Sensitive diagnostic tools and targeted drug administration strategies are needed to eliminate schistosomiasis

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Abstract

Although preventive chemotherapy has been instrumental in reducing schistosomiasis worldwide, serious challenges remain. These include the omission of certain groups from mass drug administration campaigns, the existence of persistent disease hotspots as well as the risk of recrudescent infections. Central to these challenges is the fact that the currently prescribed diagnostic tools to establish the burden of infection lack sensitivity, especially in low endemic settings, resulting in an underestimation of the true prevalence of active *Schistosoma* infections. This necessitates a re-evaluation and possible adaptation of current WHO-recommended control strategies. Recently, more targeted interventions and novel approaches have been employed, such as establishing infection burden by precision mapping to provide high resolution spatial information that delineates significant variations in schistosomiasis prevalence within a defined geographical area. Such information is instrumental in guiding targeted intervention campaigns. However, the need for highly accurate diagnostic tools in such strategies remains a crucial factor that is often neglected. The availability of highly sensitive diagnostic tests also opens up the possibility of applying sample pooling strategies, to reduce control programme costs. To achieve interruption of transmission and eventually elimination of schistosomiasis, better local targeting of preventive chemotherapy in combination with utilising more sensitive diagnostic tools is vital.

Key-points

* Preventive chemotherapy has been key in reducing the burden of schistosomiasis but serious challenges remain

* Current diagnostic tools to detect *Schistosoma* infections as part of control programmes lack sensitivity

* Re-evaluation and adaption of current WHO-recommended schistosomiasis control strategies is urgently needed

* The use of highly sensitive diagnostic tools is key in breaking the transmission cycle and moving towards sustained elimination of schistosomiasis

Introduction

Despite years of sustained control efforts, the global burden of schistosomiasis remains high with an estimated 221 million people worldwide requiring preventive chemotherapy of which 90% resides in sub-Saharan Africa (1). This immense burden is exacerbated by the fact that schistosomiasis is strongly linked to poverty, limited access to potable water, and lack of adequate sanitation (2). Since 2001, the World Health Organisation (WHO) has strongly advocated for schistosomiasis morbidity control through preventive chemotherapy (World Health Assembly resolution 54·19 (3)) with a more recent expanded goal of elimination of schistosomiasis as a public health problem (World Health Assembly resolution 65·21 (4)).

While there have been successes in reducing the intensity of infections and associated morbidity through sustained mass drug administration (MDA) campaigns, schistosomiasis remains highly prevalent (5). In regions that have successfully reduced the intensity of infection to lower thresholds, the currently prescribed diagnostic tools are no longer reliable for control programmes treating these populations. Especially in areas with a low infection intensity these methods lack sensitivity and are therefore not able to accurately detect such low intensity infections and thereby underestimate the prevalence of active *Schistosoma* infections (6, 7). To break the cycle of transmission and shift towards sustained elimination of schistosomiasis, changes to the current global schistosomiasis control strategies are urgently needed (8, 9). The availability of more sensitive diagnostic tools presents opportunities to revisit these strategies in regions where a break in transmission may be feasible.

Strategic changes to advance the global control of schistosomiasis were discussed at an international workshop hosted by Leiden University Medical Center in the Netherlands in September 2017. The workshop brought together representatives from national control programmes, industry, donors and academia (research scientists, clinicians, and mathematical modellers) to develop a vision for sustained local interruption of transmission and the eventual successful elimination of schistosomiasis.

Challenges related to the current approach

The WHO's current strategy for controlling schistosomiasis focuses on reducing disease morbidity and transmission through periodic, targeted MDA with praziquantel (40 mg/kg body weight) administered to at-risk populations (10). As part of this strategy, the mean schistosomiasis prevalence is determined in an 'implementation unit (IU)'; a geographical area where an MDA programme is being rolled-out. This IU can be a whole district or a sub-district (Figure 1A), for example an administrative, health or education district and it varies in size from country to country (11).

Usually, in 5-10 sentinel sites within such an IU a parasitological survey is performed to determine the overall prevalence in the entire IU (Figure 1B) (9, 12). The sentinel site can be a school with 50 children per school being surveyed. Based on the mean prevalence determined by the survey, the risk of schistosomiasis is categorised as low (<10%), moderate (≥10% to <50%) or high (≥ 50%) for the whole IU (Figure 1C); a classification that defines the intervention strategy applied within this geographical area (13). Even though at sub-district level the burden of infection can be determined in more detail, this strategy does not sufficiently capture the focality of schistosomiasis, resulting in areas receiving over- or more importantly under-treatment (12).

Although initial implementation of the WHO MDA strategy has been successful in reducing morbidity (14-16) there are several opportunities for optimisation. MDA strategies traditionally target school-age children, a group within which the prevalence of schistosomiasis is often higher compared to other groups and which can be conveniently reached by programmes at one location (a school). However, this strategy fails to cover other groups that are at high risk of schistosome infection, for example preschool-age children and adults exposed to infested water through their occupations (e.g. fishermen, farmers, women doing laundry and irrigation workers) (17, 18). As such, these groups remain potential active reservoirs for continued transmission in a community. Preschool-age children are excluded due to safety concerns and poor adherence to praziquantel, although this concern is likely to be addressed with the development of a paediatric formulation for praziquantel (19). Likewise, WHO guidelines recommend the inclusion of pregnant and lactating women in MDA campaigns, but these groups often remain excluded also due to safety concerns despite the growing body of evidence demonstrating efficacy and safety of praziquantel for their treatment (20, 21). Exclusion of certain groups becomes a critical issue if the goal is community-wide control and elimination of schistosomiasis.

The commitment of Merck to support the WHO through the donation of praziquantel for preventive chemotherapy in school-aged children in Sub-Saharan Africa (22) has been pivotal to schistosomiasis control efforts. However, with the scale-up of MDA programmes, many African countries have been faced with the challenge of bridging the gap between the demand for praziquantel and what is available via the donation programme (23). Moreover, the currently recommended MDA dosage for praziquantel may be leading to suboptimal cure rates and prolonged low intensity infections within some communities. These consequences will be even more substantial and pronounced when percentages of population coverage of MDA will be reduced, leaving larger numbers of infected people untreated.

Additionally, in certain areas control of schistosomiasis is hampered by the existence of 'persistent hotspots'; geographical regions where MDA programmes have been in operation for several years, yet remain unable to achieve the forecasted declines in prevalence or intensity of schistosomiasis (24-27). Persistent hotspots have been identified across Africa including Kenya (28), Mali (29, 30), Sudan (31) and Tanzania (24, 32). These hotspots likely require approaches that combine MDA with multi-sectoral efforts such as health education, improvements to sanitation and potable water supply, environmental and vector control as well as future use of vaccines (33-37).

Another challenge in the control of schistosomiasis exists in parts of Asia where the prevalent schistosome species (*S. japonicum, S. mekongi and S. malayensis*) are known to be zoonotic and have several animal definitive hosts as a reservoir of infection (38). Also in African schistosomiasis, animal reservoirs have been described (39, 40). In such areas, the control and elimination of schistosomiasis is even more problematic since the management of animal reservoirs is imperative (38). In addition, molecular studies have also found evidence of genetic interactions between human and animal schistosomes within the African continent and the emergence of hybrid species indicative of some zoonotic spill-over (41, 42).

Classic diagnosis of schistosomiasis as part of control programmes is often still based on parasitological assessment of urine or stool, depending on the schistosome species endemic in the area. These diagnostic methods are known to lack sensitivity in detecting infections of low intensity, resulting in an underestimation of the burden of infection (7). Identifying areas with low infection intensities using accurate diagnostic tools combined with cost-effective strategies for implementation is essential for achieving elimination of schistosomiasis. This is also important for dealing with 'subtle morbidities' that could have long-term impact on the quality of life of individuals including effects on cognitive development (43). Control programmes struggle with how to tackle low prevalence settings where the factors sustaining transmission at lower levels are poorly understood and interruption of transmission has not yet been achieved (9, 33, 34). In addition, low endemic areas likely require continuous surveillance with highly sensitive diagnostic tools, as the risk of prematurely stopping MDA might very well result in infection levels returning to pre-MDA levels shortly after cessation of MDA (recrudescent infections) (37, 44). As for persistent hotspots, an integrated control approach is likely required to achieve these epidemiological targets.

Importance of precision mapping and more targeted interventions

Locating exactly where active transmission occurs and which individuals within a community still harbour living worm pairs, is particularly relevant as schistosomiasis is heterogeneously distributed, meaning that an endemic region can be considered as a collection of (micro)foci (45). There is a lack of clear guidelines that account for the potential effects of this natural heterogeneity, or focality, on programme design. Recent studies by the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) have shown a large variability in MDA efficacy at the community level (24, 28). Therefore, existing control guidelines need to be adapted with greater focus on geographical areas of low endemicity that are likely to achieve transmission interruption. In these areas, sampling grids can be narrowed by increasing the number of sites being sampled; a concept that has been termed 'precision mapping' (12). In order to demonstrate the precision mapping approach in Cameroon, Tchuem Tchuenté *et al* exhaustively sampled all schools in two schistosomiasis-endemic districts representing geographical areas characterised as being low and high with respect to schistosomiasis transmission (12). This approach produced high-resolution mapping information that showed significant variations in schistosomiasis prevalence between districts and sub-districts (called implementation units, IU), which would not have been detected with conventional mapping approaches that are part of the current global control strategies. Analysis of data from precision mapping can be used to guide targeted and intensified interventions in high-risk areas, providing a cost-efficient and judicious use of donated praziquantel. Furthermore, this approach presents an opportunity to zoom in on an IU to identify areas of significant transmission and the

advantage to specifically target the identification of individuals living in a low-endemic community who harbour significant intensities of living adult worms (the so called 'super-spreaders' (46)).

Importance of highly sensitive diagnostics

The success of any strategy to tackle schistosomiasis hinges on the ability to obtain an accurate picture of the burden of infection in a given community, as 'improvement can only come from accurate measurement' (Lord Kelvin, 1883) (47). The necessity of accurate diagnostic tools with high sensitivity in these strategies is often neglected. To achieve the goal of elimination of schistosomiasis, highly sensitive and specific diagnostic tools, that ideally are field-applicable, are needed to monitor the burden of infection.

Several diagnostic tools have demonstrated to be useful alternatives compared to conventional diagnostic methods currently used by national control programmes, such as the widely used field-applicable point-of-care circulating cathodic antigen (POC-CCA) test (48, 49). Even though this test has been recommended as a replacement for traditional microscopy (50), it is limited to the detection of intestinal schistosomiasis and still lacks sensitivity in detecting infections of low intensity (51, 52). A more promising alternative is the highly sensitive and specific laboratory-based up-converting phosphor lateral flow (UCP-LF) test that detects *Schistosoma* circulating anodic antigen (CAA) (53-56). It is a genus-specific test which detects all *Schistosoma* species in blood and urine samples, and may potentially be able to detect a single worm pair by increasing sample volume (56, 57). Furthermore, the UCP-LF CAA test is amenable to pooled sample testing strategies (58). Individuals whose pooled urine samples are found negative by the UCP-LF CAA test can be assumed to all be free of schistosome worms, or at least below a set threshold in worm load, while in CAA-positive urine pools, one or more individuals harbour a worm burden which might be relevant for further transmission. Individual urine samples can then be subsequently tested to identify infected individuals within a positive sample pool, in order to only treat infected individuals and thereby save drugs. Compared to more exhaustive sampling approaches, such pooling strategies can potentially reduce control programme costs (59). Although the UCP-LF CAA test is still lab-based, steps are underway to develop a more field-applicable version of this test (55, 58, 60). Clearly, a reliable and easy-to-use rapid diagnostic test is a prerequisite for the development of test-and-treat strategies, with or without pooled sampling, as well as to facilitate the clinical diagnosis of schistosomiasis at point-of-care settings and the targeted use of praziquantel.

Other more sensitive and specific diagnostics methods include polymerase chain reaction (PCR)-based methods for the detection of schistosome-specific DNA in clinical samples (urine, faeces or blood) (7, 61). One approach that has been designed for field use is loop-mediated isothermal amplification (LAMP), an advanced DNA-based detection method that amplifies DNA without a thermocycler and in some instances, can have higher sensitivity compared to conventional PCR (62-64). Another potentially field-applicable technique is isothermal recombinase polymerase amplification (RPA) for schistosome-specific DNA detection applicable to both *S. haematobium* (65) and *S. mansoni* (66).

Integrating sensitive diagnostics into an intensified focal test-and-treat strategy

In a theoretical schistosomiasis endemic area, comprised of one or more IUs, where the prevalence of infection has been determined to be low by standard parasitological methods (i.e. less than 10% overall prevalence and less than 1% prevalence of heavy infections), an intensified focal test-and-treat strategy, using highly accurate diagnostic tools, should at least be included to shift transmission dynamics within these geographical areas towards a break in transmission.

When applying the precision mapping approach in such an area, the burden of infection within an IU should be estimated from a larger number of sentinel sites, rather than a sampling from 5-10 sites as is conventionally recommended. This increased sampling from a larger number of sentinel sites would require pooling multiple samples in order to reduce the total number of tests needed as a cost-saving measure (58, 59). Given the focal nature of schistosomiasis, sampling designs should also consider proximity to water contact points where transmission is suspected.

In one scenario discussed at the workshop, an IU at sub-district level can be divided into separate 'transmission units' (TU, Figure 1D); a proposed geographical area limited to one or few transmission sites. So, instead of the current strategy in which 5-10 sentinel sites within an IU are being sampled, the whole IU is divided into smaller TUs. By integrating a pooling strategy using a highly sensitive diagnostic test, a whole TU will be

sampled and tested, leading to a quantitative evaluation of the overall infection burden within each TU. Mathematical modelling could provide valuable information on the best pooling strategy, taking into consideration age-groups or risk groups, as well as expected infection levels based on pre-control endemicity and history of control, to determine optimal pool size (58, 59). Information from existing databases on correlation between different diagnostic tests could also be used to develop a predictive model to estimate for example CAA or DNA loads and linking these individual measurements to transmission potential within a given area. The outcome of testing pooled samples with a highly sensitive diagnostic test in combination with the predictions of the model(s) would then guide the prevalence thresholds that should be set to determine the appropriate control strategy that will be embarked on within each TU.

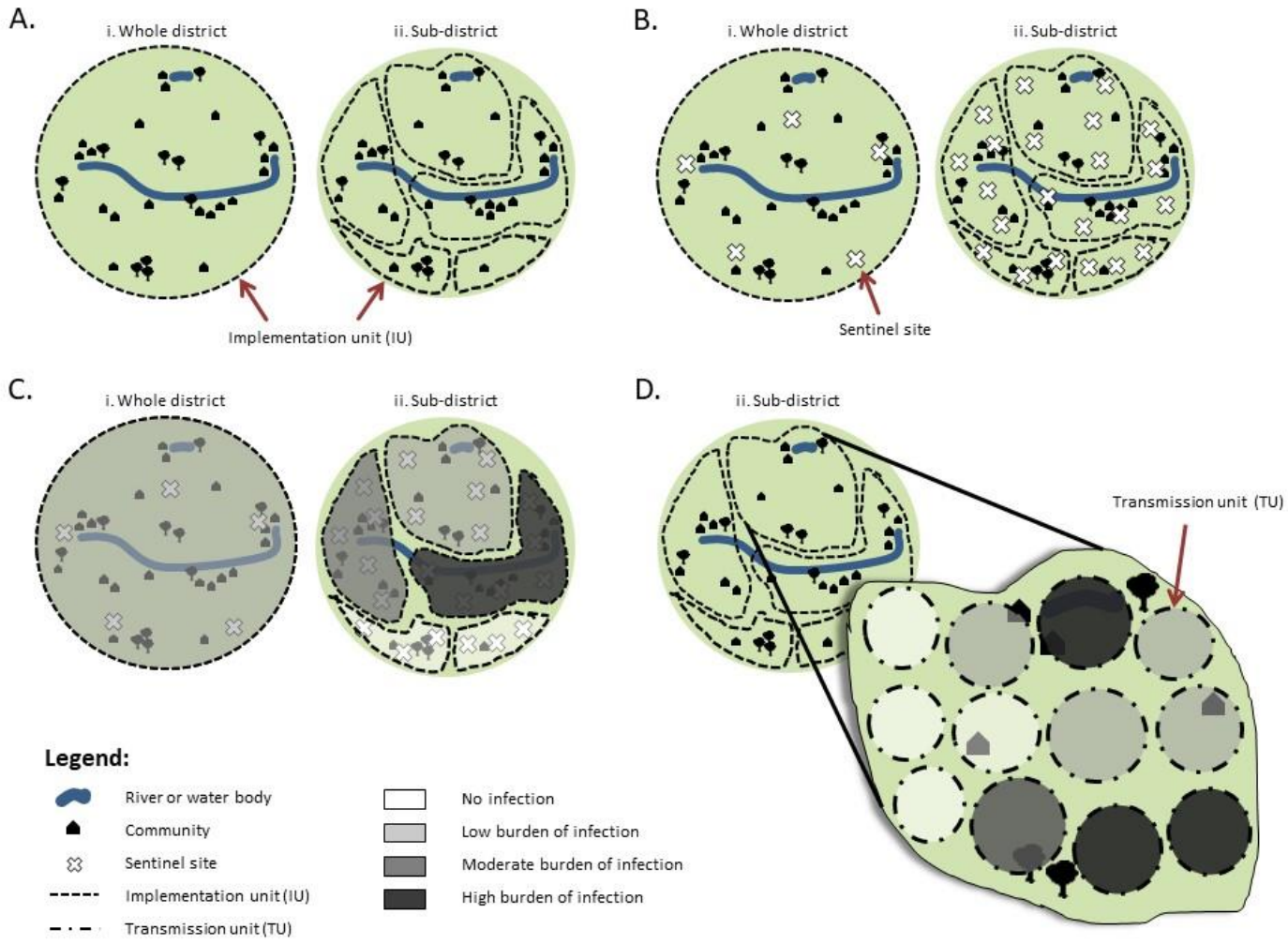

Figure 1. Schematic representation illustrating the current strategy of sampling within an intervention unit in comparison to a mapping approach at a smaller level based on a pooled sampling strategy. Currently, according to the WHO, areas are divided into implementation units (IU) (A) which can vary in size; for example a whole district (A-i) or a sub-district (A-ii). The burden of infection in each IU is determined and monitored by sampling from 5-10 sentinel sites (B) using conventional parasitological diagnostic tools. The burden of infection is then categorised as low, moderate or high for each IU (C). By further dividing sub-district IUs into smaller transmission units (TU) (D), and instead of sampling from 5-10 sentinel sites applying a pooling strategy to the whole TU, a bigger area will be sampled from. This results in more accurate data for mapping and quantifying the distribution of schistosomiasis as well as to identify communities at risk.

Table 1: Proposed treatment strategy based on infection burden

Infection burden established by sampling	Recommended treatment strategy*
I. High infection burden	Intense MDA (annual or biannual treatment of all high-risk groups as well as community-wide treatment)
II. Medium infection burden	Regular MDA (annual community-wide treatment)
III. Low infection burden (near elimination)	Intensified focal test-and-treat (multiple rounds per year) and frequent surveillance, using the most sensitive diagnostic tool available in combination with pooled sampling
IV. No infection (anymore)	No MDA, regular surveillance, using the most sensitive diagnostic tool available in combination with pooled sampling

** Combined with integrated intervention measures, see text*

From the strategy outlined above, we envisage four scenarios that may reflect the burden of infection from surveying each TU (shown in Table 1). The corresponding recommended strategy should then also be implemented at TU level. In TUs found to have a high infection burden, for instance potential 'hotspots' or 'persistent hotspots', intense MDA of yearly or twice-yearly treatment should be rolled out following existing control strategies. Additional samples should be taken not only from school-age children, but also from high-risk groups (such as fishermen, car-washers, women doing laundry, etc.) and testing stratified according to these groups. The strategy could be adapted to treatment for each positive group in addition to all school-age children; and the entire group could be monitored and followed up over a two-year period. For TUs where a medium infection burden is established, a regular MDA programme of yearly community-wide treatment should be implemented. In areas where the burden of infection is found to be low, an intensified test-and-treat strategy with multiple rounds of testing and treating per year should be implemented after identifying the high-risk groups within each community. In addition, the identification, treatment and monitoring of individuals who still harbour high worm infections also needs to be taken into account in this strategy. Furthermore, knowledge about local transmission sites with respect to aquatic biology and social behaviour patterns is indispensable in tackling and reducing exposure. Individual worm levels could also be included to guide local or regional interventions. In TUs found to be negative, no MDA would be carried out but groups should be followed-up and tested over a given period of time using a cost-efficient sample pooling strategy. It would be important to know if these areas have always been negative or are negative after prolonged control since the monitoring approach depends on the potential for transmission in the area (best reflected by the pre-control endemicity). Obviously, all strategies also need to include other integrated multisectoral approaches such as health education, snail control, and water, sanitation and hygiene (WASH) initiatives. Classic xenomonitoring augmented with DNA methods that can identify infected snail hosts is especially important to determine environmental risk accurately (67), as well as monitoring of schistosome infection in locations where zoonotic spill-over may occur. Further innovations such analysis of water for environmental DNA (eDNA) (68), signatures of schistosomes with taxon specific probes, could be very powerful to verify putative interruptions of transmission.

At the national level, a surveillance response mechanism would need to monitor these focal test-and-treat strategies. This includes modelling for prediction and guiding the intervention, monitoring of infection and mechanisms to evaluate interventions (69). Global positioning system (GPS) mapping could be used to determine precise locations of infected people of all ages and their households (70). However, privacy issues need to be taken into consideration. Innovations such as surveying snail environmental DNA (eDNA) in water bodies (68, 71) are additional tools that can be used to monitor transmission. Lessons can also be learnt from the Global Polio Eradication Initiative which uses environmental surveillance of poliovirus in sewage to monitor the virus (72).

After presumed interruption of transmission has been achieved, communities should still, ideally, be monitored longitudinally using highly sensitive and specific assays using the UCP-LF CAA test and eventually also serology. After a number of years with no new infections being detected, new-borns and young children would have to be followed to assess their exposure to schistosomes (44, 73), which could be done through for example targeted anti-schistosomal antibody testing (74, 75). In addition, the movement of individuals from regions that are still endemic for schistosomiasis into post-transmission areas would have to be monitored, and infected individuals promptly treated. The development of commercially available highly sensitive tests would be indispensable in targeting these groups in this post-transmission phase.

Given that current schistosomiasis control programmes in sub-Saharan Africa rely heavily on donated praziquantel for MDA campaigns, the proposed test-and-treat strategy will enhance cost-efficiency. The availability of a paediatric praziquantel formulation for young children will further support and strengthen a community-wide targeted treatment approach.

The successful implementation and efficient rollout of the proposed strategy would hinge on close cooperation between key international players (such as WHO) and stakeholders within endemic countries. Within these countries, engagement with national and local authorities would guarantee local ownership and responsibility for the strategy and its implementation. Targeted implementation at more local levels such as a TU could be more complex due to logistical challenges and the lack of adequate structures. Therefore, strengthening overall neglected tropical disease (NTD) coordination structures at national and sub-national levels, including the building of local capacity, would assure the proper execution of the proposed strategy, as well as effective long-term monitoring, evaluation and overall sustainability.

Additionally, it would be essential that endemic countries adopt and incorporate the strategy into the development of their NTD master plans. This would be achieved through local and international stakeholders working closely with endemic country NTD expert committees that are responsible for coordinating the direction of national NTD goals and policies (including for schistosomiasis) and ensuring that these are in line with regional and global targets. Combining all these efforts is essential for improved focal targeting of preventive chemotherapy in combination with more sensitive diagnostic tools in order to achieve interruption of transmission and the eventual elimination of schistosomiasis.

Conclusion

The persistent global burden of schistosomiasis despite continuous large-scale MDA, requires a rethinking and revision of both intervention strategies and the diagnostic tools that enable these strategies. Especially in areas of low infection intensity, non-invasive pooled sample testing with highly accurate diagnostic tools should be implemented by national control programmes in adapted control strategies that ensure cost-efficiency in monitoring and evaluation, as well as longer-term surveillance. We believe this will be the way to go to achieve interruption of transmission and eventually elimination of schistosomiasis.

Contributors

ASA, GJD and PTH led the writing of this Personal View. All authors made contributions to the writing and discussions on the scope of this Personal View, and critically reviewed revisions and approved the final paper.

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