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Review

From innovation to application: Social–ecological context, diagnostics, drugs and integrated control of schistosomiasis

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ABSTRACT

Compared to malaria, tuberculosis and HIV/AIDS, schistosomiasis remains a truly neglected tropical disease. Schistosomiasis, perhaps more than any other disease, is entrenched in prevailing social–ecological systems, since transmission is governed by human behaviour (e.g. open defecation and patterns of unprotected surface water contacts) and ecological features (e.g. living in close proximity to suitable freshwater bodies in which intermediate host snails proliferate). Moreover, schistosomiasis is intimately linked with poverty and the disease has spread to previously non-endemic areas as a result of demographic, ecological and engineering transformations. Importantly though, thanks to increased advocacy there is growing awareness, financial and technical support to control and eventually eliminate schistosomiasis as a public health problem at local, regional and global scales. The purpose of this review is to highlight recent progress made in innovation, validation and application of new tools and strategies for research and integrated control of schistosomiasis. First, we explain that schistosomiasis is deeply embedded in social–ecological systems and explore linkages with poverty. We then summarize and challenge global statistics, risk maps and burden estimates of human schistosomiasis. Discovery and development research pertaining to novel diagnostics and drugs forms the centrepiece of our review. We discuss unresolved issues and emerging opportunities for integrated and sustainable control of schistosomiasis and conclude with a series of research needs.

Contents

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1. Introduction

Unlike malaria, tuberculosis and HIV/AIDS, schistosomiasis and a host of other helminthic, bacterial, protozoan and viral diseases remain truly neglected (Hotez et al., 2006, 2007; Utzinger et al., 2009). Indeed, there is no "Global Fund to Fight Schistosomiasis" and other neglected tropical diseases (NTDs), whereas the creation of the Global Fund to Fight AIDS, Tuberculosis and Malaria in 2002 was a game changer that raised the profile and funding for research and control of the 'big three', that is HIV/AIDS, tuberculosis and malaria (Hotez et al., 2008; Moran et al., 2009). The close link with poverty, geographical isolation, underappreciated global burden, stigmatization, lack of political voice of those affected and the aforementioned absence of an established global funding mechanism are some of the factors that explain the general neglect of schistosomiasis and NTDs in general (Molyneux, 2008; Weiss, 2008; Hotez et al., 2009; Gray et al., 2010; Payne and Fitchett, 2010).

Schistosomiasis gives rise to a complex of mainly chronic and debilitating but also acute manifestations caused by the host's vigorous immunological reactions to parasite eggs, which are trapped in host tissues of the mesenteric veins, or lodged in particular organs, such as the liver (Gryseels et al., 2006; Davis, 2009). The causative agent is a blood fluke of the genus *Schistosoma*. There are five species capable of parasitizing humans: *Schistosoma haematobium*, *Schistosoma mansoni*, *Schistosoma japonicum*, *Schistosoma mekongi* and *Schistosoma intercalatum*, with the former three being the most widespread (Gryseels et al., 2006; Davis, 2009). Of scientific note, *S. intercalatum* has been grouped into two separate species: *S. intercalatum* and *Schistosoma guineensis* (Kane et al., 2003). An infection with *S. haematobium* causes urinary schistosomiasis, which is characterized by the lesions of the bladder wall and the presence of blood in urine (haematuria) (Hatz, 2001; van der Werf et al., 2003; Gryseels et al., 2006; Davis, 2009). *Schistosoma mansoni* and *S. japonicum* cause intestinal schistosomiasis, the late-stage symptoms issuing from the liver (Hatz, 2001; Gryseels et al., 2006; Lambertucci et al., 2008; Davis, 2009). *Schistosoma intercalatum* is restricted to Central Africa and might become extinct (Tchuem Tchuenté et al., 2003). *Schistosoma mekongi* occurs focally in the south of Lao People's Democratic Republic and Cambodia (Muth et al., 2010).

From a global public health point of view, schistosomiasis remains the most important water-based disease (Steinmann et al., 2006). Indeed, in the endemic parts of the world, schistosomiasis is intimately connected to the construction and operation of irrigation systems, multipurpose small dams and large hydroelectric dams for power production and irrigation-fed agriculture (Hunter et al., 1993; Jobin, 1999; Amerasinghe, 2003; Steinmann et al., 2006). This makes schistosomiasis also a typical disease of poverty, as it is widespread where access to clean water and basic sanitation is lacking, hygiene is substandard and health systems are weak or non-existent (Bruun and Aagaard-Hansen, 2008; Utzinger et al., 2009; King, 2010). Poor and marginalized rural dwellers of sub-Saharan Africa are the most severely affected by schistosomiasis, explained by a multitude of complex and interconnected factors (WHO, 2002a; Bruun and Aagaard-Hansen, 2008; Utzinger et al., 2009). Finally, schistosomiasis has shown a tendency of spreading to previously non-endemic areas in the face of water resources development and management (Fenwick, 2006; Steinmann et al., 2006; Li et al., 2007), a situation that might be further exacerbated by climate change (Yang et al., 2005, 2010; Zhou et al., 2008).

The goal of this review is to highlight advances made in innovation, validation and application of new tools and strategies for research, control and eventual elimination of schistosomiasis. We first set the stage by clarifying that schistosomiasis is genuinely entrenched in social–ecological contexts. Next, we review global statistics of at-risk populations, number of infections and burden estimates and emphasize that these data are educated guesses at best. We give a detailed account of recent progress made in the discovery and development of new tools, placing particular emphasis on diagnostics and drugs, recognizing that 'preventive chemotherapy' provides rapid and spectacular initial results in terms of morbidity reduction. However, this strategy fails to prevent re-infection, and hence, we discuss unresolved issues and opportunities for a more integrated and systemic approach to control schistosomiasis. We conclude that an understanding of the pertinent social–ecological systems is mandatory to the sustainable control and eventual elimination of schistosomiasis, and offer a series of research needs.

2. Understanding schistosomiasis from a social–ecological perspective

2.1. Social and behavioural factors

Fig. 1 shows that schistosomiasis is embedded in the social–ecological system, which in turn explains its intimate connection with habituation, poverty and general neglect. The drawing depicts the schistosome life cycle, as perceived by an 11-year-old schoolgirl from Fagnampleu, a rural setting in the Man region, western Côte d'Ivoire. In the second half of the 1990s, our teams initiated epidemiological research and control activities against schistosomiasis, soil-transmitted helminthiasis, malaria and multiparasitism in this part of Côte d'Ivoire (Utzinger et al., 1998; Keiser et al., 2002; Raso et al., 2006; Silué et al., 2008). While implementing the first randomized controlled trial with oral artemether for the prevention of patent *S. mansoni* infections (Utzinger et al., 2000b), we invited children attending the primary school of Fagnampleu to draw the schistosome life cycle. We obtained a rich collection and the one shown in Fig. 1 was selected as representative. Two key social determinants of schistosomiasis are depicted. First, a man is urinating 'in the bush' or perhaps directly into a freshwater pond. Second, a woman is standing barefoot in unprotected surface water with a bucket on her head after she has been fetching water. It therefore shows the infection of the intermediate host snails and how this infection is propagated back to other humans, whilst they are in contact with contaminated freshwater bodies. Moreover, the picture shows that water is carried back home for domestic use, and hence this behaviour is learned by children in their early years of life as common and natural behaviour.

Fig. 1. The schistosome life cycle as perceived by an 11-year-old schoolgirl living in Fagnampleu, western Côte d'Ivoire. Of note, key elements how schistosomiasis is deeply embedded in social (e.g. open human waste elimination and water contact patterns) and ecological systems (e.g. people are living in close proximity to freshwater bodies inhabited by intermediate host snails) are clearly depicted.

A deeper understanding of these social and behavioural patterns, along with knowledge, attitudes, beliefs and practices, are crucial for the design and implementation of local, setting-specific policies and strategies for the prevention and control of schistosomiasis (Huang and Manderson, 2005; Bruun and Aagaard-Hansen, 2008; Aagaard-Hansen et al., 2009; Manderson et al., 2009). Moreover, we conjecture that, for teaching purposes and raising local awareness, the life cycle as depicted in Fig. 1 is appealing and of more immediate impact in contrast to the technical life cycles presented in textbooks and the peer-reviewed literature (for recent examples, see: Gryseels et al., 2006; Davis, 2009; McManus et al., 2010; Utzinger et al., 2010a). Thus, we speculate that for children and adults living in schistosome-endemic areas, hand-drawn life cycles are particularly instructive for disease prevention and control.

2.2. Ecological factors

With regard to ecological considerations, new evidence has been generated while conducting a systematic review and meta-analysis investigating whether living in close proximity (i.e. $\leq$5 km) to large dams and irrigation systems is a risk factor for schistosomiasis (Steinmann et al., 2006). A total of 35 databases from 24 studies, all of which carried out in Africa, met the authors' inclusion criteria. Specifically, the studies compared schistosomiasis prevalence data before and after the construction of large dams or irrigation systems nearby. Moreover, inference was drawn between two settings, one with and another without a water resources development component. It was found that people living in close proximity to large dams were at a significantly higher risk of infection by either *S. mansoni* (risk ratio (RR) = 2.6, 95% confidence interval (CI) = 1.4–5.0) or *S. haematobium* (RR = 2.4, 95% CI = 1.4–3.9) than those living further away. However, with regard to living in close proximity to irrigation systems, there was a significant risk for infection by *S. mansoni* (RR = 4.7, 95% CI = 1.7–12.5), but not by *S. haematobium* (RR = 1.1, 95% CI = 0.4–3.0). In fact, ecological and demographic transformations often resulted in a shift from urinary to intestinal schistosomiasis, first documented in Egypt shortly after completion of the Aswan high dam (Abdel-Wahab et al., 1979) and more recently in Senegal after the Diama dam became operational (Southgate, 1997).

Additionally, the aforementioned review revealed that schistosomiasis has spread to previously non-endemic areas due to water resources developments. This observation has been explained by the creation of suitable freshwater bodies attracting intermediate host snails ready for the parasite to be introduced by labour-induced in-migration (Greany, 1952; Choudhry, 1975; Fenwick, 2006; Steinmann et al., 2006).

3. Global statistics, distribution and burden estimates

3.1. Global statistics and current distribution

Global statistics for mid-2003 suggest that almost 800 million individuals were at risk of schistosomiasis, 207 million were infected, 120 million suffered from clinical disease and 20 million exhibited severe morbidity (Chitsulo et al., 2000; Steinmann et al., 2006). An estimated 97% of all infected people are concentrated in Africa, which is partially explained by the social–ecological context detailed above, weak or non-existing health systems, poverty and general neglect (Bruun and Aagaard-Hansen, 2008; Hotez and Fenwick, 2009; Stothard et al., 2009a; Utzinger et al., 2009).

Fig. 2 shows a global map with estimated country-specific prevalence rates of schistosomiasis as of mid-2003. Three issues are noteworthy. First, schistosomiasis has been eliminated from Japan and Tunisia (Tanaka and Tsuji, 1997; Jordan, 2000). Second, the disease is close to elimination on some Caribbean islands and in Morocco (Hillyer et al., 1999; Laamrani et al., 2000). Third, early recognition of the public health implications of schistosomiasis, political will and commitment, and sustained implementation of the created national control programmes met with success wherever tried as in Brazil, the People's Republic of China (P.R. China) and Egypt (Engels et al., 2002; Wang et al., 2008). Estimated prevalence rates are now below 1% in Brazil and P.R. China and approximately

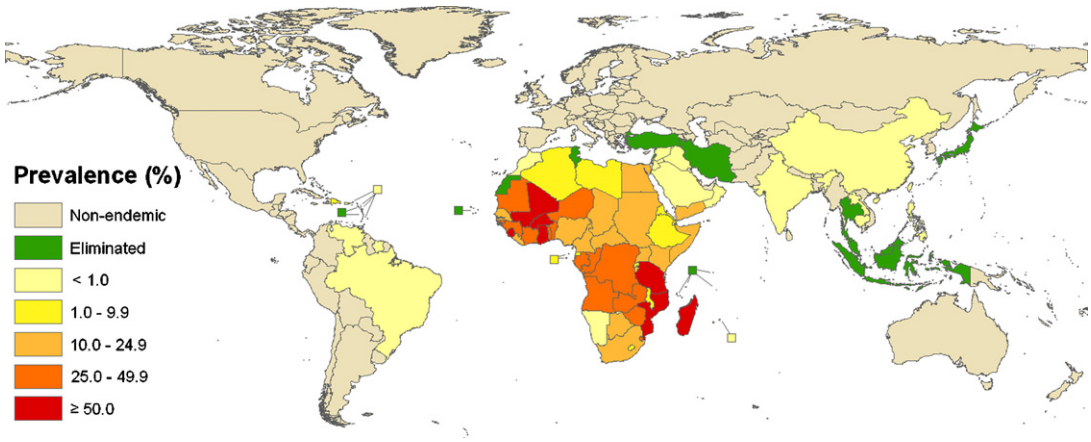

Fig. 2. Current global distribution of schistosomiasis, stratified according to country-specific prevalence estimates.
Source: Steinmann et al. (2006) and Utzinger et al. (2009).

10% in Egypt (Steinmann et al., 2006; Zhou et al., 2007; Utzinger et al., 2009). On the other hand, prevalence rates in excess of 50% have been reported for some African countries, such as Ghana (72.5%), Mozambique (69.8%), Burkina Faso (60.0%), Mali (60.0%), Sierra Leone (59.5%), Madagascar (55.0%) and the United Republic of Tanzania (51.5%) (Steinmann et al., 2006; Utzinger et al., 2009).

The accuracy of the aforementioned data, however, warrants scrutiny. In the absence of reliable and updated schistosomiasis prevalence data in the public domain, inference is usually drawn from a limited number of surveys, most of which adopted a simple cross-sectional epidemiological design, used insensitive diagnostic approaches and focused on school-aged children in rural settings. Since the peak prevalence of schistosome infections occurs in the school-aged and adolescent populations (Woolhouse, 1998), extrapolation of such data is likely to result in overestimates of the prevalence in the entire population. On the other hand, widely used diagnostic approaches, such as the Kato–Katz technique for the detection of *S. mansoni* eggs in stool samples, lack sensitivity, particularly in low endemicity areas, and hence reported prevalence rates considerably underestimate the 'true' number of infections (de Vlas and Gryseels, 1992; Utzinger et al., 2001; Enk et al., 2008). Moreover, although some studies report the occurrence of transmission in urban settings (Matthys et al., 2007), schistosomiasis is primarily a rural disease. In this regard, it is important to note that urbanization continues at a rapid pace in Africa and elsewhere in the developing world. For example, while less than a third of Africans lived in urban areas 20 years ago, the estimated proportion has grown to 40% in 2010 (UN, 2010). In some countries more people already live in urban rather than rural areas, for example in Ghana where the urban population is currently estimated at 51.5%. Hence, the reported data that 72.5% of the Ghanaian population is infected with schistosomes is not credible. It should also be noted that considerable progress has been made in schistosomiasis control in sub-Saharan African with financial and technical support from the Schistosomiasis Control Initiative (Fenwick et al., 2009). This has facilitated the (re-)establishment of national control programmes in several countries. However, the success of these programmes in terms of patients cured has yet to be translated into new estimates of the number of infections on a country-by-country basis.

We, therefore, welcome new efforts to update estimates of schistosome (and other helminth infections) prevalence data using standardized approaches, including geolocation of identified survey data, so that more accurate distribution maps can be generated, as recently exemplified for East Africa (Brooker et al., 2009). What is needed is a 'real-time', open-access database for researchers and national disease control managers alike to update the latest survey data in a spatially explicit way. One of the specific objectives of the European Union (EU)-funded CONTRAST programme is to provide such a platform capable of continuously updating information as it becomes available (Simoonga et al., 2009; Stensgaard et al., 2009; http://www.eu-contrast.eu/). Of note, mapping the distribution of schistosomiasis in West Africa by CONTRAST has been completed and work is in progress for the rest of Africa. Following on, this open-access platform will be extended from Africa to the rest of the world and, as a next step, the schistosomiasis target will be expanded to include soil-transmitted helminthiasis and other NTDs. Importantly, other groups are also working towards a global atlas of helminth infections (Brooker et al., 2010), which bodes well for joining forces with the CONTRAST team.

3.2. Estimates of burden of disease

There is considerable discussion regarding the 'true' burden of schistosomiasis (King et al., 2005; Gryseels et al., 2006; King and Bertino, 2008; King and Dangerfield-Cha, 2008). Indeed, the first global estimate published by the World Health Organization (WHO) for the year 1998 was 1,699,000 disability-adjusted life years (DALYs) lost (WHO, 1999). Table 1 shows the evolution of global burden estimates for schistosomiasis, as presented in the annex tables of the World Health Reports published between 2000 and 2003 (WHO, 2000, 2001, 2002b, 2003). Interestingly, an expert committee convened by WHO in 2001 put forth a considerably higher estimate, i.e. 4.5 million DALYs (WHO, 2002a). Based on a systematic review and analyzing performance-related symptoms and disability-associated outcomes for all forms of schistosome infections, it was concluded that even the higher value of 4.5 million DALYs is probably still an underestimation of the 'true' burden (King et al., 2005; King and Dangerfield-Cha, 2008). Indeed, the hightest estimate cited in the literature is 70 million DALYs (Hotez and Fenwick, 2009). What are the reasons for these discrepancies? To answer this question, it is important to understand the DALY metrics and how the burden of diseases and injuries is calculated.

To quantify the burden of a disease or injury, a combined measure of years of life lost due to pre-mature death and the number of healthy life year-equivalents lost due to disability is employed, i.e. the DALY (Murray and Lopez, 1996). In the case of schistosomiasis, generally believed to cause 'only' between 7000 and 15,000 deaths per year (Table 1), the burden is mainly governed by disability-linked morbidities. However, miniscule disability weights (0.005–0.006 on a scale from 0 (no disability) to 1 (death)) were assigned to all forms of schistosomiasis, which is at the root of

Table 1
Evolution of global estimates of the at-risk population, number of people infected, deaths and burden due to schistosomiasis according to different sources.

Year	World population (million)	Global estimates				Ref.
		At-risk population in million (%)	No. of people infected in million (%)	No. of deaths	Burden (million DALYs)	
1940	2166.8	n.d.	114.4 (5.3)	n.d.	n.d.	Stoll (1947)
1985	4846.2[a]	500–600(10.3–12.4)	>200 (>4.1)	n.d.	n.d.	WHO (1985)
1995	5713.1[a]	702.4 (12.3)[b]	193.2 (3.3)	n.d.	n.d.	Chitsulo et al. (2000)
1998	5884.6	–	–	7000	1.699	WHO (1999)
1999	5961.6	–	–	14,000	1.932	WHO (2000)
2000	6045.2	–	–	11,000	1.713	WHO (2001)
2001	6122.2	–	–	15,000	1.760	WHO (2002b)
2002	6225.0	–	–	15,000	1.702	WHO (2003)
2003	6313.8	779.3 (12.3)	207.3 (3.3)	n.d.	n.d.	Steinmann et al. (2006)
n.d.		–	–	280,000[c]	4.500[d]	Hotez et al. (2006)
n.d.		–	–	–	70.0	Hotez and Fenwick (2009)

DALYs, disability-adjusted life years; n.d., not determined.

[a] *Source*: World Urbanization Prospects: The 2009 Revision Population Database (http://esa.un.org/unpd/wup/unup/p2k0data.asp; accessed: 20 April 2010).

[b] Of note, the at-risk population cited in the original publication (i.e. 652.1 million) should actually read 702.4 million, as apparently the at-risk population in Egypt (i.e. 50.2 million) had been omitted from the total estimate (see Chitsulo et al., 2000; Steinmann et al., 2006).

[c] Estimate is based on a systematic review exploring the functional relationship between schistosome infection and morbidity which revealed that, for Africa in the year 2000, there were 150,000 deaths attributable to non-functioning kidney due to *S. haematobium* and another 130,000 deaths attributable to haematemesis due to *S. mansoni*) (*source*: van der Werf et al., 2003).

[d] *Source*: WHO (2002a).

the low overall global estimates for schistosomiasis. According to King et al. (2005), disregarding subtle morbidity, disability weights of 0.02–0.15 were estimated for different morbid sequelae due to schistosomiasis. New research pertaining to chronic schistosomiasis japonica found age-specific disability weights of up to 0.25 in the age group above 60 years (Jia et al., 2007; Finkelstein et al., 2008).

We applaud a new coordinated effort to systematically review the literature, coupled with modeling to obtain prevalence, incidence, morbidity and mortality data for more than 150 diseases and risk factors with the ultimate goal to produce internally consistent global burden estimates for the year 2005 (Murray et al., 2007). This scientific inquiry with coordination across disease clusters and risk factors will also identify a more unified annual mortality estimate due to schistosomiasis, which currently ranges between 15,000 and 280,000 in sub-Saharan Africa alone according to different sources (van der Werf et al., 2003; WHO, 2003).

4. Diagnostics

4.1. The paramount importance of an accurate diagnosis

The need for an accurate diagnosis of schistosomiasis and other diseases cannot be overemphasised, as it is of critical importance for the clinician in providing adequate patient management, and for epidemiologists and disease control managers for all aspects of prevention, control, monitoring and surveillance. At the population level, for example, mapping, estimating the burden of disease, evaluating anti-schistosomal drug efficacy, pharmacovigilance, monitoring of control programmes and verification of local elimination all depend on accurate diagnostics (Peeling et al., 2006; Bergquist et al., 2009; Johansen et al., 2010). Yet, the current global strategy for the control of schistosomiasis and a host of other NTDs is built around 'preventive chemotherapy', that is the regular administration of drugs to at-risk populations without prior diagnosis (WHO, 2006; Hotez et al., 2007; Baker et al., 2010; Tchuem Tchuenté, 2010). Justification for this strategy is derived from the safety and therapeutic profiles of drugs, their low costs (including delivery) and the rapid impact on ameliorating morbidity (Molyneux et al., 2005; Hotez et al., 2006, 2007; Smits, 2009). These are some of the reasons that explain why research and development of diagnostic tools are so much neglected (Ridley, 2006), which might be further amplified in the era of 'preventive chemotherapy' (Bergquist et al., 2009; Rollinson, 2009).

4.2. Parasitological methods

Direct detection of schistosome eggs in urine (e.g. *S. haematobium*) and stool samples (e.g. *S. mansoni* and *S. japonicum*) under a microscope is the most widely used diagnostic approach in epidemiological surveys of schistosomiasis. A commonly employed direct method for the diagnosis of urinary schistosomiasis is the standard urine filtration method that involves the detection and quantification of *S. haematobium* eggs in a 10-ml filtrate of a urine specimen that should be collected between 10:00 and 14:00 h to correspond with diurnal peak egg output (Plouvier et al., 1975; Mott et al., 1982). The Kato–Katz method, widely used for the diagnosis of *S. mansoni* and *S. japonicum* (and soil-transmitted helminths), will be described in more detail below.

In an early stage of a control programme, when morbidity control is the declared objective, infection prevalence and intensity are usually high, and hence direct methods show reasonable diagnostic accuracy. However, prevalence and particularly intensity of infection are reduced through treatment, and hence direct methods become less sensitive and should be augmented or replaced by immunological techniques based on antigen or antibody detections (van Lieshout et al., 2000; Doenhoff et al., 2004; Bergquist et al., 2009; Johansen et al., 2010), or molecular tools such as polymerase chain reaction (PCR)-based approaches (Pontes et al., 2003; ten Hove et al., 2008; Gomes et al., 2010).

4.2.1. The Kato–Katz technique

For quantification of faecal egg counts the Kato–Katz method, originally developed in the mid-1950s by the Japanese researchers Kato and Miura (Kato and Miura, 1954), and further modified in the early 1970s by Katz and colleagues in Brazil (Katz et al., 1972), is the most widely used technique in epidemiological surveys pertaining to intestinal schistosomiasis (and also used for other helminth infections). This technique is simple, but requires a minimum of laboratory equipment (e.g. microscope and mostly reusable test kit materials) and well-trained laboratory technicians. Although it is commonly believed that the Kato–Katz technique is inexpen-

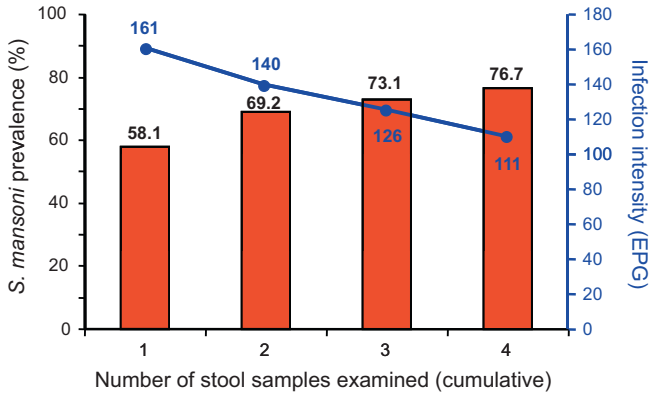

Fig. 3. Effect of sampling effort on the observed prevalence and infection intensity of *S. mansoni* in a cohort of 253 schoolchildren in Fagnampleu, western Côte d'Ivoire. *Source*: Utzinger et al. (2000a).

sive, new research in Zanzibar has shown that a single or duplicate Kato–Katz thick smears done within the frame of an epidemiological survey costs US$ 1.73 and US$ 2.06, respectively (Speich et al., 2010). Most commonly, Kato–Katz thick smears are prepared by using standardized 41.7 mg templates, and hence the theoretical sensitivity is 24 eggs per gram (EPG) of faeces. However, it is widely acknowledged that single Kato–Katz thick smear examinations underestimate the 'true' prevalence of *S. mansoni* and *S. japonicum* and this issue is particularly important in settings where infection intensities are low (de Vlas and Gryseels, 1992; Yu et al., 2007; Lin et al., 2008). Numerous studies have investigated the effect on diagnostic accuracy of stool consistency, intra-specimen and day-to-day variation in faecal egg output, and have discussed the implications for research and control (Engels et al., 1996, 1997a,b; Kongs et al., 2001; Utzinger et al., 2001; Booth et al., 2003; Enk et al., 2008).

Fig. 3 shows the effect of multiple stool sampling on the observed prevalence and intensity of *S. mansoni* infection among a cohort of 253 schoolchildren during the baseline survey of an anti-schistosomal drug efficacy trial (Utzinger et al., 2000a). Whereas the prevalence of infection increased from 58.1% after examining a single Kato–Katz thick smear to 76.7% after each child had submitted four consecutive stool samples, the overall infection intensity decreased from 161 EPG to 111 EPG. These observations are explained by the imperfect sensitivity of the Kato–Katz method for detecting light-intensity infections. Hence, caution is indicated when gauging the expected low infection intensities after drug interventions. Here, multiple stool samples with at least duplicate Kato–Katz thick smears per sample must be analyzed as the risk for missing light infections is now high. Another approach to boost diagnostic sensitivity is to employ multiple methods for the same stool sample, e.g. the Kato–Katz technique combined with the ether-concentration method (Raso et al., 2006; Legesse and Erko, 2007).

4.2.2. First experiences with the FLOTAC technique

In veterinary parasitology, simple flotation methods, such as the McMaster and Wisconsin flotation techniques have been in use for helminth diagnosis for 50+ years (Whitlock, 1948; Cox and Todd, 1962). In 2006, after more than a decade of development, a new flotation method was presented: the FLOTAC technique (Cringoli, 2006). The central feature of this technique is the FLOTAC apparatus, a cylindrically shaped device with two flotation chambers, each holding a volume of 5 ml. Up to 1 g of stool can be examined with a single FLOTAC test, and hence the theoretical sensitivity is 1 EPG, i.e. more than an order of magnitude greater than a single Kato–Katz thick smear. Standard protocols have been presented for the FLOTAC basic, dual, double and pellet techniques, and experiences gained thus far with the FLOTAC technique for the diagnosis of helminths in different animal species and humans have been summarized (Cringoli et al., 2010). Studies carried out in Côte d'Ivoire and Zanzibar revealed that a single FLOTAC is, as expected, more sensitive than multiple Kato–Katz thick smears for the diagnosis of common soil-transmitted helminths such as *Ascaris lumbricoides*, hookworm and *Trichuris trichiura*. However, the FLOTAC approach resulted in significantly lower faecal egg counts of soil-transmitted helminths compared to the Kato–Katz method and this observation warrants further investigation (Utzinger et al., 2008; Knopp et al., 2009).

More recently, a study compared the diagnostic accuracy of three direct methods – Kato-Katz, ether-concentration and FLOTAC – for the detection and quantification of *S. mansoni* eggs in stool samples from 112 schoolchildren in Côte d'Ivoire. Additionally, the effect of different preservation media (sodium acetate-acetic acid-formalin (SAF) and formalin) and duration of stool preservation was assessed. Combined results of the three methods (considering a positive test results regardless of the method employed as 'true postive') served as a diagnostic 'gold' standard and revealed a high prevalence of *S. mansoni* (83.0%). Table 2 summarizes the main results of the diagnostic accuracy of the three methods. In brief, the conservation media showed only little effect in diagnostic sensitivity of the FLOTAC technique, and hence only results with SAF are presented. Moreover, the same results were obtained after 30 and 83 days of stool preservation for subsequent FLOTAC examination, we therefore only present the results from the latter time point. Subjecting stool samples to a single FLOTAC revealed a sensitivity for *S. mansoni* diagnosis of 91.4%. This compared favourably to the ether-concentration method with stool samples preserved for 40 days (sensitivity: 85.0%) or triplicate Kato–Katz using fresh stool samples (sensitivity: 77.4%). However, the FLOTAC technique resulted in considerably lower faecal egg counts compared to the Kato–Katz and ether-concentration techniques, which warrants

Table 2
Diagnostic accuracy of single and triplicate Kato–Katz thick smears, ether-concentration technique and FLOTAC using fresh or preserved stool samples in terms of sensitivity and faecal egg counts for the diagnosis of *S. mansoni* among 112 schoolchildren in a highly endemic area of south Côte d'Ivoire.

Technique	Duration of stool preservation (days)	Number of infected schoolchildren (%)	Sensitivity in % (95% CI)	Mean faecal egg count in EPG (95% CI)
'Gold' standard	N/A	93 (83.0)	100	N/A
Kato–Katz (single)	0 (fresh stool)	63 (56.3)	67.7 (59.1–76.4)	134.9 (97.5–186.8)
Kato–Katz (triplicate)	0 (fresh stool)	72 (64.3)	77.4 (69.7–85.2)	121.2 (86.8–169.2)
Ether-concentration	40 (in SAF)	79 (70.5)	85.0 (78.3–91.6)	110.7 (76.0–161.1)
FLOTAC	0 (fresh stool, homogenized in SAF)	60 (53.6)	64.5 (55.7–73.4)	18.1 (13.2–24.7)
FLOTAC	10 (in SAF)	81 (72.3)	87.1 (80.9–93.3)	32.3 (24.7–42.3)
FLOTAC	83 (in SAF)	85 (75.9)	91.4 (86.2–96.6)	57.7 (41.5–80.2)

Source: Glinz et al. (2010).
CI, confidence interval; EPG, eggs per gram of stool; N/A, not applicable.

follow-up studies to elucidate the reasons for these discrepancies (Glinz et al., 2010).

4.3. Immunological methods

Immunodiagnosis of schistosomiasis has been proposed to overcome some of the limitations with parasitological methods, that is day-to-day and intra-specimen variation of schistosome egg output, the risk of missing low-intensity infections, relatively time-consuming methodologies and the need for well-trained laboratory technicians (Hamilton et al., 1998; van Lieshout et al., 2000; Doenhoff et al., 2004). Immunological approaches are based on the detection of antibodies or antigens. Although immunodiagnosis usually requires somewhat better equipped laboratories than direct techniques using microscopy, immunological methods may yield higher sensitivities, especially for antibody detection. However, specificity might be a problem for antibody detection, and since antibody detection is not quantitative, it is difficult to differentiate between light and heavy infections. Moreover, antibody levels remain high for prolonged periods of time following successful chemotherapy, which represents a diagnostic dilemma: failure to differentiate between active and cured infections. Finally, there might be a high degree of cross-reactivity in settings where schistosome and other trematode infections co-exist (Bergquist et al., 2009; Johansen et al., 2010). In P.R. China, a common approach for the diagnosis of *S. japonicum* is to first screen at-risk populations for antibodies, followed by stool microscopy of antibody-positive individuals (Utzinger et al., 2005; Zhu, 2005; Balen et al., 2007). In Venezuela, the combination of stool microscopy with serological methods has been proposed for detection of schistosomiasis mansoni cases in low-transmission areas (Alarcón de Noya et al., 2007).

Detection of schistosome antigens, such as circulating anodic antigens (CAA) and circulating cathodic antigens (CCA) (van Lieshout et al., 2000) or *S. mansoni* soluble egg antigen (SEA) (Chand et al., 2010) in blood or urine, using enzyme-linked immunosorbent assays (ELISAs) hold several advantages over antibody detection. Most notably, active infections can be readily demonstrated. Hence, this approach is useful for drug efficacy trials due to high specificity. Classical ELISA procedures, however, are quite slow, require well-equipped laboratories and highly qualified technicians (Deelder et al., 1989; van Lieshout et al., 2000).

Against this background, different rapid diagnostic assays have been developed. One of these tests, presented in more detail in the current review, is based on the detection of CCA in urine for the diagnosis of schistosomiasis. The principle of the test is based on a lateral-flow assay using a nitrocellulose strip of the sample with a colloidal carbon conjugate of anti-CCA monoclonal antibodies (van Dam et al., 2004). Table 3 summarizes the performance of the CCA urine strip test for the diagnosis of *S. mansoni* in different epidemiological settings across Africa, as compared to parasitological methods such as duplicate Kato–Katz thick smears, sometimes supplemented with preserved stool samples subjected to an ether-concentration method (van Dam et al., 2004; Stothard et al., 2006; Legesse and Erko, 2007, 2008; Standley et al., 2010a). Overall, the sensitivity of the CCA urine strip test was high (76.9–100%), whereas specificity was moderate to high (43.4–87%). Positive and negative predictive values (PPV and NPV) were moderate to high. A recent study carried out on the Sesse Islands in Uganda found poor diagnostic congruence between Kato–Katz thick smears and CCA urine strip tests (Standley et al., 2010b).

The CCA strip test has also undergone validation for *S. haematobium* diagnosis with test results compared to the standard urine filtration method and reagent strips for detection of microhaematuria. While CCA urine strip tests totally failed to detect *S. haematobium* or resulted in a very poor sensitivity (9%) among

Table 3
Diagnostic performance of circulating cathodic antigen (CCA) urine-dipsticks for detection of *S. mansoni* infections in different African settings.

Setting, country (time of survey)	Study population	Diagnostic 'gold' standard	No. (%) of *S. mansoni*-positive individuals		Diagnostic performance of CCA urine strip (%)				Ref.
			'Gold' standard	CCA urine strip	Sensitivity	Specificity	PPV	NPV	
Mwanza region, United Republic of Tanzania (n.k.)	Schoolchildren aged 7–18 years	Duplicate 41.7 mg Kato–Katz thick smears (1 stool sample)	39 (79.6)	49 (100)	100	87[a]	n.d.	n.d.	van Dam et al. (2004)
25 sentinel schools in Hoima and Mayuge districts, Uganda (April and July 2003)	Schoolchildren aged 11 years (n = 590)	Duplicate 41.7 mg Kato–Katz thick smears (1 stool sample)	n.d. (58)	n.d. (48)	83	81	84	84	Stothard et al. (2006)
Dudycha village, south-central Ethiopia (July 2005)	Individuals aged 5–75 years with a mean of 20 years (n = 251)	Duplicate 41.7 mg Kato–Katz thick smears plus formol–ether concentration method (1 stool sample)	179 (71.3)	189 (75.3)	82.1	75.9	77.8	48.4	Legesse and Erko (2007)
Kemmie primary school, south-central Ethiopia (June 2007)	Schoolchildren aged 5–22 years (n = 184)	Single 41.7 mg Kato–Katz thick smear plus formol–ether concentration method (1 stool sample)	78 (42.4)	120 (65.2)	76.9	43.4	50.0	71.9	Legesse and Erko (2008)
Lake Victoria shoreline schools in northern Tanzania and western Kenya (January and February 2009)	Schoolchildren aged 6–17 years (n = 171)	Duplicate 41.7 mg Kato–Katz thick smears (1 stool sample)	117 (68.6)	122 (71.3)	87.7	68.1	86.1	71.1	Standley et al. (2010a)

n.d., not determined; n.k., not known; NPV, negative predictive value; PPV, positive predictive value.
[a] Determined based on 45 urine samples from schoolchildren from a mountainous area of the United Republic of Tanzania, where schistosomiasis is not endemic, hence, serving as negative controls.

children in Zanzibar (Stothard et al., 2006, 2009b), moderate to high sensitivities and specificities were observed in Ethiopia (Ayele et al., 2008) and Ghana (Obeng et al., 2008).

Clearly, additional validation of the CCA urine strip test for the diagnosis of both urinary and intestinal schistosomiasis in different epidemiological settings is warranted. A rapid diagnostic test based on urine examination, characterized by high sensitivity and specificity would be a major asset, particularly for the diagnosis of *S. mansoni* at the point-of-care (POC). Hence, we welcome new research facilitated by the Bill & Melinda Gates Foundation sponsored Schistosomiasis Consortium for Operational Research and Evaluation (SCORE), now funding several projects pursuing rigorous validation of the CCA urine strip test for the diagnosis of *S. mansoni* in low and moderate endemicity areas, as well as in mixed *S. mansoni*–*S. haematobium* foci. Should these validations prove successful, efforts should be made to further reduce the cost per test strip (ideally below US$ 1.00) in order to render this technique a useful diagnostic approach at POC in resource-constrained settings where schistosomiasis is entrenched (Stothard, 2009).

4.4. Molecular methods

Diagnostic tools with a high sensitivity are required for the detection of light-infection intensities (e.g. for diagnosing tourists and travellers returning from schistosome-endemic countries in specialized laboratories in western travel clinics). Additionally, such tools are needed for the rigorous evaluation of drug efficacy trials and monitoring of late-stage schistosomiasis control programmes, when transmission control and local elimination become the ultimate targets. In 2002, the proof-of-concept PCR for the detection of *S. mansoni* in faecal samples was published (Pontes et al., 2002). The method is based on the amplification of a highly repeated DNA sequence, using simple DNA extraction techniques and a rapid two-step PCR approach, which facilitated the amplification of *S. mansoni* DNA in faecal samples. Subsequently, 194 individuals, aged 5–76 years, from a *S. mansoni*-endemic setting in Brazil, were invited to provide three stool specimens, all of which were subjected to the Kato–Katz method. PCR was performed on a single stool sample per individual. While triplicate Kato–Katz thick smears revealed a *S. mansoni* prevalence of 30.9%, a single stool sample subjected to the PCR-based approach found a considerably higher prevalence of 38.1% (Pontes et al., 2003). Several other groups have developed additional specific and highly sensitive PCR-based assays for schistosomiasis diagnosis (for two recent examples, see: Lier et al., 2009; Gomes et al., 2010).

Recently, a multiplex real-time PCR for the detection and quantification of both *S. mansoni* and *S. haematobium* has been developed (ten Hove et al., 2008). Employing stool samples from individuals in a schistosome-endemic area in Senegal, the PCR approach found, as expected, a higher detection rate than standard parasitological tests performed on multiple stool samples. Subsequent research in Ghana, placing emphasis on the diagnosis of *S. haematobium*, confirmed the high sensitivity and specificity of real-time PCR, compared to standard urine filtration and CCA strip tests (Obeng et al., 2008). Given the high sensitivity of PCR-based methods, operational advantages (need for only a single stool or urine sample), the potential for high throughput and the possibility for extension to other helminths or intestinal protozoa based on additional molecular targets, this approach provides a powerful diagnostic platform for epidemiological research and might become the 'gold' standard during the end game of helminth control programmes.

4.5. Metabolic profiling

In 2004, an approach for biomarker discovery in the *S. mansoni*-mouse model has been presented, using a metabolic profiling strategy (Wang et al., 2004). This strategy uses a combination of analytical tools and multivariate statistical analyses to assess and quantify the dynamics of biochemical responses of living systems to patho-physiological stimuli (Nicholson et al., 1999). With regard to analytical tools, spectroscopic methods such as nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry (MS) and capillary electrophoresis (CE) are utilized. In view of the multivariate structure of the data, commonly employed statistical analyses include principal component analysis (PCA) and projection to latent structure-discriminant analysis (PLS-DA). Metabolic profiling finds increasing applications for studying an organism's gene function, drug safety assessment and recovery of biomarkers that might give rise to novel diagnostics and prognostics, as well as drug and vaccine targets (Nicholson et al., 2002; Lindon et al., 2004a,b; Holmes, 2010).

Progress made thus far with metabolic profiling investigations to enhance our understanding of patho-physiological responses of host animals to experimental infection with schistosomes and other trematodes or nematodes has been reviewed recently (Legido-Quigley, 2010; Wang et al., 2010). Table 4 summarizes candidate biomarkers that have been recovered from urine samples obtained from mice infected with *S. mansoni* (Wang et al., 2004;

Table 4
Observed changes in the urinary metabolites of mice with a patent *S. mansoni* infection and hamsters with a patent *S. japonicum* infection using a metabolic profiling strategy (↑, denotes increased levels; ↓, denotes decreased levels).

Metabolite	*S. mansoni*-mouse model		*S. japonicum*-hamster model
	Wang et al. (2004)[a]	García-Pérez et al. (2008)[b]	Wang et al. (2006)[c]
2-Oxoglutarate	↓		
2-Oxoisocaproate	↓		
2-Oxoisovalerate	↓		
Acetate	↓		↑
Alanine	↓		
Benzoic acid	↑	↑	
Butyrate	↓		
Citrate	↓	↓	↓
Creatine		↑	
Creatinine	↑		
Glycolic acid		↑	
Hippurate	↓	↓	↓
Lactate			↓
Malonate	↓		
p-Cresol glucuronide	↑		↑
Phenylacetylglycine	↑		↑
Propionate	↓		↓
Pyruvate	↑		↑
Succinate	↓		↓
Taurine	↓		
Trimethylamine	↑		↑
Tryptophan	↑	↑	
Urea		↓	
Uric acid		↑	
β-Alanine	↑		
D-3-Hydroxybutyrate	↓		

[a] In this study, 10 NMRI female mice were infected with 80 *S. mansoni* cercariae each and urine samples were collected 49 and 56 days post-infection. Ten sex- and age-matched mice were left uninfected and served as a control. Metabolic profiling was facilitated by ^{1}H NMR and pattern recognition tools.

[b] In this study, 10 NMRI female mice were infected with 80–100 *S. mansoni* cercariae each and urine samples were collected 2 days per week during 8 weeks. Ten sex- and age-matched mice were left uninfected and served as a control. Metabolic profiling was facilitated by CE and pattern recognition tools.

[c] In this study, a total of 18 male Syrian SLAC hamsters (experiment 1: $n = 10$ hamsters; experiment 2: $n = 8$ hamsters) were infected with 100 *S. japonicum* cercariae each and urine samples were collected 34–36 days post-infection. Another 19 sex- and age-matched hamsters were left uninfected and served as a control. Metabolic profiling was facilitated by ^{1}H NMR and pattern recognition tools. Note that the metabolites presented here are the ones derived from an orthogonal signal correction PLS-DA analysis using a combination of data from both experiments.

García-Pérez et al., 2008) and hamsters infected with *S. japonicum* (Wang et al., 2006) using ^{1}H NMR spectroscopy or CE in conjunction with multivariate data analysis. In brief, the urinary metabolic fingerprint of a patent *S. mansoni* infection in the mouse consists of reduced levels of the tricarboxylic acid cycle intermediates, including citrate, succinate and 2-oxoglutarate, and increased levels of pyruvate suggesting stimulated glycolysis. Disturbance of amino acid metabolism was also associated with infection, as indicated by depletion of taurine, 2-oxoisocaproate and 2-oxoisovalerate, and elevation of tryptophan. Additionally, a range of microbial-related metabolites such as trimethylamine, phenylacetylglycine, acetate, butyrate, propionate and hippurate were perturbed due to an infection with *S. mansoni*, indicating gut microbial disturbances (Wang et al., 2004). While the metabolic signature of a patent *S. japonicum* infection in the hamster showed many similarities to the *S. mansoni*-derived signature (e.g. reduced levels of tricarboxylic acid cycle intermediates and perturbations of microbial-related metabolites), the inhibition of short-chain fatty acids was unique to the *S. japonicum* infection model, which might be relevant for species-specific diagnosis (Wang et al., 2006). Follow-up studies using CE and multivariate data analyses confirmed the decreased level of hippurate and the simultaneous increase of benzoic acid in urine obtained from *S. mansoni*-infected mice (García-Pérez et al., 2008). However, García-Pérez and colleagues challenged the microbial-related metabolite hypothesis and instead suggested an altered liver metabolism, caused by the host's immune reaction due to trapped schistosome eggs. Blood and various tissue samples from schistosome-infected and non-infected control rodents have also been subjected to metabolic profiling, with a set of common and unique biomarkers identified according to host-parasite model and tissue samples investigated (Li et al., 2009; Garcia-Perez et al., 2010a,b; Wu et al., 2010).

Although it is likely to take many more years of focused scientific inquiry and will require considerable financial and technical resources for knowledge and technology transfer to resource-constrained countries where schistosomiasis is endemic, it has been speculated that metabolic profiling provides a unique platform for biomarker discovery that might ultimately lead to the next generation of diagnostic assays (Holmes, 2010; Wang et al., 2010).

5. Drug discovery and development

Praziquantel is virtually the only drug available for the treatment of individual patients and, particularly, for population-based morbidity control of schistosomiasis, owing to the broad spectrum of activity and safety profile of praziquantel (Fenwick et al., 2003; Utzinger and Keiser, 2004; Caffrey, 2007; Cioli et al., 2008; Doenhoff et al., 2008). Two alternative anti-schistosomal drugs, metrifonate and oxamniquine, are characterized by deficiencies in their therapeutic profiles. Indeed, while metrifonate is only active against *S. haematobium*, oxamniquine shows activity against *S. mansoni* singly. Moreover, resistance is easy to select for in the case of oxamniquine and has been documented in Brazil (Conceição et al., 2000). In addition, both these drugs are no longer being used against schistosomiasis and have become difficult to obtain (Cioli, 2000; Utzinger and Keiser, 2004; Danso-Appiah et al., 2008). Should clinically relevant resistance develop to praziquantel, sustainable chemotherapeutic treatment and control would be jeopardized, and hence there is a pressing need to develop alternative anti-schistosomal drugs in advance of this calamitous prospect while praziquantel is still effective (Caffrey, 2007; Doenhoff et al., 2008; Sayed et al., 2008). Isolates with decreased sensitivity to praziquantel have indeed been reported from different epidemiological settings, e.g. Egypt, Kenya and Senegal (Ismail et al., 1996; Fallon et al., 1997; Cioli et al., 2004; Melman et al., 2009) and may be harbingers of more to come.

Drug discovery and development research with an emphasis on *Schistosoma* spp. in the new millennium has been reviewed before (Ribeiro-dos-Santos et al., 2006; Keiser and Utzinger, 2007a; Doenhoff et al., 2008; Caffrey et al., 2009; Xiao et al., 2010). The following compounds and compound classes revealed high anti-schistosomal activities: K11777 (Abdulla et al., 2007), synthetic trioxolanes (Xiao et al., 2007), oxadiazoles (Sayed et al., 2008) and aminoethanethiosulfuric acids (Caffrey et al., 2009). Here, we highlight key results obtained from the latest laboratory investigations and clinical trials. In the next section, we summarize results obtained with compounds that have been exclusively screened for *in vitro* activity, primarily against *S. mansoni*. Section 5.2 discusses compounds that have been studied in rodent models, and hence have progressed further in the drug development pipeline.

Table 5
Recent *in vitro* studies obtained in the last 2–3 years investigating the anti-schistosomal properties of various compounds against *Schistosoma* spp.

Compound, compound class	Concentration	Observation	Reference
Imidazolidines	174–640 μM	All adult *S. mansoni* dead after 24–96 h and tegumental alterations	Neves et al. (2010)
Curcumin	5–10 μM	Decreased viability and death of *S. mansoni*	Magalhães et al. (2009)
Mefloquine	1–10 μg/ml	Decreased viability, death and tegumental alterations on *S. mansoni* and *S. japonicum*	Manneck et al. (2010a), Xiao et al. (2009)
Trioxaquines	5–50 μg/ml	Death of juvenile and adult *S. mansoni*	Boissier et al. (2009)
Praziquantel analogs	1 μg/ml	Several derivatives caused morphological changes and decreased viability on adult *S. mansoni*	Dong et al. (2010)
9-(S)-[3-Hydroxy-2-(phosphonomethoxy)propyl]adenine derivatives	5–10 μM	Depending on the drug and concentration death of adult *S. mansoni*	Botros et al. (2009)
Phloroglucinol derivatives	10–100 μM	Death of adult *S. mansoni* inhibition of egg development and reduced motor activity with several derivatives observed	Magalhães et al. (2010)
Compounds from *Zanthoxylum naranjillo*	10 μM	Decreased motor activity observed with two derivatives	Braguine et al. (2009)
Multiple chemistries including FDA-approved drugs	1 μM	Alterations in *S. mansoni* schistosomula and adult phenotypes, including death	Abdulla et al. (2009)
Various Egyptian plant derivatives and extracts	Various	Death of adult *S. mansoni*	Yousif et al. (2007)
Antiandrogens	1–10 μg/ml	*Schistosoma mansoni* incubated with 10 μg/ml cyproterone actetate died within 15 h. Incubation with bicalutamide, nilutamide and flutamide at 10 μg/ml resulted in decreased viability	Keiser et al. (2010a)
Arachidonic acid	1–10 mM	*Schistosoma mansoni* and *S. haematobium* died 5 h post-exposure to 2.5 mM arachidonic acid	El Ridi et al. (2010)

FDA, Food and Drug Administration.

Finally, results from recent clinical trials are summarized in Section 5.3.

5.1. In vitro studies

Several classes of chemical compounds were evaluated *in vitro* against adult *S. mansoni*, including trioxaquines, imidazolidines, salicylanilides, antibiotics, plant derivatives, phloroglucinol derivatives and acyclic nucleoside phosphonates (Table 5).

Trioxaquines are hybrid molecules consisting of two pharmacophores, a trioxane and a 4-aminoquinoline moiety, which are currently in development for malaria (Boissier et al., 2009). These drugs, used at concentrations of 5–50 μg/ml, rapidly kill 21-day-old juvenile and 49-day-old adult *S. mansoni in vitro*. Hence, these findings further strengthen the current evidence-base that peroxidic compounds not only possess activities against *Plasmodium* spp. (White, 2008; Weinberg and Moon, 2009; Chaturvedi et al., 2010) and cancer cell lines (Krishna et al., 2008; Chaturvedi et al., 2010), but also are active against schistosomes and other trematodes (Keiser and Utzinger, 2007a,b; Utzinger et al., 2007; Xiao et al., 2007, 2010).

In vitro examination of seven ether lipid esters of acyclic nucleoside phosphonates against adult *S. mansoni* has revealed lower activities than praziquantel. However, it should be noted that derivatives of 9-(S)-[3-Hydroxy-2-(phosphonomethoxy)propyl]adenine modified by esterification and cyclization, showed high mortality rates of adult *S. mansoni* (Botros et al., 2009).

In a recent study, several derivatives of niridazole, an imidazolidin that has previously been clinically used against *Schistosoma* spp. infections, were synthesized and assessed for their *in vitro* activity against *S. mansoni*. Incubation with different imidazolidine derivatives resulted in the complete killing of adult *S. mansoni* worms within 24–96 h, but only at high concentrations (174–640 μM) (Pitta et al., 2006; Neves et al., 2010).

Natural compounds have also been studied for anti-schistosomal properties. The *in vitro* activity of two natural compound classes, phloroglucinol derivatives (i.e. aspidin, flavaspidin, methylene-*bis*-aspidinol and desaspidin) extracted from the rhizomes of the ferns *Dryopteris* spp. and compounds isolated from an evergreen tree and shrub in the family of Rutaceae, *Zanthoxylum naranjillo*, were studied against adult *S. mansoni*. Aspidin, flavaspidic acid and desapidin showed the highest activities, resulting in worm death and inhibition of egg development after *in vitro* exposure at concentrations of 25 or 50–100 μM (Braguine et al., 2009; Magalhães et al., 2010). A large-scale study of 346 methanol extracts from 281 plant species found in Egypt identified 15 extracts with a 50% lethal concentration at 5 μg/ml to adult *S. mansoni in vitro* (Yousif et al., 2007).

Finally, a partially automated, medium-throughput phenotypic screen has been developed for *S. mansoni* (Abdulla et al., 2009). The screen prosecuted a chemically diverse array of 2160 compounds, among which were 821 drugs approved for human use, thus affording the opportunity to 're-purpose' drugs already in use for other medical conditions. Multiple and dynamic phenotypes were identified and categorized for schistosomula and adult schistosomes *in vitro*, and a variety of drugs and chemistries were identified, including known anthelminthics and antibiotics.

5.2. In vivo studies

Several compounds have been studied for both *in vitro* and *in vivo* anti-schistosomal properties, with key results summarized in Tables 5 and 6. Considerable progress has been made with mefloquine, an aminoalcohol, which is widely used in the prophylaxis and treatment of malaria (Karbwang and White, 1990; Bukirwa and Orton, 2005; Jacquerioz and Croft, 2009). Activity of mefloquine against juvenile and adult *S. mansoni* was first reported towards the end of 2008 (van Nassauw et al., 2008; Keiser et al., 2009). The key findings can be summarized as follows: mefloquine exerts a rapid effect on schistosomula *in vitro*. Adult worms die within 1 and 24 h of incubation in media containing 100 and 10 μg/ml of mefloquine, respectively (Manneck et al., 2010a). A single oral dose of 200 mg/kg mefloquine administered to mice infected with either juvenile or adult *S. mansoni* resulted in worm burden reductions of 94.2% and 72.3%, respectively (Keiser et al., 2009). Scanning electron microscopic (SEM) observations revealed extensive tegumental alterations, including blebbing, shrinking and sloughing, effects particularly pronounced among female specimens (Manneck et al., 2010a). As mefloquine is a chiral drug with two dissimilar asymmetric centres, a recent study tested the *in vivo* activities of the four isomers and two racemates against adult *S. mansoni*. Worm burden reductions ranged from 65.4% (+erythro isomer) to 93.4% (erythroracemate, mefloquine) following a single 200 mg/kg oral dose (Manneck et al., 2010b). In the meantime, studies on mefloquine have been extended from *S. mansoni* to *S. japonicum*, including detailed histopathological investigations in the juvenile and adult stages of the parasite (for a review, see Xiao et al., 2010).

A major drawback with praziquantel is its significantly decreased efficacy against developing worms, particularly those 14 to 30 days post-infection in the mouse model (Sabah et al., 1986). Hence, it was investigated whether metabolically stable analogs of praziquantel might have improved activity against schistosomula.

Table 6
Recent *in vivo* studies obtained in the last 2–3 years investigating the anti-schistosomal properties of various compounds against *S. mansoni*.

Compound, compound class	Drug administration		Worm burden reduction (%)		Ref.
	Route	Dose (mg/kg)	Juvenile worms	Adult worms	
Sulfur compounds (e.g. aminoalkanethiosulfuric acids)	Oral	400–800, single	n.d.	Female: 64–100 Male: 33–61	de Oliveira Penido et al. (2008)
Curcumin	16 injections i.p.	400, single	n.d.	44	Allam (2009)
Mefloquine and isomers	Oral	200, single	94	65–93	Keiser et al. (2009), Manneck et al. (2010b)
Praziquantel analogs	Oral	400, single	0–42	0–81	Dong et al. (2010)
Antrodia camphorata polysaccharides	Oral	2.5 mg, QD for 2–6 weeks	n.d.	Chemoprophylactic properties, 27–75	Chen et al. (2008)
Salicylanilides, antibiotics, natural products	Oral	Various; 50–100 mg/kg QD or BID for 4 days	n.d.	Up to 56	Abdulla et al. (2009)
Antiandrogens	Oral	50–400, single	6–37	0–85	Keiser et al. (2010a)
Arachidonic acid	Oral	500 and 1000, single 300 for 15 days	39 43–54	38 58–64	El Ridi et al. (2010)

BID, twice a day; n.d., not determined; QD, once a day.

Six amide and four urea derivatives of praziquantel were synthesized and their *in vivo* activity assessed against both juvenile and adult stages of *S. mansoni*. Whereas just one compound yielded a significant adult worm burden reduction (total worm burden reduction of 79%), five of the drugs exhibited a moderate activity (25–42%) and one of the drugs (an ozonide) had a high activity (85%) against juvenile *S. mansoni* worms. Interestingly, the *in vitro* observations on adult *S. mansoni* did not correspond to the observed *in vivo* activities, pointing to the presence of active metabolites (Dong et al., 2010).

Another compound that has been subjected to both *in vitro* and *in vivo* testing against *S. mansoni* is curcumin. All *S. mansoni* worms died after incubation in a medium containing 50 or 100 μM (Magalhães et al., 2009). When curcumin was given intraperitoneally to mice (400 mg/kg divided into 16 injections), a moderate total worm burden reduction of 44% and reduced liver pathology was observed (Allam, 2009).

Recently, many years of *in vivo* studies with a series of amino alkane and amino phenyl thiosulfuric acids have been summarized (de Oliveira Penido et al., 2008). Although many of the compounds tested were toxic to mice, several others were well tolerated and a single 800 mg/kg oral dose yielded moderate male worm burden reductions and moderate-to-high female worm burden reductions.

Chemoprophylactic effects have been observed for natural products when mice were treated with 2.5 mg of *Antrodia camphorata* polysaccharides daily for 2–6 weeks, with total worm burden reductions ranging from 26.6 to 74.4% (Chen et al., 2008).

In the 1980s, a series of 3-arylhydantoins (e.g. Ro-13-3978) were studied for their anti-schistosomal properties at Hoffmann-La-Roche in Basel, Switzerland (Link and Stohler, 1984). Given the close resemblance of Ro-13-3978 with nilutamide, a drug marketed for the treatment of metastatic prostate cancer, nilutamide and two structurally related antiandrogens flutamide and bicalutamide were studied *in vitro* and in the *S. mansoni*-mouse model. The highest total worm burden reduction of 85% was achieved with a single 400 mg/kg dose of nilutamide in the adult infection model. Cyproterone acetate, a structurally unrelated steroidal antiandrogen, did not show any activity *in vivo* (Keiser et al., 2010a).

Arachidonic acid is a polyunsaturated fatty acid present in the phospholipids of cell membranes, which is abundant in the brain and muscles and necessary for the development of retina, brain and muscles. Schistosomes were affected *in vitro* at concentrations of 2.5 mM and above. *In vivo* doses of 500 mg/kg (juveniles) and 100 mg/kg (adults) achieved worm burden reductions of 39.3% and 37.9%, respectively in *S. mansoni*-infected mice. Slightly higher worm burden reductions (43.0–63.6%) were observed when arachidonic acid was administered at 300 mg/kg/day for 15 days (El Ridi et al., 2010).

Finally, mice harbouring adult *S. mansoni* were treated with a number of the natural products, antibiotics and salicylanilides to arise from the medium-throughput *in vitro* phenotypic screen mentioned above (Abdulla et al., 2009). Depending on compound, worm burden reductions ranged from 0 to 56% after oral dosing at 50–100 mg/kg once or twice daily for 4 days. Decreased hepatic egg counts, and liver- and spleen-associated pathologies were also measured.

5.3. Clinical trials: mefloquine and artemisinin-based combination therapy

The efficacy and safety of mefloquine (25 mg/kg) and an artesunate-mefloquine combination (3 doses of 100 mg artesunate plus 250 mg mefloquine on consecutive days) have been assessed in two randomized, exploratory open-label trials among schoolchildren in Côte d'Ivoire infected with *S. mansoni* and *S. haematobium*. Additionally, groups of children were treated with praziquantel (standard dose of 40 mg/kg) and artesunate alone (3 doses of 4 mg/kg), in order to obtain data for the current treatment of choice, i.e. praziquantel, and to investigate whether the combination of artesunate and mefloquine acts additively, antagonistically or synergistically. Findings of the *S. haematobium* trial have been published recently (Keiser et al., 2010b). In brief, a cure rate of 61% was observed among children treated with an artesunate–mefloquine combination, whereas monotherapies with mefloquine, artesunate and praziquantel achieved cure rates of 21%, 25% and 88%, respectively. Egg reduction rates in excess of 95% were observed both among praziquantel and artesunate–mefloquine recipients. Children treated with either mefloquine or artesunate showed egg reduction rates of 74% and 85%, respectively. Of note, some of the children were co-infected with *S. mansoni* and high cure and egg reduction rates were observed among praziquantel and artesunate-mefloquine recipients.

Adverse events were monitored over a 72-h period and at least one adverse event (i.e. abdominal pain, chill, coughing, diarrhoea, headache, vertigo and vomiting) was observed in 61%, 80%, 94% and 100% of the praziquantel, artesunate, artesunate-mefloquine and mefloquine recipients, respectively. Abdominal pain showed the highest incidence, particularly in children treated with mefloquine (89%) and an artesunate-mefloquine combination (83%), but was mainly mild and transient.

In previous reviews and a recent commentary, we have summarized the evidence from randomized controlled trials with the artemisinins (i.e. artemether and artesunate) against schistosome infections and the prevention of patent infections (Utzinger and Keiser, 2004; Keiser and Utzinger, 2007a; Utzinger et al., 2007, 2010b; Xiao et al., 2010). Two small investigations in Senegal and Sudan assessed the potential ancillary benefit of artemisinin-based combination therapy (ACT) against schistosomiasis in patients concurrently infected with *Plasmodium falciparum* and schistosomes (Boulanger et al., 2007; Adam et al., 2009). High cure rates (87–100%) were obtained against schistosome infections in young children treated with different ACTs (i.e. artesunate–sulfadoxine/pyrimethamine, artesunate with sulfalene (also known as sulfamethoxypyrazine) plus pyrimethamine, artesunate–amodiaquine and artemether–lumefantrine).

In view of these findings, two larger trials were conducted, the first one in Mali with 800 *S. haematobium*-infected children and the second in Kenya with 212 *S. mansoni*-infected children. Study participants were randomly assigned to either artesunate with sulfalene plus pyrimethamine (3 tablets, each containing 100 mg artesunate + 250 mg sulfalene/12.5 mg pyrimethamine, given within 24 h) or praziquantel (single dose of 40 mg/kg). In both trials, praziquantel recipients showed significantly higher cure rates than those receiving an ACT (53.0% *versus* 43.9% in the Mali trial, $P = 0.011$; 65% *versus* 14% in the Kenya trial, $P < 0.001$). With regard to egg reduction rates, in the Mali trial, both praziquantel and the ACT investigated resulted in high levels (>90% with no statistically significant difference between the two groups) (Sissoko et al., 2009). The egg reduction rate in Kenya was 84.1% in the praziquantel group and only 35.0% among ACT recipients, owing to a statistically highly significant difference (Obonyo et al., 2010). Another trial, conducted in Sudan, randomly assigned 92 *S. mansoni*-infected children to either artesunate plus sulfadoxine/pyrimethamine (3 doses of 4 mg/kg artesunate over consecutive days plus 1 dose of 25 mg/kg sulfadoxine on the first day) or praziquantel (40 mg/kg). While praziquantel recipients were completely cured, 41.4% of the children in the artesunate plus sulfadoxine/pyrimethamine group remained *S. mansoni*-egg positive 28 days post-treatment ($P < 0.001$). The egg reduction rate among the ACT recipients was 86.6% (Mohamed et al., 2009).

6. Integrated control

We are confident that recent innovations in the fields of diagnostics and drugs – as reviewed here – along with progress made in vaccine discovery and development (McManus and Loukas, 2008; Bergquist and Lustigman, 2010; McManus et al., 2010) will ultimately yield new and improved tools and strategies for schistosomiasis control. The recent publications of the draft genomic sequences of *S. mansoni* and *S. japonicum* (Berriman et al., 2009; *Schistosoma japonicum* Genome Sequencing and Functional Analysis Consortium, 2009) provide a wealth of new insights into the biology of these parasitic worms, host-parasite interactions and metabolic and signalling pathways that might reveal novel drug, diagnostic and vaccines targets (Webster et al., 2010).

While basic research needs to be continued, a next logical step is to validate new promising tools and strategies in the field, bench and bedside in schistosome-endemic settings. Some of the work highlighted here is currently undergoing validation, such as determining the accuracy of the FLOTAC technique for parasitological diagnosis and CCA urine strip tests for immunodiagnosis. Moreover, the efficacy and safety of mefloquine and different ACTs against schistosomiasis are currently being investigated. Successfully validated tools and strategies might then be applied at a larger scale.

However, let there be no doubt: there is no 'magic bullet'. Be it a more sensitive diagnostic tool or a novel anti-schistosomal drug with an improved safety and therapeutic profile over praziquantel, these tools alone will not render schistosomiasis control programmes sustainable. A deeper understanding of the social–ecological context and the intimate connection of the disease with poverty, as detailed in Section 2, are key elements to design and implement truly integrated and sustainable control programmes (Utzinger et al., 2003, 2009; Singer and Castro, 2007; Bruun and Aagaard-Hansen, 2008; Parker et al., 2008; Gray et al., 2010; Spiegel et al., 2010). In many parts of sub-Saharan Africa, where schistosomiasis is still highly endemic and causes substantial morbidity, vertical implementation of preventive chemotherapy using praziquantel, will remain the strategy of choice in the near future. However, whenever resources allow, a package of intervention, including preventive measures, should be tailored according to the prevailing social–ecological systems. Should a schistosomiasis vaccine become available (even if it shows only partial efficacy), a control approach linking chemotherapy with such a vaccine should be evaluated without delay (Bergquist et al., 2005, 2008; Bethony et al., 2008).

The most obvious platform to facilitate and deliver a package of intervention is through the health system. This requires strengthening of existing health systems using locally owned resources and leadership, in order to provide adequate, comprehensive and permanent quality health care (Marchal et al., submitted). Additionally, inter-sectoral collaboration (e.g. between the health, agriculture, education, infrastructure and water resources sectors), as well as alignment and harmonization of district-based projects and programmes, should be encouraged (Ehrenberg and Ault, 2005; Utzinger and de Savigny, 2006; Holveck et al., 2007).

With regard to inter-sectoral collaboration for integrated and sustainable control of schistosomiasis, an excellent example arises from P.R. China, where experiences and expertise have been gained over the past 50+ years and can guide current and future schistosomiasis control efforts in other endemic areas (Utzinger et al., 2005; Wang et al., 2008; Gray et al., 2010). Strong political will and commitment to use local resources for control, and implementation of an integrated control approach, readily adapted to the local ecological settings and fine-tuned over time in face of the changing challenge of control are key lessons learned. Another important lesson is that snail control was part of the interventions throughout (Utzinger et al., 2005). Importantly, once the targets for morbidity control had been achieved (e.g. prevalence of infection in humans below a pre-defined level), the emphasis shifted to transmission control and, recently, a package of interventions has been pilot-tested in the lake regions along the Yangtze River. Regular administration of praziquantel is complemented with mechanization of agriculture (i.e. replacing water buffaloes with tractors) and, where this is not possible, better livestock management (i.e. fencing of water buffaloes), improved access to clean water and sanitation and, finally, human faeces management for special occupational groups such as fishermen and boatmen. First experiences show that this comprehensive control approach can halt the transmission of schistosomiasis, and hence discussions are underway for adopting the national strategy (Wang et al., 2009a). Importantly, an impact beyond the target disease schistosomiasis has been documented, as infection rates with common soil-transmitted helminths were significantly reduced (Wang et al., 2009b). This comprehensive control strategy therefore lends further support to historic evidence: access to treatment and preventive measures facilitated the reduction and local elimination of hookworm infection in the south of the United States of America and elsewhere (Sweet et al., 1929; Stiles, 1939).

7. Conclusions and research needs

The need for discovery research will be paramount in order to refine existing and develop new tools and strategies for the control of schistosomiasis and NTDs in general. We reviewed recent innovations, placing emphasis on diagnostics and drugs for schistosomiasis. The next step in the continuum from innovation to application is validation and all three steps require coherent scientific inquiry, trained cadre to design and implement the necessary laboratory studies and clinical trials with adequate financial resources all along. Although concerns were aired at the turn of the third millennium that researchers might walk away from medical helminthology (Colley et al., 2001) and that financial resources for research and control of NTDs are still lagging behind the 'big three', we are witnessing a profoundly changing landscape of funding opportunities for the NTDs (Moran, 2005; Moran et al., 2009).

Yet, numerous basic and operational research questions remain and addressing them will be crucial to discover, develop and deploy the next generation of diagnostics and therapeutics and ultimately a vaccine for an integrated and sustainable control of schistosomiasis. With regard to operational issues, SCORE now provides a platform to address some of the most pressing ones. We offer the following points and priorities for consideration.

- Continued evidence-based, high-level advocacy, especially to grant awarding philanthropies such as the Bill & Melinda Gates Foundation that schistosomiasis is a pernicious and underrecognized disease that must be addressed through better diagnosis and drugs and hopefully a vaccine, and improved public awareness.
- The first point implies the need for a deeper understanding of the social–ecological context in which schistosomiasis is entrenched, and concerted efforts to re-estimate the 'true' global burden of schistosomiasis.
- An open-access, real-time global database for schistosomiasis risk mapping and prediction so that control interventions can be better targeted, both spatially and temporally, and cost-effectiveness enhanced. Such a database could also be utilized to map treatment coverage and monitor progress with other control interventions.
- Sensitive non-invasive POC diagnostics suitable for use by minimally trained personnel in the context of large-scale and routine surveillance of baseline prevalences, including those following interventions.

- Focussed drug research activity in the search for new chemical entities especially given the recent wealth of genome and transcriptome information, which should open up interest in identifying and validating new gene targets, a necessary first step, on the road to drug development.
- Identification of drug development candidates adhering to a target product profile, such as excellent safety and activity against all stages of the parasite in humans.
- Documenting the effect and costs of implementing an integrated control approach on prevalence, intensity and transmission of schistosomiasis and measuring the potential ancillary benefits on other NTDs.
- Establish the proof-of-concept that schistosomiasis elimination is feasible, which will provide a major boost to continued funding towards transmission control and local elimination of NTDs in general.

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