

## Human schistosomiasis

Bruno Gryseels, Katja Polman, Jan Clerinx, Luc Kestens

Lancet 2006; 368: 1106–18

Institute for Tropical Medicine  
Antwerp, Nationalestraat 155  
B-2000, Antwerp, Belgium  
(Prof B Gryseels MD,  
K Polman PhD, J Clerinx MD,  
Prof L Kestens PhD)

Correspondence to:  
Prof Bruno Gryseels  
bgryseels@itg.be

Schistosomiasis or bilharzia is a tropical disease caused by worms of the genus *Schistosoma*. The transmission cycle requires contamination of surface water by excreta, specific freshwater snails as intermediate hosts, and human water contact. The main disease-causing species are *S haematobium*, *S mansoni*, and *S japonicum*. According to WHO, 200 million people are infected worldwide, leading to the loss of 1·53 million disability-adjusted life years, although these figures need revision. Schistosomiasis is characterised by focal epidemiology and overdispersed population distribution, with higher infection rates in children than in adults. Complex immune mechanisms lead to the slow acquisition of immune resistance, though innate factors also play a part. Acute schistosomiasis, a feverish syndrome, is mostly seen in travellers after primary infection. Chronic schistosomal disease affects mainly individuals with long-standing infections in poor rural areas. Immunopathological reactions against schistosome eggs trapped in the tissues lead to inflammatory and obstructive disease in the urinary system (*S haematobium*) or intestinal disease, hepatosplenic inflammation, and liver fibrosis (*S mansoni*, *S japonicum*). The diagnostic standard is microscopic demonstration of eggs in the excreta. Praziquantel is the drug treatment of choice. Vaccines are not yet available. Great advances have been made in the control of the disease through population-based chemotherapy but these required political commitment and strong health systems.

Schistosomiasis or bilharzia is a tropical parasitic disease caused by blood-dwelling fluke worms of the genus *Schistosoma*. Adult schistosomes are white or greyish worms of 7–20 mm in length with a cylindrical body that features two terminal suckers, a complex tegument, a blind digestive tract, and reproductive organs. Unlike other trematodes, schistosomes have separate sexes. The male's body forms a groove or gynaecophoric channel, in which it holds the longer and thinner female (figure 1). As permanently embraced couples, the schistosomes live within the perivesical (*Schistosoma haematobium*) or mesenteric (other species) venous plexus. Schistosomes feed on blood and globulins through anaerobic glycolysis. The debris is regurgitated in the host's blood.

The females produce hundreds (African species) to thousands (oriental species) of eggs per day. Each ovum contains a ciliated miracidium larva, which secretes proteolytic enzymes that help the eggs to migrate into the lumen of the bladder (*S haematobium*) or the intestine (other species). The eggs are excreted in the urine or faeces and can stay viable for up to 7 days. On contact with water, the egg releases the miracidium. It searches for the intermediate host, freshwater snails, guided by

light and chemical stimuli. After penetrating the snail, the miracidia multiply asexually into multicellular sporocysts and later into cercarial larvae with embryonic suckers and a characteristic bifurcated tail.

The cercariae start leaving the snail 4–6 weeks after infection and spin around in the water for up to 72 h seeking the skin of a suitable definitive host. Cercarial shedding is provoked by light and occurs mainly during daytime. One snail, infected by one miracidium, can shed thousands of cercariae every day for months. On finding a host, the cercariae penetrate the skin, migrate in the blood via the lungs to the liver, and transform into young worms or schistosomulae. These mature in 4–6 weeks in the portal vein, mate, and migrate to their perivesicular or mesenteric destination where the cycle starts again. The lifespan of an adult schistosome averages 3–5 years but can be as long as 30 years. The theoretical reproduction potential of one schistosome pair is up to 600 billion schistosomes.

The main schistosomes infecting human beings are: *S mansoni*, which is transmitted by *Biomphalaria* snails and causes intestinal and hepatic schistosomiasis in Africa, the Arabian peninsula, and South America; *S haematobium*, transmitted by *Bulinus* snails and causing urinary schistosomiasis in Africa and the Arabian peninsula; and *S japonicum*, transmitted by the amphibian snail *Oncomelania* and causing intestinal and hepatosplenic schistosomiasis in China, the Philippines, and Indonesia (figure 2). *S intercalatum* and *S mekongi* are only of local importance. *S japonicum* is a zoonotic parasite, which infects a wide range of animals including cattle, dogs, pigs, and rodents. *S mansoni* is also found in rodents and primates, but human beings are the main host. A dozen other schistosome species are animal parasites, some of which occasionally infect people.

The distribution of the different species depends mainly on the ecology of the snail hosts. Natural streams,

### Search strategy and selection criteria

The literature research for this Seminar started from standard works and recent reviews.<sup>1–10</sup> We also used our own collections and the library holdings of the Antwerp Institute of Tropical Medicine, and searched PubMed and MEDLINE over the past 10 years for the main topics of this paper with the key words "schistosomes OR schistosomiasis OR schistosoma" PLUS "epidemiology", "transmission", "pathology", "morbidity", "mortality", "immunology", "vaccine", "treatment", "praziquantel", "diagnosis", "control", "disease burden", and "genital". We checked relevant references for accuracy and balance, and where necessary searched secondary references until the original data were found. Subjects related to molecular biology, basic immunology, and malacology are beyond the scope of this Seminar; other papers<sup>8–10</sup> are excellent starting points for the interested reader.

ponds, and lakes are typical sources of infection, but over the past few decades man-made reservoirs and irrigation systems have contributed to the spread of schistosomiasis.<sup>11</sup> The disease is largely a rural problem, but urban foci can be found in many endemic areas.<sup>12</sup>

Snail populations, cercarial density, and patterns of human water contact show strong temporal and spatial variations, resulting in a focal distribution of the infection within countries, regions, and villages (figure 3).<sup>13</sup> Typically, rates and intensities of infection increase from an early age to a peak around age 8–15 years and decrease again in adults. Within populations and age-groups, schistosomes are overdispersed; a small number of individuals carry most of the parasites.<sup>14</sup> These features have been attributed both to water-contact patterns and to innate and acquired immunity. Sex-related patterns vary in relation to behavioural, professional, cultural, and religious factors.<sup>2</sup>

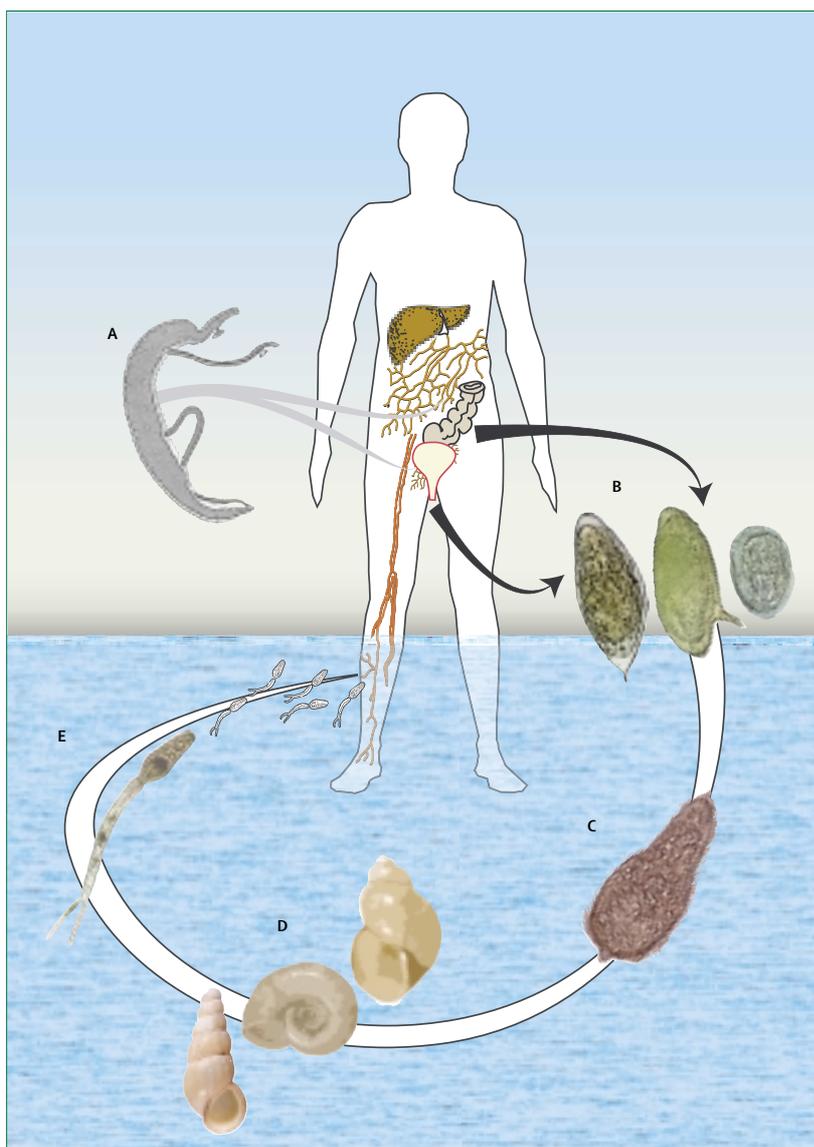
### Acute pathology

The percutaneous penetration of cercariae can provoke a temporary urticarial rash that sometimes persists for days as papulopruriginous lesions, especially after primary infections such as occur in tourists and migrants.<sup>15</sup> A similar swimmers' itch is also frequently caused by cercariae of animal trematodes in temperate climate zones.<sup>16</sup> Possibly, cercarial dermatitis often goes unrecognised in endemic areas.<sup>17</sup>

Acute schistosomiasis (Katayama fever) is a systemic hypersensitivity reaction against the migrating schistosomulae, occurring a few weeks to months after a primary infection.<sup>15,18–20</sup> The disease starts suddenly with fever, fatigue, myalgia, malaise, non-productive cough, eosinophilia, and patchy infiltrates on chest radiography. Abdominal symptoms can develop later, caused by the migration and positioning of the mature worms. Most patients recover spontaneously after 2–10 weeks, but some develop persistent and more serious disease with weight loss, dyspnoea, diarrhoea, diffuse abdominal pain, toxæmia, hepatosplenomegaly and widespread rash.

Katayama fever due to *S. mansoni* or *S. haematobium* is rarely seen in chronically exposed populations, possibly owing to underdiagnosis or in-utero sensitisation.<sup>21</sup> It is common, however, in tourists, travellers, and other people accidentally exposed to transmission.<sup>15,22,23</sup> Most cases in western travel clinics are imported from sub-Saharan Africa, many in family or group clusters. Notorious sources of infection are Lake Malawi, Lake Victoria, and Lake Volta, the Zambesi and Niger deltas, and some lake resorts in South Africa. The contacts with infected water include bathing and swimming, scuba diving, water skiing, and rafting.<sup>23</sup>

Katayama fever due to *S. japonicum* does also occur in people living in endemic areas and with a history of previous infections. In China, rebound epidemics have been reported in endemic communities exposed to



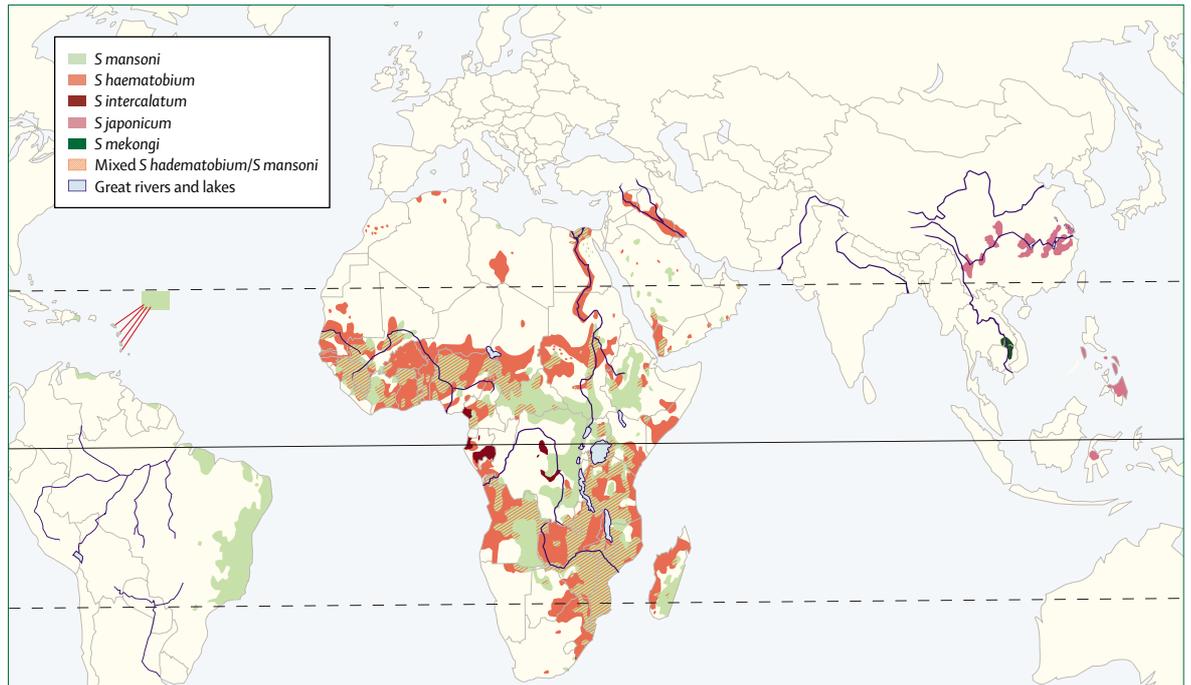
**Figure 1: Transmission cycle of *Schistosoma mansoni***

A: paired adult worms (sturdy male holding slender female). B: eggs (left to right, *S. haematobium*, *S. mansoni*, *S. japonicum*). C: ciliated miracidium. D: intermediate host snails (left to right, *Oncomelania*, *Biomphalaria*, *Bulinus*). E: cercariae.

floods.<sup>24,25</sup> The manifestations can be severe with persistent fever, organomegaly, and cachexia, which can evolve rapidly to hepatosplenic fibrosis and portal hypertension.

### Chronic pathology and morbidity

The main lesions in established and chronic infection are due not to the adult worms but to eggs that are trapped in the tissues during the perivesical or perintestinal migration or after embolisation in the liver, spleen, lungs, or cerebrospinal system. The eggs secrete proteolytic enzymes that provoke typical eosinophilic inflammatory and granulomatous reactions, which are progressively replaced by fibrotic deposits (figure 4).<sup>26</sup>



**Figure 2: Global distribution of schistosomiasis**

Based on updated and corrected data from Doumenge and Mott.<sup>1</sup> Main foci: *S. mansoni*—much of sub-Saharan Africa, northeast Brazil, Surinam, Venezuela, the Caribbean, lower and middle Egypt, the Arabian peninsula; *S. haematobium*—much of sub-Saharan Africa, Nile valley in Egypt and Sudan, the Maghreb, the Arabian peninsula; *S. japonicum*—along the central lakes and River Yangtze in China; Mindanao, Leyte, and some other islands in the Philippines; and small pockets in Indonesia; *S. mekongi*—central Mekong Basin in Laos and Cambodia; *S. intercalatum*—pockets in west and central Africa.

The severity of the symptoms is thus related both to the intensity of infection and to individual immune responses.

### Urinary schistosomiasis

The eggs of *S. haematobium* provoke granulomatous inflammation, ulceration, and pseudopolyposis of the vesical and ureteral walls.<sup>27</sup> Common early signs include dysuria, pollakisuria, proteinuria, and especially haematuria.<sup>28,29</sup> In endemic areas, this sign is the red flag of schistosomiasis in children aged 5–10 years, sometimes confused with menstruation in girls and even a coming of age in boys.<sup>5</sup> Typically, blood is first seen in the terminal urine, but in severe cases the whole urine sample can be dark coloured. Bacterial superinfection and bladder stones can complicate the clinical picture. These early signs become less common after adolescence. However, chronic lesions can evolve to fibrosis or calcification of the bladder and lower ureters, resulting in hydroneurter and hydronephrosis. Chronic compression can eventually lead to parenchymal damage and kidney failure.

In non-treated populations exposed to *S. haematobium*, microhaematuria has been found in 41–100% of infected children, gross haematuria in between none and 97%, and radiologically visible lesions in the upper urinary tract in 2–62%.<sup>29</sup> Kidney function is surprisingly well preserved in many cases. Most lesions, including hydronephrosis, heal well after antischistosomal treatment or even

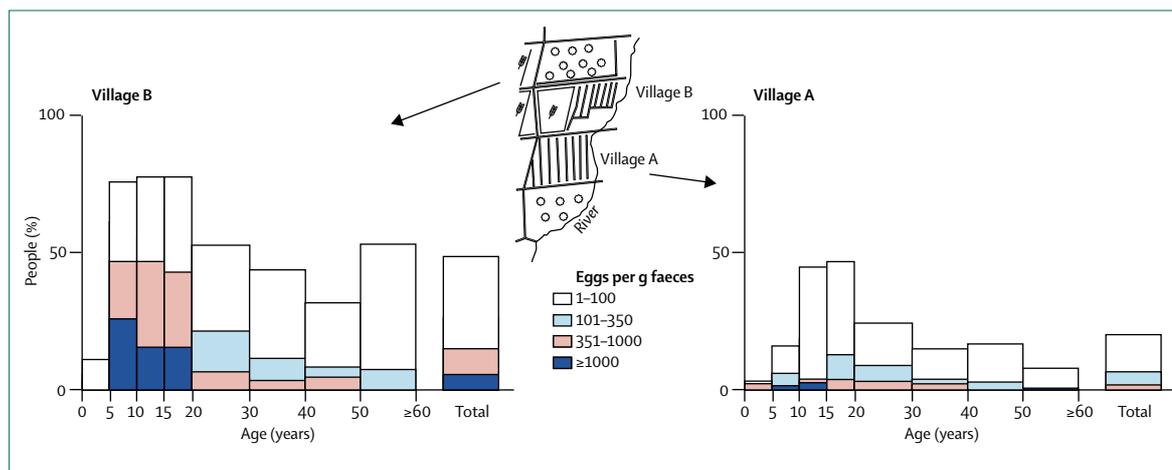
spontaneously, which suggests that the renal parenchyma is compressed but not destroyed in most cases.<sup>29</sup>

Chronic urinary schistosomiasis is epidemiologically associated with squamous bladder cancer in Egypt and other African foci. Nitrosamines,  $\beta$ -glucuronidase, and inflammatory gene damage have been put forward as possible carcinogenic factors.<sup>30</sup> However, an equally likely explanation is that schistosomiasis lesions intensify the exposure of the bladder epithelium to mutagenetic substrates from tobacco or chemicals.<sup>31,32</sup> In Egypt, the incidence of bladder cancer has decreased in line with schistosomiasis prevalence over the past few decades.<sup>33,34</sup>

Published evidence does not allow deduction of epidemiologically valid rates of mortality directly due to urinary schistosomiasis. Autopsy and clinical observations leave no doubt that patients, particularly older people, die of schistosomiasis-induced renal damage.<sup>35–37</sup> Other clinical and epidemiological surveys have not shown specific mortality, however.<sup>29,38–40</sup>

### Intestinal schistosomiasis

Schistosome eggs migrating through the intestinal wall provoke mucosal granulomatous inflammation, pseudopolyposis, microulcerations, and superficial bleeding.<sup>27,41</sup> Most lesions are situated in the large bowel and rectum. The most common symptoms and signs are chronic or intermittent abdominal pain and discomfort,



**Figure 3: Focal distribution and age dependency of schistosome infections**

Derived from Gryseels and Nkulikyinka.<sup>13</sup> Age-related distribution of infection and of heavy infection with *S mansoni* in two hamlets of one village, separated by a dirt road, in the Rusizi Plain, Burundi. In both, rates of infection and of heavy infection rise sharply in young children to a peak in adolescents, decreasing to a plateau in adults. However, both rates are much higher and rise more strikingly in one hamlet than in the other, reflecting the focal character of transmission patterns.

loss of appetite, and diarrhoea with or without blood.<sup>29,42,43</sup> These features are difficult to ascribe unequivocally to schistosomiasis in people with several infections, as is common in endemic areas. Population surveys found that diarrhoea was reported in 3–55% of infected people and bloody diarrhoea in 11–50%, of which 30–60% was attributable to schistosomal infections.<sup>29,44,45</sup> The frequency of the symptoms is related to intensity of infection. Field methods and confounding factors vary substantially, however, and the data cannot be easily compared or pooled.

### Hepatic schistosomiasis

Hepatic schistosomiasis can be caused by *S mansoni*, *S japonicum*, and *S mekongi*. The pathological effects of *S intercalatum* are limited to mild intestinal disease.<sup>46</sup>

The terms hepatic or hepatosplenic schistosomiasis amalgamate early inflammatory and late fibrotic hepatic disease, which are actually two distinct syndromes. The distinction is important not only in clinical practice, but also for morbidity control strategies and the interpretation of immunological mechanisms.<sup>47,48</sup>

Inflammatory hepatic schistosomiasis is an early reaction to ova trapped in the presinusoidal periportal spaces of the liver; it is the main cause of schistosomal hepatomegaly in children and adolescents.<sup>47,49,50</sup> Typical features include sharp-edged enlargement of the left liver lobe and nodular splenomegaly, extending from a few centimetres below the costal arch to below the umbilicus and even into the pelvis.<sup>24,51</sup> Clinical and epidemiological differentiation from malaria can be difficult.<sup>52</sup> Ultrasonography can reveal mild forms of diffuse fibrosis; in many cases, there is no apparent sign of functional disease.<sup>53</sup> This type of hepatomegaly is found in up to 80% of infected children;

it is less common and intense in adults.<sup>43,47</sup> The frequency and intensity are related to faecal egg counts, but they are also subject to methodological variations, immunogenetic predisposition, and other confounding factors.<sup>50</sup>

Fibrotic or chronic hepatic schistosomiasis develops years later in the course of infection, generally in young and middle-aged adults with long-standing intense infections and, presumably, some form of immunogenetic predisposition.<sup>54,55</sup> The disease results from a massive deposition of diffuse collagen deposits in the periportal spaces, leading to pathognomonic periportal or Symmer's pipestem fibrosis.<sup>41</sup> This fibrosis leads in turn to progressive occlusion of the portal veins, portal hypertension, splenomegaly, collateral venous circulation, portocaval shunting, and gastrointestinal varices. The liver is not necessarily enlarged but is generally hard and nodular on palpation. Ultrasonography reveals typical fibrotic streaks and portal-vein dilatation, which are not reversible in most cases. In contrast to cirrhosis, hepatocellular function and indices remain largely unaffected. In *S mansoni* infections, the fibrotic process takes 5–15 years, by which time the infection might no longer be present or detectable.<sup>41,51,54</sup> In *S japonicum*, the progression can be more rapid, in some cases with little or no interval between acute and chronic disease.<sup>24</sup>

Bleeding from gastro-oesophageal varices is the most serious, commonly fatal, complication of fibrotic hepatic schistosomiasis. In *S mansoni* infections, it tends to recur and grow more severe over time; in *S japonicum*, bleeding is sudden and massive in many cases.<sup>24,49</sup> Repeated or occult bleeding can lead to anaemia, hypoalbuminaemia, cachexia, and growth retardation. Ascites can be caused by a combination of hypoalbuminuria and portal hypertension.

Before the advent of modern schistosomicides,



**Figure 4: Schistosomiasis pathology**

A: Acute liver granuloma around *S mansoni* egg in liver of an experimentally infected mouse containing many cells, mainly eosinophils and lymphocytes, and some macrophages; large red cells are intact murine hepatocytes. B: Chronic liver granuloma around the remains of a schistosome egg in a mouse liver, with dominant (blue-coloured) fibrous tissue; courtesy and copyright of Eric Van Marck, University of Antwerp. C: Macrohaematuria due to ulceration of the bladder wall in urinary schistosomiasis. D: Ultrasonography of irregular bladder wall and polyp; courtesy of Wellcome Trust International Image Collection, copyright C Hatz. E: Intravenous pyelography showing bilateral hydronephrosis. F: Severe bloody diarrhoea due to heavy infection with *S mansoni*. G: 6-year-old boy with gross reactive hepatosplenomegaly. H: 19-year-old man with symptoms of chronic fibrotic hepatic schistosomiasis—splenomegaly, external varices, ascites, and growth retardation. I: ultrasonography of advanced periportal fibrosis and portal venodilatation; courtesy of Wellcome Trust International Image Collection, copyright R Davidson.

advanced schistosomal liver fibrosis with oesophageal bleeding was a common clinical syndrome in Egypt, Sudan, Brazil, China, and the Philippines but much less frequent in most of sub-Saharan Africa.<sup>5,6,47,50,56</sup> These regional morbidity patterns have been attributed to ethnic and genetic factors.<sup>57</sup>

In a heavily infected population in Sudan, the annual

mortality due to heavy *S mansoni* infection has been estimated at 0.05%, with a case-fatality rate for oesophageal bleeding of 1.1%.<sup>58</sup> Clinical studies from other areas with high infection rates also found substantial fatality rates among patients with advanced liver fibrosis.<sup>59–61</sup> In most cross-sectional community surveys, however, life-threatening conditions were not detected.<sup>29,50</sup> For *S japonicum*, the best available data show a case-fatality rate of 1.8% among 278 patients followed up for 12 years in the Philippines.<sup>62</sup> High mortality rates have been reported among patients with complicated and even acute schistosomiasis in China, but this evidence is not well documented.<sup>24</sup>

### Ectopic schistosomiasis

Pulmonary schistosomiasis is due to portal-caval shunting, allowing ova to leak into the perialveolar capillary beds. The ensuing granulomas can give rise to bronchial symptoms and later to fibrosis complicated by pulmonary hypertension and cor pulmonale. The symptoms can remain occult for many years.<sup>49</sup> In *S mansoni* infections, portosystemic leaking of immune complexes to the mesangial areas can lead to glomerulonephritis.<sup>63</sup>

Genital schistosomiasis, due to eggs of *S haematobium* and *S mansoni* in the reproductive organs, is quite common but mostly occult in some endemic areas and a regular finding in travellers.<sup>64,65</sup> Symptoms in female patients include hypertrophic and ulcerative lesions of the vulva, vagina, and cervix, which might facilitate sexual transmission of infections. Lesions of the ovaries and the fallopian tubes can lead to infertility. In men, the epididymis, testicles, spermatic chord, and prostate can be affected; haemospermia is a common symptom.

Neuroschistosomiasis is caused by inflammation around ectopic worms or eggs in the cerebral or spinal venous plexus, which can evolve to irreversible fibrotic scars if left untreated.<sup>66,67</sup> Ectopic *S mansoni* and *S haematobium* infections seem to cause mainly spinal pathology with transverse myelitis, which is also a potential complication of acute schistosomiasis in travellers.<sup>68</sup> *S japonicum* is associated with cerebral granulomatous lesions, which can lead to epileptic, paralytic, and meningoencephalitic symptoms.<sup>24,67</sup> Sporadically, ectopic schistosomiasis lesions are found in the skin, the peritoneum, or other organs.

### Indirect pathology and morbidity

As severe disease becomes less common thanks to modern drugs, subtle or indirect morbidity such as fatigue and physical or cognitive impairment has received more attention. Such unspecific and multifactorial morbidity is difficult to measure and to dissociate from other poverty-related health problems. Older studies could not convincingly demonstrate these effects, even in heavily infected people.<sup>29</sup> Recent studies, however, have found small but significant associations between

schistosome infection and anaemia, nutritional status, and cognitive and physiological capacities.<sup>69</sup> The underlying mechanisms could range from social determinants to complex immune interactions.<sup>69,70</sup>

## Diagnosis

The microscopic examination of excreta remains the gold standard for the diagnosis of schistosomiasis.<sup>71</sup> The eggs are easy to detect and identify by microscopy owing to their size and shape, their typical lateral or terminal spine, and the living miracidium (in fresh samples) with mobile cilia and pulsing excretory cells (figure 5). Direct wet slides are not very sensitive; if no eggs are found, concentration methods should be used but even these can miss light infections.<sup>72,73</sup>

Urine should be concentrated by sedimentation, centrifugation, or filtration, and samples should be taken around noon or after physical exercise. To obtain a quantitative assessment of the intensity of infection, a fixed amount (generally 10 mL) of urine is forced over a paper or nitrocellulose filter, which can be examined and eggs counted directly under the microscope. Intensity can then be expressed as eggs per 10 mL.

For the intestinal schistosomes, eggs must be sought in the faeces. Concentration methods, such as sedimentation in a glycerine solution or centrifugation in formolised ether are needed for detection of mild and light infections. In the field, the faecal thick smear or Kato-Katz method is commonly used, because it allows quantification of the infections by egg counts, usually expressed as per g faeces.<sup>71</sup> Rectal snips are very sensitive, even for *S haematobium* infection.<sup>74</sup>

Quantitative egg counts after standardised urine filtration or in calibrated faecal thick smears are especially useful for epidemiological surveys and control, since they correlate well with worm burdens and morbidity.<sup>57</sup> Individual egg counts should not be overinterpreted as a measure of disease, however, because they vary substantially within and between stool and urine samples.<sup>75</sup>

Antibody-based assays are quite sensitive but cannot distinguish history of exposure from active infection; they can also cross-react with other helminths and are

not easily applicable under field conditions.<sup>71,76,77</sup> Such assays are important, however, for diagnosis in travellers, migrants, and other occasionally exposed people.<sup>15</sup> They can also be useful for incidence studies in children and in low-transmission or post-control settings.<sup>78</sup> Most routine techniques detect IgG, IgM, or IgE against soluble worm antigen or crude egg antigen by EIA, indirect haemagglutination, or immunofluorescence. Seroconversion generally happens within 4–8 weeks of infection, but the interval can be as long as 22 weeks.<sup>79</sup> Most assays have positive results for at least 2 years after cure and in many cases much longer.<sup>80</sup>

Somatic schistosome antigens, such as circulating anodic antigen and circulating cathodic antigen, can be detected and quantified with labelled monoclonal antibodies in serum or urine of infected individuals.<sup>81</sup> Antigen detection in serum is not very sensitive in light infections and therefore less useful for clinical applications.<sup>82</sup> However, as a specific, direct, and stable measure of worm burdens, it is a valuable research tool for epidemiological and therapeutic studies.<sup>83</sup> The less specific urine-based antigen detection assays have potential for the development of field-applicable reagent strips.<sup>84</sup>

Reagent strips for microhaematuria and simple questionnaires for red urine are cheap, easy, and effective tools for the screening and rapid epidemiological assessment of urinary schistosomiasis.<sup>85</sup> Such indirect diagnostic methods are less satisfactory for intestinal or hepatic disease.<sup>86,87</sup> Biochemical markers of pathology are still under investigation.<sup>88</sup>

In hospital settings, cystoscopy and endoscopy are used to visualise bladder lesions and oesophageal varices.<sup>49,74,89,90</sup> Laparoscopy and wedge biopsy can reveal the macroscopic and histological appearance of granulomatous inflammation or periportal fibrosis.<sup>91,92</sup>

Radiography allows visualisation of renal, ureteral, and bladder pathology.<sup>93</sup> In hepatic schistosomiasis, contrast radiography can show portal-vein distension or gastro-oesophageal varices. CT, myelography, and MRI can be useful for detailed imaging, especially for neuroschistosomiasis.<sup>66,93,94</sup> Over the past 10 years, portable ultrasonographic equipment has allowed major

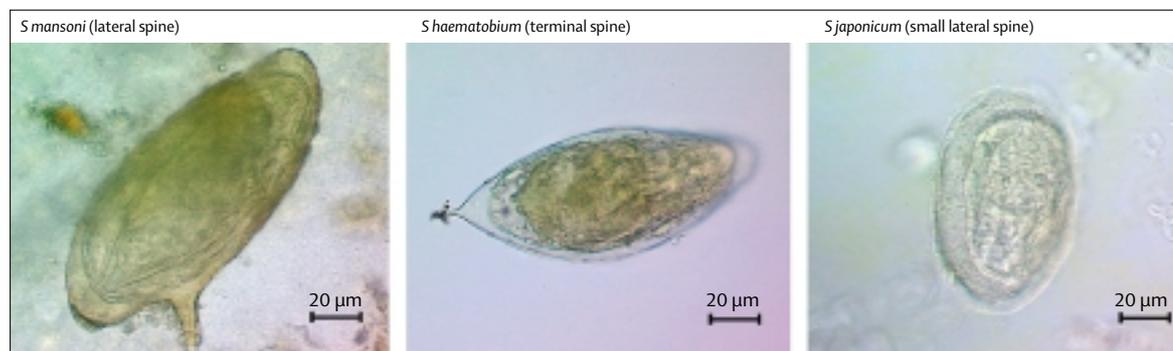


Figure 5: Schistosome eggs

advances in the study of schistosomiasis pathology.<sup>95,96</sup> Standard protocols have been developed to classify hepatic fibrosis and urinary-tract lesions. Their use requires specific expertise and experience, however, and is subject to much variation within and between observers.

### Treatment

Early treatments against schistosomiasis had severe and even lethal side-effects that had to be weighed against the benefits for the patient.<sup>4,5</sup> The 1970s heralded the advent of effective, safe, and simple drugs.<sup>34</sup>

Praziquantel, an acylated quinoline-pyrazine that is active against all schistosome species, is now the most widely used. It is mostly marketed as 600 mg tablets, with a recommended standard regimen of 40 mg/kg bodyweight in a single dose.<sup>6</sup> The drug acts within 1 h of ingestion by paralysing the worms and damaging the tegument. Side-effects are mild and include nausea, vomiting, malaise, and abdominal pain. In heavy infections, acute colic with bloody diarrhoea can occur shortly after treatment, probably provoked by massive worm shifts and antigen release.<sup>97</sup>

Praziquantel has very low toxicity in animals, and no important long-term safety difficulties have been documented in people so far.<sup>98</sup> It is judged safe for treatment of young children and pregnant women.<sup>99</sup>

Praziquantel has little or no effect on eggs and immature worms. Tissue-dwelling eggs can be excreted for several weeks after treatment, and during the same period prepatent or newly acquired infections can become productive. The preferred timing of follow-up is therefore 4–6 weeks after treatment.<sup>100</sup> After a single dose of 40 mg/kg, 70–100% of patients cease to excrete eggs. In most of those not cured, egg counts and antigen concentrations are reduced by more than 95%.<sup>97,101,102</sup> Clinical, radiographic, and sonographic studies have shown the regression over weeks to months of intestinal and vesical lesions, reactive hepatomegaly, and even severe lesions of the upper urinary tract or mild liver fibrosis.<sup>103</sup> This regimen is therefore recommended for most population-based treatment campaigns. In populations with high initial egg counts exposed to rapid reinfection, cure rates can be much lower. In these cases, the dose can be increased to 60 mg/kg, if possible split in two and taken several hours apart to avoid side-effects. 60 mg/kg or more in split doses is also advisable for individual case management or in people who have left the endemic area, to ensure complete cure.<sup>101</sup> A repeat dose 6–12 weeks later can be useful to cure prepatent infections, particularly if eosinophilia, high antibody titres, or symptoms persist.

Katayama fever is primarily treated with corticosteroids to suppress the hypersensitivity reaction and with praziquantel to eliminate the already matured worms.<sup>15,18</sup> Since immature worms are not susceptible to praziquantel, treatment should be repeated 4–6 weeks after the first

symptoms. In oesophageal bleeding,  $\beta$  blockers, endoscopic sclerotherapy, splenectomy, or a portocaval shunt might be indicated.<sup>4,49</sup> In advanced urinary schistosomiasis, damaged and non-functional kidneys might have to be removed.

Corticosteroids and anticonvulsants are needed as possible adjuvants to praziquantel in neuroschistosomiasis, which needs specialised care.<sup>67</sup> Praziquantel should be administered with great caution in the case of concurrent neurocysticercosis.<sup>104</sup>

Oxamniquine acts only on *S mansoni* and is nowadays mainly used in Brazil.<sup>4,34</sup> It is as effective as praziquantel but can provoke more pronounced side-effects, most notably drowsiness, sleep induction, and epileptic seizures.

Artemisinin derivatives are effective against the immature stages of *S japonicum*, *S mansoni*, and possibly *S haematobium*.<sup>105</sup> Their use in cure or prophylaxis for acute schistosomiasis, possibly in combination with praziquantel, is being investigated.<sup>106</sup> Widespread use in malaria-endemic areas is not recommended, because it might promote artemisinin resistance in malaria parasites.

A derivative of myrrh (an oleo-resin extract of *Commiphora molmol*; Mirazid; Pharco Pharmaceuticals, Alexandria, Egypt) was heralded as a potent new schistosomicide but appears to be completely ineffective.<sup>107</sup>

Schistosomes can become resistant to hycanthone and oxamniquine, in animals as well as in the field. Resistance to these drugs has never spread beyond local foci, however.<sup>108</sup> Under drug pressure, praziquantel-tolerant schistosome strains can be quite easily selected in animals.<sup>109</sup> In the field, very low cure rates have been observed in northern Senegal, but they could be explained by very intense transmission, reinfection, maturing prepatent infections, and possibly the epidemic nature of the focus.<sup>110</sup> In Egypt, tolerant strains have been isolated from people who did not respond well to treatment, but these observations need to be confirmed.<sup>111</sup> The catastrophic experience in cattle, with widespread resistance to anthelmintics due to systematic mass treatment, shows that caution is needed.<sup>112</sup>

### Immunology

There is longstanding epidemiological and clinical evidence that people living in endemic areas acquire some form of immune resistance after years of exposure.<sup>113</sup> In terms of parasite population dynamics, host-related factors such as innate or acquired immunity are likely to have an important role in truncating the enormous reproduction potential of schistosomes to the endemic equilibrium of one.<sup>114</sup> The acquisition of effective immunity is difficult to prove, because the decrease in infection rates after adolescence can also be explained by reduced water contact.

Immunological advances, new epidemiological approaches, and mathematical modelling corroborate

the existence of acquired immunity, however.<sup>9,113,115</sup> Comparative studies of reinfection after curative treatment have shown that children are far more susceptible than adults and that these differences cannot be explained by differing water-contact patterns. Observations in people and in animals suggest that acquired immunity is mediated by IgE against antigens of larvae and adult worms, which trigger eosinophils to release cytotoxins targeting schistosomulae.<sup>113</sup> The slow development of acquired immunity is thought to be due to blockage of the IgE receptors by excess antischistosome IgG<sub>4</sub> and possibly other immunoglobulin isotypes in the first years of infection. Some researchers suggest a role of schistosome-specific IgA, such as anti-Sm28GST, in mediating protective immunity in people, or of the slow release of somatic antigens of dying worms.<sup>115,116</sup> The latter hypothesis has been invoked to explain increased immunity after treatment, but other studies did not confirm these observations.<sup>117,118</sup>

In populations with only recent exposure to transmission, age-related infection patterns are surprisingly similar to those in long-standing endemic conditions. Since slowly acquired immunity cannot be invoked in such circumstances, some form of age-related innate resistance could also play an important part in the epidemiology of schistosomiasis.<sup>119–121</sup>

Most schistosomiasis-related pathology is induced by cellular immune responses. The granulomatous reactions around the eggs are orchestrated by CD4-positive T cells and involve eosinophils, monocytes, and lymphocytes.<sup>26</sup> In mice, a predominantly T-helper-1 reaction in the early stages of infection shifts to an egg-induced T-helper-2-biased profile, and imbalances between these responses lead to severe lesions.<sup>122</sup> Although these observations cannot readily be extrapolated, similar mechanisms could be at the basis of fibrotic pathology in human beings.<sup>48</sup>

Much effort has been devoted to the development of vaccines against schistosomiasis. Several antigens are judged to be potential vaccine candidates and have been tested in animals with varying results.<sup>123,124</sup> The recombinant rShGST-28 (Billvax; Eurogentec, Herstal, Belgium) has already undergone phase I and II clinical trials.<sup>116</sup> Questions remain about the feasibility, applicability, and relevance of schistosomiasis vaccines, however.<sup>124,125</sup>

The possible interaction between schistosomiasis and HIV/AIDS is receiving increasing attention, given the role of immune responses in both diseases and the geographic overlap in distribution in Africa.<sup>70</sup> Low CD4-positive T-cell counts resulting from HIV infection might increase susceptibility to schistosome infection and influence egg excretion.<sup>126</sup> HIV infection would not affect the efficacy of praziquantel, susceptibility to reinfection, the development of fibrosis, or the diagnosis and surveillance of schistosomiasis.<sup>126–129</sup> Conversely, schistosomiasis does not interfere with HIV screening or viral-load testing and should not exacerbate the course of HIV infection, but it might contribute to immune reconstitution syndromes

after antiretroviral treatment.<sup>130</sup> Schistosomiasis treatment can result in lower viral loads and higher CD4-cell counts.<sup>131,132</sup> The clinical and epidemiological significance of all these observations is still unclear.

### Global burden

Schistosomiasis is highly prevalent, but the associated morbidity is low and variable. Thus, its influence on public health and the priority of control measures have long been debated. The discussion has been revived in light of the renewed resources for the fight against poverty-related diseases and the Global Burden of Disease Study, which attempted to quantify and rank health problems according to disability-adjusted life years (DALY).<sup>133</sup> This index is calculated from disease-specific prevalence, mortality, and disability weights. The Global Burden of Disease Study currently attributes a disability weight of 0·06 and an annual mortality of 14000 deaths per year to schistosomiasis. Based on the generally accepted number of 200 million infected people worldwide, the total number of DALY lost to schistosomiasis is estimated at 1·532 million per year, of which 77% are in sub-Saharan Africa. Schistosomiasis would therefore account for 0·1% of the total world global burden of disease and 0·4% of that in sub-Saharan Africa, which is of the same order as leishmaniasis and trypanosomiasis. New meta-analyses of existing data have resulted in proposals to increase the schistosomiasis disability weight by a factor of between three and 30, and the mortality estimate up to 280000 deaths annually in sub-Saharan Africa alone.<sup>69,134</sup>

Both the Global Burden of Disease Study and the revisions are, however, limited by the lack of representative data and of clear case definitions. Where they have been adequately measured, true national prevalences are three to ten times lower than the WHO estimates that extrapolated local surveys without accounting for geographic heterogeneity.<sup>135–140</sup> By contrast, with standard survey methods true prevalence can be underestimated by 50% or more.<sup>72</sup> The proposed revision of the mortality rates relies on similar overestimates and would add an unexplained 10% to overall mortality in male adults in sub-Saharan Africa.<sup>134</sup> The proposed revision of the disability weight is based on a thorough meta-analysis of published morbidity data; however, owing to the differing methods and confounding factors, these cannot readily be pooled to extract precise disability weights.<sup>68</sup> New, dedicated field studies would be needed to validate the proposed changes.

### Control

The aims and strategies of schistosomiasis control have shifted fundamentally over the past few decades, since the introduction of modern schistosomicides, particularly praziquantel. As for other parasitic diseases, transmission control aiming at the intermediate host has been largely replaced by morbidity control through population-based chemotherapy. This strategy allows quick gains, but

careful long-term planning is needed to ensure sustainability and progression to the more demanding stages of infection and transmission control.

Snail control with molluscicides, toxic chemicals, is expensive and logistically complex. Substantial human and material resources are needed for efficient application, as well as detailed epidemiological and malacological surveillance. Snail populations can be greatly reduced but rarely eliminated, so regular and long-term retreatment is necessary. The toxicity of molluscicides for other aquatic organisms, including fish, gives rise to ecological and economic concerns. Large-scale chemical snail control is still used in Egypt and China, but owing to the success of population-based chemotherapy, its cost-effectiveness is increasingly being questioned.<sup>141</sup> Snail control can also be pursued by physical measures or biological competitors, but such methods are not easy to put into practice.<sup>142,143</sup>

Schistosomiasis can in principle be eliminated by behavioural changes, sanitation, and safe water supply, as has been shown in Japan.<sup>144</sup> Educational programmes can improve knowledge about the disease and health-care seeking, but behaviour can be difficult to change without other options for water contact.<sup>145,146</sup> The provision of safe water supplies and latrines is obviously useful, but for the prevention of schistosomiasis, safe contact sites are also needed.<sup>147,148</sup> In the case of *S japonicum*, transmission control necessitates interventions on the large and diverse animal reservoir.<sup>25</sup>

On the recommendation of WHO, population-based treatment with praziquantel is now the main component of most national control programmes.<sup>6</sup> The fundamental aim is to reduce morbidity by keeping down intensity of infection. Various strategies can be applied, including indiscriminate mass treatment, active case finding, and treatment of particular risk groups such as school-aged children. 20 years of experience have shown that population-based treatment is feasible, safe, and effective.<sup>6,149</sup> In the absence of ecological or behavioural changes, however, it has little durable effect on transmission; regular retreatment is therefore needed for an unknown period.<sup>6,114</sup> Sustainability is therefore a key requirement for chemotherapy-based control.

Wide-scale chemotherapy has greatly reduced the public-health impact of schistosomiasis in middle-income countries such as Egypt, China, Brazil, the Philippines, Puerto Rico, Tunisia, Morocco, and Saudi Arabia.<sup>6</sup> Key factors to success were national commitment and investments, in several cases through loans from the World Bank, implementation through regular health services, and concurrent socioeconomic development. The challenge for these countries is now to move towards control and possibly elimination of infection and transmission. The main technical difficulty lies in identification of remaining cases and pockets through an integrated surveillance and response system. The progressive elimination of transmission sources requires intensive intersectoral collaboration, and political

commitment might wane as morbidity decreases. Also the liberalisation of health care could be a threat to control programmes for schistosomiasis and other diseases. In China, market reforms might already have led to the re-emergence of schistosomiasis in some areas.<sup>150</sup>

Low-income countries, especially those in sub-Saharan Africa, have had greater difficulties in implementing and sustaining chemotherapy-based control strategies. Early pilot projects in Mali, Congo, Madagascar, and Malawi showed promising results in the short term but floundered when foreign assistance ended.<sup>6,47,135</sup> Other programmes were built up more gradually, by improving passive or active case finding through regular health-care structures. Although less spectacularly successful in the short term, they appeared to be sustainable with limited national resources.<sup>151-153</sup>

Renewed efforts are now being made to extend chemotherapy-based control of schistosomiasis to sub-Saharan Africa and to integrate these efforts with systematic anthelmintic treatment in school-aged children.<sup>154</sup> The main vehicles are the Schistosomiasis Control Initiative and the Partners for Parasite Control Consortium, public-private partnerships supported by the Bill and Melinda Gates foundation, drug-donating companies, WHO, and academic institutes. Following a resolution by the World Health Assembly, they have set a joint global target to provide annual preventive treatment to at least 75% of all school-aged children at risk of morbidity from schistosomiasis or soil-transmitted helminths by the year 2010.<sup>155</sup> The programme is by now active in Burkina Faso, Mali, Niger, Tanzania, Uganda, and Zambia. Proposals are being developed for a further integration with drug-delivery programmes for lymphatic filariasis, onchocerciasis, and nutritional deficiencies in a single package and to link these programmes with those against AIDS, malaria, and tuberculosis.<sup>156,157</sup> Another integration challenge lies, however, with the health workers in the field, who must cope with a wide variety of vertical programmes in their daily routine. For many, provision of accessible care for people with symptoms will be the first step in a strategy of morbidity control.

### The way forward

In theory, doctors and other health workers have adequate tools at hand for diagnosis and treatment of most overt cases of schistosomiasis in outpatient or primary care. However, detection of light infections and assessment of their clinical importance remains more difficult. Resistance to praziquantel should be avoided at all costs, and new drugs would be welcome. Improved diagnostic agents and therapeutic strategies are therefore main topics for further applied research on schistosomiasis. A truly evidence-based consensus should be built on how to assess and use the available data on disease burden not just at the global level, but also at national and local levels.

Scientists and funding agencies should also pursue

more vigorously hypothesis-driven research on the biology, epidemiology, and immunology of schistosomiasis. The relation between human beings and schistosomes remains one of the most baffling tricks of nature; its elucidation could teach us much about both species.

Enormous progress has been made in the control of schistosomiasis in many countries. Extension of these successes to countries with fewer resources, in particular sub-Saharan Africa, is imperative, but the lessons of the past should not be forgotten. The fight against schistosomiasis is not just a matter of distributing drugs; establishment of strong health systems that are able to take care of patients and to integrate sustainable control measures is a far greater and more important challenge. A definitive solution to the schistosomiasis problem, finally, can be achieved only by eliminating its main underlying cause—poverty.

#### Contributors

Bruno Gryseels wrote the initial drafts and the final paper. Katja Polman contributed to the sections on biology and epidemiology, diagnosis, and treatment and control. Jan Clerinx contributed to the section on pathology. Luc Kestens contributed to the section on immunology. All authors contributed to overall revisions and final editing.

#### Conflict of interest

We declare that we have no conflict of interest.

#### Acknowledgments

We dedicate this Seminar to Dr Peter (Pip) Jordan, who died on May 30, 2006. He was a great schistosomiasis expert, who made fundamental contributions to the successful control of this disease in large parts of the world. We thank Kristien Wyants for secretarial assistance, Veerle Demedts and Dirk Schoonbaert for bibliographic support, and Jean-Pierre Wenseleers for the graphic work. The work on this seminar was solely funded by the Institute of Tropical Institute of Antwerp, which had no economic interest.

#### References

- Doumenge JP, Mott KE. Global distribution of schistosomiasis: CEGET/WHO atlas. *World Health Stat Q* 1984; **37**: 186–99.
- Jordan P, Webbe G, Sturrock FS. Human schistosomiasis. Wallingford: CAB International, 1993.
- Brown DS. Freshwater snails of Africa and their medical importance, 2nd edn. London: Taylor and Francis, 1994.
- Olds GR, Dasarathy S. Schistosomiasis. *Curr Treat Options Infect Dis* 2000; **2**: 88–99.
- Jordan P. From Katayama to the Dakhla Oasis: the beginning of epidemiology and control of bilharzia. *Acta Tropica* 2000; **77**: 9–40.
- WHO Expert Committee. Prevention and control of schistosomiasis and soil-transmitted helminthiasis. Technical report series. Geneva: World Health Organisation, 2002.
- Ross AG, Bartley PB, Sleight AC, et al. Schistosomiasis. *N Engl J Med* 2002; **346**: 1212–20.
- Brindley PJ. The molecular biology of schistosomes. *Trends Parasitol* 2005; **21**: 533–36.
- Mountford AP. Immunological aspects of schistosomiasis. *Parasite Immunol* 2005; **27**: 243–46.
- Raghavan N, Knight M. The snail (*Biomphalaria glabrata*) genome project. *Trends Parasitol* 2006; **22**: 148–51.
- Oomen JMV, de Wolf J, Jobin WR. Health and irrigation. ILRI publication 45. Wageningen: ILRI, 1990.
- Mott KE, Desjeux P, Moncayo A, Ranque P, de Raadt P. Parasitic diseases and urban development. *Bull World Health Organ* 1990; **68**: 691–98.
- Gryseels B, Nkulikyinka L. The distribution of *Schistosoma mansoni* in the Rusizi plain (Burundi). *Ann Trop Med Parasitol* 1988; **82**: 581–90.
- Gryseels B, De Vlas SJ. Worm burdens in schistosome infections. *Parasitol Today* 1996; **12**: 115–19.
- Bottieu E, Clerinx J, De Vega MR, et al. Imported Katayama fever: clinical and biological features at presentation and during treatment. *J Infect* 2006; **52**: 339–45.
- Horak P, Kolarova L. Molluscan and vertebrate immune responses to bird schistosomes. *Parasite Immunol* 2005; **27**: 247–55.
- Appleton CC. Schistosome dermatitis: an unrecognized problem in South Africa? *S Afr Med J* 1984; **65**: 467–69.
- Lambertucci JR. Acute schistosomiasis: clinical, diagnostic and therapeutic features. *Rev Inst Med Trop Sao Paulo* 1993; **35**: 399–404.
- Rocha MO, Pedrosa ER, Lambertucci JR, et al. Gastro-intestinal manifestations of the initial phase of schistosomiasis mansoni. *Ann Trop Med Parasitol* 1995; **89**: 271–78.
- Rocha MO, Rocha RL, Pedrosa ER, et al. Pulmonary manifestations in the initial phase of schistosomiasis mansoni. *Rev Inst Med Trop Sao Paulo* 1995; **37**: 311–18.
- King CL, Malhotra I, Mungai P, et al. B cell sensitization to helminthic infection develops in utero in humans. *J Immunol* 1998; **160**: 3578–84.
- Hatz C. Schistosomiasis: an underestimated problem in industrialised countries? *J Travel Med* 2005; **12**: 1–2.
- Jelinek T, Nothdurft HD, Loscher T. Schistosomiasis in travelers and expatriates. *J Travel Med* 1996; **3**: 160–64.
- Chen MG. *Schistosoma japonicum* and *S japonicum*-like infections: epidemiology, clinical and pathological aspects. In: Jordan P, Webbe G, Sturrock FS. Human schistosomiasis. Wallingford: CAB International, 1993: 237–70.
- Ross AG, Sleight AC, Li Y, et al. Schistosomiasis in the People's Republic of China: prospects and challenges for the 21st century. *Clin Microbiol Rev* 2001; **14**: 270–95.
- Cheever AW, Hoffmann KF, Wynn TA. Immunopathology of schistosomiasis mansoni in mice and men. *Immunol Today* 2000; **21**: 465–66.
- Cheever AW, Kamel IA, Elwi AM, Mosimann JE, Danner R, Sippel JE. *Schistosoma mansoni* and *S haematobium* infections in Egypt, III: extrahepatic pathology. *Am J Trop Med Hyg* 1978; **27**: 55–75.
- Chen MG, Mott KE. Progress in assessment of morbidity due to *Schistosoma haematobium* infection: a review of recent literature. *Trop Dis Bull* 1989; **86**: R1–36.
- Gryseels B. The relevance of schistosomiasis for public health. *Trop Med Parasitol* 1989; **40**: 134–42.
- IARC Working Group on the evaluation of carcinogenic risks to humans. Schistosomes, liver flukes and *Helicobacter pylori*. In: IARC Monographs on the evaluation of carcinogenic risks to humans, vol 61. Geneva: World Health Organisation, 1994: 45–119.
- Bedwani R, Renganathan E, El Khwsky F, et al. Schistosomiasis and the risk of bladder cancer in Alexandria, Egypt. *Br J Cancer* 1998; **77**: 1186–89.
- Cheever AW. Schistosomiasis and neoplasia. *J Natl Cancer Inst* 1978; **61**: 13–18.
- Koraitim MM, Metwalli NE, Atta MA, el Sadr AA. Changing age incidence and pathological types of schistosoma-associated bladder carcinoma. *J Urol* 1995; **154**: 1714–16.
- Fenwick A, Savioli L, Engels D, Robert BN, Todd MH. Drugs for the control of parasitic diseases: current status and development in schistosomiasis. *Trends Parasitol* 2003; **19**: 509–15.
- Forsyth DM, Bradley DJ, McMahon J. Death attributed to kidney failure in communities with endemic urinary schistosomiasis. *Lancet* 1970; **2**: 472–73.
- Smith JH, Elwi A, Kamel IA, Von Lichtenberg F. A quantitative post mortem analysis of urinary schistosomiasis in Egypt, II: evolution and epidemiology. *Am J Trop Med Hyg* 1975; **24**: 806–22.
- Elem B, Vandal MT. Bilharziasis of the urinary tract in Zambia: observation on 100 consecutive cases. *Med J Zambia* 1981; **15**: 48–51.
- Lehman JS Jr, Farid Z, Bassily S. Mortality in urinary schistosomiasis. *Lancet* 1970; **2**: 822–23.
- Fine J. Hydronephrosis in a series of 3,400 post-mortem

- examinations in Zambia, with special reference to Bilharharzia. *Med J Zambia* 1975; **9**: 98–101.
- 40 Bradley AK, Gilles HM. Malumfashi Endemic Diseases Research Project, XXI: pointers to causes of death in the Malumfashi area, northern Nigeria. *Ann Trop Med Parasitol* 1984; **78**: 265–71.
  - 41 Cheever AW. A quantitative post-mortem study of *Schistosomiasis mansoni* in man. *Am J Trop Med Hyg* 1968; **17**: 38–64.
  - 42 Chen MG, Mott KE. Progress in assessment of morbidity due to *Schistosoma mansoni* infection: a review of recent literature. *Trop Dis Bull* 1988; **85**: R1–56.
  - 43 Chen MG, Mott KE. Progress in assessment of morbidity due to *Schistosoma japonicum* infection: a review of recent literature. *Trop Dis Bull* 1988; **85**: R1–45.
  - 44 Guyatt H, Gryseels B, Smith T, Tanner M. Assessing the public health importance of *Schistosoma mansoni* in different endemic areas: attributable fraction estimates as an approach. *Am J Trop Med Hyg* 1995; **53**: 660–67.
  - 45 Booth M, Guyatt HL, Li Y, Tanner M. The morbidity attributable to *Schistosoma japonicum* infection in 3 villages in Dongting Lake region, Hunan province, PR China. *Trop Med Int Health* 1996; **1**: 646–54.
  - 46 Chen MG, Mott KE. Progress in assessment of morbidity due to *Schistosoma intercalatum* infection: a review of recent literature. *Trop Dis Bull* 1989; **86**: R1–18.
  - 47 Gryseels B, Polderman AM. Morbidity, due to schistosomiasis mansoni, and its control in Sub-Saharan Africa. *Parasitol Today* 1991; **7**: 244–48.
  - 48 Abath FGC, Morais CNL, Montenegro CEL, Wynn TA, Montenegro SML. Immunopathogenic mechanisms in schistosomiasis: what can be learnt from human studies? *Trends Parasitol* 2006; **22**: 85–91.
  - 49 Lambertucci R L. *Schistosoma mansoni*: pathological and clinical aspects. In: Jordan P, Webbe G, Sturrock FS. Human schistosomiasis. Wallingford: CAB International, 1993: 195–235.
  - 50 Gryseels B. Morbidity due to infection with *Schistosoma mansoni*: an update. *Trop Geogr Med* 1992; **44**: 189–200.
  - 51 Gryseels B, Polderman AM. The morbidity of schistosomiasis mansoni in Maniema (Zaire). *Trans R Soc Trop Med Hyg* 1987; **81**: 202–09.
  - 52 Booth M, Vennervald BJ, Kenty L, et al. Micro-geographical variation in exposure to *Schistosoma mansoni* and malaria, and exacerbation of splenomegaly in Kenyan school-aged children. *BMC Infect Dis* 2004; **4**: 13.
  - 53 Kardorff R, Stelma FF, Vocke AK, et al. Ultrasonography in a Senegalese community recently exposed to *Schistosoma mansoni* infection. *Am J Trop Med Hyg* 1996; **54**: 586–90.
  - 54 Homeida M, Ahmed S, Dafalla A, et al. Morbidity associated with *Schistosoma mansoni* infection as determined by ultrasound: a study in Gezira, Sudan. *Am J Trop Med Hyg* 1988; **39**: 196–201.
  - 55 Dessein AJ, Hillaire D, Elwali NE, et al. Severe hepatic fibrosis in *Schistosoma mansoni* infection is controlled by a major locus that is closely linked to the interferon-gamma receptor gene. *Am J Hum Genet* 1999; **65**: 709–21.
  - 56 Macdonald G, Farooq M. The public health and economic importance of schistosomiasis. In: Ansari N, ed. Epidemiology and control of schistosomiasis (bilharziasis). Basel: Karger, 1973: 337–53.
  - 57 Jordan P, Webbe G. Epidemiology. In: Jordan P, Webbe G, Sturrock FS. Human schistosomiasis. Wallingford: CAB International, 1993: 87–158.
  - 58 Kheir MM, Eltoum IA, Saad AM, Ali MM, Baraka OZ, Homeida MM. Mortality due to schistosomiasis mansoni: a field study in Sudan. *Am J Trop Med Hyg* 1999; **60**: 307–10.
  - 59 Kloetzel K. Mortality in chronic splenomegaly due to schistosomiasis mansoni: follow-up study in a Brazilian population. *Trans R Soc Trop Med Hyg* 1967; **61**: 803–05.
  - 60 Ongom VL, Owor R, Grundy R, Bradley DJ. The epidemiology and consequences of *Schistosoma mansoni* infection in West Nile, Uganda, II: hospital investigation of a sample from the Panyagoro community. *Trans R Soc Trop Med Hyg* 1972; **66**: 852–63.
  - 61 Williams EH, Hayes RJ, Smith PG. Admissions to a rural hospital in the West Nile District of Uganda over a 27 year period. *J Trop Med Hyg* 1986; **89**: 193–211.
  - 62 Blas BL, Cabrera BD, Santos AT Jr, Nosenas JS. An attempt to study the case fatality rate in *Schistosoma japonicum* infection in the Philippines. *Southeast Asian J Trop Med Public Health* 1986; **17**: 67–70.
  - 63 Barsoum R, Harrington JT, Mathew CM, et al. The changing face of schistosomal glomerulopathy. *Kidney Int* 2004; **66**: 2472–84.
  - 64 Feldmeier H, Leutscher P, Poggensee G, Harms G. Male genital schistosomiasis and haemospermia. *Trop Med Int Health* 1999; **4**: 791–93.
  - 65 Poggensee G, Feldmeier H. Female genital schistosomiasis: fact and hypotheses. *Acta Trop* 2001; **79**: 193–210.
  - 66 Naus CW, Chipwete J, Visser LG, Zijlstra EE, Van Lieshout L. The contribution made by schistosoma infection to non-traumatic disorders of the spinal cord in Malawi. *Ann Trop Med Parasitol* 2003; **97**: 711–21.
  - 67 Ferrari TC. Involvement of central nervous system in the schistosomiasis. *Mem Inst Oswaldo Cruz* 2004; **99** (suppl 1): 59–62.
  - 68 Anon. Schistosomiasis in US Peace Corps volunteers-Malawi, 1992. *MMWR Morb Mortal Wkly Rep* 1993; **42**: 565–70.
  - 69 King CH, Dickman K, Tisch DJ. Regauging the cost of chronic helminthic infection: meta-analysis of disability-related outcomes in endemic schistosomiasis. *Lancet* 2005; **365**: 1561–69.
  - 70 Secor WE. Immunology of human schistosomiasis: off the beaten path. *Parasite Immunol* 2005; **27**: 309–16.
  - 71 Feldmeier H, Poggensee G. Diagnostic techniques in schistosomiasis control: a review. *Acta Trop* 1993; **52**: 205–20.
  - 72 De Vlas SJ, Gryseels B. Underestimation of *Schistosoma mansoni* prevalences. *Parasitol Today* 1992; **8**: 274–77.
  - 73 Engels D, Nahimana S, Gryseels B. Comparison of the direct faecal smear and two thick smear techniques for the diagnosis of intestinal parasitic infections. *Trans R Soc Trop Med Hyg* 1996; **90**: 523–25.
  - 74 Feldmeier H. Diagnosis. In: Jordan P, Webbe G, Sturrock FS. Human schistosomiasis. Wallingford: CAB International, 1993: 271–303.
  - 75 De Vlas SJ, Gryseels B, van Oortmarssen GJ, Polderman AM, Habbema JD. A model for variations in single and repeated egg counts in *Schistosoma mansoni* infections. *Parasitology* 1992; **104**: 451–60.
  - 76 Tsang VC, Wilkins PP. Immunodiagnosis of schistosomiasis. *Immunol Invest* 1997; **26**: 175–88.
  - 77 Rabello A. Diagnosing schistosomiasis. *Mem Inst Oswaldo Cruz* 1997; **92**: 669–76.
  - 78 Noya O, de Noya BA, Losada S, et al. Laboratory diagnosis of schistosomiasis in areas of low transmission: a review of a line of research. *Mem Inst Oswaldo Cruz* 2002; **97**: 167–69.
  - 79 Jones ME, Mitchell RG, Leen CL. Long seronegative window in schistosoma infection. *Lancet* 1992; **340**: 1549–50.
  - 80 Rabello AL, Garcia MM, Pinto da Silva RA, Rocha RS, Katz N. Humoral immune responses in patients with acute *Schistosoma mansoni* infection who were followed up for two years after treatment. *Clin Infect Dis* 1997; **24**: 304–08.
  - 81 Deelder AM, Qian ZL, Kremser PG, et al. Quantitative diagnosis of schistosoma infections by measurement of circulating antigens in serum and urine. *Trop Geogr Med* 1994; **46**: 233–38.
  - 82 Van Lieshout L, Polderman AM, Visser LG, Verwey JJ, Deelder AM. Detection of the circulating antigens CAA and CCA in a group of Dutch travellers with acute schistosomiasis. *Trop Med Int Health* 1997; **2**: 551–57.
  - 83 Polman K. Epidemiological application of circulating antigen detection in schistosomiasis [PhD dissertation]. Leiden: University of Leiden, 2000.
  - 84 van Dam GJ, Wichers JH, Ferreira TMF, Ghatai D, van Amerongen A, Deelder AM. Diagnosis of schistosomiasis by reagent strip test for detection of circulating cathodic antigen. *J Clin Microbiol* 2004; **42**: 5458–61.
  - 85 Lengeler C, Utzinger J, Tanner M. Screening for schistosomiasis with questionnaires. *Trends Parasitol* 2002; **18**: 375–77.
  - 86 Lengeler C, Utzinger J, Tanner M. Questionnaires for rapid screening of schistosomiasis in sub-Saharan Africa. *Bull World Health Organ* 2002; **80**: 235–42.
  - 87 Tan HZ, Yang MX, Wu ZG, et al. Rapid screening method for *Schistosoma japonicum* infection using questionnaires in flood area of the People's Republic of China. *Acta Tropica* 2004; **90**: 1–9.

- 88 Vennervald BJ, Kahama AI, Reimert CM. Assessment of morbidity in *Schistosoma haematobium* infection: current methods and future tools. *Acta Tropica* 2000; **77**: 81–89.
- 89 AbdelWahab MF, Esmat G, Farrag A, Elboraey Y, Strickland GT. Ultrasonographic prediction of esophageal varices in schistosomiasis mansoni. *Am J Gastroenterol* 1993; **88**: 560–63.
- 90 Richter J, Correia Dacal AR, Vergetti Siqueira JG, et al. Sonographic prediction of variceal bleeding in patients with liver fibrosis due to *Schistosoma mansoni*. *Trop Med Int Health* 1998; **3**: 728–35.
- 91 Homeida M, Abdel-Gadir AF, Cheever AW, et al. Diagnosis of pathologically confirmed Symmers' periportal fibrosis by ultrasonography: a prospective blinded study. *Am J Trop Med Hyg* 1988; **38**: 86–91.
- 92 Hayashi S, Ohtake H, Koike M. Laparoscopic diagnosis and clinical course of chronic schistosomiasis japonica. *Acta Trop* 2000; **77**: 133–40.
- 93 Palmer PES, Reeder CC. International Registry of Tropical Imaging. Radiology Department, Uniformed Services University USA 2005. <http://tmcr.usuhs.mil> (accessed April 10, 2006).
- 94 Lambertucci JR, Serufo JC, Gerspacher-Lara R, et al. *Schistosoma mansoni*: assessment of morbidity before and after control. *Acta Trop* 2000; **77**: 101–09.
- 95 Hatz CF. The use of ultrasound in schistosomiasis. *Adv Parasitol* 2001; **48**: 225–84.
- 96 Richter J, Hatz C, Haussinger D. Ultrasound in tropical and parasitic diseases. *Lancet* 2003; **362**: 900–02.
- 97 Stelma FF, Talla I, Sow S, et al. Efficacy and side effects of praziquantel in an epidemic focus of *Schistosoma mansoni*. *Am J Trop Med Hyg* 1995; **53**: 167–70.
- 98 Dayan AD. Albendazole, mebendazole and praziquantel: review of non-clinical toxicity and pharmacokinetics. *Acta Trop* 2003; **86**: 141–59.
- 99 WHO. Report of the WHO informal consultation on the use of praziquantel during pregnancy/lactation and albendazole/mebendazole in children under 24 months (WHO/CDS/CPE/PVC/2002.4). Geneva: World Health Organization, 2002.
- 100 Renganathan E, Cioli D. An international initiative on praziquantel use. *Parasitol Today* 1998; **14**: 390–91.
- 101 Davis A. Antischistosomal drugs and clinical practice. In: Jordan P, Webbe G, Sturrock FS. Human schistosomiasis. Wallingford: CAB International, 1993: 367–404.
- 102 Utzinger J, N'Goran EK, N'Dri A, Lengeler C, Tanner M. Efficacy of praziquantel against *Schistosoma mansoni* with particular consideration for intensity of infection. *Trop Med Int Health* 2000; **5**: 771–78.
- 103 Richter J. The impact of chemotherapy on morbidity due to schistosomiasis. *Acta Trop* 2003; **86**: 161–83.
- 104 Fong GC, Cheung RT. Caution with praziquantel in neurocysticercosis. *Stroke* 1997; **28**: 1648–49.
- 105 Xiao SH, Tanner M, N'Goran EK, et al. Recent investigations of artemether, a novel agent for the prevention of schistosomiasis japonica, mansoni and haematobia. *Acta Trop* 2002; **82**: 175–81.
- 106 Utzinger J, Keiser J, Shuhua X, Tanner M, Singer BH. Combination chemotherapy of schistosomiasis in laboratory studies and clinical trials. *Antimicrob Agents Chemother* 2003; **47**: 1487–95.
- 107 Barakat R, ElMorshedy H, Fenwick A. Efficacy of myrrh in the treatment of human *Schistosomiasis mansoni*. *Am J Trop Med Hyg* 2005; **73**: 365–67.
- 108 Cioli D, Pica-Mattoccia L, Archer S. Drug resistance in schistosomes. *Parasitol Today* 1993; **9**: 162–66.
- 109 Fallon PG, Doenhoff MJ. Drug-resistant schistosomiasis: resistance to praziquantel and oxamniquine induced in *Schistosoma mansoni* in mice is drug specific. *Am J Trop Med Hyg* 1994; **51**: 83–88.
- 110 Gryseels B, Mbaye A, De Vlas SJ, et al. Are poor responses to praziquantel for the treatment of *Schistosoma mansoni* infections in Senegal due to resistance? An overview of the evidence. *Trop Med Int Health* 2001; **6**: 864–73.
- 111 Botros S, Sayed H, Amer N, El Ghannam M, Bennett JL, Day TA. Current status of sensitivity to praziquantel in a focus of potential drug resistance in Egypt. *Int J Parasitol* 2005; **35**: 787–91.
- 112 Geerts S, Gryseels B. Drug resistance in human helminths: current situation and lessons from livestock. *Clin Microbiol Rev* 2000; **13**: 207–22.
- 113 Butterworth AE. Immunology of schistosomiasis. In: Jordan P, Webbe G, Sturrock FS. Human schistosomiasis. Wallingford: CAB International, 1993: 331–66.
- 114 Gryseels B. Uncertainties in the epidemiology and control of schistosomiasis. *Am J Trop Med Hyg* 1996; **55** (suppl): 103–08.
- 115 Woolhouse ME, Hagan P. Seeking the ghost of worms past. *Nat Med* 1999; **5**: 1225–27.
- 116 Capron A, Riveau G, Capron M, Trottein F. Schistosomes: the road from host-parasite interactions to vaccines in clinical trials. *Trends Parasitol* 2005; **21**: 143–49.
- 117 Mutapi F, Hagan P, Woolhouse ME, Mdluluza T, Ndhlovu PD. Chemotherapy-induced, age-related changes in antischistosome antibody responses. *Parasite Immunol* 2003; **25**: 87–97.
- 118 van den Biggelaar AH, Borrmann S, Kremsner P, Yazdanbakhsh M. Immune responses induced by repeated treatment do not result in protective immunity to *Schistosoma haematobium*: interleukin (IL)-5 and IL-10 responses. *J Infect Dis* 2002; **186**: 1474–82.
- 119 Gryseels B. Human resistance to schistosoma infections: age or experience? *Parasitol Today* 1994; **10**: 380–84.
- 120 Ouma JH, Fulford AJ, Kariuki HC, et al. The development of schistosomiasis mansoni in an immunologically naive immigrant population in Masongalemi, Kenya. *Parasitology* 1998; **117**: 123–32.
- 121 Kabatereine NB, Vennervald BJ, Ouma JH, et al. Adult resistance to schistosomiasis mansoni: age-dependence of reinfection remains constant in communities with diverse exposure patterns. *Parasitology* 1999; **118**: 101–05.
- 122 Pearce EJ. Priming of the immune response by schistosome eggs. *Parasite Immunol* 2005; **27**: 265–70.
- 123 Bergquist RN, Colley DG. Schistosomiasis vaccine: research to development. *Parasitol Today* 1998; **14**: 99–104.
- 124 Hewitson JP, Hamblin PA, Mountford AP. Immunity induced by the radiation-attenuated schistosome vaccine. *Parasite Immunol* 2005; **27**: 271–80.
- 125 Gryseels B. Schistosomiasis vaccines: a devils' advocate view. *Parasitol Today* 2000; **16**: 46–48.
- 126 Karanja DMS, Colley DG, Nahlen BL, Ouma JH, Secor WE. Studies on schistosomiasis in western Kenya, 1: evidence for immune-facilitated excretion of schistosome eggs from patients with *Schistosoma mansoni* and human immunodeficiency virus coinfections. *Am J Trop Med Hyg* 1997; **56**: 515–21.
- 127 Mwanakasale V, Vounatsou P, Sukwa TY, Ziba M, Ernest A, Tanner M. Interactions between *Schistosoma haematobium* and human immunodeficiency virus type 1: the effects of coinfection on treatment outcomes in rural Zambia. *Am J Trop Med Hyg* 2003; **69**: 420–28.
- 128 Mwinzi PNM, Karanja DMS, Kareko I, et al. Evaluation of hepatic fibrosis in persons co-infected with *Schistosoma mansoni* and human immunodeficiency virus 1. *Am J Trop Med Hyg* 2004; **71**: 783–86.
- 129 Kallestrup P, Zinyama R, Gomo E, et al. Schistosomiasis and HIV-1 infection in rural Zimbabwe: implications of coinfection for excretion of eggs. *J Infect Dis* 2005; **191**: 1311–20.
- 130 Fernando R, Miller R. Immune reconstitution eosinophilia due to schistosomiasis. *Sex Transm Infect* 2002; **78**: 76.
- 131 Elliott AM, Mawa PA, Joseph S, et al. Associations between helminth infection and CD4+ T cell count, viral load and cytokine responses in HIV-1-infected Ugandan adults. *Trans R Soc Trop Med Hyg* 2003; **97**: 103–08.
- 132 Kallestrup P, Zinyama R, Gomo E, et al. Schistosomiasis and HIV-1 infection in rural Zimbabwe: effect of treatment of schistosomiasis on CD4 cell count and plasma HIV-1 RNA load. *J Infect Dis* 2005; **192**: 1956–61.
- 133 Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL. Global burden of disease and risk factors. New York/Washington: Oxford University Press/The World Bank, 2006.
- 134 van der Werf MJ, De Vlas SJ, Brooker S, et al. Quantification of clinical morbidity associated with schistosome infection in sub-Saharan Africa. *Acta Trop* 2003; **86**: 125–39.
- 135 Chitsulo L, Engels D, Montresor A, Savioli L. The global status of schistosomiasis and its control. *Acta Trop* 2000; **77**: 41–51.
- 136 Utroska JA, Chen MG, Dixon H, et al. An estimate of global needs for praziquantel within schistosomiasis control programmes (WHO/SCHISTO/89.102). Geneva: World Health Organization, 1989.
- 137 Brooker S, Rowlands M, Haller L, Savioli L, Bundy DA. Towards an

- atlas of human helminth infection in sub-Saharan Africa: the use of geographical information systems (GIS). *Parasitol Today* 2000; **16**: 303–07.
- 138 Ratard RC, Kouemeni LE, Bessala MM, Ndamkou CN. Estimation of the number of cases of schistosomiasis in a country: the example of Cameroon. *Trans R Soc Trop Med Hyg* 1992; **86**: 274–76.
- 139 Gryseels B. The epidemiology of schistosomiasis in Burundi and its consequences for control. *Trans R Soc Trop Med Hyg* 1991; **85**: 626–33.
- 140 Brinkmann UK, Werler C, Traore M, Korte R. The National Schistosomiasis Control Programme in Mali, objectives, organization, results. *Trop Med Parasitol* 1988; **39**: 157–61.
- 141 Zhang W, Wong CM. Evaluation of the 1992–1999 world bank schistosomiasis control project in China. *Acta Trop* 2003; **85**: 303–13.
- 142 Cowie RH. Can snails ever be effective and safe biocontrol agents? *Int J Pest Manag* 2001; **47**: 23–40.
- 143 Laamrani H, Boelee E. The role of irrigation design and water management parameters in the ecology of transmission and control of schistosomiasis in central Morocco. *Cahiers d'études et de recherches francophones/Agricultures* 2002; **11**: 23–29.
- 144 Minai M, Hosaka Y, Ohta N. Historical view of schistosomiasis japonica in Japan: implementation and evaluation of disease-control strategies in Yamanashi Prefecture. *Paras Int* 2003; **52**: 321–26.
- 145 Sow S, De Vlas SJ, Mbaye A, Polman K, Gryseels B. Low awareness of intestinal schistosomiasis in northern Senegal after 7 years of health education as part of intense control and research activities. *Trop Med Int Health* 2003; **8**: 744–49.
- 146 Engels D, Ndoricimpa J, Gryseels B. Schistosomiasis mansoni in Burundi: progress in its control since 1985. *Bull World Health Organ* 1993; **71**: 207–14.
- 147 Kloetzl K. Some personal views on the control of schistosomiasis mansoni. *Mem Inst Oswaldo Cruz* 1992; **87** (suppl 4): 221–26.
- 148 El Katsha S WS. Gender, behavior, and health; schistosomiasis transmission and control in rural Egypt. Cairo: American University in Cairo Press, 2002.
- 149 Magnussen P. Treatment and re-treatment strategies for schistosomiasis control in different epidemiological settings: a review of 10 years' experiences. *Acta Trop* 2003; **86**: 243–54.
- 150 Bian Y, Sun Q, Zhao Z, Blas E. Market reform: a challenge to public health: the case of schistosomiasis control in China. *Int J Health Plann Manag* 2004; **19** (suppl 1): S79–94.
- 151 Ali MI, Byskov J, Mokgweetsinyana SS, Sibiya J, Mott KE. Integration of control of schistosomiasis due to *S. mansoni* within primary health care in Ngamiland, Botswana. *Trop Med Parasitol* 1989; **40**: 195–200.
- 152 Jarallah JS, al Shammari SA, Khoja TA, al Sheikh M. Role of primary health care in the control of schistosomiasis: the experience in Riyadh, Saudi Arabia. *Trop Geogr Med* 1993; **45**: 297–300.
- 153 Engels D, Sindayigaya B, Gryseels B. Sustainability of schistosomiasis case detection based on primary health care. *Trans R Soc Trop Med Hyg* 1995; **89**: 599.
- 154 Fenwick A. New initiatives against Africa's worms. *Trans R Soc Trop Med Hyg* 2006; **100**: 200–07.
- 155 Fifty-fourth World Health Assembly. Resolution WHA54.19. Schistosomiasis and soil-transmitted helminths. Geneva: World Health Organization, 2001.
- 156 Molyneux DH, Hotez PJ, Fenwick A. "Rapid-impact interventions": how a policy of integrated control for Africa's neglected tropical diseases could benefit the poor. *PLoS Med* 2005; **2**: e336.
- 157 Hotez PJ, Molyneux DH, Fenwick A, Ottesen E, Ehrlich SS, Sachs JD. Incorporating a rapid-impact package for neglected tropical diseases with programs for HIV/AIDS, Tuberculosis, and Malaria. *PLoS Med* 2006; **3**: e102.