Schistosomiasis

Subjects: Infectious Diseases

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Schistosomiasis is a common neglected tropical disease of impoverished people and livestock in many developing countries in tropical Africa, the Middle East, Asia, and Latin America.

schistosomiasis Schistosoma haematobium Schistosoma mansoni sub-Saharan Africa Africa

1. Life Cycle of Schistosoma sp.

Schistosomes have a complex life cycle involving both intermediate gastropod hosts and a definitive mammalian host (**Figure 1**). Unlike other trematode species, *Schistosoma* spp. are dioecious (separate male and female worms) which undergo sexual reproduction in the mammalian definitive host. Schistosome eggs are produced and excreted into the environement via the faeces (*S. mansoni*) or urine (*S. haematobium*). Miracidia are released when the eggs come in contact with water and infect the snail host. There, miracidia develops into mother sporocysts and undergo asexual reproduction to produce daughter sporocysts which produce cecariae. Infected snails shed cercariae into the water and upon locating a suitable definitive host, penetrate the skin, transform into schistosomula and migrate through the circulatory system to the lungs, heart and liver where they mature into adult worms (**Figure 1**). The adult worms then exit the liver and pair up to mate in the mesenteric vessels of the bowel (*S. mansoni, S. intercalatum*) or bladder (*S. haematobium*).

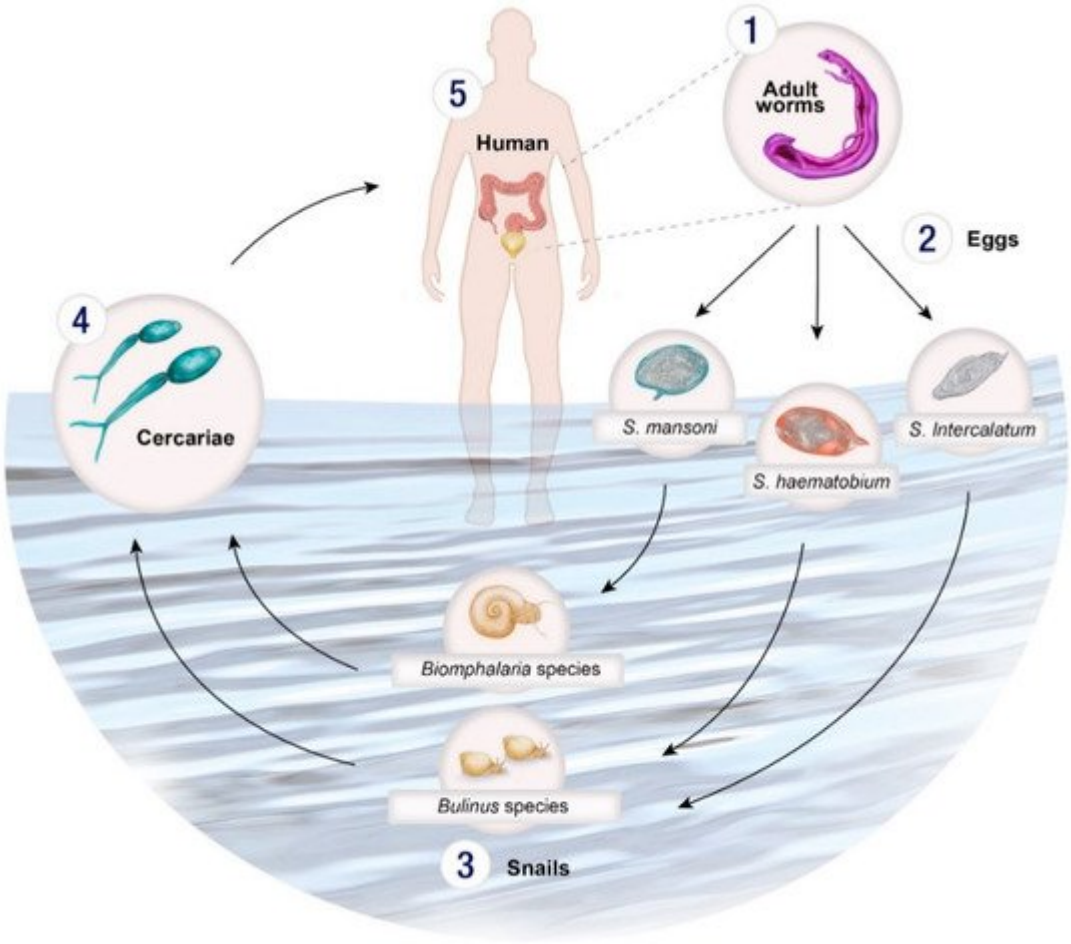

Figure 1. Life cycle of *Schistosoma* spp. (1) Male and female adult worms reproduce sexually in the venous system of the bladder (*S. haematobium*) or the bowel (*S. mansoni, S. intercalatum, S. guineensis*) producing eggs which are excreted in urine or via faeces, or are retained in body tissues, such as the liver. (2) The eggs hatch upon contact with water releasing miracidia which then penetrate a specific intermediate molluscan host. (3) Within the snail host, the miracidia develop into sporocysts and asexually reproduce daughter sporocysts which in turn produce cercariae. (4) The cercariae emerge from the snail and directly penetrate the skin of the (5) human host and transform into schistosomula. The schistosomula migrate via the circulatory system to the lungs and then the heart before arriving in the liver where they mature. Once mature the adult worms exit the liver and pair up to mate in the mesenteric vessels of the bowel bowel (*S. mansoni, S. intercalatum, S. guineensis*) or bladder (*S. haematobium*).

A proportion of the eggs are carried by the bloodstream to other areas of the body where they can become lodged in tissues, and trigger an inflammatory response, causing acute or chronic disease. (**Figure 1**). Schistosomes have an average life span of 3–10 years but can live up to 40 years in their human hosts in permanent copulation [1][2].

The control and elimination of schistosomiasis requires interruption of a complex pathway of transmission governed by the interplay of humans, intermediate host snails and human–water contact patterns. The snail hosts are crucial for determining the range of schistosomiasis and are responsible for the focal nature of the disease (i.e.,

highly variable infection prevalence and intensity even within a small area such as from one village to another). Two genera of snails (*Bulinus* and *Biomphalaria*) are responsible for the distribution of schistosomes in Africa. These molluscs can be an important focus of control efforts involving environmental modification (e.g., digging water drainage ditches or tunnels to flood and bury the snail habitats to disrupt snail habitats), or through the use of chemicals, such as niclosamide [3][4]. Concerning, however, are the detrimental impacts that such chemicals can have on the environment including the general pollution they cause and being toxic to larger animals such as fish [5][6].

2. Clinical Presentation of Schistosomiasis in Africa

Schistosome infection has three distinct disease phases beginning with an initial dermatitis reaction following skin penetration by the cercariae resulting in an allergic inflammatory maculopapular lesion [7]. The infection may then proceed to a symptomatic acute schistosomiasis stage also known as Katayama fever or Katayama syndrome. Acute schistosomiasis is rarely reported in individuals living in areas endemic for *S. mansoni* or *S. haematobium*. One possible explanation for this being that in-utero sensitisation might decrease the severity of common symptoms of Katayama syndrome in chronically exposed individuals resulting in lowered immune responsiveness to schistosome antigens in infants born to infected mothers; it may also be equally likely that cases from endemic areas are simply unrecognised or under-reported [7][8]. The most common symptoms of acute schistosomiasis include prolonged fever, weakness, vomiting, nausea, diarrhoea, malaise and rapid weight loss [9][10]. The third and final disease stage, chronic schistosomiasis, occurs when eggs are deposited in various body tissues, commonly affecting the liver, bladder and urogenital system, and less commonly in the central nervous system [9][11]. Adult worms can avoid detection by the immune system by camouflaging their outer layer with host antigens and tegmental shedding and are able to reside for long periods in their hosts [12]. In contrast, schistosome eggs are fully exposed to the immune system, and this results in the formation of granulomatous and fibrotic lesions around the eggs in various tissues resulting in necrosis, ulceration and bleeding that can have long-term detrimental effects [9][10][13][14]. Chronic schistosomiasis is associated with hepatosplenomegaly, portal fibrosis and, in the case of *S. haematobium*, haematuria (blood in urine), ureter fibrosis, and squamous cell carcinoma of the urinary bladder [9].

S. mansoni is the leading cause of intestinal schistosomiasis in Africa. Around 50% of eggs deposited by adult worms are retained in the liver, causing chronic disease [15]. Pathogenesis due to *S. intercalatum* is less severe than *S. mansoni* and *S. haematobium* and most infected patients, particularly children, do not show symptoms of the disease [16].

2.1. Female Genital Schistosomiasis

Female genital schistosomiasis (FGS) is characterised by the presence of *S. haematobium* eggs in the vagina and cervix and affects up to 20 million women in sub-Saharan Africa and the Middle East [17][18]. The eggs penetrate the urogenital system, causing uterine enlargement, menstrual disorders, cervicitis and infertility [19]. Schistosomiasis in pregnant women presents with symptoms ranging from anaemia during pregnancy to newborns with low birth weight, and increased infant and maternal mortality rates [20][21][22][23]. Urogenital schistosomiasis has also been

linked with increased risk of HIV infection in women resulting from the production of genital mucosal lesions surrounding the eggs [24][25]. The immune response caused by *S. haematobium* infection leads to chronic inflammatory granulomatous lesions, genital epithelial bleeding and sandy patches in the cervix and vagina that, if left untreated, can become an easy entry point for the HIV virus, as well as leading to infertility [1][24][26][27][28][29]. Concurrent infection with HIV and *S. haematobium* leads to increased disease pathology while HIV infection may lead to an increased chance of contracting schistosomiasis [24][30][31]. Schistosomiasis has also been suspected of increasing disease progression and death in HIV patients by increasing the HIV RNA load in the blood plasma [32][33]. More than 70% of HIV infections worldwide occur in sub-Saharan Africa and thus HIV remains a major health challenge in Africa and an important confounding factor for schistosome infection. Diagnosis of FGS can be challenging due to different transformation stages of the *S. haematobium* parasite and immune response in the affected tissues. In cases where the infected patient is asymptomatic, the disease may be mistaken for sexually transmitted diseases (STDs) or cervical cancer [34][18][35]. Stigma against STDs can lead to misdiagnosis, or reluctance of young women to present to a doctor when experiencing clinical symptoms of FGS.

2.2. Primary and Secondary Infertility in *S. haematobium* Infections

Infertility is the inability to become pregnant after regular and unprotected sexual intercourse for more than one year [36]. It can be diagnosed as either primary–where the woman has never conceived, or secondary-when the woman has experienced previous labour. Suspected cases of infertility resulting from *S. haematobium* infection in the genital tracts have been widely reported in Africa [37][38][39][40][41][42][43]. While the presence of an adult worm infection in the urogenital system is generally asymptomatic, the deposition of *S. haematobium* eggs along the urogenital tract, including the cervix and vagina, trigger a hypersensitive immune response, causing scarring and fibrosis in the genital tract, ovaries and fallopian tubes. The eggs may appear as papillary white lesions [37][38], causing thickening, nodular lesions and adhesions which eventually lead to obstruction and blockage of the fallopian tubes. The resulting fibrosis and blockage is suspected to lead to infertility. A case study in Nigeria reported the inability of a woman to get pregnant with her second child despite having a regular menstrual cycle; tuboplasty (surgery undertaken to restore the functionality and integrity of the fallopian tubes) revealed lesions and blockage of the patient's fallopian tubes due to the presence of *S. haematobium* eggs [38]. Urogenital schistosomiasis has also been linked to ectopic pregnancies as a result of blockage of the fallopian tubes [39][40]. Patients can recover with administration of PZQ if the infection is treated sufficiently early [38][39].

2.3. Male Genital Schistosomiasis

Male genital schistosomiasis (MGS) was first reported in 1911 [44] and is described as the presence of schistosome (*S. haematobium*) eggs in the male genital organs and fluids. The awareness and severity of this disease especially in endemic areas is often overlooked and underreported as it can be misdiagnosed as a sexually transmitted infection (STI) [31][45][46]. Symptoms of this disease include painful urination, painful ejaculation, irregular ejaculations, hermatospermia, prostatitis, epididymitis (inflammation of the epididymitis at the back of the testicles), which could mimic tuberculosis and associated funiculitis, erectile dysfunction, enlarged genital organs and infertility [31][47][48][49].

2.4. Bladder Cancer in *S. haematobium* Infections

Globally, 275,000 people are diagnosed with bladder cancer annually and 108,000 people die of the disease. Bladder cancer caused by translational cell carcinoma (TCC) occurs in industrialised and developing countries not endemic for urogenital schistosomiasis, while bladder cancer caused by squamous cell carcinoma (SCC) is a long-term sequela of chronic infection and occurs in many parts of Africa plagued with urogenital schistosomiasis [50][51]. Bladder cancer is one of the foremost serious complications of chronic *S. haematobium* infection and it is estimated that the schistosome-associated bladder cancer incidence is 3–4 cases per 100,000 infections [52].

TCC arises from the transitional epithelium lining of the bladder and presents in its early stage as a painless haematuria. In contrast, a squamous hyperplasia (usually not present in a normal urothelium which is a highly specialized epithelium lining the lower urinary tract) gives rise to SCC due to injuries caused by the immunological responses to deposited eggs in the bladder [53]. This is followed by painful haematuria, chronic inflammation and necroturia [53]. SCC often presents with symptoms only at a late stage and can be challenging to treat by surgery or with chemotherapy.

A study in Egypt reported that 82% of patients with SCC had *S. haematobium* eggs lodged in their bladder wall and infected individuals had the tendency to develop cancer at a younger age than uninfected individuals [54]. Kitinya et al. [55] reported that of 172 individuals with bladder cancer in Egypt over a nine year period (1971–1980), 72% were SCC cases. Similarly, a study in Northern Tanzania reported 46% of SCC patients had *S. haematobium* eggs in the tumour tissues [55]. Another study from Angola, situated in the western part of Western Africa, reported a >70% (215/300) *S. haematobium* prevalence with 3 of the infected patients having calcified bladders and one SCC case was recorded [56]. A decrease in the prevalence of urogenital schistosomiasis in Egypt has seen a decline in the SCC and an increase in the median age of infected individuals with bladder cancer [57].

The mechanisms associated with *S. haematobium* and the development of SCC are largely unknown although the carcinogenic process appears to be closely related to tissue inflammation [58]. Botelho et al. [59] described the relationship between *S. haematobium* and cancer by exposing normal epithelial cells (Chinese Hamster Ovary (CHO) cells) in culture with *S. haematobium* total antigen and observed increased cell proliferation, decreased apoptosis, migration, invasion and tumourigenesis [59][60]. This suggested that *S. haematobium* has the ability to induce the formation of cancer-like cells [59]. Furthermore, *S. haematobium* exposed cells injected into mice with no immune system resulted in the development of tumours similar to those found in bladder cancer [61].

3. Treatment and Control

Preventive chemotherapy (PC) through MDA with PZQ is the cornerstone of the treatment and control of schistosomiasis in endemic regions of Africa. PZQ has been proven a safe and effective oral drug active against adult worms of all *Schistosoma* species [62][63], although its mechanism of action is still not fully understood. However, it cannot be used for chemoprophylaxis due to its short half-life, and it is ineffective against migrating schistosomula [64]. Corticosteroids, in addition to PZQ, are effective as an adjuvant when patients present with

Katayama syndrome, usually within two months of exposure to cercariae [8][65] to suppress immunological reactions and prevent acute disease. Other drugs that proved effective for the treatment of schistosomiasis include oxamniquine for *S. mansoni,* and metrifonate for *S. haematobium* [9][10] but these are either no longer readily available or have been withdrawn due to unacceptable toxicity. Co-infections of *Schistosoma* spp. and soil-transmitted helminths (STH) are common in many endemic areas in Africa, and as such, combination PC with both PZQ and albendazole is recommended by WHO [66] particularly for SAC and other high risk groups.

PZQ is given to SAC between the ages of 5 and 15 years who have the highest infection rates and are more readily reached through school programs. PC is usually carried out by firstly assessing the prevalence of the disease which determines the frequency of treatment in that area [67]. For example, areas showing disease prevalence with 50% or more usually should receive a single annual treatment while areas with 10% prevalence will receive triennial treatment [67]. As of 2019, 57.1% (61.8 million) SAC who require treatment have received PZQ [68].

Re-infection remains a major challenge to control efforts in Africa due to a number of factors including: high levels of infection prevalence and intensity, poor or non-compliance of PZQ treatment and low coverage, recontacting contaminated water as a result of daily activities and seasonal factors. Hence, a multifaceted intervention approach will be needed to move from wide-spread control to elimination including: snail control; treatment; effective risk mapping and epidemiological surveillance; accurate diagnostics; improved access to clean water, sanitation and hygiene (WASH); and public health education to bring about behavioural changes to prevent infection and reinfection [69][70][71][72][73]. These integrated approaches, together with the development and deployment of future anti-schistosome vaccines effective in humans (albeit no schistosomiasis vaccine has yet been accepted for public use) will contribute greatly to reducing and interrupting transmission in endemic areas leading to eventual elimination [74][75]. Another challenge to be faced is climate change and the resultant elevated temperatures which may increase the geographical distribution of the parasite through expansion of suitable environments for snails into higher altitudes and into further locations in Africa currently unaffected by the disease. While most studies focus on increasing temperature, it has been shown that snails and schistosomes within their hosts survive during the winter months and produce viable cercariae that complete their life cycles when optimal temperature is reached [76]. Furthermore, snails from temperate region demonstrate better resistance to harsh winter conditions than tropical snails [76].

4. Diagnosis

There are a number of approaches used for schistosomiasis diagnosis and schistosome detection. The standard method used in Africa is the detection of eggs in urine or stool by microscopy [77][78], although a number of immunological [79][80][81][82][83][84][85] and molecular [86][87][88][89][90][91][92][93] diagnostic assays have been developed with some deployed in Africa. Polymerase chain reaction (PCR) and quantitative PCR (qPCR)-based molecular methods are now increasingly being employed for diagnosis in high-resource settings globally but they are expensive, take time, require a significant laboratory infrastructure and training which hampers their current use in low socio-economic endemic field settings. Isothermal amplification detection (IAD) methods can overcome some

of these obstacles including the limitations of costly thermal cyclers required for the PCR-based detection of parasite DNA in stool or urine. IAD assays work similar to that of conventional PCR in that they utilise DNA or RNA polymerase in the extension of target-specific primers. However, isothermal amplification facilitates amplification without the repeated cycles of denaturation and annealing required for PCR. The most established IAD method for schistosome detection is loop-mediated isothermal amplification (LAMP) [94][95][96][97][98][99][100][101][102][103]. Other isothermal methods for parasite detection include helicase-dependent isothermal amplification (HDA) [104], recombinase polymerase amplification (RPA) [105] and nucleic acid sequence-based amplification (NASBA) [106], but only RPA has been applied in the detection of *Schistosoma* spp. [107][108][109][110].

As indicated earlier, the microscopic detection of eggs in urine (*S. haematobium*) and faeces (*S. mansoni*) is the most commonly used method for the diagnosis of schistosomiasis. The Kato-Katz (KK) method is used to detect *S. mansoni* eggs in faeces, while urine microscopy, preceeded by urine filtration, is used to identify *S. haematobium* infections [77][78]. *S. haematobium* eggs were identified in the semen of fishermen as part of a cross-sectional study along the southwestern shoreline of Lake Malawi in Sub-Saharan Africa, suggestive of high lodgement of eggs in the reproductive organs of men [49]. The precise origin of eggs found in semen is unresolved but they may have originated in the bladder, carried with drops of urine through the urethra and released with the semen [31]. Eggs of *S. haematobium* can be readily detected by light microscopy, and cell-free circulating schistosome DNA has been detected in semen several weeks after a single dose of PZQ [111].

In addition to egg detection, active infections can be detected from worm-derived circulating anodic antigens (CAAs) and circulating cathodic antigens (CCAs) in serum and urine using enzyme-linked immunosorbent assay (ELISA) or monoclonal- antibody-based lateral flow tests [112][113]. These detection methods have the ability to detect infection before the worms begin producing eggs, [114][115][116]. However, they do not discriminate between past, active or re-infections, especially in endemic areas where patients can remain seropositive several years after treatment [114][117].

Haematuria and proteinuria reagent strip testing can also be used as indirect diagnostic methods for *S. haematobium* infection [118]. Strip testing has previously been shown to provide sensitivity and specificity levels of 75% and 87%, respectively, for detection of *S. haematobium* [119] and has been suggested as an alternative form of diagnostic to the usual urine microscopy. Strip testing may be useful in sub-Saharan Africa due to its substantially higher sensitivity than microscopic methods and ease of storage of the strips [112]. However, the strip tests also detect haematuria not associated with *S. haematobium* infection, and the method exhibits poor sensitivity in detecting egg-positive urine post-treatment and low-intensity infections [112].

4.1. Environmental Monitoring

As indicated earlier, schistosomiasis is a highly focal disease with transmission being highly dependent on the presence of fresh water and appropriate snail intermediate hosts, as well as water contact activities by humans who become infected. The risk of infection is dependent on seasonal changes in snail populations, water levels, infection rates and cercarial output. Flooding events may also cause temporarily higher rates of infection in human

communities. Information on snail hosts and the distribution of cercariae are important tools in the control and elimination of schistosomiasis [58][109][120].

Molecular xenomonitoring is a useful disease surveillance tool for the detection of infection rates in field population of snails and could be useful in identifying infection risk areas to help guide intervention measures for schistosomiasis control and elimination [121][122][123][124]. There are a number of methods used for xenomonitoring including sentinel mice which have been used to identify transmission sites in natural water bodies in China; however, this process is time-consuming and expensive [122][125]. Morphological identification of miracidia and cercariae collected from water sources can be inaccurate due to disintegration of the larvae and misidentification of human and non-human cercariae that co-exist in most endemic areas; the latter issue is also applicable to identifying cercariae from infected snails [126] (**Figure 1**).

PCR-based detection methods have been developed that detect cercariae in water samples and schistosome species in snail intermediate snail hosts, and these have proved useful in identifying and monitoring schistosomiasis transmission areas in Africa [122][127]. An example is the DraI PCR, which has been used to monitor snail transmission *S. haematobium* cercariae in Morocco [128]. The DraI ribosomal sequence is specific to the *S. haematobium* group and can detect low amounts of DNA due to its abundant sequences in the *S. haematobium* genome [129][130][131][132]. Another example is a two-step multiplex PCR approach which first identifies *Schistosoma* infected snails, followed by species-specific identification using internal transcribed spacer (ITS) rRNA primers [133][134].

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