Schistosomiasis

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Abstract | Schistosomiasis (bilharzia) is a neglected tropical disease caused by parasitic flatworms (blood flukes) of the genus *Schistosoma*, with considerable morbidity in parts of the Middle East, South America, Southeast Asia and, particularly, in sub-Saharan Africa. Infective larvae grow in an intermediate host (fresh-water snails) before penetrating the skin of the definitive human host. Mature adult worms reside in the mesenteric (*Schistosoma mansoni* and *Schistosoma japonicum*) or pelvic (*Schistosoma haematobium*) veins, where female worms lay eggs, which are secreted in stool or urine. Eggs trapped in the surrounding tissues and organs, such as the liver and bladder, cause inflammatory immune responses (including granulomas) that result in intestinal, hepato-splenic or urogenital disease. Diagnosis requires the detection of eggs in excreta or worm antigens in the serum, and sensitive, rapid, point-of-care tests for populations living in endemic areas are needed. The anti-schistosomal drug praziquantel is safe and efficacious against adult worms of all the six *Schistosoma* spp. infecting humans; however, it does not prevent reinfection and the emergence of drug resistance is a concern. Schistosomiasis elimination will require a multifaceted approach, including: treatment; snail control; information, education and communication; improved water, sanitation and hygiene; accurate diagnostics; and surveillance-response systems that are readily tailored to social-ecological settings.

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Following an autopsy in Egypt in 1851, the German physician Theodor Bilharz first described a parasitic disease that would later be termed bilharzia¹. Currently, the most widely accepted term for this disease is schistosomiasis, although bilharzia is still used². Schistosomiasis is highly debilitating and is intimately linked to poverty, leading to chronic ill health. The infection is widespread in the tropics and subtropics and is caused by one of six species of trematode worms of the genus *Schistosoma*^{3–5}.

The most common disease-causing species are *Schistosoma haematobium*, *Schistosoma mansoni* and *Schistosoma japonicum*, whereas *Schistosoma guineensis*, *Schistosoma intercalatum* and *Schistosoma mekongi* have lower global prevalence. Adult schistosome parasites dwell in the blood vessels of vertebrate hosts, including humans, but their life cycle requires a phase of asexual multiplication or development within an intermediate host — a snail (*Biomphalaria* spp. snails for *S. mansoni*, *Bulinus* spp. snails for *S. haematobium* and *Oncomelania* spp. snails for *S. japonicum*)⁶. Schistosome infection in humans occurs by contact with fresh water contaminated by cercariae, the free-swimming, infectious stage of schistosomes that are released by the intermediate host snail (FIG. 1) and that penetrate the intact human skin^{2,3}. In zoonotic schistosomiasis, other mammalian hosts are also involved. Transmission is highly dependent on environmental

factors, especially those affecting the intermediate host snail. It is conceivable that climate change will affect aquatic environments, and hence, alter the transmission and distribution of water-borne and water-based diseases, such as schistosomiasis^{7,8}.

There are three distinct phases of clinical disease progression: acute infection, established active infection and late chronic infection. Acute schistosomiasis occurs in travellers to schistosomiasis-endemic areas after a primary infection; common presenting symptoms are myalgia, abdominal pain in the right upper quadrant, diarrhoea (with or without blood), fatigue, malaise, fever and, in case of *S. haematobium* infection, haematuria (blood in urine)⁹. Established active and late chronic disease affects mainly individuals from poor rural areas with long-standing infections¹⁰. In established active and late chronic infections, immunopathological reactions against schistosome eggs trapped in host tissues lead to inflammatory and obstructive disease; the tissues and organs affected depend on the infecting *Schistosoma* spp., as the worms nest in different preferential anatomical locations. Late chronic infection with *S. guineensis*, *S. intercalatum*, *S. mansoni*, *S. mekongi* and *S. japonicum* (which all reside in the mesenteric veins of the bowel) causes intestinal disease, and advanced disease involves the liver and spleen (hepato-splenic schistosomiasis). Late chronic infection with *S. haematobium*

(which nests in the pelvic venous plexus) causes urogenital schistosomiasis, which mainly involves lesions of the bladder wall^{4,11,12}. Morbidity is particularly severe in high-intensity infections (infections with high worm burden), most importantly with *S. mansoni* and *S. japonicum*^{4,11,12}. Schistosomiasis is also associated with undernutrition, exercise intolerance (that is, decreased ability to perform physical exercise at what would be considered the normally expected level or duration), diarrhoea (sometimes bloody), chronic pain and anaemia, and urogenital schistosomiasis may be a factor in the spread of HIV^{13–15}.

Although substantial strides have been made in the control of schistosomiasis through programmes of population-based preventive chemotherapy (that is, the periodic administration of praziquantel (an oral anti-schistosomal drug) to at-risk populations without prior diagnosis), additional interventions

(including the development of schistosomiasis vaccines) and multisectoral approaches will be required to achieve elimination¹⁶.

In this Primer, we describe the main features of schistosome biology and the epidemiology, pathogenesis, clinical features, diagnosis, management and control of schistosomiasis, identifying key areas in which further clinical and basic research are needed for improved management, control and eventual elimination of this human disease.

Epidemiology

The parasites

The six *Schistosoma* spp. that can infect humans have different geographical distributions. *S. haematobium* has been reported in 54 countries⁵ and is the most common species, occurring in sub-Saharan Africa and the Middle East, although a 2013 outbreak of urogenital

Fig. 1 | **Schistosome life cycle exemplified by *Schistosoma mansoni*.** *Schistosoma mansoni* has a life cycle involving an intermediate fresh-water snail host and the definitive human host. Eggs (excreted in the faeces of the human host) hatch upon contact with water, releasing miracidia (free-swimming ciliated larvae), which penetrate the intermediate host snail (*Biomphalaria* spp.). Within the snail, the miracidia develop into sporocysts, which in turn produce new daughter sporocysts by asexual reproduction; numerous cercariae (free-swimming larval stage in which the parasites pass from the intermediate to the final host) are then produced again asexually within the daughter sporocysts. After ~30 days, cercariae emerge from the snail in response to sunlight and penetrate the skin of a human host; in the skin, the tails drop off and the larvae transform into schistosomula. The schistosomula enter the venous blood vessels (directly or after invading the lymphatic system) and are transported to the lungs via the right heart, before reaching the left heart, and then enter the arterial circulation. Once they arrive in the hepatic portal system, the schistosomula migrate to the mesenteric veins of the liver, where they mature into separate-sex adults. The male worm grasps the female in the gynaecophoral canal and the worms migrate to the mesenteric veins of the bowel, where the female produces eggs (~5 weeks post-infection). Eggs are released in the bloodstream, pass through the intestinal wall and are excreted in the faeces. Image (top left) reproduced from Oxford Textbook of Medicine 5th Edition edited by Warrell, Cox, and Firth (2010) Figs.7.11.1.3. By permission of Oxford University Press. Image (top right) courtesy of P. Nielsen, Ross University School of Veterinary Medicine, Saint Kitts and Nevis. Image (bottom left) courtesy of A. Azugati. Image (bottom right) courtesy of H. Madsen, University of Copenhagen, Denmark.

Fig. 2 | **Prevalence of schistosomiasis.** Worldwide distribution of schistosomiasis in 2012. ^aSchistosomiasis status needs to be evaluated to verify whether interruption of transmission has been achieved. Figure adapted from Map: Distribution of schistosomiasis, worldwide, 2012, WHO, © 2012.

schistosomiasis was observed in Corsica¹⁷. *S. mansoni* is endemic in sub-Saharan Africa, Brazil, the Caribbean islands, Puerto Rico, Suriname and Venezuela¹⁸, and *S. japonicum* is endemic in the People's Republic of China and the Philippines, with small foci in Indonesia⁴. *S. japonicum* used to be endemic in Japan, but extensive control efforts led to its elimination in the late 1970s (REF.¹⁶). The remaining species have lower global prevalence, with *S. guineensis* and *S. intercalatum* endemic in West Africa and Central Africa^{19,20} and *S. mekongi* restricted to the southern parts of Cambodia and along the Mekong river in Lao People's Democratic Republic²¹. Although *S. haematobium*, *S. mansoni*, *S. guineensis* and *S. intercalatum* primarily infect humans, *S. japonicum* and *S. mekongi* are zoonotic species. Indeed, >40 different mammalian species serve as reservoir hosts for *S. japonicum*, with bovines (water buffalo and cattle) being the most important²². The main reservoir hosts for *S. mekongi* seem to be dogs and domestic pigs, but other animals, notably bovines, may also be involved in transmission²¹. Of note, *Schistosoma malayensis* n. sp., a species related to *S. japonicum* that was first described in 1988, is responsible for a few autochthonous cases of human schistosomiasis in Peninsular Malaysia²³. It is zoonotic, utilizing *Robertsiella* spp. snails as intermediate hosts and mainly rodents (*Rattus muelleri* (also known as *Sundamys muelleri*) and *Rattus tiomanicus*) as definitive hosts²⁴.

The disease

Prevalence. The WHO considers schistosomiasis a neglected tropical disease that mainly occurs in tropical and subtropical areas (FIG. 2). Globally, an estimated 779 million people are at risk of infection^{6,25}. Over 250 million people are infected with *Schistosoma* spp. worldwide, with 201.5 million of them living in Africa^{6,25,26}. Over the past decade, considerable progress has been made in mapping and advanced geostatistical modelling,

which enables a more-precise display and prediction of the prevalence and intensity of schistosome infection at different scales of analysis (for example, within a single village or at the district, national or continental level)^{27,28}. The application of geographical information system and remote sensing technologies for determining environmental features (such as land surface temperature, rainfall and fresh-water bodies) has been utilized for schistosomiasis risk profiling and estimating treatment needs with the anti-schistosomal drug praziquantel (according to guidelines and treatment thresholds put forth by the WHO)^{27,29,30}. These studies also determined the role of environmental risk factors (for example, living in close proximity to open fresh-water bodies) in explaining patterns and geographical heterogeneity in risk of infection.

A key epidemiological feature of schistosomiasis is its focal distribution (that is, highly variable prevalence and intensity of infection even within a small area, from one village to another), which is governed by the interplay of humans, intermediate host snails and human–water contact patterns. Lack of access to clean water, poor sanitation and hygiene and activities involving contact with water, whether domestic (for example, washing cloths and dishes in open fresh-water bodies), recreational (for example, playing and swimming in ponds, lakes and rivers) or professional (for example, car washing and sand collection), put children, adolescents and adults at risk of schistosome infection when exposed to contaminated water bodies³¹.

Disease burden. If left untreated, schistosomiasis can result in substantial morbidity and even mortality, although the precise extent is disputed (see Quality of life). According to the Global Burden of Disease Study 2016, the global burden of schistosomiasis is estimated at 1.9 million disability-adjusted life years (DALYs)³². Prior studies estimated the global burden of

schistosomiasis at 1.7–4.5 million DALYs^{33–35}, whereas a meta-analysis suggested a severalfold higher burden; such higher estimates can be mainly explained by the inclusion in the analysis of undernutrition, anaemia and growth faltering in children, which are partially due to schistosome infection but are usually not attributed to schistosomiasis³⁶. The morbidity and mortality associated with untreated *S. japonicum* infection are especially high, probably owing to the relatively higher number of eggs produced by this species than by the others^{37,38}.

Mechanisms/pathophysiology

The progression of schistosome infections can be divided into three general overlapping stages influenced by the duration of the individual's infection: acute, established active and late chronic infection. These stages differ in egg excretion rates in stool or urine as well as in clinical manifestations and symptoms.

Acute stage

Cercarial dermatitis. After cercarial skin penetration of intact skin, a portion of the infectious larvae will die in the skin, whereas the rest enter the venous circulation through a small blood vessel directly or by first entering a lymphatic vessel. The larvae are transported via the blood flow to their maturation site in the liver. In the skin, innate immune responses to dying or dead larvae give rise to hypersensitivity reactions and can cause a maculopapular pruritic reaction, called cercarial dermatitis, on parts of the body that have been exposed to water containing cercariae. Cercarial dermatitis can occur in individuals exposed to human *Schistosoma* spp. infection for the first time, such as travellers and migrants from a schistosomiasis-endemic area. Swimmer's itch is a type of cercarial dermatitis caused by cercariae of avian schistosomes⁹. Swimmer's itch is more-frequent in some parts of Europe, such as in the Czech Republic, where fresh-water lakes are used for recreational purposes. Whereas the initial exposure to avian cercariae usually causes a relatively mild cutaneous reaction, later exposures in individuals who were previously sensitized generate more-severe symptoms more rapidly. However, infections with avian *Schistosoma* spp. do not proceed past the initial swimmer's itch stage.

Acute schistosomiasis. After successful cercarial penetration and maturation of the schistosome, the infection may proceed to a symptomatic acute stage. Symptomatic acute schistosomiasis is also known as Katayama fever or Katayama syndrome after a district of Hiroshima, Japan, where *S. japonicum* was detected for the first time in a human³⁹. It usually occurs in naive individuals exposed to *Schistosoma* spp. for the first time, between 2 weeks and 3 months after exposure⁹. The symptoms are caused by systemic hypersensitivity reactions and formation of immune complexes in response to antigens released during schistosome migration or initiation of egg deposition⁹. Symptoms are often accompanied by eosinophilia and transient pulmonary infiltrates (as observed on chest radiography)^{3,9,40}. Acute schistosomiasis is rarely

observed in people living in *S. mansoni*-endemic or *S. haematobium*-endemic areas. This lack of susceptibility to acute symptoms may be due to in utero desensitization, resulting in lowered immune responsiveness to schistosome antigens in infants born to infected mothers⁴¹, or possibly due to repeated exposure to skin-penetrating cercariae, which induce IL-10 production by CD4⁺ T cells in the skin, resulting in a regulatory immune response⁴². However, acute schistosomiasis has been reported in the People's Republic of China, when flooding has exposed communities living in *S. japonicum*-endemic areas to new outbreaks of infection^{38,43}.

Established active infection

In most cases, especially in people living in endemic areas, symptomatic acute schistosomiasis is not observed and the disease reaches a stage of established active infection, with mature adult worms and well-established egg production. This stage is characterized by excretion of live eggs in stools or urine. The live adult worms residing in the blood vessels do not stimulate any local inflammation and normally do not directly cause symptoms. This observation can be explained by several factors, such as the fact that adult worms have somatic stem cells that enable the worms to regenerate their surface tegument (the outer protective layer) and binding of host antigens to the surface tegument, thereby hiding the worm antigens on the surface from the host's immune system⁴⁴. The main symptoms and organ-related lesions of patent infections are caused by inflammatory responses against parasite eggs (FIG. 3). Schistosome eggs actively secrete antigenic glycoproteins, which have the function of facilitating the passage of the eggs from the blood vessel (where they are laid) to the lumen of the intestine or urinary bladder (thereby promoting transmission) by inducing an inflammatory response. However, these soluble egg antigens also induce the formation of granulomas around eggs that are trapped in the surrounding tissue; granulomas are a collection of inflammatory cells such as eosinophils, neutrophils, lymphocytes and macrophages that accumulate in response to the presence of the eggs.

Organ-specific clinical symptoms often positively correlate with infection intensity, as indicated by excreted egg counts, and are mediated by egg-induced inflammation and granulomatous reactions. Established active schistosomiasis is characteristically observed in children in endemic areas and is entirely reversible following treatment and removal of the adult worms³. The high lymphocyte proliferative responses induced by soluble egg antigens at this stage in the infection then progressively decrease as the infection becomes chronic.

Late chronic infection

In most people continuously exposed to infection in schistosomiasis-endemic areas, their worm burdens gradually decline after their early teenage years as a partial immunity to new infections develops, while the number of established worms from earlier infections is reduced over time by natural worm deaths⁴⁵. This

Fig. 3 | Hepatic granulomas. Granulomas form around eggs trapped in liver tissue. **a** | Major cellular populations located within and adjacent to the hepatic granuloma induced in either *Schistosoma mansoni* or *Schistosoma japonicum* infection. There is a dense population of eosinophils at the core of a *S. mansoni*-induced hepatic granuloma, whereas in *S. japonicum* infection the core is composed mainly of neutrophils. Chemokine-binding proteins secreted by *S. mansoni* eggs can bind neutrophil chemoattractant CXC-chemokine ligand 8 (CXCL8) and block the infiltration of neutrophils to the granuloma; however, these proteins do not bind to eosinophil chemoattractant CC-chemokine ligand 11 (CCL11) and, therefore, do not inhibit the recruitment of eosinophils. **b** | Hepatic granuloma from a *S. mansoni*-infected mouse. HSC, hepatic stellate cell. Part **a** adapted with permission from REF.²¹⁷, Elsevier. Part **b** courtesy of A. M. O. Kildemoes, University of Copenhagen, Denmark.

reduction in worms means that fewer new eggs are excreted or deposited in the tissue. At the same time, new granulomas are smaller in size with less inflammation as a result of immunological downregulation, and the previously formed granulomas gradually resolve when eggs within them are destroyed. These granulomas are then replaced by fibrous tissue (scarring), and this process contributes to a reduction in symptom severity.

Immunology and host–parasite interactions

The interaction between the host's immune system and schistosomes is complex and involves several different stages of the life cycle of the parasite, which may be present in the body of the host, such as penetrating cercariae, migrating schistosomula, mature adult worms and parasite eggs trapped in the tissue. Immune responses against cercariae and possibly other parasite stages are important for development of resistance to reinfection, whereas responses towards egg antigens are responsible for the pathology in schistosomiasis. Protective immune responses against schistosomes develop slowly over a period of 10–15 years, and children of <10 years of age in schistosomiasis-endemic areas are susceptible to reinfection after treatment of the schistosome infection, whereas adults are usually resistant. This observation may also explain the characteristic age-prevalence and age-intensity curves observed in schistosomiasis-endemic areas. The human responses linked to resistance to reinfection are T helper 2 (T_H2) cell-associated responses characterized by eosinophilia, production of specific immunoglobulin E (IgE) against schistosomes and cytokines such as IL-4 and IL-5. Many studies from a variety of epidemiological settings have shown associations between specific IgE, eosinophils and

post-treatment production of IL-4 and IL-5 with resistance to new infections after treatment, whereas specific IgG4 has been associated with susceptibility to infection⁴⁴. A hypothesis is that death of adult worms – either naturally or after treatment with praziquantel – leads to the release of antigens that may cross-react with larval antigens and stimulate protective IgE responses, suggesting that the more dead worms a person has experienced, the stronger the protective responses⁴⁶. As the average lifespan of a worm is 3–10 years, this hypothesis could in part explain why children, who have had few dying worms during their lifetime, are susceptible to infection and accumulating more worms through continuous exposure, whereas adults who have experienced many dying worms have developed protective immune responses. This hypothesis may also explain why it takes many years for immunity to develop.

Our knowledge on host–parasite interactions derives from human epidemiological studies analysing immune correlates to resistance to reinfection. Mouse models of schistosome infections cannot be used for this purpose, as mice are naive hosts and do not live long enough to develop protective immune responses after primary infection. However, mouse models are useful for teasing out factors important in immunopathology and formation of granulomas.

The most widely studied experimental animal models of schistosomiasis are murine infections with *S. mansoni*⁴⁷ or *S. japonicum*⁴⁸. In recent years, these models, particularly using gene knockout or transgenic mice, have substantially advanced the understanding of the immunopathological mechanisms that may be important in various forms of both schistosomiasis and fibrotic disease⁴⁹.

Pathophysiology

Organ-specific morbidity can develop during established acute and late chronic stages, caused by the accumulation of parasite eggs and development of fibrosis; the severity of symptoms generally correlates with the intensity of the infection. What organs are affected depends on the infecting *Schistosoma* spp. as the adult worms of different species localize and lay eggs in specific preferred sites. In addition, serious effects result if adult worms locate and lay eggs in aberrant sites⁹.

Intestinal schistosomiasis. *S. mansoni* and *S. japonicum* adult worms live in the mesenteric veins and can cause intestinal schistosomiasis. Symptoms of intestinal schistosomiasis are associated with parasite eggs passing through, or becoming trapped in, intestinal tissues, which induces mucosal granulomatous inflammation with micro ulcerations, superficial bleeding and, sometimes, pseudopolyps^{3,50,51}. Pseudopolyps are projecting masses of inflammatory tissue that develop during the healing phase in repeated cycles of ulceration.

Hepato-splenic schistosomiasis. The venous blood flow sweeps a proportion of *S. japonicum* or *S. mansoni* eggs from the mesenteric veins into the small portal branches of the liver, via the portal vein, where they are trapped in the pre-sinusoidal periportal tissues. Granulomas form around the eggs (FIG. 3) and, in high-intensity established active infections, this can cause substantial enlargement of the spleen and liver, especially the left liver lobe, characteristic of hepato-splenic schistosomiasis^{3,52,53}. High-intensity childhood infections in particular are often accompanied by hepato-splenomegaly⁵⁴, and this can be exacerbated by chronic exposure to *Plasmodium* spp. (the aetiological agent of malaria) infection⁵³. With time and repeated or long-term infections, the worm burden and egg excretion and deposition decrease, and in most adolescents there is an associated decrease in hepato-splenomegaly. However, in some individuals, egg-induced granulomatous responses lead to severe periportal fibrosis, known as Symmer's pipestem fibrosis, with deposition of collagen around the portal vein, occlusion of the smaller portal branches and severe, often irreversible, pathology^{55,56}. Of note, what factors can contribute or predispose to the development of these complications have yet to be fully understood.

Urogenital schistosomiasis. Adult *S. haematobium* worms live in the pelvic venous plexus, and the symptoms and pathological changes of urogenital schistosomiasis are closely associated with the passage of parasite eggs through the urinary bladder wall and egg deposition in bladder tissue and genital organs^{3,55}. During an established active infection, clusters of living eggs in the urogenital tissues can be found surrounded by intense inflammatory reactions and intense tissue eosinophilia^{57,58}. The passage of egg clusters into the lumen of the bladder is often accompanied by the sloughing off of the epithelial surface, ulceration and bleeding. The intense egg-induced tissue inflammation can result in bladder wall thickening and development of masses

and pseudopolyps^{59,60}. Inflammation and granuloma formation around the ostium (the opening of the ureter in the bladder) blocking the passage of urine can lead to hydronephrosis (swelling of a kidney as a result of a build-up of urine), which may, in some cases, result in a non-functioning kidney⁶¹. Urogenital schistosomiasis is associated with squamous cell carcinoma of the urinary bladder, and *S. haematobium* is now classified by the International Agency for Research on Cancer (IARC) as a carcinogen^{62,63}. The carcinogenic process is closely related to tissue inflammation. Bladder cancer may occur after many years of exposure, infection and urinary tract inflammation⁶³, when an established active infection, with eggs in the urine, is no longer detectable. Generally, late chronic infections are characterized by little or no detectable egg excretion and an accumulation of dead calcified tissue eggs, which may appear as yellow sandy patches in cystoscopic examination of the bladder mucosa^{58,59}.

During established active infection, eggs are frequently deposited in genital organs such as the cervix^{57,64}, seminal vessels and prostate⁶⁵. Very characteristic cervical lesions are found in *S. haematobium* infections, including active-stage lesions with intense tissue inflammation with live eggs and chronic-stage sandy patches with clusters of calcified eggs^{57,66}. Analysis of semen samples shows a higher prevalence of leukocytes and increased levels of inflammatory cytokines in men with genital schistosomiasis⁶⁷. In both women and men, the manifestations of *S. haematobium* infection may play a part in HIV transmission by increasing the number of inflammatory cells and possibly viral load in semen and causing friable bleeding lesions on the cervical mucosa in women⁶⁸.

Diagnosis, screening and prevention

Clinical presentations

Acute schistosomiasis. Symptoms may present suddenly and include fever, myalgia, general malaise and fatigue, headache, non-productive cough and intestinal symptoms such as abdominal tenderness or pain. Symptoms are often relatively mild and transient in the weeks or months after exposure. These mild and transient symptoms can lead to misdiagnosis, owing to similarities with many other febrile infectious diseases with acute onset, including malaria, salmonellosis and acute hepatitis⁴⁰. Many patients recover spontaneously as the symptoms of acute schistosomiasis subside after 2–10 weeks, but the illness follows a more-severe clinical course in some individuals, with weight loss, dyspnoea, diarrhoea and hepatomegaly^{9,40}. Although the clinical manifestations associated with established active and late chronic infections can present in individuals with low-intensity infections (such as naive patients from non-endemic areas), more-severe disease is usually associated with high-intensity infections.

Intestinal schistosomiasis. Intestinal schistosomiasis may be accompanied by intermittent abdominal pain, discomfort, loss of appetite and, sometimes, bloody diarrhoea. These symptoms tend to be more-pronounced with greater intensities of infection⁵¹. *S. intercalatum* and *S. guineensis*

Fig. 4 | **Established active and late chronic schistosomiasis.** **a** | Child with established active schistosome infection, with early inflammatory hepatosplenomegaly. **b** | Fibrosis around the portal vein (arrow) visualized by ultrasonography. **c** | Oesophageal varices (arrow) visualized by ultrasonography. **d** | Severe late chronic fibrotic disease increased portal pressure and ascites in a young adult man. Image in part **a** courtesy of N. Kabatereine, Imperial College London, UK. Image in part **b** reproduced from Oxford Textbook of Medicine 5th Edition edited by Warrell, Cox, and Firth (2010) Figs.7.11.1.9. By permission of Oxford University Press. Images in parts **c** and **d** courtesy of B.J. Vennervald, University of Copenhagen, Denmark.

cause generally milder intestinal manifestations than *S. mansoni*, *S. mekongi* or *S. japonicum*.

Hepato-splenic schistosomiasis. Periportal fibrosis is usually seen in adults and, sometimes, in adolescents living in areas with very high schistosomiasis transmission; the severity of periportal fibrosis correlates in part with the intensity and duration of infection⁶⁹ (FIG. 4). Portal branch occlusion as a result of periportal fibrosis may lead to marked portal hypertension, frequently accompanied by severe enlargement and hardening of the spleen. Of note, whereas portal hypertension is associated with periportal fibrosis in chronic hepatosplenic schistosomiasis in older individuals (often of >15 years of age), in children with severe hepato-splenic schistosomiasis, increased portal pressure may be evident in the absence of detectable periportal fibrosis⁵².

In some cases, portal hypertension leads to the development of oesophageal varices, which may rupture with high risk of fatal haematemesis (vomiting of blood)⁷⁰. Other complications include ascites (accumulation of fluid in the abdominal cavity), delayed growth and puberty and severe anaemia. However, in contrast to toxin-induced and alcohol-induced liver cirrhosis, in schistosomiasis, even with marked periportal fibrosis and portal hypertension, no hepatocyte damage is observed and liver enzymes remain normal⁷⁰.

Urogenital schistosomiasis. A common characteristic of established active *S. haematobium* infection is blood in the urine, and in endemic areas many school-aged children present with visible haematuria⁷¹. Children may present with dysuria with frequent urination⁷² as a direct effect of egg-induced urothelial inflammatory responses. However, bladder wall lesions resolve 3–6 months after treatment with praziquantel^{61,73}.

Genital schistosomiasis can cause pelvic discomfort and pain, abnormal vaginal discharge, itch and contact bleeding in girls and women⁷⁴ and haematospermia and painful ejaculation in men^{65,75}. In both sexes, genital schistosomiasis has been associated with increased risk of HIV infection⁷⁶.

Other manifestations. Schistosome worms and eggs can sometimes locate in ectopic sites such as the spleen, lungs, skin and central nervous system, causing site-specific manifestations and symptoms.

Neuroschistosomiasis (affection of the central nervous system by *Schistosoma* spp.) may be one of the most severe clinical outcomes of schistosomiasis and is caused by the inflammatory response around eggs in the cerebral or spinal venous plexus^{77–79}. *S. mansoni* and *S. haematobium* worms abnormally locate most often in the spinal venous plexus, where they may cause transverse myelitis⁷⁹, a complication also seen in individuals with acute schistosomiasis⁴⁰. Neuroschistosomiasis caused by *S. japonicum* is mainly associated with granulomatous lesions in the brain, which can result in epileptic seizures, encephalopathy with headache, visual impairment, motor deficits and ataxia (reduced coordination of voluntary muscle movements)⁷⁸.

Pulmonary schistosomiasis is caused by portal-caval shunting, in which venous blood bypasses the liver through collateral veins connecting the portal vein with the vena cava, and eggs are thereby transported to the lung capillaries, where they induce granulomas in the perialveolar area. These granulomas may lead to fibrosis and may result in pulmonary hypertension and cor pulmonale (an enlargement of the right ventricle of the heart due to increased pressure in the lung capillaries)⁸⁰.

Diagnosis

The diagnosis of acute schistosomiasis requires different diagnostic methods than those used to diagnose established active or late chronic infections^{40,81}. In endemic areas, where individuals typically have established active or late chronic infection, diagnosis is often based on detection of schistosome eggs in faeces or urine by microscopy. However, these methods are often not sensitive enough to detect acute infections, which have low intensity, in returning travellers or recent immigrants from a schistosomiasis-endemic area. In this case, anamnestic information such as recent travels to endemic areas and exposure to fresh-water bodies through recreational or other activities is important and may provide

Box 1 | Making a positive diagnosis of a schistosome infection in a returning traveller or recent immigrant**Medical history**

- Recent travel to or from an endemic country; note that different *Schistosoma* spp. migrate to different anatomical sites, corresponding to different symptoms. As the different species have different geographical distributions, determining the country visited can guide in the diagnosis
- Contact with water from lakes, rivers or streams

Physical examination

- Urticarial rash on the skin at the site of cercariae entry, with discrete erythematous raised lesions that vary in size from 1 to 3 cm
- Hepatomegaly (tender left lobe) and in approximately one-third of patients splenomegaly on palpation of the abdomen (indicative of established active or late chronic infection)
- Dry or moist rales (crackling noises) in the lungs on auscultation (acute infection)
- Generalized lymphadenopathy

Laboratory investigations

- Stool and/or urine examination to detect schistosome eggs
- Full blood count: eosinophilia is present in >80% of patients with acute infections, whereas anaemia and thrombocytopenia may be present in established active and late chronic schistosomiasis
- Coagulation profile: prolonged prothrombin time indicated by an increased INR (international normalised ratio) may be evident in established active and late chronic schistosomiasis
- Urea, electrolytes and liver function: elevated urea and creatinine levels may be evident, and hyperglobulinaemia and hypoalbuminaemia may be present in late chronic and advanced schistosomiasis
- Serology may be diagnostic in patients with acute schistosomiasis

Radiology

- Chest radiography: pulmonary infiltrates are common in acute schistosomiasis
- Abdominal ultrasonography can establish the extent of liver and spleen pathology in intestinal schistosomiasis
- Pelvic ultrasonography can establish the extent of bladder, ureteral and renal pathology in urogenital schistosomiasis

Adapted from REF.⁵⁵.

an indication of schistosomiasis⁸² (BOX 1). Eosinophilia is a common finding in these individuals and is often a sign of helminth infection, such as schistosomiasis⁸³.

Parasitological diagnosis. The standard for diagnosing an established active infection is the detection of eggs in faeces, urine or rectal biopsy samples by microscopy⁸¹ (TABLE 1). Parasitological diagnosis of schistosomiasis in populations living in endemic areas most often relies on filtering a standardized small amount of urine or stool sample and microscopically counting all eggs in that volume^{84,85}. The level of infection is then expressed as eggs per 10 ml of urine or eggs per gram of stool (EPG)⁸⁶. These methods have a low sensitivity (estimated at <50%)^{86,87}, and the observation of 1 egg in a slide corresponds to detection of 20–40 EPG, or 5,000–10,000 eggs per diurnal faecal portion of 250 g (in *S. mansoni* infections, 1–99 EPG are considered low-intensity infections). However, egg excretion may show a high degree of day-to-day⁸⁸ as well as intraspecimen and diurnal variation⁸⁹. This variability warrants collection of multiple biological samples over consecutive days or examination of a single specimen multiple times. Furthermore, as the infection reaches the late chronic stage, egg excretion can be very low or even absent despite severe clinical manifestations³. For travellers or previously exposed people, this diagnostic approach is rarely sensitive enough to detect the often very low levels of infection; thus, larger amounts of urine or stool will have to be examined and other

methods employed, such as formol-ether concentration and sedimentation, in which a larger amount of stool is centrifuged^{81,86}.

Schistosome eggs can be detected in tissue biopsy samples^{66,90} and rectal snip samples, which are very sensitive even for detection of *S. haematobium* and useful in diagnosing infections in travellers³. *S. haematobium* can be located in veins around the genital organs in both men and women, and eggs have been detected in semen samples⁶⁵ and Pap smears⁵⁴.

Detection of worm antigens, worm DNA and anti-schistosome-specific antibodies. When schistosomes feed on red blood cells, they regurgitate waste products into the bloodstream⁹¹. These products are proteoglycans known as circulating anodic (negatively charged) antigens (CAAs) and circulating cathodic (positively charged) antigens (CCAs) and they can be detected in serum and urine by enzyme-linked immunosorbent assay (ELISA) or monoclonal-antibody-based lateral flow assays⁹². The presence of CAAs or CCAs is an indication of an established active infection with presence of live worms, and circulating antigens can be detected before the worms have started producing eggs⁹³. The levels of antigens correlate well with the intensity of infection⁹⁴, and the assays for circulating antigens have proved very valuable as research tools in schistosomiasis epidemiology. However, these assays may be less suited for diagnosis in areas with low endemicity and in travellers, who are likely to have very few worms⁹⁵.

There is a commercially available point-of-care (POC) assay (Rapid Medical Diagnostics; Pretoria, South Africa) that detects *S. mansoni* CCA in urine. This assay is now used for screening of *S. mansoni*-infected communities in relation to mass drug administration (MDA) programmes⁹⁶, although the costs of POC-CCA screening may be prohibitive for widespread use in some areas. Concentration of urine samples can improve the sensitivity of the POC-CCA assay⁹⁷.

PCR-based detection of parasite DNA in stool⁹⁸ or urine⁹⁹ is more sensitive¹⁰⁰ than parasitological methods and is now increasingly being employed for diagnosis in high-resource settings. *Schistosoma* spp. DNA can also be detected in vaginal lavage and cerebrospinal fluid samples for diagnosis of urogenital schistosomiasis⁸¹ or neuroschistosomiasis, respectively¹⁰¹. Multiplex PCR analysis, which includes detection of several intestinal parasites in a single stool sample, can be an advantage when diagnosing infections in travellers¹⁰².

Detection of anti-schistosome-specific antibodies with serological assays can be very useful in travellers who present with clinical symptoms and very low or no egg excretion¹⁰³. Production of antibodies against adult worm antigens starts ~4–7 weeks after exposure, and in most cases seroconversion takes place within 3 months¹⁰³. However, serology cannot distinguish between current infection or past exposure in people living in a schistosomiasis-endemic area, where people remain seropositive for several years after treatment¹⁰⁴. Antibody detection assays such as rapid diagnostic POC tests¹⁰⁵ may prove useful as infection intensities decline following

control programmes, as has been the case in the People's Republic of China¹⁰⁶.

Radiology

Ultrasonography can be used to visualize pathological changes associated with established active and late chronic schistosomiasis¹⁰⁷. Portable ultrasonography equipment has been used in population-based studies for >20 years to assess the organ-specific pathological changes, such as periportal fibrosis and signs of portal hypertension (such as severe dilatation of the portal vein and presence of collateral veins) in intestinal schistosomiasis¹⁰⁸ and bladder wall abnormalities and hydronephrosis in *S. haematobium* infection¹⁰⁸. Ultrasonography is a valuable tool for monitoring the direct effect of interventions on schistosomiasis morbidity¹⁰⁹, and standardized protocols for classification and grading of pathological lesions are available¹¹⁰. Radiological examinations such as intravenous pyelography (radiographic examination with injected contrast material) to visualize renal, ureteral and bladder pathology complements ultrasonography for diagnosis of kidney damage⁵⁹. Endoscopy and cystoscopy can be used to detect oesophageal varices and urinary bladder lesions, respectively^{111,112} (FIG. 5). In neuroschistosomiasis, CT and especially MRI are the methods of choice¹¹³. Of note, these diagnostic tools are generally not available in rural health-care facilities, the primary point of care for many patients with schistosomiasis. Furthermore, they are of limited use in assessing the level of morbidity in endemic populations. However, lesions in the female genital tract,

Table 1 | Diagnostic tests for *Schistosoma* spp. infection

Test	Sample	Quantitative	Sensitivity	Specificity	Target setting		
					Endemic areas		Non-endemic areas
					PHCU	Laboratory	
Microscopic detection of eggs							
Kato-Katz	10–50 mg of fresh faeces	Yes	Low	High	Yes	Yes	NA
FECT	10 g of fresh faeces	No	Medium	High	No	Yes	Low–medium sensitivity
Urine filtration ^a	10 ml of fresh, well-suspended urine	Yes	Medium	High	Yes	Yes	Medium–high sensitivity ^b
Antigen detection							
ELISA ^c	Serum, urine and vaginal lavage	Yes	High	High	No	No	Low sensitivity
POC-CCA ^d	Urine	Semi-quantitative ^e	High	High	Yes	Yes	Low sensitivity
UCP-LF CAA	Urine	Yes ^f	High	High	No	Yes/no ^g	Low sensitivity
Antibody detection							
ELISA	Serum	No	High	Low	No	Yes/no	Yes
IHT	Serum	No	High	Low	No	Yes/no	Yes
DNA detection							
PCR	Fresh or frozen faeces, urine, vaginal lavage and rectal snip	Yes	High	High	No	Yes/no	Yes
LAMP	Fresh or frozen faeces and urine	Yes	High	High	No	Yes/no	Yes

CAA, circulating anodic antigen; CCA, circulating cathodic antigen; ELISA, enzyme-linked immunosorbent assay; FECT, formalin-ether concentration technique; IHT, indirect haemagglutination test; LAMP, loop-mediated isothermal amplification; LF, lateral flow; NA, not applicable; PHCU, public health care unit; POC, point-of-care; UCP, up-converting phosphor. ^aFor *Schistosoma haematobium* eggs only. ^bFiltration can be used in non-endemic areas but requires a large sample (normally a 24-hour urine sample). ^cFor both CAA and CCA. ^dFor *Schistosoma mansoni* CCA only. ^eThe POC-CCA test can be read as 'trace', +, ++ and +++. ^fThe test is quantitative but requires specific equipment for reading the strips. ^gYes/no indicates that the test requires reagents, equipment and trained personnel.

Fig. 5 | **Urogenital schistosomiasis.** Active *Schistosoma haematobium* infection, with egg excretion in urine (parts a–c), and late chronic infection, with calcified eggs (parts d and e). *S. haematobium* eggs on a nucleopore filter after urine filtration (part a). Urinary bladder wall polyps (arrows) visualized by ultrasonography (part b). Dilatation of ureters and bladder wall thickening (arrows) visualized by ultrasonography (part c). Radiography picture showing bladder calcifications (arrow; part d). Cystoscopy showing yellow sandy patches with calcified *S. haematobium* eggs (arrow; part e). Images in parts a, c and d courtesy of M. Sacko, Institut National de Recherche en Santé Publique, Mali. Image in part b reproduced from Oxford Textbook of Medicine 5th Edition edited by Warrell, Cox, and Firth (2010) Figs.7.11.1.6. By permission of Oxford University Press. Image in part e reproduced from REF.²¹⁸, Springer Nature Limited.

especially cervical lesions, can be detected by colposcopy (direct visualization of the cervix using a special microscope), and a pocket atlas with pictures showing the lesions has been developed for use in health-care facilities in endemic areas^{57,114}.

Biomarkers

Several biomarkers have been tested for diagnosing or predicting severe schistosomiasis-associated disease. These include different markers for identification of liver fibrosis in *S. mansoni* or *S. japonicum* infections^{10,81} and inflammatory pathological changes in the urogenital tract in *S. haematobium* infection¹¹⁵. However, such markers are not currently used in routine diagnosis. Several studies have investigated urine biomarkers associated with schistosomiasis and related bladder cancer¹¹⁶, but currently no urine biomarkers have undergone large-scale clinical studies or follow-up studies assessing the cancer-predictive or prognostic value of the tests.

Screening

Screening of populations living in endemic areas is relevant in relation to control programmes, to assess infection prevalence and intensity (that is a proxy for worm burden) before and/or after an intervention, such as MDA^{81,86}. One of the most widely employed, easy-to-use screening methods is testing for *S. haematobium*-related microhaematuria using a reagent strip test¹¹⁷. This approach has been especially useful in school-aged children, in whom microhaematuria strongly correlates with urogenital schistosomiasis⁹⁶, and it has also proved to be useful following intervention¹¹⁷. A meta-analysis has shown an overall sensitivity of the reagent strip test for detection of *S. haematobium* egg-positive urines of 81%, but the overall sensitivity decreased to 72% in previously treated populations¹¹⁷. Direct parasitological methods are inexpensive and easy to use, but a major drawback is their low sensitivity⁸⁷. The POC-CCA assay may prove useful for detection of *S. mansoni* infection and has the logistic advantage that it can be performed directly on a urine sample rather than a more-cumbersome stool or blood sample⁸⁷. The POC-CCA assay is more

sensitive than standard parasitological techniques¹¹⁸, but its applicability is limited in low-endemicity areas where people with *Schistosoma* spp. infection have very few worms.

Tools for detecting *Schistosoma* spp. transmission in the intermediate host snail and the environment are important to achieve the ultimate goal of schistosomiasis elimination^{4,81}. Traditionally, detection of transmission has been done through collection of intermediate host snails followed by incubation or crushing of the snails to detect shedding of schistosome cercariae¹¹⁹ or sporocysts, respectively¹¹⁹. However, the proportion of collected snails shedding cercariae is generally low, and the direct methods are time consuming with low sensitivity. PCR-based methods or loop-mediated isothermal amplification (LAMP) assays have been used to detect prepatent (that is, sporocysts) or patent (that is, cercariae) infection in intermediate host snails¹²⁰. Prediction of *S. japonicum* prevalence and mapping of the risk of infection have been undertaken on the basis of LAMP analysis of its intermediate host snail, *Oncomelania hupensis*¹²¹.

Prevention

Travellers to a schistosomiasis-endemic area should be aware of the risk of infection when engaging in activities involving direct contact with water⁴⁰. However, for people living in rural areas where schistosomiasis is endemic, it may be very difficult if not impossible to avoid water contact. Schistosomiasis is a poverty-related disease, and preventive measures such as access to clean water and good sanitary facilities are important in reducing the risk of infection but often are not present¹²². Furthermore, these measures will have little effect on reducing the risk through occupational exposure, such as fishing in the rivers and lakes, and such activities are often the main or only source of income for families¹²³. *S. japonicum* infection is a zoonosis; thus, preventive measures will have to be directed towards infections in animals as well, particularly water buffaloes, which act as major reservoirs for the parasite¹²⁴.

Despite intensive development efforts, currently no schistosomiasis vaccines are available^{125,126}.

Management

Management of schistosomiasis involves the targeted treatment of patients diagnosed with schistosomiasis in an endemic area (in a hospital or some other medical facility if available) and in returning travellers or migrants. The aim of treatment with the anti-schistosomal drug praziquantel is curative therapy, and treatment can be repeated several times until the infection is eliminated (that is, no eggs are detected upon microscopic examination of faeces or urine). The recommended dose is generally lower for *S. mansoni* and *S. haematobium* infections than for *S. japonicum* and *S. mekongi* infections; higher doses are generally split into two administrations a few hours apart⁵⁵. Global community-based schistosomiasis control programmes, focusing on MDA, are important to reduce morbidity. Of note, in MDA programmes, praziquantel is given only once; thus, as the drug is ineffective against migrating schistosome, if these larvae are present in an individual, a new patent infection will arise.

Praziquantel

The most effective and widely used compound is praziquantel, an acylated quinoline-pyrazine derivative that has been the mainstay of schistosomiasis treatment for >30 years. Randomized controlled trials showed that oral praziquantel is safe and efficacious against adult worms of all *Schistosoma* spp., although its precise mechanism of action remains to be established (BOX 2), and it is the current therapeutic drug of choice for treating patients diagnosed with schistosomiasis¹²⁷. Praziquantel is also the cornerstone of global community-based schistosomiasis control programmes, focusing on MDA, to reduce morbidity^{128,129}. Controlled trials (one in Uganda, testing praziquantel against *S. mansoni* infection, and the other in the Philippines, testing praziquantel against *S. japonicum* infection) provide support for the use of praziquantel for the treatment of pregnant women after the third trimester, in line with WHO recommendations¹³⁰.

Praziquantel was discovered in the mid-1970s, commenced trials in humans as an anti-schistosomal drug candidate by 1978 and came on the market as Biltricide (Bayer) in 1988 (REF. 131). Subsequently, the efficacy, in terms of cure rate (CR) and egg reduction rate (ERR), and safety of praziquantel have ensured its widespread use. A meta-analysis showed that the WHO-recommended dose of praziquantel (40 mg/kg) achieved CRs of 94.7% for *S. japonicum* infections, 77.1% for *S. haematobium* infections, 76.7% for *S. mansoni* infections and 63.5% for mixed *S. haematobium* and *S. mansoni* infections; mean ERR was 95% for *S. japonicum*, 94.1% for *S. haematobium* and 86.3% for *S. mansoni*¹³². Praziquantel is effective within 1 hour after being ingested; although well absorbed, it undergoes extensive first-pass hepatic clearance (that is, a fraction of the drug (~80%) is metabolized in the liver to inactive metabolites that are excreted in the urine via the kidneys). Praziquantel is also secreted in its active form in breast milk², but in minute levels; thus, adverse events for the child are not expected, although it is recommended that women should not breastfeed on the day of praziquantel treatment and during the subsequent 72 hours. Praziquantel can be used to

treat young children (of >4 years of age) and pregnant women after the first trimester⁴.

In MDA-based schistosomiasis control programmes, a single dose of praziquantel is recommended by the WHO¹³³, although this regimen has been questioned¹³⁴ and recent pharmacodynamic and pharmacokinetic data support a higher dose, particularly for children of <6 years of age¹³⁵. A dose or 'tablet' pole is used in the field to estimate the number of tablets given on the basis of height rather than weight of the patient¹³⁶, and this has been modified recently for treating preschool-aged children (<5 years of age)¹³⁷ as CRs in this age group are low¹³⁸.

Co-infections of *Schistosoma* spp. and soil-transmitted helminths are very common in areas where these worms are co-endemic, such as in Africa and Asia. In these areas, joint preventive therapy of albendazole (another anthelmintic drug for treating soil-transmitted helminth infections) and praziquantel is recommended by the WHO, with schedules related to community prevalence of the two infections¹³⁹.

Adverse events associated with praziquantel therapy are generally regarded as minimal, including dizziness, headache, abdominal pain, transient nausea, pruritus (itch) and rash, and are likely due to the consequences of antigenic release from dead or dying worms and not the drug itself^{3,55,127}. Allergic reactions to praziquantel are rare¹⁴⁰. In individuals with schistosomiasis and concurrent cysticercosis (*Taenia solium* (pork tapeworm) infection that results in the development of cysts in the central nervous system, skin, eyes and muscle), praziquantel can induce seizures and/or cerebral infarction and permanent eye lesions as a result of the severe inflammatory reactions caused by the dying *T. solium* worms¹⁴¹. Currently there is no monitoring or evaluation of MDA for schistosomiasis in African communities where schistosomiasis and *T. solium* cysticercosis are

Box 2 | Praziquantel mechanism of action

Praziquantel induces tetanic contractions of the parasites and the appearance of tegumental vacuoles, resulting in surface damage that causes the adult worms to detach from venous walls and die². The presence of host antibodies (presumably recognizing the worm antigens that become exposed as a result of praziquantel-induced damage) has been shown to be essential for praziquantel efficacy in animal models¹²⁷. Nevertheless, the precise mechanism of action of praziquantel remains unknown. Indirect evidence suggests that praziquantel increases schistosome calcium uptake via calcium ion channels in the adult worm tegument and subtegument. However, some doubt has been raised whether calcium influx is central to the anthelmintic effect of praziquantel, and alternative mechanisms of action have also been proposed, including interference with the function of myosin regulatory light chains²⁰² or antagonism of adenosine uptake²⁰³. The tegument antigen (also known as tegumental-allergen-like (TAL) protein 1 (SmTAL1) or antigen SmA22.6) from *Schistosoma mansoni* binds both calcium ions and praziquantel, and it has been suggested that the drug acts, in part, through antagonism of the activities of this protein, although this hypothesis warrants further investigation²⁰⁴.

co-endemic; thus, the risk of adverse events in individuals with *Schistosoma* spp. and *T. solium* co-infections could be substantially underestimated¹⁴².

Limitations of praziquantel

Praziquantel has no effect on immature schistosomes and cannot prevent reinfection or alter the schistosome life cycle^{134,143}. Furthermore, there have been some reports of *S. mansoni* and *S. haematobium* infections that are either poorly or not responsive to praziquantel in areas where there has been heavy use of the drug^{2,3,127,144}. In addition, some experimental evidence in mice indicates that schistosome parasites residing in mice that received repeated *in vivo* praziquantel treatments matured into adult worms that had reduced drug sensitivity; this phenomenon seems to be amplified over each generation of worms¹⁴⁵. Furthermore, drug-tolerant schistosome worms have increased levels of P-glycoprotein¹⁴⁶, which may correlate with reduced drug efficacy, as increased expression of this member of the ATP-binding cassette superfamily of proteins is known to be associated with multidrug resistance in tumour cells. However, there is no clear confirmation that clinically relevant praziquantel resistance has developed, on the basis of a considerable number of studies in different endemic settings, which have indicated no loss in efficacy in individuals with schistosomiasis who have received multiple courses of treatment over many years¹⁴⁷. In addition, there are no reports to date of the development of praziquantel-resistant *S. japonicum* parasites following extensive use of the drug in the People's Republic of China¹⁴⁸. Notwithstanding, praziquantel resistance cannot be discounted in the future, and there is also widespread concern of the risk associated with relying on a single drug, particularly as MDA is being further scaled up.

The potential for the development of drug resistance and the incomplete efficacy of praziquantel further highlight the need to continue research into developing new compounds and for improved formulations of praziquantel. A series of endoperoxide and praziquantel conjugates had *in vitro* activity against both adults and schistosomula of *S. japonicum* and against adult *S. mansoni*¹⁴⁹. Furthermore, a combination of praziquantel and the proton pump inhibitor omeprazole had a synergistic effect against adult worms of *S. mansoni* *in vitro*¹⁵⁰. By contrast, praziquantel, in combination with the anti-malarial Synriam (Ranbaxy), did not increase efficacy compared with praziquantel alone in a randomized, exploratory phase II trial in adolescents infected with *S. mansoni* in West Africa¹⁵¹.

The large size of praziquantel tablets and the characteristic bitter taste of the drug mean that treating preschool-aged children is challenging as they may be unable to swallow the whole tablet and, if they chew it, vomiting can occur. The drug is manufactured and administered as a racemic mixture of (S) and (R) stereoisomers, and although the anti-schistosomal properties are associated with (R)-praziquantel, the bitterness is mostly due to (S)-praziquantel. Thus, there are approaches to change the synthesis of praziquantel to remove the (S) isomer¹⁵², and another programme (the Pediatric Praziquantel Consortium, a public-private

partnership established in 2012) is developing a paediatric formulation suitable for treating schistosomiasis in preschool-aged children¹⁵³, which, once available, could be included as a primary health-care option through the Integrated Management of Childhood Illnesses (IMCI) platform developed by the WHO and UNICEF (United Nations Children's Fund)¹⁵⁴.

Artemisinin and its derivatives

Despite its effectiveness against adult schistosomes, praziquantel cannot be used as a chemoprophylactic drug (chemoprophylaxis refers to the use of drugs (given at prophylactic doses) to temporarily protect individuals entering an area of high endemicity) owing to its short half-life (1–1.5 h) and because 3–21-day-old migrating schistosomula are refractory to the drug. The potent anti-malarials artesunate and artemether, derived from artemisinin, the active ingredient of the medicinal plant *Artemisia annua*, are effective against schistosomula during the first 21 days of infection in humans and animals and are capable of killing all immature schistosomula if given every 2 weeks. The mechanism of action of these schistosomicides is not known, although artemether interacts with haemin (an iron-containing molecule that can be formed from haem, the cofactor of human haemoglobin) to exert a toxic effect on schistosomes¹⁵⁵. The anti-schistosomal activity of the artemisinin derivatives on schistosome infections in animals and in clinical trials has been extensively reviewed¹⁵⁶. Artemether has been used effectively in the chemoprophylaxis of high-risk groups, such as fishermen and flood relief workers, in schistosomiasis-endemic areas of the People's Republic of China¹⁵⁷ and might be useful for individuals travelling to schistosomiasis-endemic areas, yet further evidence is required to support this claim¹⁵⁸. Adverse events such as fever, giddiness, sweating and abdominal discomfort are minimal and temporary. The dose required for schistosomiasis chemoprophylaxis is lower than that used for the treatment of malaria; nevertheless, the use of artemether and artemisinin-based combinations for schistosomiasis chemoprophylaxis is not recommended in malaria-endemic areas because of the possible selection of artemisinin-resistant *Plasmodium* spp. parasites.

It has been suggested that, in areas where continuous schistosomiasis transmission occurs, artemether and other artemisinins can be used as a combined therapy with praziquantel to improve CRs. In support of this approach, controlled trials in animals indicated that the combination of praziquantel plus artemether was safe, resulting in higher CRs than therapy with praziquantel alone¹⁵⁷, and a meta-analysis indicated twice higher CRs in humans with the combination therapy than with praziquantel monotherapy¹⁵⁹. By contrast, however, in a randomized, placebo-controlled double-blind trial in the People's Republic of China, combinations of artemether and praziquantel for the treatment of acute schistosomiasis japonica (caused by *S. japonicum*) did not result in increased levels of efficacy compared with praziquantel monotherapy¹⁶⁰. Praziquantel monotherapy was also more efficacious in the treatment of children with *S. mansoni* infection in western Kenya than another combination therapy comprising artemether with

sulfalene plus pyrimethamine, an effective artemisinin-based anti-malarial drug combination¹⁶¹. Furthermore, the addition of mefloquine (a quinine-derived anti-malarial) or mefloquine–artemether (fixed-dose combination) did not increase the efficacy of praziquantel against chronic *S. haematobium* infection in school-aged children in Côte d'Ivoire¹⁶². Thus, overall, the role of artemether-based combination therapy in the treatment of schistosomiasis is still unclear¹⁶³.

Adjuvant care

In addition to worm elimination (or at least reduction of the intensity of infection), the management of schistosomiasis includes treatment of the complications that may arise following infection.

Corticosteroids, such as prednisone, are used to treat acute schistosomiasis (within 2 months of cercarial exposure)⁹. If the diagnosis and treatment of neuroschistosomiasis are timely, the prognosis is generally good. In individuals with neuroschistosomiasis, corticosteroids and anticonvulsants may be required in addition to praziquantel^{2,55}. Corticosteroids help to reduce acute allergic reactions, should they occur, and prevent or reduce damage induced by excessive inflammation associated with schistosome egg granulomas in the central nervous system. Anticonvulsants are used to treat seizures associated with neuroschistosomiasis; however, lifelong use is generally unnecessary. Corticosteroids are also used to treat intracranial hypertension and hydrocephalus (accumulation of cerebrospinal fluid within the brain) in neuroschistosomiasis¹⁶⁴. Surgery (that is, a ventriculoperitoneal shunt, connecting a brain ventricle with the peritoneal cavity) should be undertaken only on patients who deteriorate, despite clinical management, and for special cases such as those with symptoms of medullary compression¹⁶⁴.

Approximately 5–10% of patients with intestinal schistosomiasis progress to the most severe form, hepato-splenic schistosomiasis¹⁶⁵. This form is associated with portal hypertension and splenomegaly and can result in the formation of oesophageal varices with episodes of gastrointestinal bleeding, even with liver function preserved. Treatment of variceal bleeding includes band ligation, endoscopic sclerotherapy, splenectomy, portal systemic shunts and combinations of gastro-oesophageal devascularization¹⁶⁶. Praziquantel should always be given to patients with advanced disease to prevent cardiopulmonary schistosomiasis (a severe clinical manifestation occurring when prolonged and extensive obstruction of the pulmonary arterioles by schistosome eggs leads to pulmonary hypertension and cor pulmonale) and to arrest fibrosis¹⁶⁶.

Quality of life

The assessment of the quality of life of individuals with schistosomiasis is a difficult endeavour because the life cycles of the parasites are complex, the disease shows considerable spatial and temporal heterogeneity and there is a paucity of readily available tools for accurate diagnosis in the field, particularly in settings where infection intensities are low⁸⁷. For example, the sensitivity of the Kato-Katz technique for the diagnosis of

S. mansoni and *S. japonicum* infections in epidemiological surveys might be <25% in low-endemicity areas^{167,168}. Moreover, there is considerable day-to-day and intraspecimen variation of faecal egg output, which makes reaching a definitive diagnosis difficult¹⁶⁷. Of note, infection occurs several weeks before *Schistosoma* spp. eggs are detected in stool or urine, and it might take many months and multiple infections until people feel that quality of life is affected¹⁶⁹. Clearly, this has ramifications on people's perception of the disease and its morbidity and how to measure and quantify quality of life.

Being a debilitating disease, schistosomiasis has negative implications for human socio-economic activities in endemic areas. Late chronic infection in children compromises cognitive development, growth and physical fitness. In adults, late chronic infection may affect work efficiency, resulting in reduced economic productivity. Schistosomiasis can lead to nonspecific morbidity such as anaemia, impaired childhood growth and malnutrition^{170,171} as a result of continued inflammation during established active infection. This morbidity is common among school-aged children living in endemic areas, where schistosomiasis may also result in substandard school performance⁴. Indeed, evidence from randomized drug intervention trials suggests that children had increased physical fitness 1–2 months post-treatment, their skin-fold thickness (a measure that estimates subcutaneous body fat) improved 1–8 months post-treatment, they gained weight 3–12 months post-treatment and they had improved cognition 3 months post-treatment. Meanwhile, levels of perceived pain and anaemia were lower at a 6-month treatment follow-up (C. King, personal communication).

Published estimates show considerable variation with regard to the number of at-risk population, number of people infected with *Schistosoma* spp., annual mortality and the global burden of disease. In 1998, the first published estimate of the burden of schistosomiasis was 1.7 million DALYs¹⁷². Another estimate by the WHO, in 2002, gave a threefold higher estimate of 4.5 million DALYs³³. A systematic review, coupled with an analysis of performance-related symptoms and disability-associated outcomes for the human infections associated with the different schistosome species, concluded that the 4.5 million DALY estimate was probably a serious underestimation of the 'true' burden³⁶. The highest burden estimate for schistosomiasis reported in the peer-reviewed literature is 70 million DALYs¹⁷³. New efforts by hundreds of disease experts who systematically review the literature and employ mathematical models to obtain prevalence, incidence, morbidity and mortality data for more than 300 diseases, injuries and risk factors resulted in refined, internally consistent global burden of disease estimates; in 2016, the burden of schistosomiasis was estimated at 1.9 million DALYs³². This most recent trend of declining DALYs is indicative of progress made in schistosomiasis control, most likely as a result of large-scale MDA campaigns²⁷. Overall, the variability of these estimates underscores the challenge of precisely measuring and quantifying the quality of life of individuals with schistosomiasis.

Box 3 | Research priority areas

Tools and interventions

- Develop inexpensive, field-applicable diagnostic assays to determine worm burden, to distinguish a current from a past infection, to monitor successful drug cure of individuals in low-prevalence areas and to assess treatment failures
- Develop and test new drugs
- Test combinations of praziquantel with new drugs
- Monitor spread of praziquantel drug resistance and its effect on *Schistosoma* spp. transmission
- Develop and evaluate integrated control interventions with the long-term goal of elimination
- Develop mathematical models incorporating these control measures and assessing their cost-effectiveness

Transmission

- Undertake genetic studies on host–parasite strain interactions and compatibility
- Determine the extent of introgression (the movement of a gene from one species into the gene pool of another by the repeated backcrossing of an interspecific hybrid with one of its parent species) between *Schistosoma* spp. infecting humans and ruminants and the prevalence and distribution of their hybrids
- Undertake comprehensive evaluation of the economic burden of livestock and zoonotic schistosomiasis to determine whether extending preventive treatment to include animal hosts in a 'One Health' approach is desirable
- Determine the effect of environmental changes (climate change, dams, irrigation projects, etc.) on the epidemiology and transmission of schistosomiasis
- Apply remote sensing and geographical information system techniques in combination with direct ground truth verification to determine future transmission patterns of schistosomiasis and at-risk areas
- Increase public awareness of the risks and effect of schistosomiasis on the community and the health benefits of disease control

Disease burden and epidemiology

- Determine the true economic costs and disability-adjusted life years due to both established schistosomiasis-associated morbidity and following reinfection
- Determine the effects of host genetics on morbidity, risk of infection and infection course
- Further understand immunopathology, immunoregulation and immune evasion mechanisms in schistosomiasis
- Assess the effect of other infections on the burden of schistosomiasis and vice versa
- Monitor the effects of schistosomiasis on vaccination programmes

Basic science

- Discover new vaccine targets and test these with new adjuvant formulations in nonhuman primates before human clinical trials
- Assess new and old vaccine candidates as prophylactic, therapeutic or anti-fecundity (reduction in the number of eggs produced) vaccines
- Test vaccine candidates in rigorous field and clinical trials
- Continue genomics and post-genomics studies of schistosomes and intermediate host snails
- Undertake post-genomics studies to address unanswered questions on the basic biology of schistosomes

Outlook

The WHO set a target of potential global elimination of schistosomiasis as a public health problem by 2025 (REF.¹⁷⁴). To this end, there has been an increased emphasis on reducing schistosomiasis prevalence and intensity of infection, and hence morbidity, mainly through the use of large-scale administration of praziquantel to school-aged children and sometimes other high-risk groups. However, the introduction of such programmes has not been a totally unqualified success on its own despite important health benefits in terms of achieving decreased morbidity in several settings¹⁷⁵. Furthermore, these large-scale preventive treatment programmes may, in the longer term, profoundly affect *Schistosoma* spp. biology and immunoepidemiology with potentially important consequences for public health; thus, careful surveillance and monitoring will be required in the future as MDA programmes are rolled out¹⁷⁶. Furthermore, the development of new complementary interventions and new approaches to control are required.

To achieve the WHO target, the 2007 comprehensive schistosomiasis research agenda should be revisited¹⁷⁷. The agenda comprised elements ranging from basic science to public health and categorized the research into four themes: tools and interventions for schistosomiasis (including drugs, diagnostics and control programmes and their implementation); ecological, biological and societal aspects of schistosomiasis transmission; schistosomiasis disease burden and epidemiology; and basic science of relevance to schistosomiasis, including vaccines, immunology and pathology. We summarize the most important outstanding areas and emphasize some of the pressing research needs in BOX 3.

Diagnosis and prevention

Precise diagnosis of *Schistosoma* spp. infections, in both snail and mammalian hosts, will be crucial in achieving morbidity reduction and eventually disease elimination, particularly in areas where extensive control has reduced schistosomiasis prevalence and infection

intensity to very low levels. Thus, the development of improved, more-cost-effective and field-friendly diagnostic tests represents a key area for future applied schistosomiasis research^{81,87}.

Vaccines. No schistosomiasis vaccine has yet been accepted for public use. One vaccine candidate, monovalent recombinant protein *S. haematobium* glutathione (S)-transferase (Sh28GST) with adjuvant (Bilhvax, Eurogentec)¹⁷⁸, has been tested in a clinical phase III trial, the results of which are still pending¹²⁵. Schistosomiasis vaccine development is hindered not only by current limited funding but also by the complicated immunology associated with the disease¹⁷⁹. Protective responses in natural settings favour IgE production; a schistosomiasis vaccine that is dependent on IgE would be potentially problematic and would likely be affected by regulatory and safety factors owing to potential vaccine-induced anaphylaxis (as IgE is associated with allergic responses)^{179,180}. A step-by-step approach involving identification of protective antigens, selection and cloning of the most promising among them and then ensuring the feasibility of large-scale production has resulted in the identification of a large number of putative, protective antigens as vaccine candidates¹⁸¹. Support for development of schistosomiasis vaccines (both a human schistosomiasis vaccine and a veterinary vaccine for bovine use) and their evaluation in public health programmes has been reinforced by the National Institute of Allergy and Infectious Diseases of the NIH in the United States and the Bill & Melinda Gates Foundation; although in some areas schistosomiasis control could be achieved through current MDA programmes, global control would require an approach integrated with additional interventions, including suitably adjuvanted vaccines^{125,126}.

Indeed mathematical modelling supports the view that even partially protective schistosomiasis vaccines would contribute to reducing schistosome infections and interrupting transmission in endemic areas¹⁸².

Snail control

Elimination of a human parasitic disease such as schistosomiasis requires interruption of a complex pathway of transmission. In the case of *S. japonicum*-associated schistosomiasis, control is especially challenging as *S. japonicum* can persist in a range of nonhuman mammalian hosts.

Control efforts are hindered by rapid reinfection of previously treated individuals. The removal of infected snails would reduce the number of water-borne infectious cercariae, thereby reducing the risk of reinfection. Snail control through the use of chemicals, such as niclosamide, released directly into water, has been implemented in many areas. However, to be most effective, chemicals should be used at least biannually, making the strategy time consuming and expensive, especially when large areas are involved. Additional concerns are the toxicity of molluscicides to larger animals such as fish and the general pollution they cause. Other snail control approaches are environmental methods, such as digging water drainage tunnels or ditches to flood and bury the snail habitats, and the use of biological and ecological measures, including using snail predators such as fish and crustacea¹⁸³ or introducing schistosome-resistant snail strains into the wild snail population¹⁸⁴. Despite the concerns, affordable snail control, combined with MDA using praziquantel, could be part of the optimum strategy leading to schistosomiasis elimination¹⁸⁵.

New anti-schistosomal drugs

No anti-schistosomal drug candidates are presently undergoing human clinical trials, a fact that reflects the general current drug discovery and development landscape for parasitic helminth infections¹⁸⁶. Nevertheless, although it is unlikely that a new anti-schistosomal drug will be developed to compete with praziquantel in the near future¹³¹, owing to the incomplete efficacy of praziquantel and the possibility of resistance developing, there is an urgent need to find an alternative or complementary treatment. Research should continue to develop new compounds or repurposed drugs as an alternative for treatment¹⁸⁷ (BOX 4).

The availability of the annotated genomic sequences for the three major *Schistosoma* spp. infecting humans^{188–190} has been pivotal in re-stimulating the search for new anti-schistosomal drug targets. In addition, in vitro and in vivo drug screening has been undertaken of anticancer compounds and other agents with potential for repurposing to treat schistosomiasis^{191,192}. Currently, approaches used in schistosomiasis drug discovery programmes include molecular modelling methods, drug repurposing studies, structure-based drug design and target-focused compound screening^{189,193,194}. These approaches have enabled biochemical mapping of metabolic pathways to predict metabolic rate-limiting steps in schistosomes, which can help to identify molecules that could be new drug targets or are known drug targets in other organisms.

Box 4 | Examples of anti-schistosomal drugs under development

Oxamniquine is a safe anti-schistosomal drug that is highly effective in killing adult worms and immature schistosomula, but only of *Schistosoma mansoni* species, and this drug is no longer readily available. However, a combination of genetic and structural analyses determined the structure of oxamniquine in complex with its target enzyme in the schistosome, providing new insight for structure-guided modifications of the drug to make new derivatives that are also effective against *Schistosoma haematobium* and *Schistosoma japonicum*²⁰⁵.

HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) reductase, the target for statins (a class of cholesterol-lowering drugs), was first identified as a metabolic rate-limiting step in *S. mansoni* and was later confirmed by chemical and genetic methods to be a validated drug target in schistosomes²⁰⁶.

Another compound that has shown promise as an anti-schistosomal drug is imatinib, a protein kinase inhibitor commonly used in cancer therapy²⁰⁷.

The zinc-dependent histone deacetylases (HDACs) have received much attention as targets for epigenetic therapies, notably anticancer treatments. The most studied HDAC in schistosomes is HDAC8 (smHDAC8); compelling evidence provides proof of concept that targeting this and other epigenetic enzymes is a valid approach to treat schistosomiasis and possibly diseases caused by other eukaryotic pathogens²⁰⁸. The related sirtuins are a superfamily of evolutionarily conserved NAD⁺-dependent protein N-ε-acetyl-lysine (AcK) deacetylase enzymes and key epigenetic players, carrying out important histone modifications. Thus, sirtuins also represent highly relevant targets for the development of new anti-schistosomal drugs²⁰⁹.

Other identified schistosome targets with potential for the development of rationally designed anti-schistosomal drugs include heat shock 70 kDa protein (HSP70)²¹⁰, thioredoxin-glutathione reductase²¹¹, prolol oligopeptidase²¹², glucose transporters²¹³, a serotonergic G protein-coupled receptor (GPCR)²¹⁴, ion (transient receptor potential (TRP)) channels²¹⁵ and acetylcholinesterase²¹⁶.

One of the major signalling pathways in schistosomes is apoptosis, and the key molecular components have been identified through advances in genomics and transcriptomics sequencing¹⁹⁵. Apoptosis has been extensively targeted with drugs, particularly those used in cancer treatment. Some of these drugs target the BCL-2 family of proteins, which regulate the intrinsic apoptotic pathway, and these compounds are now considered as potentially important anti-schistosomal agents¹⁹⁶. The epigenome and epigenetic components represent further anti-schistosomal drug targets in view of the tight control of gene transcription associated with the complexity of the schistosome life cycle¹⁹⁷.

The large number of putative drug targets identified through these approaches will require extensive screening to determine which ones are most capable of yielding suitable downstream drug candidates. Subsequently, selected compounds, such as organometallic agents¹⁹⁸, or those derived from natural products¹⁹⁹, will require rigorous, costly scrutiny and testing for toxicity and efficacy²⁰⁰ before full-scale clinical application.

Disease burden

A precise evidence-based consensus should be developed on how to evaluate and implement the available data on schistosomiasis disease burden locally, nationally and globally. Control efforts have been successful,

notably in the People's Republic of China, but it is now crucial to extend these achievements to areas with limited resources, in particular many countries in sub-Saharan Africa. The battle against schistosomiasis will not be won solely through the distribution and deployment of praziquantel. The creation of strong and efficient health-care systems and the implementation of integrated, cost-effective schistosomiasis control measures that are sustainable in the long term represent important challenges for the public health community well into the 21st century. At the same time, climate change and elevated temperatures may increase the geographical distribution of schistosomiasis through expansion of suitable environments for snails into higher altitudes and into further northern latitudes. When the consequences of climate change become more-pronounced, an increase in the number of migrants will likely result, governed by individuals' vulnerability and resilience strategies, and it is recognized that several aspects of population movements are directly linked to the spread of schistosomiasis²⁰¹. Similar to many other neglected tropical diseases, schistosomiasis is a disease of poverty, and strong local and international governmental involvement and support will be needed to finally consign this disease to history.

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Author contributions

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