RTI Press

Research Report

March 2017

New Tools for the Schistosomiasis Elimination Toolbox: Barriers and Opportunities for the Development of a Topical Cercarial Anti-Penetrant

Philip W. Downs, Natasha Massoudi, Anna Dick, Achille Kabore, Ginger Rothrock, and Bruce Blough

RTI INTERNATIONAL

RTI Press publication RR-0029-1703

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Suggested Citation

Downs, P.W., Massoudi, N., Dick, A., Kabore, A., Rothrock, G., and Blough, B. (2017). *New Tools for the Schistosomiasis Elimination Toolbox: Barriers and Opportunities for the Development of a Topical Cercarial Anti-Penetrant*. RTI Press Publication No. RR-0029-1703. Research Triangle Park, NC: RTI Press. https://doi.org/10.3768/rtipress.2017.rr.0029.1703

This publication is part of the RTI Press Research Reports series.

RTI International
3040 East Cornwallis Road
PO Box 12194
Research Triangle Park, NC
27709-2194 USA

Tel: +1.919.541.6000
E-mail: rtipress@rti.org
Website: www.rti.org

Cover photo: Andrea Petersen.

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About the Authors

Philip W. Downs, DrPh, MPH, is a senior manager of health policy on neglected tropical diseases in RTI International's Global Health division. He served as study coordinator for this study.

Natasha Massoudi, MPH, an independent consultant, conducted the literature review and interviewed key informants.

Anna Dick, MPH, is a project operations manager with the division of International Education and advised on public/private partnerships.

Achille Kabore, MD, also a senior manager of RTI's Global Health division, is a schistosomiasis control expert and technical advisor on neglected tropical diseases.

Ginger Rothrock, PhD, directs the chemistry group in RTI International's Industrial Technologies division. For this project she advised on regulations for new product development.

Bruce Blough, PhD, is a senior researcher in RTI's Discovery Science Technology division and served as a study advisor.

Acknowledgments

This study was supported by internal RTI funding.

Abstract

Schistosomiasis is a neglected tropical disease (NTD) affecting about 260 million people worldwide. Elimination of schistosomiasis remains a challenge because of high reinfection rates and limitations of current treatment guidelines and disease control interventions. Despite over 70 years of research on *Schistosome cercariae* anti-penetrants, a personal protective product (PPP) remains elusive for the prevention of schistosomiasis. In this paper we explore perceptions of topical PPPs to identify potential opportunities and barriers in the development, promotion, and use as a tool to control and prevent schistosomiasis.

Results from key informant interviews suggest that despite recognized benefits of a cercarial anti-penetrant, translation of research into a practical PPP for endemic areas is hindered by two critical issues: (1) minimal available evidence to demonstrate effective and practical use of topically applied products in community-based settings and (2) limitations of current business models to sustain product availability among high-risk groups in low-income settings. Additionally, introduction of a PPP would require an intensive behavioral change communication strategy to reinforce and enable routine use of the product.

The potential additive impact of a PPP on reducing point of source infections, in combination with a comprehensive elimination strategy that includes preventive drug treatment, snail control, and improved water and sanitation, may still present an effective strategy to reduce moderate to high intensity of infection among high-risk groups, but requires additional translational research and business model development.

Background

Schistosomiasis is a neglected tropical disease (NTD) that affects approximately 260 million people. In fact, a total of 700 million people, or more than 10 percent of the world's population, are at immediate risk for infection. Schistosomiasis is caused by schistosomes, parasitic flatworms commonly known as blood-flukes. Disease in humans is primarily caused by three species of schistosomes: *Schistosoma mansoni, S. haematobium,* and *S. japonicum.* Sources of fresh water, such as rivers and lakes, become contaminated with schistosome eggs when infected people urinate or defecate in or near the water. Eggs hatch into free-swimming larva (miracidia), which, if they penetrate certain species of freshwater or amphibious snails, develop and multiply into schistosome cercariae (larvae). Cercariae emerging from snails can survive for approximately 48 hours in the water (Grimes et al., 2015) and within seconds can penetrate the exposed skin of a person wading, swimming, bathing, or washing in the contaminated water.

Cercariae then migrate through the person's circulatory system to intestinal blood vessels, where they mature into adult worms. The adult worms then migrate to and live in very small blood vessels (venules)—the mesenteric venules (*S. mansoni* and *S. japonicum*) or the vesicular venules (*S. haematobium*). After mating, mature female worms produce between 200 and 2,000 eggs per day over an average of 5 years, depending on species (Kini, Dayoub, Raja, Pickering, & Thong, 2009). Only about half the eggs produced are excreted in the affected person's feces or urine. The remaining eggs become trapped in body tissues, causing major inflammation and cellular damage. This includes blood in urine and feces, periportal fibrosis and portal hypertension, bladder cancer, kidney problems, diarrhea, anemia, tiredness, and abdominal pain.

Women infected with *S. haematobium* may develop lesions of the cervix and vagina, vaginal bleeding, and pain during sexual intercourse (Kjetland, Leutscher, & Ndhlovu, 2012). Studies have shown that female genital schistosomiasis is a risk factor for HIV transmission to women (Mbabazi et al., 2011; Secor, 2006). Infected men may develop long-term or irreversible consequences, including infertility. Most people have no symptoms when they are first infected, except for minor fever and chills typically occurring within 2 months.

In 2012, a resolution by the World Health Assembly (Number 65.21) recommended that the World Health Organization (WHO) develop guidelines for initiating schistosomiasis elimination campaigns and that it elaborate a process to evaluate and certify the elimination of transmission (WHO, 2012). Elimination of schistosomiasis remains a challenge because of high reinfection rates in heavily infected communities and the limitations of current disease control strategies. The development of new complementary tools and strategies for the control of schistosomiasis remains of interest to a broad range of stakeholders.

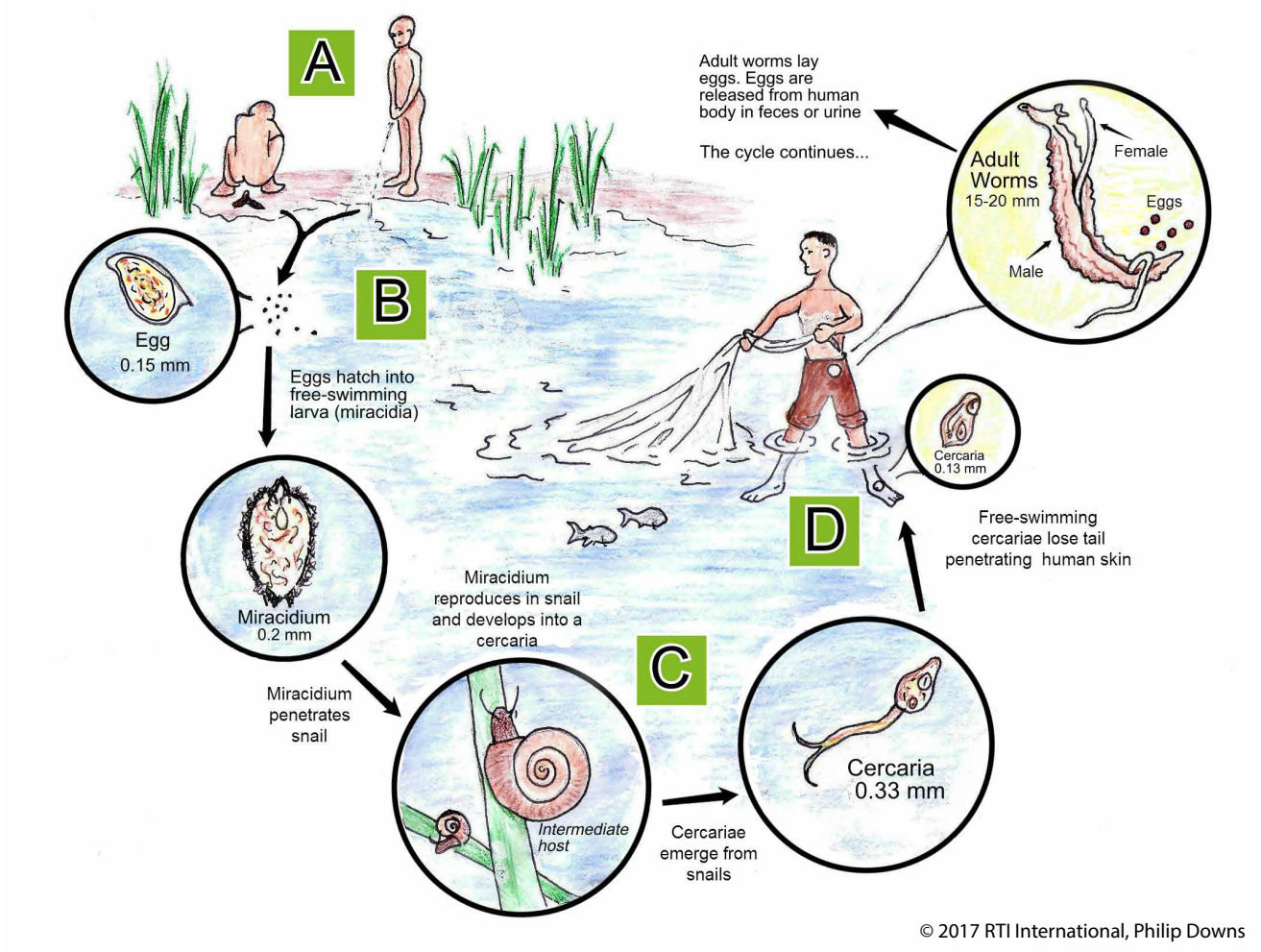
Figure 1 (following page) shows points in the disease transmission cycle where the spread of infection can be reduced: (A) treatment of human hosts, (B) environmental improvements, (C) snail control, and (D) point of contact restrictions. These intervention points are described further below.

A. Reduce the prevalence and intensity of infection within the population. Infected individuals and at-risk populations can be treated through mass distribution of the antiparasitic drug praziquantel (PZQ). Preventative chemotherapy with PZQ is currently promoted in endemic countries as a safe and effective public health strategy to reduce the intensity and prevalence of infection by treating both infected individuals and entire communities determined to be at risk. Depending on the surveyed prevalence of schistosomiasis, school-aged children and high-risk adults in endemic areas are regularly treated with a dose of PZQ either annually, biennially, or triennially. Current formulations are restricted from being administered to children younger than 5 years of age; consequently, infected preschool aged children are typically not targeted despite their potential for contaminating water sources.[1] The World Health Organization (WHO) currently facilitates

[1] The aim of the nonprofit Pediatric Praziquantel Consortium is to develop, register, and make available a praziquantel formulation for preschool-aged children (www.pediatricpraziquantelconsortium.org).

https://doi.org/10.3768/rtipress.2017.rr.0029.1703

Figure 1. Schistosomiasis transmission cycle and disease control entry points



the donation of PZQ 600 mg tablets to countries for the treatment of school-aged children. The donated PZQ is manufactured by Merck KGaA (Darmstadt, Germany). The current lack of an oral drug therapy that can be safely administered to children younger than 5 years of age, coupled with growing concern over PZQ resistance among highly endemic communities (Doenhoff, Kusel, Coles, & Cioli, 2002), supports diversification of disease control strategies.

B. Improve environmental conditions. Improvement of water, sanitation, and hygiene (WASH) facilities and practices has been shown to reduce contamination of water sources by infected individuals (Grimes et al., 2015). For many endemic communities, sustainable WASH infrastructures take years to develop and may still not benefit individuals with moderate to heavy infection, such as fishermen and people in other professions who are frequently exposed to water sources but have limited access to basic sanitary facilities.

C. Snail control. Where feasible, water sources can be routinely treated with a cercaricide or molluscicide to reduce infective stage larvae (Evan Secor, 2014). The prohibitive costs of routine chemical treatment, concerns over safety and the environmental impact on other aquatic species, and limitations to size of the water body that can be treated all restrict when and where snail control is practical and effective.

D. Reduce contact with infected water. Preventing physical contact with known infectious water sources obviously reduces the potential for cercarial penetration of the skin. However, for many endemic communities who lack access to a safe source of drinking water and who perform daily activities in or near open bodies of water, limiting or preventing physical contact with infectious water sources is difficult, if not impossible. However, individuals exposed to an infected water source could fight transmission by routinely using a product to repel cercariae or inhibit cercarial penetration; such a PPP is referred to here as a cercarial anti-penetrant.

Among the available approaches to prevent and control schistosomiasis, the use of cercarial anti-penetrants is the least developed; WHO does not recommend their use as part of an evidence-based strategy for schistosomiasis control or elimination. Until additional evidence can show PPPs effectively reducing the intensity of infection, and until they can be supplied in a cost-effective way to endemic populations, PPPs are unlikely to become part of a globally endorsed strategy to prevent, control, and eventually eliminate schistosomiasis.

That is not to say that topical cercarial anti-penetrant products do not have a potential role to play in schistosomiasis control. PPPs are successfully used in other infectious disease control and prevention strategies, such as the distribution and use of filter cloths and pipe filters for the prevention of Guinea worm disease (dracunculiasis), the promotion of long-lasting insecticidal nets (LLINs) for the prevention of malaria, and the adoption of condoms to prevent sexually transmitted diseases. By placing a tangible disease prevention tool into the hands of at-risk individuals and households, PPPs can create new entry points for health workers to discuss disease prevention and reinforce health promotion strategies among community members.

Schistosome Cercarial Anti-Penetrants

Many compounds and formulations have been described in the peer-reviewed literature as containing anti-penetrant properties (repellent, barrier, or cercaricide) for *S. mansoni,* *S. haematobium,* and *S. japonicum cercariae.* These include various formulations of DEET, dimethicone, and niclosamide.

Table 1 summarizes studies we identified through a literature search on cercarial anti-penetrants. Among these studies, only two used a topical anti-penetrant for *S. mansoni* and *S. haematobium* as part of a randomized, double-blind, placebo-controlled field trial—and both were 1 percent niclosamide trials (Podgore et al., 1994; Abu-Elyazeed et al., 1993). In studies that included laboratory testing on human subjects, four compounds showed a positive impact in significantly reducing infection of *S. mansoni* or *S. haematobium:* DEET (N,N-diethyl-m-toluamide) and LipoDEET (a liposome-based formulation); 1 percent niclosamide; and dimethicone.

Although 1 percent niclosamide-based lotion was shown to provide a high level of cercarial impairment that significantly reduced the likelihood of infection in a controlled laboratory setting (Bruce et al., 1992; Abu-Elyazeed, Podgore, Mansour, & Kilpatrick, 1993; Wulff, Haeberlein, & Haas, 2007), a subsequent population-based study suggested that a 1 percent niclosamide lotion self-applied to the limbs and torso twice a week failed to prevent *S. haematobium* reinfection among Egyptian farmers (Podgore et al., 1994). The conflicting results from the population-based study may have been influenced by variation in skin coverage among study participants when applying the compound, including differences in the frequency of application and techniques used to rub the lotion on the skin.

Various concentrations of LipoDEET appear to provide anti-schistosomiasis properties in both human and animal models; a single skin application of 20 percent LipoDEET conferred 100 percent protection against all three species of human schistosomes (Ramaswamy, He, Salafsky, & Shibuya, 2003). LipoDEET is commercially available in such products as Ultra 30 (Sawyer Products, Inc.) and Ultrathon (3M), which are marketed as insect repellents.

Among studies that involved animal models, concentrations of a cyclohexanecarboxamide derivative formulated in jojoba oil successfully

Table 1. Summary of studies evaluating compounds having schistosome cercariae anti-penetrant properties, 1945–2012

Category of Compond Tested	Compound Tested	Schistosome Species Targeted	Citation
DEET formulations	DEET (N,N-diethyl-m-toluamide)	*S. mansoni*	Salafsky, B., Ramaswamy, K., He, Y. X., Anderson, G. L., Nowicki, D. K., & Shibuya, T. (1998). Evaluation of N,N-diethyl-m-toluamide (DEET) as a topical agent for preventing skin penetration by cercariae of *Schistosoma mansoni. The American Journal of Tropical Medicine and Hygiene, 58*(6), 828–834.
	DEET (N,N-diethyl-m-toluamide)	*S. mansoni*	Twfeek, G. M. (1999). The potential use of N,N-diethyl-m-toluamide (DEET) as a prophylactic agent in the control of schistosomiasis. *Journal of the Egyptian Society of Parasitology, 29*(3), 763–776.
	DEET incorporated into liposomes (LipoDEET)	*S. mansoni; S. haematobium*	Salafsky, B., Ramaswamy, K., He, Y. X., Li, J., & Shibuya, T. (1999). Development and evaluation of LipoDEET, a new long-acting formulation of N,N-diethyl-m-toluamide (DEET) for the prevention of schistosomiasis. *The American Journal of Tropical Medicine and Hygiene, 61*(5), 743–750.
	DEET (N,N-diethyl-3-methylbenzamide); 1-(3-Cyclohexen-1-yl-carbonyl)-2-methylpiperidine (AI3-37220)	*S. mansoni*	Secor, W. E., Freeman, G. L., Jr., & Wirtz, R. A. (1999). Short report: Prevention of *Schistosoma mansoni* infections in mice by the insect repellents AI3-37220 and N,N-diethyl-3-methylbenzamide. T*he American Journal of Tropical Medicine and Hygiene, 60*(6), 1061–1062.
	DEET incorporated into liposomes (LipoDEET)	*S. mansoni, S. japonicum,* and *S. haematobium*	Ramaswamy, K., He, Y. X., Salafsky, B., & Shibuya, T. (2003). Topical application of DEET for schistosomiasis. *Trends in Parasitology, 19*(12), 551–555. http://doi.org/10.1016/j.pt.2003.10.001
	DEET (N,N-diethyl-m-toluamide)	*S. mansoni, S. japonicum,* and *S. haematobium*	Jackson, F., Doherty, J. F., & Behrens, R. H. (2003). Schistosomiasis prophylaxis in vivo using N,N-diethyl-m-toluamide (DEET). *Transactions of the Royal Society of Tropical Medicine and Hygiene, 97*(4), 449–450. http://doi.org/10.1016/S0035-9203(03)90087-3
	DEET (N,N-diethyl-m-toluamide): "free" DEET, controlled-release DEET, and white precipitate ointment	*S. mansoni, S. japonicum,* and *S. haematobium*	Negm, A. Y., Ibrahim, I. R., El-Temsahy, M. M., & El-Azzouni, M. Z. (2004). Effect of topical agents on cercariae of *Schistosoma mansoni. Journal of the Egyptian Society of Parasitology, 34*(3), 903–913.
	DEET (N,N-diethyl-m-toluamide); dimethicone	*S. mansoni, S. japonicum,* and *S. haematobium*	Cooper, E., Iqbal, A., Bartlett, A., Marriott, C., Whitfield, P. J., & Brown, M. B. (2004). A comparison of topical formulations for the prevention of human schistosomiasis. *The Journal of Pharmacy and Pharmacology, 56*(8), 957–962. http://doi.org/10.1211/0022357043996
Dimethicone formulations	Dimethicone-based barrier cream	*S. mansoni*	Ingram, R. J., Bartlett, A., Brown, M. B., Marriott, C., & Whiffield, R. J. (2002). Dimethicone barrier cream prevents infection of human skin by schistosome cercariae: Evidence from Franz cell studies. *The Journal of Parasitology, 88*(2), 399–402. http://doi.org/10.1645/0022-3395(2002)088[0399:DBCPIO]2.0.CO;2

(continued)

Table 1. Summary of studies evaluating compounds having schistosome cercariae anti-penetrant properties, 1945–2012 *(continued)*

Category of Compond Tested	Compound Tested	Schistosome Species Targeted	Citation
Niclosamide formulations	Niclosamide: four different concentrations (0.5%, 1%, 2%, and 4%)	*S. mansoni*	Hassan, M. M., el-Gamal, R. L., Farghaly, A. M., & Ibrahim, M. N. (1991). Topical niclosamide as a protective agent against schistosome infection. *Journal of the Egyptian Society of Parasitology, 21*(3), 817–822.
	1% (W/V) formulation of niclosamide (2',5-Dichloro-4'-nitrosalicylanilide)	*S. mansoni*	Bruce, J. I., Miller, R., Lightner, L., & Yoganathan, S. (1992). Efficacy of niclosamide as a potential topical antipenetrant (TAP) against cercariae of *Schistosoma mansoni* in monkeys. *Memorias do Instituto Oswaldo Cruz, 87*(Suppl 4), 281–289. http://doi.org/10.1590/S0074-02761992000800044
	1% niclosamide	*S. mansoni*	Abu-Elyazeed, R. R., Podgore, J. K., Mansour, N. S., & Kilpatrick, M. E. (1993). Field trial of 1% niclosamide as a topical antipenetrant to *Schistosoma mansoni* cercariae. *The American Journal of Tropical Medicine and Hygiene, 49*(4), 403–409.
	1% niclosamide	*S. haematobium*	Podgore, J. K., Abu-Elyazeed, R. R., Mansour, N. S., Youssef, F. G., Hibbs, R. G., & Gere, J. A. (1994). Evaluation of a twice-a-week application of 1% niclosamide lotion in preventing *Schistosoma haematobium* reinfection. *The American Journal of Tropical Medicine and Hygiene, 51*(6), 875–879.
	(1) Safe Sea, a cream protecting against jellyfish, and (2) niclosamide in water-resistant sunscreen cream formulations at concentrations as low as 0.05%	*S. mansoni; Trichobilharzia szidati* cercariae	Wulff, C., Haeberlein, S., & Haas, W. (2007). Cream formulations protecting against cercarial dermatitis by *Trichobilharzia. Parasitology Research, 101*(1), 91–97. http://doi.org/10.1007/s00436-006-0431-5
Other treatments	Five tropical ointments to reduce penetration: CL-28A without carboset resins, CL-28 with carboset resins, 25% *Pterodon pubescens* oil extract in ether; 1:4 *P. pubescens* and CL-28A; 1:100 lapachol with CL-28A	*S. mansoni*	Austin, F. G., & Frappaolo, P. J. (1973). *Schistosoma mansoni:* Chemoprophylaxis studies with antipenetration compounds. *The American Journal of Tropical Medicine and Hygiene, 22*(6), 743–747.
	Oxamniquine, mixed with PlastiFix dissolved in benzene	*S. mansoni*	Pellegrino, J., Gilbert, B., & Valadares, T. E. (1976). Preliminary studies on the antischistosomal activity of topically applied oxamniquine. *Revista do Instituto de Medicina Tropical de Sao Paulo, 18*(6), 456–458.
	1,4- and 1,2-naphthoquinones applied topically	*S. mansoni*	Pinto, A. V., Pinto, M. D., Gilbert, B., Pellegrino, J., & Mello, R. T. (1977). *Schistosomiasis mansoni:* Blockage of cercarial skin penetration by chemical agents: I. naphthoquinones and derivatives. *Transactions of the Royal Society of Tropical Medicine and Hygiene, 71*(2), 133–135. http://doi.org/10.1016/0035-9203(77)90078-5
	Coumarin derivatives	*S. mansoni*	Lopes, J. L., Lopes, J. N., Mello, R. T., Pellegrino, J., & Vieira, P. C. (1980). [Chemoprophylactic study of schistosomiasis. IV: Inhibition of the penetration of cercariae by coumarin derivatives]. *Revista Brasileira de Biologia, 40*(2), 283–285.

(continued)

Table 1. Summary of studies evaluating compounds having schistosome cercariae anti-penetrant properties, 1945–2012 *(continued)*

Category of Compond Tested	Compound Tested	Schistosome Species Targeted	Citation
Other treatments *(continued)*	Amoscanate (0.1% w/v) in methanol solution	*S. mansoni*	Greene, L. K., Grenan, M. M., Davidson, D. E., Jr., Jones, D. H., & Shedd, T. R. (1983). Amoscanate as a topically applied chemical for prophylaxis against *Schistosoma mansoni* infections in mice. *The American Journal of Tropical Medicine and Hygiene, 32*(6), 1356–1363.
	Salicylanilide	*S. mansoni*	Miller, R. E., & Reid, W. A., Jr. (1986). *Schistosoma mansoni:* Salicylanilides as topical prophylactic against cercarial penetration of mice. *Experimental Parasitology, 61*(3), 359–368. http://doi.org/10.1016/0014-4894(86)90191-8
	Hexachlorophene (1.25% w/v) in absolute methanol or 70% isopropanol	*S. mansoni*	Grenan, M. M., Greene, L. K., Davidson, D. E., Jr., Jones, D. H., Shedd, T. R., & Hiestand, G. (1985). Hexachlorophene as a topically applied chemical for prophylaxis against *Schistosoma mansoni* infections in mice. *Revista do Instituto de Medicina Tropical de Sao Paulo, 27*(4), 190–196. http://doi.org/10.1590/S0036-46651985000400006
	Peptide-based irreversible inhibitors and non-peptide, reversible inhibitors applied in a 3:1 propylene glycol:isopropyl alcohol formulation	*S. mansoni*	Lim, K. C., Sun, E., Bahgat, M., Bucks, D., Guy, R., Hinz, R. S., . . . McKerrow, J. H. (1999). Blockage of skin invasion by schistosome cercariae by serine protease inhibitors. *The American Journal of Tropical Medicine and Hygiene, 60*(3), 487–492.
	"Sucupira" oil and the lactone eremanthine, extracted from *Pterodon pubescens* and *Eremanthus elaeagnus*	*S. mansoni*	Dias, F. L., Takahashi, C. S., Sakamoto-Hojo, E., Vichnewski, W., & Sarti, S. J. (1995). Genotoxicity of the natural cercaricides "sucupira" oil and eremanthine in mammalian cells in vitro and in vivo. *Environmental and Molecular Mutagenesis, 26*(4), 338–344. http://doi.org/10.1002/em.2850260410
	Millettia thonningii (West African legume)	*S. mansoni*	Perrett, S., Whitfield, P. J., Sanderson, L., & Bartlett, A. (1995). The plant molluscicide *Millettia thonningii* (Leguminosae) as a topical antischistosomal agent. *Journal of Ethnopharmacology, 47*(1), 49–54. http://doi.org/10.1016/0378-8741(95)01253-A
	IR3535-ethyl butylacetylaminopropionate	*Cercarial dermatitis*	Caumes, E., Felder-Moinet, S., Couzigou, C., Darras-Joly, C., Latour, P., & Léger, N. (2003). Failure of an ointment based on IR3535 (ethyl butylacetylaminopropionate) to prevent an outbreak of cercarial dermatitis during swimming races across Lake Annecy, France. *Annals of Tropical Medicine and Parasitology, 97*(2), 157–163. http://doi.org/10.1179/000349803235001633
	An iridoid mixture extracted from leaves of *Citharexylum quadrangular* formulated in jojoba oil	*S. mansoni, S. japonicum,* and *S. haematobium*	Bahgat, M., Shalaby, N. M., Ruppel, A., & Maghraby, A. S. (2005). Humoral and cellular immune responses induced in mice by purified iridoid mixture that inhibits penetration of *Schistosoma mansoni* cercariae upon topical treatment of mice tails. *Journal of the Egyptian Society of Parasitology, 35*(2), 597–613.
	MNRC-5: N-phenyl-N-[1-(piperidine-1-carbonyl) cyclohexyl] benzamide, cyclohexanecarboxamide derivative	*S. mansoni*	Bahgat, M., Aboul-Enein, M. N., El Azzouny, A. A., Maghraby, A., Ruppel, A., & Soliman, W. M. (2009). A cyclohexanecarboxamide derivative with inhibitory effects on *Schistosoma mansoni* cercarial serine protease and penetration of mice skin by the parasite. *Acta Poloniae Pharmaceutica – Drug Research, 66*(3), 333–340.

blocked cercarial penetration; Bahgat and colleagues (2009) observed a significant reduction (75 percent; $p < 0.05$) in the recovered *S. mansoni* worms from treated mice in comparison with controls. Eucalyptus oil, used in Swimmer's Itch Guard (Resolutions, LLC), has cyclohexanecarboxamide properties but did not conclusively provide protection against *S. mansoni* in human clinical trials. Swimmer's Itch Guard is sold as a topically applied gel to prevent cercarial dermatitis in swimmers. Cercarial dermatitis (swimmer's itch) is a common noncommunicable disease that causes a skin rash. It is mostly associated with bird schistosomes of *Trichobilharzia spp.* (Kolářová, et al., 2013).

Despite the evidence of cercarial anti-penetrant properties in certain compounds, endemic countries for *S. mansoni, S. haematobium,* or *S. japonicum* have been unsuccessful in leveraging a topical PPP to measure the impact that routine use has on moderate to heavy intensity of infection among different high-risk populations.

In this paper we seek to identify opportunities for and barriers to leveraging generic compounds as part of operations research efforts to understand the potential role of known anti-penetrants in the control and prevention of schistosomiasis.

Methods

Based on the results of our systematic literature search, presented in Table 1, we initially identified nine subject matter experts on the use and application of cercarial anti-penetrants. The literature review used the search terms "Schistosomiasis or cercarial" and "topical or ointment or repellents" in PubMed. The search was restricted to publications between 1945 and 2012, and meta-analyses were excluded. Only studies that specified *S. mansoni, S. haematobium,* or *S. japonicum* as part of the abstract were included.

After contacting the nine initial subject matter experts, we used a snowball sampling technique to identify additional informants. In total, we identified 35 key informants through a mixture of internet searches for key terms, authors identified through the literature, and referrals from interviewees. We initially contacted each key informant by e-mail and invited the contact to participate in the study. We conducted interviews by telephone or Skype and asked for consent to record the interview using QuickTime. Interviews lasted on average 45 minutes. Informants were provided with the name of the primary investigator, the primary investigator's contact information, and the scope of the study. Individuals were encouraged to participate in an interview even if they felt they were not directly involved in studies involving cercarial anti-penetrants. Informants were also informed that answers would be confidential and that they could decline to answer any question or terminate the interview at any point.

Our key informant questionnaire was designed to collect information about

- the key informants' sociodemographics and professional affiliation and experience, including their experience with anti-penetrants
- their opinions on cercarial anti-penetrants and challenges to research and development
- population(s) that should be targeted for anti-penetrants and advocacy
- behavioral and resource factors that may influence successful use of anti-penetrants.

A copy of the survey guide is provided in the appendix.

Broad themes were identified by cutting and sorting quotes and expressions of the key informants into various groupings. Themes were then confirmed within and across each group through analysis of word and subject matter repetition, comparison of similarities and differences between key informants, and assessment of missing data—that is, information that was not shared by informants.

Limitations

The methodologies used in this study were not intended to demonstrate causation between the use of anti-penetrants and the reduction of schistosomiasis infections, nor elucidate the costs and feasibility of distributing anti-penetrants to high-risk groups. Rather, our intent was to identify and describe key factors that need to be addressed to reach

 https://doi.org/10.3768/rtipress.2017.rr.0029.1703

consensus on the role of cercarial anti-penetrants for schistosomiasis control, and the potential opportunities to facilitate this research. Given some key informants' limited awareness of the management and implementation of routine disease control interventions and what constitutes a cost-effective product, key informants may have underestimated or overestimated the practicality of developing and scaling up the use of a PPP as part of a globally recognized evidence-based strategy to control and eliminate schistosomiasis.

Results

The majority of the 15 key informants interviewed were affiliated with a university or research institute (n=10), followed by those affiliated with international nonprofit organizations/institutions (n=3) and private industry (n=2). Informants' roles ranged from microbiologists and parasitologists to directors of international schistosomiasis projects, physicians, and scientific advisors.

Results of the key informant interviews highlighted two major obstacles to translating research into the development of a PPP for schistosomiasis control programming:

- minimal available evidence to show the effective use of topically applied products in community-based settings
- limitations of current development models to sustain product availability among high-risk groups in low-income settings.

Challenges to Assessing Effectiveness

Informants recognized that although the proof of concept for a schistosome cercarial anti-penetrant has been established in animal models, manufacturers have minimal support or incentive to prove efficacy in larger population-based studies in high-risk populations. These populations often have insufficient disposable income to purchase preventive health products or are not aware of the links between environment and health outcome and therefore do not value a topical product. One informant expressed concern that there may not be a viable market for a topical product without investment by a large global entity to insure that manufacturers can get a return on investment.

Informants strongly agreed that the lack of funding/grant opportunities is a major problem for schistosomiasis researchers who wish to test the use and efficacy of PPPs among at-risk populations. While academia generates a lot of innovative ideas, researchers expressed frustration with being unable to find partnerships that secure the needed funding to publish results and apply research findings to routine implementation. In general, informants felt that there is a lack of enthusiasm to fund projects because, as one informant said, there is "no incentive for pharmaceutical companies to fund research. Researchers are interested in an academic view, but are not interested in the question 'Is there a commercial product at the end of the day?'" Certain informants suggested that researchers need to be more proactive in approaching their respective university chief information officers to disclose research so that more ideas, even those considered accidental findings, can penetrate through the schistosomiasis research community.

Developing large double-blinded field trials to prove efficacy is extremely difficult and expensive, including the long time frame to obtain approval, secure access to parasites, and determine end points to establish proof of principle. While animal models are straightforward as a preliminary screen for effectiveness, there remains a need for clinical studies (and subsequent field studies) on humans. Human skin needs to be used given its unique cytokine and hormonal components. New topical products for schistosomiasis prevention would first need to be tested on a group of persons never exposed to the cercariae. In this regard, the use of compounds that have already gone through rigorous regulatory review and approval for use in a topical product at established concentrations and frequencies could save considerable time and resources.

Challenges to Product Availability

The majority of informants indicated that the actual development of a compound would not be difficult—many of the formulations are simple, and previous studies discovered compounds that were "whipped

up in people's labs" and cost "pennies to make." One informant noted that the production schemes are not complicated, only that products would need to be tested for shelf life in tropical settings. Again, informants suggested that manufacturers could adjust the pharmacokinetics of existing products (e.g., commercially available products used for the prevention of cercarial dermatitis, or products marketed as insect repellents) to avoid lengthy safety testing processes.

In general, the informants said they believe that manufacturers do not see NTDs as a top priority because manufacturers do not believe or perceive that NTDs cause mortality. In addition, without assurances that products would reach end users, manufacturers do not have a strong motivation to invest in product development. Some informants said enough of the population would need to purchase the product to ensure a manufacturers' profit expectations, or the manufacturer would require a substantial tax incentive for donating unsold product if another global entity did not pay for it. As one informant indicated, if adequate supply and return on investment for the manufacturer are not addressed, then "the product will remain stagnant."

One informant suggested that a smaller market be created in wealthy countries first, particularly among travelers, and then expanded to endemic countries where manufacturers could benefit from improved public relations by aligning with WHO's schistosomiasis elimination efforts. Another informant said that the market will remain unclear as long as the emphasis of endemic countries is on obtaining donated quantities of PZQ for school-aged children and not on developing long-range plans and more nuanced approaches to address transmission in high-risk populations.

PPPs are currently not among WHO's advised strategies for the control and elimination of schistosomiasis. Informants had a strong sense that in order for any new product to be recommended, the product (1) could not be "in adversarial competition with current treatment programs," as one informant said, and (2) would need to be perceived as complementary to the primary strategy that espouses that schistosomiasis can be treated with PZQ, which remains the main global strategy to reduce burden of disease. Informants suggested that a topical product could complement other public health strategies including improved sanitation, use of molluscicides, and health education.

Other Considerations

Responses related to the effectiveness and availability of PPPs could be further categorized by the following:

- characteristics of the targeted population (high-risk groups)
- qualitative properties of the product
- behavioral changes required to support product use.

Target population. Key informants suggested that children, individuals in high-risk occupations, and international development professionals living near or around known sources of infection would benefit from a topical anti-penetrant. It was noted that primary school children (5–14 years of age) are more likely to be exposed to infection when swimming and are quickly reinfected after treatment. Similarly, children less than 5 years of age living in high-risk areas can become exposed simply by wading in water and are not typically targeted with PZQ during mass drug administration campaigns. Informants identified occupations that are at a higher risk for infection: farmers, rice field workers, clothes washers, car washers, fishermen, sand harvesters, and canal cleaners.

Depending on the frequency of exposure to water sources suspected of being infected, people in these occupations would need to consider the practicality of routinely using a PPP in order for the product to be effective. In contrast, tourists, humanitarian workers, soldiers, missionaries, and Peace Corps volunteers may only need to apply an anti-penetrant in special circumstances.

Product properties. We identified several product characteristics that would make a topical product more attractive to users. Formulations should be long lasting, nontoxic, not damaging to clothing, hydrophobic, stable in tropical climates, and effective at killing or repelling multiple species of cercariae. Tactile and sensory preferences would likely influence use. To encourage multiple applications, a product

would need to be easy to apply, perhaps with a spray-on or other mechanism that could facilitate appropriate skin coverage with minimal effort, and would need to offer sufficient skin coverage. The product packaging should also be designed for mobility (easy for users to carry). Although regulatory agencies may restrict products from having a dual purpose, informants encouraged PPPs for schistosomiasis to have a dual purpose, such as also being a soap for washing the body or a cream for moisturizing the skin. Other ideas included adding a mosquito repellent or an attractive fragrance for use as a deodorant or perfume. Informants specified the product should not feel greasy or oily and not cause skin irritation (Table 2).

Table 2. Key characteristics of a personal protective product (PPP) for schistosomiasis identified in key informant interviews

Type	Desired characteristics
Physical properties	Attractive color, nice smell, not greasy or oily, doesn't cause skin roughness or irritation
Chemical properties	Waterproof, long-lasting, nontoxic, not damaging to clothing, no environmental residue
Ease of use	Spray-on or mist applicator, easy to remove, does not attract flies, easy to carry
Dual purpose	Repellent or cercaricide *plus* body soap, insect repellent, lotion/moisturizer, deodorant, perfume, or sunblock

Behavioral change requirements: Informants expressed concern over the practicality of expecting targeted populations to adopt the necessary behavioral changes to use a topical product effectively. As noted by one informant, since schistosomiasis is a "slow disease" it would be important for those at risk to understand the connection between use of the product and its benefits. Unlike mosquito repellents and sunblock lotions, which prevent the immediate negative stimulus of an insect bite and sun burn, respectively, symptoms of schistosomiasis infection are not experienced immediately, so people in endemic areas may not connect environmental exposure with the disease, or use of the product with benefits.

For this reason, introduction of a schistosomiasis PPP would require an intensive behavioral change communication strategy to reinforce the routine indicated use of the product—correct application, correct amount, correct coverage, correct time. Even if such behavioral changes could be made, national schistosomiasis control program managers may not be interested in promoting use of the product unless the product can be made available to endemic communities free of charge, similar to other drug therapies provided for preventive chemotherapy distribution campaigns.

Discussion

As a complement to current control interventions, the comparative costs and comparative effectiveness of PPPs over strategies like mass drug administration are perhaps less important than articulating the overall business model to guide product use and availability among endemic communities. The business model to develop a topical anti-penetrant for schistosomiasis should therefore be considered concurrently with the design of randomized control trials. One of the most feasible strategies suggested by informants is to modify existing compounds and products—preferably products that have already been approved for use through a well-documented regulatory process. Indeed, this approach quickly establishes a new product's legitimacy and safety and decreases manufacturer testing time and costs. While the manufacture of product in endemic countries could further reduce costs by eliminating overseas shipping, promoting local manufacture does not necessarily ensure sustained product availability to high-risk individuals in low-income communities.

The following proposed business models, if leveraged, could promote research to test the efficacy of topical anti-penetrant products in low-income communities and could promote long-term accessibility.

Venture Philanthropy. Venture philanthropic approaches have successfully leveraged therapeutic development networks to advance product development and use. For example, the use of eflornithine to treat African

https://doi.org/10.3768/rtipress.2017.rr.0029.1703

trypanosomiasis (Robays, Raguenaud, Josenando, & Boelaert, 2008), rather than its original marketed purpose as a facial hair remover, is an example of how venture philanthropy can help repurpose a commercially marketed product into a product for global health use. In the case of schistosomiasis, a venture philanthropic model could enable a donor organization to provide early-stage funding to manufacturers, such as 3M or Sawyer International, to further test the impact of existing commercial products that contain cercarial anti-penetrant properties on a broad spectrum of schistosome species. Linking this model with a therapeutics development network composed of specialists in schistosomiasis clinical research and behavioral science could expedite and promote quality, safety, and efficiency in clinical trial research and help accelerate the delivery of a topical anti-penetrant among high risk-groups in schistosomiasis-endemic communities for research.

One-for-One and Drug Donation Programs. Once the effectiveness of a topical anti-penetrant is established, disease control programs will need to ensure long-term availability of the product among those most in need. This could be achieved either through a one-for-one model or through the creation of a drug donation program.

In a one-for-one marketing strategy, consumers who purchase the product are covering the cost of providing the new product for free to individuals in low-income countries; costs of the provided product are built into the retail price. This business model is used by companies like TOMS shoes and Bombas socks. Similarly, international development professionals or tourists traveling to schistosomiasis-endemic countries, or swimmers who seek a product to prevent cercarial dermatitis, could purchase a broad spectrum anti-penetrant for schistosome infections and in doing so help offset costs for the company to provide the product for free to those in need and unable to pay.

To sustain product availability, NTD control and elimination programs for lymphatic filariasis, onchocerciasis, trachoma, soil-transmitted helminths, and schistosomiasis have benefited from effective drug donation programs. For example, the Merck Mectizan Donation Program has provided ivermectin (Mectizan) to combat onchocerciasis (river blindness) around the world since 1987 (Sturchio, 2001). In 1998, Merck expanded the successful program and began providing Mectizan for lymphatic filariasis in areas where the two diseases occur at the same time. The Mectizan Donation Program leverages support in distributing the donated medicine through the WHO, the World Bank, ministries of health, and numerous nongovernmental organizations. By taking advantage of tax breaks offered by the US government to pharmaceutical companies who donate safe and effective drugs to endemic countries, the donation program has substantially contributed to the elimination of river blindness in Mexico, Ecuador, Guatemala, and Columbia, as well as significant reductions in transmission in a number of African countries. A similar approach could be taken with manufacturers of FDA-approved topical products that are empirically shown to reduce transmission of schistosomiasis in high-risk groups.

Even if the biological effectiveness of a topical anti-penetrant to prevent schistosomiasis is established and product availability is addressed through alternative business models, the remaining obstacle in operationalizing use of a product will be around repeated and continuous application. As demonstrated by a study conducted by Podgore and colleagues (1994), which used a 1 percent niclosamide lotion in communities in Egypt, operationalizing wide-scale use of a PPP requires a strong behavior change communication framework. More recently this was demonstrated in a study looking at the additive impact of topical repellents with LLINs on plasmodium species-specific prevalence among malaria endemic villages in Cambodia. Despite instruction and promotion of the repellent's daily use, usage was suboptimal and in combination with LLINs showed no difference in plasmodium prevalence compared to LLINs alone (Sluydts et al., 2016).

Further behavior change communication research on PPPs would need to be an integral part of the research protocol developed for randomized control trials to explain which factors would contribute to reinforcing or enabling product use behaviors. In particular, additional research focused on the knowledge,

attitudes, and practices of high-risk groups could improve the design and structure of communication channels and messages to

- reinforce behaviors (e.g., What are the most effective strategies to encourage routine application of topical product to the skin?)
- remove policy constraints (e.g., What impact does WHO endorsement of a topical product have on use and availability?)
- change ideational factors (cognitive, social, and emotional) related to PPPs (e.g., How do topical product design and purpose affect PPP use and skin coverage? How does perception of disease risk influence adherence to routine use of a product?).

Conclusions

Given the high reinfection rates of schistosomiasis in various parts of the world and limitations of current treatment guidelines and control activities, achieving elimination targets for *S. mansoni, S. haematobium,* and *S. japonicum* through preventative drug therapy alone is challenging without adopting more comprehensive control and prevention strategies, including snail/cercariae control and improved water and sanitation. A lack of evidence to conclusively dismiss the use of cercarial anti-penetrants as part of a PPP approach to prevent schistosomiasis at the point of contact continues to feed aspirations to identify and develop new anti-penetrants.

Results of key informant interviews suggest that future pathways to study the impact of topical anti-penetrants in low-resource endemic areas must consider the business modalities to enable product availability and sustain supply, as well as the behavioral factors that influence effective product use. Furthermore, future funding opportunities depend on the capacity and willingness of researchers to actively engage with manufacturers of commercially available products and explore alternative business models. Early public-private partnerships, including engagement with product manufacturers, behavioral researchers, therapeutic networks, and coordination with international policy groups (e.g. WHO) and Ministries of Health in endemic countries, could address the financial and logistical challenges of human testing and provide a pathway to new evidence-based topical anti-penetrants for the prevention of schistosomiasis.

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