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Schistosomiasis: Current and future perspectives

Abstract

Schistosomiasis is one of the neglected tropical diseases (NTD) that has challenged the medical community and affects 200 million people annually. Despite early appreciation of the schistosomal life cycle, breaking transmission is very difficult due to deficiencies in sanitation, presence of animal reservoirs and chronicity of disease in the absence of symptoms. New and effective methods to control schistosomiasis are required to counteract the dire consequences it poses and reduce associated morbidity and disability adjusted life years (DALYs).

Keywords: schistosomiasis, neglected tropical disease, control, epidemiology

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Background

Neglected tropical disease (NTDs) is an umbrella term used to describe a group of conditions, which disproportionately contribute to morbidity and mortality in developing countries. Poverty, poor sanitation and lack of healthcare infrastructure were found to be the main reasons for its persistence.[1] Among several parasitic infections, Schistosomiasis (genus schistosoma), was found to be most prevalent with ~200 million people requiring treatment in 2019 alone.[2] Schistosomiasis is a water borne helminth and the second most widespread parasitic disease after malaria and first in disability adjusted life years (DALYs) a measure of premature mortality and years of healthy life lost.[3] As such Schistosomiasis represents a considerable global health problem but particularly in Sub-Saharan Africa where >90% infections take place.[3,4]

Of the schistosomal species *S. mansoni, S.haematobium* and *S.japonicum* are the most important. Of these two thirds of cases are caused by *S.haematobium* which leads to urogenital infection causing haematuria. Chronic inflammation is linked with the development of squamous cell carcinoma of the bladder. The remaining cases are associated with S.mansoni (and to a lesser extent *S.japonicum*) which result in intestinal disease manifesting leading to chronic and bloody diarrhoea and is an important cause of chronic liver disease worldwide.[5,6] While the process of mass drug administration is recommended by the World Health Organization (WHO) there has been no meaningful reduction in cases. Moreover, given the perennial risks of reinfection, lack of sustained immunity, poor access to healthcare of affected individuals, and emerging resistance to therapies it is unlikely the elimination of Schistosomiasis by 2030 can be achieved without new methods of control.[7] To do this a thorough understanding of the natural life cycle and contribution of various hosts in the dissemination and persistence of Schistosoma infection in the environment is required. Here we explore the biology of schistosomiasis as a means to evaluate both current control methods and highlight possible means by which elimination might be achieved.

Schistosomiasis pathogenesis

The life cycle of Schistosoma was first elucidated in 1908 and is complicated by multiple hosts and reservoirs of the parasite. Common to all schisotosomal species is their development within freshwater snails from the genus *Biomphalaria* (S.mansoni), *Bulinus* (S.haematobium) and *Oncomelania* (S.japonicum) that serve as the intermediate host for their development and subsequent ability to infect the definitive host.[8] While asexual reproduction takes place in the freshwater snail, humans serves as the definitive host and site of sexual reproduction whereby the mature female parasite produces eggs which are eliminated through the lumens of the gastrointestinal or urinary system depending on the schistosomal species thereby completing the lifecycle. Importantly, other mammalian hosts including dogs, pigs, mice and baboons serve as reservoirs of the disease in endemic areas (Figure 1).[4,6]

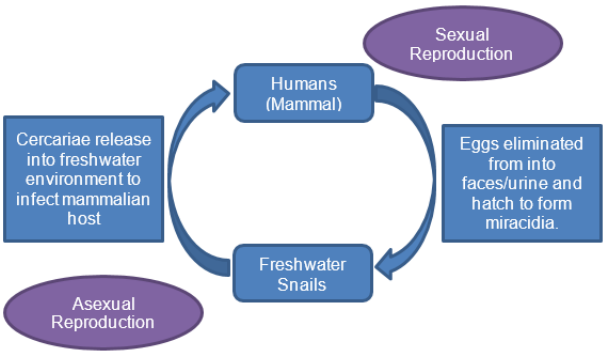

Figure 1 The life cycle of Schistosomiasis.

In the presence of poor sanitation as well as bathing in rivers, schistosoma eggs from infected humans and other mammals can pass into the freshwater environment of the snail intermediate host. The eggs may be differentiated by species according to the location of their spine, which is lateral in *S.mansoni* terminal in *S.haemtobium* and absent in *S.japonicum* eggs.[6] Here eggs hatch and release miracidia larvae which are capable of swimming and infecting particular freshwater snails. As little as one miracidia is needed to infect a freshwater snail and on doing so they develop into sporocysts which divide to form daughter sporocysts through asexual reproduction. These can either produce Cercariae which emerge around 30 days after initial infection and are characterised by the presence of a fork tail and the capability of infecting humans or more daughter sporocysts.

This process is highly efficient with approximately 200 (*S.haemtobium*), 15-160 (*S.japonicum*) and 250-600 (S.mansoni) cercariea being produced daily with sunlight triggering their release into the aquatic environment.[9,10] During activities such as washing, fishing etc. humans can therefore come into contact with cercariae which migrate to the skin through chemical and temperature gradients which they then penetrate, the only known route of human infection.[10] Upon contact the Cercariae continue to develop and in doing so lose their tails to become schistosumula. Schistosumula invade through

the epidermis by means of variable serine protease secretion aiding the breakdown of epidermal collagen and elastin. This explains the variation in dermal invasion rates with *S. mansoni* and *S. haemtobium* taking approximately 3 days to achieve dermal blood vessel invasion while S. japonicum can achieve this in as little as 8 hours.[11] After reaching the circulation they travel through the lungs and heart to the liver where the schistosumula mature into male and female adult worms which interact with one another through the gynaecophoral canal and migrate to species specific preferred organs. *S. haemtobium* adult worms for instance preferentially infects the bladder venules while *S. japonicum* and *S.mansoni* prefer the mesenteric vessels of the small and small/large bowel respectively.[4,11] Upon reaching their destination the female worms produce eggs ~5 weeks after infection which can be in excess of 2000 eggs/day in the case of *S. japonicum* which can result in Katayama fever. These eggs assisted by their sharp spines bury themselves through the blood vessel wall to reach the bowel/bladder lumen for expulsion into the feaces and urine thereby completing the life cycle. It is clear however that a large proportion of eggs are unable to fully invade through the blood vessel walls upon failing to do so these result in an inflammatory response which leads to granulomatous disease and chronic inflammation linked to both fibrosis and oncogenesis. Importantly eggs may be deposited to ectopic sites with the liver predominant however the lung and central nervous system (CNS) may also occur.[9,11]

For successful infection of the intermediate and definitive hosts Schistosomal species must bypass the immune system in order to complete their life cycle. In *Bulinus Glabrata* the snail host of *S. mansoni*, sporocysts can utilise the ability of molecular mimicry whereby they can exhibit similar surface glycans and glycosylation patterns as the host snail as a means of camouflage while their surface polymorphic mucins further enable their failed recognition by the snail innate and adaptive immune system enabling them to persist. Other mechanisms in the mollusc host include the release of schistosome excretion products which reduce key phosphorylation pathways important in haemocyte development.[12] In humans during dermal invasion, schistosomula interact with cells of the innate and adaptive immune system in several ways. Firstly as they become coated with immunoglobulins and complement proteins they can cleave these through protease production while utilising host antigens (e.g. blood group antigens) to effectively camouflage from the immune system. Moreover, schistosomula produce high levels of Sm16 an immunomodulatory protein, which decreases proinflammatory cytokine expression in keratinocytes, reduce neutrophil chemotaxis and attenuates Toll-like receptor signalling. In the setting of chronic infection, an immunosuppressive environment through IL-10 secretion and predominantly regulatory T-cell responses is produced.[13,14]

Control strategies

As for a multitude of conditions, the mantra prevention is better than cure holds true. Of management strategies mass chemoprophylaxis is often employed to reduce overall prevalence and transmission particularly in children who are both more commonly and severely affected from schistosomal infection. Currently, a 10% infection rate among schoolchildren (5-14 year old) is used as a threshold for their mass treatment alongside high-risk adults (e.g fishermen). However, incomplete uptake and access of chemoprophylaxis is an issue as in 2010 only 19% of schoolchildren requiring chemoprophylaxis received it. Chemoprophylaxis however does not provide long-term immunity or protection from reinfection with the costs of this approach considerable. Moreover, there is evidence of diminishing efficacy of Praziquantel when it is used iteratively as chemoprophylaxis in a given population.[15,16] This therefore highlights that while chemoprophylaxis is an important facet of schistosomiasis control the contributions of the local environment, sanitation and health behaviours in endemic areas cannot be ignored.

Biological control strategies are direct when natural predators of the organism or host are introduced to reduce transmission without causing environmental damage or indirect when the habitat and fauna of the organism or host are modified to negatively impact on its survival. Both direct/indirect biological control does however have challenges in so far as identifying suitable species or environmental changes without unintended consequences to the local ecosystem.[17] As all schistosomal infections require snail species as an intermediate host they are often the target of such control strategies. Traditional molluscicides are among the most prevalent and historic methods to control schistosomiasis infections and prevent onward transmission. These have been trialled in many countries with success however they have also been linked with significant off target toxicities to surrounding species. Currently, Nicolosamide is the only molluscicide currently recommended by the WHO with concerns of emerging resistance reported. As such, discovery of new agents is required with botanical molluscicides, with plant families *Phytolaccaceae* and *Euphorbiceae* among the most promising candidates. These have the benefits of being low cost, easily cultivated, efficacious and very specific to schistosomal snail species.[18]

River prawns are a natural predator of uninfected and infected freshwater snails and are therefore larvicidal. In one study utilising this approach in Senegal where the Diama dam had drastically increased schistosomiasis infection while decimating river prawn populations, their reintroduction led to an 80% decline in infected snails and ~18% decreased schistosomiasis prevalence in an 18 month period. This not only represents a viable solution and food source for the local people but also highlights how human behaviour can modify risk in endemic areas with schistosomiasis epidemics often reported after dam projects, which in part is linked to reduced migration of local prawn populations.[19,20]

Sanitation is often poor in resource limited settings is an important means to avoid infected faeces from humans and other known reservoirs of infections being introduced to freshwater snails. Therefore, for any meaningful impact, population based measures targeting both sanitation and hygiene are needed.[10] For instance ensuring separate human and animal water and waste disposal as well as water treatments can aid in schistosomal control as well as other important pathogens, which are common in developing countries. Such treatments include water filtration using sand filters with 0.18-0.35mm grain size which can remove cercariae and the chlorination of water. At concentrations of >1.5mg/L chlorine has been found to render water cercariae free within minutes however this is affected by water temperature and pH. The use of this approach is of benefit in particular in feeding animals can help reduce animal reservoirs of schistosomiasis while through altered human behaviours e.g. protective clothing in water, can help reduce reinfection rates.[10] In a computational modelling experiment of schistosomiasis in a Kenyan village it was shown that combination mass chemoprophylaxis and snail population control was both the most cost-effective and efficacious method of Schistosoma control with DALYs reduced by up to 40%.[21] Possible future control methods include genetic manipulation of snail hosts or schistosoma eggs mirroring such approaches as used in malaria, however this is complicated by the fact *Bulinus* snails are hermaphrodites and thus able to self-fertilize potentially limiting its efficacy.[22] Other ideas include the development of a Schistosomal vaccine with multiple human trials underway, this would need to result in a minimal 75%

reduction in worm burden in infected patients to be effective and be able circumvent the immune evasive mechanisms currently employed by schistosomal species.[23] Integrating therefore schistosomal control programmes with other NTD programmes could thus be a meaningful way to address this alongside renewed community engagement.

Conclusion

Schistosomiasis is an important NTD, which leads to high levels of morbidity and disability in the affected individuals. Due to its intricate life cycle involving reservoirs and intermediary and definitive hosts it is difficult to control unless simultaneous approaches are taken to modify the environment and behaviours which contribute to this risk but are perpetuated by the resource poor setting schistosomal infection occurs in. While effective traditional molluscides are hampered by their off target effects however new phytochemical molluscides as well as biologic control measures may circumvent this through restoring natural food chains which may have been altered by human behaviour.

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Conflicts of interest

I have no conflicts of interest

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