Journal of Agricultural Research, Development, Extension, and Technology, 3(1), 71-87 (2021)
Review Article

Schistosoma japonicum in the Philippines: Its epidemiology, diagnostics, control, and elimination

Jan Clyden B. Tenorio[1,2] and Elizabeth C. Molina[1]

[1]*Department of Veterinary Paraclinical Sciences, College of Veterinary Medicine, University of Southern Mindanao, Kabacan 9407, Cotabato, Philippines*
[2]*Department of Veterinary Paraclinical Sciences, College of Veterinary Medicine, University of the Philippines Los Baños, College, Laguna 4031, Philippines*

Received: August 5, 2021
Revised: September 18, 2021
Accepted: October 8, 2021

Abstract

Schistosoma japonicum infections continue to be a public health concern in China, the Philippines, and Indonesia. In the Philippines, it has a focal distribution wherein an estimated 12.4 million people are at risk of infection, while 2.7 million are directly exposed across 12 regions. The country's latest national prevalence revealed that some endemic communities had already reached infection control status. Recent advancements in schistosomiasis diagnostics have resulted in the development of assays that have superior diagnostic performance. The cost of adopting these novel techniques remains a huge bottleneck for those with developing economies and underfunded control and elimination programs like the Philippines. Mass Drug Administration (MDA) has significantly reduced the schistosomiasis morbidity rates in the Philippines through its protracted implementation. MDA fatigue among beneficiaries resulting in non-compliance has been reported. Control and elimination efforts still need continued local and national governmental support. A One Health approach is called for if the goal of transmission interruption in all endemic communities is to be achieved by 2025. This paper reviews the recent research and updates on *S. japonicum* infections in terms of disease occurrence, advancements in diagnostic techniques and approaches, and its treatment, prevention, control, and elimination in the Philippines and its neighboring countries.

Keywords - *diagnostics, neglected tropical diseases, one health, schistosoma japonicum, schistosomiasis, the Philippines*

Introduction

Schistosomiasis infections have been reported in 78 countries, including the People's Republic of China, the Philippines, and Indonesia (Gordon et al., 2019; World Health Organization [WHO], 2020a, 2021). It was reported that an estimated 290.8 million people required preventive chemotherapy for schistosomiasis, but only 97.2 million people were treated for this Neglected Tropical Disease (NTD) (Casulli, 2021; Chen et al., 2021; WHO, 2020a). *Schistosoma mansoni*, *S. haematobium* and *S. japonicum*, the primary human schistosomiasis agents, were reported to cause losses of about 1.5 to 4.5 million disability life years (DALYs) (McManus et al., 2010; Hailgebriel et al., 2020). The Philippine Schistosomiasis Control and Elimination Program reported that the national prevalence was 4.68% in 2017 (Philippine Department of Health [DOH], 2018). *Schistosoma japonicum* infections are endemic in 1,609 barangays (communities), in 196 municipalities and 15 cities, in 28 provinces, and in 12 regions (Palasi, 2021). An estimated 12.4 million Filipinos are at risk, while 2.7 million are directly exposed to the parasite (Leonardo et al., 2020a, 2020b; Palasi, 2021).

Trematodes of the genus *Schistosoma* are the cause of schistosomiasis or bilharziasis. These parasites belong to the family Schistosomatidae, order Strigeidida (Taylor et al., 2016). These worms are primarily parasites of blood vessels of the gastrointestinal tract and the genitourinary system. Six major *Schistosoma* species cause disease in humans (Tenorio & Molina, 2020; WHO, 2020a). *S. mansoni* causes intestinal schistosomiasis in Africa, the Caribbean, the Middle East, and parts of South America (Kurup & Hunjan, 2010; WHO, 2020a). *S. guineensis* and *S. intercalatum* are found in central Africa (McManus et al., 2018). *S. haematobium*

Corresponding author email: Jan Clyden B. Tenorio, jcbtenorio@usm.edu.ph

causes urogenital schistosomiasis in Africa, the Middle East, and Corsica in France (Boissier et al., 2016; McManus et al., 2018). *S. japonicum*, the etiologic agent of schistosomiasis japonica, is different among the aforementioned species due to its zoonotic nature which can involve several species of wild and domestic animals. It causes intestinal schistosomiasis in China, Indonesia, and the Philippines (Gordon et al., 2019; Olveda et al., 2014). Similarly, *S. mekongi*, which causes a similar disease in several areas in Lao PDR and Cambodia, is also recognized as a zoonotic parasite, but the animal species involved has yet to be elucidated (Khieu et al., 2019; WHO, 2020a).

Oncomelania hupensis quadrasi is the only known intermediate host of *S. japonicum* in the Philippines. This snail species prefers aquatic environments, such as wet soils, rice paddies, ponds, streams and shaded areas in riverbanks (Gordon et al., 2019). Various studies and governmental reports have noted varying *S. japonicum* infection rates among snails collected in endemic areas, majority of which are in Mindanao (Abao-Paylangco et al., 2019; Fornillos et al., 2019a). Snail-infested bodies of water are sources of direct infection transmission due to a large amount of parasite cercariae infective stages released by *S. japonicum*-infected *O. hupensis quadrasi*.

In the Philippines, dogs, rats, pigs, cats, cattle, and water buffaloes reportedly have been affected by schistosomiasis japonica (Fernandez et al., 2007; Gordon et al., 2012, 2015c; McGarvey et al., 2006). Bubalines, and to a lesser extent bovines, have been implicated as the main reservoir hosts of schistosomiasis japonica in the Philippines (Angeles et al., 2015; Olveda & Gray, 2019). High prevalence has been reported among water buffaloes in schistosomiasis hot spots (Gordon et al., 2012, 2015c; Wu et al., 2010). However, the actual status of the disease among these animals and in other reservoir host species in most endemic areas in the country remains largely unknown.

A variety of tests have been developed to effectively diagnose schistosomiasis caused by various schistosome species. These include the conventional microscopy-based tests, antibody- or antigen-based serologic methods, molecular assays, and the use of inflammatory and metabolic products as biomarkers of disease (Chen et al., 2021; Gordon et al., 2019; Weerakoon et al., 2015). In addition, various control, prevention, and elimination efforts have been put into place to eliminate *S. japonicum* infections in China, the Philippines, and Indonesia, and *S. mekongi* in Lao PDR and Cambodia. These include preventive chemotherapy or Mass Drug Administration (MDA), provision of clean water, and practice of sanitation and hygiene (WASH), snail control programs, community education towards behavioral modification, and veterinary management of animal reservoir hosts (Leonardo et al., 2020b; WHO, 2017).

This paper is a review of recent updates on schistosomiasis with a special highlight to schistosomiasis japonica in the Philippines. The aim of this paper is to collate recent research and updates on *S. japonicum* infections in terms of disease occurrence, advancements in diagnostic techniques and approaches, and the disease treatment, prevention, control and elimination efforts in the country.

Life Cycle and Zoonotic Transmission of *S. japonicum*

Snail Intermediate Host

S. japonicum has a complex life cycle that utilizes a snail intermediate host and a mammalian final host (Figure 1). Various snail species are known to be the intermediate host of the parasite in different parts of Asia: *O. hupensis nosphora* and *O. hupensis formosana* in Japan, *O. hupensis hupensis* in China, and *O. hupensis quadrasi* in the Philippines (Gordon et al., 2019; Leonardo et al., 2020b). In China, four subspecies of *O. hupensis* were identified: *O. hupensis guangxiensis*, *O. hupensis tangi*, *O. hupensis hupensis*, and *O. hupensis robertsoni* (Guan et al., 2016; Gordon et al., 2019; Li et al., 2009; Zhao et al., 2010). The former two species' populations have been reduced through control measures and the latter two were noted as the remaining dominant species; *O. hupensis hupensis* is the most widespread in China (Gordon et al., 2019; Zhao et al., 2010). These snails are prevalent near water bodies, wherein they release the infective stage of the parasite (Fornillos et al., 2019; Leonardo et al., 2020b). Moreover, Fornillos et al. (2019a) reported that water-logged areas with thick vegetation, riverbanks, rice fields, ponds, irrigation cannals, swamps, and streams were common characteristics of habitats of *O. hupensis quadrasi* in the Philippines. These conditions provide adequate moisture and shade for the snails

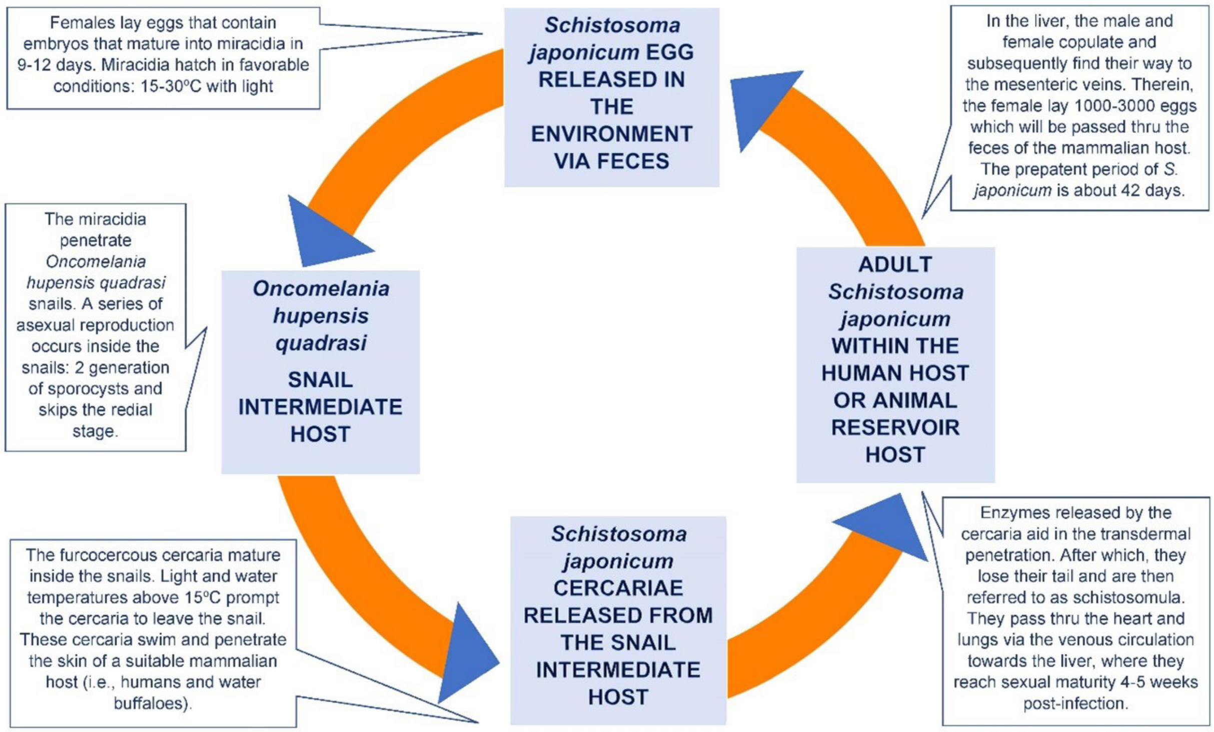

Figure 1. The zoonotic life cycle of *Schistosoma japonicum* in the Philippines. The parasite utilizes the amphibious Oncomelania hupensis quadrasi snail as the intermediate host and suitable mammalian hosts (e.g., humans and water buffaloes) as final host (Carabin et al., 2011). Water buffaloes serve as non-human sources of schistosome eggs that may in turn develop into infective cercariae that can cause human infections. .

to proliferate, as noted by Calata et al. (2019). In endemic areas, the presence of snail intermediate hosts together with suitable animal reservoir hosts complicate the control and prevention of human *S. japonicum* infections.

S. japonicum infection rates among *O. hupensis quadrasi* snails in endemic areas in the Philippines have been reported and studied by various papers and agency reports. In 2016, Leonardo et al. reported that from 2013 to 2015, the snail infection rate (SIR) of *S. japonicum* was highest in Northern Samar at more than 12%, followed by Sorsogon, Davao de Oro and Surigao del Norte at more than 1%. These were followed by Mindoro Oriental, Negros Occidental, Agusan del Sur, Leyte, Lanao del Norte, Bukidnon, New Corella in Davao del Norte, and Negros Occidental which had snails infected with *S. japonicum* but with infection rates at lower than 1%. Recently, Fornillos et al. (2019a) determined the *S. japonicum* SIR and positive sampling sites (PSS) of *O. hupensis quadrasi* in different edemic areas of the country. They reported that Maragusan, Compostela Valley had the highest infection rate (1.51 %), with 3 out of the 4 sampling sites having snails infected with *S. japonicum*. It was followed by Alegria, Surigao del Sur (SIR: 0.98%; PSS: 3/5), Kapatagan, Lanao del Norte (SIR: 0.87%; PSS: 3/4), Valencia, Bukidnon (SIR: 0.75%; PSS: 1/3), Alang-alang, Leyte (SIR: 0.57%; PSS: 3/5), Trento, Agusan del Sur (SIR: 0.36%; PSS: 3/7). All of the snails obtained from Talibon, Bohol were not infected with *S. japonicum*. This does not come as a surprise because Bohol has been noted as the only endemic province that has achieved near *S. japonicum* elimination status in the country (Leonardo et al., 2016). In Lake Mainit, Agusan del Sur, Abao-Paylangco et al. (2019) reported an over-all prevalence of 67.71% among *O. hupensis quadrasi* collected from rice fields within the vicinity of the lake.

Mammalian Reservoir Hosts

Over 40 species of mammals, including humans, are known to harbor *S. japonicum* (He et al., 2001). Moreover, several species of animals have been implicated as reservoirs of human infections. In China, dogs, rats, pigs, cats, goats and sheep, cattle, and water buffaloes were initially thought to play such roles (McManus et al., 2010). Likewise, some of these animals have also been found to harbor the parasite in the Philippines (Fernandez et al., 2007; Gordon et al., 2012, 2015c; McGarvey et al., 2006; Tenorio & Molina, 2020). In China, however, transmission modeling studies have found that around 75-99% of human infections in different endemic areas can be attributed to water buffaloes (Gray et al., 2007, 2008, 2009; Williams et al., 2002). Hence, the recent reports of high prevalences of schistosomiasis japonica in water buffaloes and cattle in endemic foci in the country (Gordon et al., 2012, 2015c; Jumawan & Estaño, 2021; Navarro et al., 2021; Tenorio & Molina 2020; Wu et al., 2010) had resulted to the notion that these animals may also be the important reservoirs of human infections in the Philippines (Angeles et al., 2015; Olveda et al., 2014; Olveda & Gray, 2019). Thus, it has been advocated that these animals be included in the control and elimination efforts of *S. japonicum* in the country.

Epidemiology of *S. japonicum* in the Phlippines

Schistosoma japonicum has a long history in the Philippines. It was first reported in a patient that had amoebiasis and bacterial infection in 1906 (Leonardo et al., 2020a, 2020b; Olveda et al., 2014). Moreover, it was first recognized as a disease of public health concern in 1953 (Olveda et al., 2014). Schistosomiasis has been reported to have a clustered distribution in Luzon, Visayas, and Mindanao (Leonardo et al., 2020b; Soares Magalhães et al., 2014). All the provinces in Mindanao are affected except Sulu and its neighboring islands, Misamis Oriental and Sarangani (Leonardo et al., 2008, 2020b). The Philippine Schistosomiasis Control and Elimination Program (SCEP) reported that the national prevalence is 4.68% based on a focal survey in 2017 (Palasi, 2021; DOH, 2018). Moreover, among the 1,442 barangays surveyed from 2015 to 2020, 30% have high endemicity (i.e., prevalence of >5%), 27% have moderate endemicity (i.e., prevalence of ≥1% but <5%), and 33% are under low endemicity classification (i.e., prevalence that is <1%) (Palasi, 2021). An estimated 12.4 million Filipinos are at risk, while 2.7 million are directly exposed to the parasite (Leonardo et al., 2020b; Palasi, 2021).

Multiple published studies have reported the national baseline prevalence and the prevalence in each schistosomiasis endemic province in the Philippines, the most comprehensive of which was conducted between 2005-2008. Leonardo et al., (2008, 2012) reported that the national baseline prevalence was 1.3% (range: 0.08% to 6.30%). Furthermore, the group discovered that Mindoro Oriental had the highest prevalence among endemic provinces at 6.3%. Agusan del Sur in Mindanao followed with a prevalence of 3.9% and then Sorsogon at 3.6%. Northern Samar and Eastern Samar in Eastern Visayas rounded out the top five endemic provinces with a prevalence of 2.4% and 1.8%, respectively. It is important to note that the Kato-Katz technique was used to assess multiple stool samples collected from study participants in endemic areas. In 2013-2015, another national schistosomiasis prevalence survey was conducted by the SCEP (Figure 2) (Leonardo et al., 2016; Manalo, 2020). It was reported that Northern Samar was the top endemic province with a prevalence of 10.0%. Agusan del Norte and Sorsogon followed with prevalences of 4.34% and 4.0%, respectively. Two provinces from Central Mindanao rounded out the top five endemic provinces in the 2013-2015 survey, with Bukidnon ranking fourth at 3.83% prevalence and Cotabato Province (formerly North Cotabato) occupying the fifth spot with 3.45%. With these reports, Leonardo et al. (2016) noted that some of the endemic provinces with prevalences of <5% had already reached morbidity control status.

Risk Factors of Schistosomiasis in the Country

Certain demographics of Filipinos have a higher risk of infection than others. Water contact behaviors are the root of most risk factors to human schistosomiasis infections (Buchwald et al., 2021; Carabin et al., 2011). *S. japonicum* infections are considered an occupational hazard to those who have extensive exposure to infected bodies of water (i.e., fisher folks), as well as those working in sites where the snail intermediate hosts may proliferate (i.e., farmers in rice paddies) (Leonardo et al., 2008, 2012). Groups within these demographics are associated with higher prevalence (Carabin et al., 2011). Also, there is evidence of differences in schistosomiasis prevalence between sexes, with males being more at risk than females (Leonardo et al., 2008, 2012, 2015). Leonardo et al. (2015) posited that this might be due to the occupational hazard of rice farming duties among male inhabitants

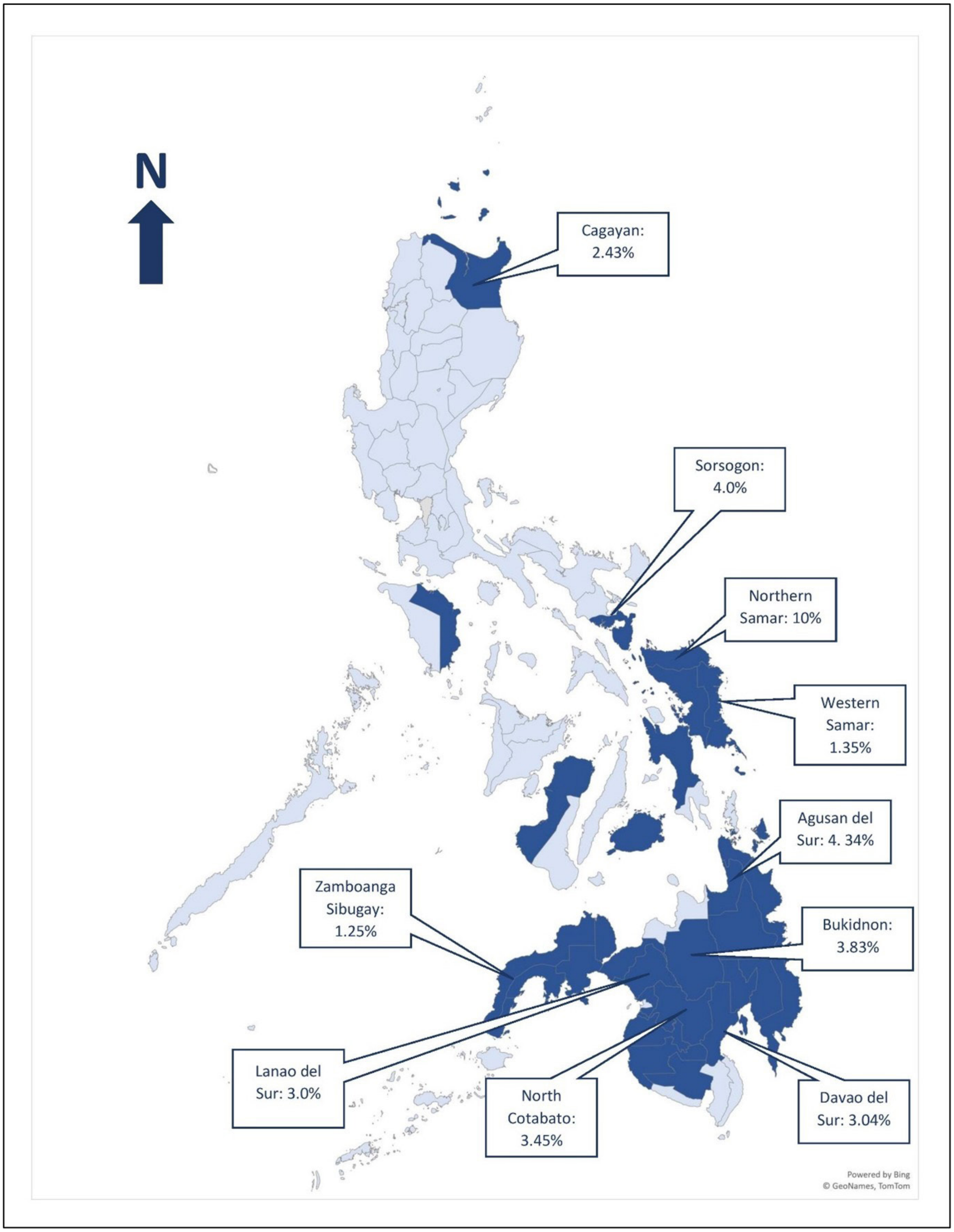

Figure 2. Map of the 28 *Schistosoma japonicum* endemic provinces in the Philippines (in blue) according to Palasi (2021). Highlighted are the ten provinces with the highest prevalence based on a survey conducted in 2013-2015, as reported by Leonardo et al. (2016) and Manalo (2020).

in endemic foci. The authors also noted that females also participate in rice farming activities but to a lesser extent. *S. japonicum* infections tend to peak with older age, which could be due to more prolonged exposure to infected environments (Leonardo et al., 2008, 2012, 2015). It has been noted that the probability of schistosomiasis is higher in adults aged 20 years old and above (Soares Magalhães et al., 2014).

An increased risk of infection was also reported in school-aged children in Calatrava, Negros Occidental (Belizario et al., 2015). Schistosomiasis in school-aged children has been noted to cause anemia, malnutrition, stunting, and poor cognitive performance (Cabanacan-Salibay et al., 2016). Socio-economic status had also been reported as a key determinant of *S. japonicum* infections. High economic status is a protective factor, while lower-income status and living in rural, endemic farming areas are seen to be a predisposition to infection (Carabin et al., 2011). The capacity to provide for a sufficient WASH facility, whether at home or in the community at large, is an example of how economic status influences the risk of acquiring the disease among people from different economic demographics.

The findings reiterate that schistosomiasis is a disease of poverty, and those living and working in contact with infected bodies of water are at a greater risk of acquiring *S. japonicum* infections. Farmers who use water buffaloes or cattle as draft animals are at risk of infection as these animals may serve as reservoir hosts. Within an endemic setting where an infected reservoir host (i.e., water buffaloes wallowing in mud) is cohabitating with the snail intermediate hosts, human inhabitants are at extreme risk of infection, and perpetuation of schistosomiasis in such areas is inevitable if control and prevention efforts are not enacted. The risk of infection among school-aged children should not be taken lightly due to the pathologies caused by infections that may have long-lasting effects in their age group.

Advancements in Diagnostic Approaches

Various tests have been developed throughout the years to effectively diagnose schistosomiasis caused by various schistosome species. These include the conventional microscopy-based parasitological techniques that detect the agent's eggs or immature forms, serological methods, molecular assays, and the use of inflammatory and metabolic products as biomarkers of disease (Chen et al., 2021; Gordon et al., 2019; Weerakoon et al., 2015). This section will briefly highlight and discuss the principles, uses, pros, and cons of these techniques.

Parasitological Techniques

Tests that fall under this category are those used to demonstrate schistosome eggs or immature forms using microscopy. The most valuable and perhaps the most widely used is the Kato-Katz (KK) technique. It involves detecting schistosome eggs in a thick fecal smear under a microscope (Ajibola et al., 2018; Belizario et al., 2014). The WHO (2019) recommends KK for monitoring control programs (e.g., mass drug administrations) of NTDs, including schistosomiasis. The technique is easy to conduct, inexpensive, less laborious, and has good sensitivity in settings of high disease burdens (Ajibola et al., 2018; Weerakoon et al., 2015). However, in areas of low prevalence (i.e., those receiving mass prophylactic treatments), its sensitivity is decreased (Gordon et al., 2019; Olveda et al., 2016; Weerakoon et al., 2015). Increasing the sensitivity of KK may involve increasing the number of samples collected from the study population. Samples may be collected on separate but succeeding days (i.e., 2-4 days). Bärenbold et al. (2017) showed that if the *S. mansoni* egg per gram (EPG) was 100, examination of one sample via KK would have a sensitivity of 50% but an examination of two samples increased KK's sensitivity to 80%. The KK technique has been used extensively in national prevalence surveys in the Philippines (Belizario et al., 2015; Leonardo et al., 2008, 2012, 2015).

Other less used copro-parasitologic techniques include the FLOTAC technique (Cringoli et al., 2010) and the Danish Bilhaziasis Laboratory (DBL) technique. The DBL technique has been used in detecting *S. japonicum* eggs in animals in the Philippines (Fernandez et al., 2007; Leonardo et al., 2015; Wu et al., 2010). The Miracidial Hatching Technique (MHT) is used to test the viability of excreted schistosome eggs (Juberg et al., 2008). For the detection and quantification of schistosome eggs in fecal samples of bovines and bubalines, Formalin Ethyl Acetate–Sendimentation & Digestion (FEA-SD) technique was developed by Xu et al. (2012). It involves sedimentation of fecal samples using ethyl acetate and formalin and digestion with potassium hydroxide. The former allows for the separation of debris, and the latter enables a clearer observation of the schistosome eggs by rendering the undigested fibers translucent. The authors noted that FEA-SD might be of considerable value to schistosomiasis surveillance in bovine reservoir hosts (Xu et al., 2012). Tenorio and Molina (2020), Navarro et al. (2021), and Jumawan and Estaño (2021) utilized this technique to survey *S. japonicum* infections among water buffaloes and cattle in different regions in Mindanao.

Serological Techniques

Serological tests include assays that determine previous exposure to schistosomes by detecting antibodies against the parasite or circulating parasite antigens. Anti-schistosome antibodies are mainly detected using various forms of Enzyme-Linked Immunosorbent Assays (ELISA) and Circumoval Precipitation Test (COPT) (Gordon et al., 2019). ELISA tests the reactivity of antibodies from a serum sample to extracted Soluble Egg Antigens (SEA-ELISA), larval antigens, and Adult Worm Antigens (AWA-ELISA) (Weerakoon et al., 2015). Various studies have been conducted to assess the performance of target ELISA antigens using human and animal samples from the Philippines. The recombinant thioredoxin peroxidase-1 (SjTPx-1) and *S. japonicum* tandem repeat protein-7 (Sj7TR) were found to be promising ELISA target antigens; both had a sensitivity of 85.71% (Angeles et al., 2011). With the aims of assessing the utilization of target antigens via ELISA for the diagnosis of zoonotic schistosomiasis in animals, various studies have been performed using animal samples from endemic provinces in the country (Angeles et al., 2012, 2019, 2020). A cocktail ELISA combining SjTPx-1, Sj7TR, and Sj1TR (*S. japonicum* tandem repeat protein-1) had high sensitivities (84.1% in humans, 80.0% in water buffaloes and dogs) when tested with sera from patients from Negros Occidental, Mindoro Occidental, Leyte, and Northern Samar (Moendeg et al., 2015). Cai et al. (2017) found that an ELISA test combining the SjSAP4 (*S. japonicum* saposin protein-4) and Sj23-LHD (*S. japonicum* tegumental protein-23 -large hydrophilic domain) antigens provided a great diagnostic performance, and recommended such test to be useful in serodiagnosis of schistosomiasis japonica in the Philippines. The recombinant *S. japonicum* cathepsin B (SJCatB) has shown great promise as a diagnostic antigen for an indirect ELISA assay: 100% sensitivity and 95.0% specificity in experimentally infected mice; 86.7% sensitivity and 96.7% specificity in human sera from Sorsogon Province (Macalanda et al., 2019). An ELISA assay that combined the Sj23-LHD and SjSAP-4 had good diagnostic performance when compared to fecal droplet digital PCR (Cai et al., 2019).

A positive COPT test is signified by the formation of a precipitate when a serum sample is exposed to lyophilized eggs (Weerakoon et al., 2015). The test has been noted to have high sensitivity and specificity but is labor-intensive, complex, and has a lengthy procedure (Weerakoon et al., 2015). Leonardo et al. (2015) used both ELISA and COPT with KK and ultrasonography in determining the prevalence of schistosomiasis in the new endemic foci of Gonzaga, Cagayan, and Calatrava, Negros Occidental. Belizario et al. (2018) assessed the diagnostic performance of parasitologic (KK, FECT) and serologic assays (COPT, Antibody and Antigen ELISA) and found that the ELISA tests had the highest sensitivities in near-elimination areas and endemic areas. They concluded that population screening of *S. japonicum* infections using serological assays may be of value in low-endemic areas in the country.

Screening for circulating schistosome antigen can be done using monoclonal antibody-based antigen detection techniques (Utzinger et al., 2015; Ajibola et al., 2018). These tests detect circulating anodic antigens (CAA) and circulating cathodic antigens (CCA) in serum or urine using an up-converting phospho-lateral flow (UCP-LF) reporter technology (Utzinger et al., 2015). Point-of-care (POC) CCAs have been noted to have higher sensitivity than KK, and the lack of need for any special equipment make them more feasible for field use than molecular and serological assays (Ajibola et al., 2018; Diab et al., 2021). Perhaps the greatest advantage of CAA- and CCA-based assays is that they can detect active infections because CAA and CCA are only produced by live blood flukes, and their half-life in the circulation is relatively short (WHO, 2017). Although POC CCA has been appraised as a more sensitive replacement of KK in surveillance monitoring in endemic areas, it still needs to be validated for cross-reactivity against other trematodes in the Western Pacific Region, which may subvert the validity of its results (WHO, 2017). A study found that a combination UCP-LF CAA and POC CCA had a sensitivity comparable to triplicate KK in assessing schistosomiasis using urine samples from Indonesia and the Philippines (van Dam et al., 2015). Recently, a POC-CCA assay was found to have a sensitivity and specificity of 63.3% and 93.3%, respectively, in assessing schistosomiasis in a cohort with infection intensity of more than 10 egg per gram in Northern Samar (Cai et al., 2021). When compared to ELISA and ddPCR, the assay showed a low sensitivity and thus has a limited potential for routine use in areas of low infection intensity.

Imaging and Sonographic Techniques

Ultrasonography is a noninvasive, inexpensive, radiation-free, and mobile imaging tool for schistosomiasis diagnosis (Sah et al., 2015). The B-mode grayscale ultrasonography can be used to demonstrate hepatic lesions of schistosomiasis (Hashim & Berzigotti, 2021; Sah et al., 2015). Hepatic schistosomiasis is characterized by periportal fibrosis, which appears as echogenic pipe-stem fibrosis (Hashim & Berzigotti, 2021; Hussain et al., 1984). This method was used in Japan to monitor advanced hepatic fibrosis in formerly endemic areas (WHO, 2017). Target organ damage and peculiar calcifications (e.g., turtle shell-like septal calcification as seen in chronic *S. japonicum* infections) are findings often seen when using Computer Tomography (Sah et al., 2015). Magnetic Resonance Imaging (MRI) holds a special significance in diagnosing neuroschistosomiasis involving the brain and spinal cord (Sah et al., 2015). The value of sonographic tests is that they can demonstrate the pathology of the disease in affected organs in real-time. This is particularly helpful in determining the extent of hepatic damage that a schistosomiasis infection has caused. However, these advantages are undermined by the fact that other infectious and noninfectious conditions may manifest the same imaging results.

Molecular Techniques

DNA amplification assays have been at the forefront of schistosomiasis diagnostic advancements in recent years. These techniques have been noted to be more sensitive and specific than conventional copro-parasitological techniques (Weerakoon et al., 2015; Gordon et al., 2019). Hence, several Polymerase Chain Reaction (PCR)-based techniques that detect schistosome DNA have been developed, which include conventional PCR , quantitative PCR (qPCR), digital droplet PCR (ddPCR), Nested PCR, and Direct PCR (Weerakoon et al., 2015 & 2018a). Other amplification assays developed for assessing schistosomiasis morbidity include Loop-mediated isothermal amplification (LAMP) and recombinase polymerase amplification (RPA) (Weerakoon et al., 2018a). Preferred schistosome target sequences in amplification assays should have two qualities: it must be species-specific and thus highly conserved, and it must have considerable copies, thus in great abundance (He et al., 2016). Pelovello et al. (2019) found that candidate primers for the *cox1* and *nad5* mitochondrial genes were suitable for *S. japonicum* molecular diagnostics. The *cox3* had a high 100% specificity when compared to KK and COPT using spiked stool and serum samples, but its sensitivity was low (Pelovello et al., 2019).

A recent advancement is the detection of Schistosoma cell-free DNA (cfDNA) using qPCR and ddPCR from a variety of samples (e.g., serum, urine, and saliva) (Ajibola et al., 2018; Weerakoon et al., 2017). This allowed the diagnosis of intestinal schistosomiasis using samples other than stool which can be of significance to epidemiologic studies wherein participants may hesitate to provide fecal samples repeatedly. More importantly, assays using cfDNA can detect both prepatent and patent *S. japonicum* infections.

A couple of studies have utilized molecular methodologies to assess schistosomiasis in endemic foci, primarily in the hotspot provinces in Eastern Visayas. Gordon et al. (2015a) assessed schistosomiasis in six barangays in Palapag, Northern Samar using KK and qPCR; the NADH dehydrogenase 1 (*nad1*) gene was amplified. An overall prevalence of 90.2% was detected using qPCR from 550 fecal samples, whereas KK only detected 22.9%. Another study utilizing multiplex qPCR to detect soil-transmitted helminthiases and schistosomiasis reported a prevalence of 90.64% in 545 human fecal samples (Gordon et al., 2015b). In 2017, Weerakoon et al. assessed *S. japonicum* infections in 18 barangays of Laoang and Palapag, Northern Samar via ddPCR that detected cell-free Schistosoma DNA in 412 fecal, serum, urine, and saliva samples. The fecal ddPCR had the highest positivity rate at 74.5%, followed by serum ddPCR at 67.2%, urine ddPCR at 47.6% and saliva ddPCR at 25.5% (Weerakoon et al., 2017). Notably, using the same samples, co-parasitism with various protozoans was found: 58.7% of the samples had *Blastocystis* spp., 21.8% had *Cryptosporidium* spp., 12.1% had amoebiasis, and 19.2% had giardiasis (Weerakoon et al., 2018b). These studies proved that high polyparasitism occurs in schistosomiasis endemic foci in the country. Co-infections of multiple parasitic agents can have profound implications on the health of inhabitants in endemic areas which are often poverty-stricken.

The aforementioned studies had yet again proved that molecular methods are far more sensitive than the conventional KK and serological techniques. Interestingly, although studying only a small fraction of the country's endemic areas, all of these molecular schistosomiasis studies seem to contradict the reported national schistosomiasis surveys that used KK, making one question the latter's validity and value in baseline prevalence studies (Olveda et al., 2016). Despite their plentiful advantages, some major drawbacks inhibit the routine utilization of molecular techniques in the country. Financial constraints and the lack of trained personnel are problems in the disease detection arm of the country's schistosomiasis control program (Leonardo et al., 2016). The need for expensive equipment (e.g., thermocycler) and extensive training for technicians are significant cons. Also, the expensive DNA isolation and preservation kits add to the already expensive cost of running DNA-based assays.

Other Uses of Molecular Techniques

Molecular techniques have also been utilized in detecting *S. japonicum* and *O. hupensis quadrasi* eDNA in the Philippines. Fornillos et al. (2019b) reported a method of assessing *S. japonicum* and *O. hupensis quadrasi* eDNA from environmental water samples from different endemic foci in the county. They used a qPCR assay that targeted the cytochrome c oxidase subunit 1 (*cox1*) gene. In another study, Calata et al. (2019) reported that qPCR was better than cPCR in detecting *O. hupensis quadrasi* eDNA from soil samples from two endemic barangays in Gonzaga, Cagayan. Also, they found that edaphic factors such as increased pH, phosphorous, zinc, copper, and potassium content lead to increased eDNA detection, which may indicate that these factors favor snail habitation. Aside from these, other uses of molecular methods, such as genetic characterization, have given some valuable insights on schistosomiasis in the country. Moendeg et al. (2017) genotyped parasite samples obtained from different endemic locales using different microsatellite loci. They found that *S. japonicum* from areas with high schistosomiasis prevalence in humans and snails have higher genetic diversity, while the reverse was true for low prevalence areas. Thus, they posited that the ongoing gene flow brought about by the active movement of infected humans and animals from one endemic area to another may explain why *S. japonicum* transmission continues to persist despite the control measures (i.e., mass drug administration) that were being implemented.

Control and Elimination Efforts

Various control and elimination efforts have been put into place with the goal of eliminating S. japonicum infections in China, the Philippines, and Indonesia and *S. mekongi* in Lao PDR and Cambodia. These include preventive chemotherapy or mass drug administration (MDA) among inhabitants of high-risk areas, provision of WASH facilities and its many iterations, snail control programs, community education towards behavioral modification, and veterinary management of animal reservoir hosts (WHO, 2017, 2021). Vaccine development against schistosomiasis for humans and reservoir animals, specifically water buffaloes, are ongoing. Elimination of schistosomiasis transmission in the Western Pacific Region was targeted to be accomplished by 2025, with validation by 2030 (Leonardo et al., 2020b; WHO, 2017). Earlier this year, however, the WHO (2021) launched the roadmap for the control and elimination of NTDs by the year 2030. According to the roadmap, schistosomiasis is targeted to be eliminated as a public health concern–the reduction of the proportion of those with heavy intensity infections to less than 1% (Casulli, 2021; WHO, 2021). This section briefly describes various anti-schistosomiasis control and prevention measures instituted in the Philippines and in other countries.

Clinical Treatment and Mass Drug Administration

Praziquantel is the drug of choice against schistosomiasis (Bauerfeind, et al., 2016; Yu et al., 2021). It is effective against the five major schistosome species affecting humans, but its efficacy depends on the dose (Olveda et al., 2014; Yu et al., 2021). A clinical trial conducted in the Philippines established that the dose of 40 $mg{\cdot}kg^{-1}$

of Praziquantel is effective and is better tolerated for mass drug administration (MDA) than the alternative dose of 60 mg·kg^{-1} (Olveda et al., 2014). However, the latter dose was used to treat in clinical cases (i.e., KK positive patients), and is given two times fortnightly as per national regulation (Olveda et al., 2014).

Praziquantel is also the drug of choice for MDA against schistosomiasis (Leonardo et al., 2016; WHO, 2017). Eliminating the risk of schistosomiasis morbidity is the goal of community-based drug administration using Praziquantel (Inobaya et al., 2015; Olveda & Gray 2019). The drug was introduced in 1979 in the Philippines (Inobaya et al., 2015). Its introduction marked a shift in the control measures employed against schistosomiasis: from expensive snail control to active case finding and treatment with praziquantel (Inobaya et al., 2015; Leonardo et al., 2016, 2020b). In 1996, the DOH replaced the latter with MDA in all endemic areas, especially if the passive prevalence was >10% (Inobaya et al., 2015). Since then, MDA has been the backbone of schistosomiasis control for over two decades (Inobaya et al., 2015). At least eighty-five percent (85%) coverage was the target in high endemicity areas (Leonardo et al., 2016; Inobaya et al., 2018). Considerable reduction in the prevalence of schistosomiasis in endemic regions has been attributed to protracted MDA (Inobaya et al., 2015; Leonardo et al., 2016; Olveda & Gray, 2019). However, it has been noted that if the goal is the elimination of schistosomiasis as a public health concern in the country (i.e., prevalence of < 1% in the country), MDA will not suffice as the sole bullet in the fight against schistosomiasis (Inobaya et al., 2015; Olveda & Gray 2019).

The protracted MDA programs in highly endemic areas have prompted the development of 'MDA-fatigue,' resulting to non-compliance (Inobaya et al., 2015). Concerning this, Inobaya et al. (2018) conducted a cross-sectional study that assessed factors associated with non-compliance to MDA in Northern Samar. They found an overall non-compliance rate of 27%; a greater percentage of these were women. Among the reasons for non-compliance raised by the study subjects were fears of adverse reactions and misconceptions about the use of the drug for non-deworming purposes.

Praziquantel treatments in animal reservoir hosts, most notably among water buffaloes, were also considered in China (Cao et al., 2017; WHO, 2017). The drug is used in reservoir host MDA efforts at doses of 30 mg·kg^{-1} to 10 g PO for cattle, 25 mg·kg^{-1} to 10 g PO for water buffaloes, 60 mg·kg^{-1} PO for pigs and 25 mg·kg^{-1} PO for horses (Cao et al., 2017; WHO, 2017).

Snail Control Measures

Control and prevention measures targeting the snail intermediate hosts were the earliest thrusts against schistosomiasis prior to the discovery and use of praziquantel as an anti-schistosome agent. Measures included environmental modification and the application of molluscicide to reduce the number of intermediate hosts (Esquilla et al., 2021; Leonardo et al., 2020a; WHO, 2017). The WHO recommends the use of niclosamide, which is applied directly to the snail-infested environment, as a means of snail control in endemic countries; concentrations of 0.6-1 mg·L^{-1} were found to be effective (Leonardo et al., 2020a). However, the use of niclosamide may lead to harmful environmental effects (Esquilla et al., 2021; Leonardo et al., 2020a).

In Japan, snail control became the main mode of *S. japonicum* infection control. Measures employed included concreting ditches, applying molluscicides, and using flame throwers to kill snails and converting agricultural lands from wet rice production to dry fruit tree cultivation (WHO, 2017). These efforts reduced the population and distribution of snail intermediate hosts leading to schistosomiasis elimination in Japan in 1996 (WHO, 2017). China also had its fair share of snail control efforts implemented. Among these were ecological control with agricultural land use conversion, water resource projects, forestry projects, mechanical control using black plastic films for heat treatment, and chemical molluscicides (McManus et al., 2010; WHO, 2017). These measures have also successfully reduced the population of two of the four known intermediate hosts in China (Gordon et al., 2019). Both China and Japan have proven that controlling the snail intermediate hosts population leads to reduced human infection rates (WHO, 2017). However, snail control programs put much financial burden on the already limited funding of schistosomiasis control efforts in developing countries (Leonardo et al., 2020b).

Safe Water, Sanitation and Hygiene, and Community Education (WASHED)

The provision of clean water and the practice of adequate sanitation and proper hygiene are integral to the control and elimination of NTDs (Boissier et al., 2016; WHO, 2015). Thus, WASH is one of the five public health interventions advocated by the WHO for the control and elimination of NTDs, together with disease management and rehabilitation, preventive chemotherapy or MDA, vector control, and veterinary public health (Tenorio & Molina, 2021; WHO, 2015, 2020b). Regarding schistosomiasis and WASH, a meta-analysis by Grimes et al. (2014) revealed that the odds of acquiring schistosomiasis for those with safe water supplies and practiced proper sanitation were significantly less than those who do not. They had proven that access to clean water and proper hygiene are important protective factors that lessen the odds of developing schistosomiasis.

In countries affected by *S. mekongi* like Lao PDR and Cambodia, MDA is paired with Community-Led WASH (CL-SWASH) initiatives to eliminate schistosomiasis (Khieu et al., 2019). Lao PDR's approach is a multi-risk management approach involving community participation geared towards environmental health risk assessment of schistosomiasis transmission (Khieu et al., 2019). The key goals of their Water Safety Plan were increasing access to clean water through improving hydro-infrastructure and eliminating open defecation to interrupt transmission among inhabitants of endemic areas (Khieu et al., 2019).

In the Philippines, several WASH efforts have been enacted to combat prevalent helminthiases, including schistosomiasis. In 2006, the Integrated Helminth Control Program (IHCP) was launched to control soil-transmitted helminths and other helminthiases (DOH, 2006). Access to safe water, community toilets and latrines, and school-supervised WASH practices were advocated by different local government units and national departments through the IHCP (DOH, 2006). The Community-Led Total Sanitation (CLTS) program aimed to eliminate open defecation, provide hygiene facilities, practice hygienic food handling, implement proper waste disposal, and provide a clean and safe environment was launched in 2007 (DOH, 2010). The education sector also had its fair share of WASH initiatives, including the Implementation of the Essential Health Care Program (EHCP) and WASH in Schools (WINS) program – these programs provided WASH facilities in schools, highlighted health education in the basic education curriculum, and facilitated deworming efforts among pre-school-aged and school-aged children (Belizario et al., 2013; Philippine Department of Education (DepEd), 2009, 2016). Also, the Philippines is an awardee of the Sustainable Development Goals (SDG) fund, specifically to achieve Goal 6, which pertains to Sustainable Water and Sanitation. The iWASH (Integrated Safe Water, Sanitation and Hygiene) program is a multi-sectorial initiative supported by the Spanish Government, various United Nations sub-organizations, many Departments and offices of the Philippine government, private organizations, and community groups, especially women. The program aims to promote Water and Sanitation Access, Integrity, Empowerment, Rights and Resiliency (Pro-WATER). Program beneficiaries include municipalities in the schistosomiasis endemic provinces of Northern Samar and Zamboanga. Molina et al. (2021) assessed the status of WASH practices in endemic barangays in Davao region and compared it to national and global WASH targets. They reported that access to improved water sources, sanitary toilet coverage, and hand washing facilities with soap within households in the studied barangays were below the national guidelines and global recommendations.

Schistosomiasis Transmission Interruption by 2025: The Target

Despite the COVID-19 Pandemic, the Philippine Schistosomiasis Control and Elimination Program remains hopeful that it can achieve its goal of schistosomiasis transmission interruption by 2025. To enable this, the DOH has institutionalized its 7-year (2019-2025) Strategic Plan towards transmission interruption of schistosomiasis infection in the country (DOH, 2020). The main goal is to attain zero schistosomiasis incidence in humans and animal reservoir hosts, and zero infection rate in snail intermediate hosts in endemic communities by 2025 (DOH, 2020). Moreover, schistosomiasis endemic barangays (communities) would be the implementation unit of integrated intervention packages that are customized to their endemicity status. Also, focal schistosomiasis surveys and updating of snail maps will be enacted in these endemic communities. Lastly, the Department of Agriculture (DA), specifically through the Bureau of Animal Industry (BAI), and the Local Government Unit (LGU) Veterinary offices will be engaged for capacity building in handling animal schistosomiasis (DOH, 2020).

Conclusion

The Philippines has had a long-standing battle to eliminate schistosomiasis. The current national prevalence data indicate that the country has reached infection control level. However, the decreasing sensitivity of the feco-assays in areas of low endemicity warrants care in interpreting the results of epidemiologic studies that utilize it. Hence, MDA must continue in highly endemic areas despite reports of MDA fatigue resulting in non-compliance. The development of cheaper yet more sensitive and specific tests give a glimmer of hope on the diagnostics front. The underfunded schistosomiasis control program of the country needs much political commitment: from the national government down to the local leaders of endemic communities. A One Health approach that will engage the communities and their leaders, medical professionals, veterinarians, malacologists, and environmental scientists is essential in achieving the goal of parasite transmission interruption by 2025 in the Philippines and be one with the global goal of eliminating the illness as a public health concern by 2030.

Disclosure Statement

No potential conflict of interest was declared by the authors.

Acknowledgement

The first author would like to acknowledge the Department of Science and Technology-Accelerated Science and Technology Human Resource Development Program- National Science Consortium (DOST-ASTHRDP-NSC) Scholarship for funding his graduate studies.

References

Abao-Paylangco, R., Balamad, M., Paylangco, J., Japitana, R., & Jumawan, J. (2019). *Schistosoma japonicum* in selected rice fields surrounding Lake Mainit, Philippines. *Journal of Ecosystem Science and Eco-Governance, 1*(1), 15-24.

Ajibola, O., Gulumbe, B.H., Eze, A.A. & Obishakin, E. (2018). Tools for detection of Schistosomiasis in resource limited settings. *Medical Science*, *6*(2), 39.

Angeles, J.M., Goto, Y., Kirinoki, M., Asada, M., Leonardo, L.R., Rivera, P.T., et al. (2012). Utilization of ELISA using Thioredoxin Peroxidase-1 and tandem repeat proteins for diagnosis of *Schistosoma japonicum* infection among water buffaloes. *PLoS Neglected Tropical Diseases*, *6*(8), e1800.

Angeles, J.M., Goto, Y., Kirinoki, M., Leonardo, L.R., Moendeg, K.J., Ybañez, A.P., et al. (2019). Detection of canine *Schistosoma japonicum* infection using recombinant thioredoxin peroxidase-1 and tandem repeat proteins. *Journal of Veterinary Medical Science*, *81*, 1413–1418.

Angeles, J.M., Goto, Y., Kirinoki, M., Leonardo, L.R., Tongol-Rivera, P., Villacorte, E.A., et al. (2011). Human antibody response to thioredoxin peroxidase-1 and tandem repeat proteins as immunodiagnostic antigen candidates for *Schistosoma japonicum* infection. *American Journal of Tropical Medicine and Hygiene*, *85*, 674-679.

Angeles, J.M., Goto, Y., Kirinoki, M., Villacorte, E.A., Moendeg, K.J., & Rivera, P.T. (2020). Field evaluation of recombinant antigen ELISA in detecting zoonotic schistosome Infection among water buffaloes in endemic municipalities in the Philippines. *Frontiers of Veterinary Science*, *7*, 592783.

Angeles, J.M., Leonardo, L.R., Goto, Y., Kirinoki, M., Villacorte, E.A., Hakimi, H., et al. (2015). Water buffalo as sentinel animals for schistosomiasis surveillance. *Bulletin of the World Health Organization*, *93*, 511-512.

Bärenbold, O., Raso, G., Coulibaly, J. T., N'Goran, E. K., Utzinger, J., & Vounatsou, P. (2017). Estimating sensitivity of the Kato-Katz technique for the diagnosis of Schistosoma mansoni and hookworm in relation to infection intensity. *PLoS Neglected Tropical Diseases*, *11*(10),

Bauerfeind R, Graevenitz A, Kimmig P, Sheifer H, Schwartz T, Slenczka W., & Washington, H.Z. (2016). *Zoonoses: Infectious diseases transmissible between animals and humans*. Washington DC: ASM Press.

Belizario Jr, V.Y., Destura, R., Gabunada, R.R., Petronio-Santos, J.A., dela Tonga, A., Amarillo, M.L., et al. (2018). Evaluation of fecal and serological tests for the diagnosis of schistosomiasis in selected near-elimination and endemic areas in the Philippines. *Southeast Asian Journal of Tropical Medicine and Public Health*, *49,* 198-207.

Belizario Jr, V.Y., Erfe, J.M., Naig, J., & Chua, P. (2015) Evidence of increasing risk of schistosomiasis among school-age children in municipality of Calatrava, Province of Negros Occidental, Philippines. *Asian Pacific Journal of Tropical Medicine*, *8*, 373-377.

Belizario Jr, V.Y., Plan, A.O. & de Leon W.U. (2014). Laboratory diagnosis of selected neglected parasitic diseases in the Philippines: Can we do better? *Acta Medica Philipina, 48*, 4-10.

Belizario Jr, V.Y., Tuliao, A.H., Totanes, F.G. & Asuncion, C.L. (2013). Optimizing school-based intestinal helminth control interventions in the Philippines. *PIDSP Journal*, *14*, 2-13.

Boissier, J., Grech-Angelini, S., Webster, B.L., Allienne, J.F., Huyse, T., Mas-Coma, S., et al. (2016). Outbreak of urogenital schistosomiasis in Corsica (France): an epidemiological case study. *The Lancet Infectious Diseases*, *16*(8), 971–979.

Buchwald, A. G., Grover, E., Van Dyke, J., Kechris, K., Lu, D., Liu, Y., et al. (2021). Human mobility associated with risk of *Schistosoma japonicum* Infection in Sichuan, China. *American Journal of Epidemiology, 190*(7), 1243-1252.

Cabanacan-Salibay, C., Torres, M., Luyon-Tabo, H. & Salibay, S. (2016). Schistosomiasis in children in the Philippines: Beyond health issues. *Journal of Pediatric Infectious Diseases*, *12*, 238-248.

Cai, P., Mu, Y., Weerakoon, K. G., Olveda, R. M., Ross, A.G. & McManus, D.P. (2021). Performance of the point-of-care circulating cathodic antigen test in the diagnosis of *Schistosomiasis japonica* in a human cohort from Northern Samar, the Philippines. *Infectious Diseases of Poverty 10*(1), 121.

Cai, P., Weerakoon, K.G., Mu, Y., Olveda, D.U., Piao, X., Liu, S., et al. (2017). A parallel comparison of antigen candidates for development of an optimized serological diagnosis of *Schistosomiasis japonica* in the Philippines. *EBioMedicine*, *24*, 237-246.

Cai, P., Weerakoon, K.G., Mu, Y., Olveda, R.M., Ross, A.G., Olveda, D.U., et al. (2019) Comparison of Kato Katz, antibody-based ELISA and droplet digital PCR diagnosis of schistosomiasis japonica: Lessons learnt from a setting of low infection intensity. *PLOS Neglected Tropical Diseases*, *13*(3), 1-17.

Calata, F., Caranguian, C.Z., Mendoza, J., Fornillos, R., Tabios, I.K., Fontanilla, I.K., et al. (2019). Analysis of environmental DNA and edaphic factors for the detection of the snail intermediate host *Oncomelania hupensis quadrasi*. *Pathogens*, *8*, 160.

Cao, Z.G., Huang, Y. & Wang, T. (2017). *Schistosomiasis japonica* control in domestic animals: Progress and experiences in China. *Frontiers of Microbiology*, *8*, 2464. https://doi.org/10.3389/fmicb.2017.02464

Carabin, H., Johansen, M., Friedman, J., McGarvey, S., Madsen, H., Zhou, X.N., et al. (2011). Zoonotic schistosomosis (schistosomiasis). In S. Palmer, L. Soulsby, P. Torgenson, & D. Brown, *Textbook of zoonoses: Biology, clinical practice, and public health control*. (2nd ed., pp. 700-709). Oxford University Press.

Casulli A., 2021. New global targets for NTDs in the WHO roadmap 2021-2030. *PLOS Neglected Tropical Diseases*, 15, e0009373.

Chen, C., Guo, Q., Fu, Z., Liu, J., Lin, J., Xiao, K., et al. (2021). Reviews and advances in diagnostic research on *Schistosoma japonicum*. *Acta Tropica*, *213*, 105743.

Cringoli, G., Renaldi, L., Maurelli, M. & Utzinger, J. (2010). FLOTAC: New multivalent techniques for qualitative and quantitative copromicroscopic diagnosis of parasites in animals and humans. *Nature Protocols*, *5*, 503-515.

Diab, R.G., Tolba, M.M., Ghazala, R.A., Abu-Sheasha, G.A., Webster, B.L., & Mady, R.F. (2021). Intestinal schistosomiasis: Can a urine sample decide the infection? *Parasitology International*, *80*, 102201.

Esquilla, M.G., Sanchez C.B. & Tenorio, J.C.B. (2021). Molluscicidal activity of Makabuhay (*Tinospora rumphii* Boerl) stem ethanolic extract against Radix (Lymnaea) spp. snails. *Journal on New Biological Reports, 10*(2), 64-71.

Fernandez Jr., T.J., Tarafder, M.R., Balolong Jr., E., Joseph, L., Willingham III, A.L., Bélisle, P., et al. (2007). Prevalence of *Schistosoma japonicum* infection among animals in fifty villages of Samar province, the Philippines. *Vector Borne Zoonotic Diseases*, *7*, 147-155.

Fornillos, R.J., Fontanilla, I.K.C., Kikuchi, M., Kirinoki, M., Kato-Hayashi, N., Kawazu, S., et al. (2019a). Infection rate of *Schistosoma* *japonicum* in the snail *Oncomelania hupensis quadrasi* in endemic villages in the Philippines for snail surveillance technique. *Tropical Biomedicine*, *36*, 402-411.

Fornillos, R.J., Sato, M.O., Tabios, I.K., Sato, M., Leonardo, L.R., Chigusa, Y., et al. (2019b). Detection of *Schistosoma japonicum* and *Oncomelania hupensis quadrasi* environmental DNA and its potential utility to schistosomiasis japonica surveillance in the Philippines. *PLOS One*, *14*, e0224617.

Gordon, C.A., Acosta, L., Gobert, G., Jiz, M., Olveda, R.M., Ross, A.G., et al. (2015c). High Prevalence of *Schistosoma japonicum* and *Fasciola gigantica* from Northern Samar, the Philippines. *PLOS Neglected Tropical Diseases 9*(2), e0003108.

Gordon, C.A., Acosta, L.P., Gobert, G.N., Olveda, R.M., Ross, A.G., Williams, G.M., et al. (2015a). Real-time PCR demonstrates high prevalence of Schistosoma japonicum in the Philippines: Implications for surveillance and control. *PLOS Neglected Tropical Diseases*, *9*, e0003483.

Gordon, C.A., Acosta, L., Gray, D., Olveda, R., Jarilla, B., Gobert, G.N., et al. (2012). High Prevalence of *Schistosoma japonicum* infection in carabao from Samar province, the Philippines: Implications for transmission and control. *PLOS Neglected Tropical Diseases 6*, e1778.

Gordon, C.A., Kurscheid, J., Williams, G.M., Clements, A., Li, Y., Zhou, X.N., et al. (2019). Asian schistosomiasis: Current status and prospects for control leading to elimination. *Tropical Medicine and Infectious Diseases*, 4, 40.

Gordon, C.A., McManus, D.P., Acosta, L.P., Olveda, R.M., Williams, G.M., Ross A.G., et al. (2015b). Multiplex real-time PCR monitoring of intestinal helminths in humans reveals widespread polyparasitism in Northern Samar, the Philippines. *International Journal of Parasitology*, *45*, 477-483.

Gray, D.J., Williams, G.M., Li, Y., Chen, H., Forsyth, S.J., Li, R.S., et al. (2009). A cluster-randomised intervention trial against *Schistosoma japonicum* in the Peoples' Republic of China: bovine and human transmission. *PLOS One 4*(6), e5900.

Gray, D.J., Williams, G.M., Li, Y., Chen, H., Li, R.S., Forsyth, S.J., et al. (2007). A cluster-randomized bovine intervention trial against *Schistosoma japonicum* in the People's Republic of China: design and baseline results. *American Journal of Tropical Medicine and Hygiene, 77*, 866-874.

Gray, D.J., Williams, G., Li, Y. & McManus, D. (2008). Transmission dynamics of *Schistosoma japonicum* in the lakes and marshlands of China. *PLOS One, 3*(12), e4058.

Grimes, J.E., Croll, D., Harrison, W.E., Utzinger, J., Freeman, M.C. & Templeton, M.R. (2014). The relationship between water, sanitation and schistosomiasis: a systematic review and meta-analysis. *PLOS Neglected Tropical Diseases*, *8*, e3296.

Guan, W., Li, S. Z., Abe, E. M., Webster, B. L., Rollinson, D., & Zhou, X. N. (2016). The genetic diversity and geographical separation study of *Oncomelania hupensis* populations in mainland China using microsatellite loci. *Parasites & Vectors* 9, 28.

Hailgebriel, T., Nibret, E. & Munshea, A. (2020). Prevalence of *Schistosoma mansoni* and *Schistosoma haematobium* in snail intermediate hosts in Africa: A systematic review and meta-analysis. *Journal of Tropical Medicine*, 8850840.

Hashim, A. & Berzigotti, A. (2021). Noninvasive assessment of *Schistosoma*-related periportal Fibrosis. *Journal of Ultrasound in Medicine*. https://doi.org/10.1002/jum.15623

He, Y., Salfsky, B. & Ramaswamy, K. (2001). Host–parasite relationship of *Schistosoma japonicum* in mammalian hosts. *Trends in Parasitogy, 17*, 320-324.

He, P., Song, L.G., Xie, H., Liang, J.Y., Yuan, D.Y., Wu, Z.D., et al. (2016). Nucleic acid detection in the diagnosis and prevention of schistosomiasis. *Infectious Diseases of Poverty*, *5*, 25.

Hussain, S., Hawass, N., & Zaidi, A. (1984). Ultrasonographic diagnosis of schistosomal periportal fibroses. *Journal of Ultrasound in Medicine*, *3*, 449-452.

Inobaya, M.T., Chau, T.N., Ng, S.K., MacDougall, C., Olveda, R.M., Tallo, V.L. et al. (2018). Mass drug administration and the sustainable control of schistosomiasis: an evaluation of treatment compliance in the rural Philippines. *Parasites and Vectors*, 11, 441.

Inobaya, M.T., Olveda, R.M., Tallo, V.L., McManus, D.P., Williams, G.M., Harn, D.A., et al. (2015). Schistosomiasis mass drug administration in the Philippines: Lessons learnt and the global implications. *Microbes Infection*, *17*(1), 6-15.

Jumawan, J.C. & Estaño, L.A. (2021). Prevalence of *Schistosoma japonicum* in bovines and *Oncomelania hupensis quadrasi* from ricefields surrounding Lake Mainit, Philippines. *Journal of Parasitic Diseases*, *45*(1), 1-8.

Jurberg, A., de Oliveira, A., Lenzi, H., & Coelho, P. (2008). A new miracidia hatching device for diagnosing schistosomiasis. *Memórias do Instituto Oswaldo Cruz*, *103*, 112-114.

Khieu, V., Sayasone, S., Muth, S., Kirinoki, M., Laymanivong, S., et al. (2019). Elimination of *Schistosomiasis Mekongi* from endemic areas in Cambodia and the Lao People's Democratic Republic: Current status and plans. *Tropical Medicine and Infectious Diseases 4*(1), 30.

Kurup, R., & Hunjan, G. S. (2010). Epidemiology and control of Schistosomiasis and other intestinal parasitic infections among school children in three rural villages of south Saint Lucia. *Journal of Vector Borne Diseases, 47*(4), 228-234.

Leonardo, L.R., Chigusa, Y., Kikuchi, M., Kato-hayashi, N., Kawazu, S., Angeles, J.M., et al. (2016). Schistosomiasis in the Philippines: Challenges and some success in control. *Southeast Asian Journal of Tropical Medicine and Public Health*, *47*, 651-666.

Leonardo, L.R., Hernandez, L., Magturo, T.C., Palasi, W., Rubite, J.M., de Cadiz, A., et al. (2020b). Current status of neglected tropical diseases (NTDs) in the Philippines. *Acta Tropica*, *203*, 105284.

Leonardo, L.R., Rivera, P., Saniel, O., Solon, J.A., Chigusa, Y., Villacorte, E., et al. (2015). New endemic foci of schistosomiasis infections in the Philippines. *Acta Tropica*, *141*, 354-360.

Leonardo, L.R., Rivera, P., Saniel, O., Villacorte, E., Crisostomo, B., Hernandez, L., et al. (2008). Prevalence survey of schistosomiasis in Mindanao and the Visayas, The Philippines. *Parasitology International, 57*, 246-251.

Leonardo, L.R., Rivera, P., Saniel, O., Villacorte, E., Lebanan, M.A., Crisostomo, B., et al. (2012). A national baseline prevalence survey of schistosomiasis in the Philippines using stratified two-step systematic cluster sampling design. *Journal of Tropical Medicine*, 2012, 936128.

Leonardo, L.R., Varona, G., Fornillos, R.J., Manalo, D., Tabios, I.K., & Moendeg, K.J. (2020a). Oncomelania hupensis quadrasi: Snail intermediate host of Schistosoma japonicum in the Philippines. *Acta Tropica, 210*, 105547.

Li, S. Z., Wang, Y. X., Yang, K., Liu, Q., Wang, Q., Zhang, Y., et al. (2009). Landscape genetics: the correlation of spatial and genetic distances of Oncomelania hupensis, the intermediate host snail of *Schistosoma japonicum* in mainland China. *Geospatial Health*, *3*(2), 221-231.

Macalanda, A., Angeles, J.M., Moendeg, K.J., Dang-Trinh, M.A., Higuchi, L., Kirinoki, M., et al. (2019). *Schistosoma japonicum* cathepsin B as potential diagnostic antigen for Asian zoonotic schistosomiasis. *Parasitol Research*, *118*, 2601-2608.

Manalo, D. (2020). Prediction of snail habitats of *Oncomelania hupensis quadrasi* and identification of risk areas for schistosomiasis japonica in endemic and neighboring non-endemic barangays of Gonzaga, Cagayan, Philippines. Philippine Veterinary Medical Association 87th Annual Convention and Scientific Conference. Davao City.

McGarvey, S., Carabin, H., Balolong, E., Belisle, P., Fernandez, T., Joseph, L., et al. (2006). Cross-sectional associations between intensity of animal and human infection with *Schistosoma japonicum* in Western Samar province, Philippines. *Bulletin of the World Health Organization*, *84*, 446-452.

McManus, D. P., Dunne, D. W., Sacko, M., Utzinger, J., Vennervald, B. J., & Zhou, X. N. (2018). Schistosomiasis. *Nature Reviews Disease Primers, 4*(1), 13.

McManus, D.P., Gray, D.J., Li ,Y., Feng, Z., Williams, G.M., Stewart, D., et al. (2010). Schistosomiasis in the People's Republic of China: the era of the Three Gorges Dam. *Clinical Microbiology Reviews, 23*, 442–466.

Moendeg, K.J., Angeles, J.M., Goto, Y., Leonardo, L.R., Kirinoki, M., Villacorte, E.A., et al. (2015). Development and optimization of cocktail-ELISA for a unified surveillance of zoonotic schistosomiasis in multiple host species. *Parasitology Research, 114*, 1225-1228.

Moendeg, K.J., Angeles, J.M., Nakao, R., Leonardo, L.R., Fontanilla, I.K., & Goto, Y. (2017). Geographic strain differentiation of *Schistosoma japonicum* in the Philippines using microsatellite Calmarkers. *PLOS Neglected Tropical Diseases 11*, e0005749.

Molina, V., Sison, O., Medina, J.R., Lumangaya, C., Ayes, C.N. & Joe, J.A. (2021). Water, sanitation and hygiene practices in the Philippines: Meeting national and global targets at the local level. *Journal of Environmental Science and Management, 24*(1), 1-14.

Navarro, R.C., de Cadiz, A.E., Fronda, J.M., Ong, L.A.D., & Belizario Jr, V.Y. (2021). Prevalence of *Schistosoma japonicum* infection in water buffaloes in selected areas in Davao del Norte and Davao de Oro, the Philippines. *International Journal of One Health*, *7*, 12-18.

Olveda, R.M. & Gray, D.J. (2019). Schistosomiasis in the Philippines: Innovative controlapproach is needed if elimination is the goal. *Tropical Medicine and Infectious Diseases, 4*, 66.

Olveda, D.U., Li, Y., Olveda, R.M., Lam, A.K., McManus, D.P., Chau, T.N., et al. (2014). Bilharzia in the Philippines: past, present, and future. *International Journal of Infectious Diseases*, *18*, 52-56.

Olveda, R.M., Tallo, V., Olveda, D.U., Inobaya, M.T., Chau, T.N. & Ross, A.G. (2016). National survey data for zoonotic schistosomiasis in the Philippines grossly underestimates the true burden of disease within endemic zones: implications for future control. *International Journal of Infectious Diseases*, *45*, 13-17.

Palasi, W. (2021). Control and Elimination of Schistosomiasis (SCH) and soil transmitted helminths (STH) amid the COVID-19 pandemic in the Philippines. Parasitic neglected tropical diseases: Scaling up for control and elimination in the new normal, public health in the time of COVID-19 in the new normal, British Embassy of Manila-UP College of Public Health Webinar Series for Public Health Workers. College of Public Health, University of the Philippines Manila.

Pelovello, M.V., Santos, J.A.P., del Rosario, J.M.M., Schwem, B.E., Obleopas, R.A., Belizario Jr, V.Y., et al. (2019). A PCR-based Assay for the Detection of Schistosoma japonicum from Human Samples. *Philippine Journal of Health Research Development*, *23*, 1-8.

Philippine Department of Education [DepEd]. (2009). Order No. 65 s. 2009: Implementation of Essential Health Care Program.

Philippine Department of Education [DepEd]. (2016). Order No. 10 s. 2016: Policy and guidelines for the comprehensive Water, Sanitation, and Hygiene in Schools (WINS) Program.

Philippine Department of Health [DOH]. (2006). Administrative Order 2006–0028: Strategic and operational framework for establishing Integrated Helminth Control Program.

Philippine Department of Health [DOH]. (2010). *Guidebook for Community-Led Total Sanitation.* Retrieved July 1, 2021, from https://doh.gov.ph/sites/default/files/publications/Community_Led_Total_Sanitation.pdf

Philippine Department of Health [DOH]. (2018). Schistosomiasis Control Program. Retrieved July 1, 2021, from Philippine Department of Health: https://www.doh.gov.ph/schistosomiasis-control-program

Philippine Department of Health [DOH]. (2020). Department Circular No. 2020-0129: Adoption of the National Strategic Plan Towards Interruption of Schistosomiasis Transmission in the Philippines (2019-2025).

Sah, V.K., Wang, L., Min, X., Rizal, R., Feng, Z., Ke, Z., Deng, M., Li, L., & Li, H. (2015). Human schistosomiasis: A diagnostic imaging focused review of a neglected disease. *Radiology of Infectious Diseases, 2*, 150-157.

Soares Magalhães, R.J., Salamat, M.S., Leonardo, L., Gray, D.J., Carabin, H., Halton, K, McManus, D.P., et al. (2014). Geographical distribution of human *Schistosoma japonicum* infection in The Philippines: tools to support disease control and further elimination. *International Journal of Parasitology, 44*, 977-984.

Taylor, M., Coop, R., & Wall, R. (2016). Veterinary Parasitology 4th Ed. The Atrium, Southern Gate, Chichester, West Sussex: John Wiley & Sons, Ltd.

Tenorio, J.C.B. & Molina, E.C. (2020). *Schistosoma japonicum* infections in cattle and water buffaloes of farming communities of Koronadal City, Philippines. *International Journal of One Health 6*, 28-33.

Tenorio, J.C.B. & Molina, E.C. (2021). Monsters in our food: Foodborne trematodiasis in the Philippines and beyond. *Veterinary Integrative Sciences, 19*(3), 467-485.

Utzinger, J., Becker, S.L., van Lieshout, L., van Dam, G.J. & Knopp, S. (2015). New diagnostic tools in schistosomiasis. *Clinical Microbiology and Infection*, *21*, 529-542.

van Dam, G.J., Odermatt, P., Acosta, L., Bergquist, R., de Dood, C.J., Kornelis, D., et al. (2015). Evaluation of banked urine samples for the detection of circulating anodic and cathodic antigens in *Schistosoma mekongi* and *S. japonicum* infections: a proof-of-concept study. *Acta Tropica 141*(Pt B), 198-203.

Weerakoon, K.G., Gobert, G.N., Cai, P. & McManus, D.P. (2015). Advances in the diagnosis of Human Schistosomiasis. *Clinical Microbiology Reviews*, *28*, 939–967.

Weerakoon, K.G., Gordon, C.A., & McManus, D.P. (2018a). DNA Diagnostics for Schistosomiasis Control. *Tropical Medicine and Infectious Diseases*, *3*(3), 81.

Weerakoon, K.G., Gordon, C.A., Williams, G.M., Cai, P., Gobert, G.N., Olveda, R.M., et al. (2017). Droplet Digital PCR Diagnosis of Human Schistosomiasis: Parasite Cell-Free DNA Detection in Diverse Clinical Samples. *Journal of Infectious Diseases*, *216*, 1611-1622.

Weerakoon, K.G., Gordon, C.A., Williams, G.M., Cai, P., Gobert, G.N., Olveda, R.M., et al. (2018b). Co-parasitism of intestinal protozoa and Schistosoma japonicum in a rural community in the Philippines. *Infectious Diseases of Poverty*, *7*, 121.

Williams, G.M., Sleigh, A.C., Li, Y., Feng, Z., Davis, G.M., Chen, H., Ross, A.G.P., Berquist, R., & Mcmanus, D.P. (2002). Mathematical modelling of schistosomiasis japonica: comparison of control strategies in the People's Republic of China. *Acta Tropica*, *82*, 253–262.

World Health Organization. (2015). Water, sanitation & hygiene for accelerating and sustaining progress on negected tropical diseases A global strategy 2015-2020.

World Health Organization. (2017). Expert Consultation to Accelerate Elimination of Asian Schistosomiasis, Shanghai, China. Manila: WHO Regional Office for the Western Pacific.

World Health Organization. (2019). Bench aids for diagnosis of intestinal parasites, 2nd Edition. Geneve: World Health Organization.

World Health Organization. (2020a). Schistosomiasis Fact Sheet. World Health Organization Website: https://www.who.int/news-room/fact-sheets/detail/schistosomiasis

World Health Organization. (2020b). Regional Action Framework for Control and Elimination of Neglected Tropical Diseases in the Western Pacific. Manila, Philippines: World Health Organization Regional Office for the Western Pacific.

World Health Organization. (2021). *Ending the neglect to attain the Sustainable Development Goals: A road map for neglected tropical diseases 2021-2030*. Retrieved July 1, 2021, from https://www.who.int/neglected_diseases/Ending-the-neglect-to-attain-the-SDGs--NTD-Roadmap.pdf

Wu, H.W., Qin, Y.F., Chu, K., Meng, R., Liu, Y., McGarvey, S.T., et al. (2010). High prevalence of *Schistosoma japonicum* infection in water buffaloes in the Philippines assessed by real-time polymerase chain reaction. *American Journal of Tropical Medicine Hygiene*, *82*, 646–652.

Xu, B., Gordon, C.A., Hu, W., McManus, D.P., Chen, H.G., Gray, D.J., et al. (2012). A novel procedure for precise quantification of Schistosoma japonicum eggs in bovine feces. *PLOS Neglected Tropical Diseases*, 6: e1885. https://doi.org/10.1371/journal.pntd.0001885

Yu, Q.F., Zhang, J.Y., Sun, M.T., Gu, M.M., Zou, H.Y., Webster, J.P., et al. (2021). In vivo praziquantel efficacy of Schistosoma japonicum over time: A systematic review and meta-analysis. *Acta Tropica*, *222*, 106048.

Zhao, Q.P., Jiang, M.S., Littlewood, D.T. & Nie, P. (2010). Distinct genetic diversity of Oncomelania hupensis, intermediate host of *Schistosoma japonicum* in mainland China as revealed by ITS sequences. *PLoS Neglected Tropical Diseases, 4*(3), e611.