiasis has been eradicated in Japan and in the coastal plain of the People's Republic of China, by way of comprehensive multidisciplinary campaigns. However, transmission continues in the lake and marshland regions below the Yangtze River and in the mountainous areas of Sichuan and Yunnan Provinces. The disease remains highly endemic in the Philippines and to a lesser extent in isolated pockets in Indonesia.⁴⁻⁸

[Figure 1 here]

The first case of schistosomiasis in the Philippines was reported in 1906.⁹ The case was a Filipino man who had never been out of the country. He eventually died with clinical impressions of amebiasis and bacterial infection. Autopsy confirmed the diagnosis of amebiasis, but with additional findings of *Schistosoma* ova in sections of the large intestine, liver, and lungs. Subsequently, schistosome ova were found in several cases among 500 autopsies reported in 1908 and in the feces of some prisoners admitted to Bilibid Prison, in the City of Manila in 1914.¹⁰ Several years later, in 1928, a case of Katayama disease (a toxemic syndrome with fever in the acute, early egg-laying phase of schistosomiasis) presenting as chronic appendicitis was reported.¹¹ Attempts to demonstrate the intermediate host of the parasite were not successful until the discovery of the snail *Oncomelania hupensis quadrasi* in Palo, Leyte in 1932.¹² *S. japonicum* infection in mice, rabbits, and monkeys was then established by infecting the animals with cercariae (*Schistosoma* larvae) obtained from the *Oncomelania* snails (Figure 1).

Following identification of the intermediate host, research on delineating schistosomiasis-endemic areas and studies on the clinical and pathological aspects of schistosomiasis japonica were conducted. Research activities were disrupted during World War II, but were given impetus when an outbreak of schistosomiasis occurred among Americans and the Allied Armed Forces, who landed on the island of Leyte in 1945.¹³ In 1953, schistosomiasis was recognized as a public health problem in the Philippines. From the early 1960s to the latter part of the 1970s, extensive research activities ranging from studies on parasite biology, transmission, and control to clinical and pathological aspects of the disease were carried out. Morphological characteristics and the biology of *O. hupensis quadrasi* cercarial shedding patterns, and survival in the environment, and studies elucidating the lifecycle of the parasite

were documented. In 1975 *S. japonicum*-endemic regions in the Philippines were determined.¹⁴ It was estimated that five million people lived in schistosomiasis-endemic areas, with over 800 000 individuals with active infection. The major foci of schistosomiasis were in the islands of Leyte, Samar, and Mindanao, which cover 24 provinces of eight regions of the country, and this situation remains today (Figure 2). These endemic regions have no distinct dry season. The region comprises predominantly rice growing areas, which maximize contact between humans and fresh water snails.¹⁴ In 2003, new foci of infection were found in the provinces of Negros Occidental and in Cagayan in the north of the country¹⁵ (Figure 2).

[Figure 2 here]

Morbidity due to *S. japonicum* infection

Clinical manifestations of schistosomiasis japonica among residents in endemic communities, non-immune individuals, and hospitalized patients, have been reported.^{13,16} Three clinical stages in schistosomiasis japonica infection in the Philippines are recognized and classified: the first or early phase, the second or acute phase, and the third or chronic phase.¹⁶

Early phase

The first stage includes the period from cercarial penetration to establishment of paired worms in the mesenteric venules. Exposure to cercariae via fresh water contact immediately (but not necessarily) results in pruritus, erythema, and a papular rash

known as ‘swimmer’s itch’. People living in endemic areas are seldom seen with the erythema and papular rashes. However, in non-immune individuals, the incidence is highly variable. For instance, among 158 American soldiers landing on the island of Leyte during World War II, 9% showed signs and symptoms of swimmer’s itch.¹⁸ During the period corresponding to larval migration, infected individuals may have chills, fever, headache, an unproductive cough due to pulmonary involvement, and abdominal cramps. The time of onset and intensity of the above clinical manifestations varies widely.¹⁹

Acute phase

Maturation and pairing of adult worms along with the onset of oviposition 42–70 days post-exposure, leads to the second or acute phase of the disease. At this stage, worm metabolic products that are expelled into the systemic circulation contribute to a serum sickness-like condition called Katayama syndrome.²⁰ This syndrome has been well described among 337 American soldiers who were affected by schistosomiasis during the Leyte campaign.¹⁸ Moderate to severe disease is characterized by marked eosinophilia, malaise, generalized muscle pain, and pulmonary symptoms and lymphadenopathy. Tender hepatomegaly was seen in 92% of the soldiers and splenomegaly occurred in 30% of the cases. Diarrhea or dysentery was seen in about 67% of the men.^{18,20} Neurological symptoms suggestive of meningoencephalitis were seen in 9.3%.¹⁸ The severity of clinical disease was also noted to be correlated with the intensity of infection.¹⁸

Chronic phase

During chronic schistosome infection, a variety of clinical manifestations may result from infection depending on the organ involved, and these range from mild to severe, with several gradations in between. Sequelae are categorized into hepatosplenic, hepatointestinal, pulmonary, cerebral, and ectopic forms.^{17,21} Cardiac and renal localizations of lesions are rarely encountered.

In the hepatosplenic form, hemodynamic changes are due to *S. japonicum* eggs trapped in the presinusoidal areas of the liver. These eggs induce classical pipe-stem fibrosis (PSF) around the intrahepatic radicals of the portal vein, leading to increases in splenic pulp and portal vein pressures and signs of severe portal hypertension.²² The severity of portal hypertension correlates with the severity of fibrosis as demonstrated by Doppler ultrasonography.²³ Patients with severe periportal thickening have dilated portal and splenic veins, high portal vein velocity, and portal vein collateral formation. Recently we conducted community-based ultrasound examinations in endemic villages in Northern Samar Province to determine the prevalence of schistosomiasis-induced hepatic fibrosis and hepatosplenic disease. Individuals within these villages have been receiving annual mass drug administration (MDA) with praziquantel for more than 10 years. Approximately 50% of the individuals have some form of hepatic fibrosis, with 20% having grade III fibrosis (severe fibrosis) according to the World Health Organization (WHO) staging criteria (unpublished data). The chronic pulmonary form is due to eggs that have reached the pulmonary circulation as emboli via the portosystemic collaterals. The eggs obstruct the arterioles or pass through the walls and lie in the parenchyma just outside the vessels, giving rise to two types of lesions, namely arterial and parenchymatous lesions, and this can lead to pulmonary hypertension or cor pulmonale. Bronchial

asthma, bronchitis, bronchiectasis, and pulmonary emphysema have also been associated with schistosomiasis.^{13,17}

Chronic schistosomiasis of the central nervous system can present clinically with a wide spectrum of signs and symptoms including: headache, nausea, vertigo, visual and speech defects, rigidity, spasm, mental confusion, and hemiplegia.^{13,17} Focal epilepsy due to schistosomiasis in the Philippines has been estimated to be from 2% to 5% among *S. japonicum*-infected individuals.¹³ Ectopic forms of schistosomiasis have been demonstrated in many organs, including the heart, appendix, ovary, fallopian tubes, and uterus.^{13,17}

Other manifestations

Over the past 20 years, many studies have examined the impact of *S. japonicum* infection on growth, nutrition, hemoglobin levels, and cognitive functions in Filipino children. For example, in 1990 it was demonstrated that the intensity of infection was associated with decreased fat, muscle, and long bone growth in adolescents; males aged 16 to 18 years were 7.8 cm shorter and 5.8 kg lighter than non-infected adolescents in the same community.^{24,25} The effects were greater in villages not yet receiving annual screening and treatment. In other studies, *S. japonicum* infection in children was associated with malnutrition, anemia, and lower cognitive performance, such as learning, memory, and verbal fluency.^{26–28} Studies in infected women have shown that maternal schistosomiasis has adverse effects on pregnancy outcomes. Babies born from mothers with schistosomiasis have markedly decreased birth weights. Circulating mediators of inflammation are elevated in the peripheral blood, placental blood, and placental tissues of *S. japonicum*-infected pregnant women. In

addition, placental interferon gamma is associated with both *S. japonicum* infection status and markedly decreased birth weight.²⁹

Chemotherapy

Praziquantel has proven to be effective against the five species of schistosomes affecting humans. However, efficacy depends on the treatment dose. In an attempt to optimize praziquantel use for the treatment of schistosomiasis, the WHO Special Programme for Research and Training in Tropical Diseases (TDR) launched in 2003 a series of multi-country trials, comparing the efficacy and safety of 40 mg/kg and 60 mg/kg in schistosome-infected patients in Asia, Africa, and the Americas (Add a reference here [Au?4]). In the clinical trial in the Philippines, the 40 mg/kg dose was effective and better tolerated than the higher 60 mg/kg dose. The national policy-makers in the Philippines subsequently adopted the 40 mg/kg dose for its MDA program against schistosomiasis. However, those found infected by stool examination (case finding) were treated with 60 mg/kg and given the same dose 2 weeks later as per the national protocol.

Past and present control strategies

The schistosomiasis problem in the Philippines is a formidable one. Climatic conditions and rice farming methods have made snail control difficult. Before the introduction of praziquantel in the Philippines, approaches used were aimed at decreasing transmission by reducing the number of snail intermediate hosts and by limiting human exposure to the infective form of the parasite. Environmental

manipulation (e.g., irrigation) in combination with molluscicides was used. However, these approaches were reported to be expensive and have shown limited impact on human transmission in pilot studies.³⁰ Improved sanitation was an essential component of the control program, but was difficult to sustain in communities, as no more than one third of the population had satisfactory latrines. Chemotherapy was used only on a case-by-case basis, as the drugs available at that time produced significant side effects before therapeutic levels were reached. There were significant achievements, but they were not effective in reducing the prevalence, incidence, or morbidity of *S. japonicum* infection.

With the introduction of praziquantel in the Philippines in 1980, schistosomiasis control shifted to a chemotherapy-based program. Case finding and treatment led to a decline in the national prevalence of schistosomiasis. In 1990 the Philippine National Schistosomiasis Control Program (PNSCP) under the Philippine Health Development Plan received a substantial loan, enabling the PNSCP to intensify case finding and treatment in all endemic areas. The PNSCP managed to reduce the national prevalence from more than 10% before 1990 to less than 5% in 1995. Unfortunately, the funds ceased in 1995. Subsequent marked budget reductions resulted in significantly decreased financial support and a loss of schistosomiasis control teams in each of the endemic municipalities.³¹ After 1995 the chemotherapy-based control program shifted from case finding and treatment to MDA. Despite the marked reduction in financial and manpower support for the control program, the annual national prevalence data on schistosomiasis in the Philippines reported by the PNSCP has been maintained at less than 5%. This reported low national prevalence data has given the mistaken impression that schistosomiasis is no longer a major public health problem there and can even be eliminated in some endemic areas by

MDA. However, bodies of evidence generated from endemic areas in the country are suggesting that elimination of schistosomiasis in the Philippines using MDA as the major approach will not be sustainable in the long run. For example, in a study looking at the long-term impact of intensive case finding treatment with praziquantel (compliance more than 85% throughout the 9-year period of the study), dramatic drops in the prevalence and incidence of infection occurred in the first 3 to 4 years, followed by significant rebound.³²

Recent studies by Leonardo and colleagues,^{33,34} funded by the WHO Western Pacific Region (WPRO), reported that the national schistosomiasis prevalence in the Philippines is less than 1% (mean 0.49%; range 0.08–3.95%). However, these findings grossly understate the current human schistosomiasis prevalence there. We recently (2011) conducted a cross-sectional epidemiological survey to determine the current schistosomiasis burden across six barangays in Northern Samar, the Philippines. The overall human prevalence was found to be 26.4% ($n = 1955$; 95% confidence interval 24.5–28.4%), while in carabao (water buffaloes) it was found to be 65.4% ($n = 211$; 95% confidence interval 58.9–71.9%).³⁵ The study was expanded in 2012 to 18 barangays, and the human schistosomiasis prevalences in the barangays under study were found to range from 5% to 48%.³⁵ The results are contrary to those recently reported for Northern Samar where the mean human prevalence was reported to be only 2.45%.^{33,34} Advanced schistosomiasis cases and deaths are now being reported by the media and confirmed by the National Department of Health for Mindanao, Samar, Leyte, and Oriental Mindoro.³⁵ This latest evidence clearly demonstrates that schistosomiasis has not been eliminated from the Philippines and, indeed, remains a major public health problem there. Moreover, the compliance to MDA has decreased over time as people living in endemic villages in the Philippines

prefer case finding and treatment to MDA done empirically.^{36,38} There are now strong bodies of evidence to show that water buffalo (called carabao in the Philippines), cattle, dogs, and a range of feral animals, also contribute significantly to disease transmission.^{39–44} Given the zoonotic nature of schistosomiasis in the Philippines, there is a need for cheap innovative control strategies to combat the disease.

Future control strategies leading to elimination

Over the last five decades, schistosomiasis japonica has been eliminated from Japan (in 1996) and transmission has been interrupted in the coastal plain region of the People's Republic of China, by integrated approaches involving snail control, mass chemotherapy of the human population, health education, provision of sanitary facilities, environmental modification, and improved farming methods. The successful schistosomiasis control measures deployed in Japan and China cannot be easily duplicated in the Philippines given the nature of year-round transmission there (only 5 months in China) and limited health care dollars to combat the disease.

The current (2012) national funding for schistosomiasis control in the Philippines is PHP \$ 47 684 000 (USD \$ 1 126 477.54).²⁵ This amount represents only a small fraction (<1%) of what is currently spent on the national schistosomiasis elimination program in China.³⁵ Moreover, the manpower and infrastructure in China far surpass those of the Philippines. In the Philippines, the population in rural endemic areas is growing exponentially; thus more and more individuals are becoming at risk of contracting schistosomiasis. Filipinos residing within schistosomiasis-endemic areas are typically very poor rice farmers with family incomes far below the national average.³⁵ Over 50% of the endemic population live in poverty, with rudimentary

water, sanitation, and hygiene; therefore, the rates of parasitic diseases, acute respiratory infections, diarrheal diseases, and other communicable diseases are high.³⁵ The only way forward is to break the *S. japonicum* lifecycle through multi-component integrated control.

The disappointing results obtained with MDA for schistosomiasis control reflect the complex nature of the human–schistosome parasite interaction. There is a need to formulate innovative approaches that are economically sustainable in the Philippines. Currently, a combination of human mass treatment, targeted molluscicides, and bovine (water buffalo and cattle) treatment and vaccination is being trialed in 22 highly endemic villages in the province of Northern Samar. In a pre-clinical trial in China, the vaccine (SjCTPI-Hsp70 construct) provided a 51.2% reduction in worm burden, a 61.5% reduction in liver eggs, and a 52.1% reduction in fecal eggs and hatching of fecal miracidia (free swimming larvae).⁴⁵ If the bovine vaccine, along with the other integrated measures, proves to be successful, it may lead to sustainable schistosomiasis control and elimination in the Philippines.

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Figure captions

Figure 1 The zoonotic lifecycle of *Schistosoma japonicum* in the Philippines.

Figure 2 Map of the current schistosome-endemic areas in the Philippines highlighted in blue. The red dot represents a new focus of infection discovered in 2003.

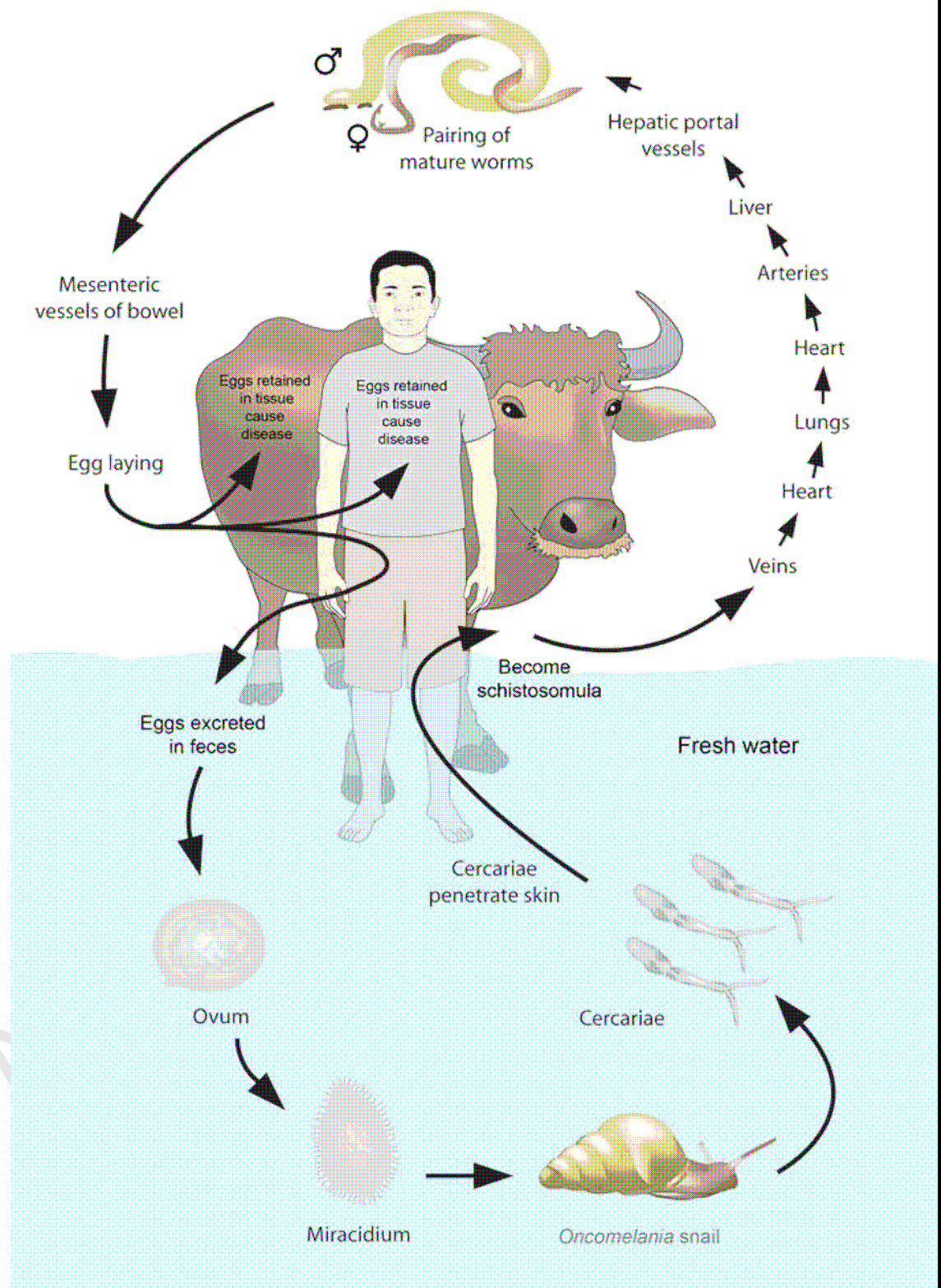


Figure 1

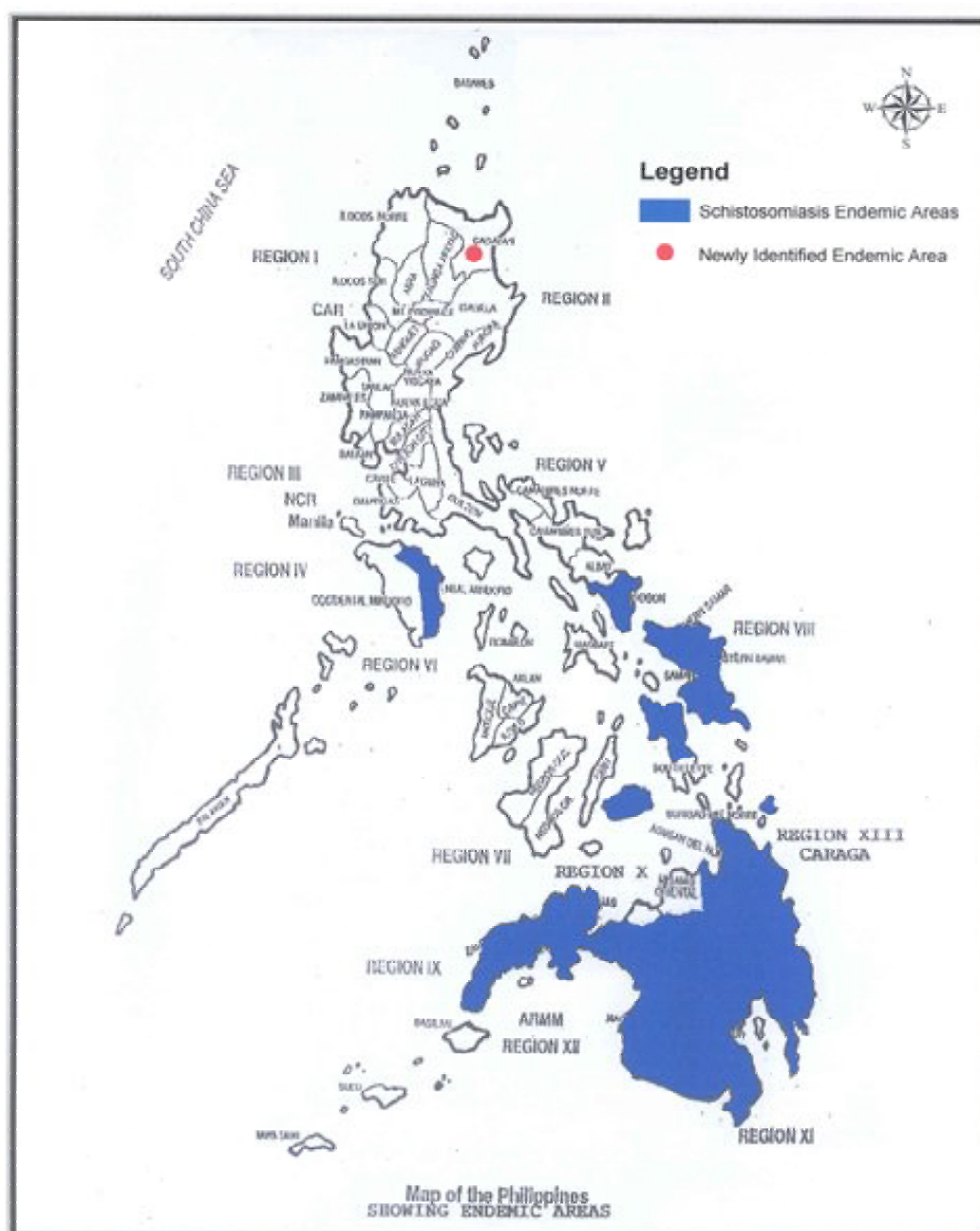


Figure 2