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Diagnosis and treatment of schistosomiasis in children in the era of intensified control

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In the current era of intensified and integrated control against schistosomiasis and other neglected tropical diseases, there is a need to carefully rethink and take into consideration disease-specific issues pertaining to the diagnosis, prevention, control and local elimination. Here, we present a comprehensive overview about schistosomiasis including recent trends in the number of people treated with praziquantel and the latest developments in diagnosis and control. Particular emphasis is placed on children. Identified research needs are offered for consideration; namely, expanding our knowledge about schistosomiasis in preschool-aged children, assessing and quantifying the impact of schistosomiasis on infectious and noncommunicable diseases, developing new antischistosomal drugs and child-friendly formulations, designing and implementing setting-specific control packages and developing highly sensitive, but simple diagnostic tools that are able to detect very light infections in young children and in people living in areas targeted for schistosomiasis elimination.

Keywords: behavior change • co-infection • control • diagnosis • elimination • praziquantel • sanitation • schistosomiasis • snail control • treatment

Schistosomiasis is a chronic neglected disease of poverty caused by blood flukes of the genus *Schistosoma* [1–3]. Hence, schistosomiasis mainly affects people who live in deprived or marginalized communities in the tropics and subtropics. According to the Global Burden of Disease Study 2010 (GBD 2010), schistosomiasis ranks third after leishmaniasis and soil-transmitted helminthiasis among the neglected tropical diseases and is responsible for an estimated 3.3 million disability-adjusted life years [4]. In 2012, the WHO announced the new goals for 2020, namely to eliminate several of the neglected tropical diseases and to intensify control of other neglected tropical diseases, so that they no longer pose public health problems [5]. WHO gets support from public (e.g., Ministries of Health) and private partners (e.g., pharmaceutical companies) and nongovernmental organizations. These partners collectively signed the London Declaration and are thus committed to tackle neglected tropical diseases including schistosomiasis [301]. Specifically, the aim for schistosomiasis-endemic countries is to periodically administer the antischistosomal drug praziquantel to populations at risk of infection and hence prevent morbidity. This strategy is phrased 'preventive chemotherapy.' The primary target, as endorsed by Member States in World Health Assembly (WHA) resolution 54.19 in 2001 – but still far from being met – is to treat at least 75% and up to 100% of school-aged children (SAC) who are at highest risk of morbidity [6,7]. In May 2012, WHA resolution 65.21 has been endorsed, acknowledging progress in schistosomiasis control and hence considering elimination as the next logical step and an attainable goal in some low-endemicity areas [8]. Hence, Member States are encouraged to work toward the interruption of transmission and to initiate elimination campaigns wherever appropriate [8]. Additionally, the Schistosomiasis Consortium for Operational Research and Evaluation is currently supporting a multiyear integrated program aiming at schistosomiasis elimination on Zanzibar [9]. Lessons learnt will be important for shaping the elimination agenda [10]. Although the primary tool for large-scale schistosomiasis control programs is preventive chemotherapy [11], Member States and the international community should not only provide means for treatment, but instead

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improve the water and sanitation infrastructure, alongside setting-specific hygiene interventions and snail control [8,12].

In this review, we summarize the epidemiology of, and morbidity due to, the three main *Schistosoma* species infecting man. The centerpiece of our review focuses on tools and strategies to diagnose, prevent, treat and control/eliminate schistosomiasis. In view of intensified control efforts, we highlight available drugs and regimens, different control approaches, novel diagnostic tests and the potential impact of schistosomiasis on co-infections and comorbidities due to HIV/AIDS, tuberculosis, malaria and intestinal protozoa infections. Since children are the main carriers and spreaders of schistosomiasis, particular emphasis is placed on this age group with child-related aspects discussed in detail toward the end of each subchapter.

Epidemiology of *Schistosoma* infections

Schistosomiasis is a water-based parasitic disease, and the causative agents are blood flukes of the genus *Schistosoma* [2,13–15]. There are six *Schistosoma* species that can infect humans. However, of particular public health importance are only three species, namely *S. haematobium*, *S. japonicum* and *S. mansoni*. Schistosomiasis has a fairly complex life cycle. In brief, the adult female and male worms live in permanent pairs in the perivesical (*S. haematobium*) or portal veins and mesenteric blood vessels (other species). Eggs produced by the female worms reach the bladder or intestine, respectively, from where they can be excreted with urine or feces [3]. In case the eggs get in contact with freshwater, the parasitic first-stage larva, the miracidium, hatches. Miracidia infect species-specific intermediate hosts, freshwater snails of the genus *Bulinus* (*S. haematobium*, *S. intercalatum* and *S. guineensis*), *Biomphalaria* (*S. mansoni*), *Oncomelania* (*S. japonicum*) and *Neotricula* (*S. mekongi*), in which they multiply asexually. Snails shed hundreds to thousands of cercariae (4–6 weeks after infection), and this larval stage is infective for humans. If humans get in contact with natural freshwater, cercariae are able to penetrate their skin, are transported with the blood stream via the lungs to the liver, mature into adult worms in the portal veins and finally mate and migrate to their final destination. Although most *Schistosoma* species have humans as the only definitive host, *S. japonicum* also infects a large range of domestic and wild animals, including cattle, dogs, pigs, water buffaloes and rodents, thus contributing to disease transmission [13,16].

High schistosomiasis transmission areas are located in sub-Saharan Africa (mainly *S. haematobium* and *S. mansoni*), Brazil (*S. mansoni*) and the Philippines (*S. japonicum*). A low risk of acquiring *Schistosoma* infections occurs in the Middle East (*S. haematobium* and *S. mansoni*), Surinam, Venezuela and some of the Caribbean islands (*S. mansoni*), Indonesia and the People's Republic of China (*S. japonicum*), Lao People's Democratic Republic and Cambodia (*S. mekongi*) [2,10].

Age prevalence curves for *Schistosoma* infection typically rise from early childhood, peak in SAC or adolescents and decline to reach low levels in adulthood [13,17,18]. There is evidence that, depending on exposure history, resistance to infection can be acquired over time, resulting in lower infection rates and intensities in adults [19,20]. However, data obtained from a cross-sectional survey done in western Côte d'Ivoire suggest that a second peak in prevalence occurs in individuals aged 45 years and above [21]. People living in endemic areas, who are using unprotected open water bodies as domestic sources or are exposed to natural freshwater due to occupational or recreational activities, have an elevated risk of infection or reinfection [14,22,23]. Living in close proximity to natural freshwater bodies constitutes an important risk factor for children and other community members, as it leads to frequent exposure to open water bodies (e.g., while washing clothes or fetching water, or during recreational activities such as swimming, bathing, playing or fishing) [23–26].

Discussion point

Several studies have explored ways to change the behavior of children to reduce their risk of becoming infected with schistosomiasis. For example, health education through active teaching and learning, using songs, poetic dramas, short plays and peer discussions result in increased knowledge of how to prevent schistosomiasis and reduce risky behavior in schoolchildren [27]. A study carried out in Mwanza, United Republic of Tanzania found that participatory hygiene and sanitation transformation (PHAST) interventions increased peoples' knowledge about schistosomiasis transmission and succeeded in changes in their perceptions and attitudes toward water contacts [28]. Children below the age of 15 years had less water contact after the PHAST activities. Alternative play areas and safe play options, or water recreation areas such as artificial pools, are considered as effective means for reducing the infection risk for children, particularly when used in combination with health education and treatment [29,30].

Morbidity due to *Schistosoma* infection

The clinical manifestations of schistosomiasis can be grouped into several phases, and they differ between people living in endemic areas and nonimmune travelers upon primary infection. In the earliest stage, a cutaneous rash might develop at the site where the percutaneous penetration of the cercariae occurred. This localized eruption typically appears within the first week of infection and disappears after some hours. A first generalization of disease can be seen in the so-called 'Katayama fever' (sometimes also referred to 'Katayama syndrome'), which is named after a Japanese district that was once endemic for schistosomiasis japonica [31]. This immune-mediated syndrome constitutes a hypersensitivity reaction and may develop around 2–8 weeks after *Schistosoma* infection when maturing schistosomes migrate within the host and start egg production. Katayama fever is mainly seen in nonimmune individuals after their first exposure to schistosomes, and hence is an important differential diagnosis in returning travelers with fever. However, Katayama fever is rarely seen in endemic areas [32]. Despite the syndrome's name, fever is absent in at least one-third of symptomatic patients, and a good knowledge of other typical

symptoms is mandatory to suspect acute schistosomiasis in affected individuals [33]. Dry cough, abdominal pain, general fatigue, myalgia, headache and diarrhea or abdominal tenderness are commonly seen and often accompanied by a peripheral blood eosinophilia [34]. Severe, possibly life-threatening complications are rare and include cardiac and central nervous involvement. Table 1 summarizes the clinical symptomatology of acute schistosomiasis.

Although acute schistosomiasis is a relevant health problem in returning travelers, morbidity due to chronic schistosomiasis is by far more significant in affected populations who live in schistosome-endemic areas. Adult schistosomes produce and excrete eggs, about half of which get trapped in small blood vessels of the bladder (*S. haematobium*) or liver (*S. japonicum* and *S. mansoni*) where the eggs and their secretions constitute a continuous antigenic stimulus, leading to granuloma formation around the eggs as an attempt to protect the affected organs from damage [35]. This persistent inflammatory immune response mechanism, however, leads to chronic genitourinary and renal disease (*S. haematobium*) as well as hepatic, gastrointestinal and even pulmonary morbidity (other species). Chronic complications account for most of the schistosomiasis burden [4,36,37]. *Schistosoma mansoni* and *S. japonicum* commonly cause hepatic fibrosis that favors the development of portal hypertension with devastating health consequences, such as variceal bleeding and hypersplenism, whereas *S. haematobium* typically leads to bladder lesions [38]. Inflammation and ulceration of the bladder give rise to persistent hematuria and dysuria, and the ever present urothelial alterations constitute an important risk factor for the development of squamous cell bladder cancer. Obstructive changes of the bladder wall in hosts chronically infected with *S. haematobium* might eventually lead to life-threatening upstream renal complications (hydronephrosis, nephrotic syndrome and glomerulonephritis) [38,39]. In contrast, bloody diarrhea, colonic obstruction and abdominal pain are common features of *S. mansoni* and *S. japonicum* infections. Much less frequent, aberrant schistosome oviposition (all species) leads to neuroschistosomiasis that may present as acute paraplegia (when the spinal cord is affected) or encephalomyelitis (when brain involvement occurs) [40,41].

The chronic complications of schistosomiasis only occur after years of infection, and hence are generally seen in the adult population. However, schistosomiasis has an enormous impact on SAC and preschool-aged children (PSAC). Although SAC are the age group in which the highest prevalence and intensities of infection are usually observed [42], there is growing recognition that PSAC might be considerably affected by schistosomiasis where the disease is highly endemic [43,44]. Negative effects on the nutritional status and anemia, impaired cognitive development, reduced physical fitness and higher susceptibility to co-infections have been reported [37,45]. However, subtle morbidity is much more complex to assess than specific organ alterations, and the causal attribution to a chronic infection is difficult. Most frequently, cognition is assessed by a battery of tests examining the learning and memory domains [46], whereas the physical fitness can be assessed by using quality of life questionnaires and measurement of the oxygen uptake in a standardized 20-m shuttle run test [47–50]. Infants and PSAC are estimated to be most heavily affected by growth faltering and chronic morbidity, and recent epidemiological studies found that schistosomiasis can be quite prevalent in this age group [43,51–54]. However, research and schistosomiasis control activities have largely neglected PSAC.

Discussion point

There is a paucity of high-quality, confounder-controlled studies examining morbidity in SAC and PSAC, and additional scientific evidence base with regard to a potentially negative impact of schistosomiasis on aerobic fitness and children's cognition needs to be generated. Growing awareness that schistosomiasis affects children at very young age will hopefully lead to new research in this neglected age group to further our understanding of the epidemiology and the acute and chronic morbidity patterns. Due to the manifold clinical manifestations of schistosomiasis, clinicians may not recognize the disease in young patients presenting with diffuse symptomatology. Hence, there is a need for the development of easily applicable algorithms for diagnosis and treatment of common syndromes in resource-constrained settings. Such algorithms should take schistosomiasis into account whenever necessary, for example, for the assessment of persistent diarrhea [55] or unexplained neurological disorders [56], to improve our knowledge of its contribution to common clinical problems in schistosome-endemic countries. The 5-year multicountry NIDIAG study, funded by the European Commission (EC), aims to develop improved diagnosis–treatment algorithms for three clinical syndromes that frequently occur in resource-constrained tropical settings (i.e., persistent fever, neurological disorders and digestive disorders) [302]. Hence, ongoing research by the NIDIAG consortium will contribute to fill an important identified gap.

Treatment of schistosomiasis

At present, treatment and morbidity control of schistosomiasis rest on a single drug, praziquantel [57–59]. Discovered in the mid-1970s, praziquantel is active against all human *Schistosoma* species [60,61]. The drug has several properties that explain its wide use; it is safe, orally active, absorbs promptly and has a rapid onset of action. Praziquantel is acting by disrupting the Ca^{++} homeostasis in schistosomes, leading to spastic paralysis caused by rapid Ca^{++} influx [62]. However, the precise mechanism of action has yet to be fully elucidated. In large-scale programs, praziquantel is usually administered at a single oral dose of 40 mg/kg bodyweight, and the recommended treatment frequency depends on the local prevalence [60,61]. A dose pole has been developed and widely validated that allows treatment of children based on their height rather than weight [63,64].

A median egg reduction rate of 98.7% and cure rates ranging between 63 and 100% determined 1–3 months after treatment have been reported in randomized controlled trials for praziquantel against *S. haematobium* [65]. As summarized

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Table 1. Symptomatology and clinical manifestations of schistosomiasis caused by the three main *Schistosoma* species parasitizing man.

	Schistosoma mansoni	*Schistosoma japonicum*	*Schistosoma haematobium*	Clinical presentations and typical symptomatology
Early (hours to days after infection)	+	+	+	Localized maculopapular eruption at the site of cercarial transcutaneous penetration (cercarial dermatitis), pruritus
Acute = Katayama syndrome (2–8 weeks after infection)				
General findings	+	+	+	Fever (typically nocturnal, often absent), arthralgia, myalgia (neck pain!), fatigue
Respiratory tract	+	+	+	Dry cough, chest pain, wheezing
GI tract	+	+	+	Abdominal pain, tenderness, diarrhea, hepatomegaly
Central nervous system	+	+	+	Headache, confusion, rarely severe complications (hemiplegia, focal deficiencies, seizures, visual impairment, ataxia, incontinence)
Cardiac involvement	+	+	+	Pericarditis, myocarditis, myocardial ischemia, electrocardiogram: repolarization abnormalities (ST segment, abnormal T waves)
Cutaneous	+	+	+	Urticarial rash, angioedema
Genitourinary			+	Hematuria, dysuria
Laboratory findings	+		+	Eosinophilia, elevated serum liver enzymes (ALT, AST)
Chronic (months to years after infection)				The clinical manifestation depends on the site of schistosome egg deposition.
Respiratory tract	+	+		Remodeling of pulmonary vessels, pulmonary hypertension and related complications (cor pulmonale)
GI tract	+	+		Colitis, intestinal obstruction, ulceration, hyperplasia, (bloody) diarrhea, enteric protein loss
Hepatobiliary system	+	+		Hepatomegaly, periportal fibrosis, portal hypertension and development of related complications (variceal bleeding, splenomegaly, hypersplenism, hepatopulmonary and hepatorenal syndrome)
Central nervous system	+	+	+	Acute transverse myelitis (paraplegia, lumbar pain, altered sensitivity, vegetative dysfunctions), progressive myeloradiculopathy, seizures, alteration of mental state, focal deficiencies
Renal and urological involvement			+	Haematuria, dysuria, suprapubic dyscomfort, calcification, obstruction with consecutive ureteric and renal involvement (nephrotic syndrome [edema, proteinuria, arterial hypertension], megaureter, hydronephrosis, bacterial pyelonephritis, renal colic, membranoproliferative glomerulonephritis), important risk factor for squamous cell carcinoma of the bladder
Genital			+	Genital lesions and ulcers, genital bleeding and pain, vulval involvement, facilitation of HIV transmission
Cognitive and physical morbidity in chronic infections	+	+	+	Impaired growth, anemia, reduced physical fitness, susceptibility to co-infections, impaired cognitive and mental development (e.g., in educational tests for short-term memory)

Table 2. Summary of cure rates determined for antischistosomal drugs against *S. mansoni* and *S. haematobium*.

Drug	Dosage	Cure rates on schistosome species (%)		Ref.
		Schistosoma haematobium	*Schistosoma mansoni*	
Praziquantel[a]	1 × 40 mg/kg	63–100	52–92	[65,66]
Metrifonate[b]	3 × 7.5–10 mg/kg	52–81	–	[65]
Oxamniquine[b]	1 × 40 mg/kg	–	82	[66]
Artesunate[c]	3 × 4 mg/kg/day	27	NA	[65]
	4 mg/kg for the first day and 2 mg/kg daily for the next 4 days; total dose 12 mg/kg	NA	31	[228]
Mefloquine[c]	2 × 15 mg/kg	36–70	NA	[90]
	1 × 25 mg/kg	21	NA	[89]

NA: Not assessed.
a: Current drug of choice against all schistosome species. b: Previously marketed antischistosomal drugs. c: Antimalarial drugs that have been tested against schistosomiasis.

in Table 2, the cure rates against *S. mansoni*, determined 1 month post-treatment, vary from 52 to 92% [66]. A recent systematic literature review revealed an overall cure rate of 71.3% of praziquantel against *S. haematobium* and *S. mansoni* [61]. Most common adverse events such as nausea, headache and dizziness are usually mild and last <24 h [65,66].

Until recently, children below the age of 4 years (or <94 cm in height) have been excluded from praziquantel treatment. However, evidence is growing that this young age group is at risk of schistosomiasis, which raises the question of whether PSAC should be included in preventive chemotherapy campaigns [43,44]. Recently, the dose pole has been optimized and its downward extension now allows single, 3/4 and 1/2 tablet divisions of the standard 600 mg praziquantel tablet to be administered with high fidelity to PSAC, according to a broad validation using biometric data from PSAC from 36 African countries [64]. Crushed or broken praziquantel tablets administered to young children are efficacious against *S. mansoni* and *S. haematobium* and, in the absence of appropriate paediatric formulations, recommended for administration to young children [44,67].

Noteworthy, praziquantel has several shortcomings. Most importantly, the drug lacks activity against the young developing stages of the parasite [68]. With regard to the oral formulation of praziquantel, there are additional drawbacks. Due to the activity of only one enantiomer (*R*-praziquantel) of the racemate in use, tablets are large in size and they are very bitter in taste, which leads to decreased compliance, especially among young patients [69,70]. The safety and efficacy of praziquantel syrup (Epiquantel) have recently been investigated in studies in PSAC in Niger and Uganda. In Niger, Epiquantel was well tolerated and yielded moderate-to-high efficacy against *S. haematobium*, but a considerably lower efficacy against *S. mansoni* [54]. The syrup had a similar efficacy to crushed praziquantel tablets against *S. mansoni* in Uganda [71]. Furthermore, operational issues such as storage, transport and adequate dosing are a concern. In the frame of a public-private partnership (PPP), including Merck KGaA, Astellas Pharma, the Swiss Tropical and Public Health Institute and TI Pharma, efforts are underway to develop a pediatric formulation of praziquantel, either a racemate praziquantel or a *R*-praziquantel formulation. The project is currently in the preclinical phase, and a candidate oral dispersible tablet has been developed.

Two additional antischistosomal drugs – oxamniquine and metrifonate – had been recommended by WHO until the late 1990s, but both drugs are not available any longer [58,59]. Oxamniquine was mainly used in Brazil in the frame of the national schistosomiasis control program aimed at *S. mansoni*. The mechanism of action of oxamniquine is well understood: the nucleic acid metabolism is irreversibly inhibited by alkylation. Oxamniquine used at a dosage of 40 mg/kg shows high cure rates at 1 month post-treatment (82%) and achieves egg reduction rates of 68–100%. Should praziquantel resistance emerge, oxamniquine could be reintroduced as an alternative drug against *S. mansoni* [66]. Metrifonate is an organophorus cholinesterase inhibitor and its activity profile is restricted to *S. haematobium*. The recommended treatment is three oral doses at 14-day intervals (7.5–10 mg/kg each) [65]. Egg reduction rates after administration of metrifonate are above 90% and observed cure rates range between 52 and 81% [65].

Recently, WHO set the goal to scale up access to praziquantel, aiming for an annual treatment of 235 million people in 2018 (Figure 1) [72]. This ambitious endeavor with only one available drug in hand will place additional selective pressure on schistosomes, which may accelerate the emergence of resistance [73]. Observed cure rates following standard single 40 mg/kg oral doses of praziquantel show considerable variation [66,74], and low cure rates observed against *S. mansoni* in Senegal in the 1990s raised concern about tolerance or resistance [75,76]. Reduced susceptibility to praziquantel has indeed been detected

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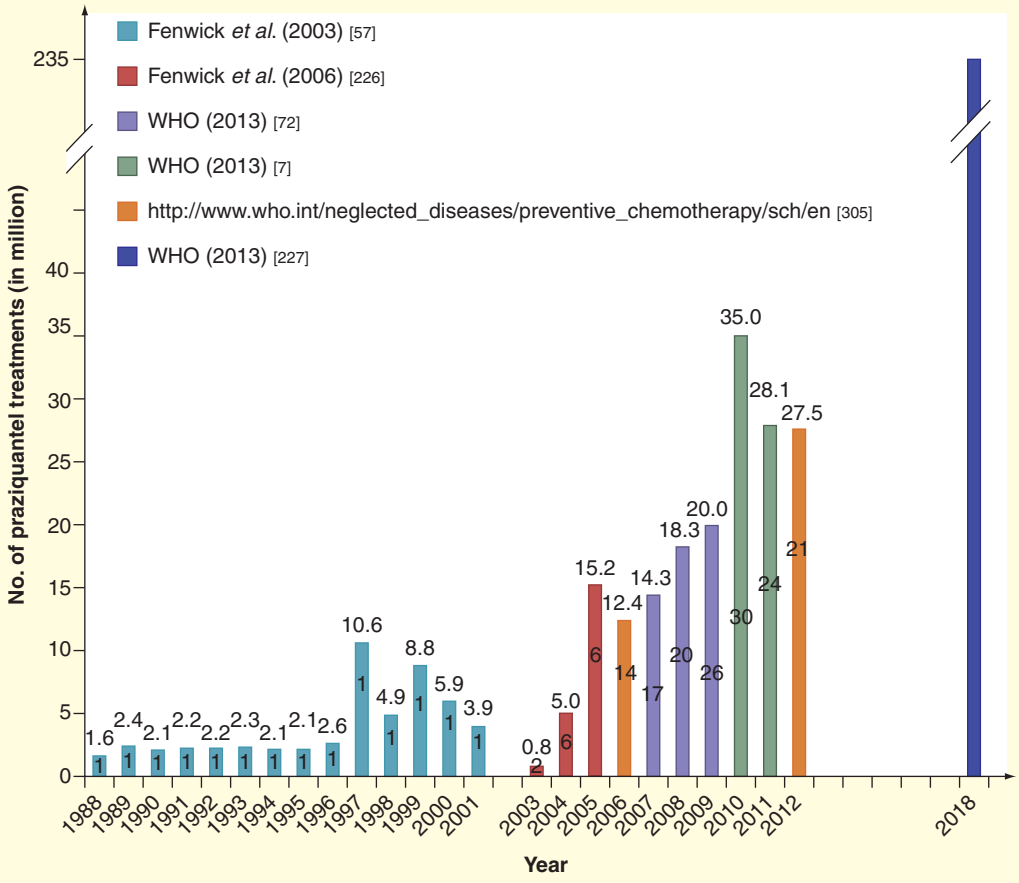

Figure 1. Reported number of countries (within bars) and people treated with praziquantel (above bars) against schistosomiasis since 1988 and projections for 2018.

for schistosomes isolated from Egyptian patients who failed to be cured after multiple treatments [77]. New drugs with novel mechanisms of action and activity against all *Schistosoma* stages and drugs that are eligible for combination chemotherapy are therefore urgently needed [62,66,78].

An attractive starting option for drug development for neglected diseases where only limited resources are available is to work with existing drugs, the so-called repositioning or repurposing of drugs [73,79,80]. This strategy is at the root of detailed scientific inquiry with marketed antimalarials against *Schistosoma* [81]. Indeed, the antischistosomal activities of artemisinin derivatives (i.e., artemether and artesunate) were extensively studied *in vitro*, *in vivo* and in clinical trials. Key findings from these laboratory and clinical investigations have been summarized elsewhere [58,81–84]. It is worth highlighting that artemether and artesunate show highest activity against juvenile worms and are therefore interesting partner drugs for combination chemotherapy with praziquantel [82,85–87]. However, the superior efficacy of the combination over single praziquantel remains uncertain and has to be investigated in more detail as concluded in a recent systematic review and meta-analysis [66].

Mefloquine is another antimalarial that has been widely studied for its antischistosomal properties since the discovery of its *in vitro* and *in vivo* activities against *S. mansoni* in 2009 [88]. In combination with artesunate, cure rates of 61% were achieved in *S. haematobium*-infected children [89]. Similarly, when mefloquine was used as intermittent preventive treatment against malaria in pregnancy, it showed an ancillary benefit against *S. haematobium*: high egg reduction rates were observed in women co-infected with *Plasmodium* and *S. haematobium* [90].

Discussion point

Although some progress has been registered, the antischistosomal drug pipeline is still empty. Although antimalarials might have some impact against schistosomiasis in malaria co-endemic settings where artemisinin-based combination therapy and mefloquine are being used, these antimalarials will not replace praziquantel, given the superior clinical, economic and operational profile of praziquantel against schistosomiasis. The necessity of developing alternatives to praziquantel, now that this drug is still efficacious and in view of growing drug pressure, cannot be overemphasized [62]. Additionally, there is a pressing need to optimize existing drugs for the usage in PSAC [91]. It should be noted that using drugs in monotherapy enhances the risk of resistance development and that there is considerable concern that using antimalarials against schistosomiasis in malaria-endemic settings might select for resistance in malaria parasites [59,92]. Hence, despite there is evidence that artemisinin

derivatives used in combination with praziquantel have the potential to increase the cure rates in schistosomiasis treatment [84], at present, the application of this regimen should not be recommended in co-endemic settings.

The recent establishments of PPPs and new consortia illustrate an important and fruitful step toward a more productive and faster drug discovery and development as seen in malaria (e.g., Medicines for Malaria Venture [303]). These platforms bring together a diversity of expertise that is necessary to advocate the neglected field of drug development. Another issue of high priority is the appraisal of the impact of *Schistosoma* infection on the disposition kinetics of applied drugs. In addition, it will be important to study the drug disposition of antischistosomals in young children, as it is conceivable that preventive chemotherapy programs will further expand, perhaps also targeting PSAC. Recent studies have shown that cure rates in young children are lower than in their older counterparts, which might be explained by differences in pharmacokinetics [93].

Prevention & control of schistosomiasis

SAC are at highest risk of infection with *Schistosoma* worms. Hence, most large-scale control efforts focus on the prevention of morbidity in this age group, which is facilitated by preventive chemotherapy, often through the education sector. Preventive chemotherapy follows a vertical approach and, on the day of drug administration, schoolchildren are encouraged to take a morning meal to enhance bioavailability [93,94] and to lower the odds of adverse events [95]. Additionally, SAC should bring along their nonschool-enrolled siblings, so that all children of this age group are being treated. Praziquantel treatment often goes hand-in-hand with the administration of albendazole or mebendazole against soil-transmitted helminthiasis, vitamin A supplementation, malaria control efforts (e.g., distribution of long-lasting insecticidal nets) and/or with vaccinations targeting measles [96–98]. Obvious advantages of treating children in schools are that they are easily accessible, teachers can assist with the treatment, and drug intake by the children can be directly observed. There are, however, concerns that treatment coverage might not be optimal [99,100]. For example, children who lack knowledge about schistosomiasis transmission and prevention and who were not directly supported by a teacher in taking the drugs had significantly lower odds of taking praziquantel in a Kenyan study. These issues, alongside local perceptions and beliefs toward praziquantel administration need to be explored in greater detail [100]. Community-wide treatment campaigns are considered to achieve higher coverage rates of nonschool-enrolled children than school-based treatment [101]. Nevertheless, coverage strongly depends on local circumstances, including sensitization of the community, relation between the drug distributors and targeted groups, experiences on adverse events and understanding of the need and purpose of periodic treatment without prior diagnosis [102,103].

Although preventive chemotherapy is able to temporarily reduce the prevalence in the targeted population and is thought to lower transmission by the decrease of infection intensity, and hence egg excretion into the environment, it is unlikely to interrupt transmission. Particularly in high-transmission areas, prevalence and intensity of infection can quickly reach pretreatment levels if no other means of control are applied, even if the coverage is high [104]. To achieve the highest impact of praziquantel treatment, it should be applied when the likelihood for re-infection is lowest, and hence be timed to the beginning of the low-transmission season, if there is any [105]. To clear matured schistosomes in the body that were not targeted by the first praziquantel application due to their juvenile stage and to accelerate a more rapid reduction of infection-related disease, a second treatment 2–8 weeks after the first treatment round is recommended [106].

Snail control using molluscicides to reduce the infected intermediate host snail population at human water contact sites is an important, well-tried and effective tool to complement preventive chemotherapy against schistosomiasis [107]. The most effective time of application is shortly before or shortly after a preplanned chemotherapy campaign to avoid rapid re-infection of people [108,109]. The molluscicide niclosamide has been recommended by the WHO to control schistosomiasis in humans [110–112]. Niclosamide has been widely and effectively used for snail control in schistosomiasis control programs in different parts of the world, most extensively in the People's Republic of China, but also in Egypt, Kenya and Morocco [109,113–116] and is currently applied and evaluated in a randomized intervention trial that aims at elimination of urogenital schistosomiasis in Zanzibar [9,23]. It must be noted, however, that chemical molluscicides, such as niclosamide, not only kill snails but also are toxic for fish and other organisms, and hence there are significant risks for the environment and biodiversity. New molluscicidal-only formulations or products are highly desirable to remedy the negative impact on species other than snails. Alternatively, indirect snail control measures such as the destruction of the snails' natural habitat, for example, by the removal of vegetation from riverbanks, or biological control with fish, ducks, crayfish or competitor snails have been successfully applied to reduce intermediate host snail populations [10,117,118].

Although preventive chemotherapy and snail control are measures that need to continuously be applied to reduce morbidity and transmission, more sustainable and long-lasting efforts to prevent infection and reinfection include health education and behavior change interventions as well as improvements in the water and sanitation infrastructure in at-risk communities [9,12,119–122]. Behavior change interventions have been described earlier on in the current review, but one needs to be aware that increased knowledge about how to prevent infection and how to reduce transmission and the motivation for behavioral change in deprived communities need to go hand-in-hand with the accessibility of safe water sources and improved sanitation. Transmission of schistosomiasis is closely linked with human practices related to water contact and sanitation [2,102]. Ceasing urination into open water bodies can inhibit the transmission of *S. haematobium*. While also refraining from open defecation in or near water bodies can lower the

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transmission of *S. guineensis*, *S. intercalatum*, *S. japonicum*, *S. mansoni* and *S. mekongi*, there remains the risk that eggs are trapped in the perianal folds and are released into water while people take a (hygienic) bath and hence contributes considerably to transmission [123]. There is, however, a paucity of studies assessing or showing any clear impact of improved sanitation on schistosomiasis endemicity [122,124–126]. On the other hand, multiple studies have shown that people who lack safe water supply, use water from natural freshwater bodies for washing purposes or children spending time playing in open water bodies are at a higher risk of acquiring schistosomiasis than their less exposed counterparts [23,25,124]. Improving access to safe water in endemic populations has been shown to have a positive effect in reducing the prevalence and intensity of schistosomiasis a long time ago [127,128]. In 2001, WHA resolution 54.19 urged Member States to promote access to safe water, sanitation and health education through intersectoral collaboration to sustain the control of schistosomiasis (and soil-transmitted helminthiasis), and this has been re-emphasized in 2012 in WHA resolution 65.21 [6,8], but more action in this regard must be taken. Additional, well-designed studies to assess the impact of improved sanitation and safe water on schistosomiasis, including information about user uptake, maintenance, sustainability and affordability, are warranted [122].

Finally, a vaccine would be the key to sustainably control and eliminate schistosomiasis. A vaccine could reduce worm fecundity and/or prevent *Schistosoma* infection and re-infection not only in humans but also in reservoir hosts (e.g., water buffaloes) that significantly contribute to the transmission of *S. japonicum* [129]. Over the past 20–30 years, multiple vaccine candidates based on, for example, recombinant-derived schistosome proteins [130,131], radiation-attenuated schistosome larval stages [132,133] or DNA-delivered proteins have been identified [129]. Although protection against various schistosome species was achieved in a wide range of host reservoir animals, there are currently only very few vaccine candidates (e.g., recombinant Sm14/FABP antigen, rSh28GST antigen), which are studied in clinical trials [134–138]. The identification of the whole *S. haematobium*, *S. japonicum* and *S. mansoni* genomes and the rich resources of genomic data of other *Schistosoma* species [139–142], as well as the availability of high-quality outcomes of the additional '-omics' sciences will contribute to the development of a human antischistosome vaccine and novel antischistosomal drugs [137].

Discussion point

Since SAC are the main spreaders of schistosomiasis, it will be very important to tailor behavioral change and health education interventions to children's understanding, so that the goal of modifying their behavior to not urinating or defecating into open water, or be in contact with this water while playing or washing, to interrupt transmission can be met. Behavioral interventions should also target children's peers (parents, older siblings and teachers) so that they can exemplify adequate behavior through their own life. Sensitizing children, parents and teachers to the importance and benefit of periodic deworming might increase the coverage of drug intake. When constructing latrines or urinals, it is important to design them in a way that favors the use by children. It should be considered that children might not use latrines because they do not like the smell or are afraid of darkness or of falling into too big holes [143].

It is clear that for sustainable control, interruption of transmission and finally elimination of schistosomiasis, integrated control approaches that are tailored to the local situation are necessary. The People's Republic of China is a trailblazer in integrated and intersectoral schistosomiasis control demonstrating that transmission can be effectively interrupted by combining preventive chemotherapy with snail control, health education, improved sanitation and environmental and reservoir host management [144]. Lessons from the multifaceted schistosomiasis control program implemented in the People's Republic of China's over the past 60 years can guide the progression from schistosomiasis control to elimination in other endemic areas [145,146].

Diagnosis of schistosomiasis

For a rapid and inexpensive epidemiological assessment of *S. haematobium* infection to identify high-risk communities in need of treatment, questionnaires have been proven to be a valuable tool [147,148]. The proportion of schoolchildren reporting to have had blood in urine (macrohematuria) or to have had schistosomiasis in the past 2–4 weeks showed a correlation with the *S. haematobium* prevalence in a multicountry study [149,150].

Reagent strips to assess microhematuria in urine are also considered as good diagnostic indicator for heavy *S. haematobium* infections in the community and can be used for the identification of high-transmission areas [151,152]. Recent work has shown that microhematuria, identified by reagent strips, is still a useful indicator of *S. haematobium* in a setting with a history of two decades of preventive chemotherapy [23]. Hematuria levels decrease after treatment against schistosomiasis, and hence reagent strips can also be applied as indirect measure to assess drug efficacy, with the most appropriate assessment time ~6 weeks after treatment [153].

For the identification and mapping of *S. mansoni*-endemic areas, the recently developed point-of-care circulating cathodic antigen (POC-CCA) dipstick or cassette test in urine is recommended as noninvasive, sensitive and rapid diagnostic tool [93,154]. A recent multicountry study revealed that a single POC-CCA, applied on urine samples, is more sensitive than multiple Kato–Katz thick smears using stool samples [154]. The POC-CCA is particularly useful in low-infection intensity settings, without showing cross-reactivity with *S. haematobium* infections [154,155]. Due to its rapid test cassette format, it is easy to apply and a single person can, after a short introduction and training, perform hundreds of tests per day without the need of an equipped laboratory. The POC-CCA assay is therefore a promising tool for rapid mapping, large-scale epidemiological surveys and individual patient management in remote health facilities without trained laboratory technicians or sophisticated equipment. The cost of the POC-CCA assay (above US$ 1.00 per test [154]) is an issue though.

The color grading on the hematuria reagent strips or the color intensity on the POC-CCA dipstick and cassette test band are correlated with the number of eggs excreted in urine or stool [23,155,156], and hence allows a semiquantification of the intensity of infection. Although reagent strips for hematuria assessment have a color chart that helps to classify the intensity of hematuria, the POC-CCA tests currently lack this useful grading option and the color intensity of the test band has to be interpreted by the reader.

Of note, the intensity of an infection is linked with morbidity [157]. Hence, diagnostic methods allowing a quantification of the intensity help to assess the level of morbidity. *Schistosoma haematobium* infection is quantified by means of filtering 10 ml of a vigorously shaken mid-day urine sample through a polycarbonate filter and by subsequently counting the eggs trapped on the filter using microscopy [158]. An infection is considered as heavy, if 50 or more eggs per 10 ml of urine are counted on the filter [159]. The current cutoff to differentiate between low and heavy infection intensities was only set a decade ago [6], whereas studies conducted in the 1980s and 1990s used considerably higher egg count thresholds [160].

The method most widely used for the diagnosis and quantification of *S. mansoni* and *S. japonicum* infections in epidemiological studies is the Kato–Katz technique [161–163]. A thick smear containing ~41.7 mg of filtered stool is examined under a microscope. Eggs from *S. mansoni*, *S. japonicum* and other intestinal helminths are counted and, after multiplication with a factor of 24, reveal an estimate of eggs per 1 g of stool (EPG). Thresholds for moderate and heavy *S. mansoni* and *S. japonicum* infection intensities are 100 and 400 EPG, respectively [159]. The recently developed FLOTAC technique allows examination of up to 1 g of stool. The FLOTAC technique is based on the flotation of helminth eggs by using a flotation solution with a specific gravity [164]. This method requires more sophisticated laboratory equipment than the Kato–Katz technique, such as a centrifuge and different chemicals, and is relatively low throughput. While Kato–Katz thick smears are prepared from fresh stool samples, and require rapid work-up, FLOTAC can be done on fixed stool samples many weeks after stool collection. A recent study in Côte d'Ivoire compared the accuracy of Kato–Katz and FLOTAC for *S. mansoni* diagnosis and concluded that FLOTAC is as sensitive as Kato–Katz, but egg counts using FLOTAC are considerably lower compared with Kato–Katz [165]. The influence of the diagnostic accuracy of Kato–Katz and FLOTAC for assessing drug efficacy against soil-transmitted helminth infections has been studied [166,167] and needs to be done for *S. mansoni*. Additional direct parasitological methods for the detection of *Schistosoma* infections are summarized in Table 3.

Detection of *Schistosoma* spp. DNA via polymerase chain reaction (PCR) is reported to have a high sensitivity and specificity, particularly in low-transmission settings [168]. However, the PCR cycle thresholds are correlated with microscopic egg counts for both *S. haematobium* and *S. mansoni* [169], and in view of a decrease in sensitivity when infection intensities drop [170], applicability of PCR in areas where people have mostly light-intensity infections must be promoted with care. The advantages of PCR are that parasitic DNA can be extracted from serum, plasma, feces and urine [169,171–173], with particularly the latter being a patient- and technician-friendly noninvasive approach; samples can be frozen or stored on filter papers without the need for direct processing; there is potential for a high throughput of patients (i.e., one well-trained technician can extract DNA from at least 96 urine samples and process all within 1 day); and the isolated DNA can be simultaneously screened for other infections [168,169,174]. Disadvantages of a PCR approach are that the methodology requires highly skilled laboratory personnel and well-equipped laboratory infrastructure. Costs for a single test are therefore considerably higher than for more conventional diagnostic assays. The potential of the application of PCR in resource-constrained countries is therefore limited. Recent publications identified the loop-mediated isothermal amplification (LAMP) of *S. japonicum* DNA in human sera as more sensitive than PCR and highlighted that due to its lower price and ease of application it might be a valuable tool for field diagnosis and disease surveillance in schistosomiasis- endemic areas [175]. The LAMP assay is also used for the detection of *S. haematobium* and *S. mansoni* DNA in intermediate host snails, and considered as an easily applicable tool, which could be used in low-technology parasitology laboratories in areas where interruption of schistosomiasis transmission or elimination of the diseases needs verification [176,177].

Although antibody-based detection assays have a limited applicability for confirmation of cases and success of treatment, because they cannot readily distinguish past from present infections, they are very useful for the purpose of confirming interruption of transmission, because they are able to show the contact of people with *Schistosoma* parasites. For example, in the People's Republic of China, where integrated schistosomiasis control efforts reduced *S. japonicum* infections to very low levels, indirect immunodiagnostic assays such as the circumoval precipitin test, dipstick dye immunoassay, indirect hemagglutination assay or enzyme-linked immunosorbent assay are applied for population screenings to detect potential cases, which are then confirmed by subsequent stool examination [178–180].

A promising diagnostic approach is the detection of a *Schistosoma* worm antigen in serum or urine applying the circulating anodic antigen (CAA) test procedure via the up converting phosphor (UCP) technology lateral flow assay [181,182]. The CAA test is highly sensitive and able to diagnose light infections and might, if designed in a high-throughput rapid test format, be a suitable tool for the verification of schistosomiasis transmission interruption and surveillance in formerly endemic areas. The CAA–UCP technology needs validation in endemic settings, particularly in areas where prevalence and intensities of infections are very low.

Additional new diagnostic paradigms, which still need further evaluation are, for example, a modified version of the miracidium hatching test, which can be used for the diagnosis

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Table 3. Methods to diagnose schistosomiasis at different levels of infection intensity and control.

	Infection intensity				Control				Ref.
	Very light[†]	*Light*	*Moderate*	*High*	*Morbidity*	*Prevalence*	*Transmission*	*Elimination/surveillance*	
Questionnaire									[148]
Schistosoma haematobium				x	x				
Dipstick for hematuria									[151]
Schistosoma haematobium		(x)		x	x	(x)			
Direct parasitological methods			*						
Urine filtration			*						[158]
Schistosoma haematobium		(x)		x	x	x	(x)		
Kato-Katz									[161]
Schistosoma mansoni		(x)	x	x	x	x	(x)		
Schistosoma japonicum		(x)	x	x	x	x	(x)		
Formalin–ether concentration									[229,230]
Schistosoma mansoni		(x)	x	x	x	x	(x)		
Schistosoma japonicum		(x)	x	x	x	x	(x)		
FLOTAC									[164]
Schistosoma mansoni	(x)	x	x	x	x	x	(x)		
*Schistosoma japonicum***									
Miracidium hatching test									[183,184]
Schistosoma haematobium				x	x	x			
Schistosoma mansoni			x	x	x	x			
Schistosoma japonicum			x	x	x	x			

[†]Very light infection intensity is defined as infections that are below the detection limit of a single urine filtration and Kato-Katz thick smear: *S. haematobium*: >0 and <1 eggs/10 ml urine, *S. mansoni* and *S. japonicum*: >0 and <24 eggs per 1 g of stool. *moderate infection intensity for *S. haematobium* does not exist. **no data on FLOTAC for *S. japonicum* detection exist to our knowledge. x is defined as method suitable for detection of infection at the given level of intensity. x is defined as method moderately suitable for detection of infection at the given level of intensity.

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Table 3. Methods to diagnose schistosomiasis at different levels of infection intensity and control (cont.).

	Infection intensity				Control			Ref.
	Very light[†]	*Light*	*Moderate*	*High*	*Morbidity*	*Prevalence*	*Transmission*	*Elimination/surveillance*	
Indirect methods									
Antibody detection									[190,231]
Schistosoma haematobium							(x)	(x)	
Schistosoma mansoni							(x)	(x)	
Schistosoma japonicum							(x)	(x)	
Antigen detection									[181]
Schistosoma haematobium	(x)	x		x	x	x	(x)	(x)	
Schistosoma mansoni	(x)	x	x	x	x	x	(x)	(x)	
PCR									[169,171,174,232]
Schistosoma haematobium	(x)	x		x	x	x	(x)	(x)	
Schistosoma mansoni	(x)	x	x	x	x	x	(x)	(x)	
Schistosoma japonicum	(x)	x	x	x	x	x	(x)	(x)	

[†]Very light infection intensity is defined as infections that are below the detection limit of a single urine filtration and Kato-Katz thick smear: *S. haematobium*: >0 and <1 eggs/10 ml urine, *S. mansoni* and *S. japonicum*: >0 and <24 eggs per 1 g of stool. *moderate infection intensity for *S. haematobium* does not exist. **no data on FLOTAC for *S. japonicum* detection exist to our knowledge. x is defined as method suitable for detection of infection at the given level of intensity. x is defined as method moderately suitable for detection of infection at the given level of intensity.

of any schistosome species [183,184], or the saline gradient technique [185] and the Mini-FLOTAC for the detection of *S. mansoni* or *S. japonicum* [186,187]. Moreover, new rapid diagnostic tests (RDTs) have been developed that are visualizing human IgG attached to *S. haematobium* eggs in filtered urine [188] or detecting antischistosome antibodies in finger-prick blood samples that are binding to *S. mansoni* cercarial transformation fluid suitable for the detection of *S. haematobium* and *S. mansoni* [189–191]. A proof of concept for mobile phone microscopy has recently been established for soil-transmitted helminth infection diagnosis [192] and hence warrants validation for schistosomiasis diagnosis. Other mobile diagnostic tools have been assessed and their strengths and limitations discussed [193]. A sampling strategy well established in the veterinary field but only recently adapted to human parasitology is the pooling of stool or urine samples for a rapid assessment of infection intensity and drug efficacy [187,194].

Discussion point

The typical age prevalence and intensity curves for *Schistosoma* infections rise from early age and peak in SAC [13]. Since most direct parasitological methods are not sensitive enough to detect very light infections, they have a limited suitability to detect schistosomiasis in young children. Moreover, stool samples from infants and PSAC are difficult to obtain and are often not of a consistency that allows adequate examination with, for example, the Kato–Katz technique [67]. Therefore, serological examinations using either antibody detection assays to determine the contact of the child with the parasite, or the POC-CCA or CAA-UCP tests that can be applied on urine samples might reveal more reliable results on *Schistosoma* infection in children. The highlighted insensitivity of direct parasitological methods can generally result in an underestimation of prevalence or overestimation of treatment efficacy, which have important ramifications on treatment decisions in helminth control programs [166]. It is crucial to adapt the diagnostic approach to the epidemiological situation in the area, the current stage of control and population under investigation [195]. Hence, while in population subgroups with high-intensity infection potential (i.e., SAC in a high-transmission area not yet targeted by schistosomiasis control), simple methods such as the Kato–Katz technique for *S. mansoni* or *S. japonicum*, or the urine filtration for *S. haematobium*, will reveal an accurate picture of the prevalence and transmission potential, other more sensitive methods are needed to detect light infections with high

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sensitivity. Of note, light infections might not only occur in PSAC, but also in individuals with single exposures to the infective agent such as returning travelers or tourists [3,196], or among individuals who developed partial immunity by regular and frequent exposure in a high-transmission area [197]. Mostly, light infection levels are also expected in populations that are periodically treated against schistosomiasis in the current era of intensified control. Hence, over the course of helminth control programs, it is important to change the diagnostic approaches from simple low-cost methods applied in high-transmission settings to highly sensitive and specific methods that identify infections in areas targeted for transmission control, surveillance or elimination [195,198]. It is clear that, particularly for the latter three points, new diagnostic tools and strategies, supported with standard protocols need to be developed [187,199]. The ultimate goal is to get away from testing multiple samples, increasing the amount or volume of tested samples or combining the results of different diagnostic methods, which are approaches currently recommended in the absence of tools that meet predefined target product profiles [200,201].

Schistosomiasis co-infections

In most schistosome-endemic areas, several other viral, bacterial and parasitic pathogens are commonly found, thus leading to a substantial amount of co-infections. The impact of multiple concurrent infections on acute and chronic morbidity and on the susceptibility to other infections is poorly understood and thus constitutes an important research need. We present some key co-infections and discuss their clinical significance.

HIV/AIDS

Experimental studies in mice and monkeys led to the hypothesis that *S. mansoni* infections would accelerate replication of HIV and possibly the clinical course in co-infected individuals [45]. These observations are generally explained by the effects of schistosomiasis on the host's immune response, specifically on the two important subsets of CD4-positive T lymphocytes, that is, Th1 and Th2 [202]. Intestinal schistosomiasis stimulates the Th2-type cytokine production (e.g., interleukins 4, 5 and 13) that leads to eosinophilia. In contrast, the Th1-type response (e.g., cytotoxic T lymphocytes, γ-interferon production) is reduced, which results in less efficient control of HIV replication in the host. Additionally, mast cells of the intestinal mucosa have been identified as a potential link between HIV infection and schistosomiasis [203]. Although the exact immunological mechanisms still need to be elucidated, there is a growing body of evidence from clinical and epidemiological studies of a cause–effect relationship between both urogenital and intestinal schistosomiasis and HIV infection. Schistosomiasis appears to favor an elevated susceptibility to HIV, a more rapid disease progression, and transmission of HIV to others [45,204]. The potential public health impact of antischistosomal treatment, particularly preventive chemotherapy targeting entire communities, on HIV/AIDS remains to be elucidated.

Viral hepatitis

Viral hepatitis and schistosomiasis are co-endemic in many tropical areas. The hepatitis B and C viruses share some important features with schistosomiasis, particularly the hepatotropism and the high rate of chronic infections. Co-infections are common [205], yet rarely taken into account in the clinical assessment of patients from co-endemic areas [206]. A schistosome co-infection in patients with hepatitis C is significantly associated with failure to respond to antiviral therapy [207]. Similar to tuberculosis, schistosomiasis might alter the host's immune response, thus leading to a weak or absent response to the hepatitis B vaccine. A recent *in vivo* study with *S. japonicum* in the mouse model demonstrated that this inhibited vaccine response was reversible following anthelmintic treatment, thus underscoring the potential of periodic deworming as an important public health measure in co-endemic areas [208].

Tuberculosis

A study from Tanzania reported a co-infection with *S. mansoni* in every third hospitalized patient with tuberculosis [209]. Moreover, several studies made an interesting observation according to which schistosomiasis may reduce the host's immune response to the bacille calmette–guerin vaccine, which is widely used in endemic areas for protection against *Mycobacterium tuberculosis*, and hence may lower the protective efficacy of the vaccine [210].

Salmonellosis

Typhoidal and nontyphoidal serovars of *Salmonella enterica*, a Gram-negative bacterium, are important water- and foodborne pathogens of diarrheal and systemic infections, with the highest morbidity observed in tropical and subtropical areas. Systemic infections can often be fatal and require immediate antibiotic treatment. In co-infected patients where both *Salmonella* and adult schistosomes are present in blood vessels, the bacterium can attach to the parasite's tegument via a specific fimbrial adherence protein. Interestingly, this docking mechanism protects *Salmonella* against systemic antibiotic therapy. Several studies found that different antibiotics commonly used to treat salmonellosis were not effective in individuals co-infected with schistosomiasis. Even if antibiotics tested to be active against *Salmonella* strains *in vitro* were administered, they were of no clinical use to cure salmonellosis [211]. Moreover, once the refuge-providing schistosomes are eliminated following praziquantel treatment, life-threatening *Salmonella* bacteremia may rapidly develop in co-infected patients [212]. Hence, this co-infection is of considerable clinical relevance and new research is urgently required.

Malaria (infection with Plasmodium *spp.)*

A considerable amount of work has been carried out over the past decade to investigate potential links between malaria and

schistosomiasis (and other helminth infections). Although many studies suggest a positive association between the infection intensities in people harboring a concurrent *Plasmodium–Schistosoma* infection [213,214], others reported antagonistic results. For example, in comparison to individuals without schistosomiasis, a Senegalese study observed less severe *P. falciparum* infection intensities in children who were co-infected with *S. haematobium* at a light intensity [215]. Such conflicting results may be due to the fact that most co-infection studies were carried out in SAC or adults, while there is a paucity of data in very young children who are at highest risk of developing severe malaria. Hence, studies of malaria in schistosomiasis-endemic regions in PSAC have been identified as an urgent research need for a comprehensive understanding of the interactions between both parasites [216].

Soil-transmitted helminthiasis

Co-infections between schistosomes and the soil-transmitted helminths (i.e., *Ascaris lumbricoides*, *Trichuris trichiura*, *Strongyloides stercoralis* and hookworm) have been studied in laboratory animals and humans. Data are conflicting with some studies reporting a multiplication of disease severity, whereas in other studies, infection with one helminth appeared to confer protection from a subsequent infection with another helminth species. However, epidemiological studies observed a strong association between hookworm and *S. mansoni* co-infection [217,218] and higher infection intensities and elevated levels of anemia in co-infected individuals [217,219]. Moreover, several recent case reports draw attention to severe co-infections of *S. mansoni* and *S. stercoralis* that warrant further investigation [220,221].

Other infections

Co-infection studies have been conducted for several other bacteria (e.g., *Helicobacter pylori* and *Staphylococcus aureus*), protozoa (e.g., *Entamoeba*, *Leishmania* and *Toxoplasma*) and helminths (e.g., *Fasciola* and *Echinostoma*) [222]. Very recently, a first report suggested an association between schistosomiasis and eumycetoma, a neglected fungal disease that frequently occurs in tropical settings [223].

Discussion point

There is ample evidence for associations (positive and negative) and interactions between schistosomiasis and other infectious diseases, and many of them are co-endemic in tropical and subtropical areas. The health effects of schistosomiasis are not limited to the disease itself, but also the trematodes' ability to negatively influence on the course and prognosis of other infections and to impair the effectiveness of preventive measures such as vaccines. There is a particular lack of research targeting the interactions between schistosomiasis and viral hepatitis, tuberculosis and invasive salmonellosis. Hence, in-depth experimental studies and well-designed epidemiological studies should be launched without delay. Moreover, studies assessing the impact of praziquantel treatment on the incidence and severity of the aforementioned co-infections in populations with different *Schistosoma* infection levels are sorely needed. The EC-funded multi-country IDEA project will generate new evidence about the interaction of schistosomiasis with HIV, tuberculosis and malaria and the impact of antischistosomal treatment on disease outcome and immunological markers [304]. Indeed, IDEA will longitudinally follow-up well-characterized HIV, tuberculosis and malaria cohorts, and study the effect of helminth co-infections, which are rigorously assessed by a suite of diagnostic methods (i.e., examination of stool and urine samples with a broad set of quality-controlled parasitological methods).

Expert commentary

In the current era of intensified and integrated control targeting schistosomiasis and other neglected tropical diseases, it must be emphasized that tools and strategies with proven track records are available to fight schistosomiasis. However, we need to constantly adapt and fine-tune intervention packages as control programs progress, and carefully monitor whether they have the desired impact. Innovation, validation and application of new tools and strategies, and thinking outside the box, must be seen as integral parts [2]. As highlighted in this review, numerous research gaps remain, and there is a need to show flexibility in the approaches taken, particularly now that we are escalating from schistosomiasis control to interruption of transmission and finally elimination.

To further our understanding of the burden and impact of schistosomiasis, there is a need to conduct additional high-quality, confounder-controlled studies to measure and quantify acute and chronic morbidity in SAC and PSAC. Additionally, physical fitness, cognition and nutritional disorders should be measured in *Schistosoma*-infected and non-infected children and it should be determined whether these indicators improve over the course of praziquantel treatment. Moreover, the effect, mediating pathways and impact of schistosomiasis on co-infections such as malaria need further scientific inquiry, particularly in PSAC who are at greatest risk of developing severe malaria. The effect of intensified schistosomiasis control/elimination efforts on the susceptibility toward other infectious and noncommunicable diseases, on vaccine responses and on the clinical management of concomitant infections needs to be carefully assessed. With regard to treatment of schistosomiasis, we have praziquantel, a safe, inexpensive and efficacious drug against all human schistosome species. However, praziquantel lacks activity against the young developing stages of the parasite. The artemisinins and mefloquine are active against juvenile worms, and hence present interesting candidates for combination chemotherapy with a drug that is active against the adult schistosome stages (i.e., praziquantel). It must be noted, however, that the artemisinins or mefloquine should always be used in combination with an antimalarial partner drug (e.g.,

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lumefantrine) to avoid selection for resistance development in malaria parasites. At present, there is no praziquantel formulation that is convenient for the uptake by infants and PSAC, which is of considerable concern as new research showed that schistosomiasis already affects children at very young age. Studies on drug disposition in young children and the development of a child-friendly formulation of praziquantel are thus of great importance. The growing pressure of praziquantel raises the risk of parasites developing resistance to this drug. Because the antischistosomal drug development pipeline is empty, the risk of praziquantel resistance cannot be overemphasized. Drugs that have been used before (e.g., oxamniquine) could again be utilized, but new drugs – and also vaccines – must be developed.

Large-scale control programs will only effectively reduce schistosomiasis transmission if preventive chemotherapy is complemented by measures to reduce the number of infected intermediate hosts (e.g., snail control) and reservoir hosts (e.g., chemotherapy targeting water buffaloes or fencing of these animals), to improve sanitation and access to clean water, and to educate at-risk populations in a way that they take action in preventing infection and transmission. To achieve the highest level of success in the control/elimination of schistosomiasis, governments and international donors must be highly committed and provide the necessary financial, technical and human resources. Moreover, integrated control packages can only be successfully implemented, if the health sector builds bridges with the agricultural, education, financial and water and sanitation sectors [12,120,122,224]. The voice and proposals of the affected communities must be considered. Indeed, developing and implementing interventions together with communities will render them more accepted and effective. If people's concerns and suggestions are considered, higher drug intake coverage might be achieved in mass treatment programs, water supply and latrines might be constructed at appropriate places and be used and maintained by children and the community, and contact with open water bodies be reduced or avoided if there are alternative water sources and play options for children. More research is needed to determine and evaluate the impact of different control approaches, particularly of sanitation, snail control and behavior change interventions. Qualitative research to deepen the understanding of community perceptions about schistosomiasis prevention and the use and acceptance of an improved sanitary infrastructure in different social–ecological settings are crucial for getting interventions right. The development and evaluation of alternatives to toxic molluscicides for snail control constitutes another important research need.

The implementation of control measures over multiple years will reduce infection intensities in targeted settings. To avoid an underestimation of the number of infected people, particularly those with low-intensity infections, highly sensitive diagnostic tools are needed. Although the widely used urine filtration and Kato–Katz techniques are suitable for assessing prevalence and infection intensity in high-endemicity settings, those two assays are less suitable in low-intensity settings. Hence, more sensitive methods such as POC-CCA, CAA-UCP and PCR must be considered. The reliability of these diagnostic approaches needs, however, further validation in low-endemicity areas, and standard protocols for high throughput are needed. A drawback of the more sensitive methods is their higher cost and the need for sophisticated laboratory equipment. The development of highly sensitive and specific RDT formats for monitoring and surveillance of schistosomiasis would therefore be an important achievement.

Five-year view

New bold goals and a roadmap for the control/elimination of schistosomiasis and other neglected tropical diseases by 2020 are now in place. Importantly, the control of neglected tropical diseases is explicitly stated in the post-2015 agenda of sustainable development [225]. In light of these recent developments, we have every reason to believe that control/elimination of schistosomiasis will be further intensified. Political will and support from local governments, intersectoral collaboration and community ownership are crucial to consolidate achievements made and register additional progress. The development of efficacious and child-friendly drugs and vaccines that are easily administrable is crucial. Although there are current efforts to develop a child-friendly formulation of praziquantel, the current drug and vaccine pipelines are virtually empty, and hence new products will not enter the market anytime soon. With regard to diagnostics, considerable progress has been made in recent years, and hence we are convinced that new or further improved highly sensitive assays will be available in 5 years from now. High-quality operational research studies will be required to rigorously field test and scientifically evaluate the new or improved tools and strategies. We see the CAA-UCP test as a particularly promising tool that could be transformed into a rapid format. In our opinion, this test has the potential to become an indispensable assay for detecting low-intensity infections and for verification purposes of schistosomiasis elimination. Lots remains to be done and in view of the generation gap reported in parasitology, vector biology and disease control, it will be of particular importance that scientists, control managers and public health experts work closely together, being open to experience from the past as well as not reluctant to new ideas, to move toward large-scale and sustainable control and elimination of schistosomiasis and other neglected tropical diseases.

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Key issues

- The impact of acute and chronic schistosomiasis on children's physical fitness, cognition and nutritional disorders remains to be investigated in well-designed, confounder-adjusted trials to contribute to accurate burden estimates.
- The impact of schistosomiasis on the susceptibility, development and transmission of co-infections and on their treatment and prevention remains to be studied.
- There is a pressing need to develop new drugs and vaccines that are efficacious against all stages of the *Schistosoma* parasites, particularly in view of up-scaling the current administration of praziquantel, which holds the risk of developing drug-resistant parasites.
- Highly sensitive diagnostic tools to detect light-intensity infections are needed for an accurate assessment of control interventions, and for monitoring and surveillance once interruption of transmission has been achieved and for verification of local elimination.
- Integration of preventive chemotherapy with other control measures such as snail control, access to clean water, improved sanitation and health education is necessary to escalate from morbidity control to transmission interruption and ultimately elimination.
- Control interventions must be adapted to the social–ecological settings and accepted and supported by the local government and communities to become successful.
- Effective partnerships between scientists, control managers and public health experts, the private sector and intersectoral collaboration are necessary for long-term sustainable control/elimination of schistosomiasis.

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