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## Human schistosomiasis

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### Abstract

Human schistosomiasis—or bilharzia—is a parasitic disease caused by trematode flukes of the genus *Schistosoma*. By conservative estimates, at least 230 million people worldwide are infected with *Schistosoma* spp. Adult schistosome worms colonise human blood vessels for years, successfully evading the immune system while excreting hundreds to thousands of eggs daily, which must either leave the body in excreta or become trapped in nearby tissues. Trapped eggs induce a distinct immune-mediated granulomatous response that causes local and systemic pathological effects ranging from anaemia, growth stunting, impaired cognition, and decreased physical fitness, to organ-specific effects such as severe hepatosplenism, periportal fibrosis with portal hypertension, and urogenital inflammation and scarring. At present, preventive public health measures in endemic regions consist of treatment once every 1 or 2 years with the isoquinolinone drug, praziquantel, to suppress morbidity. In some locations, elimination of transmission is now the goal; however, more sensitive diagnostics are needed in both the field and clinics, and integrated environmental and health-care management will be needed to ensure elimination.

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DGC organised and edited the drafts. All authors contributed equally to the writing of this Seminar.

Declaration of interests

We declare that we have no competing interests.

For more on the **Schistosomiasis Control Initiative** see <http://www3.imperial.ac.uk/schisto>

For more on the Schistosomiasis Consortium for Operational Research and Evaluation see <http://score.uga.edu>

## Introduction

Schistosomiasis—also known as bilharzia—is an infectious disease that affects more than 230 million people worldwide, according to conservative estimates.<sup>1,2</sup> It is caused by trematode parasites of the genus *Schistosoma*;<sup>3</sup> the adult male and female worms live within the veins of their human host, where they mate and produce fertilised eggs. The eggs are either shed into the environment through faeces or urine, or are retained in host tissues where they induce inflammation and then die. The eggs that reach freshwater will hatch, releasing free-living ciliated miracidia that then infect a suitable snail host. In the snail, the parasite undergoes asexual replication through mother and daughter sporocyst stages, eventually shedding tens of thousands of cercariae (the form infectious for human beings) into the water. The asexual portion of the lifecycle in the snail (figure 1) requires 4–6 weeks before infectious cercariae are released. After cercariae penetrate the skin of the mammalian host, the maturing larvae (schistosomula) need about 5–7 weeks before becoming adults and producing eggs. These intervals (in both the snail and human being) are termed prepatent periods, when the infection is ongoing but release of cercariae (from snails) or eggs (from humans) cannot be detected. Cercariae can remain infective in freshwater for 1–3 days, but deplete their energy reserves greatly over a few hours.<sup>4</sup> Eggs—whether excreted or retained in the body—die within 1–2 weeks after being released by the female worm.

Three main species of schistosomes infect human beings, *Schistosoma haematobium*, *Schistosoma mansoni*, and *Schistosoma japonicum*. *S. haematobium* and *S. mansoni* both occur in Africa and the Middle East, whereas only *S. mansoni* is present in the Americas. *S. japonicum* is localised to Asia, primarily the Philippines and China. Three more locally distributed species also cause human disease: *Schistosoma mekongi*, in the Mekong River basin, and *Schistosoma guineensis* and *Schistosoma intercalatum* in west and central Africa (figure 2). Each species has a specific range of suitable snail hosts, so their distribution is defined by their host snails' habitat range. *S. mansoni* and *S. haematobium* need certain species of aquatic freshwater *Biomphalaria* and *Bulinus* snails, respectively. *S. japonicum* uses amphibious freshwater *Oncomelania* spp snails as its intermediate host.

Schistosomes live an average of 3–10 years, but in some cases as long as 40 years, in their human hosts.<sup>6,7</sup> Adult male and female worms live much of this time *in copula*, the slender female fitted into the gynaecophoric canal of the male, where she produces eggs and he fertilises them (appendix). Adult worms digest erythrocytes and although most of their energy is obtained by glucose metabolism,<sup>8,9</sup> egg production is dependent on fatty acid oxidation<sup>10</sup>—both glucose and fatty acids being derived from the host. They live within either the perivesicular (*S. haematobium*) or mesenteric (*S. mansoni*, *S. japonicum*, and others) venules. Schistosomes have no anus and cannot excrete waste products, so they regurgitate waste into the bloodstream. Some of these expelled products are useful for blood-based and urine-based diagnostic assays. *S. japonicum* and *S. mekongi* are zoonoses that also infect a wide range of mammalian hosts, including dogs, pigs, and cattle, which greatly complicates control and elimination efforts. Although *S. mansoni* can infect rodents and non-human primates, human beings are thought to be its predominant mammalian reservoir. Understanding the schistosome lifecycle (figure 1) and the parasite's movement between intermediate (snail) and definitive (mammalian) hosts is fundamental to the control and

elimination of human schistosomiasis. Environmental changes can either increase<sup>11</sup> or decrease<sup>12</sup> transmission. Changes in snail habitat and predators are crucial determinants of transmission, and prepatent periods can affect the efficacy of treatment regimens.<sup>13</sup> Effective treatment of people (such that their excreta do not contain eggs), the prevention of sewage contamination of freshwater, the elimination of intermediate host snails, and the prevention of human contact with water containing infected snails can help to prevent transmission.

Although still in its infancy, studies of schistosome genomics will prove crucial for identification of candidates for drug targets and prophylactic vaccines.<sup>14</sup> Schistosome populations are very genetically heterogeneous<sup>15,16</sup> and genomic characterisation of human schistosomes can be used to establish epidemiological patterns of transmission, including insights into interspecies hybridisation among some schistosome species. For example, in areas with high transmission of both *S haematobium* and the *S bovis* parasites of cattle, bidirectional introgressive hybridisation occurs, yielding schistosomes of mixed heritage in people and snails.<sup>17</sup> The implications of these findings are unclear for human disease, but these populations of hybrid schistosomes could prove problematic if they can replace existing species and parasite strains or extend intermediate host ranges.

## Epidemiology

In regions endemic for schistosomiasis the most prevalent form of the disease is chronic schistosomiasis, resulting from repeated exposure to infectious cercariae. In such settings, a child's initial infection often occurs by age 2 years with the burden of infection increasing in intensity during the next 10 years as new worms colonise the child's body. Typically, the highest prevalence and intensities of infection occur in young adolescents (figure 3), after which both intensity and prevalence of infection generally decrease in adulthood. However, high prevalence can persist among subpopulations of adults who have frequent contact with water during their daily activities—eg, laundry, bathing, fishing, washing cars. In endemic regions, serosurveys show that almost every long-term resident becomes infected with schistosomes at some point in their life. In regions with typical transmission patterns, 60–80% of school-age children and 20–40% of adults can remain actively infected.

The frequency of schistosome infections among infants and young children is being increasingly recognised.<sup>20</sup> This situation was overlooked, partly, because of an emphasis on school-aged children, the low parasite egg output at this age, and the low sensitivity of standard diagnostics. Early childhood infection undoubtedly has a substantial role in host immunomodulation and the establishment of chronic antischistosome-egg inflammation that contributes to pathological effects in endemic paediatric populations.<sup>21</sup>

## Pathogenesis and morbidity

All evidence suggests that schistosome eggs, and not adult worms, induce the morbidity caused by schistosome infections.<sup>22</sup> Many eggs are not excreted and become permanently lodged in the intestines or liver (for *S mansoni*, *S japonicum*, and *S mekongi*) or in the bladder and urogenital system (for *S haematobium*). There, the eggs induce a granulomatous host immune response largely characterised by lymphocytes (which mainly produce T-

helper-2 cytokines; eg, interleukins 4, 5, and 13), eosinophils, and, alternatively, activated macrophages (figure 4).<sup>23,24</sup> These granulomas contain egg proteolytic enzymes to prevent tissue necrosis, but the process of granuloma formation induces chronic inflammation that leads to the disease manifestations of schistosomiasis.<sup>25</sup>

Acute schistosomiasis occurs most often in travellers or immigrants to schistosome-endemic regions who are exposed to schistosome antigens for the first time at an older age than usual. It occurs weeks to months after infection, as a consequence of worm maturation, egg production, release of egg antigen, and the host's florid granulomatous and immune complex responses. Acute schistosomiasis is sometimes referred to as Katayama syndrome and the typical clinical presentation is a sudden onset of fever, malaise, myalgia, headache, eosinophilia, fatigue, and abdominal pain lasting 2–10 weeks. This aspect of schistosomiasis has been reviewed in detail.<sup>26</sup> The limited presentation of this syndrome in residents of endemic regions is probably a result of in-utero priming of T-lymphocyte and B-lymphocyte responses of babies born to mothers with helminthic infections.<sup>27,28</sup>

Over time, the granulomatous response to eggs is downregulated through several mechanisms in most individuals, leading to progression to the chronic intestinal form of the disease for *S mansoni*, *S japonicum*, and *S mekongi*. This form of the disease presents as non-specific intermittent abdominal pain, diarrhoea, and rectal bleeding, with the frequency of symptoms often related to the intensity of infection.<sup>29</sup> Such gastrointestinal features are often focal with isolated mucosal hyperplasia, pseudopolyposis, and polyposis interspersed with normal bowel (appendix).<sup>30</sup> Some people with intestinal schistosomiasis only poorly immunoregulate their response to parasite egg antigens<sup>31</sup> and consequently develop extensive fibrosis and subsequent hepatosplenic disease with periportal fibrosis.<sup>32</sup> Patients with periportal fibrosis—also called Symmer's pipe-stem fibrosis—retain hepatocellular function,<sup>33</sup> differentiating the disease from cirrhosis and other liver diseases. Clinical features include upper abdominal discomfort with palpable nodular and hard hepatomegaly, often with splenomegaly. Ascites and haematemesis from oesophageal varices as a complication of portal hypertension can rapidly lead to death.<sup>34</sup> Substantial pulmonary hypertension caused by granulomatous pulmonary arteritis can also occur in patients with advanced hepatic fibrosis disease.<sup>35</sup> The time from initial infection to advanced fibrosis is usually 5–15 years.<sup>36</sup> However, periportal fibrosis can occur in children as young as 6 years,<sup>37</sup> showing the need for screening and treatment of preschool children.<sup>20</sup>

By contrast, the defining symptom for urogenital schistosomiasis (*S haematobium*) is haematuria, often presenting with urinary frequency, burning micturition, and suprapubic discomfort. In endemic regions, haematuria is so widespread that it is thought a natural sign of puberty for boys, and is confused with menses in girls.<sup>18</sup> As with severe intestinal schistosomiasis, severe urogenital schistosomiasis results from poor immunoregulation of antischistosome-egg responses,<sup>38</sup> leading to chronic fibrosis of the urinary tract presenting as obstructive uropathy (hydronephrosis and hydronephrosis<sup>39</sup>), which—along with resulting bacterial superinfection and renal dysfunction—can have lethal consequences. Squamous-cell carcinoma of the bladder is also strongly associated with *S haematobium* infection.<sup>40</sup> This tumour is often multifocal, and in regions endemic for *S haematobium*, occurs at a younger age than do transitional-cell bladder carcinomas.

Female genital schistosomiasis caused by *S haematobium* strongly affects women's reproductive health.<sup>41</sup> Eggs in the vesical plexus migrate to the genital tract causing inflammatory lesions in the ovaries, fallopian tubes, cervix, vagina, and vulva. Lower genital tract sandy patches are pathognomonic for female genital schistosomiasis and are associated with neovascularisation and friable mucosa that can result in contact bleeding (appendix).<sup>41,42</sup> Female genital schistosomiasis causes pain and has been associated with stress incontinence, infertility, and increased risk of abortion. Unfortunately, treatment might not resolve these advanced forms of genital tract damage and there is growing evidence that such lesions can increase transmission of HIV.<sup>43</sup> For men, urogenital schistosomiasis can present with haematospermia, orchitis, prostatitis, dyspareunia, and oligospermia. These conditions resolve more readily after antischistosomal treatment than do those of female genital schistosomiasis.<sup>44,45</sup> *S mansoni* and *S japonicum* rarely affect the genital tract.<sup>41</sup>

All *Schistosoma* species cause non-specific but disabling systemic morbidities including anaemia, malnutrition, and impaired childhood development,<sup>46</sup> as a result of the effect of continued inflammation on normal growth, iron metabolism, physical fitness, and cognitive function.<sup>47–49</sup> Most anaemia in patients with schistosomiasis is anaemia of inflammation, linked with blood loss (and high parasitic loads), that contributes to total-body iron deficiency.<sup>21,50,51</sup> Anaemia of inflammation is caused by iron trapping within the body mediated by the hepatic hormone hepcidin, the release of which is stimulated by infection-related production of the pro-inflammatory cytokine interleukin 6.<sup>52</sup> As a downstream consequence of chronic anaemia, decreased aerobic capacity negatively affects physical work output in regions endemic for schistosomes.<sup>49,53</sup> Reduced intellectual function scores and acute and chronic undernutrition in children are also significantly associated with schistosomiasis.<sup>47,48,54</sup> Fortunately, these deficits lessen with treatment,<sup>54,55</sup> although the effective window for preventive treatment is probably short.<sup>56,57</sup>

Ectopic deposition of schistosoma eggs can lead to unexpected morbidities. The most common involves migration of parasite or eggs to the CNS, with symptoms of spinal compression or encephalopathy. Cerebral schistosomiasis occurs most commonly during *S japonicum* infections. Clinical presentation includes symptoms of meningoencephalitis with pyrexia, headache, vomiting, blurred vision, and altered sensorium or Jacksonian epilepsy. Spinal cord involvement—more common with acute schistosomiasis—can present as acute transverse myelitis or subacute myeloradiculopathy, and can result in paralysis or lumbar and leg pain, with muscle weakness, sensory loss, and bladder incontinence.<sup>58</sup>

### Comorbidities

Schistosomiasis often occurs alongside other infectious diseases, with a wide range of co-infecting organisms. In addition to its direct morbidities, schistosomiasis can affect immunological and physiological relations between the host and co-infecting pathogens. Thus, better control of schistosomiasis could provide adjunctive benefits in such areas. The most compelling example might be the effect of schistosomiasis on susceptibility to HIV infection. Among women with female genital schistosomiasis, the inflammation, friability, and neovascularisation of the genital epithelial tissue can lead to a compromised physical

barrier to exposure to HIV through sexual activity. In population-based studies, female genital schistosomiasis has been associated with a three to four times increased risk of HIV infection.<sup>43,59,60</sup> This effect is compounded by increased concentrations of CD4-positive cells in semen of men with high intensity *S haematobium* infection.<sup>61</sup> Furthermore, during active schistosomiasis, CD4-positive cells express increased concentrations of HIV coreceptors, providing more targets for HIV infection.<sup>62</sup> HIV-positive people who have delayed treatment for schistosomiasis have a more rapid increase of viral load and CD4 T-cell loss than do those treated early for schistosomiasis.<sup>63</sup> However, a randomised trial detected no significant effect of schistosome or other helminth infection on the length of time before patients with HIV became eligible for antiretroviral therapy.<sup>64</sup> So far no studies have been done of paediatric HIV and schistosomiasis co-infection, in which perinatally acquired HIV infection would normally precede schistosomiasis.

Schistosomiasis could also alter immune responses to co-infecting pathogens, allergens, or vaccines. The immunoregulatory responses during schistosome infection could downregulate T-helper-1-type immune response associated with control of viral or protozoan infections, or interfere with immunisation. In one of the most studied co-infections, schistosomiasis seems to modulate malaria but studies have yielded conflicting results. In some,<sup>65–67</sup> malaria prevalence, anaemia, and pathological effects are higher in children with schistosomiasis than in children without schistosomiasis, whereas antimalarial immune responses are diminished. However, other studies report no, or even a protective effect of schistosome infection on malaria, accompanied by increased immune responses.<sup>68,69</sup> Schistosome and malaria-related antigens can cross-react to a degree,<sup>70</sup> further complicating the situation. The particular schistosome species involved could have an important effect—perhaps *S haematobium* promotes protective responses whereas *S mansoni* increases susceptibility to malaria.<sup>65,69</sup> This difference could be a result of whether malaria sporozoites pass through a liver micro-environment immunologically affected by *S mansoni* egg granulomas.

## Diagnosis

The diagnostic standard for active schistosomiasis is viable eggs in urine (*S haematobium*), faeces (*S japonicum*, *S mansoni*), or tissue biopsies. At present, the presence of infecting schistosomes cannot be ruled out definitively because of the low sensitivity of standard urine and faecal examinations.<sup>71</sup> Microscopic examination of polycarbonate filters for eggs in the urine, urine dipstick assays for heme,<sup>72,73</sup> or the Kato-Katz faecal examination for schistosome eggs<sup>74</sup> are recommended by WHO for mapping and field-based control of schistosomiasis. Molecular techniques to detect schistosome DNA in faecal specimens have greater sensitivity than does microscopy<sup>75</sup> but they still suffer from sampling limitations because of the irregular distribution of eggs in the excreta. DNA detection for serum or urine is also being assessed.<sup>76,77</sup> Serological assays have proven useful clinically<sup>78</sup> for diagnosis by detection of antibodies against schistosomal antigens, especially for symptomatic travellers, but for people in regions endemic for schistosomiasis, serology is unable to discriminate between active infection and past exposure. Detection of circulating schistosomal antigen overcomes this difficulty, and a point-of-contact circulating cathodic antigen assay is commercially available (Rapid Medical Diagnostics, Pretoria, South



Africa). This lateral flow cassette assay works on urine and seems to be more sensitive than the Kato-Katz assay for mapping of *S mansoni*-endemic regions.<sup>79</sup> Its use permits on-site mapping of *S mansoni* without stool collections.

Better diagnostic tests for schistosomiasis are still needed—both in the field and in the clinic—and new technologies are being studied. For example, PET scans<sup>80</sup> have been used experimentally to detect adult parasites in vivo and microfluidics now offer the potential to miniaturise both antibody and parasite antigen detection assays.<sup>81</sup> In addition to the importance of diagnostic improvements for clinical diagnoses, such advances will also be essential for drug development, elimination programmes, and vaccine assessment, in which infection must be accurately monitored over time. For the present, the absence of a true gold standard for quantitative correlations to actual worm burden remains a significant challenge.

An important public health aspect of monitoring control and elimination programmes is detection of schistosome infections in the snail host. Snail xenodiagnosis enables the identification of environmental contamination during control and elimination programmes, whether through the use of so-called sentinel snails<sup>82</sup> or wild caught snails. Fully patent snail infections are detected by inducing cercarial shedding and prepatent infections can be identified by histological examination of snail tissues and by molecular parasitological techniques such as PCR<sup>83</sup> or loop-mediated isothermal amplification assays.<sup>84</sup> Comparisons of molecular assays and shedding assays show that most schistosome-infected snails do not progress to patency.<sup>85</sup>

## Treatment

Praziquantel is the drug of choice for schistosomiasis. It is effective against all *Schistosoma* species, but its mechanism of action is not clearly understood. For full efficacy it needs an effective host antibody response.<sup>86,87</sup> Praziquantel acts against adult schistosome worms, but has poor activity against immature schistosome larvae. A standard dose of 40 mg/kg is thought effective for treatment of *S haematobium* and *S mansoni* and can safely be used in pregnancy after the first trimester. For *S japonicum* and *S mekongi*, the recommended dose is 60 mg/kg. A dose pole is used in the field to determine the number of tablets to use.<sup>88</sup> For preschool children (generally, younger than age 5 years), a new dose pole extends below 94 cm.<sup>89</sup> However, cure rates among preschool children are low,<sup>90</sup> perhaps because of incorrect extrapolation of adult dosing. Praziquantel tablets are large and taste bitter; and no readily available paediatric formulation exists.<sup>91</sup> Therefore, treatment of young children involves crushing tablets in carriers such as orange juice. Common side-effects of praziquantel include abdominal pain, headache, dizziness, and transient passage of blood in stool. High-burden infections correlate with high risk of side-effects, which peak about 2–4 h after drug intake and are self-limited.

Artemisinin derivatives (such as artemether and artesunate) were developed as antimalarial drugs but also kill immature larval forms of developing schistosomes.<sup>92</sup> However, because the time of cercarial exposure is normally unknown, the drug's use is limited, except after common point-source exposures. In areas of continuous transmission, artemisinin derivatives could be used in conjunction with praziquantel to improve overall cure rates and infection control. Meta-analysis has shown two-times higher cure rates after treatment with a

combination of praziquantel and artemisinin compared with praziquantel monotherapy.<sup>93</sup> However, research of dosing, formulation, and drug interactions is needed before combination treatments will become standard. Also, the potential for induction of artemisinin-resistant malaria parasites should be considered before standard use of such combinations in regions endemic for malaria.

Oxamniquine—a tetrahydroquinolone compound—is effective against only *S mansoni* and is no longer readily available.<sup>94</sup> As with praziquantel, it has few side-effects, although some reports of heightened seizure activity in patients with underlying epilepsy have been noted.<sup>95</sup>

Even after extensive use in many endemic countries, no clear evidence of praziquantel resistance exists. However, such resistance can be induced experimentally,<sup>96</sup> thus the threat of emerging resistance caused by mass monotherapy remains. Because its mechanism of action is unknown, no test for praziquantel resistance exists except clinical failure. Although praziquantel-tolerant schistosomes have been reported,<sup>96,97</sup> such strains have not become established in field settings. Determination of clinical resistance is confounded by praziquantel's inactivity on immature worms—eg, in areas of constant reinfection, praziquantel might effectively kill adult worms but immature worms would then develop and present as adults, implying drug failure.<sup>97</sup> In such settings, repeated praziquantel treatment 3–6 weeks apart kills initially resistant juvenile worms and improves drug treatment.<sup>98</sup>

## Immunology

Immune responses during schistosomiasis can be thought of in terms of three topics: immunopathogenesis, resistance to reinfection, and immunodiagnosics. All three are affected by the development and establishment of chronic infection in the presence of chronic antigenic exposure. Faced with multiple antibody and cellular immune responses, adult schistosome worms persist in the bloodstream for decades, seemingly impervious to attack from immune effector mechanisms. This immune evasion by adult schistosomes is a result of several mechanisms<sup>99</sup> and leads to a stalemate: the worms thrive and the host survives. Indeed, morbidity seems to be associated with immunopathology against only eggs that remain trapped in tissues. That immune responses are essential for effective treatment<sup>86,87,100</sup> and that many anti-worm and anti-egg antibody responses are detected by serodiagnostic assays shows that adult worm antigens are readily detected by the host immune system, although intact worms effectively evade immune attack.

The immunopathology and immunoregulation associated with morbidity of schistosomiasis has been studied extensively. However, the immune mechanisms related to resistance, to reinfection, or in response to candidate vaccines are much less defined. Although adult worms are refractory to immune attack, immature, developing worms (skin-stage and lung-stage schistosomulae) are the probable targets of protective immunity.<sup>101</sup> Whether a protective resistance to reinfection exists is subject to ongoing debate,<sup>102</sup> but several lines of evidence suggest that such resistance does develop, albeit slowly.<sup>103–105</sup> The feasibility of inducing protective immunity has been shown through immunisation of various experimental hosts with irradiated cercariae.<sup>106,107</sup> Data from endemic populations



(appendix) suggest that age-associated decreases in infection result from development of antiparasite immunity, rather than reduced contact with water.<sup>108</sup>

Although the responsible antigens and host immune responses are not fully defined, resistance to reinfection is consistently associated with IgE antibodies against worm antigens,<sup>103</sup> low concentrations of IgG4 antibodies to worm antigens, and high blood eosinophilia.<sup>104</sup> Resistance to reinfection is partial, which means that sterile immunity either does not develop or is rare. Studies of resistance to reinfection in human beings suggest that worm death, whether natural or after treatment, leads to release of immunogens that stimulate these protective responses, which then react with antigens expressed by susceptible incoming, migrating schistosomulae.<sup>103</sup> Treatment of schistosomiasis increases common correlates of resistance: eosinophilia, parasite-specific IgE, and interleukin 5 production in response to worm antigens<sup>109–111</sup> and repeated treatment and retreatment of reinfections can lead to longer intervals before reinfection, even accounting for similar exposure patterns in highly exposed patients.<sup>105</sup> Nevertheless, despite substantial effort and successful vaccination of experimental and reservoir hosts,<sup>112</sup> no clinical trials for a human vaccine to schistosomiasis have been successful.

### Burden of disease

Official estimates<sup>113</sup> of the prevalence of *Schistosoma* infection were based on insensitive egg-detection techniques, which substantially under-represent active infection.<sup>114–116</sup> Schistosomiasis initiated by infection in early life persists into adulthood, even after infection terminates.<sup>117</sup> Thus, although more than 230 million people are thought to be actively infected with schistosomes,<sup>1</sup> a similar number are in a post-infection stage but continue to have residual morbidity. As a result, the number of people with schistosomiasis (ie, infection-related disease) could be closer to 440 million.

Classic descriptions of schistosomiasis-related morbidity focus on the pathologies unique to schistosome infection: periportal fibrosis for intestinal schistosomiasis and bladder deformity and hydronephrosis for urogenital schistosomiasis. In fact, these morbidities are much less common (5–10% of cases) than the less obvious, but disabling complications of anaemia, growth stunting, cognitive impairment, and decreased aerobic capacity (figure 5). These morbidities are systemic, associated with continuous inflammation during the first decades of life as a child has multiple, recurrent schistosome infections.<sup>56,117–120</sup> These disabling complications are particularly relevant in low-income countries, where they contribute to impaired physical performance and limited educational attainment—disabilities that become irreversible if infection cannot be prevented or suppressed throughout childhood. Schistosomiasis does not occur in isolation. It is a disease of poverty that often occurs where other parasites are prevalent and food insecurity is common. Thus, fully determining the global attributable fraction of schistosomiasis toward these morbidities is difficult. However, schistosomiasis alone is clearly a sufficient cause of these morbidities in many endemic locations.<sup>121</sup>

## Mapping and surveillance

Implementation of population-based control programmes by WHO guidelines requires prevalence estimates, to decide where to use school-based versus community-based delivery of praziquantel. A crucial consideration for the effective integration of preventive chemotherapy for neglected tropical diseases is whether schistosoma infection overlaps with filariasis, onchocerciasis, intestinal worm infections, and trachoma,<sup>122</sup> which are all targeted for control through preventive chemotherapy. Climate measures and digital topography linked with data from past population-based surveys can broadly predict where schistosome transmission is possible. But schistosome prevalence can be focal, resolving into a patchwork mosaic of high-prevalence, medium-prevalence, and low-prevalence villages across a permissive landscape.<sup>123,124</sup> Therefore, random cluster sampling across district-level administrative units can substantially overestimate or underestimate infection risk in individual communities and schools.<sup>125–127</sup> Randomised subsampling could be improved by testing paired locations at various distances apart to estimate the controlling distance factor for autocorrelation of infection prevalence within a given region.<sup>128</sup> However, because prevalence can vary significantly over 2–5 km, it might be best to briefly survey all intended treatment locations (implementation units) with rapid sampling techniques (limited to 15–50 people per site). For initial allocation of *S haematobium* treatment, the WHO's Red Urine Group consortium showed that a prevalence of visible (gross) haematuria of 10% or greater effectively identifies high-prevalence communities.<sup>129</sup> However, for *S mansoni* infection, symptom scores or occult blood testing—although indicative of severe disease<sup>130,131</sup>—are not sufficient to map levels of infection for preventive chemotherapy. Instead, Lot-Quality Assurance or Multiple Category Lot-Quality Assurance approaches are used for limited testing of a single stool to classify communities as having high or low prevalence.<sup>132</sup> Point-of-care urine assays might supplant stool testing for this crucial mapping and decision process.<sup>79</sup> A shortcoming of rapid testing strategies is that test sensitivity will probably fall as programmes succeed and prevalence and intensity falls. More sensitive testing of more residents will be needed to define regions that still have high transmission and to establish if elimination has been achieved. For *S haematobium* infection, dipstick diagnosis of microscopic haematuria still seems to be adequate to detect low-level infection. However, for *S mansoni* and *S japonicum* new elimination diagnostic tests are needed.

## Control and elimination

It is an exciting time for control and elimination of schistosomiasis. In 1984, the WHO endorsed a strategy to control morbidity caused by schistosomiasis through preventive chemotherapy with praziquantel.<sup>133</sup> Because of its excellent tolerability and generally good ability to either cure or drastically reduce egg output (70–90%),<sup>134,135</sup> praziquantel can be distributed yearly (or in alternate years) by moderately trained school teachers or community health workers to obtain sufficient coverage to control morbidity in children, even despite the possibility of reinfection, resulting in prevention of severe hepatosplenic or urogenital disease.<sup>73,115</sup> WHO has recommended the inclusion of preschool children in preventive chemotherapy efforts.<sup>20,136</sup>

In 2012—through World Health Assembly Resolution 65.19—the WHO recommended that countries, if possible, aim beyond control of morbidity toward elimination of

schistosomiasis. This change of policy was a bold and important step. It is partly predicated on the pledge by Merck Serono (Geneva, Switzerland) to donate up to 250 million tablets of praziquantel per year<sup>137</sup> and the demonstration by the Schistosomiasis Control Initiative, that nationwide rollout of preventive chemotherapy with praziquantel can be accomplished. The decision by a country to move towards elimination should not be made lightly. It must be based on years of extensive control and reliable prevalence mapping that justifies the decision. Countries will need diagnostic tests suitable for use in the field, suitable survey sampling schemes, and the human capacity to implement the necessary interventions. Meeting these requirements needs a strong platform of government commitment over a substantial period. After elimination, the programme must provide an adequately designed surveillance scheme based on sound epidemiological and statistical techniques and improved diagnostic instruments. Aside from drug donations, many countries will need international and binational assistance for implementation of elimination interventions.

Because preventive chemotherapy alone will not eliminate schistosomiasis from most regions, additional control measures should be integrated into national and regional programmes.<sup>138</sup> For the first 60 years of large-scale efforts to control schistosomiasis, snail control was the primary method used to prevent infection because no drugs were suitable for mass distribution. Although chemicals, habitat change, predators, and biological competitors have been used to reduce snail populations, efforts at present primarily use the molluscicide niclosamide, which kills snails at low concentrations and is non-toxic to people. However, it is toxic to some freshwater fish and amphibians.<sup>139,140</sup> Niclosamide is a licensed pesticide in the USA, and is widely used for control of snails<sup>141,142</sup> and sea lampreys.<sup>143</sup> When used properly in suitable habitats, it has been an important contributor to schistosomiasis elimination campaigns.<sup>144–146</sup>

Behavioural modification is a possible, but challenging, approach to management of any health problem. However, with proper community involvement, it could be useful for reduction of both exposure of people to schistosome-containing water and contamination of snail habitat by human excreta containing schistosome eggs. Behavioural modification—without provision of feasible alternatives—is destined to fail, but in conjunction with improvements in water and sanitation, it could prove successful. Provision of schistosome-safe water for washing, bathing, and recreation is effective but expensive.<sup>147</sup>

Ongoing studies of the Schistosomiasis Consortium for Operational Research and Evaluation in five African countries will help determine the regimens needed to gain and sustain control of morbidity. In Zanzibar, studies are underway to understand the thresholds and combined activities needed for elimination.<sup>148</sup> Widespread elimination will almost certainly need integrated use of many or all the methods that can be applied: preventive chemotherapy, snail control, behavioural modification, water and sanitation improvements, and perhaps eventually a prophylactic or transmission-blocking vaccine.

The coordination and logistics needed at national, regional, and continental scales to reach sustained control of morbidity, then elimination, are daunting. Nevertheless, now is the time to move towards this goal. World Health Assembly resolution 65.21 calls on all countries to intensify interventions to control schistosomiasis and to strengthen surveillance of

schistosomiasis transmission. It also recommends that endemic countries embark on elimination programmes and develop means to document their progress. The resolution calls on WHO to report on progress towards elimination of schistosomiasis to the Executive Board and the World Health Assembly every 3 years.<sup>149</sup> The ultimate vision is a world free of schistosomiasis, with the intermediate goals of controlling morbidity caused by schistosomiasis by 2020, eliminating schistosomiasis as a public health problem by 2025, and interrupting transmission of schistosomiasis in most regions and in selected countries in Africa by 2025.<sup>150</sup>

## Conclusion

Schistosomiasis is an ancient human disease with effects worldwide, particularly in the poorest communities. Effective early treatment is possible, thereby preventing the substantial immune-mediated effects of *Schistosoma* infection on human health. New diagnostic tests and new approaches to treatment implementation are aimed at local, then regional elimination, thus changing the public health agenda from curative approaches to a truly preventive strategy.

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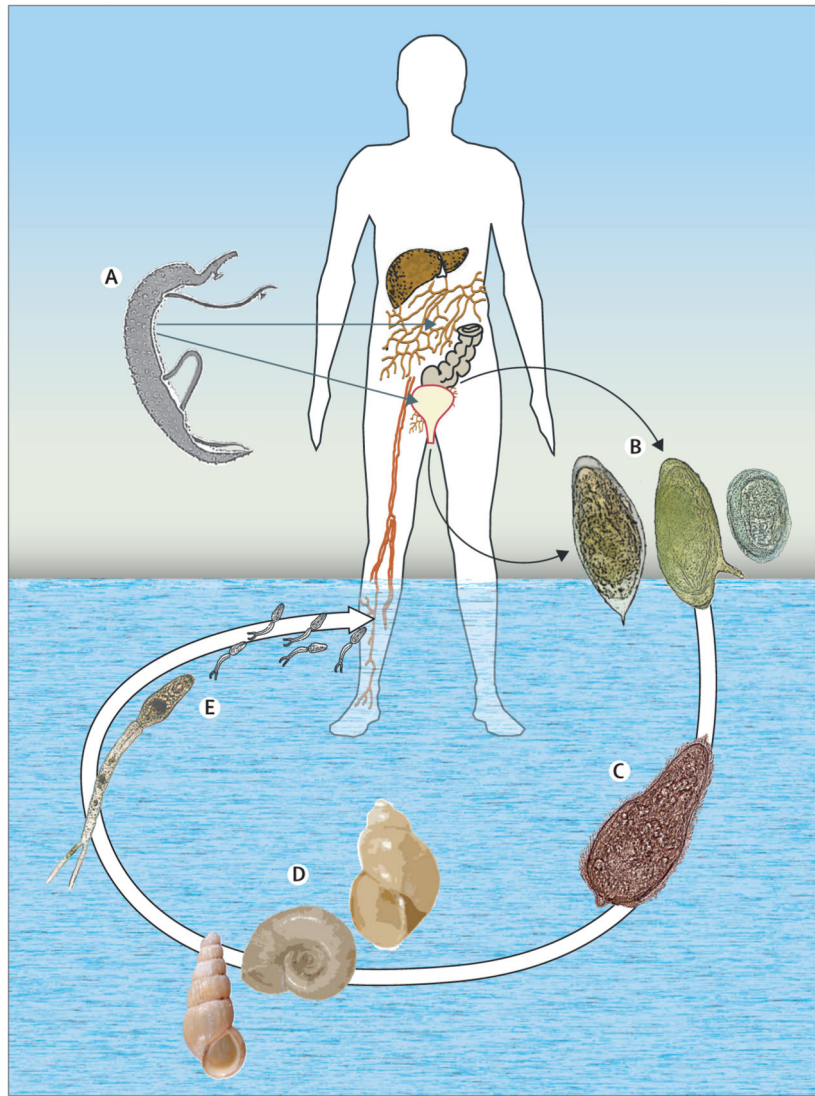
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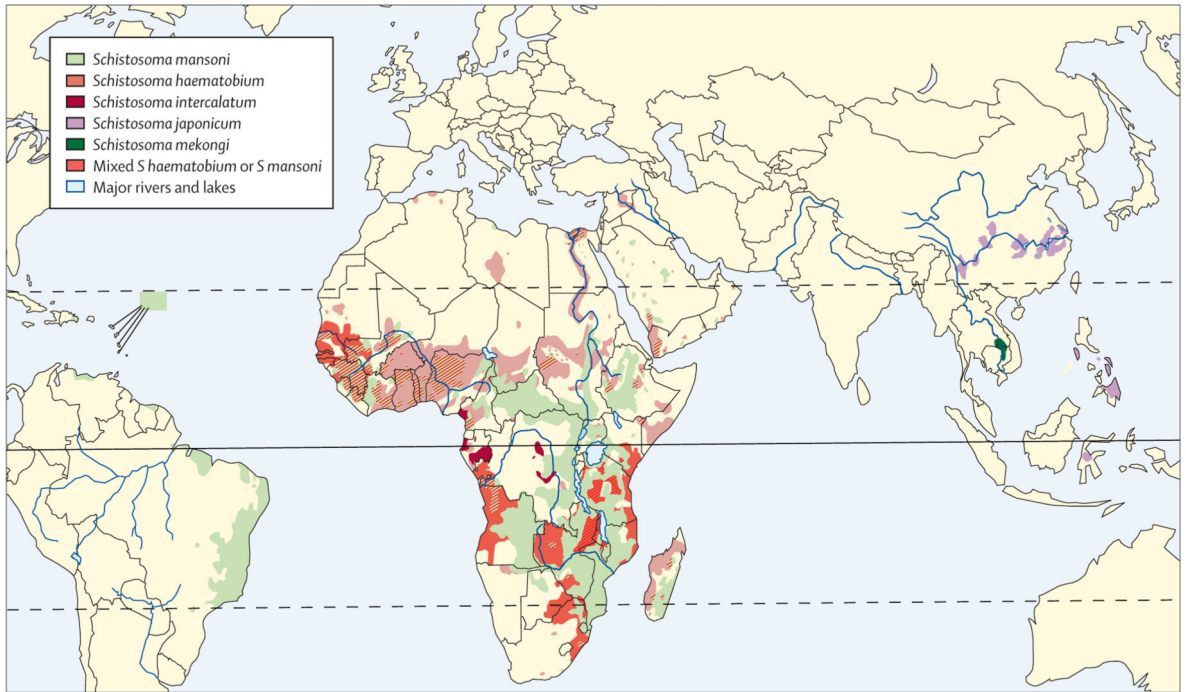
### Search strategy and selection criteria

We did a systematic search of PubMed, Medline, Google Scholar, and Embase for relevant studies, with the wildcard search terms “schistosome\*”, “bilharz\*”, and related subject headings for reports published between Jan 1, 2006 and Dec 31, 2013. Selection of studies was not limited by language. Reports were independently reviewed for inclusion by at least two authors. Older references were included on the basis of their importance.

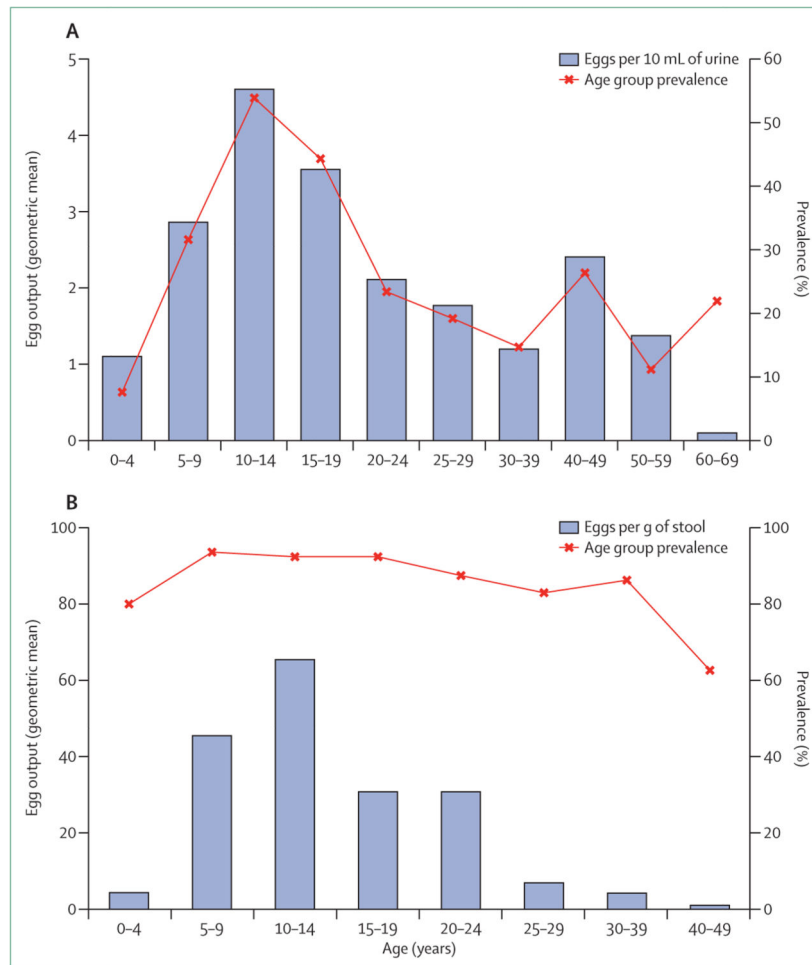


**Figure 1. Lifecycles of *Schistosoma mansoni*, *Schistosoma haematobium*, and *Schistosoma japonicum***

(A) Paired adult worms (larger male enfolding 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.

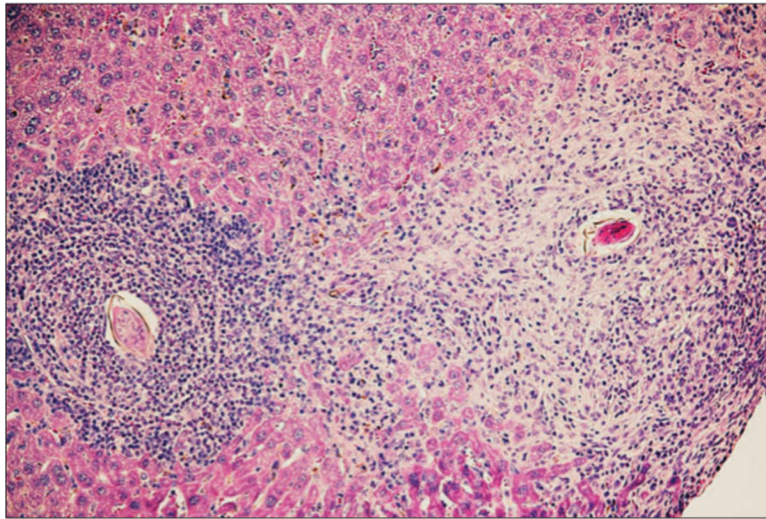


**Figure 2. Global distribution of countries where human schistosomiasis is transmitted**  
Adapted from Gryseels and colleagues.<sup>5</sup>

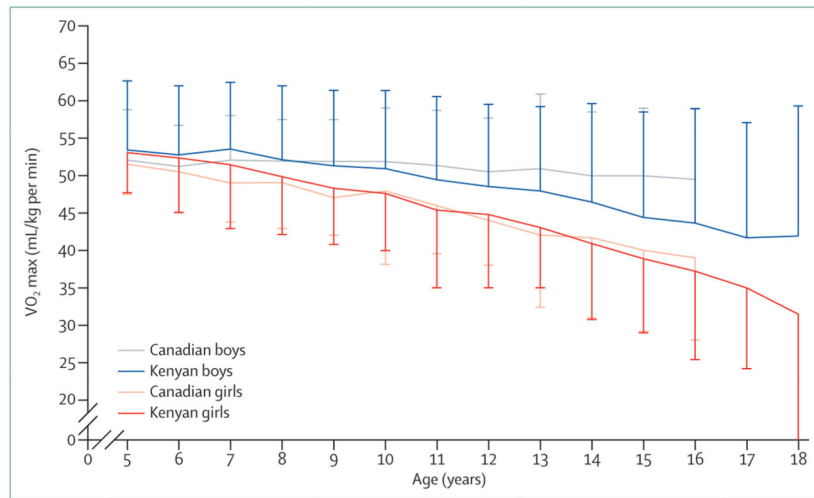


**Figure 3. Age-prevalence and age-intensity of infection curves for *Schistosoma haematobium* (A) and *Schistosoma mansoni* (B)**

Data from King and colleagues<sup>18</sup> and DeStigter and colleagues.<sup>19</sup>



**Figure 4.** *Schistosoma mansoni* egg-induced granulomas in the liver of an infected mouse  
Eggs are roughly 120–180  $\mu\text{m}$  long, 45–70  $\mu\text{m}$  wide.



**Figure 5. Effect of schistosomiasis on aerobic capacity in children in Kenya and Canada**  
Data taken from Bustinduy and colleagues.<sup>49</sup>