Transmission control for schistosomiasis – why it matters now

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Current population-based schistosomiasis treatment programs are a first step to reducing the global burden of Schistosoma-related disease; however, they might not dramatically reduce parasite transmission in highly endemic areas. Consequently, the benefits of these programs remain in doubt because recurring low-level reinfection is likely to be associated with subtle but persistent morbidities such as anemia, undernutrition and diminished performance status. The real health benefits of transmission control need to be reconsidered and attention given to more aggressive and, ultimately, more affordable parasite elimination strategies. The next generation of schistosomiasis control can be optimized using new monitoring tools and effective transmission containment.

A shift in our thinking about schistosomiasis

What is wrong with having schistosomiasis?

Since the reassessment of parasitic disease burdens by the international health community in the late 1980s and 1990s [1–3], the worldwide problem of schistosomiasis seems to have lost priority in the global health agenda. Compared with treatment and prevention of more lethal diseases (such as malaria, HIV and tuberculosis), control of schistosomiasis has not been considered such a high priority. This is unfortunate, because 200–300 million people suffer schistosomiasis-related disability on a daily basis and will experience recurrent episodes of Schistosoma infection for as much as half of their lives [4].

The burden of disease as a result of schistosomiasis has been traditionally tallied in terms of quantifiable, objective physical morbidities, such as hepatosplenomegaly, hepatic fibrosis, or, for urinary schistosomiasis, as bladder and kidney inflammation [5,6]. However, the average person with schistosomiasis does not experience these advanced forms of disease. Instead, he or she is prone to suffer from less obvious, but nonetheless significant, disabilities owing to growth stunting (Figure 1), anemia, abdominal pain, exercise intolerance, poor school performance and lowered work capacity [7].

Such conditions might not lead one to seek medical attention in an underdeveloped area having only limited healthcare resources. Nevertheless, any infection-associated performance deficit might have a significant impact on important activities of daily life. The average disability of uncomplicated schistosomiasis has been dismissed by some as unimportant, but in the setting of the developing-world ‘poverty trap’, in which a family must invest its entire capital for survival each year [8], even a 2–3% disability associated with chronic parasitic infection [9] can become highly relevant to their annual success (Figure 2). Although an infected person might get by, he or she might never be able to emerge from a subsistence level of productivity.

Revisiting current strategies for schistosomiasis control

Taken from the older, objective-morbidity view of schistosomiasis disease burden, the perception is that Schistosoma infection, per se, is normally ‘asymptomatic’ and does not need to be treated [10]. From this perspective, the main objective of schistosomiasis control should be reduction of infection intensity and the prevention of late forms of severe disease.

By contrast, on meta-analysis of the available evidence, it is apparent that schistosomiasis, whether caused by

Glossary

DALY: disability-adjusted life year, as defined in WHO/World Bank Global Burden of Disease Initiative [3].

Donor fatigue: a state in which donors no longer contribute to a cause because they have become tired of receiving appeals for donations.

Passive case treatment: treatment delivered to symptomatic patients who seek care at health facilities outside the scope of population-based drug treatment programs.

PCR: polymerase chain reaction technique for detection of specific DNA content of clinical or field samples.

Prepatent infection: snail infection by Schistosoma parasitic forms during the period of sporocyst development, before shedding of infectious cercariae. Depending on environmental conditions and snail susceptibility, the prepatent period might last from 1–2 months up to >1 year in duration. However, only a fraction of infected snails progress from prepatency to become patent shedders of cercariae.

Th1: T-helper cell type 1, associated with induction of immune responses active against viruses and intracellular pathogens.

Th2: T-helper cell type 2, associated with immune responses against helminths.

Xenomonitoring: testing of field-sampled vector or intermediate hosts for evidence of ongoing infectious disease transmission within human communities.
The impaired growth of children in a schistosomiasis-endemic area (data from Ref. [72]). Graph lines indicate significant retardation of median growth among Schistosoma haematobium-afflicted Kenyan boys (red lines with squares) relative to US median growth (black lines with circles) in terms of both height (upper lines; cm) and weight (lower lines; kg) after the age of 8 years old. Values below the US 3rd percentile (blue lines) are considered evidence of severe undernutrition. Here, the fall-off in average growth rates begins at ~8 years of age at the onset of peak S. haematobium infection prevalence (black line) (>90%) and later, intensity [11]. Not shown, similar deficits are observed for girls from the same village areas and in areas endemic for Schistosoma mansoni, both in Kenya [72] and in Brazil [73].

Schistosoma haematobium, S. mansoni or S. japonicum, and whether of light or heavy intensity, is a significant chronic inflammatory disease that contributes substantially to chronic morbidities resulting in significant personal disability for the average person who experiences the infection [7] (Figure 3). On a global scale, given the average impact of schistosomiasis combined with the large number of people estimated to have the disease (200 to 300 million), the number of healthy years of life lost to schistosomiasis becomes large, with revised estimates in the order of 6–13.5 million DALYs (see Glossary) lost. From this newer, disability-focused perspective, prevention of schistosome infection and reinfection becomes the priority for control.

**Drug treatment does not reliably affect transmission**

Although large-scale school- or community-based treatment programs (Table 1) can have an excellent impact on the average intensity of schistosome infection in participating communities [11–13], there is evidence that broad treatment coverage per se will not reliably affect local levels of parasite transmission and the consequent risk of reinfection with schistosomiasis [11,14,15]. ‘Wormy’ villages with high, persistent risk for new Schistosoma infection, despite high levels of school-based treatment coverage, can be readily identified [14]. New forms of environmental analysis, based on Geographic Information Systems (GIS) mapping and local or focal clustering assessment, indicate that transmission is often highly focal [16], sporadic [17,18] and predominantly limited to a few key sites in each village complex [19]. Overlapping networks of water use at different sites, combined with their intermittent contamination, create highly nonlinear patterns of transmission and make it possible that a single, heavily infected person can maintain transmission in any ecologically high-risk community [19]. Even if broad-based treatment reduces average infection levels to a new, lower equilibrium, if that one heavily infected person escapes treatment, then the campaign might not reduce transmission to the point at which community-wide risk of disease is effectively curtailed [20,21].

Experience has shown that in high-risk settings, cessation of drug treatment for even a few years can result in recurrence of high levels of schistosome infection among adults and children, as if the community had never been treated [14,15,22–24]. Without the ‘externality’ of transmission reduction, non-participant residents in treated communities do not receive any clear benefit from treatment campaigns [21]. Whereas advanced forms of schistosomiasis-associated morbidity (e.g. hepatosplenomegaly and urinary tract obstruction) might be suppressed...
among those who are treated, the impact on chronic, infection-associated disabilities, such as anemia and exercise intolerance, might be minimal owing to rapid reinfection or persisting infection. Based on a nine-year study of school-based treatment campaigns in communities at high-risk for continuing S. haematobium transmission [14], it is estimated that the average resident’s cumulative life-years of infection might only be reduced from 14.6 to 8.8 life-years of infection after implementation of a drug-based treatment program.

The next challenge: deciding to reduce transmission and prevent infection
Why should we be concerned about continuing transmission if it results in mostly light infections? Risk of advanced disease is undoubtedly multifactorial. However, newer evidence suggests that it is the strength of an individual’s immune response to parasite eggs, more than intensity of infection, that determines risk for severe tissue inflammation in schistosomiasis [25,26]. In addition, inflammation is also linked to individual genetic predisposition [27]. The importance of these findings is that individuals who experience only light infections are still at significant risk for schistosomiasis-associated disease. Thus, the current focus on infection intensity control will not necessarily prevent the development of serious disease.

Given the issues of the inflammation-associated anemia and disability outcomes described earlier [7,25,28], there is concern that infected women who remain anemic during pregnancy will be more likely to experience fetal loss or maternal mortality, and that their children will suffer intra-uterine growth retardation. Physical and intellectual performance of these children is also likely to be impaired [9,29–31]. We also know that children who are exposed to their mother’s helminthic infections in utero are born with anti-parasite immune responses that are frequently polarized to be either highly active or significantly suppressed (i.e. hyperimmune or tolerized). An important consequence of this skewing of immune responses is that children with highly active anthelminthic (Th2-type) immune responses are less responsive to routine childhood vaccination against pathogens that require Th1 immunity, such as tuberculosis [32].

Without changes in Schistosoma transmission potential, even multiple years of annual treatment will not be adequate to prevent Schistosoma infection in many high-risk areas. It would not be surprising to see the onset of both community- and donor-fatigue in large-scale drug treatment projects if disease control is not fully effective and durable over the long term [33].

In summary, because any schistosomiasis infection will significantly affect individual and community health, prevention of infection (i.e. transmission control) should be considered as a potential new standard for control of both the disease and the disability caused by schistosomiasis.

How can we best achieve prevention of infection?
At present, there is no clear-cut answer to this question. Experience from the 1950s–1970s in Japan [34], China [13], the Philippines [34], St Lucia [35] and Iraq [36] indicates that schistosomiasis transmission can be interrupted in high-risk communities by implementing significant changes in local snail abundance and/or water use, consequently changing high-risk patterns of water exposure. It seems that supplemental transmission control could offer dramatic leverage in reducing lifetime exposure to schistosome infection in many high-risk communities [19,37].

This step-up to transmission control (i.e. augmentation of drug-based disease control programs to include a component of transmission control) might seem beyond the scope or financial means of present-day schistosomiasis disease control initiatives. However, the larger and more durable effects of long-term transmission reduction must be seen as more cost-effective and, ultimately, more affordable in the long run [8]. The objective of reducing exposure to infection via access to safe water could be viewed as part of a ‘combined approach matrix’ for control of multiple infectious diseases [38]. Such an approach would also be well aligned with the Millennium Development Goals for health and poverty reduction [39,40].

Alternatively, the integration of schistosomiasis control as part of a ‘deworming’ multi-parasite control initiative offers possible economies-of-scale and economies-of-scope in terms of overall health impact, which are highly attractive for regions afflicted by multiple endemic parasite species [41]. We do not yet know if modest augmentation of drug-based campaigns by integration with focal snail control could provide effective and economical interruption of transmission, even to the point of local parasite eradication [19,37]. This latter form of ‘integrated pest management’, an approach that is familiar for disease control in agricultural programs, remains an underexplored mechanism for achieving

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**Table 1. Current recommendations for community-based control of schistosomiasis-associated diseases in endemic areas**

<table>
<thead>
<tr>
<th>Community category</th>
<th>Intervention in schools (enrolled and non-enrolled children)</th>
<th>Health services and community-based intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. High prevalence</td>
<td>Targeted treatment of school-aged children, once a year</td>
<td>Access to PZQ for passive case treatment; community-directed treatment for high-risk groups recommended</td>
</tr>
<tr>
<td>II. Moderate prevalence</td>
<td>Targeted treatment of school-aged children, once every two years</td>
<td>Access to PZQ for passive case treatment</td>
</tr>
<tr>
<td>III. Low prevalence</td>
<td>Targeted treatment of school-aged children twice during primary schooling (once on entry, again on leaving)</td>
<td>Access to PZQ for passive case treatment</td>
</tr>
</tbody>
</table>

*a*Data from WHO [13].

*b*Abbreviation: PZQ, praziquantel.

*c*Treatment strategies should always be accompanied by efforts to improve water supply and sanitation.

*d*Can be done on presumptive grounds, according to diagnostic algorithms adapted to the endemic situation.
the objective of long-term schistosomiasis transmission control [35].

**Technology for generating the next wave of transmission studies and control programs**

If transmission control becomes an important objective for schistosomiasis control, the next question becomes how can we easily and economically measure and monitor transmission potential? This is an important prerequisite for evaluating both the impact of any population-based drug treatment programs [42] and of implementing any new transmission-control endeavors [35].

Until recently, the impact of control programs on transmission potential has been determined by monitoring local rates of *Schistosoma*-infected snails shedding cercariae or by measurement of cercarial numbers at transmission sites (cercariometry) [43]. Cercariometry has not been applied routinely and still presents problems in practice and in data analysis [44]. By contrast, the observation of infection rates among populations of field snails has been the mainstay for many studies of schistosomiasis control [45]. However, as the rate of snails shedding cercariae is often low, even in areas of high transmission [46], large numbers of snails are required to detect statistically significant changes in transmission potential over time, especially following implementation of control measures.

**Can prepatent infection serve as an indicator of human-to-snail transmission?**

Considering that prepatent infection (incubation before shedding) can last for several weeks with only a proportion of infections reaching the stage of cercarial shedding [47,48], that mortality of infected snails can be higher after cercarial shedding [49], and that sporocyst development is delayed in cold seasons [50], it can be assumed that prepatent infection rates will always be substantially higher than patent (shedding) infection rates among sampled snails. Thus, measuring prepatent infection is perhaps more suitable than measuring patent infection for quantitative assessment of the impact of control programs on human-to-snail transmission (Box 1). Until recently, data on prepatency in field snails have not been widely studied because the detection methods that were employed, namely, crushing of snails in search of larvae or repeated shedding of field snails taken to the laboratory, were unsuitable for large-scale, sensitive monitoring [51]. Although detection of schistosomal antigens in snail hemolymph is potentially suitable for large-scale screening and detection, it is unsuitable for detecting early prepatent infection [52,53].

Identification of early snail infection, perhaps the most relevant outcome for linking snail infection to water contamination, has been accomplished recently using various molecular tools. As an example, PCR amplification of tandem repeated DNA sequences (Sm1–7 repeat of *Schistosoma mansoni* [54] and DraI repeat of *S. haematobium* [55]) has been shown to enable detection of snail infection throughout prepatency [17,56]. Large-scale monitoring of field snails by DraI-PCR recently provided year-round data on prepatent *S. haematobium* infections in bulinid snails recovered from transmission sites in the Msambweni area of Kwale District, Coast Province, Kenya [17]. In Brazil, similar results have been obtained for detection of *S. mansoni* in field samples of *Biomphalaria* snails [57]. These findings demonstrate that prepatent infections are indeed significantly more abundant and stable over time than cercarial shedding. In Kenya, even when community-wide therapy was applied, 30–50% of field snails recovered in the study area were found to be infected with *S. haematobium*, suggesting a high residual of water contamination by parasite eggs despite the fact that there were significant reductions in mean community infectious burden following treatment [17] (Box 2).

**Box 1. Advantages of molecular monitoring of pre-patent snail infection by *Schistosoma* species**

- Greater specificity of schistosome species identification
- Greater sensitivity for detection of snail infection
- Increased ability to detect effective water contamination by schistosome eggs through more sensitive monitoring of human-to-snail transmission
- Greater power to detect significant increases or decreases in transmission
- Lower dependence on participation by local population
- Amenable to automation and high-throughput testing

Post-control resurgence of snail infection rates, if detected efficiently, can be expected to precede the reappearance of symptoms among reinfected local human populations [15]. Thus, monitoring of continuing transmission potential (measured as snail prepatent infection rates) could help to select the most effective modes of targeting and timing chemotherapy. It could also enable rapid, performance-based decisions about applying additional snail control measures (e.g. by focal molluscicide application) for prevention of recurring infection and disease. The ultimate objective will then be to reduce all risk of schistosome infection in a sustainable manner.

This proposed snail-monitoring approach is in fact a form of xenomonitoring, because it involves monitoring of infection in the intermediate host for indirect assessment of infection levels among local human populations as a result of human-to-intermediate host transmission. A similar monitoring approach has been proposed for surveillance following filariasis control [58–60]. In the case of snail xenomonitoring, however, much higher rates of schistosome prepatent infection can be expected and fewer specimens are required when using a properly designed sampling strategy. Compared with mosquito monitoring, snail collection is done at local water contact sites (i.e. at water bodies and not in homes), and hence fewer local residents will refuse sampling.

Repeated surveys of schistosomiasis infection in human populations can be hindered by problems of subject adherence [61], limited availability for testing (e.g. timing of school hours) and difficulties in obtaining sufficient treatment coverage [62]. Schools are significant sites of human aggregation, and are often selected for both monitoring and treatment of schistosomiasis [39,62]. Water bodies represent another aggregation site for humans (and, naturally, for snails), but selective monitoring and treatment of humans gathering at high-risk water sites might be too challenging, and, to our knowledge, has not been
attempted. By contrast, sampling of snails can be carried out undisturbed at most times, with wide area coverage. Snails can be collected for monitoring purposes [63] and also targeted for mollusciciding during the same visit [35,64]. People from nearby villages can be assigned and trained for snail collection [17]. In fact, these are the people most likely to be motivated for schistosomiasis control because they are the ones most likely to be affected.
– proximity to transmission sites frequently determines intensity of site usage by individual households [16].

In areas where large-scale monitoring and control of schistosomiasis needs to continue for long periods, training and participation of local workers in collecting and identifying snails should be simpler, because neither task requires the laboratory equipment, facilities or the expertise that would be needed for identification of *Schistosoma* eggs in excreta. After suitable training, focal snail collection can be coupled with focal mollusciciding at the same sites. Such activities could be considered part of area-wide initiatives for health and water management [40,65]. Control of *S. japonicum* poses special challenges owing to the amphibious nature of *Onchomelania* spp. snails and the presence of multiple animal reservoirs for the parasite. For this form of the parasite, rapid detection of the presence of infection will enable more focused implementation of snail control and habitat modification [13,15,34].

**Molecular monitoring of prepatency in snails as a large-scale application in schistosomiasis control**

There are technical issues remaining in the implementation of molecular monitoring of schistosome transmission and some further development is required. To exclude false-positive test results caused by genetic overlap with related trematodes, full species specificity should be available for the *Schistosoma* monitoring assays of snail specimens. Such specificity has recently been achieved for *S. haematobium* with the use of a novel inter-repeat PCR assay (I. Abbasi et al., unpublished). Application of molecular monitoring requires selection of suitable time slots for snail collection during the transmission season. The appropriate numbers of snails and sites that are required for representative sampling (and the most cost-effective operation) have also to be determined. In monsoon areas, snail numbers at transmission sites usually rise rapidly as the rainy season subsides and then decline gradually during the following dry season[43]. This variation must be considered in the design of suitable sampling schemes. Previous molecular monitoring for *S. haematobium* transmission over the course of an entire year revealed that prepatency rates can exhibit a succession of peaks [17], which might dictate systematic collection of repeated samples over time to cover both high and low values of prepatent infection in local snails. Large-scale PCR monitoring of prepatent snail infection has so far been carried out in only one geographic region (coastal Kenya) and with only one host snail, *Bulinus nasutus*. These results require further validation in different geographic regions where different host–parasite combinations exist.

**Future directions**

Although many thousands of snails have been examined by PCR in research laboratory settings [17,57,66], this method would be unsuitable for routine large-scale application in most field laboratories. Discovery of user-friendly, inexpensive molecular diagnosis and identification tools for field programs in endemic regions is an issue relevant to large-scale monitoring of control programs for infectious diseases (e.g. malaria, filariasis and tuberculosis) in many developing countries. Development of molecular detection tools for parasites is ongoing [67], and should ultimately lead to adequate detection sensitivity, operational simplicity and low cost, which are vital criteria of field-worthiness for such molecular techniques. Several technologies described so far claim these qualities; for example, the loop-mediated isothermal amplification (LAMP) method. This method relies on auto-cycling strand-displacement DNA synthesis, and is capable of amplifying a few copies of DNA to over one billion copies in less than an hour under isothermal conditions [68,69]. It avoids the use of expensive high precision instruments and elaborate multi-step methods to detect the amplification products. Rather, it relies on simple DNA extraction plus direct detection of amplification products, and has already been employed for detecting protozoan parasites [70,71].

Such developments in lower-tech molecular recognition are expected to lead to better detection of disease-agents under most field conditions. In many developing countries, central reference laboratories, which have already incorporated standard PCR molecular detection tools, can be expected to provide the required local backup for the standardization and dissemination of simplified assays. Sustainable control and elimination of schistosomiasis transmission, and hence long-term elimination of schistosomiasis-associated morbidity, requires the development of monitoring tools suitable for continued application and, without doubt, the essential involvement of some form of community participation, including health education [65].

**Concluding remarks**

The view of the social and medical importance of schistosomiasis is changing with the greater appreciation of its day-to-day impact on individual health and disability. The well known infection-associated advanced morbidities that occur late in infection, i.e. liver fibrosis, intestinal bleeding, urinary tract obstruction, superinfection and cancer, seem to represent only a small fraction of *Schistosoma* infection-associated disease. It now seems likely that chronic complications, such as anemia, undernutrition (e.g. short stature or underweight), abdominal and pelvic pain, and possibly infertility, play a much more substantial part in the daily and lifetime health burden of affected individuals and populations. Such outcomes are associated with both the presence and, to a lesser extent, the intensity of infection. Because post-treatment risk of reinfection can remain high and because variations in anti-parasite immune responses can drive individual risk for disease formation even in light infection, new thought is being given to transmission control in high-risk areas. New molecular amplification technologies offer a positive step towards community monitoring of local water contamination by schistosome eggs and transmission to snails. Use of these sensitive and specific techniques will provide essential data for the development of the next generation of schistosomiasis control, based on reduction and ultimate elimination of local transmission.

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