CellPress
REVIEWS

Opinion

To Reduce the Global Burden of Human Schistosomiasis, Use 'Old Fashioned' Snail Control

Susanne H. Sokolow,[1,2,*] Chelsea L. Wood,[3] Isabel J. Jones,[1] Kevin D. Lafferty,[4] Armand M. Kuris,[2] Michael H. Hsieh,[5,6,7] and Giulio A. De Leo[1]

Control strategies to reduce human schistosomiasis have evolved from 'snail picking' campaigns, a century ago, to modern wide-scale human treatment campaigns, or preventive chemotherapy. Unfortunately, despite the rise in preventive chemotherapy campaigns, just as many people suffer from schistosomiasis today as they did 50 years ago. Snail control can complement preventive chemotherapy by reducing the risk of transmission from snails to humans. Here, we present ideas for modernizing and scaling up snail control, including spatiotemporal targeting, environmental diagnostics, better molluscicides, new technologies (e.g., gene drive), and 'outside the box' strategies such as natural enemies, traps, and repellants. We conclude that, to achieve the World Health Assembly's stated goal to eliminate schistosomiasis, it is time to give snail control another look.

Trends

Despite a rise in the global effort towards preventive chemotherapy, just as many people suffer from schistosomiasis today as did 50 years ago.

Snail control can complement medical treatment, especially where transmission is endemic and reinfection after treatment is a common occurrence.

Modernizing snail control is a priority and might benefit from more research on spatiotemporal targeting, environmental diagnostics, better molluscicides, new technologies, and 'outside the box' strategies such as natural enemies, traps, and repellants.

Targeting Snails Is a Key to Success for Schistosomiasis Control

Soon after Japanese researchers resolved the schistosome life cycle and identified its snail hosts in 1913, Japan launched a 'snail picking' effort that offered children a 0.5-yen bounty per container of snails they collected and destroyed [1]. After seven years, Japan shifted from this labor-intensive (and ineffective) effort [1], to controlling snails by cementing irrigation canals, draining wetlands, and applying molluscicides. By 1994, this sustained snail control effort, plus drug treatment of infected people, led to the eradication of schistosomiasis in Japan [2]. Other countries, such as Guadeloupe, Iran, Iraq, Lebanon, Martinique, Morocco, Oman, Puerto Rico, Saint Lucia, Saudi Arabia, Tunisia, and Venezuela, have also controlled or eliminated schistosomiasis using snail control [3] (Table 1). Brazil, China, Egypt, Indonesia, the Philippines, and Zanzibar have long used snail control alongside preventive chemotherapy and other strategies to suppress schistosomiasis prevalence, whereas countries that have not pursued snail control have been less successful [3]. Snail control appears to be a key intervention needed to achieve the World Health Assembly's stated goal to eliminate schistosomiasis [3,4] (Table 1).

Despite these many successes, the modern orthodoxy paints snail control as old fashioned, preferring to focus instead on preventive chemotherapy via mass drug administration (MDA) of praziquantel [5–7]. Praziquantel's introduction in the late 1970s and early 1980s, and the release of its generic form in the 1990s, led the World Health Assembly to adopt, in 2001, preventive chemotherapy as the recommended global strategy for schistosomiasis reduction[i] [7,8]. This is in line with recent emphasis on integrated preventive chemotherapy (distributing drugs against various preventable diseases). But despite distributing millions of pills in recent decades, sub-Saharan Africa's schistosomiasis problem is as serious now as it was before

[1]Hopkins Marine Station, Stanford University, Pacific Grove, CA 93950, USA
[2]Marine Science Institute, University of California, Santa Barbara, CA 93106, USA
[3]School of Aquatic and Fishery Sciences, University of Washington, Box 355020, Seattle, WA 98195-5020, USA
[4]U.S. Geological Survey, Western Ecological Research Center, c/o Marine Science Institute, University of California, Santa Barbara, CA 93106, USA
[5]Children's National Health System, Washington DC, 20010, USA
[6]The George Washington University, Washington DC, 20037, USA
[7]Biomedical Research Institute, Rockville, MD 20850, USA

*Correspondence:
ssokolow@stanford.edu
(S.H. Sokolow).

Table 1. Outcomes and Control Strategies of All National Schistosomiasis Control Programs during the Past Century[a]

Country/ territory name	Control outcome	Successful prevalence reduction (%)	Successful population-at-risk reduction (%)	Molluscicides	Snail habitat reduction	Snail biological control	Human tx by MDA	Other controls	Details of other control measures	Refs
Iran	E	100	100	•	•	•		•	Land reclamation, draining swamps, providing latrines	[100,101]
Japan	E	100	100	•	•			•	Human test and tx; cementing irrigation canals	[1,2,102,103]
Jordan	E	100	100	•				•	Low coverage; human test and tx	http://www.who.int/schistosomiasis/resources/EMRO_report_Schistosomiasis.pdf
Lebanon	E	100	100	•	•			•	Cementing irrigation canals; improved water and sanitation	[101]
Martinique	E	100	100			•		•	Improved water and sanitation	[104]
Mauritius	E	100	100	•					Some enigmatic snail declines	[105]
Morocco	E	100	100	•	•			•	Mobile envoys to support human test and tx	[21,106–112]
Puerto Rico	E	100	100	•		•		•	Human test and tx; improved water; health education	[113]
Tunisia	E	100	100	•				•	Human test and tx	[114]
Saudi Arabia	N	99.8	ND	•	•		•	•	Little MDA; land reclamation, cementing canals	[23,115–120]
Indonesia	N	99.5	ND	•			•	•	Little MDA; agro-engineering; sanitation improvement	[121]
Iraq	N	99.5	ND	•				•	Targeted tx of schoolchildren in early years	[120,122]
Egypt	N	99	ND	•	•		•	•	Safe water supply and agricultural drainage projects	[101,120,123–128] http://documents.worldbank.org/curated/en/756051468036566715/pdf/444660PPAR0P0051520Box327410B01PUBLIC1.pdf
China	N	98.9	79	•	•		•	•	Tx of cattle and buffalo; agricultural engineering and safe water	[129,130]
Venezuela	N	98.6	ND	•	•			•	Human test and tx; invasive competitor snails	[22,131–133]
Philippines	N	98.3	ND	•	•		•	•	Shift from early focus on snails and targeted tx to later MDA	[134,135]
St. Lucia	N	98.2	84.3	•	•	•		•	Site of early Rockefeller studies on control of schistosomes	[136]
Guadeloupe	N	96	ND	•	•	•		•	Bridges; canal engineering to reduce snail habitat	[133,137]

Table 1. (continued)

Country/ territory name	Control outcome	Successful prevalence reduction (%)	Successful population-at-risk reduction (%)	Molluscicides	Snail habitat reduction	Snail biological control	Human tx by MDA	Other controls	Details of other control measures	Refs
Zanzibar	N	84.7	ND	•	•		•	•	Recent initiation of elimination program	[138–140]
Laos	N	84.6	ND				•	•	Limited health education and improved sanitation	[141–143]
Cambodia	N	83	90				•	•	Limited health education and improved sanitation	[141,144]
Brazil	N	80	69	•			•	•	Early human test and tx; improved water and sanitation	[145–148]
Burundi	N	74.4	ND	•			•	•	Focal molluscicide and sanitation were implemented rarely	[149–151]
Ghana	N	73.9	ND				•		Low coverage	[152]
Madagascar	N	73.8	ND	•			•	•	Molluscicides used rarely; improved water and sanitation	[153,154] http://www.who.int/neglected_diseases/preventive_chemotherapy/PCTNewsletter12_En.pdf?ua=1, http://digitalcollections.sit.edu/isp_collection/1675/, http://apps.who.int/medicinedocs/pdf/whozip48e/whozip48e.pdf
Rwanda	N	69.5	ND				•	•	Mapping and training health personnel	[155]
Libya	N	66.7	ND	•	•			•	Human test and tx	http://www.who.int/schistosomiasis/resources/EMRO_report_Schistosomiasis.pdf
Surinam	N	61.5	69.3	•	•			•	Human test and tx; education	[156,157] http://www.who.int/schistosomiasis/resources/PAHO_report_Schistosomiasis_carribean.pdf
Burkina Faso	N	61.2	ND				•			[29,158,159]
Tanzania	N	60	0	•			•	•	Limited molluscicide and human test and tx	[160,161]
Uganda	N	55.4	ND				•			[162,163]
Mali	N	51.8	ND				•			[41,164]
Sierra Leone	N	51.4	ND				•			[165,166]
Kenya	N	51	ND			•	•		Limited biological control in early years with Louisiana Crayfish	[74,167]
Niger	N	44	ND				•			[168–171]

Table 1. (continued)

Country/ territory name	Control outcome	Successful prevalence reduction (%)	Successful population-at-risk reduction (%)	Molluscicides	Snail habitat reduction	Snail biological control	Human tx by MDA	Other controls	Details of other control measures	Refs
Yemen	N	44	ND				•			[172]
Malawi	N	43.3	ND	•	•		•	•	Limited experimental molluscicide and biological control	[173–176]
Congo	N	41.7	ND	•			•	•	Limited molluscicide, education and health training	http://apps.who.int/medicinedocs/pdf/whozip48e/whozip48e.pdf
Togo	N	30.9	ND				•			[162,177]
Mozambique	N	28.9	ND				•			http://www3.imperial.ac.uk/schisto/wherewework/mozambique/mozambiquestrategy
Zambia	N	26.6	ND				•			[178,179]
Cameroon	N	16.7	ND				•			[180]
Swaziland	N	9.6	ND				•			[181]
Senegal	N	1	ND		•		•		Limited trials for biological control with river prawns	[9,182] http://apps.who.int/iris/bitstream/10665/65978/1/WHO_CDS_CPC_SIP_99.2.pdf
Oman	N	0.6	ND	•				•	Low coverage of control; human test and tx; concrete reservoirs	http://www.who.int/schistosomiasis/resources/EMRO_report_Schistosomiasis.pdf
Benin	N	−2	ND				•	•	Improved water and sanitation (incidental to development)	http://www.evaluategroup.com/Universal/View.aspx?type=Story&id=153562
Somalia	N	−24	NA				•		Low coverage of control	http://www.who.int/neglected_diseases/preventive_chemotherapy/databank/en/
Sudan	N	−29.7	47				•		Low coverage of control	[183–187]
Central African Republic	N	−58	ND				•		Low coverage of control	http://apps.who.int/iris/bitstream/10665/69740/1/WHO_CDS_NTD_2007.4_eng.pdf
Dominican Republic	N	ND	ND	•	•				Lacking quantitative data on success	[13,157,188]
Syria	N	ND	ND					•	Early human test and tx; cementing canals; conflict hinders effort	http://www.who.int/schistosomiasis/resources/EMRO_report_Schistosomiasis.pdf

[a]The most successful programs have focused on widespread and early snail control activities. Countries and territories are ordered by most to least successful in terms of reducing schistosomiasis prevalence. More details and data are available at [3], http://schisto.stanford.edu and https://purl.stanford.edu/yt060bn1019. Abbreviations: E, schistosomiasis eliminated from the country/territory; N, schistosomiasis is not yet eliminated; ND, no data; tx, treatment campaigns.

praziquantel's discovery, in part because reinfection after treatment can thwart long-term control [3]. Given this disappointing outcome, the World Health Assembly's 2012 resolution 65.21 advocates adding modernized snail control and other control methods to preventive chemotherapy in order to achieve schistosomiasis elimination[ii].

Together, preventive chemotherapy and snail-control techniques offer our best opportunity for schistosomiasis elimination – and current technology for snail control has come a long way from snail picking. Here we argue that it is time to refocus on snail control in the fight against schistosomiasis. We discuss which strategies remain relevant, and propose what future snail control might look like.

Snails and the Schistosome Life Cycle

The schistosome life cycle encompasses two transmission processes: human-to-snail transmission and snail-to-human transmission (Figure 1). Schistosome eggs from human urine or feces reach fresh water, where eggs hatch and release the miracidia larvae that infect freshwater snails. After completing asexual reproduction in the snails, the schistosomes then

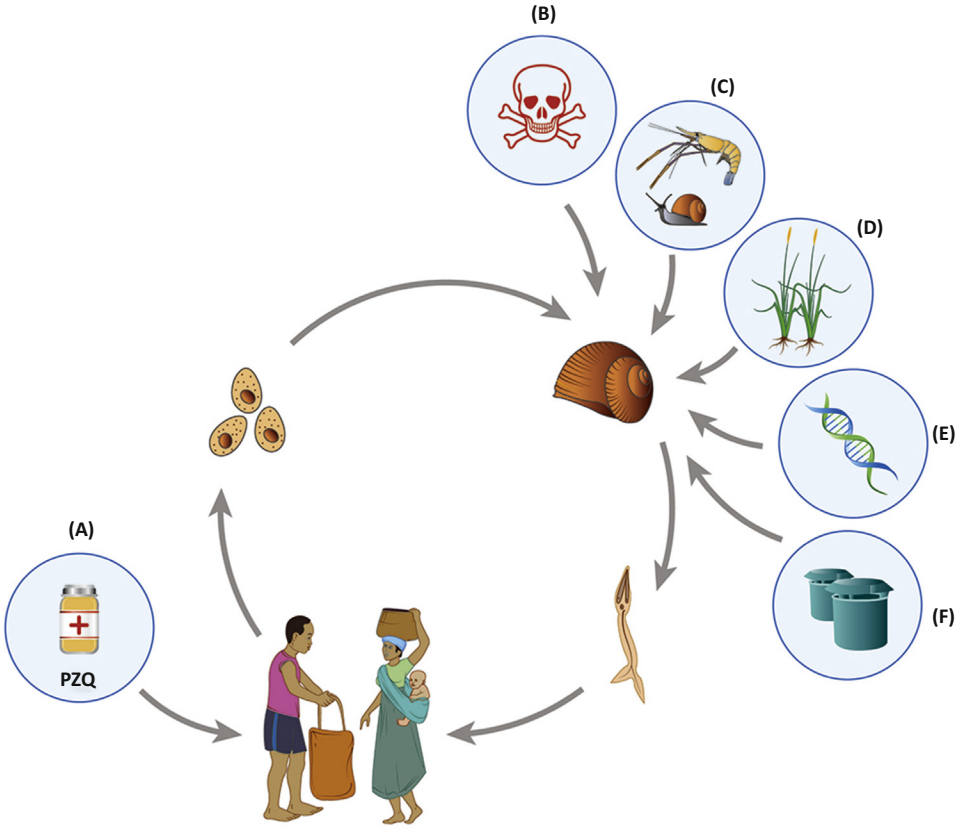

Figure 1. The *Schistosoma* sp. Lifecycle and Snail Control Strategies. Human-to-snail transmission occurs via free-living miracidia released from eggs in urine and feces; and snail-to-human transmission occurs through free-living cercariae that exit infected snails into the water, seeking new vertebrate hosts. Control strategies should combine (A) human drug treatment or preventive chemotherapy with praziquantel (PZQ) with (B–F) creative methods to control infected snails such as: (B) chemical molluscicides; (C) natural enemies; (D) habitat modification; (E) creative technologies such as gene drive; (F) traps or repellants and other 'out of the box' strategies.

release free-swimming cercariae that penetrate human skin, eventually migrating to the portal or pelvic veins, depending on the schistosome species.

It is not easy to eradicate snails, but snail eradication is not necessary for the elimination of schistosomes. To break the schistosome life cycle, snail densities must be driven below a threshold where snail infection rates are lower than snail death rates [9]. Schistosome and snail compatibility is complex, and there are many strain differences across the world [10,11], but despite this complexity, the simple fact remains that, where schistosome-susceptible snails have been reduced, schistosomiasis has often been eliminated from large areas (even whole countries). In Japan, where schistosomiasis has been eliminated since the 1990s, the snail intermediate host, *Oncomelania nosophora,* persists to this day – although its abundance is low enough to merit a vulnerable ranking on the International Union for Conservation of Nature (IUCN) red list[iii] [12]. In Guadeloupe, where snail reductions interrupted schistosomiasis transmission (with few to no documented cases during the past several decades [13,14]), *Biomphalaria glabrata* intermediate host snails are still present and still susceptible to infection, at least up to 2005 [15]. The recalcitrance of snails to eradication means that snail control must be deployed with other approaches to reduce the chance that infected humans will reintroduce the parasite.

'Old-fashioned' snail control has included chemical molluscicides, habitat modification, and biological control, but modern methods could add 'outside the box' strategies – including some under development or yet to be devised. Given that snail populations persist, these snail-control interventions are best complemented with traditional, human-centric schistosomiasis control strategies, like human drug treatment (such as MDA or targeted testing and treatment), water, sanitation, and hygiene infrastructure (WASH), or behavior modification through education. Snail control – or any environmental intervention that reduces schistosomiasis transmission and slows reinfection after treatment – should decrease the frequency at which preventive chemotherapy is required and thus would spare drugs, increase MDA efficacy, reduce costs, and improve scalability. Simply put, elimination is possible if human infections can be interrupted via preventive chemotherapy, and snail densities can be reduced (Figure 1).

Looking Back

Effective 'old-fashioned' snail control strategies have included chemical molluscicides, reducing snail habitat, and biological control (i.e., intentional or unintentional introductions of competitor snails or snail predators), and snail control has sometimes been combined with a number of other strategies including MDA, human testing and treatment campaigns, and engineering interventions (Table 1).

Success with Chemical Molluscicides

During the 20th century, molluscicides were among the most commonly used snail-control strategies by governments and public health agencies, but molluscicides fell out of favor as costs of the chemicals increased, and concurrently, the cost of praziquantel fell, beginning in the 1990s [3]. Although the environmental impacts associated with chemical applications limit their acceptability in some circumstances, molluscicides have been effective in controlling schistosomiasis [3,4,16]. Since the 1960s, the most-used chemical has been niclosamide, a formulation with lethal effects for snails up to 24 h after application and low lethal concentration (LC90) for snails, at <1 ppm [4]. In theory, these low concentrations are nontoxic to vertebrates, including fish and humans, but uneven dispersal can lead to fish kills and health concerns [17]. Some countries have imposed restrictions on the use of niclosamide in the environment due to health concerns and to concerns regarding its nontarget effects [18]. However, it is interesting

to note that niclosamide has been approved for many decades as an anthelmintic treatment in people and has recently been explored as an anticancer therapy and a treatment for Zika virus [19,20].

Success with Snail Habitat Modification

Snail habitat modification for schistosomiasis control has taken several forms – including vegetation removal, land reclamation (e.g., wetland drainage), cementing canals, and occasionally, hydrological interventions to increase or alter stream flow (Table 1). For example, these strategies have controlled snails in Japan, Morocco, Saudi Arabia, and Venezuela [2,21–23]. By contrast, habitat changes linked to dam construction, irrigation expansion, and other water-related changes have resulted in unintentional and sometimes dramatic schistosomiasis outbreaks [24,25].

Success with Biological Control

Schistosome-transmitting snails have various natural enemies. Some crustaceans, birds, and fishes eat them. Other snail species compete with them. Non-schistosome trematodes castrate them. Such natural enemies can regulate snail populations, but most enemies have limited natural ranges, and could have nontarget effects where they are non-native. Biological control has a bad reputation for nontarget effects – but this stems from a few examples where spectacular collateral impacts have accompanied ill-conceived strategies [26]. Biological control can be both safe and effective in a modern context, especially when native species that are natural enemies of pests are used [9,27].

Many biological control strategies have been researched for schistosomiasis control (e.g., introduction of predators, competitors, and parasites of snails), but few strategies have been used widely in practice. One exception is the widespread use of competitor snail species that are not competent hosts for schistosome infection in Caribbean countries such as Antigua, Guadeloupe, Martinique, Montserrat, Puerto Rico, and St Lucia; noncompetent snails were introduced and successfully displaced schistosome-competent intermediate host snails. Schistosomiasis control has been pursued through snail introductions with species such as *Pomacea glauca, Marisa cornuarietis, Melanoides tuberculata*, or *Tarebia granifera* [3,13]. Displacement can be long-lasting if competitor snail populations are self-sustaining [13,28].

No One-Size-Fits-All Solution

No single strategy will reduce schistosomiasis transmission everywhere. For example, past attempts at widespread biological control using snail competitors worked to eliminate schistosomiasis on some Caribbean islands but not others [28]; and MDA using praziquantel has durably reduced schistosomiasis in some parts of Burkina Faso but not others [29]. What worked well in one place or time can be ineffective or inappropriate in another. Deploying multiple strategies may help to balance the control portfolio. In particular, snail control is likely to be synergistic with traditional drug-distribution campaigns employed in preventive chemotherapy and other well-established interventions like WASH infrastructure improvements, education, and sustainable development.

Looking Forward

Future snail-control strategies should build on past successes while responding to changing conditions and incorporating modern technologies. History has shown that controlling complex life-cycle parasites, such as *Schistosoma* spp., requires interrupting transmission from humans to intermediate hosts and vice versa. Embracing a synergistic approach might deliver lasting disease reductions beyond those achievable by focusing on any single aspect of transmission

[9]. Public health, conservation and sustainable development goals could be aligned if health interventions capitalize on cobenefits – as has been suggested, for example, in recent studies that focus on complementing human drug treatment with species restoration (of snail predators) to reduce snails, control schistosomiasis transmission, alleviate poverty, and restore ecosystems [9,30–32].

Schistosomiasis, today, is linked to poverty [33,34], and the long time course required to reduce or eliminate schistosomiasis can erode interest by philanthropic organizations and individual donors [3]. Economic sustainability therefore remains a pressing concern for the future of schistosomiasis control.

For snail control, cost-effectiveness could benefit from strategic improvements such as: (i) targeting control to where and when most transmission occurs to increase effectiveness while reducing coverage needs (e.g., considering hubs and hotspots of transmission in space and time); (ii) using complementary natural enemies (e.g., predator ducks and their echinostome trematodes) that offer affordable win–win solutions that simultaneously reduce schistosomiasis and generate revenue or other cobenefits; (iii), applying novel technologies to improve snail management and control (such as gene drive); (iv) discovering molluscicide formulations that are less harmful and more sustainable; and finally, (v) integrating snail control with other available tools, including preventive chemotherapy, education, and sanitation.

Understanding the Landscape of Schistosomiasis Infection Risk: Ecological Surveillance, Network Theory, and Optimal Control

Snail populations and their schistosome parasites can be dynamic and difficult to predict at the spatial and temporal scales relevant to control campaigns. Theory and empirical data from other disease systems indicate that strategic timing and spatial distribution of control effort improves the efficiency of control, but little schistosomiasis-specific research on this topic exists [35–39].

Although there are few empirical data on snails and their schistosome parasites, especially for sub-Saharan Africa, where most human schistosome infections occur today, the existing data suggest that schistosome-infected snails have aggregated distributions, so that infection risk is distributed in hotspots [40,41]. A hotspot might be a particular water access site or village, with infection risk varying from village to village (across tens to hundreds of meters; e.g., [42–44]). Furthermore, water flow can move cercariae away from high densities of infected snails [45], making it harder to pinpoint the source of infection risk to humans.

Planning and assessing the success of snail control requires mapping and tracking snail abundance and infection prevalence, but the most common traditional snail sampling technique is timed snail counts (Box 1). Although useful for evaluating relative risk among sites or across time within a single study, the relative abundance method does not measure absolute risk, which is best expressed as infected snail density (combined with information on the density of cercariae emitted from snails through time, Box 1). The use of relative abundance snail-sampling methods has been rationalized by invoking investigator safety, time constraints, and the need for simple, straightforward sampling designs when working in challenging field conditions. Absolute sampling using quadrats – that is, the kind of quantitative invertebrate sampling used in other aquatic habitats [46] – is time-consuming and logistically challenging, but yields a more useful, quantitative measure of snail abundance.

Box 1. Quantifying Snails and Their Trematode Infections

Researchers define and measure human risk for schistosomiasis transmission in several ways: prevalence or density of infected snails assessed through snail surveys [189,190], cercarial density measured via cercariometry or molecular detection in water, [191,192], or density of infective cercariae derived through mouse exposure [193]. Because snail densities vary widely, the prevalence of infected snails is a poor way to estimate infection risk in humans. Infection rates in sentinel mice are the most direct way to measure risk in humans. However, mouse exposures are expensive and pose ethical concerns to some [192]. Next best is cercarial density, but filtering for cercariae is challenging because waters are often turbid, cercariae have short lifespans (hours), are small, and have soft bodies [194]. Newly available environmental DNA sampling still requires ground truthing and cannot distinguish cercariae (infective to humans) from miracidia (infective to snails). Therefore, snail sampling via timed searches (e.g. [9,52,59]) has been by far the most common way to measure risk in research studies and monitoring efforts for the last several decades. In a traditional search, trained technicians spend a set time (e.g., 15 min) searching for potential snail habitat at water-access points, then agitate the substrate or vegetation with fine-mesh scoops (~1–2 mm mesh size, pictured) – and retrieve the scoops and pull out the snails [194] (Figure I). Collected snails are put in vials under bright light to shed cercariae, which can then be identified and used to estimate which snails are infected [194]. Such timed searches are quick and inexpensive, but by targeting snail habitat, the actual measure probably reflects snail density within snail habitat rather than overall snail density, perhaps explaining why many past studies conclude that infected snail density at a site does not correlate well with measured human infection rates [195,196]. On the contrary, studies using systematic or random quadrat sampling (including dissecting snails to examine for trematode infections) have found more robust correlations between infected snail density and human infection rates [197]. Future work should aim to develop cost-effective and accurate ways to assess infection risk.

In recent years, advances in molecular genetic techniques, spatial statistics, and GIS mapping have made it possible to examine schistosomiasis transmission risk at fine-grained spatial scales [198]. These technologies, coupled with more robust and spatially quantitative snail-sampling techniques – borrowed from ecological studies on freshwater invertebrates (e.g., [46,197]) – could improve prediction capabilities for schistosomiasis transmission.

Figure I. Two Different Snail Scoops Designed and Deployed to Sample Snails in Schistosomiasis Transmission Sites in Senegal. Image courtesy of The Upstream Alliance (http://wwwtheupstreamalliance.org), under the terms of the Creative Commons Attribution License CC BY 2.0.

In addition to improved methodologies to assess snail abundance and to sample transmission stages, species distribution models (habitat suitability models), environmental DNA, network models, and optimal control theory might improve current snail sampling efforts. Some indirect sampling methods might become cost-effective with additional refinement. For example, species distribution modeling [47,48] encompasses various methods to correlate species

occurrences to underlying habitat variables, such as temperature, rainfall, vegetation cover, etc. This technique could help generate maps that predict schistosomiasis transmission hotspots using readily available data, such as land features and environmental variables [49]. For example, recent reviews [50,51] concluded that spatial risk profiling for schistosomiasis using remotely sensed data is an under-used strategy in schistosomiasis research and control. Species distribution modeling might be particularly effective where strong seasons lead to dramatic snail-habitat ephemerality that is easily mapped, as in Burkina Faso and Cote d'Ivoire [52,53]. These models still require ground truthing using environmental data for training and validation. An alternative indirect approach is to use environmental DNA (eDNA) to track snail density or parasite presence by detecting genetic material directly from water, soil, or other environmental samples without evidence of their biological source [54,55]. The eDNA technique also requires more refinement and validation [54], especially before it can be calibrated for quantitative assessments. Furthermore, because schistosome eDNA might arise from DNA in living or dead miracidia, or living or dead infectious cercariae, it might be hard to translate an eDNA signal to infection risk.

Schistosomiasis transmission maps onto where people work, live, and travel. Understanding the spatial and seasonal connectivity among snail and human populations (e.g., through network modeling, which tracks populations and their interconnections) could indicate critical links where control would be most effective. For example, targeting snail control based on identification of villages that are important hubs of transmission could reduce costs and improve scalability [37].

In Senegal, network models including human mobility – tracked through mobile phone records – predicted schistosomiasis prevalence better than models assuming homogenous mixing of people across cities and villages [37]. Ciddio *et al*. showed how a network model tracking human mobility and water-mediated snail and cercarial dispersal could be used to target environmental interventions to reduce human exposure and contamination risks [56].

In addition to network modeling, there is little published work on how to apply optimal control theory to neglected tropical diseases, including schistosomiasis. Yet, this approach, which is often used in optimization problems from engineering and economics [57], and more recently from biology and epidemiology [58], could provide a platform to tackle schistosomiasis transmission control, considering a complex landscape of competing costs and benefits [52,59]. By incorporating economic considerations in the form of a cost function, and considering control strategies that can vary continuously through time along an optimal path (rather than an 'either or' or a 'one size fits all' approach), these models could offer insight needed for ecosystem-specific decision-making on complex trade-offs in health, economic, and environmental factors influencing the management and control of schistosomiasis.

Future Molluscicide Formulations

New molluscicides (or new niclosamide formulations) that are safer, more effective, more specific, or that disperse more evenly, would be beneficial in the fight against schistosomiasis. For example, some promising research areas include slow-release niclosamide formulations [16], extracts from molluscicidal plants such as endod and others [4,16,60], and surfactant formulations that help disperse niclosamide or other molluscicides more evenly, delivering snail-killing efficacy with less opportunity for accumulating unsafe concentrations. Although some of these strategies have been investigated at small scales for many decades (e.g., molluscicidal plants), the investment of time, energy, and funding has not yet been sufficient to allow scale-up [61]. Understanding the spatiotemporal heterogeneity in snail and

trematode abundance, as discussed above, could contribute to better targeting of molluscicide applications in space and time, and improve safety, efficacy, and cost-effectiveness for this historically successful, chemical-based snail control strategy.

Gene-Drive Technologies for Snail Control

We might soon engineer snail hosts with new genetic properties similar to gene-drive-engineered malaria-resistant *Anopheles gambiae* mosquitos [62]. In 2016, a CRISPR-Cas9-based gene drive was used to insert genes conferring sterility to female *A. gambiae* mosquitos, revealing the potential for gene-drive technologies to reduce malaria transmission [63]. Despite the fitness costs to the mosquitoes that result from sterility-inducing genes, the gene-drive system successfully increased the allele frequency of these genes in laboratory-reared populations over six generations.

The CRISPR-cas9 gene-drive system deserves to be explored as an avenue to schistosomiasis control. Some barriers to employing this technology have already been surmounted: genes that confer schistosome resistance have been identified in wild snail populations [15]; the *B. glabrata* genome has been sequenced [64], and CRISPR-cas9 gene editing has been carried out in a marine gastropod [65]. However, a caveat is that *Biomphalaria* and *Bulinus* spp. snails (but not *Onchomelania* spp.), are hermaphroditic and can self-fertilize, making gene-drive systems for population suppression more challenging, because drives intended to suppress population growth might lead to compensation by the wild-type snails in the form of more asexual reproduction (selfing) [66]. Gene drives that confer schistosome resistance are an alternative strategy, but seem limited in application given that existing resistance genes do not spread to fixation in host snails [67] (presumably due to associated fitness costs of resistance in uninfected snails). Though it is often implied to be highly precise, CRISPR-cas9 gene editing can produce off-target mutations with unpredictable effects, so more work is required to ensure safety of releasing gene-edited snails into the wild [68]. Ethical limitations and methodological hurdles notwithstanding [69], the potential for this new gene-drive technology to revolutionize control for human disease, including schistosomiasis and other vector-borne and environmentally transmitted diseases, is tantalizing, so long as safety, efficacy, and implementation constraints can be surmounted.

Thinking Outside the Box: Traps, Repellants, and Natural Enemies

Attempts to trap and kill snails, or schistosomes emitted from snails, or repel them from humans, have not yet been applied widely in practice, but such 'outside the box' strategies could prove useful if new technologies make them more effective, feasible, or scalable. For instance, snails are attracted to lettuce homogenates (specifically, the amino acids glutamate and proline [70]) and wheat germ cereal [71] which could be used to bait traps. Snails can be repelled by molluscicides [71], or artificial shade [72], and schistosomes emitted from snails can be repelled by topical lipid formulations of N,N-diethyl-meta-toluamide (DEET) applied to exposed skin [73].

Snail predators – particularly crustaceans, fish and birds – have been effective at reducing snail populations in the past, warranting more research to develop and scale-up the use of snail predators for disease control. For example, Louisiana crayfish (*Procambarus clarkii*), introduced to Kenya and Egypt, can reduce snail abundance and therefore human schistosomiasis transmission [3,74,75]. More recently, native river prawns have been proposed as snail-control agents in their native coastal ranges, where human-driven environmental change (e.g., dam building) has reduced prawn numbers [24,32]. Dams are associated with greater increases in human schistosomiasis risk within river prawn native ranges than outside them, suggesting that prawns might have once controlled snail populations [24]. Indeed, reintroducing native river

prawns (*Macrobrachium volenhovenii*) into Senegalese water-access points – where they had been present before the nearby Diama Dam was built [32] – resulted in a reduction in snail density and human schistosomiasis reinfection rates [9]. In theory, prawn ladders designed to help juvenile prawns surmount dams could help restore river prawn migration pathways [76]. Other crustaceans might suppress snails and thus schistosomiasis transmission. For example, the Malaysian river prawn, *Macrobrachium rosenbergii* – in the same genus as the African river prawn – also eats schistosome-hosting snails [77]; unlike the African-native, *M. rosenbergii* is domesticated, and could therefore be deployed as a biological control agent in managed landscapes with the co-benefit of revenue generation through commercial-scale aquaculture [9,31,77].

Some fish eat snails [78,79]. The observation that fish might control snails has inspired efforts to use fish as a biological control tool, with mixed results [80]. However, one snail-eating cichlid, *Trematocranus placodon,* has shown promise [78], as has the African catfish, *Clarias gariepinus* [81].

With respect to birds, non-native, domestic ducks reduced snail density in Zimbabwean ponds, but presented many logistical challenges – including high costs for duck breeding, maintenance, and protection against poaching [82]. Another role for birds might be in the trematodes they carry. Nonschistosome trematodes that use birds as final hosts, such as *Ribeiroia guadeloupensis,* castrate host snails and outcompete schistosomes inside infected snails [83], and other similar trematode species have been investigated for similar applications [84].

Competition with other species can suppress snails or schistosomes. Past schistosomiasis control strategies have been successful in using competitor snails, and this strategy could be revisited for deployment in modern schistosomiasis hotspots (see the 'Looking Back' section). In addition, schistosome species are outcompeted in their snail hosts by other trematode species that produce rediae – jawed reproductive structures that can kill sporocysts [85]. Indeed, many echinostome species, including *Echinostoma* spp. [86,87] as well as *Exorchis* sp. [88], *Cotylurus lutzi* [89], paramphistomoids [90], and others, have been investigated for this purpose. However, other trematode species might facilitate schistosome infection, possibly by reducing the host's immune defenses; evidence for this comes from *Calicophoron microbothrium* [91] and *Zygocotyle lunata* [92]. Such differences must be well understood before deploying trematodes as natural enemies for schistosomiasis control.

'Decoy hosts' – noncompetent snails and other aquatic organisms, such as fish and amphibians – absorb schistosome miracidia without becoming infected, potentially diverting miracidia from competent snail hosts and reducing infected snail prevalence. Though this effect has been observed in laboratory [93] and meso-cosm experiments [94], its success in scaled-up control programs has not yet been demonstrated. The parasites' free-living stages also have predators that consume them directly (such as *Chaetogaster* spp., filter feeders, and small fish [95]); the use of trematode predators in schistosomiasis biological control is beyond the scope of this paper but remains an interesting and relatively unexplored alternative strategy that may – in some instances – complement snail control for schistosomiasis reduction.

Concluding Remarks

'Without snails, there can be no schistosomiasis.' This quote, from the World Health Organization Working Group on Schistosomiasis in 2005[iv] represents a necessary but insufficient assessment. Indeed, where the snail intermediate hosts for schistosome parasites cannot persist, there is no opportunity for schistosomiasis transmission, but even where snails and

Outstanding Questions

Can network analysis of schistosomiasis transmission reveal hotspots and hubs to target for more efficient snail control?

At what spatial scale does schistosomiasis transmission occur? Can understanding transmission improve control (i.e., the spatial extent that must be treated to protect humans using a given water body).

Might CRISPR-cas9 gene editing and gene-drive technologies be a safe and effective way to reduce schistosomiasis-infected snails?

Are molluscicides outdated or are there future formulations that could deliver successful snail control with fewer nontarget effects?

How can natural enemies, repellants, traps, and decoys be used for snail control?

What is the most efficient and synergistic use of preventive chemotherapy and environmental controls, including snail control, in the global fight against schistosomiasis?

Can environmental DNA (eDNA) technology be used to indirectly track snail or schistosome presence and distribution in the environment?

Can optimal control theory contribute to an improved strategy for schistosomiasis elimination?

schistosomes coexist, schistosome transmission might be unsuccessful. Therefore, more ecological research on schistosome-hosting snails and the conditions permissive to schistosome transmission is warranted.

For the past century, snail control has been successful in reducing schistosomiasis transmission in many countries, but has fallen out of favor in the last few decades. Here, we have discussed how both new and old fashioned snail control technologies can be used to reduce the risk of schistosome transmission from snails to humans, but many questions remain unanswered (see Outstanding Questions). We presented some ideas for modernizing, improving, and scaling up snail control, such as spatial targeting, temporal targeting, gene-drive technologies, affordable environmental diagnostics, and 'outside the box' strategies such as traps, repellants, natural enemies, and decoys. The goal of snail control is to reduce transmission. This can be maximized by better synergy between MDA and environmental interventions that affordably slow human reinfection after treatment. A synergistic approach spares drugs and likely improves efficacy, cost effectiveness, and scalability.

Most of the two and a half billion dollars disbursed each year to treat and control neglected tropical diseases [96,97] is directed toward MDA. Although treatment has been effective, control has not, because there is not enough praziquantel to reach all 800 million people at risk today, and drugs, alone, cannot address the environmental components of transmission [98,99]. Coupling drug delivery with snail control has proven effective in the past, and seems the most cost effective option for the future global fight against schistosomiasis [199].

Acknowledgments

The authors thank Lee Marom, Greg Galin, and Elsevier Workshop services for artwork, and John McLaughlin and Andy Chamberlin for useful comments and discussions. SHS, IJJ, and GADL were funded by NSF CNH grant # 1414102, NIH Grant 1R01TW010286-01, a GDP SEED grant from the Freeman Spogli Institute at Stanford University, and a grant from the Bill and Melinda Gates Foundation. Any use of trade, product, or firm names in this publication is for descriptive purposes only and does not imply endorsement by the U.S. government.

Resources

[i] http://apps.who.int/gb/archive/pdf_files/WHA54/ea54r19.pdf

[ii] www.who.int/neglected_diseases/mediacentre/WHA_65.21_Eng.pdf

[iii] www.iucnredlist.org

[iv] http://apps.who.int/iris/bitstream/10665/69482/1/TDR_SWG_07_eng.pdf

References

1. Kajihara, N. and Hirayama, K. (2011) The war against a regional disease in Japan. A history of the eradication of *Schistosomiasis japonica*. *Trop. Med. Health* 39, 3–44
2. Tanaka, H. and Tsuji, M. (1997) From discovery to eradication of schistosomiasis in Japan: 1847–1996. *Int. J. Parasitol.* 27, 1465–1480
3. Sokolow, S.H. *et al.* (2016) Global assessment of schistosomiasis control over the past century shows targeting the snail intermediate host works best. *PLoS Negl. Trop. Dis.* 10, e0004794
4. King, C.H. and Bertsch, D. (2015) Historical perspective: snail control to prevent schistosomiasis. *PLoS Negl. Trop. Dis.* 9, e0003657
5. Gray, D.J. *et al.* (2010) Schistosomiasis elimination: lessons from the past guide the future. *Lancet Infect. Dis.* 10, 733–736
6. Fenwick, A. and Savioli, L. (2011) Schistosomiasis elimination. *Lancet Infect. Dis.* 11, 346 author reply 346–347
7. Bergquist, R. *et al.* (2017) Controlling schistosomiasis with praziquantel: How much longer without a viable alternative? *Infect. Dis. Poverty* 6, 74
8. Engels, D. *et al.* (2002) The global epidemiological situation of schistosomiasis and new approaches to control and research. *Acta Trop.* 82, 139–146
9. Sokolow, S.H. *et al.* (2015) Reduced transmission of human schistosomiasis after restoration of a native river prawn that preys on the snail intermediate host. *Proc. Natl. Acad. Sci. U. S. A.* 112, 9650–9655
10. Rollinson, D. *et al.* (2001) Interactions between intermediate snail hosts of the genus Bulinus and schistosomes of the *Schistosoma haematobium* group. *Parasitology* 123 (Suppl), S245–S260
11. Galinier, R. *et al.* (2017) A multistrain approach to studying the mechanisms underlying compatibility in the interaction between *Biomphalaria glabrata* and *Schistosoma mansoni*. *PLoS Negl. Trop. Dis.* 11, e0005398

12. IUCN (2017) *IUCN Red List of Threatened Species.* http://www.iucnredlist.org
13. Pointier, J. *et al.* (2011) The biological control of the snail hosts of schistosomes: the role of competitor snails and biological invasions. In *Biomphalaria Snails and Larval Trematodes* (Toledo, R., ed.), pp. 215–238, Springer Science+Business Media
14. Rollinson, D. *et al.* (2013) Time to set the agenda for schistosomiasis elimination. *Acta Trop.* 128, 423–440
15. Allan, E.R.O. *et al.* (2017) Schistosome infectivity in the snail, *Biomphalaria glabrata*, is partially dependent on the expression of Grctm6, a Guadeloupe Resistance Complex protein. *PLoS Negl. Trop. Dis.* 11, e0005362
16. McCullough, F.S. *et al.* (1980) Molluscicides in schistosomiasis control. *Bull. World Health Organ.* 58, 681–689
17. Dai, J.R. *et al.* (2008) A novel molluscicidal formulation of niclosamide. *Parasitol. Res.* 103, 405–412
18. Coelho, P. and Caldeira, R.L. (2016) Critical analysis of molluscicide application in schistosomiasis control programs in Brazil. *Infect. Dis. Poverty* 5, 57
19. Li, Y. *et al.* (2014) Multi-targeted therapy of cancer by niclosamide: A new application for an old drug. *Cancer Lett.* 349, 8–14
20. Xu, M. *et al.* (2016) Identification of small-molecule inhibitors of Zika virus infection and induced neural cell death via a drug repurposing screen. *Nat. Med.* 22, 1101–1107
21. Laamrani, H. *et al.* (2000) Evaluation of environmental methods to control snails in an irrigation system in Central Morocco. *Trop. Med. Int. Health* 5, 545–552
22. Incani, R.N. (1987) The Venezuelan experience in the control of schistosomiasis mansoni. *Mem. Inst. Oswaldo Cruz* 82 (Suppl. 4), 89–93
23. al-Madani, A.A. (1990) Schistosomiasis control in Saudi Arabia with special reference to the period 1983–1988. *Public Health* 104, 261–266
24. Sokolow, S.H. *et al.* (2017) Nearly 400 million people are at higher risk of schistosomiasis because dams block the migration of snail-eating river prawns. *Philos. Trans. R. Soc. B Biol. Sci.* 372 (1722), 20160127
25. Steinmann, P. *et al.* (2006) Schistosomiasis and water resources development: systematic review, meta-analysis, and estimates of people at risk. *Lancet Infect. Dis.* 6, 411–425
26. Howarth, F.G. (1991) Environmental impacts of classical biological control. *Annu. Rev. Entomol.* 36, 485–501
27. Bale, J.S. *et al.* (2008) Biological control and sustainable food production. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 363, 761–776
28. Pointier, J.P. and Jourdane, J. (2000) Biological control of the snail hosts of schistosomiasis in areas of low transmission: the example of the Caribbean area. *Acta Trop.* 77, 53–60
29. Ouedraogo, H. *et al.* (2016) Schistosomiasis in school-age children in Burkina Faso after a decade of preventive chemotherapy. *Bull. World Health Organ.* 94, 37–45
30. Swartz, S.J. *et al.* (2015) Infection with schistosome parasite in snails leads to increased predation by prawns: implications for human schistosomiasis control. *J. Exp. Biol.* 218, 3962–3967
31. Sokolow, S.H. *et al.* (2014) Regulation of laboratory populations of snails (*Biomphalaria* and *Bulinus* spp.) by river prawns, *Macrobrachium* spp. (Decapoda Palaemonidae): implications for control of schistosomiasis. *Acta Trop.* 132C, 64–74
32. Alkalay, A.S. *et al.* (2014) The prawn *Macrobrachium vollenhovenii* in the Senegal River basin: towards sustainable restocking of all-male populations for biological control of schistosomiasis. *PLoS Negl. Trop. Dis.* 8, e3060
33. King, C.H. (2010) Parasites and poverty: the case of schistosomiasis. *Acta Trop.* 113, 95–104
34. Garchitorena, A. *et al.* (2017) Disease ecology, health and the environment: a framework to account for ecological and socio-economic drivers in the control of neglected tropical diseases. *Philos. Trans. R. Soc. B Biol. Sci.* 372 (1722), 20160128
35. Chades, I. *et al.* (2011) General rules for managing and surveying networks of pests, diseases, and endangered species. *Proc. Natl. Acad. Sci. U. S. A.* 108, 8323–8328
36. McVinish, R. *et al.* (2016) Limiting the spread of disease through altered migration patterns. *J. Theor. Biol.* 393, 60–66
37. Mari, L. *et al.* (2017) Big-data-driven modeling unveils country-wide drivers of endemic schistosomiasis. *Sci. Rep.* 7, 489
38. King, C.H. (2009) Toward the elimination of schistosomiasis. *N. Engl. J. Med.* 360, 106–109
39. Gurarie, D. and King, C.H. (2005) Heterogeneous model of schistosomiasis transmission and long-term control: the combined influence of spatial variation and age-dependent factors on optimal allocation of drug therapy. *Parasitology* 130, 49–65
40. Brown, D.S. (1994) *Freshwater Snails of Africa and Their Medical Importance,* Taylor & Francis
41. Clements, A. *et al.* (2009) A comparative study of the spatial distribution of schistosomiasis in Mali in 1984–1989 and 2004–2006. *PLoS Negl. Trop. Dis.* 3 (5), e431
42. Kloos, H. *et al.* (1983) Water contact behavior and schistosomiasis in an upper Egyptian village. *Soc. Sci. Med.* 17, 545–562
43. Babiker, A. *et al.* (1985) Focality and seasonality of Schistosoma mansoni transmission in the Gezira Irrigated Area, Sudan. *J. Trop. Med. Hyg.* 88, 57–63
44. Woolhouse, M.E. and Chandiwana, S.K. (1989) Spatial and temporal heterogeneity in the population dynamics of *Bulinus globosus* and *Biomphalaria pfeifferi* and in the epidemiology of their infection with schistosomes. *Parasitology* 98, 21–34
45. Muhoho, N.D. *et al.* (1997) Cercarial density in the river of an endemic area of schistosomiasis haematobia in Kenya. *Am. J. Trop. Med. Hyg.* 57, 162–167
46. Kuris, A.M. *et al.* (2008) Ecosystem energetic implications of parasite and free-living biomass in three estuaries. *Nature* 454, 515–518
47. Beale, C.M. and Lennon, J.J. (2012) Incorporating uncertainty in predictive species distribution modelling. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 367, 247–258
48. Wardrop, N.A. *et al.* (2014) Interpreting predictive maps of disease: highlighting the pitfalls of distribution models in epidemiology. *Geospat. Health* 9, 237–246
49. Stensgaard, A.S. *et al.* (2006) Modeling freshwater snail habitat suitability and areas of potential snail-borne disease transmission in Uganda. *Geospat. Health* 1, 93–104
50. Walz, Y. *et al.* (2015) Use of an ecologically relevant modelling approach to improve remote sensing-based schistosomiasis risk profiling. *Geospat. Health* 10, 398
51. Walz, Y. *et al.* (2015) Risk profiling of schistosomiasis using remote sensing: approaches, challenges and outlook. *Parasites Vectors* 8, 163
52. Perez-Saez, J. *et al.* (2016) Hydrology and density feedbacks control the ecology of intermediate hosts of schistosomiasis across habitats in seasonal climates. *Proc. Natl. Acad. Sci. U. S. A.* 113, 6427–6432
53. Walz, Y. *et al.* (2015) Modeling and validation of environmental suitability for schistosomiasis transmission using remote sensing. *PLoS Negl. Trop. Dis.* 9, e0004217
54. Bass, D. *et al.* (2015) Diverse applications of environmental DNA methods in parasitology. *Trends Parasitol.* 31, 499–513
55. Thomsen, P.F. and Willerslev, E. (2015) Environmental DNA – An emerging tool in conservation for monitoring past and present biodiversity. *Biol. Conserv.* 183, 4–18
56. Ciddio, M. *et al.* (2017) The spatial spread of schistosomiasis: A multidemensional network model applied to Saint-Louis region, Senegal. *Adv. Water Resour.* 108, 406–415
57. Lee, E.B. and Markus, L. (1967) *Foundations of Optimal Control Theory,* John Wiley
58. Lenhart, S. and Workman, J.T. (2007) *Optimal Control Applied to Biological Models,* Chapman & Hall/CRC
59. Sturrock, R.F. *et al.* (2001) Seasonality in the transmission of schistosomiasis and in populations of its snail intermediate hosts

in and around a sugar irrigation scheme at Richard Toll, Senegal. *Parasitology* 123, S77–S89

60. Kloos, H. and McCullough, F. (1982) Molluscicidal effects of eucalyptus. *Vet. Rec.* 111, 148
61. Chimbari, M.J. (2012) Enhancing schistosomiasis control strategy for Zimbabwe: building on past experiences. *J. Parasitol. Res.* 2012, 353768
62. Windbichler, N. *et al.* (2011) A synthetic homing endonuclease-based gene drive system in the human malaria mosquito. *Nature* 473, 212–215
63. Hammond, A. *et al.* (2016) A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector *Anopheles gambiae*. *Nat. Biotechnol.* 34, 78–83
64. Adema, C.M. *et al.* (2017) Whole genome analysis of a schistosomiasis-transmitting freshwater snail. *Nat. Commun.* 8, 15451
65. Perry, K.J. and Henry, J.Q. (2015) CRISPR/Cas9-mediated genome modification in the mollusc, *Crepidula fornicata*. *Genesis* 53 (2), 237–244
66. Esvelt, K.M. *et al.* (2014) Concerning RNA-guided gene drives for the alteration of wild populations. *Elife* Published online July 17, 2014. http://dx.doi.org/10.7554/eLife.03401
67. Allan, E.R. *et al.* (2017) Schistosome infectivity in the snail, *Biomphalaria glabrata*, is partially dependent on the expression of Grctm6, a Guadeloupe Resistance Complex protein. *PLoS Negl. Trop. Dis.* 11, e0005362
68. Schaefer, K.A. *et al.* (2017) Unexpected mutations after CRISPR-Cas9 editing in vivo. *Nat. Methods* 14, 547–548
69. Baltimore, D. *et al.* (2015) Biotechnology. A prudent path forward for genomic engineering and germline gene modification. *Science* 348, 36–38
70. Uhazy, L.S. *et al.* (1978) *Schistosoma mansoni*: identification of chemicals that attract or trap its snail vector, *Biomphalaria glabrata*. *Science* 201, 924–926
71. Etges, F.J. and Gilbertson, D.E. (1966) Repellent action of some chemical molluscicides on schistosome vector snails. *Am. J. Trop. Med. Hyg.* 15, 618–624
72. Loreau, M. and Baluku, B. (1991) Shade as a means of ecological control of Biomphalaria pfeifferi. *Ann. Trop. Med. Parasitol.* 85, 443–446
73. Ramaswamy, K. *et al.* (2003) Topical application of DEET for schistosomiasis. *Trends Parasitol.* 19, 551–555
74. Mkoji, G.M. *et al.* (1999) Impact of the crayfish *Procambarus clarkii* on *Schistosoma haematobium* transmission in Kenya. *Am. J. Trop. Med. Hyg.* 61, 751–759
75. Khalil, M. and Sleem, S.H. (2011) Can the freshwater crayfish eradicate schistosomiasis in Egypt and Africa? *J. Am. Sci.* 7, 457–462
76. Benstead, J. (1999) Effects of a low-head dam and water abstraction on migratory tropical stream biota. *Ecol. Appl.* 9, 656–668
77. Roberts, J.K. and Kuris, A.M. (1990) Predation and control of laboratory populations of the snail *Biomphalaria glabrata* by the freshwater prawn *Macrobrachium rosenbergii*. *Ann. Trop. Med. Parasitol.* 84, 401–412
78. Evers, B.N. *et al.* (2006) The schistosome intermediate host, *Bulinus nyassanus*, is a 'preferred' food for the cichlid fish, *Trematocranus placodon*, at Cape Maclear, Lake Malawi. *Ann. Trop. Med. Parasitol.* 100, 75–85
79. Madsen, H. and Stauffer, J.R. (2011) Density of *Trematocranus placodon* (Pisces: Cichlidae): a predictor of density of the schistosome intermediate host, *Bulinus nyassanus* (Gastropoda: Planorbidae), in Lake Malawi. *Ecohealth* 8, 177–189
80. Slootweg, R. *et al.* (1994) The biological control of intermediate hosts of schistosomiasis by fish. *Rev. Fish Biol. Fish.* 4, 67–90
81. Gashaw, F. *et al.* (2008) Assessment of the potential of competitor snails and African catfish (*Clarias gariepinus*) as biocontrol agents against snail hosts transmitting schistosomiasis. *Trans. R. Soc. Trop. Med. Hyg.* 102, 774–779
82. Ndlela, B. and Chimbari, M.J. (2000) A preliminary assessment of the potential of the Muschovy duck (*Cairina maschata*) as a biocontrol agent of schistosomiasis intermediate host snails. *Cent. Afr. J. Med.* 46, 271–275
83. Nassi, H. *et al.* (1979) Evaluation of a trial to control *Biomphalaria glabrata* in Guadeloupe by using a sterilizing trematode (author's transl). *Ann. Parasitol. Hum. Comp.* 54, 185–192 (in French)
84. Pointier, J.P. and Jourdane, J. (2000) Biological control of the snail hosts of schistosomiasis in areas of low transmission: the example of the Caribbean area. *Acta Trop.* 77, 53–60
85. Hechinger, R.F. *et al.* (2011) Social organization in a flatworm: trematode parasites form soldier and reproductive castes. *Proc. Biol. Sci.* 278, 656–665
86. Jourdane, J. *et al.* (1990) Influence of intramolluscan larval stages of *Echinostoma liei* on the infectivity of *Schistosoma mansoni* cercariae. *J. Helminthol.* 64, 71–74
87. Jourdane, J. and Mounkassa, J.B. (1986) Topographic shifting of primary sporocysts of *Schistosoma mansoni* in *Biomphalaria pfeifferi* as a result of coinfection with *Echinostoma caproni*. *J. Invertebr. Pathol.* 48, 269–274
88. Tang, C.T. *et al.* (2009) Development of larval *Schistosoma japonicum* blocked in *Oncomelania hupensis* by pre-infection with larval *Exorchis* sp. *J. Parasitol.* 95, 1321–1325
89. Basch, P.F. (1969) *Cotylurus lutzi* sp. n. (Trematoda: Strigeidae) and its life cycle. *J. Parasitol.* 55, 527–539
90. Laidemitt, M.R. *et al.* (2017) Loads of trematodes: discovering hidden diversity of paramphistomoids in Kenyan ruminants. *Parasitology* 144, 131–147
91. Southgate, V.R. *et al.* (1989) The influence of *Calicophoron microbothrium* on the susceptibility of *Bulinus tropicus* to *Schistosoma bovis*. *Parasitol. Res.* 75, 381–391
92. Spatz, L. *et al.* (2012) Susceptibility of wild populations of *Biomphalaria* spp. from neotropical South America to *Schistosoma mansoni* and interference of *Zygocotyle lunata*. *J. Parasitol.* 98, 1291–1295
93. Johnson, P.T. *et al.* (2009) Community diversity reduces *Schistosoma mansoni* transmission, host pathology and human infection risk. *Proc. Biol. Sci.* 276, 1657–1663
94. Upatham, E.S. (1972) Interference by unsusceptible aquatic animals with the capacity of the miracidia of *Schistosoma mansoni* Sambon to infect *Biomphalaria glabrata* (Say) under field-simulated conditions in St Lucia, West Indies. *J. Helminthol.* 46, 277–283
95. Hopkins, S.R. *et al.* (2013) Parasite predators exhibit a rapid numerical response to increased parasite abundance and reduce transmission to hosts. *Ecol. Evol.* 3, 4427–4438
96. Molyneux, D.H. (2012) The 'Neglected Tropical Diseases': now a brand identity; responsibilities, context and promise. *Parasites Vectors* 5, 23
97. Bergquist, R. *et al.* (2008) Trick or treat: the role of vaccines in integrated schistosomiasis control. *PLoS Negl. Trop. Dis.* 2 (6), e244
98. Remais, J.V. and Eisenberg, J.N. (2012) Balance between clinical and environmental responses to infectious diseases. *Lancet* 379, 1457–1459
99. Secor, W.E. and Montgomery, S.P. (2015) Something old, something new: is praziquantel enough for schistosomiasis control? *Future Med. Chem.* 7, 681–684
100. Arfaa, F. *et al.* (1970) Progress towards the control of bilharziasis in Iran. *Trans. R. Soc. Trop. Med. Hyg.* 64, 912–917
101. El-Halawani, A. (1978) Evaluation of molluscicidal control of schistosomiasis in the Middle East. In *Proceedings of the International Conference on Schistosomiasis* (Abdallah, A., ed.), pp. 349–357, Egypt Ministry of Health
102. Jordan, P. (2000) From katayama to the Dakhla Oasis: the beginning of epidemiology and control of bilharzia. *Acta Trop.* 77, 9–40
103. Ebisawa, I. (1998) Epidemiology and eradication of *Schistosomiasis japonica* in Japan. *J. Travel Med.* 5, 33–35

104. Pointier, J.-P. (2001) Invading freshwater snails and biological control in Martinique Island, French West Indies. *Mem. Inst. Oswaldo Cruz* 96 (Suppl), 67–74
105. Dhunputh, J. (1994) Progress in the control of schistosomiasis in Mauritius. *Trans. R. Soc. Trop. Med. Hyg.* 88, 507–509
106. Amarir, F. *et al.* (2011) National serologic survey of *Haematobium schistosomiasis* in Morocco: evidence for elimination. *Am. J. Trop. Med. Hyg.* 84, 15–19
107. Barkia, H. *et al.* (2014) Contribution of mobile teams to efforts to eliminate schistosomiasis at *Schistosoma haematobium* in Morocco – narrative review article. *Iran. J. Public Health* 43, 1167–1175
108. Boelee, E. and Laamrani, H. (2004) Environmental control of schistosomiasis through community participation in a Moroccan oasis. *Trop. Med. Int. Health* 9, 997–1004
109. Khallaayoune, K. and Laamrani, H. (1992) Seasonal patterns in the transmission of *Schistosoma haematobium* in Attaouia, Morocco. *J. Helminthol.* 66, 89–95
110. Laamrani, H. *et al.* (2000) New challenges in schistosomiasis control in Morocco. *Acta Trop.* 77, 61–67
111. Laamrani, H. *et al.* (2000) *Schistosoma haematobium* in Morocco: moving from control to elimination. *Parasitol. Today* 16, 257–260
112. Nuttall, I. *et al.* (1994) GIS Management tools for the control of tropical diseases: applications in Botswana, Senegal, and Morocco. In *GIS for Health and the Environment* (De Savigny, D. and Wijeyaratne, P., eds), pp. 59–73, International Development Research Center
113. Haddock, K.C. (1981) Control of schistosomiasis: the Puerto Rican experience. *Soc. Sci. Med. D* 15, 501–514
114. Rey, L. *et al.* (1982) Schistosomiasis in Tunisia. Results after 10 years of the endemics control. *Bull. Soc. Pathol. Exotique Ses Filiales* 75, 505–522
115. Al-Madani, A.A. (1990) Schistosomiasis control in Saudi Arabia with special reference to the period 1983–1988. *Public Health* 104, 261–266
116. Barakat, R. *et al.* (2014) Human schistosomiasis in the Middle East and North Africa Region. In *Neglected Tropical Diseases – Middle East and North Africa* (McDowell, M.A. and Rafati, S., eds), pp. 23–57, Springer
117. Hotez, P.J. *et al.* (2012) Neglected tropical diseases of the Middle East and North Africa: review of their prevalence, distribution, and opportunities for control. *PLoS Negl. Trop. Dis.* 6, e1475
118. Lotfy, W.M. and Alsaqabi, S.M. (2010) Human schistosomiasis in the Kingdom of Saudi Arabia: A review. *J. Med. Res. Inst.* 31, 1–6
119. WHO (2007) Inter-country meeting on strategies to eliminate schistosomiasis from the Eastern Mediterranean Region. In *World Health Organization of the EMR*. World Health Organization
120. Youssef, A.R. *et al.* (1998) Schistosomiasis in Saudi Arabia, Egypt, and Iraq. *Urology* 51, 170–174
121. Izhar, A. *et al.* (2002) Recent situation of schistosomiasis in Indonesia. *Acta Trop.* 82, 283–288
122. Baquir, H. (1974) Letter: Present status of Hor Rajab bilharziasis control project Iraq 15, WHO-TA. *Trans. R. Soc. Trop. Med. Hyg.* 68, 345
123. Lotfy, W.M. (2009) Human schistosomiasis in Egypt: Historical review, assessment of the current picture and prediction of the future trends. *J. Med. Res. Inst.* 30, 1–7
124. Khalil, M. and Sleem, S.H. (2011) Can the freshwater crayfish eradicate schistosomiasis in Egypt and Africa? *J. Am. Sci.* 7, 457–462
125. Farooq, M. *et al.* (1966) The effect of area-wide snail control on the endemicity of bilharziasis in Egypt. *Bull. World Health Organ.* 35, 369–375
126. El-Khoby, T. *et al.* (2000) The epidemiology of schistosomiasis in Egypt: Summary findings in nine governorates. *Am. J. Trop. Med. Hyg.* 62, 88–99
127. El Khoby, T. *et al.* (1998) The USAID/Government of Egypt's Schistosomiasis Research Project (SRP). *Parasitol. Today* 14, 92–96
128. Barakat, R.M.R.R. (2013) Epidemiology of schistosomiasis in Egypt: Travel through time: Review. *Cairo Univ. J. Adv. Res.* 4, 425–432
129. Zhou, X.-N. *et al.* (2005) The public health significance and control of schistosomiasis in Chinan – then and now. *Acta Trop.* 96, 97–105
130. Xianyi, C. *et al.* (2005) Policy and practice schistosomiasis control in China: The impact of a 10-year World Bank Loan Project (1992–2001). *Bull. World Health Organ.* 83, 43–48
131. de Noya, B.A. *et al.* (1992) New approaches for the control and eradication of schistosomiasis in Venezuela. *Mem. Inst. Oswaldo Cruz* 87, 227–231
132. De Noya, B.A. *et al.* (1999) The last fifteen years of schistosomiasis in Venezuela: Features and evolution. *Mem. Inst. Oswaldo Cruz* 94, 139–146
133. Pointier, J.P.P. and Jourdane, J. (2000) Biological control of the snail hosts of schistosomiasis in areas of low transmission: the example of the Caribbean area. *Acta Trop.* 77, 53–60
134. Bergquist, R. and Tanner, M. (2010) Controlling schistosomiasis in Southeast Asia: a tale of two countries. *Adv. Parasitol.* 72, 109–144
135. Blas, B.L. *et al.* (2004) The schistosomiasis problem in the Philippines: a review. *Parasitol. Int.* 53, 127–134
136. Jordan, P. (1985) *Schistosomiasis: The St Lucia Project,* Cambridge University Press
137. Pointier, J.P. and Théron, A. (1995) Ecology and control of the snail intermediate hosts of trematodes in an heterogenous environment: the *Biomphalaria glabrata* model in the insular focus of. *Res. Rev. Parasitol.* 55, 121–133
138. Stothard, J.R. *et al.* (2009) The epidemiology and control of urinary schistosomiasis and soil-transmitted helminthiasis in schoolchildren on Unguja Island, Zanzibar. *Trans. R. Soc. Trop. Med. Hyg.* 103, 1031–1044
139. Knopp, S. *et al.* (2013) From morbidity control to transmission control: time to change tactics against helminths on Unguja Island, Zanzibar. *Acta Trop.* 128, 412–422
140. Knopp, S. *et al.* (2012) Study and implementation of urogenital schistosomiasis elimination in Zanzibar (Unguja and Pemba islands) using an integrated multidisciplinary approach. *BMC Public Health* 12, 930
141. Urbani, C. *et al.* (2002) Epidemiology and control of mekongi schistosomiasis. *Acta Trop.* 82, 157–168
142. Sornmani, S. (1976) Current status of schistosomiasis in Laos, Thailand and Malaysia. *Southeast Asian J. Trop. Med. Public Health* 7, 149–154
143. Ohmae, H. *et al.* (2004) Schistosomiasis mekongi: From discovery to control. *Parasitol. Int.* 53, 135–142
144. Sinuon, M. *et al.* (2007) Control of *Schistosoma mekongi* in Cambodia: results of eight years of control activities in the two endemic provinces. *Trans. R. Soc. Trop. Med. Hyg.* 101, 34–39
145. Coura, J.R. and Amaral, R.S. (2004) Epidemiological and control aspects of schistosomiasis in Brazilian endemic areas. *Mem. Inst. Oswaldo Cruz* 99 (Suppl. 1), 13–19
146. Barbosa, F.S. *et al.* (1971) Control of *Schistosomiasis mansoni* in a small Northeast Brazilian community. *Trans. R. Soc. Trop. Med. Hyg.* 65, 206–213
147. Amaral, R.S.d *et al.* (2006) An analysis of the impact of the Schistosomiasis Control Programme in Brazil. *Mem. Inst. Oswaldo Cruz* 101 (Suppl. 1), 79–85
148. Almeida Machado, P. (1982) The Brazilian program for schistosomiasis control, 1975–1979. *Am. J. Trop. Med. Hyg.* 31, 76–86
149. Ndayishimiye, O. *et al.* (2014) Control of neglected tropical diseases in Burundi: partnerships, achievements, challenges,

and lessons learned after four years of programme implementation. *PLoS Negl. Trop. Dis.* 8, e2684

150. Gryseels, B. (1991) The epidemiology of schistosomiasis in Burundi and its consequences for control. *Trans. R. Soc. Trop. Med. Hyg.* 85, 626–633
151. Engels, D. *et al.* (1993) *Schistosomiasis mansoni* in Burundi: Progress in its control since 1985. *Bull. World Health Organ.* 71, 207–214
152. Linehan, M. *et al.* (2011) Integrated implementation of programs targeting neglected tropical diseases through preventive chemotherapy: proving the feasibility at national scale. *Am. J. Trop. Med. Hyg.* 84, 5–14
153. Ollivier, G. *et al.* (1998) La schistosomose intestinale à *Schistosoma mansoni* à Madagascar: extension et focalisation de l'endémie. *Parasitologie* 1966, 1–5
154. Mccullough, F.S. *et al.* (1980) Molluscicides in schistosomiasis control. *Bull. World Health Organ.* 58, 681–689
155. Ruxin, J. and Negin, J. (2012) Removing the neglect from neglected tropical diseases: the Rwandan experience 2008–2010. *Glob. Public Health* 7, 812–822
156. Locketz, L. (1976) Health education in rural Surinam: use of videotape in a national campaign against schistosomiasis. *Bull. Pan Am. Health Organ.* 10, 219–226
157. Hotez, P.J. *et al.* (2008) The neglected tropical diseases of Latin America and the Caribbean: a review of disease burden and distribution and a roadmap for control and elimination. *PLoS Negl. Trop. Dis.* 2, e300
158. Touré, S. *et al.* (2008) Two-year impact of single praziquantel treatment on infection in the national control programme on schistosomiasis in Burkina Faso. *Bull. World Health Organ.* 86, 780–788
159. Poda, J.N. *et al.* (2004) Schistosomiasis endemic in Burkina Faso. *Bull. Soc. Pathol. Exot.* 97, 47–52
160. Fenwick, A. *et al.* (2006) Implementation of human schistosomiasis control: Challenges and prospects. *Adv. Parasitol.* 61, 567–622
161. Mazigo, H.D. *et al.* (2012) Epidemiology and control of human schistosomiasis in Tanzania. *Parasites Vectors* 5, 274
162. Moné, H. *et al.* (2010) Human schistosomiasis in the Economic Community of West African States. *Adv. Parasitol.* 71, 33–91
163. Kabatereine, N.B. *et al.* (2004) Epidemiology and geography of *Schistosoma mansoni* in Uganda: Implications for planning control. *Trop. Med. Int. Health* 9, 372–380
164. Landoure, A. *et al.* (2012) Significantly reduced intensity of infection but persistent prevalence of schistosomiasis in a highly endemic region in Mali after repeated treatment. *PLoS Negl. Trop. Dis.* 6, e1774
165. Sesay, S. *et al.* (2014) *Schistosoma mansoni* infection after three years of mass drug administration in Sierra Leone. *Parasites Vectors* 7, 14
166. Hodges, M. *et al.* (2011) Improved mapping strategy to better inform policy on the control of schistosomiasis and soil-transmitted helminthiasis in Sierra Leone. *Parasites Vectors* 4, 97
167. Samuels, A.M. *et al.* (2012) *Schistosoma mansoni* morbidity among school-aged children: A SCORE Project in Kenya. *Am. J. Trop. Med. Hyg.* 87, 874–882
168. Dabo, A. *et al.* (2000) Reinfection with *Schistosoma haematobium* and *mansoni* despite repeated praziquantel office treatment in Niger, Mali. *Med. Trop. (Mars.)* 60 (4), 351–355
169. Fenwick, A. *et al.* (2009) The Schistosomiasis Control Initiative (SCI): rationale, development and implementation from 2002–2008. *Parasitology* 136, 1719–1730
170. Garba, A. *et al.* (2006) Implementation of national schistosomiasis control programmes in West Africa. *Trends Parasitol.* 22, 322–326
171. Leslie, J. *et al.* (2011) Schistosomiasis and soil-transmitted helminth control in Niger: cost effectiveness of school based and community distributed mass drug administration [corrected]. *PLoS Negl. Trop. Dis.* 5, e1326
172. Oshish, A. *et al.* (2011) Towards nationwide control of schistosomiasis in Yemen: a pilot project to expand treatment to the whole community. *Trans. R. Soc. Trop. Med. Hyg.* 105, 617–627
173. Madsen, H. *et al.* (2011) Schistosomiasis in Lake Malaŵi villages. *EcoHealth* 8, 163–176
174. Stauffer, J.R. *et al.* (1997) Controlling vectors and hosts of parasitic diseases using fishes. *Bioscience* 47, 41–49
175. Stauffer, J.R. *et al.* (2006) Schistosomiasis in Lake Malawi: Relationship of fish and intermediate host density to prevalence of human infection. *EcoHealth* 3, 22–27
176. Wolff, T. and Malewezi, J.G. (1989) Organization and decentralization of the Malawi National Bilharzia Control Programme. *Trop. Med. Parasitol.* 40, 201–204
177. Agbo, K. *et al.* (1999) Prevalence des schistosomoses au Togo etude transversale realisee en milieu scolaire. *Med. Trop.* 59, 51–54
178. Kabatereine, N.B. *et al.* (2006) The control of schistosomiasis and soil-transmitted helminths in East Africa. *Trends Parasitol.* 22 (7), 332–339
179. Fenwick, A. (2011) The control of schistosomiasis in Africa and the evaluation of integrated control of neglected tropical diseases in Africa. Grant ID# 13122 and 36202 edn, Bill & Melinda Gates Foundation
180. Tchuente, L.A. *et al.* (2013) Mapping of schistosomiasis and soil-transmitted helminthiasis in the regions of Centre, East and West Cameroon. *PLoS Negl. Trop. Dis.* 6, e1553
181. Maseko, T.S. *et al.* (2016) Schistosomiasis knowledge, attitude, practices, and associated factors among primary school children in the Siphofaneni area in the Lowveld of Swaziland. *J. Microbiol. Immunol. Infect.* Published online January 11, 2016. http://dx.doi.org/10.1016/j.jmii.2015.12.003
182. Huyse, T. *et al.* (2013) Regular treatments of praziquantel do not impact on the genetic make-up of *Schistosoma mansoni* in Northern Senegal. *Infect. Genet. Evol.* 18, 100–105
183. el Gaddal, A.A. (1989) Control of schistosomiasis in the Gezira. *Mem. Inst. Oswaldo Cruz* 84 (Suppl. 1), 117–123
184. el Gaddal, A.A. (1985) The Blue Nile Health Project: a comprehensive approach to the prevention and control of water-associated diseases in irrigated schemes of the Sudan. *J. Trop. Med. Hyg.* 88, 47–56
185. El-Nagar, H. (1958) Control of schistosomiasis in the Gezira, Sudan. *J. Trop. Med. Hyg.* 61, 231–235
186. Finn, T.P. *et al.* (2012) Integrated rapid mapping of neglected tropical diseases in three States of South Sudan: survey findings and treatment needs. *PLoS One* 7, e52789
187. Humaida, S. *et al.* (2011) Schistosomiasis: epidemiology and burden of disease in the Sudan. *Sudan Med. J.* 47, 63–68
188. Ault, S.K. (1994) Environmental management: a re-emerging vector control strategy. *Am. J. Trop. Med. Hyg.* 50, 35–49
189. Olivier, L. and Schneidermann, M. (1956) A method for estimating the density of aquatic snail populations. *Exp. Parasitol.* 5, 109–117
190. Hairston, N.G. (1961) Suggestions regarding some problems in the evaluation of molluscicides in the field. *Bull. World Health Organ.* 25, 731–737
191. Theron, A. (1986) Cercariometry and the epidemiology of schistosomiasis. *Parasitol. Today* 2, 61–63
192. Hung, Y.W. and Remais, J. (2008) Quantitative detection of Schistosoma japonicum cercariae in water by real-time PCR. *PLoS Negl. Trop. Dis.* 2, e337
193. Yang, K. *et al.* (2013) Spatio-temporal analysis to identify determinants of *Oncomelania hupensis* infection with *Schistosoma japonicum* in Jiangsu province, China. *Parasites Vectors* 6, 138
194. Sturrock, R.F. (1986) Snail collection to detect schistosome transmission sites. *Parasitol. Today* 2, 59–61
195. Aoki, Y. *et al.* (2003) Cercariometry for detection of transmission sites for schistosomiasis. *Parasitol. Int.* 52, 403–408

196. Gryseels, B. and Nkulikyinka, L. (1988) The distribution of *Schistosoma mansoni* in the Rusizi plain (Burundi). *Ann. Trop. Med. Parasitol.* 82, 581–590

197. Zhou, Y.B. *et al.* (2016) Multi-host model and threshold of intermediate host Oncomelania snail density for eliminating schistosomiasis transmission in China. *Sci. Rep.* 6, 31089

198. Rollinson, D. *et al.* (2009) Genetic diversity of schistosomes and snails: implications for control. *Parasitology* 136, 1801–1811

199. Lo, NC., Gurarie, D, Yoon, N, Coulibaly, JT, Bendavid, E, Andrews, JR, King, CH. Snail control to achieve disease control targets for schistosomiasis: a cost-effectiveness modeling study. PNAS (in press).