

DIAGNOSIS OF ONE MOST DEVASTATING PARASITIC DISEASE SCHISTOSOMIASIS: NEED TO AWARE BOTH PUPIL AND PEOPLE

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Abstract: An endemic and long lived infection by multicellular intravascular of trematodes, neglected, wide spectrum including both acute and chronic forms, affecting multiple target organs diseases' is Schistosomiasis. This major tropical and sub-tropical diseases caused by parasite of the genus *Schistosoma* (*S. mansoni*, *S. mekongi*, *S. intercalatum*, *S. hematobium*, and *S. japonicum*). Schistosomiasis, also known as bilharzia, lives in certain types of freshwater snails. The infectious form of the parasite, known as cercariae, can become infected when your skin comes in contact with contaminated freshwater in which certain types of snails (*Biomphalaria* and *Bulinus* genus), that carry schistosomes are living and affect mostly on liver diseases. Praziquantel (PZQ), albendazole (ABZ), praziquantel-artemisinin, mebendazole (MEB) etc anti-helminthic drugs are using to recovery treatment of Schistosomiasis diseases. After recovery many people are suffered from liver effect. In this review article focus that at present how to the proper management of high intensity of liver infection depends on determination of morbidity levels by biological markers and imaging diagnostic tests. Now a day's parasitological survey team and pupil take responsible to aware the society and reflecting empowerment with regard to local health condition.

Keywords: Schistosomiasis, cercariae, anti-helminthic drug, trematodes, praziquantel, albendazole, morbidity, empowerment.

Overview: Schistosomiasis, dengue, Chagas disease, leprosy, leishmaniasis, malaria, and tuberculosis (WHO, 2010) all are belonging under the 17th neglected topical infectious parasitic diseases in the World according to the World Health Organization (WHO). People those who are expose them to infested water during routine agriculture, domestic, occupational, recreational activities in infested water are affected by this diseases. Schistosomiasis, one of the world's most important neglected diseases, is distributed across 78 countries in tropical and subtropical areas, where around 236.6 million people are exposed to the risk of infection by trematodes of the genus *Schistosoma*^[1]. This vulnerable infection generally occurred lack of hygiene and certain play habits of school-aged children such as swimming or fishing in infested water. The species endemic in the Americas is *Schistosoma mansoni*, and the WHO estimates that 25 million people live in risk areas for schistosomiasis, particularly in Brazil and Venezuela^[2]. Between 2015 and 2018, Brazil's National Schistosomiasis Prevalence Survey conducted among schoolchildren, which estimated the prevalence of schistosomiasis at 1.0%, suggesting a significant decline since two earlier surveys conducted in the 1950s (10.0%) and 70s (6.9%)^[3]. Despite efforts to combat the disease in recent years, there are still places in Brazil where prevalence continues as high as 20.0%, where basic sanitation is lacking and Human Development Index (HDI) scores are low^[4,5].

Schistosomiasis also called bilharziasis or bilharzias or bilharziosis, snail fever or in the acute form katayama fever. Theodore Bilharz identified the parasite *Schistosoma hematobium* in Egypt in 1851. The different species of *Schistosoma* have different types of snails serving as their intermediate hosts. These are – (i) *Biomphalaria* for *S. mansoni*; (ii) *Oncomelania* for *S. japonicum*; (iii) *Tricola* (*Neotricula aperta*) for *S. mekongi*; (iv) *Bulinus* for *S. haematobium* and *S. intercalatum*. Trapping the schistosoma eggs activate immunological reaction and induce schistosomiasis to release the antigen. A granulomatous reaction is involving in T cells, macrophages, and eosinophil that cause to clinical disease. Symptoms and signs depend on the number and location of eggs^[6]. The initial inflammatory reaction is readily reversible. However, as the disease progresses, there is collagen deposition and fibrosis, resulting in organ damage that may be only partially reversible^[7].

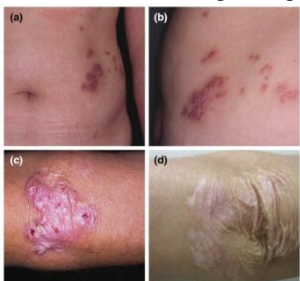


Figure-1



Figure-2



Figure-3

Figure-1: Cutaneous schistosomiasis and leishmaniasis coinfection; Figure-2: Patient has worm removed from his foot after mistaking itchy bulge for varicose vein; Figure-3: The schistosomiasis infection is spreaded.

Infection and transmission: Based on habitat *Schistosoma* sp. is either blood flukes or liver flukes or intestinal flukes or lung flukes. Basically this water born diseases (Africa, Asia, and Latin America) flukes lives in venous plexus in body of definitive host (Human) and cercariae have forked tails which penetrating unbroken skin of definite host, migrate to blood vessels, and through lung blood capillaries reach the portal blood or vesicular (bladder) blood systems. During this migration, the cercariae

change and develop from schistosomula into male and female adult parasitic worms. After mating parasite able to produce eggs. Some are staying in portal blood system some are passing out through bowel in to the soil. Those eggs are staying into blood vessel move to infected different organ such as eye, liver etc. Intermediate host of *Schistosoma* is fresh water snail and infective form is cercaria larva. The neglected tropical disease (NTDs) is classified depending on stages in evolution of infection (a) during incubation period; (b) during oviposition; (c) during tissue proliferation and repair.

Life cycle: *Schistosoma*'s life cycle is described in ray diagram under follow.

Eggs hatch in water→First stage larva→Motile ciliated Miracidium→Infects snail→Cilia shed to become sporocyst→Cell proliferation to form germ balls→Second generation sporocyst→Cercariae formed by sexual reproduction→On maturity, escape from parent→Free living in water→Infection by direct skin penetration→sheds tail-schistosomulae→Enters peripheral venules→Grow and it's sexually differentiated in 20 days in intrahepatic portal veins→Reaches vesical and pelvic venous plexus mature, mate, and lay eggs→Pierces vesical wall→Enter lumen of urinary bladder→Discharged in urine (end of maturation during micturition). Cercaria is elongated ovoid body with forked tail. Swarms of cercaria swim in water for about 3days. Once infected eggs appear in urine, it stays 10 to 20 weeks. In adult worm could live up to 20 to 30 years.

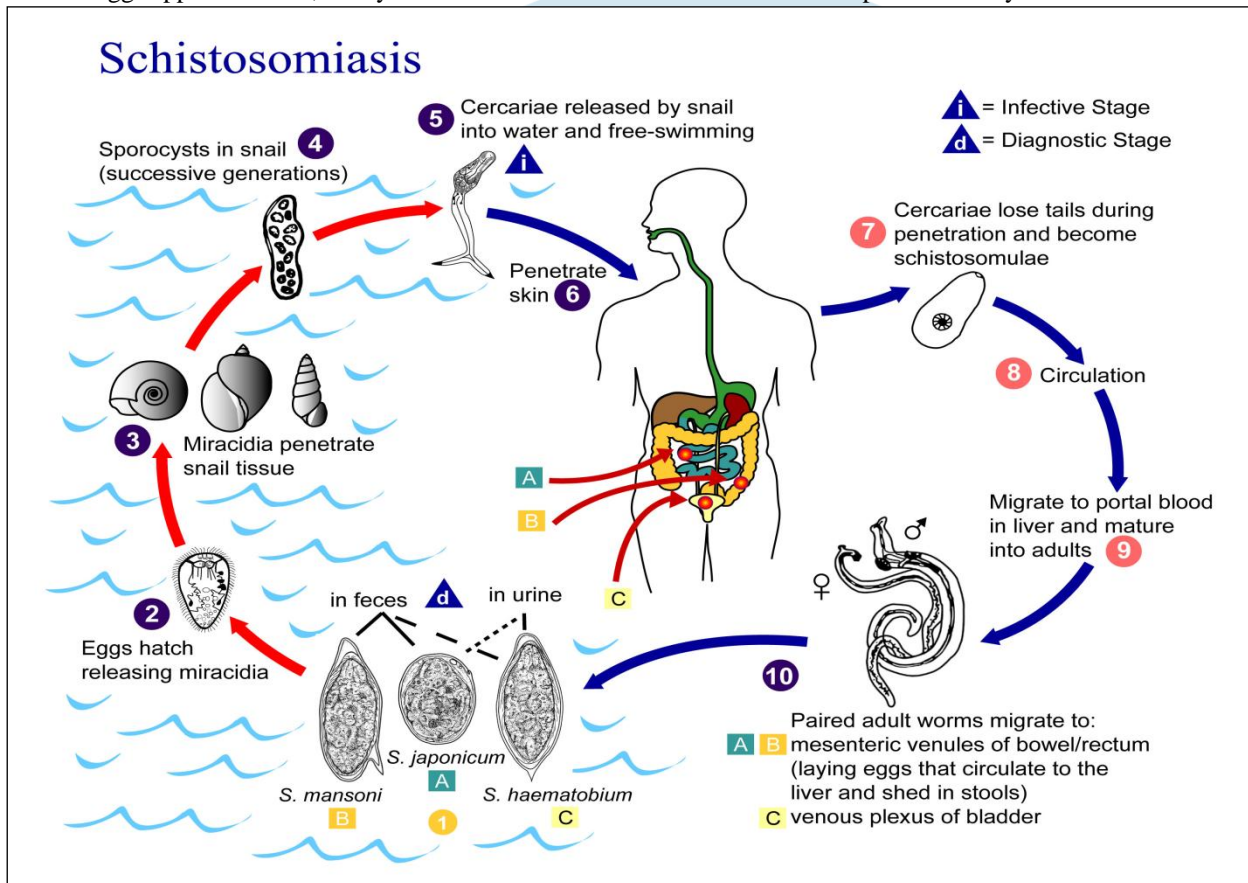


Figure-4: life cycle of Schistosomiasis in both definite and intermediate host.

Mechanisms/Pathophysiology: The progression of schistosome infections can be divided into three general overlapping stages influenced by the duration of the individual's infection: acute, established active and late chronic infection. These stages differ in egg excretion rates in stool or urine as well as in clinical manifestations and symptoms^[8]. The acute and chronic symptoms of schistosomiasis are mainly dependent on due to the egg migration through tissue and the human immune response to the eggs. Chronic symptoms are mainly due to eggs that are not shed from the body.

Acute stage: Symptomatic acute schistosomiasis is also known as Katayama fever or Katayama syndrome after a district of Hiroshima, Japan, where *S. japonicum* was detected for the first time in a human^[9]. It usually occurs in naive individuals exposed to *Schistosoma* sp. For the first time, between 2 weeks and 3 months after exposure^[10]. The symptoms are caused by systemic hypersensitivity reactions and formation of immune complexes in response to antigens released during schistosomula migration or initiation of egg deposition^[10]. Symptoms are often accompanied by eosinophilia and transient pulmonary infiltrates (as observed on chest radiography)^[10,11,12]. Acute schistosomiasis is rarely observed in people living in *S. mansoni*-endemic or *S. haematobium*-endemic areas^[8]. This lack of susceptibility to acute symptoms may be due to in utero desensitization, resulting in lowered immune responsiveness to schistosome antigens in infants born to infected mothers^[13], or possibly due to repeated exposure to skin-penetrating cercariae, which induce IL-10 production by CD4+ T cells in the skin, resulting in a regulatory immune response^[14]. However, acute schistosomiasis has been reported in the People's Republic of China, when flooding has exposed communities living in *S. japonicum*-endemic areas to new outbreaks of infection^[15,16].

Symptomatic acute schistosomiasis is observed only when mature adult worms establish egg production. No symptoms can be found in the live adult worms residing in the blood vessels. This observation can be explained by several factors, such as the fact that adult worms have somatic stem cells that enable the worms to regenerate their surface tegument (the outer protective layer) and binding of host antigens to the surface tegument, thereby hiding the worm antigens on the surface from the host's immune

system^[17]. Schistosome eggs actively secrete antigenic glycoproteins, which have the function of facilitating the passage of the eggs from the blood vessel (where they are laid) to the lumen of the intestine or urinary bladder (thereby promoting transmission) by inducing an inflammatory response^[8]. Organ-specific clinical symptoms often positively correlate with infection intensity, as indicated by excreted egg counts, and are mediated by egg-induced inflammation and granulomatous reactions. Established active schistosomiasis is characteristically observed in children in endemic areas and is entirely reversible following treatment and removal of the adult worms^[11].

Late chronic infection: In most people continuously exposed to infection in schistosomiasis-endemic areas, their worm burdens gradually decline after their early teenage years as a partial immunity to new infections develops, while the number of established worms from earlier infections is reduced over time by natural worm deaths^[18]. Some fewer new eggs are excreted or deposited in the tissue. At the same time, new tiny granulomas gradually resolve and then replaced by fibrous tissue (scarring).

Immunology and host–parasite interactions: The secondary targets, upper urinary tract, liver, lungs are involved as a result of spill over due to various mechanisms like obstruction or reflux at vesico-ureteric junction and drifting of ova through portal vein stream or to pulmonary circulation via normal portosystemic anastomoses^[19]. Occasionally, ova infect the ectopic target organs like brain, spinal cord, genitals, eyes, skin, through their respective venous anastomoses with inferior vena cava^[19].

Urinary schistosomiasis: Adult worms (*Schistosoma haematobium*) infected in lower ureters, urinary bladder, seminal vesicles and occasionally vas deferens, prostate and female genital organs. The disease may affect the general well-being resulting in reduced productivity and school performance of children^[22]. In adults, hematuria disappears and the disease evolves into fibrosis, calcification, hydronephrosis, and eventually renal failure^[19]. Chronic urinary schistosomiasis is also associated with squamous cell carcinoma of urinary bladder^[23]. In both sexes, genital schistosomiasis has been associated with increased risk of HIV infection^[24]. Each day, about 300 eggs are eliminated by the female inside the venules; the presence of a lateral spine is the most prominent feature of these eggs^[20]. Inflammation, caused by the presence of the eggs in the host, can result in rupture of the venule wall, releasing the eggs into the perivascular tissues and finally into the intestinal lumen^[20,21].

Intestinal schistosomiasis: *S. intercalatum* and *S. guineensis* cause generally milder intestinal manifestations than *S. mansoni*, *S. mekongi* or *S. japonicum*. Large bowel and rectum are mainly infected in this asymptomatic disease. The eggs of parasite get trapped in the wall of mesentery and provoke the granulomatous inflammatory reaction causing micr-ulceration, pseudopolyps and bleeding^[19]. However, this chronic condition can have significant impact on general health among children^[22].

Hepatosplenic Schistosomiasis: Adults *S. mansoni* and *S. japonicum* reside in the venules of the intestine and the major disease manifestations are due to the deposition of eggs in the liver and the consequent liver fibrosis^[25, 26]. The most important complication is periportal or Symmers' pipestem fibrosis of the liver caused by deposition of eggs^[25,26]. The liver may be enlarged or shrunken and portal hypertension develops resulting in splenomegaly and gastroesophageal varices^[27]. Hepatocellular carcinoma and bladder cancer may develop in patients with chronic infection^[28, 29, 30, 31]. Clinical diagnosis is based on the presence of living eggs in stool examination or by a positive serologic test in endemic area. In *S. mansoni* infection, eggs are deposited along the large portal veins of the hilum of the liver^[26], whereas in *S. japonicum* infection, eggs are deposited along the small portal veins of the peripheral part of the liver^[32,33]. This is probably because eggs of *S. japonicum* are smaller (70– 100 μ m in length) than those of *S. mansoni* (110–170 μ m in length)^[26]. Therefore, periportal fibrosis is predominant in the central part of the liver in a *S. mansoni* infection, while it is predominant in the peripheral part of the liver in a *S. japonicum* infection^[27]. In *S. mansoni* infection, there are bands of periportal fibrosis in the liver encompassing the large portal tracts^[26, 32], that can cause Symmers' pipe-stem fibrosis; the liver looks like a "turtle back"^[27]. Unlike in *S. japonicum* infection, eggs of *S. mansoni* do not have a tendency to calcify^[33]. The portal venous tracts are replaced with fibrous tissue and this leads to presinusoidal blockage, hepatomegaly, portal hypertension, splenomegaly, and gastroesophageal varices^[27]. Sonographic findings are thickening of the walls of the portal veins in the porta hepatis with increased echogenicity^[32, 33, 34]. Calcification of *S. mansoni* eggs in human tissues is not seen as commonly as calcification of *S. japonicum* eggs^[26].

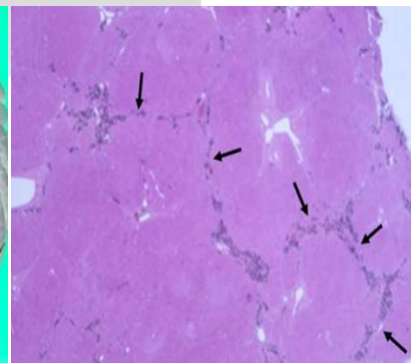


Figure:5

Figure:-6

Figure:7

Figure:5-Chronic fibrotic diseases increased portal pressure and ascites in a young adult man.; Figure:6- mimicking "turtle-back" liver; Figure:7- Photomicrograph of liver specimen infected with *S. japonicum* shows clusters of calcified schistosome eggs along the periportal fibrous septae around the hepatic lobules.

In *S. japonicum* infection, eggs are carried to the portal vein and deposited in the periportal spaces of the small portal venous radicles in the hepatic parenchyma^[30]. Eggs die, degenerate and are calcified, and produce granulomas and fibrosis. Polygonal network of periportal fibrosis looks like "honeycomb" or "tortoise shell"^[28]. Eggs are also deposited in the liver capsule and produce fibrous thickening^[28]. The eggs' smaller size and increased number allows for wide dissemination via the small portal venule^[26].

Ectopic schistosomiasis: In advanced disease stage, eggs are transported to various ectopic sites ending up with disease conditions according to the site involved^[19]. Eggs, when transported to lungs in advanced hepatic schistosomiasis through portal-caval shunting, results in granuloma formation and fibrosis eventually leading into pulmonary hypertension and right heart failure^[35,36,37]. Chronic, untreated infection of *Schistosoma mansoni* may cause immune complex mediated glomerulonephritis^[38].

Other manifestations: Devastating neurological damage can result when the eggs or parasite specially *Schistosoma mansoni*, *Schistosoma hematobium* or *Schistosoma japonicum* get transported to the brain or spinal cord^[39, 40, 41, 42]. Neuroschistosomiasis (affection of the central nervous system by *Schistosoma* spp.) may be one of the most severe clinical outcomes of schistosomiasis and is caused by the inflammatory response around eggs in the cerebral or spinal venous plexus^[43, 44, 45]. *S. mansoni* and *S. haematobium* worms abnormally locate most often in the spinal venous plexus, where they may cause transverse myelitis^[45], a complication also seen in individuals with acute schistosomiasis^[47]. Neuroschistosomiasis caused by *S. japonicum* is mainly associated with granulomatous lesions in the brain, which can result in epileptic seizures, encephalopathy with headache, visual impairment, motor deficits and ataxia (reduced coordination of voluntary muscle movements)^[44].

Pulmonary schistosomiasis is caused by portal-caval shunting, in which venous blood bypasses the liver through collateral veins connecting the portal vein with the vena cava, and eggs are thereby transported to the lung capillaries, where they induce granulomas in the perialveolar area^[8]. These granulomas may lead to fibrosis and may result in pulmonary hypertension and corpulmonale (an enlargement of the right ventricle of the heart due to increased pressure in the lung capillaries)^[46].

Diagnosis: The diagnosis of acute schistosomiasis requires different diagnostic methods than those used to diagnose established active or late chronic infections^[47, 48]. Mainly parasitological, serological/molecular methods are used to detect schistosomiasis. The gold standard diagnostic tool is detection and demonstration of eggs in stool or urine^[49,50]. However, if eggs are not detected in stool and urine, the tissue biopsy specimens of bladder and rectal mucosa may be used^[51]. Antibody-based serological assays can also be used in body fluids including blood serum and CSF to detect antibodies which remain positive for long time after active infection has resolved^[52,53]. The infection can also be confirmed with molecular detection of schistosomal DNA by PCR in sera of infected patients^[54,55]. Sometimes the affected organ is life threatening. Ultrasonographies, CT scan, MR scan are required for diagnosing in to serious condition of a patient.

Box 1 | Making a positive diagnosis of a schistosome infection in a returning traveller or recent immigrant^[55].

Medical history

- Recent travel to or from an endemic country; note that different *Schistosoma* spp. migrate to different anatomical sites, corresponding to different symptoms. As the different species have different geographical distributions, determining the country visited can guide in the diagnosis
- Contact with water from lakes, rivers or streams.

Physical examination.

- Urticarial rash on the skin at the site of cercariae entry, with discrete erythematous raised lesions that vary in size from 1 to 3cm
- Hepatomegaly (tender left lobe) and in approximately one-third of patients splenomegaly on palpation of the abdomen (indicative of established active or late chronic infection)
- Dry or moist rales (crackling noises) in the lungs on auscultation (acute infection)
- Generalized lymphadenopathy.

Laboratory investigations

- Stool and/or urine examination to detect schistosome eggs
- Full blood count: eosinophilia is present in >80% of patients with acute infections, whereas anaemia and thrombocytopenia may be present in established active and late chronic schistosomiasis
- Coagulation profile: prolonged prothrombin time indicated by an increased INR (international normalised ratio) may be evident in established active and late chronic schistosomiasis
- Urea, electrolytes and liver function: elevated urea and creatinine levels may be evident, and hyperglobulinaemia and hypoalbuminaemia may be present in late chronic and advanced schistosomiasis
- Serology may be diagnostic in patients with acute schistosomiasis.

Radiology

- Chest radiography: pulmonary infiltrates are common in acute schistosomiasis
- Abdominal ultrasonography can establish the extent of liver and spleen pathology in intestinal schistosomiasis
- Pelvic ultrasonography can establish the extent of bladder, ureteral and renal pathology in urogenital schistosomiasis.

Parasitological diagnosis of schistosomiasis in populations living in endemic areas most often relies on filtering a standardized small amount of urine or stool sample and microscopically counting all eggs in that volume^[57,58]. The level of infection is then expressed as eggs per 10 ml of urine or eggs per gram of stool (EPG)^[59]. These methods have a low sensitivity (estimated at <50%)^[59,60], and the observation of 1 egg in a slide corresponds to detection of 20–40 EPG, or 5,000–10,000 eggs per diurnal faecal portion of 250 g (in *S. mansoni* infections, 1–99 EPG are considered low-intensity infections). However, egg excretion may

show a high degree of day-to-day^[61] as well as intraspecimen and diurnal variation^[62]. When schistosomes feed on red blood cells, they regurgitate waste products into the bloodstream^[63]. These products are proteoglycans known as circulating anodic (negatively charged) antigens (CAAs) and circulating cathodic (positively charged) antigens (CCAs) and they can be detected in serum and urine by enzyme-linked immunosorbent assay (ELISA) or monoclonal-antibody-based lateral flow assays^[64].

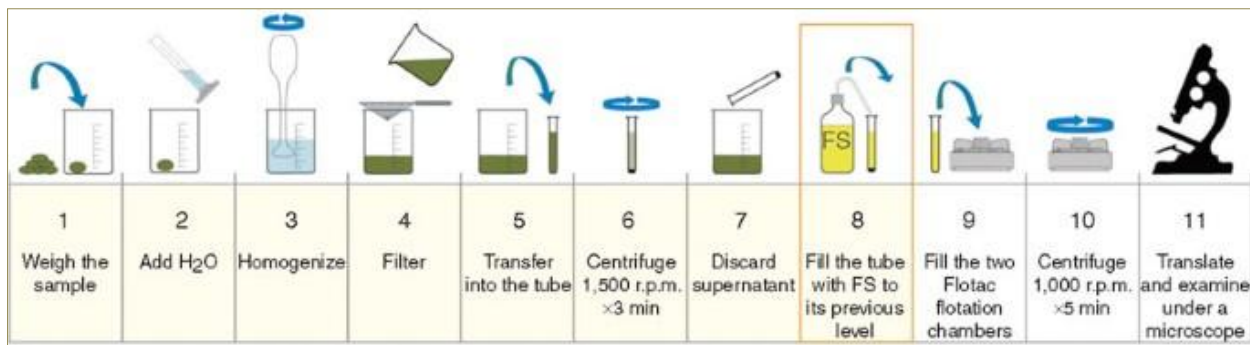


Figure-8 ; Schistosomiasis Diagnosis

Table 1 | Diagnostic tests for Schistosoma spp. Infection^[8]

Test	Sample	Quantitative	Sensitivity	Specificity	Target	setting	
					Endemic areas		Non –endemic areas
					PHC U	Laboratory	
Microscopic detection of eggs							
Kato-Katz	10–50mg of fresh faeces	Yes	Low	High	Yes	Yes	NA
FECT	10g of fresh faeces	No	Medium	High	No	Yes	Lowmedium sensitivity
Urine filtration ^a	10ml of fresh, well-suspended urine	Yes	Medium	High	Yes	Yes	Medium-high sensitivity ^b
Antigen detection							
ELISA ^c	Serum, urine and vaginal lavage	Yes	High	High	No	No	Low sensitivity
POC-CCA ^d	Urine	Semi-quantitative ^e	High	High	Yes	Yes	Low sensitivity
UCP-LF CAA	Urine	Yes ^f	High	High	No	Yes/no ^g	Low sensitivity
Antibody detection							
ELISA	Serum	No	High	Low	No	Yes/no	Yes
IHT	Serum	No	High	Low	No	Yes/no	Yes
DNA detecton							
PCR	Fresh or frozen faeces, urine, vaginal lavage and rectal snip	Yes	High	High	No	Yes/no	Yes
LAMP	Fresh or frozen faeces and urine	Yes	High	High	No	Yes/no	Yes

CAA, circulating anodic antigen; CCA, circulating cathodic antigen; ELISA, Enzyme-linked immunosorbent assay; FECT, formalin-ether concentration technique; IHT, indirect haemagglutination test; LAMP, loop-mediated isothermal amplification; LF, lateral flow; NA, not applicable; PHCU, public health care unit; POC, point-of-care; UCP, up-converting phosphor. ^aFor Schistosoma haematobium eggs only. ^bFiltration can be used in non-endemic areas but requires a large sample (normally a 24 – hour urine sample). ^cFor both CAA and CCA. ^dFor Schistosoma mansoni CCA only. ^eThe POC-CCA test can be read as ‘trace’, +, ++ and +++. ^fThe test is quantitative but requires specific equipment for reading the strips. ^gYes/no indicates that the test requires reagents, equipment and trained personnel.

Several biomarkers are used to diagnosis of Schistosomiasis. Screening of populations living in endemic areas is relevant in relation to control programmes, to assess infection prevalence and intensity (that is a proxy for worm burden) before and/or after an intervention, such as MDA^[48,59]. One of the most widely employed, easy-to use screening methods is testing for S. haematobium related microhaematuria using a reagent strip test^[65]. This approach has been especially useful in school-aged children, in whom microhaematuria strongly correlates with urogenital schistosomiasis^[66], and it has also proved to be useful following intervention^[65]. A meta-analysis has shown an overall sensitivity of the reagent strip test for detection of S. haematobium egg-positive urines of 81%, but the overall sensitivity decreased to 72% in previously treated populations^[65]. Direct parasitological methods are inexpensive and easy to use, but a major drawback is their low sensitivity^[60]. The POC-CCA assay

may prove useful for detection of *S. mansoni* infection and has the logistic advantage that it can be performed directly on a urine sample rather than a more-cumbersome stool or blood sample^[60]. The POC-CCA assay is more sensitive than standard parasitological techniques^[67].

Prevention: Precise diagnosis of *Schistosoma* spp. infections, in both snail and mammalian hosts, will be crucial in achieving morbidity reduction and eventually disease elimination, particularly in areas where extensive control has reduced schistosomiasis prevalence and infection intensity to very low levels^[8]. Schistosomiasis is a poverty-related disease, and need to be awareness of the local people, snail control, will have to be directed bathing place for cattle, cleaning for kitchenware and drinking water place. Despite intensive development efforts, currently no schistosomiasis vaccines are available^[68,69]. The aim of treatment with the anti-schistosomal drug praziquantel is curative therapy, and treatment can be repeated several times until the infection is eliminated (that is, no eggs are detected upon microscopic examination of faeces or urine)^[8]. A single dose of PZQ 40 mg/kg is effective in *S. mansoni* infection. Praziquantel is not work in effect on immature schistosomes. Also albendazole (ABZ), praziquantel-artemisinin, mebendazole (MEB) etc anti-helminthic drugs are using to recovery treatment of Schistosomiasis diseases. The WHO set a target of potential global elimination of schistosomiasis as a public health problem by 2025^[70].

Conclusion: This study has offered an outlook of Schistosomiasis and suggestions and possible health education approaches the people. It should be need to develop sustainable, permanent education programmes tailored culturally to local realities for combating schistosomiasis in endemic areas.

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