Schistosomiasis

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Abstract Schistosomiasis, a neglected tropical disease, is caused by the blood fluke that resides in the blood vessels in the human hosts. It presents as an acute, but mostly chronic, illness and is commonly found in the least developed countries with poor healthcare systems. Forty countries in Africa were endemic for schistosomiasis in sub-Saharan Africa (SSA) in 2010. Of the five species, *Schistosoma haematobium*, *S. mansoni*, *S. japonicum*, *S. intercalatum* and *S. mekongi*, that can infect humans, it is *S. haematobium* which causes urogenital schistosomiasis and *S. mansoni* and *S. japonicum* which cause intestinal schistosomiasis, which have public health importance, being responsible for most of the disease in SSA. Children, women and farmers in rural communities who depend on water contact for recreational, domestic or occupational activities are most vulnerable to the infection. Cross-border movements from unstable and conflict zones in SSA have contributed to the spread of the disease to previously non-endemic foci, and emigration from rural areas into the cities for economic opportunities has introduced the disease into some urban areas. Schistosomiasis causes around 4.5 million DALYs annually, with around 90 % of the burden of disease concentrated in SSA. Annual loss from disability due to schistosomiasis in Africa was estimated to be nearly half a billion US dollars approximately 70 % of the global cost. The life cycle involves an intermediate planorbid freshwater snail hosts – *Bulinus truncatus and Biomphalaria pfeifferi* – in the transmission of the infection with sexual and asexual stages. Man is the definitive host. Pathology and clinical morbidity of schistosomiasis are caused by eggs trapped in tissues and symptoms and signs of the disease present among other things, as haematuria in urinary schistosomiasis and abdominal pain, diarrhoea which can be bloody and blood in stool in intestinal schistosomiasis. Long-term complications from schistosomiasis include urinary tract infections, bladder calcification, hydronephrosis/hydroureter, kidney failure, lesions of the liver, portal vein, and spleen, leading to periportal fibrosis, hepatomegaly, splenomegaly, pipe-stem portal fibrosis, ascites, nodules in the vulva and bladder cancer. Microscopic examination for parasite eggs in the urine or stool is considered definitive for the diagnosis of the infection. Control of schistosomiasis is by transmission and morbidity control using health education, safe water supply, molluscicding, environmental management, chemotherapy praziquantel (PZQ) as drug of choice or combination of these measures. Whether or not schistosomiasis can only be controlled or can be eliminated using the current MDA with anthelminthes is an ongoing debate.

Keywords Urinary/urogenital • *S. mansoni*/intestinal schistosomiasis • *S. haematobium*/urinary/urogenital schistosomiasis drug/medicine/treatment

Epidemiology of the Disease

Geographic Distribution

Schistosomiasis is mostly a tropical disease caused by the blood fluke, a group of flat worms that reside in the blood vessels in the human hosts. It presents as an acute, but mostly chronic illness. Due to its geographic and demographic distribution, the disease is listed as one of the neglected tropical diseases (NTDs). It is commonly found in countries among the least developed whose health systems face difficulties to provide basic care at the primary health level (Chitsulo et al. 2000). Five species, namely, *Schistosoma haematobium*, *S. mansoni*, *S. japonicum*, *S. intercalatum* and *S. mekongi*, can infect humans, but the three with public health importance are *S. haematobium* (mostly endemic in Africa and the Middle East), *S. mansoni* (common in the tropics and subtropics) and *S. japonicum* (mainly found in the People's Republic of China and the Philippines) (WHO 2012). *S. haematobium* causes urogenital schistosomiasis, while *S. mansoni* and *S. japonicum* cause intestinal schistosomiasis. According to WHO AFRO Regional Report, 40 countries were endemic for schistosomiasis in sub-Saharan Africa (SSA) in 2010 with the most severely affected countries being Angola, Central African Republic, Chad, Ghana, Madagascar, Malawi, Mali, Mozambique, Nigeria, Senegal, Uganda, The United Republic of Tanzania, Zambia and Zimbabwe (Fig. 1).

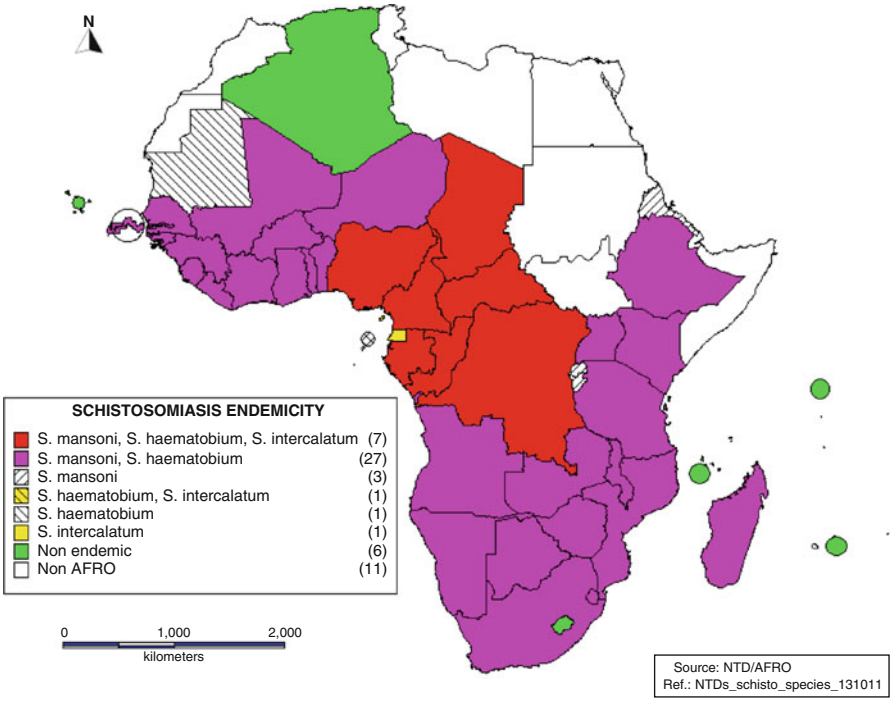


Fig. 1 Schistosomiasis endemic countries in Africa (Source: WHO AFRO)

Demographic Distribution

A major feature of the infection is that it shows a characteristic aggregated distribution and overdispersion of worms. In a typical endemic setting, it has been estimated that 20 % of the population usually carry approximately 80 % of the total infection; the remaining 80 % of the population harbour few worms that constitute only about 20 % of the overall population of worm load (Anderson and May 1992; Woolhouse et al. 1991). The infection also displays age-intensity profile that is typically convex, with prevalence and intensity of infection rising in childhood, peaking in adolescence and decreasing in adulthood to a relatively stable phase (King et al. 1988; Mitchell et al. 2008). Children, women and farmers in disadvantaged rural communities without access to adequate sanitation or clean water and who depend on water contact for recreational, domestic or occupational activities are most vulnerable to the infection. Poverty is a major determinant of schistosomiasis but attempts to improve the livelihood of poor farmers through the creation of water-related economic schemes have in turn led to the promotion of transmission of the infection (Chitsulo et al. 2000; Poda et al. 2004; Steinmann et al. 2006).

Urogenital schistosomiasis and intestinal schistosomiasis are responsible for most of the disease in SSA. In some countries, there is an overlap in distribution, resulting in mixed infection in majority of the infected persons. *S. intercalatum* which causes another form of intestinal schistosomiasis is endemic in six countries in Central and West Africa, namely, Democratic Republic of Congo, Gabon, Cameroon, Central African Republic, Chad and Sao Tome. It has recently been reported in travellers returning from Mali, West Africa, but this is yet to be officially confirmed. This chapter focuses on the two common schistosome types in SSA, namely, *S. haematobium* and *S. mansoni*, with reference to the other species where necessary.

Impact of Conflict, Migration and Tourism on Spread of the Disease

Cross-border movements from unstable and conflict zones in SSA have contributed to the spread of the disease to previously non-endemic foci (Chitsulo et al. 2000). As the economy of most of these countries is concentrated in the urban centres and cities, there has been a trend of emigration from rural areas into the cities for economic opportunities. The rural-to-urban migration has introduced the disease into some urban areas. In non-endemic countries in Europe, such as Denmark, England, Germany, Netherlands, Spain and Switzerland, the prevalence of imported schistosomiasis is rising, partly because of an increase in travelling to endemic areas and partly to emigration from these areas. The rise in the number of imported cases of schistosomiasis is creating a new diagnostic and management challenge to the health systems of these countries (Grobusch et al. 2003; Bierman et al. 2005;

Helleberg and Thybo 2010). Travellers embarking on ecotourism and diving tours in endemic destinations in Africa are the most at risk (Schwartz et al. 2005; Kinkel et al. 2012). However, records show that in 2005, two thirds of all imported cases of schistosomiasis to Europe were mostly immigrants and refugees who had fled conflicts and wars in some parts of SSA (Hatz 2005).

Life Cycle and Mode of Transmission

Schistosomiasis has a complex life cycle that involves an intermediate snail host and sexual and asexual stages (Fig. 2). Man is the definitive host and some species of the planorbid freshwater snails are the intermediate hosts in the transmission of the infection: *Bulinus truncatus* for *S. haematobium* and *Biomphalaria pfeifferi* for *S. mansoni*. The asexual reproduction occurs in the snail, whereas the sexual reproduction takes place in the human host (Hoffmann and Dunne 2003). The worms do not multiply in the human host. People infected with *S. haematobium* worms excrete the parasite eggs in their urine and *S. mansoni* eggs in faeces. Under optimal conditions, the eggs hatch to release miracidia (larvae) which swim to locate and penetrate a specific freshwater snail, the intermediate host. Within the snail, the miracidia undergo a two-staged developmental process to produce the infective larvae called

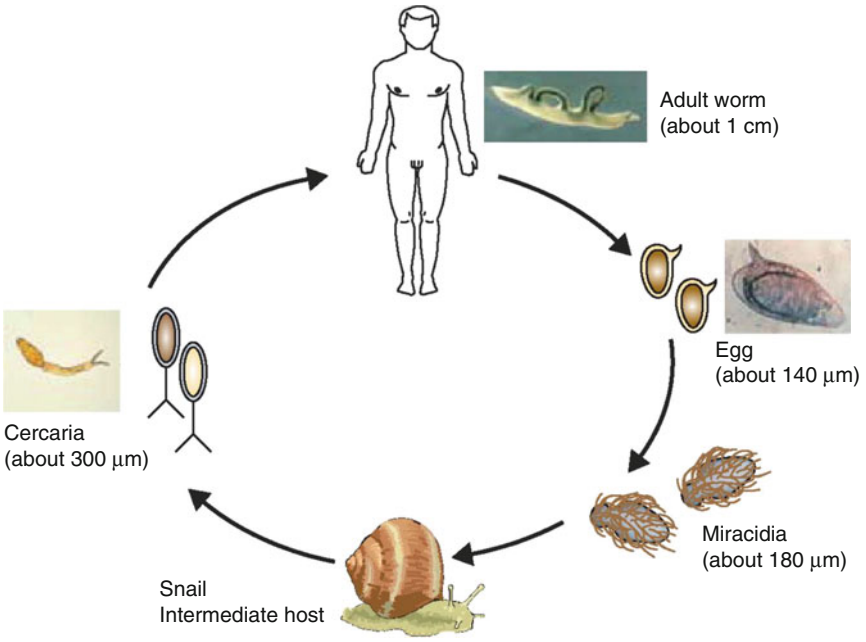


Fig. 2 Life cycle of schistosome worm and mode of transmission of schistosomiasis (Courtesy: Hoffmann and Dunne *Genome Biology* 2003)

cercariae within 4–6 weeks. Cercariae are phototropic and their release from the snail is triggered by sunlight, mostly around midday, in the tropics which tends to coincide with the peak hours of water contact activities by children and women. It has been reported that a snail infected by one miracidium can release thousands of cercariae every day for months (Gryseels et al. 2006). Upon release into the water, the cercariae can swim for up to 72 h when they must locate and penetrate the skin of the human host. Their infectivity potential slows and plateaus around nine hours post-release (Whitfield et al. 2003). The infection is acquired when the infective cercariae penetrate a person's skin upon contact with contaminated water bodies. Upon entering the skin of the human host, the cercariae shed their tail and become schistosomulae which remain in the skin for up to 2 days before locating a post-capillary venule, migrate through the venous system, the right chamber of the heart, the lungs, the mesenteric arteries and the liver via the portal vein.

Eight to 10 days post-penetration of the host's skin, the worm migrates to the liver sinusoids, develops an oral sucker and begins to feed on red blood cells. Schistosomes undergo developmental processes throughout their migratory phases until finally locating and residing in the venous plexus of the urinary bladder (*S. haematobium* worms) or superior mesenteric veins draining the large intestine (*S. mansoni* worms). A schistosome worm reaches maturity in 6–8 weeks when a male and a female worm pair up in a groove formed by the male called the gynaecophoric channel. Here, the male worm holds the longer and slender female where mating takes place and the female worms begin to produce a large number of eggs ($\approx$ 300 eggs per day) (Davis 2009). An adult worm usually lives for 3–5 years, but some can live up to 30 years (Warren 1982) and produce up to 600 billion schistosomes during their lifetime (Gryseels et al. 2006). Schistosome eggs can survive for up to 7 days.

Pathology and Disease Presentation

Pathology and clinical morbidity of schistosomiasis are caused by eggs trapped in tissues but not the worms themselves, and symptoms and signs of the disease are location specific. Within the human body, eggs produced by the worms are moved progressively across the walls of blood vessels towards the lumen of the bladder and ureters for excretion with the urine (*S. haematobium*) or the intestine to be excreted with the faeces (*S. mansoni*). In the process, a substantial number, up to half, of the eggs released by the worm become trapped in tissues and initiate immune-induced inflammatory reactions that lead to pathology and morbidity (Richter 2003; King and Dangerfield-Cha 2008). Although most individuals with few schistosome worms, especially adults, remain asymptomatic, about 80 % of infected children present with one or more symptoms of the disease in the early stages of the infection (Mott et al. 1983; Gryseels and Polderman 1987; Olds and Dasarathy 2000). The main signs and symptoms related to schistosomiasis are summarised in Table 1.

Table 1 Schistosomiasis-related pathology and clinical presentation

Stage of symptom	*S. haematobium*	*S. mansoni*	Both (non-specific)
Katayama syndrome[a]	Itchy skin	Itchy skin	Fever
	Nephropathy	Abdominal pain	Fatigue
		Diarrhoea (with or without blood)	Muscle ache
		Nephropathy	Non-productive cough
			Lymphadenopathy
			Eosinophilia
Early[b]	Haematuria	Diarrhoea	Anaemia
	Dysuria	Blood in stool/bloody diarrhoea	Fatigue
		Abdominal pain	
		Gastrointestinal bleeding	
		Hepatomegaly	
		Splenomegaly	
Late stage[c]	Bladder wall thickening	Colonic polyps	Anaemia
	Bladder wall calcification	Cirrhosis of the liver	Fatigue
	Bladder stones	Pipe-stem portal fibrosis	Nutritional deficiencies
	Secondary bacterial infection	Portal hypertension	Poor growth
	Higher risk for ectopic pregnancies	Varicose veins	Memory loss
	Infertility	Haematemesis	Slower reaction time
	Bladder abnormal pyelon dilation	Haemorrhage from rupturing varicose veins	Lower scores in cognitive ability
	Distal ureter hydronephrosis	Haemorrhagic shock	Low birth weight
	Pyelonephritis	Gallbladder cancer	
	Anuria	Liver cancer	
	Hydroureter		
	Kidney failure		
	Squamous cell carcinoma		

Source: Adapted from Danso-Appiah (2009)
Haematuria (blood in urine), dysuria (painful urination), hepatomegaly (enlargement of the liver), splenomegaly (enlargement of the spleen), anuria (no urine excretion)
[a]Occurs a few days or weeks after exposure to the infection
[b]May occur a few weeks or months after the infection
[c]Insidious and may take a long time depending on the intensity of infection

Katayama Syndrome

The acquisition of cercariae may be followed by an initial rash or itchy skin at the site of penetration. This may be followed by an acute illness called Katayama's syndrome within 4–8 weeks following exposure to the infection that may result in a systemic hypersensitivity reaction characterised by fever, fatigue, muscle aches, abdominal pain, diarrhoea, non-productive cough, lymphadenopathy and eosinophilia. There may also be pain in the upper right part of the abdomen just below the rib cage. Katayama syndrome is most common with *S. mansoni* and *S. japonicum* infections. It mainly occurs following primary infection in individuals with low or no protective immunity, such as tourists visiting an endemic area for the first time. Katayama syndrome is thought to be triggered by maturation and migration of schistosomula within the host (Zuidema 1981; Istre et al. 1984). The patient recovers spontaneously after 2–10 weeks, but some develop persistent and more serious disease. If symptoms do not abort, it can lead to other complications such as weight loss, dyspnoea, diarrhoea, diffuse abdominal pain, widespread rash, hepatosplenomegaly and toxaemia.

Early Symptoms of an Established Disease

The main early symptom of established infection with *S. haematobium* is blood in the urine (haematuria) or terminal blood after urination, appearing 10–12 weeks after the infection. This may be accompanied by painful urination (dysuria). There is evidence that parasite-induced pathological changes of the bladder and abnormal pyelon dilation of at least one of the kidneys are common in children in the early stages of the infection (Brouwer et al. 2003). This suggests that development of pathology begins far earlier in children than previously thought. For intestinal schistosomiasis due to *S. mansoni*, the early symptoms are non-specific but usually include abdominal pain, diarrhoea (which can be bloody) and blood in stool (Gryseels et al. 1992; Lengeler et al. 2002). These symptoms are caused by cellular granulomatous inflammatory reactions around eggs trapped in the intestinal tissues. In spite of the fact that a large number of eggs are deposited in the small intestine, most severe infection-related lesions such as colonic polyps occur in the large intestine (Cheever et al. 1978). It is commonly accepted that intensity and duration of infection determine severity of the disease, but some recent studies have challenged this assumption and suggested that the mere presence of the infection and not necessarily intensity determines morbidity (King and Dangerfield-Cha 2008), although further evidence is warranted to confirm or refute this. Inflammatory reactions in the liver lead to hepatosplenic schistosomiasis, which can manifest as hepatomegaly and splenomegaly within a couple of months from heavy infections or many years

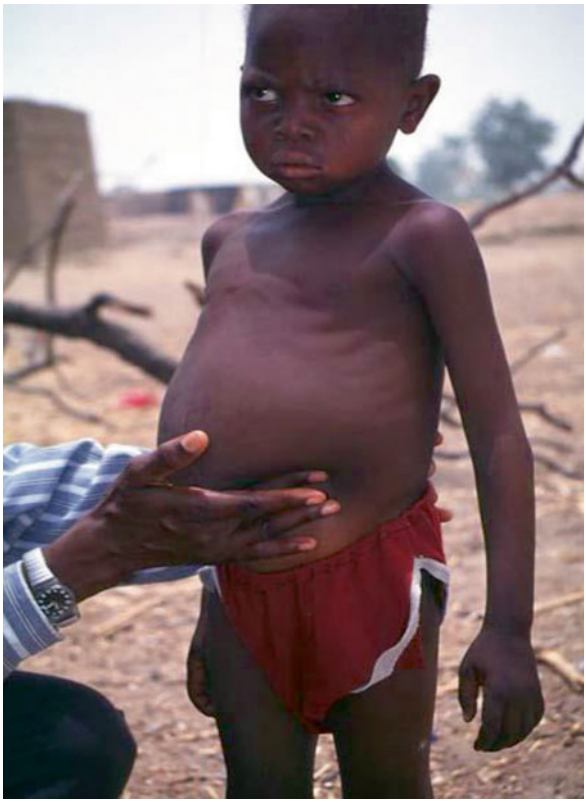


Fig. 3 Hepatosplenomegaly in schistosomiasis patient

after light infections (Fig. 3). It should be noted that chronic schistosomiasis affects mainly individuals with long-standing or repeated infections.

Late-Stage Symptoms and Complications

Long-term complications caused by schistosomiasis are mostly insidious. For *S. haematobium* infection, granulomatous changes and ulcers of the bladder wall and ureter can lead to bladder obstruction, dilatation, secondary urinary tract infections and subsequent bladder calcification. Photomicrography of the bladder in *S. haematobium* infection may show clusters of the parasite eggs with intense eosinophilia (Fig. 4). Diffused or localised wall thickening of the bladder and distal ureter hydronephrosis or hydroureter may eventually lead to kidney failure (Kardorff and Doehring 2001; WHO 2002a). In females, genital lesions resulting from the infection may present with vaginal bleeding, pain during sexual intercourse and nodules

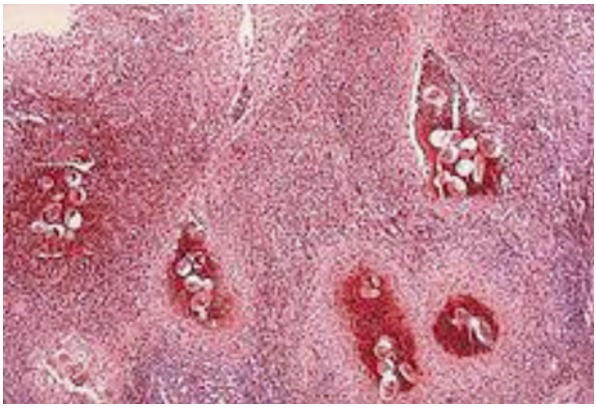


Fig. 4 Photomicrography of the bladder in *S. haematobium* infection, showing clusters of the parasite eggs with intense eosinophilia (Source: Centre for Disease Control (CDC))

in the vulva. In men, urogenital schistosomiasis can induce pathology of the seminal vesicles, prostate and other organs that may decrease male vitality and fertility. Urogenital schistosomiasis is also associated with increased risk of bladder cancer. A review on this topic showed that bladder carcinoma is ranked seventh on the list of most common cancers worldwide in men with the highest incidence occurring among men in Egypt (Murta-Nascimento et al. 2007), which may be related to *S. haematobium* infection (Jordan 2000).

Structural changes or damage resulting from complications of the infection may allow intravascular shift of worms between locations. The superior mesenteric veins have numerous anastomoses with the veins draining the internal genital organs and the vulval area towards the inferior vena cava. The structural damage to valves allows unrestricted migration of worms to the genital organs where they deposit eggs to initiate genital organ pathology (Poggensee and Feldmeier 2001). There are also communications between the spermatic ducts with the superior and inferior mesenteric veins allowing eggs to move into the semen (Arean 1956). In females, the linkage between the ovarian and uterine plexus through anastomoses allows free movement of eggs to the cervix and the vagina thereby affecting the female reproductive organs (Arean 1956; Camara 1959). In recent studies, evidence has emerged that urogenital schistosomiasis is a potential risk factor for HIV infection, especially in women with schistosomiasis-related lesions (WHO 2010a; Mbabazi et al. 2011). There is also an increased risk of hepatocellular carcinoma and mortality from co-infection of schistosomiasis and hepatitis and HIV or malaria.

The late-stage complications commonly associated with *S. mansoni* infection include lesions of the liver, portal vein and spleen, leading to periportal fibrosis, hepatomegaly, splenomegaly, pipe-stem portal fibrosis and ascites (Hatz 2001; Richter 2003). The fibrotic lesions in turn lead to liver cirrhosis that progressively occludes the portal system giving rise to Symmers' pipe-stem periportal fibrosis and portal hypertension. The portal hypertension eventually causes enlargement of the hepatic arteries that leads to varicose veins (oesophageal varices). These may rupture and cause heavy blood loss, haemorrhagic shock and finally death. The patient

may also suffer repeated episodes of variceal bleeding, the primary cause of death in hepatic schistosomiasis (Anderson and Chung 2007).

Public Health Impact of the Disease

Risk of Infection, Morbidity and Mortality Estimates

Schistosomiasis is mostly recurrent and a person may be reinfected repeatedly even when regular treatment is provided, creating long-lasting public health, social and economic burden in endemic populations (WHO 2002b; King and Dangerfield-Cha 2008). Although most individuals with schistosomiasis show few or no early symptoms, significant morbidity can develop if untreated. Current statistics suggest that the burden due to schistosomiasis may even be comparable to that of malaria (Hotez et al. 2009). Globally, it is estimated that around 800 million people are at risk of acquiring the infection and 207 million people are already infected (Hotez et al. 2006; Steinmann et al. 2006). Of those with infection, 120 million are estimated to manifest symptoms and signs of the disease while 20 million experience long-term infection-related complications (WHO 2002a). The statistics are staggering as it shows that around 580 million (~72 %) of the global total estimate of people are at risk of acquiring the infection live in SSA; over 130 million are school-age children.

From mathematical modelling, it was predicted that the two schistosome worms commonly found in SSA may contribute to the deaths of more than a quarter of a million people annually from disease-specific or infection-related complications (van der Werf et al. 2003). However, given that it is uncommon for schistosomiasis to directly result in the death of the infected person, mortality estimates provide only little insight about the public health impact of the disease. Measures such as disability-adjusted life years (DALYs) are considered to provide a better picture of the burden of disease due to schistosomiasis.

Disability-Adjusted Life Years (DALYs)

Using the DALYs approach, it has been estimated that schistosomiasis causes around 4.5 million DALYs annually, with around 90 % of the burden of disease concentrated in SSA (Hotez et al. 2006; Steinmann et al. 2006). Other analyses have challenged this value arguing that the burden of the disease has been significantly underestimated (King et al. 2005; Engels and Savioli 2006; WHO 2012), given the difficulty in establishing and quantifying cause-specific deaths due to schistosomiasis. For example, exposure to the infection usually takes place in childhood but severe-chronic disease occurs later in adulthood making it difficult to

establish the link between infection and long-term complications. Another reason for the underestimation of the burden of the disease is a limitation inherent in the DALYs approach itself, as the DALYs systematically undervalue chronic diseases, including schistosomiasis (King and Bertino 2008; Utzinger et al. 2009). Researchers and public health practitioners disagree on the current morbidity and mortality assessment methods used for the estimation of burden attributable to schistosomiasis.

Subtle Morbidity and Other Schistosomiasis-Related Complications

Heavy infection in schoolchildren may be associated with short-term memory loss, slower reaction time, lower scores in some tests of cognitive ability and poor growth (WHO 2002b). Iron deficiency anaemia and other nutritional deficiencies have been linked with heavy infection (Awasthi et al. 2003). The social and economic implications of schistosomiasis are thought to be even greater (Wright 1972; WHO 2012). In Brazil, Egypt, Sudan and Tanzania, researchers found substantial reduction in labour productivity of working adults and high school absenteeism of children suffering from schistosomiasis. For example, a substantial drop in labour output by as much as 35 % of adults infected with schistosomiasis has been reported in Egypt (Salehe and Hassan 2012). Similar results have been reported from studies investigating adults working in sugar plantations in Tanzania and Sudan that showed a decrease in work output by up to 15 % in workers infected with schistosomiasis (Salehe and Hassan 2012). Further studies from Tanzania showed that apart from spending more time in seeking treatment and hence having fewer working hours per month, irrigation rice farmers suffering from schistosomiasis also spent much more money from their harvest on seeking health care (Salehe and Hassan 2012). A group of researchers from Nigeria found similar findings with reduced worker productivity, cash income, rates of land clearing and farm size of those with the disease (Umeh et al. 2004). Generally, individuals suffering from schistosomiasis in rural areas show severely impaired work capacity and performance due to lethargy (WHO 2002b).

For schistosomiasis-related complications, evidence is also emerging from recent research that urogenital schistosomiasis may pose a significant risk for HIV infection, especially in women with schistosomiasis-related lesions (WHO 2010a, b; Mbabazi et al. 2011). Co-infection of schistosomiasis and hepatitis and HIV or malaria can increase the risk of hepatocellular carcinoma and risk of mortality. Genital lesions resulting from the infection may present with vaginal bleeding, pain during sexual intercourse and nodules in the vulva. In men, urogenital schistosomiasis can induce pathology of the seminal vesicles, prostate and other organs that may decrease male vitality and fertility.

Economic Implications of Schistosomiasis

In the early 1970s, some staggering results from analyses of the economic impact of schistosomiasis in terms of disability and loss of work capacity were published in the Bulletin of the WHO (Wright 1972). The main objective of the analysis was to quantify resource loss attributable to reduced productivity. The analysis estimated the total global annual loss to be greater than 600 million US dollars (US $641, 790, 130) excluding the cost of public health programmes, medical care or compensation for illness (Wright 1972). Annual loss from complete and partial disability due to schistosomiasis in Africa alone was estimated to be nearly half a billion US dollars (US $445, 866, 945), constituting approximately 70 % of the global cost. This value excluded Mauritius with an estimated cost of US $755, 480. Southeast Asia accounted for US $16, 527, 275, Southwest Asia US $118, 143, 675 and the Americas US $60, 496, 755. These costs estimates were based on an estimated 124, 905, 800 prevalence of the infection in those days. The authors acknowledged that the data were based on prevalence estimates obtained from less sensitive diagnosis of a single stool (for intestinal schistosomiasis) or single urine (for urogenital schistosomiasis) examinations which could lead to serious underestimation of the actual number of cases. With current estimates well over 200 million people having the infection, far higher than estimates used in this calculation (around 124 million), it is expected that the cost will be far higher.

Diagnosis of the Infection and Disease

Parasitological Diagnosis

Microscopic examination for parasite eggs in the urine (for urogenital schistosomiasis) or stool (for intestinal schistosomiasis) is considered definitive for the diagnosis of the infection. For urinary schistosomiasis, the diagnostic technique involves a Nucleopore membrane of a standard 10 ml volume of urine. This method can quantify egg count and very useful in epidemiological investigations. For *S. mansoni* infection, the use of the Kato-Katz technique (Katz et al. 1972) to examine a single or multiple stool specimens remains the gold standard. The Kato-Katz technique is both specific and sensitive and able to quantify eggs into different intensity levels. It also has low operational cost and can be used in settings with minimal infrastructure (Rabello 1992). However, sensitivity of parasitological diagnosis by microscopy decreases considerably when egg excretion is low, particularly in low endemicity areas or after chemotherapy.

Rectal biopsy for all schistosome species and biopsy of the bladder for *S. haematobium* are more sensitive and occasionally done when repeated stool or urine

examinations are negative for schistosome eggs (Rabello 1992). Rectal biopsies are particularly useful when conducting clinical trials into new treatments when it is necessary to observe egg morphology in tissues. The disadvantage is that biopsies are invasive and cumbersome to perform and not recommended for mass field application (Allan 2001).

Immunological Diagnosis

Monoclonal antibody-based technique to detect schistosome specific by-products is gaining prominence in the diagnosis of the infection (Bosompem et al. 1996, 2004; Polman et al. 2001, 2002). Reagent strips are applied for the detection of schistosomiasis-related blood and proteins released in the urine, but this technique is unable to quantify the infection. Recent studies on monoclonal antibody-based dipsticks have shown promising results (Legesse and Erko 2007, 2008; Caulibaly et al. 2011). Polymerase chain reaction (PCR) is increasingly being used in some reference laboratories in Europe, and it is hoped that this can be assessed for evidence of test accuracy and cost-effectiveness for application in endemic settings (Sandoval et al. 2006; Cnops et al. 2012; Enk et al. 2012). More recently, the FLOTAC has evolved as a novel technique for the detection and quantification of *S. mansoni* eggs in stools (Glinz et al. 2010; Cringoli et al. 2013).

Clinical Diagnosis

Clinically, schistosomiasis is diagnosed on the basis of blood in the urine of the patient (for *S. haematobium* infection) and blood in stool, diarrhoea and abdominal pain (for *S. mansoni* infection). Diagnosis based on presence of blood in urine is reliable in children but less so in adults where blood in the urine may be caused by other diseases than urogenital schistosomiasis, for example, sexually transmitted diseases. For intestinal schistosomiasis, diarrhoea, abdominal pain and splenohepatomegaly are non-specific and could be due to other causes such as malaria. Also, blood in stool can be caused by dysentery but not necessarily schistosomiasis.

Mass Screening

For mass or field control, questionnaires have been suggested as operationally cost-effective for rapid screening of the infection in high-endemic communities. Questionnaire-based assessment relies on self-reporting of symptoms; it is not reliable as recall bias can be high. For urogenital schistosomiasis, blood in urine and painful urination show moderate-to-high sensitivity, depending on age and

prevalence of the infection (Bogoch et al. 2012). In high-prevalence areas, sensitivity and specificity tend to be high, whereas in areas with low prevalence of the infection, sensitivity and specificity of this method are low. For intestinal schistosomiasis, the main signs and symptoms (blood in stool, diarrhoea and abdominal pain) are neither sensitive nor specific (Danso-Appiah et al. 2004, 2010), and questionnaire-based diagnosis is less encouraging (Raso et al. 2005). Another major challenge is that questionnaire application is influenced by age and gender of the infected person.

Control Strategies and Challenges of Implementation

The goal of schistosomiasis control, like any infectious disease, is to prevent new infections or transmission of the infection, usually by interrupting the parasites' life cycle. As this has been difficult to achieve, control guidelines have changed several times over the years. Historically, schistosomiasis control measures implemented across SSA have centred around two main strategies, namely, (i) transmission control and (ii) morbidity control, using one or more of the following measures: health education, safe water supply, molluscicding, environmental management, chemotherapy or combination of measures.

Transmission Control

Molluscicding

The application of molluscicide formed the primary control option prior to the introduction of safe and effective antischistosomal drugs in the 1970s (WHO 1985; Sturrock 2001). The objective was to interrupt transmission of the infection by targeting the intermediate snail host. Mass application of molluscicide has been conducted in various settings in SSA, particularly where outbreaks of schistosomiasis have occurred as a result of the creation of dams (Shiff et al. 1973; Chu 1978). In Ghana, for example, control measures adopted following the outbreaks of schistosomiasis after the construction of the Akosombo Dam focused primarily on chemical (molluscide) control targeting the intermediate host snails. Generally, large-scale molluscicide control proved to be very expensive and impractical in the long term and also raised a number of operational and health concerns (Chu 1978; Sturrock 2001).

Environmental Management

Environmental management attempts to reduce the snail population and thereby transmission of the infection. It has generally not been used as one of the approaches undertaken in SSA due to the high cost and paucity of information about the exact

areas where this can be implemented. Positive experiences with this have been mainly documented in Morocco and Egypt, outside SSA. There is the need for identification of areas where environmental management for snail control can be intensified in the SSA to improve effort towards control of the infection.

Health Education

Health education focuses on promoting good hygiene and sanitation, especially among school-age children and caregivers, discouraging practices such as bathing in streams and indiscriminate disposal of refuse that underpin spread of the infection. The main objective of this strategy is to decrease the number of eggs reaching and contaminating bodies thereby force of transmission and acquisition of the infection in endemic communities. The impact of most health education programmes appears to be encouraging in the short term (Asaolu and Ofoezie 2003; Mascie-Taylor et al. 2003; Guo et al. 2005; Minamoto et al. 2012), but are unsustainable in the long run (Minamoto et al. 2012). A systematic review that pooled data to evaluate the effect of health education showed that health education helps to sustain the benefits of other control measures such as chemotherapy (Asaolu and Ofoezie 2003). The review also found that health education is effective, easy and cheap to deliver and will remain the only tool for creating enabling environment for both chemotherapy and sanitation to succeed.

Safe Water Supply

The goal of safe water supply is to reduce frequency of water contact by poor rural inhabitants. However, in some settings in SSA, water contact may not be avoidable as this is the only means rural inhabitants can conduct their domestic activities such as washing clothing or fetching water for drinking, as well as children swimming in streams infested with the intermediate host snails responsible for transmission of the infection. A study examining the impact of improved water supply and sanitation facilities on schistosomiasis and other NTDs by analysing 144 independent studies and calculating disease-specific median reduction levels of the infection found marked reductions in diarrhoea (26 %), trachoma (27 %) and ascariasis (29 %) (Esrey et al. 1991). The median reduction of new infection with schistosomiasis was 77 % and dracunculiasis 78 %, with overall child mortality decreasing by 55 % (Esrey et al. 1991). The authors concluded that properly maintained water supply alone was highly effective for controlling NTDs. Investigating the value of individual household water supplies in curtailing the transmission of schistosomiasis in Saint Lucia, households in five villages were provided with their own water supply, as well as community laundry shower units between 1970 and 1975 (Jordan et al. 1982). Evaluation of the impact of water supply showed a marked reduction in the incidence of *S. mansoni* infections. Chemotherapy was introduced thereafter for 3 years (1975–1977) with oxamniquine to all the infected persons. The results

showed a further reduction in the transmission of the infection to a very low level which remained low for over 4 years, with no sign of an increase in infection rates in spite of reservoirs of the infection and poor level of sanitation in the villages remaining unchanged after the treatment (Jordan et al. 1982). The authors concluded that properly maintained water supply alone appeared to be effective in keeping transmission of infection low and that effectiveness improved further when safe water supply was combined with chemotherapy.

Drug Treatment

Chemotherapy focuses on the human host and aims at killing the worms residing in the human body thereby reducing the worm burden and infection-related pathology and morbidity. Various medicines have been tried and abandoned because of poor effect or adverse events. Egypt was the first country in Africa to use the Antimonies, one of the earliest antischistosomal medicines developed after the First World War around 1918. However, the low compliance associated with the long course of administration, pain from the injections and the serious side effects meant that the antimonies were limited to only hospital patients (Shekhar 1991; Cioli et al. 1995; Wu and Halim 2000). Treatment-associated death rates were very high, estimated at 3 per 1000 patients treated (Jordan 2000; Sturrock 2001). Ghana too tried the Antimonies in the 1960s when schistosomiasis became a big public health problem following the construction of the Akosombo Dam across the Volta River, but discontinued its use few years later because of serious adverse events (Wolfe et al. 1966).

The 1970s marked the turning point in schistosomiasis control when safe and effective medicines were introduced onto the market shifting control emphasis to chemotherapy of the human host (Cioli et al. 1995). Praziquantel (PZQ), a broad-spectrum, safe and easy-to-administer medicine immediately became the treatment of choice for schistosomiasis. The WHO endorsed selective treatment (i.e. identification of high-prevalence communities, screening the people and treating those identified to have the infection) as a more cost-effective option (WHO 1985). PZQ was delivered through small-to-medium, or large-scale selective programmes across endemic countries in SSA, funded by foreign donor organisations. The objective was to reduce or interrupt transmission of the infection; morbidity was a secondary objective.

Selective treatment programmes were implemented mainly as ‘vertical’ strategies where control decisions were mainly the responsibility of the donor agencies and expatriate experts. The outcome of this approach showed short-term promise in reducing prevalence of the infection. It was expected that any initial gains would lead to a takeover of the maintenance phase by national health authorities (Bruun et al. 2008), but transmission and reinfection rates usually remained unchanged in most treated areas. Lack of sustainability after withdrawal of donor funds and the expatriates at the end of a project was a major problem (Chitsulo et al. 2000; Engels et al. 2002). The high cost of PZQ at the time before expiry of its patent made universal coverage impossible.

Morbidity Control

Realising the minimal impact and lack of sustainability of selective treatment, WHO issued a guideline endorsing morbidity control as a new and cost-effective approach (WHO 1985). This approach was to limit coverage to symptomatic individuals or those with heavy worm load and likely to suffer complications from the infection. Morbidity control was delivered mainly through 'vertical' strategies. After about 10 years of its adoption, the WHO Expert Committee reviewed the strategy in the early 1990s and agreed that morbidity control was feasible and effective (WHO 1993). However, the Expert Committee identified that a leading role of the existing health service was necessary for its success and sustainability. It was acknowledged that if the patients themselves recognise signs and symptoms of the disease and self-report to a clinic or hospital ('passive case finding') for appropriate treatment, most severe infection-related pathology and complications may be averted. Passive case finding by local clinics looks promising because it is based on the primary healthcare concept already embraced by many endemic countries in Africa (Danso-Appiah et al. 2004, 2010).

Other potential success signs of passive case finding are that (1) control within the regular health service will strengthen the local health services including material and human resource; (2) related activities can be easily combined in an integrated concept, for example, the control of schistosomiasis can be combined with other helminthiases of public health relevance such as soil-transmitted helminths (STHs) or malaria as these diseases tend to coexist and (3) many parts of Africa where the highest burden of the disease is concentrated did not benefit from the donor-supported vertical control programmes (WHO 1998).

The morbidity control strategy was reviewed in 1998 by programme managers, scientists and public health experts from various endemic countries who reset the agenda for future control activities (WHO 1998). The Expert Committee recognised the leading role of the WHO in developing control strategies since its establishment after the Second World War but acknowledged that in SSA only a few countries had ongoing schistosomiasis control programmes as at 1990 (WHO 1998). It noted that PZQ was often not available at the peripheral health facilities where it is needed most. At the same time, major challenges were identified: (1) how to make PZQ widely available to communities where the medicine is needed most at an affordable cost; (2) how to organise and finance the distribution of PZQ to those who need it in a sustainable way and (3) how to adjust control measures to the varying distribution pattern and public health relevance of schistosomiasis in different communities.

It was also felt that drug supply from a strong centralised purchasing system with distribution through the existing health services according to local needs would facilitate decentralised planning and implementation of control strategies (WHO 1998). However, paucity of information on whether availability of PZQ alone in health facilities would influence rate of hospital uptake was a worry to policy makers. Therefore, the Expert Committee recommended the need to build local capacity and strengthen existing health systems, with main emphasis on

integration of control and decentralised decision-making and service delivery. Schistosomiasis is a focal problem and often its importance is diluted when control activities are planned and managed at the national centralised level.

Schistosomiasis was not acknowledged as a serious problem in preschool children until recently. Therefore, children under 5 years have been excluded from mass population treatment programmes (Stothard and Gabrielli 2007; WHO 2012). A major reason for their exclusion is that there is limited information about the safety of PZQ in this age group. Also, the dose pole used for determining the dose of PZQ, recommended by the WHO and used in these control programmes, only works for those over 94 cm in height. There are also no readily available syrup or paediatric formulations of PZQ.

A WHO-sponsored meeting that reviewed the results of studies on the treatment of schistosomiasis in preschool-age children in several countries in Africa (WHO 2010b) confirmed results from earlier publications (Bosompem et al. 2004; Odogwu et al. 2006; Johansen et al. 2007; Stothard and Gabrielli 2007) that (i) schistosomiasis can represent a significant public health problem in children aged less than 5 years; (ii) preschool-age children living in areas where endemicity for schistosomiasis is high, levels of infection are comparable with those of school-age children; (iii) prevalence of the infection may exceed 50 % and pathological lesions may be detectable by ultrasonography and (iv) administration of PZQ to preschool-age children is acceptable, safe and efficacious in the context of individual case management and in group settings, such as reported in the studies reported (WHO 2012).

Based on the above considerations, a series of recommendations were formulated. Among these, it was recommended that preschool-age children should be regarded as a high-risk group in areas endemic for schistosomiasis and that WHO should consider formally recommending the use of PZQ in preschool-age children in areas where schistosomiasis is endemic. However, the studies reviewed in this report had some limitations in design and methodology. Recognising the existence of knowledge, operational, regulatory and evidence gaps in existing data, it was re-emphasised that (i) treatment of this age group should be within an appropriate healthcare setting (WHO 2012), (ii) systematic review(s) involving preschool-age children, or well-designed multi-country randomised controlled trials (RCTs) using a standard protocol are warranted to contribute further evidence and (iii) a pharmacokinetic study investigating PZQ is warranted (WHO 2011). The case for health facility-based passive case reporting is strengthened given that this is the only way for preschoolers to benefit from treatment of their infection.

Chemotherapy

At present, chemotherapy is the cornerstone of schistosomiasis control and applied in endemic countries in SSA. PZQ remains the only drug for control and treatment programmes of schistosomiasis. Pressure on this drug is growing, and it is expected that this will increase exponentially given the endorsement of the implementation of

mass drug administration (MDA) in endemic countries across SSA. The risk of PZQ resistance remains a big threat and its prevention requires adequate and continued monitoring. A well-designed systematic review and meta-analysis of clinical and laboratory evidence are highly warranted to inform on the drug's performance, dynamics and resistance.

Metrifonate

Metrifonate is an effective antischistosomal drug introduced around 1952, initially as an insecticide (Lorenz et al. 1955) before it was approved for use in humans in the 1960s (Snellen 1981). It is one of only few treatments where clinical trials were initiated before detailed testing in animals were concluded (Aldridge and Holmstedt 1981). It has been used extensively giving at a dose of 7.5–10 mg/kg three times at 14-day intervals (Feldmeier and Doehring 1987). The only limitation is that it is active against only *S. haematobium*. Adverse effects are mainly associated with cholinergic stimulation and include fatigue, muscular weakness, tremor, sweating, salivation, fainting, abdominal colic, diarrhoea, nausea, vomiting and bronchospasm. Its use was limited after the publication that it was inferior clinically, economically and operationally to PZQ (Feldmeier and Chitsulo 1999). The chemistry, pharmacological properties and therapeutic efficacy as well as adverse events in clinical human use have been discussed in detail elsewhere (Cioli 2000; Utzinger and Keiser 2004).

Oxamniquine

Oxamniquine belongs to the same group of drugs as hycanthone with activity against only *S. mansoni*. It was introduced onto the market for clinical use in the early 1970s and has since been used widely with good effect, particularly in Brazil where it has been a major component of the national schistosomiasis control programme (NSCP). It acts by dislodging the worms from the mesenteric veins to the liver and destroying the male worms. Although oxamniquine allows the female worms to return to the mesentery, they are made sterile and are no longer able to produce eggs. In South America (mainly Brazil) and West Africa, a single lower dose of 15 mg/kg is given to adults and 20 mg/kg to children. In other countries of Africa and the Arabian Peninsula, higher doses are given, the total dose varying from 30 to 60 mg/kg (Foster 1987). Differences in the susceptibility of parasites to the drug seem to account for the variation in dosage. Adverse events are mild and transient and include dizziness with or without drowsiness, headache and gastrointestinal effects such as nausea, vomiting and diarrhoea. Few serious events such as seizures have been reported but all were associated with higher doses. Oxamniquine's use has declined considerably in favour of PZQ, even in Brazil, where it has long been preferred to PZQ.

Praziquantel

Praziquantel is a broad-spectrum antischistosomal drug effective against all schistosome worms. PZQ is distributed mainly as 600 mg tablet, with two or three grooves for ease of breaking. In China, it is distributed as 200 mg pills while some manufacturers provide syrup formulation containing 600 mg/5 ml (e.g. epiquentel from EIPICO). The shelf life of PZQ is usually 4 years in temperate climates and 3 years in hot humid environments. When administered orally, the drug is rapidly and almost completely absorbed, appearing in the blood within 15 min and attaining peak concentration 1–2 h after treatment (Valencia et al. 1994). Approximately 80 % of the drug is cleared within 24 h of treatment mainly through urine (Cioli et al. 1995). There are many brands and generic forms in the system including Distocide manufactured by Shin Poong in Korea, Bilharzid from Egypt and Prazitel from Kenya (Cioli and Pica-Mattoccia 2003). There are other brands produced in the Netherlands and Malta. PZQ is administered orally at a standard single dose of 40 mg/kg body weight and well tolerated. Most common adverse events are mild and transient, mostly related to the gastrointestinal tract: abdominal pain, nausea, vomiting, anorexia and diarrhoea. Currently, it is the only drug on the WHO Model List of Essential Medicines for treating schistosomiasis. Although its effectiveness is unequivocal, PZQ is less effective against immature schistosome worms (Sabah et al. 1986). Therefore, it has been suggested that a combination therapy with drugs of unrelated mechanisms of action and targeting the different developmental stages of the schistosomes may improve therapeutic efficacy and slow the development of resistance. Drugs with potential for combination with PZQ include the artemisinin derivatives, metrifonate and oxamniquine.

Other Medicines

Several drugs have been tried for the treatment of schistosomiasis and later abandoned because of poor effect or adverse events. These include the *antimonials*, *niridazole*, *lucanthone*, *hycanthone*, *oltipraz*, *cyclosporin A* and *levamisole*, extensively reviewed by Cioli et al. (1995). More recently, the efficacy of *myrrh* (*Mirazid*) in the treatment of intestinal schistosomiasis was tested in Egypt at a single daily dose of 300 mg for 3 days, and virtually no activity was observed as almost all the treated participants failed treatment at 3–6 weeks (Barakat et al. 2005; Botros et al. 2005).

Status of Medicines Used for Treating Schistosomiasis

In the late 1990s, amidst the argument that metrifonate acts against only *S. haematobium* coupled with clinical, economic and operational suitability when compared with PZQ (Feldmeier and Chitsulo 1999), this medicine was withdrawn from the

WHO Model List of Essential Medicines. The application of oxamniquine (which acts against only *S. mansoni*) infection has declined considerably, and in areas where it was formally used as the drug of choice, it is being replaced with PZQ (Cioli 2000; Beck et al. 2001; Reich and Fenwick 2001; Utzinger and Keiser 2004; WHO 2012). Oxamniquine has subsequently been removed from the WHO Model List of Essential Medicines.

At present, there is no effective and acceptable antischistosomal vaccine (Utzinger et al. 2007; Bergquist et al. 2008), and evidence on the artemisinins are inconclusive (Utzinger et al. 2007; Utzinger et al. 2010; Liu et al. 2011; del Villar et al. 2012; Wikman-Jorgensen et al. 2012; Danso-Appiah et al. 2013). Therefore, PZQ remains the only drug available for the treatment of millions of persons suffering from schistosomiasis. At the same time, PZQ use in SSA has increased enormously following the endorsement of Resolution 54.19 at World health Assembly (WHA) in the early millennium. Endemic countries in SSA have been encouraged to adopt MDA as their national control strategy. PZQ distribution is expected to increase exponentially, raising fears about potential resistance emerging against this medicine. Given aforementioned, it is critical to find and appraise available data for evidence on resistance against PZQ.

Resistance to Praziquantel

In the early 1990s, PZQ treatment in Senegal (West Africa) resulted in unacceptably low cure rates, raising concerns about possible emergence of resistance against PZQ (Gryseels et al. 1994; Stelma et al. 1995). Meanwhile, analysis of *S. mansoni* strains obtained from patients treated with PZQ but not cured in the areas where low cure rates had been registered in Senegal, also Egypt, yielded isolates less susceptible to higher doses of the drug. Around the same time, laboratory experiments in mice yielded isolates of *S. mansoni* strains from Senegal that were less sensitive to PZQ (Fallon et al. 1995). The development of resistance against PZQ was cited as one of the main reasons for the observed low drug performance. Other reasons given were the very high pretreatment intensity of infection observed in Senegal, presence of immature worms less susceptible to PZQ and rapid acquisition of a large number of new infections immediately following treatment. This prompted the European Commission to set up the European Commission-Concerted Action on PZQ in the late 1990s (Renganathan and Cioli 1998) to review reports of low efficacy of trials from Senegal and Egypt. However, it was difficult to distinguish between normal performance and failure of PZQ as it was not possible to analyse data quantitatively. Notwithstanding, the EC-Concerted Action on PZQ advocated continued monitoring and evaluation of resistance to PZQ.

In order to ascertain the availability of evidence on clinical resistance against PZQ, various electronic databases and sources were searched for systematic reviews and meta-analysis. The search retried only one meta-analysis of observational studies that has assessed this question quantitatively (Danso-Appiah and De Vlas 2002). The meta-analysis used robust Bayesian approach of evidence synthesis, accounting for various

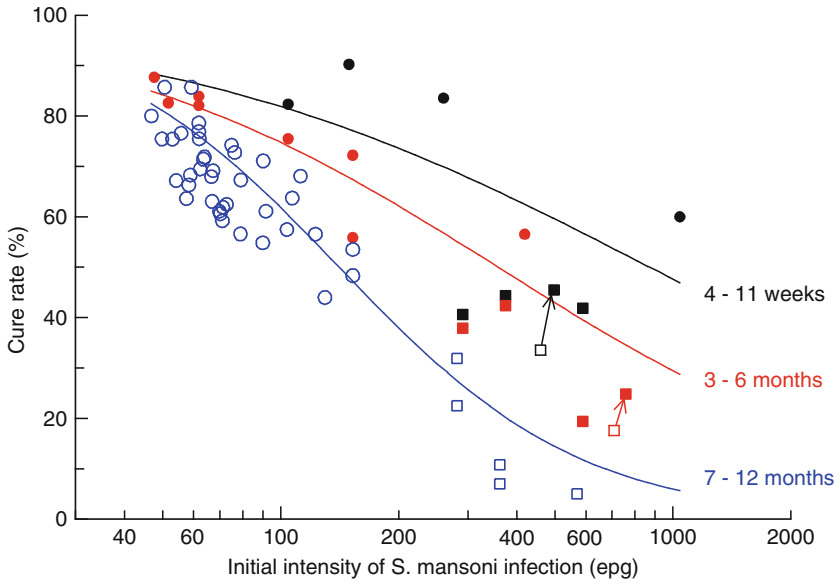


Fig. 5 The impact of pretreatment intensity of *Schistosoma mansoni* infection, diagnostic sensitivity and follow-up time on cure rate using the standard PZQ dose of 40 mg/kg body weight in population-based, selective chemotherapy. Intensity of infection (logarithmic scale) is the geometric mean of egg count per gram of faeces (epg) for individuals positive for *S. mansoni* eggs. Cure rate denotes percentage of treated subjects who appeared negative for *S. mansoni* eggs at follow-up. The dots represent different follow-up time categories: 4–11 weeks; 3–6 months; 7–12 months. Data points located on same vertical axis indicate successive follow-ups of a treatment in the same community. *Squares* represent observations from Senegal; *circles*, studies from other locations. *Arrows* illustrate shifts from published observations from Senegal based on duplicate stool specimens (*open squares*) to the corresponding cure rate and intensity from a single stool specimen. For the three follow-up time categories, curves give best fitting associations of *cure rate* and *ln epg* through cure rate = $100/(1+e^{-Lp})$, where $Lp = \alpha + \beta \ln epg$.. α and β coefficient values are 4.7 and −0.70 (4–11 weeks follow-up); 5.0 and −0.85 (3–6 months); 6.9 and −1.40 (7–12 months). Coefficients α and β are estimated by generalised linear mixed modelling (GLMM). Out of the 13 data points from Senegal, 12 are located below the respective lines. Thus, even when initial intensity, follow-up time and sensitivity of diagnosis are accounted for, cure rates from Senegal are consistently lower than expected (Reproduced from Danso-Appiah and De Vlas (2002), *Trends in Parasitology*)

risks of biases and confounding effects. Although no formal quality assessment of the included studies was conducted, rigorous standardisation measures were used to ensure comparability across studies and that biases and errors were minimised.

The results showed that the low cure rates observed in Senegal was largely the result of high pretreatment intensity of infection in persons treated there. The relatively sensitive diagnostic technique used in the studies from Senegal to some extent contributed to the observed low cure rates.

However, after correcting for pretreatment intensity and sensitivity of diagnosis, cure rates from Senegal remained somewhat lower than expected (Fig. 5). Various

studies on biological and methodological aspects were reviewed to help explain the Senegal situation (Geerts and Gryseels 2001; Gryseels et al. 2001; Cioli 2000; Doenhoff 1998).

The meta-analysis concluded that although high pretreatment intensity of infection, sensitive diagnostic methods and presence of high baseline numbers of immature worms in treated patients explained most of the low performance of PZQ in Senegal, the suspicion about resistance could not be ruled out completely. This is because tools and methods for assessing resistance were not adequate or unavailable.

Combination Therapy

As far as it is known, no new medicines are being developed although some scientists suggest that the combination of PZQ and metrifonate or PZQ and oxamniquine would be potentially cost-effective treatment. The rationale is that PZQ and metrifonate or PZQ and oxamniquine are independently effective against *S. haematobium* and *S. mansoni* infections that their targets of action in the parasite are not linked. Therefore, combination may improve therapeutic efficacy and slow or prevent the development of drug resistance. However, both oxamniquine and metrifonate are active against single schistosome species, while in most endemic settings in SSA, there is an overlap of *S. haematobium* and *S. mansoni*. As it is operationally less suitable within the MDA PC strategy, pharmaceutical companies may be less motivated to invest in the development of these combination therapies.

Amoscanate

Another potentially useful drug is amoscanate, a broad-spectrum anthelminthic medicine with activity against all the major schistosome species (Striebel 1976). It was discovered before the 1970s and showed effect against some systemic parasites including filariae and gastrointestinal nematodes such as the hookworms. It was tested extensively in China from locally produced brand called 'nithiocyaminum' (Bueding et al. 1976; Striebel 1976). Toxicity was low in animal models but mutagenicity tests in bacteria gave positive results. Also, mutagenic metabolites were constantly found in the urine of mammals administered this treatment (Batzinger and Bueding 1977). Coupled with concerns about liver toxicity, amoscanate was abandoned when PZQ became available (Cioli 1995). Given its broad-spectrum schistosomicidal properties, new and well-designed research that will investigate structural modifications of the chemical structure to decrease liver toxicity is warranted (Cioli et al. 1995).

Artemisinin Derivatives

The artemisinins act against immature schistosomes (schistosomulae) that are less sensitive to PZQ (Le et al. 1982, 1983; Utzinger et al. 2003, 2007); the invasive and adult worms are less susceptible to the artemisinins. Adverse effects are minor and last for less than 24 h. The combination of artemisinin with existing drugs effective against other stages of the parasite such as PZQ may improve efficacy and slow or prevent the development of resistance against PZQ. Therefore, combination therapy with the artemisinins should be pursued vigorously given that current evidence is inconclusive.

Supportive Evidence for Diagnostic Tools and Treatment

In order to investigate whether application of diagnostic tests and techniques in sub-Saharan Africa is supported by systematic reviews and other forms of evidence synthesis, relevant electronic databases including MEDLINE, LILACS, DARE and the Cochrane Collaboration Databases were searched in September 2013. The reference lists of published studies were also searched, and experts in the field of schistosomiasis were contacted for additional or unpublished systematic reviews that might have been missed through the search. The search identified only one published systematic review protocol which intends to assess rapid screening and diagnostic tests for schistosomiasis in endemic areas, but data are not yet available (Ochodo et al. 2012) and six published systematic reviews of varying qualities assessed treatment options and effects (Danso-Appiah et al. 2008, 2013; Liu et al. 2011; del Villar et al. 2012; Wikman-Jorgensen et al. 2012; Stothard et al. 2013).

Given that the search did not retrieve any systematic review or carefully synthesised evidence on diagnostic accuracy, it is not possible to establish whether available evidence supports the use of current diagnostic tools and methods used in SSA. The WHO recently commissioned a systematic review and meta-analysis to assess the circulating cathodic antigen (CCA) test in the diagnosis of schistosome infections which may provide valuable information (Danso-Appiah et al. submitted). The six systematic reviews on treatment options and effects retrieved are of variable quality and thus reliability. Detailed assessment as to whether they support current treatment options and policies in SSA is beyond the remit of this study. Therefore, a new and well-designed study is warranted to examine this.

The Millennium Control Strategies

With the exceptions of Egypt and Morocco, hardly any observable progress was made in the control of schistosomiasis in the African continent up to the 1990s (Utzinger et al. 2009). The reasons for this were attributed to the absence of safe and

easy-to-apply medicines prior to the 1970s and high price of available medicines after their introduction onto the market. The expiry of patency of PZQ in the early 1990s allowed the production of brands leading to a sharp fall in the price of this medicine from about US$1 at 1990 to less than UD$ 0.06 per tablet in the early millennium. PZQ use has since increased considerably. One other major reason for the surge in PZQ distribution may be due to evidence that dispelled fears about the likelihood of resistance against PZQ (Doenhoff 1998; Cioli 2000; Gryseels et al. 2001; Danso-Appiah and De Vlas 2002) together with increased advocacy for control of NTDs (Hotez et al. 2007; Fenwick et al. 2009; Garba et al. 2009; Utzinger et al. 2011).

The adoption of Resolution WHA54.19 in 2001 urged member states to treat at least 75 % of schoolchildren infected with schistosomiasis and high-risk individuals or entire 'at-risk' populations (e.g. school-age children) through mass distribution of PZQ, usually without prior diagnosis – an approach termed 'preventive chemotherapy' (PC). This is the millennium control strategy endorsed by WHO and applied in many endemic countries. Usually, PZQ at a standard single oral dose of 40 mg/kg is used.

In 2002, WHO convened an Expert Committee meeting to develop operational guidelines to translate the recommendations of WHA54.19 into concrete action with emphasis on morbidity control (WHO 2002b). The strategy had a goal of control of morbidity to be achieved through large-scale distribution of PZQ to populations at risk, using defined thresholds of prevalence as criteria for selecting the appropriate interval of retreatment. Schools were identified as the most efficient delivery entry point. On the other hand, if school enrolment is low, community-based interventions are to be implemented to reach out to children not attending school. The adoption of Resolution WHA54.19 has led to thousands of school-age children in countries in SSA to receive multiple doses of PZQ initially through the Schistosomiasis Control Initiative (SCI) which started in 2003 and funded by the Bill and Melinda Gates Foundation (Fenwick et al. 2006, 2009; Linehan et al. 2011) and more recently through the integrated control approach of NTDs supported by the United States Agency for International Development (USAID), the British Department for International Development (DFID) and the Global Network for NTDs and its partners (Hotez 2009, 2011).

New evidence that emerged that morbidity is not necessarily determined by the intensity of infection led to a revised version of the operational details of PC in 2006 (WHO 2006a, b). The target population was expanded to include all adults in high-risk areas where prevalence of infection in school-age children is 50 %, as well as special-risk groups such as people occupationally exposed to risk of infection. The targets for moderate and low-risk areas were also revised (Table 2).

With new evidence that preschool-age children in endemic areas may be at a similar risk of infection and morbidity (WHO 2011), the recommendation is that children aged up to 5 years who are excluded from population-based mass chemotherapy should be treated in health facilities as part of national control programmes. The 2006 guidelines came out with additional component about coordinated use of anthelminthic medicines to control and eliminate four main helminth infections,

Table 2 Recommended treatment strategy for schistosomiasis

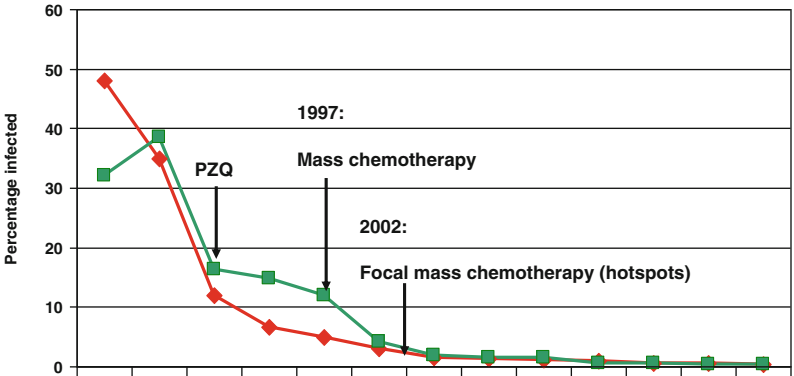
Category	Baseline prevalence among school-age children	Action to be taken	
High-risk community	50 % by parasitological methods (both) or 30 % by questionnaire for history of haematuria (for urinary schistosomiasis)	Treat all school-age children (enrolled and not enrolled) once a year	Also treat adults considered to be at risk (from special groups to entire communities living in endemic areas)
Moderate-risk community	10 % but <50 % by parasitological methods (both), or <30 % by questionnaire for history of haematuria (for urinary schistosomiasis)	Treat all school-age children (enrolled and not enrolled) once every 2 years	Also treat adults considered to be at risk (special groups only)
Low-risk community	<10 % by parasitological methods (for both urinary and intestinal schistosomiasis)	Treat all school-age children (enrolled and not enrolled) twice during their primary schooling age (e.g. once on entry and once on exit)	Praziquantel should be available in dispensaries and clinics for treatment of suspected cases

Adapted from WHO (2012)

namely, lymphatic filariasis, onchocerciasis, schistosomiasis and soil-transmitted helminths (STHs) which usually coexist and for which the medicines used for their treatment can safely be co-administered (Utzinger and Keiser 2004; Olsen 2007; Hotez 2009).

Political Will, Functional Health Service and Sustainable Control

Most countries that have been successful in schistosomiasis control have used multifaceted approach combining various control measures together with political will. For example, Japan, China, Iran, Laos, Mauritius, Morocco, Saudi Arabia, Tunisia, the endemic Caribbean Islands, Brazil and Venezuela have been successful in their control effort because they made functional health services key component of the control of schistosomiasis. Also, their governments showed political will and commitment. Therefore, an adequately resourced or functional health service can play a crucial role as control is far more effective when placed in the context of a general health system (WHO 2002b). Although in terms of cost-effectiveness and sustainability the concept which underpins this strategy is sound, the process has been slow in SSA due to lack of material and human resource and political will. The experiences of schistosomiasis control from Egypt and Uganda have been presented to



	1935	1983	1988	1993	1996	2000	2004	2005	2006	2007	2008	2009	2010
S.haematobium	48	35	11.9	6.6	5	3	1.6	1.4	1.2	0.9	0.6	0.5	0.4
S.mansoni	32	38.6	16.4	14.8	11.9	4.2	1.9	1.6	1.5	0.6	0.6	0.4	0.3

Fig. 6 The impact of mass chemotherapy with praziquantel on schistosomiasis control in Egypt (Adapted from WHO (2012). Schistosomiasis: progress report 2001–2011 and strategic plan 2012–2020)

highlight the importance of multifaceted approach as a way to successful and sustainable control.

Egypt is endemic for both urinary and intestinal schistosomiasis. Implementation of a National Schistosomiasis Control Program started in 1977, through the primary healthcare system. First, pilot projects were implemented using either snail control or chemotherapy with little success. From 1988, PZQ was made available free of charge for all diagnosed cases of schistosomiasis in all governmental health facilities. Then from 1997 to 2002, mass treatment campaigns without prior diagnosis in communities with a prevalence of infection above 20 % were actively embarked on. As the programme progressed and the disease prevalence decreased, the threshold for mass chemotherapy was changed. As the infection levels went down, the 1997 threshold of prevalence for mass treatment was reduced to >10 % in 1999, 5 % in 2000 and >3.5 % in 2002, to >3 % in 2003. Since 2003, mass chemotherapy has been applied only in hotspots (micro-focal control).

Available statistics show that before the mass chemotherapy campaigns in 1996 (Fig. 6), there were 168 villages with prevalence >30 %, 324 villages with prevalence 20–30 % and 654 villages with schistosomiasis prevalence of 10–20 %. However, during the programme evaluation by the end of 2010, only 20 villages in the whole country had prevalence more than 3–5 %, and none had prevalence >10 %. The prevalence of both *S. mansoni* and *S. haematobium* has consistently decreased under sustained treatment effort supported by political will.

Tracing Egypt's success story, the prevalence of the two species was 38.6 % and 35 %, respectively, in 1983, reduced to 11.9 % and 5 % in 1996 and to 2.7 % and 1.9 % in 2002. Mass chemotherapy began to be targeted on "hotspot" areas in 2003 when the prevalence of *S. mansoni* was 2.6 % and that of *S. haematobium* was 1.7 %, but by 2010, these were 0.3 % and 0.4 %, respectively (WHO 2011).

The achievements in Egypt were made possible after treating a total of 38.8 million and a further nine million people with PZQ. In parallel to the national programme and functional health service as a key component, attention was also focused on snail control, universal access to potable water to almost every household and significant increase in access to adequate sanitation.

SCI and other partners began the support to Uganda from 2003. Like Egypt, control began with a pilot phase in 2003, in one subregion in each of the 18 most affected districts, mainly mass treatment and health education. Activities included planning, advocacy, training of teachers and supervisors, selection and training of community drug distributors, health education, supervision, monitoring of treatment side effects, reporting of treatment coverage and drug accountability.

During the pilot phase, 400,000 people were treated and this increased to 1.4 million in 2004, 3 million in 2005. Annual meetings were held regularly at national level to review constraints and plan the way forward. In 2006, two million people were treated in 27 of the 38 endemic districts. In addition health centre-based treatment was conducted alongside mass chemotherapy in 11 of the districts. The main aspects monitored were programme performance and the impact of treatment campaigns, severe adverse events and drug utilisation and efficacy. The impact of yearly mass treatment with PZQ on infection status and morbidity of *S. mansoni* infection in school-age children was evident in several ways. Anaemia was also reduced. In adults, yearly treatment significantly reduced both the prevalence and the intensity of *S. mansoni* infection between 2003 and 2006, as well as the incidence and severity of fibrosis (WHO 2011).

Similar success stories have been reported from countries selected and supported for mass PZQ distribution as part of the SCI (2003).

Control or Elimination

From a recent survey for NTD disease-specific experts' opinions on the role of MDA for the elimination of lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminths (STHs) and trachoma, most experts in lymphatic filariasis, onchocerciasis and trachoma thought elimination was the appropriate goal of treatment programmes with MDAs. For schistosomiasis and STHs, the majority of experts thought that MDA programmes were intended to control (Keenan et al. 2013) and that MDA plus other control measures would be required for their elimination.

In a debate in PLoS Medicine titled '*Which new approaches to tackling NTDs show promise*?' (Spiegel et al. 2010), while some experts held the view that there has been too much focus on the biomedical mechanisms and drug development for NTDs at the expense of attention to the social determinants of disease and that the weak health systems and poor socio-environmental conditions that cause and/or perpetuate NTDs have largely been ignored, others argue that the best return on investment will continue to be MDA for NTDs.

In the same paper, one school of thought suggested that the designation of a set of tropical diseases as 'neglected' has indeed provoked interest in strategies for their control and research on new tools for alleviation of their burden. This initiative, however, has also exposed the over-medicalisation of contemporary tropical disease control strategies. A primary example is the emphasis on drug administration alone to alleviate the burden of schistosomiasis and STHs, two groups of disease that would benefit more from a combination of MDA and other control methods. Others of contrary views advance the points that in terms of both health impact and cost-effectiveness, few other interventions can rival MDA for NTDs, particularly schistosomiasis. Furthermore, MDA increasingly is being recognised for its beneficial effects on strengthening health systems, improving economic development and achieving the Millennium Development Goals (Spiegel et al. 2010). The successful control of blindness in SSA through free community-directed treatments with ivermectin of the Onchocerciasis Control Program (OCP) and the African Programme for Onchocerciasis Control (APOC) is cited as positive examples. Furthermore, there is considerable epidemiological overlap of NTDs, and in more than 75 % of countries in SSA at least six of the seven these diseases coexist in the same community and that there is ample evidence about the cost-effectiveness of simultaneous MDA to tackle these diseases.

Outlook of Control in the Next Decade

Schistosomiasis is widely recognised as a disease that is socially determined but most programmes have ignored the key issues about understanding the social and behavioural factors that underpin transmission and control of the disease. Therefore, social determinants of schistosomiasis should be considered as vital in designing strategies and policies for prevention and control (Bruun et al. 2008). Given the lack of suitable and appropriate water supplies in rural areas, the rural folk have no alternative but to be in constant contact with schistosomiasis infested water bodies for their daily use. There is therefore, the suggestion that preventive programmes could be updated and made relevant to real-life situations in remote rural areas by using insights from social scientists including medical anthropologists, health geographers, sociologists and others whose skills enable them to explore the social context of schistosomiasis transmission and control at the micro level, in the setting in which the infection is transmitted and where efforts are made to control it (Bruun et al. 2008).

Mass distribution of PZQ to endemic countries in SSA as set out in The WHA Resolution 54.19 has been adopted by the endemic countries. Caution is, however, called for in (i) what is a solely large-scale anthelminthic drug administration to the exclusion of preventive strategies for control which include access to clean water, improved sanitation and hygiene in an integrated and sustainable disease control

programmes (Utzinger et al. 2003) and (ii) the disconnection between engineering projects and community-led initiatives in the developing world on clean water and sanitation and the vertical 'drugs only' programmes (Singer and Castro 2007; Utzinger et al. 2009).

Utzinger et al. (2009) predict PZQ treatment needs in SSA and estimate that approximately 128 million school-age children would need to be given PZQ. This amounts to 384 million tablets of PZQ every year for treatment in Africa alone. Although PZQ has now been made available free of charge by multilateral collaboration between donor organisations and pharmaceutical companies to poor endemic countries in SSA, issues of supplies, cost, whether or not free PZQ alone will be enough to achieve the objectives of schistosomiasis control and elimination, and possible drug resistance need to be kept in mind and addressed effectively.

Experiences from schistosomiasis control as, for example, in Burundi and Mali where the German Technical Cooperation (GTZ) funded large-scale vertical control programmes with PZQ show that these programmes were not sustainable in the long run. Usually, gains in prevalence reductions were offset by rapid reinfection after withdrawal of external funds and technical capacity at the end of the programmes given practical and operational problems which resurface in the absence of adequate funding. These operational problems are not unique to Burundi and Mali. They exist in many of the endemic countries presently and will need further attention in the future. These include availability of material, human resource, operational funds and infrastructure, political will to sustain the benefit achieved with chemotherapy, availability of reliable data and adequate technical capacity for delivery, monitoring and evaluation of national control programmes. Any one of these or a combination of some of them has led to the situation where after nearly 10 years of MDA campaign only 18 countries were yet to start MDAs as at 2010, and just over half (23) of the 42 schistosomiasis endemic countries in SSA had national control programmes, mostly of limited scale. Only about five countries had reached all their at-risk populations, but prevalence rates were still 100 % in some endemic settings. In some conflict and post-conflict areas, e.g. the Democratic Republic of Congo, the actual schistosomiasis problem situation is still unknown. The next decade should see an amelioration of some of these challenges given the current goodwill and enthusiasm of ministries of health, partners and donors to eliminate several of the NTDs including schistosomiasis.

The current WHO monitoring guideline which has not been specific on how parasitological and morbidity monitoring should be conducted should see updating together with the production of guidelines on how to assess drug sensitivity and timely detection of emergence of resistance.

Very few partners provide financial support for research and development; despite the devastating public health impact of NTDs and their effect on development (Hotez et al. 2009; Manderson et al. 2009; McCoy et al. 2009; Hotez and Pecoul 2010), there is however, a cautious optimism that such a situation could change in the coming decade (Hotez and Pecoul 2010).

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