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Bilharzia: Pathology, Diagnosis, Management and Control

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Abstract

More than one billion people travel internationally each year and approximately 100 million to the tropics. Schistosomiasis is a neglected tropical disease caused by trematode blood flukes of the genus *Schistosoma*. It currently infects over 250 million people worldwide and results in approximately 25 million disability adjusted life years lost. Clinical manifestations depend on the affected organ. Subtle morbidities have also been documented including: growth retardation, anaemia and poor cognitive function in children. While schistosomiasis has been eradicated from Japan and significantly reduced in parts of China and Egypt, transmission in many other regions remains ongoing due to the wide-spread distribution of the intermediate snail host, poor sanitation, lack of health education and decreasing compliance to mass drug administration. Integrated control has significantly reduced the burden of disease in China but considerable financial capital is needed if similar results are to be duplicated elsewhere. Human vaccination is in various stages of development, and once found, will become an integral part of future control. This comprehensive review examines the epidemiology, pathology, diagnosis, clinical management, prevention and control of the disease.

Keywords: Bilharzia; Schistosomiasis; Neglected tropical disease; Diagnosis; Management; Treatment

Global Burden of Schistosomiasis

The World Health Organization estimates that schistosomiasis and geohelmiths represent more than 40% of the global disease burden caused by all tropical diseases, excluding malaria [1]. Schistosomiasis is the third most devastating tropical disease globally (after malaria and intestinal helminthiases) and is a major cause of morbidity and mortality for developing countries in Africa, South America, the Caribbean, the Middle East, and Asia [2]. Schistosomiasis or Bilharzia is caused by schistosomes, which are parasitic trematode worms of the genus *Schistosoma*. Five species infect humans, namely: *Schistosoma mansoni, Schistosoma japonicum, Schistosoma mekongi, Schistosoma intercalatum, and Schistosoma haematobium*. In 74 countries where the disease is endemic, an estimated 250 million people are infected and approximately 700 million people are at risk of infection [3,4]. The burden of disease attributable to the three major human schistosome species (*Schistosoma mansoni, S. haematobium,* and *S. japonicum*) is estimated to be between 24-29 million disability adjusted life years [5,6] (Table 1).

Schistosoma mansoni is widespread in Africa, the Eastern-Mediterranean, the Caribbean, and South America (Figure 1). Almost 300,000 people die annually from schistosomiasis in Africa alone [7]. Approximately 90% of the 250 million people infected worldwide live in Sub-Saharan Africa where *S. mansoni* is the prevalent species [7]. About 10 million women in Africa are infected during pregnancy [8]. Zoonotic transmission is possible with these species, because the parasite infects not only humans but also wild rodents [9-11].

Schistosoma haematobium infection is a significant cause of clinical morbidity and disability in the endemic countries of Africa and the Middle East, where more than 110 million people are infected [12]. In sub-Saharan Africa, two-thirds of schistosomiasis cases are due to *S. haematobium*, which represents an important cause of severe urinary tract disease. In a survey in 2000, it was estimated that 70

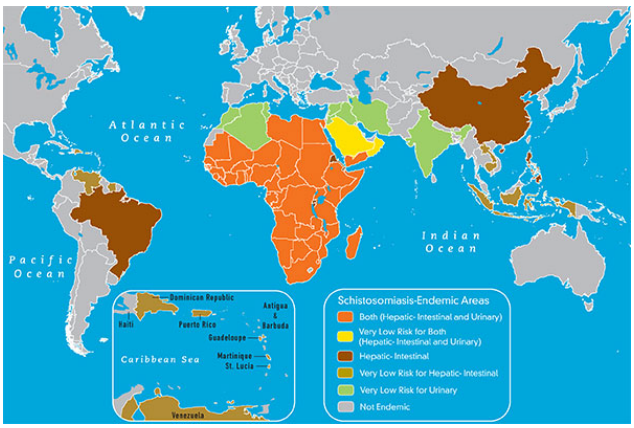

Figure 1: Map of the current global distribution of schistosomiasis. Source: US Centers for Disease Control and Prevention,<http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/schistosomiasis#2696>).

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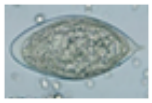
Species	Geographic Distribution	Signs and Symptoms	Diagnosis	Adult Treatment	Pediatric Treatment	Vaccine Candidate
Schistosoma mansoni	Africa, the Middle East, the Caribbean, Brazil, Venezuela, Suriname	In non-immune individuals (migrants or tourists), mild In non-immune individuals (migrants or tourists), mild maculopapular eruption may arise at the site of skin penetration by schistosome cercariae , few hours to a week later. Weeks later, acute phase (Katayama syndrome), when present, manifest with fever, malaise, myalgia, fatigue, non-productive cough, diarrhoea (with or without the presence of blood) and right upper quadrant pain. More likely to happen in non-immune people. Months or years later, infected individuals may develop signs and symptoms referable to the affected organ. Gastrointestinal involvement cause colicky hypogastric pain or pain in the left iliac fossa, diarrhoea (particularly in children) that may alternate with constipation, and haematochezia (blood in the faeces). Liver patholgy leads to hepato-splenomegaly, enlargement of the abdomen with dilated superficial abdominal veins and upper GI bleeding. Cerebral disease include encephalopathy with headache, visual impairment, delirium, seizures, motor deficit, and ataxia; spinal symptoms comprise lumbar pain, lower limb radicular pain, muscle weakness, sensory loss, and bladder dysfunction. Growth retardation, malnutrition anemia and poor cognitive functions in children.	*Schistosoma* mansoni eggs are large (114 to 180 µm long by 45-70 µm wide) and have a characteristic shape, with a prominent lateral spine near the posterior end. The anterior end is tapered and slightly curved.	Praziquantel, 40 mg/kg in two divided doses for 1day, 4-6 hours apart.	Praziquantel, (4 to 19 years old), 40 mg/kg in two divided doses for 1 day, 4–6 hours apart Praziquantel, (<4 years old) at the dose 40 mg/kg in two divided doses for 1 day, 4-6 hours apart has been proven safe and effective.	FSmTSP-2c (tetraspanin D), SmTSP-1 (Tetraspanin), Sm29 (C-terminal transmembrane domain), Sm23 (Tetraspanin), Sm-p80 (Calpain), Sm14 (Fatty Acid Binding Protein (FABP)), Sm28-GST(Glutathione S-transferase), Sm28-TPI, Sm97 paramyosin, CT-SOD (Cytosolic Cu-Zn SOD)
Schistosoma haematobium 	Africa, the Middle East	Acute signs and symptoms are similar to *S. mansoni*. Haematuria, appears 10-12 weeks after infection. Dysuria and haematuria occur in early and late disease. Late disease manifestations also include proteinuria, renal colic and renal failure. Vaginal bleeding and dyspareunia in females and infertility in males. Signs and symptoms of transverse myelitis like lumbar pain, lower limb radicular pain, and bladder dysfunction are common compared to *S. Mansoni, S. japonicum* and *S. mekongi* infections.	The eggs of *Schistosoma* haematobium are large (110-170 µm long by 40-70 µm wide) and bear a conspicuous terminal spine	Praziquantel, 40 mg/kg in two divided doses for 1 day, 4-6 hours apart	Praziquantel (4 to 19 years old), 40 mg/kg in two divided doses for 1 day, 4–6 hours apart Praziquantel (<4 years old) at the dose 40 mg/kg in two divided doses for 1 day, 4–6 hours apart has been proven safe and effective	SjSh28 GST (Glutathione S-transferase, recombinant)

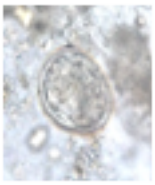
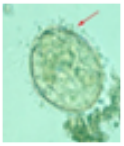
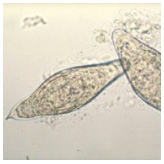
Schistosoma japonicum 	China, Indonesia, the Philippines	Similar to *S. mansoni* infection but notably more severe in manifestations.	The eggs of are large and more rounded than other species, measuring 70-100 µm long by 55-64 µm wide. The spine on *S. japonicum* eggs is smaller and less conspicuous than other species.	Praziquantel, 60 mg/kg in two divided doses for 1 day, 4 – 6 hours apart.	Praziquantel (4 to 19 years old), 60 mg/kg in two divided doses for 1 day, 4-6 hours apart	Sj97 (Paramyosin (native), Sj97 (Paramyosin, recombinant fragment), Sj97 (Parmyosin, recombinant full length), SjASP (Aspartic protease), Calpain (Calpain large subunit, recombinant), Sj26GST (26kDa Gluthione S-transferase), Sj28GST (28kDaGST), Sj14-3-3 (Signaling protein 14-3-3, recombinant), Sj14 (FABP, recombinant), Serpin (Serpin, recombinant), SjSVLBP (SVLBP, recombinant), SjFer (Ferritin, recombinant), SjC23 (Tetraspanins).
Schistosoma mekongi 	Several districts of Cambodia and the Lao People's Democratic Republic	Manifestations are similar to *S. mansoni* and *S. japonicum* but milder compare to *S. japonicum* infection.	The eggs are similar to *S. japonicum,* but are generally smaller (50-80 µm by 40-65 µm). They also contain a small, inconspicuous spine and are shed in stool.	Praziquantel, 60 mg/kg in two divided doses for 1 day, 4-6 hours apart.	Praziquantel (4 to 19 years old), 60 mg/kg in two divided doses for 1 day, 4-6 hours apart	
Schistosoma intercalatum 	Rain forest areas of central Africa	Unlike the more pathogenic species, infection with *S. intercalatum* is usually only associated with bloody stool, and sometimes splenomegaly. Majority of nfections are asymptomatic and go unnoticed	The eggs are similar to *S. haematobium* in general shape and in possessing a terminal spine, but are usually longer (140-240 µm), often have an equatorial (central) bulge and are shed in stool, not urine.The eggs of Schistosoma intercalatum have a terminal spine and tend to be moderately larger than those of *S. haematobium* (approximately 130×75 µm).	Praziquantel, 40 mg/kg in two divided doses for 1 day, 4-6 hours apart.	Praziquantel (4 to 19 years old), 40 mg/kg in two divided doses for 1 day, 4-6 hours apart	

Table 1: Summary clinical table for schistosomiasis globally.

million individuals out of 682 million had experienced haematuria and 32 million had dysuria associated with *S. haematobium* infection. It was also estimated that 18 million suffered bladder wall pathology and 10 million have hydronephrosis [7]. Renal failure accounts for a large percentage of the estimated 150,000 deaths from urinary tract schistosomiasis. Significant association was observed between major bladder wall pathology and squamous cell carcinoma [13]. Also, large percentage of women and men with urinary schistosomiasis acquire genital ulcers and other lesions [14].

Schistosoma intercalatum is a minor schistosomal species limited to a few western and central African countries [15]. Two main distinct species are recognized: one in Zaire and one in Lower Guinea (mainly Cameroon) [16]. Environmental factors and possible mating with the more predominant species *S. hematobium* contribute to the limited species distribution and number [17].

Schistosoma japonicum infection occurs in China, Indonesia and the Philippines. Zoonotic transmission is noted to be important

in *S. japonicum*. Wide varieties of domestic and feral animals are infected. In China and the Philippines, cattle and water buffalo contribute significantly in the transmission of infection [18-26]. Sj approximately 60 million individuals are at risk of infection and close to two million are currently infected [27,28]. A small focus of infection and transmission persists on the island of Sulawesi in Indonesia [29]. The disease has been eradicated in Japan through integrated multidisciplinary approach. The last case of human infection documented was in 1977 and the last infected snails were detected in 1982 [30].

Schistosoma mekongi is endemic along the Mekong River and certain tributaries in the lower Mekong basin [31]. Approximately, 140,000 people are at risk for infection with 80,000 found in Cambodia and a further 60,000 in Laos [32]. While infection in animals, such as dogs and pigs, have been reported, the contribution of these various animal reservoir hosts to the transmission of *S. mekongi* has not been established [33-35]. Integrated control measures have greatly reduced the incidence of human infection.

Life Cycle

The life cycles of all five human schistosome species are similar and involve a snail intermediate host (Figure 2). Human or animal hosts (as with *S. japonicum*) get infected when they come in contact with fresh water contaminated by cercariae, the infective stage of the parasite [4,36,37]. Upon host location, the cercariae attach to and penetrate the host skin via glandular secretions [37]. The parasites lose their tails as they penetrate the skin, and transform into young schistosomes called schistosomula [4,36,37]. After spending at least two days in the skin, the parasites burrow through the dermis, penetrate a blood vessel wall, and gain access into the circulatory system [38]. The parasites migrate to the lungs and remain there for several days before travelling to the liver were they blood-feed on red blood cells, mature and mate within the liver vessels [4,36,37]. Afterwards, they emerge as male-female worm pairs, and inhabit either the portal or pelvic vessels [36,37]. This habit of the parasite is exemplified by the four schistosome species except *S. hematobium* which prefers the urinary bladder venous plexus [36,38]. The female begins to lay eggs within the mesenteric or pelvic vessels [36,37]. Most of the eggs are carried upstream to the liver via the portal veins and its branches and get trapped in the pre-sinusoidal portal venules [36,37]. Some of the eggs migrate and penetrate the intestines and shed in the stool. Eggs laid in the pelvic venous plexus migrate towards the urinary bladder, pass through the bladder wall, and are excreted in urine [4,36,37]. When eggs contact water, they hatch into ciliated larval forms called miracidia that can sense compatible intermediate snail hosts [4,36,37]. Miracidia penetrate the snail by proteolytic activity and mechanical movement [37]. Inside the snail host, miracidia undergo asexual development and transform into cercariae which emerge from the snails and seek out the definitive host [4,37,39]. The parasite life cycle is thus completed [40].

Pathology and Morbidity

In schistosomiasis, adult worms reside in the mesenteric and pelvic venules in various sites where they lay eggs [36,37]. These sites tend to be specific for each species (e.g. *S. japonicum* prefers the superior mesenteric veins draining to the small intestine, while *S. mansoni* prefers the superior mesenteric veins of the large intestine) [41]. Many eggs are carried upstream where they get lodged in various organs,

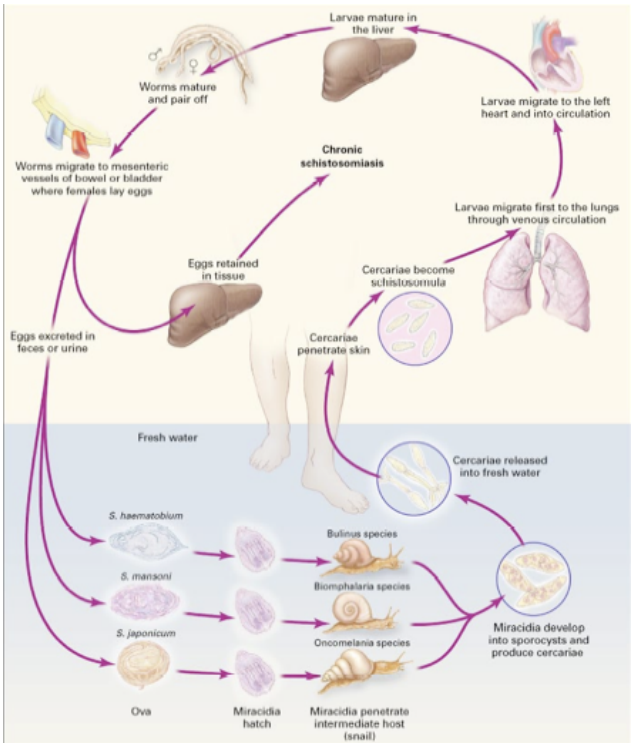


Figure 2: The schistosome life cycle (Ross et al., 2002 [4]).

especially in the liver, bowel, and genitourinary tract [4]. In acute disease (Katayama syndrome), schistosomula antigens/secretions orchestrate a T helper type 1 (Th1) cell-driven inflammatory response (involving tumour necrosis factor, interleukin-1, and interleukin-6 cytokines) and cause febrile illness [42-45]. As mature female worms lay eggs, products of worm and egg metabolism induce formation of immune complexes resulting to a serum like-sickness called Katayama syndrome [4]. In chronic disease, eggs are the cause of pathology; they evoke a Thelper type 2 (Th2) cell-driven granulomatous reaction (involving interleukin-4, interleukin-5, and interleukin-13 cytokines) resulting in tissue fibrosis and chronic morbidity [36,40,41-44]. Interleukin-13 has been observed to produce fibrosis in animal models [46]. Both Th1 and Th2 arms play a role in granuloma formation, the latter being the dominant player [45].

Gastrointestinal schistosomiasis due to *S. mansoni, S. japonicum* and *S. mekongi* can cause bowel lesions such as ulceration, pseudopolyps, and microabcesses. The semanifest clinically as abdominal pain, altered bowel habits, and blood in stools [4]. Liver enlargement and periportal fibrosis are common in advanced cases, and is generally linked with ascites and portal hypertension. Clinical signs including: superficial abdominal blood vessel dilatation, spleen enlargement, and bleeding-prone esophageal varices have been well documented [4]. Patients with severe hepatosplenic schistosomiasis may die from ruptured esophageal varices. Some studies suggest an association of *S.mansoni* and *S. japonica* and cancer development in the liver and colon, but no hard evidence exists to support the association [46-54].

The classic sign of urogenital schistosomiasis is haematuria and is specifically noted with S. haematobium [4]. Bladder, ureter fibrosis and kidney damage are sometimes seen in advanced cases [4]. The

urogenital form may present with genital lesions (e.g. vulvar nodules), vaginal bleeding, dyspareunia, and fallopian tube damage (in the late stages) in females [4]. Genital infection in males may resultin damage to seminal vesicles, prostate and other related organs; this may lead to irreversible infertility [4]. Urogenital schistosomiasis in both sexes is a significant risk factor for Human Immunodeficiency Virus (HIV) infection due to both local genital tract and systemic immunological effects [55]. Schistosomal co-infection may hasten HIV disease progression in individuals already infected with HIV, and facilitate viral transmission to sexual partners [55].

The link between *S. haematobium* and urinary bladder cancer has been documented. For example, squamous cell carcinoma of the urinary bladder has been associated with *Schistosoma haematobium* infection in studies in many areas of Africa [55-63]. In addition, studies from Africa have shown that the estimated incidence of urinary bladder cancer is higher in areas with a high prevalence of infection with *S. haematobium*, compared to areas with a low prevalence. Urinary bladder cancer as a proportion of all cancers appears to be 10 times more common among men in Egypt than among men in Algeria [54]. Furthermore, the estimated incidence of urinary bladder cancer is related to the proportion of cancerous urinary bladder specimens containing *S. haematobium* eggs is more common in men, who are more involved in agricultural work, than in women. A higher proportion of urinary bladder cancers are seen in areas where there is histological evidence of infection compared to areas without these characteristics [54].

Neurological involvement by schistosomiasis may present clinically due to space-occupying lesions in the brain and spinal cord. Neuroschistosomiasis cases have been noted in up to 5% of clinically diagnosed cases [4,64,65]. Lumbrosacral myelopathy is most commonly noted with *S. mansoni* and *S. hematobium*, while encephalic disease is mostly seen with *S. japonicum* infection [65]. Subtle morbidities due to schistosomiasis such as growth retardation, anaemia, malnutrition, and impaired cognitive functions are seen in children [66-69]. Anaemia burden worsens with other geohelminth co-infections [68]. Poor pregnancy outcomes in infected women are also seen [8].

Diagnosis

Detection of parasite eggs in the stool and urine is the gold standard for diagnosis of schistosomiasis. For people from non-endemic areas or living in low transmission areas, serological and immunological tests may be useful in showing exposure to infection and the need for thorough examination and treatment. For rapid diagnosis of *S. mansoni, S. japonicum, S. mekongi* and *S. intercalatum* infection, stool samples are examined for the presence of parasite eggs using a Kato-Katz thick smear or rapid Kato techniques [70,71]. Kato-Katz has low sensitivity if only one stool sample from each subject is examined. Sensitivity of the test can be increased by multiple stool sample examinations from the same individual, but this makes the technique impractical for wide-scale field diagnosis [72]. Concentration techniques have been developed and evaluated [73,74]. Examples of these tests are the Merthiolate-Iodine Concentration technique (MIFC), Merthiolate-Formaldehyde concentration techniques (MFCT) and Formaldehyde-Ether. These tests, however, are time consuming, laborious to perform, and also impractical for field-based screening.

For urogenital schistosomiasis, examination of urine using a filtration technique and microscopy to detect *S. haematobium* eggs was the basis of early studies on this species of schistosome [75]. As for the concentration techniques for stool examinations, the urine filtration technique has been modified to increase the sensitivity of the test [76-78]. Diagnosis of *Schistosoma* infection by the Miracidia Hatching Technique (MHT) was also introduced in China [79]. Studies in China, comparing this test to Kato-Katz, showed that the latter is still preferred over MHT for large-scale screening of *S. japonicum* infection. MHT is much more tedious, provides inconsistent and only qualitative results, and is less sensitive than Kato-Katz [80].

In an attempt to improve diagnosis of schistosome infection, serologic tests (e.g. Circumoval Precipitin test [COPT] and Indirect Hemaglutination Assay [IHA]) were developed to detect the presence of antibody against different schistosome stages [81,82]. Although these tests were found to be more sensitive, acute infection cannot be distinguished from chronic infection. With advances in parasite antigen isolation and purification, schistosome antigen detection methods in the body fluids of infected individuals were developed. An example of these methods is the use monoclonal antibodies to detect schistosome antigens that are circulating in the blood and excreted in the urine. The most promising and extensively studied are tests that can detect major circulating antigens such as the Circulating Anodic Antigen (CAA) and Circulating Cathodic Antigen (CCA) [83-91].

Commercially available CAA/CCA kits, with excellent sensitivity (98%) and specificity (100%), have been utilised to detect both *S. mansoni* and *S. haematobium* infections in urine and serum samples [89,92]. Recently, a point-of-care (POC) urine assay test using CCA has been evaluated in five countries in order to determine its use as a future diagnostic screening tool. POC testing of urine with CCA was found to be more sensitive than the Kato-Katz technique in detecting low intensities of *S. mansoni* infection [93]. More specifically, 72% prevalence among 9-12 years olds by POC-CCA corresponded to 50% prevalence by Kato-Katz, whereas, 46% POC-CCA prevalence corresponded to 10% Kato-Katz prevalence [93].

Infection with human schistosome species including *S. haematobium* can also be diagnosed through microscopic examination of tissues obtained by biopsies of the rectal mucosa [94]. This procedure, however, is invasive and can be performed only in health facilities where there are experienced physicians and microscopists. For organ pathology detection, sophisticated imaging methods, such as ultrasound, computed tomography scan (CT scan), and Magnetic Resonance Imaging (MRI), can demonstrate evidence of liver fibrosis and portal hypertension, and can visualize urinary tract fibrosis, polyps, and ulcers [95-98].

Chemotherapy

In the past, antischistosomal pharmacologic agents against *S. hematobium* or *S. mansoni* (hyacanthone, metrifonate, oxamiquin and others) or against *S. japonicum* (niridazole, antimonials) have been used but were found less effective due to the development of toxicities before therapeutic levels were reached. The situation dramatically changed when praziquantel was released in 1979. Praziquantel was proven to be effective against the five species of schistosomes affecting humans. However, efficacy depends on the dose used in the treatment. Meta-analyses of 52 clinical trials published in peer-reviewed journals showed that a dosage of 30-60 mg/kg praziquantel compared with placebo, produced a cure rate of around 76% (range from 67-83%) for human schistosomiasis. No significant differences in cure rates

were found among the subspecies *S. haematobium, S. japonicum* or *S. mansoni*. Cure rate of the drug at 40 mg/kg was 52% (range from 49-55%) compared to 91% (range from 88%-92%) when divided dosages were increased to 60, 80, 100 mg/kg [99].

In 2003, TDR (Research and Training in Tropical Disease WHO), in an attempt to optimize praziquantel use for the treatment of schistsomiasis, launched a series of multi-country trials, comparing efficacy and safety of 40 mg and 60 mg/kg in schistosome infected patients in Asia, Africa and the Americas. In the Philippines clinical trial, where *S. japonicum* is predominant, the 40 mg/kg dose was effective and better tolerated than the higher 60 mg/kg dose. The national policy-makers in the Philippines adopted the 40 mg/kg dose for its mass drug administration (MDA) program against schistosomiasis. However, those found infected by stool examination were treated with 60 mg/kg and given the same dose, two weeks later. In Brazil, where *S. mansoni,* is predominant, the reinfection rate post-treatment was lower in the 60 mg/kg group than among those who received the 40 mg/kg dose. Brazil supported the use of the higher dose for their country. It is important to note that the overall rates of schistosomiasis reinfection with 40 mg/kg were high at 30-50% depending on the species and the region [100].

Artemether or Artesunate for the prevention of schistosomiasis was introduced in the early 1990s. Multiple doses of artemether or artesunate over weekly or biweekly intervals resulted in protection rates from 65% to 97% due to its killing of juvenile schistosomula. Increasing doses and shortening medication intervals improved the efficacies of the drug. Praziquantel and artemisinin derivatives when used in combination resulted in a higher protection rate of 84% (range 64%-91%) than praziquantel used alone. The combination of praziquantel and artesunate greatly increased the protection rate to 96% (range 78%-99%) for preventing schistosome infection [99]. Side effects of abdominal discomfort, fever, sweating, and giddiness, were minimal and transient. Chemotherapy aids greatly in reducing schistosomiasis infection burden but does not prevent reinfection. However, it decreases infection intensity, reverses liver and spleen enlargement, and resolves anaemia [101]. Furthermore, chemotherapy can resolve (and sometimes reverse) hepatic fibrosis, prevent the rise of advanced hepatosplenic cases, and eliminate blood in stool and urine [101-103].

Prevention and Control

The integrated control of schistosomiasis advanced considerably with the introduction of praziquantel (PZQ) in the late 1970's. After decades of extensive use, severe schistosome-related morbidities decreased significantly, but high re-infection rates and transmission remained. In addition, to sustain the gains accomplished with PZQ, the agent has to be administered periodically through MDA for an indefinite period of time and without relaxation to prevent rebound of morbidities. Furthermore, continuous and extensive drug use may lead to PZQ- resistant strains of schistosomes [104]. Therefore, the search for alternative approaches is vital. Development of new pharmacological agents should be pursued aggressively. Vaccines that can help sustain MDA must be well supported.

Several promising vaccine candidates against schistosomiasis are in various stages of development. Some of the candidates are in the pre-clinical trial stage, and some have entered phase one and phase two clinical trials. These candidates include: GST, Paramyosin, Fatty Acid Binding Protein (FABP), Calpain, Triose-phosphate isomerase, and Tetraspanins.

Among the GST candidate vaccine molecules, the 28kDa GST recombinant protein (sSh28GST) from *S. haematobium* has already been tested in safety, immunogenicity and toxicity clinical trials studies, and Phase I and II trials [105]. Paramyosin (rSj97) candidate vaccine molecules are undergoing pre-clinical studies. The paramyosin recombinant fragment has been observed to provide protection and immunogenicity in BALB/c mice [106]. On the other hand, the full length recombinant protein, aside from exhibiting protection in mice, has also shown antibody responses in humans associated with re-infection resistance [107]. More importantly, the full length paramyosin molecule production has been up-scaled, and is now undergoing pre-clinical testing in water buffaloes in the Philippines [108]. One of the FABP candidate vaccine molecules called Sm14-FABP, as for sSh28GST, has already reached an advanced developmental stage. A noteworthy development with this candidate vaccine is its ability to induce cross-protection against *Schistosoma* and *Fasciola*. Up-scaled production of this molecule has been successful and the procedure for its industrial GMP-grade production has been developed. Phase I and II clinical trials are already being planned for Sm14-FABP [109].

Another promising vaccine candidate called Sm-p80, a calpain subunit, has been tested for its anti-infective and anti-fecundity efficacy in different vaccine formulations and approaches. Mice vaccinated with DNA plasmids encoding Sm-p80 and interleukin-2 (IL-2) provide 59% protection, while vaccination with plasmid formulated with Sm-p80 and interleukin-12 (IL-12) provides 45% protection. In addition, the Sm-p80-VR1020 vaccine elicited strong immune responses to the specific antigen Sm-p80, including immunoglobulin IgG (along with subtypes IgG1 and IgG2), IgA, and IgM in vaccinated animals [110-113].

Triose-phosphate isomerase (TPI) and the tetraspanins are other groups of antigens that have great vaccine candidate potential. Two randomised double-blind control vaccine trials were performed in buffaloes to determine the efficacy levels of the SjCTPI (TPI) and the SjC23 (Tetraspanin) vaccines, both on their own, and fused together with the dendritic cell targeting molecule, heat-shock protein 70 (Hsp70) (SjCTPI-Hsp70 and SjC23-Hsp70). The most successful vaccine construct was the SjCTPI-Hsp70, which produced a 51.2% reduction in worm burden, a 61.5% reduction in liver eggs, a 52.1% reduction in faecal eggs and a 52.1% reduction in the hatching of faecal miracidia [114,115]. These are very important findings because buffalo account for approximately 80% of the transmission to humans for *S. japonicum* in China and the Philippines [13-20]. Bovine vaccination in combination with other control measures may lead to the elimination of the disease in Asia.

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