SCHISTOSOMIASIS

The business case for new diagnostics

PATH

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Executive summary

Efforts to control schistosomiasis have made great strides in recent years through deworming programs for school-aged children. These programs depend on large-scale donation of the antischistosomal drug praziquantel (PZQ) by the UK Department for International Development, US Agency for International Development, and Merck KGaA.1,2

These mass drug administration (MDA) programs include surveillance for *Schistosoma* infection using diagnostic tools approved by the World Health Organization. Currently, microscopic examinations of stool and urine samples to detect the presence of *Schistosoma* parasite eggs are the "gold standard" methods for informing decisions regarding MDA.[2] However, coproscopy and uroscopy are not sensitive to the low-intensity infections that characterize populations that have been treated with PZQ.[3-8] In addition, although the presence of eggs in excreta is a good proxy for morbidity at high worm burdens, it is not the best proxy for future transmission risk with lower worm burdens.[9] Thus, the international schistosomiasis community has increasingly recognized the need for improved diagnostic tools to support late-stage control program decisions, such as when to stop MDA.[1,2] Failure to adequately address the need for new diagnostics could jeopardize achievement of the 2010 London Declaration goals related to schistosomiasis.

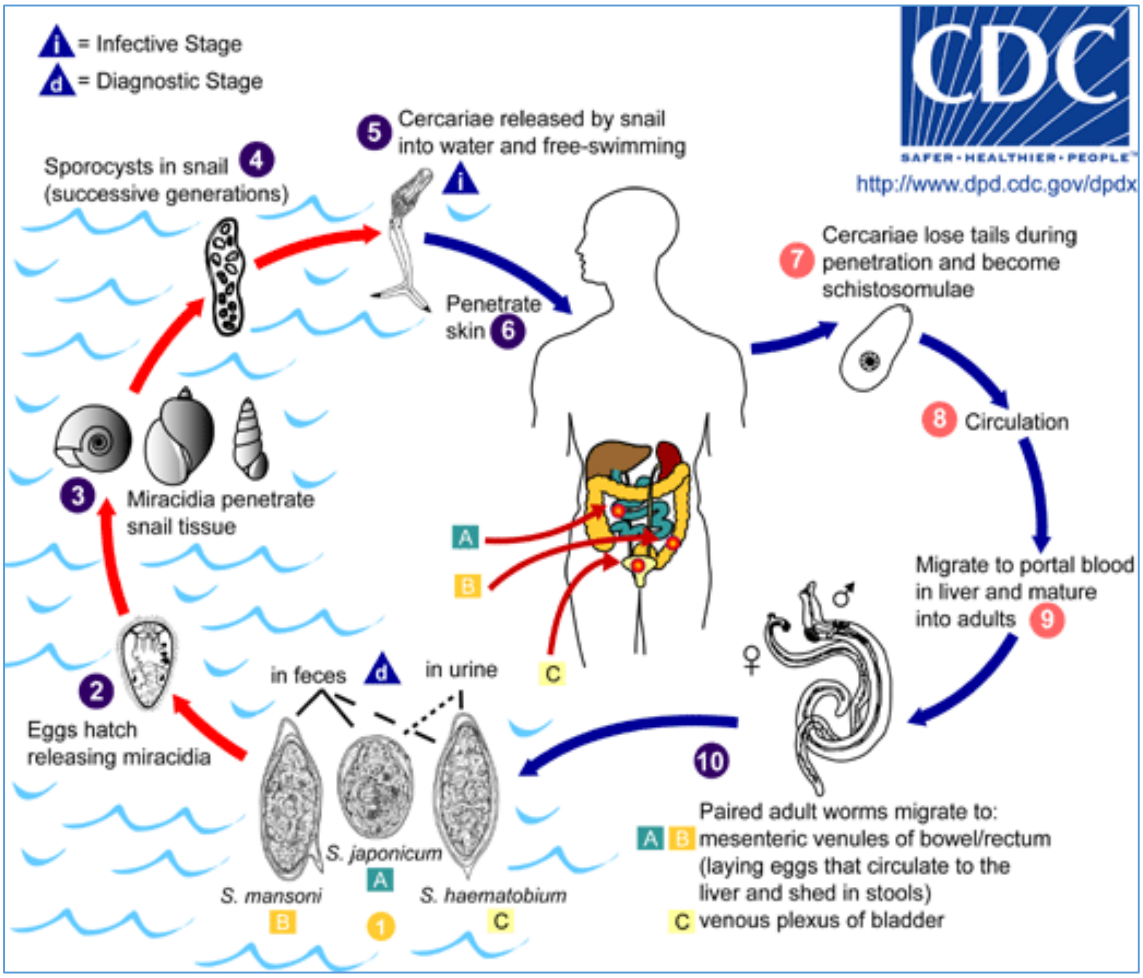
This document synthesizes primary scientific literature, technology landscape analyses, and drug development principles as it describes key considerations related to the diagnosis and control of schistosomiasis and outlines a business case for financing, developing, and deploying new diagnostics for detection of *Schistosoma* infection.

Disease overview

Schistosomiasis is a potentially debilitating disease resulting from infection with sexually reproducing trematode worms of the genus *Schistosoma*.[10,11] Approximately 700 million people worldwide are at risk of infection, and 240 million are actually affected, including several million with severe disease. In sub-Saharan Africa, schistosomiasis accounts for an estimated 250,000 deaths each year.[2]

The life cycle of the parasite (Figure 1) includes egg shedding from human excreta into local water sources, infection of an intermediate snail vector (species specific), and subdermal reinfection of humans by a free-swimming larval stage. Because of this natural history, the World Health Organization (WHO) has recommended an overall control strategy abbreviated as **PHASE** (**P**reventive chemotherapy, **H**ealth education, **A**ccess to clean water, **S**anitation improvement, and **E**nvironmental vector control).[2]

Figure 1. The life cycle of the three main Schistosoma species that cause human schistosomiasis. Note that the "diagnostic stage" in this diagram assumes that coproscopic or uroscopic methods to detect eggs are being employed as diagnostic tests, as per current World Health Organization guidelines.[12]



Although seven species of schistosomes infect humans, most morbidity is caused by *Schistosoma (S.) haematobium* (Africa), *S. mansoni* (Africa and South America), and *S. japonicum* (Asia).[a] The mature adult worms of all *Schistosoma* species take up residence in the peripheral blood vessels of their mammalian hosts. *S. haematobium* is responsible for urogenital schistosomiasis, and the other species mainly affect the intestines and the liver.[10,11]

The parasite eggs are the primary source of chronic human morbidity. Large numbers of eggs are produced, and most are not shed quickly into the excreta. Residual eggs cause inflammation, hyperemia, abnormal growths, and internal hemorrhage progressing to fibrosis and thickening of the tissues. *S. haematobium* infection can cause bladder cancer, and other *Schistosoma* species induce embolization of eggs in the intestine to the liver through the portal system (responsible for progressive liver fibrosis, portal hypertension, and ascites.[10,11,13]

The fecund adult worm pair is the best indicator of future transmission risk. A single worm pair may generate approximately 300 eggs per day and live for decades—potentially leading to massive numbers of future infections.[10,14-18] Egg generation is proportional to the intensity of infection at high worm burdens but is not constant over time, cyclically waxing and waning as well as declining when the worms are stressed, such as after chemotherapy treatments.[19-22] Thus, although egg counts may be the best proxy for morbidity in high-burden populations, direct indicators of worm burden are the best proxy for transmission risk and for informing control program decisions.

Geographic distribution patterns of schistosomiasis are outlined in Table 1 and Figures 2 and 3.

Table 1. Geographic distribution of intestinal and urogenital schistosomiasis[23]

Organ system affected	Species	Geographic distribution
Intestinal	*S. mansoni*	Africa, the Middle East, the Caribbean, Brazil, Venezuela, Suriname
	S. japonicum	China, Indonesia, the Philippines
	S. mekongi	Several districts of Cambodia and the Lao People's Democratic Republic
	S. guineensis and related *S. intercalatum*	Rain forest areas of central Africa
Urogenital	*S. haematobium*	Africa, the Middle East

[a] S. haematobium, S. japonicum , S. mansoni, S. intercalatum, S. mekongi, S. malayensis (public health significance undetermined), and S. guineensis (recently separated from S. intercalatum).

Figure 2. Schistosomiasis prevalence map published by the World Health Organization.[24]

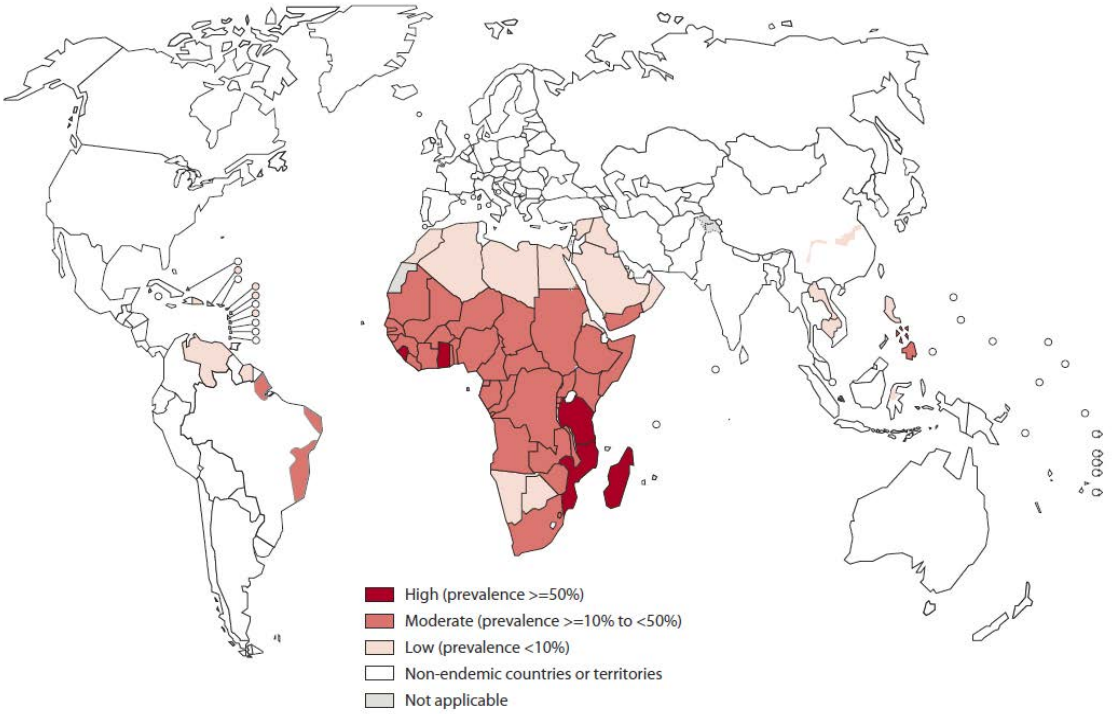
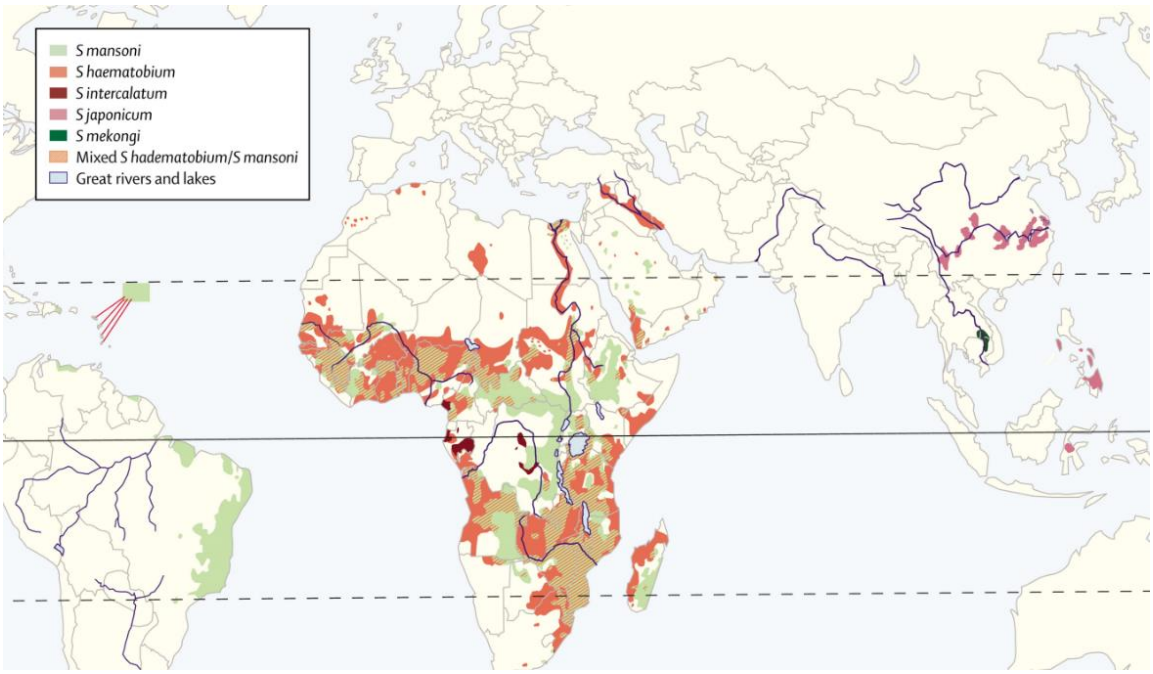


Figure 3. Geographic distribution of various *Schistosoma* species published by the World Health Organization.[25]



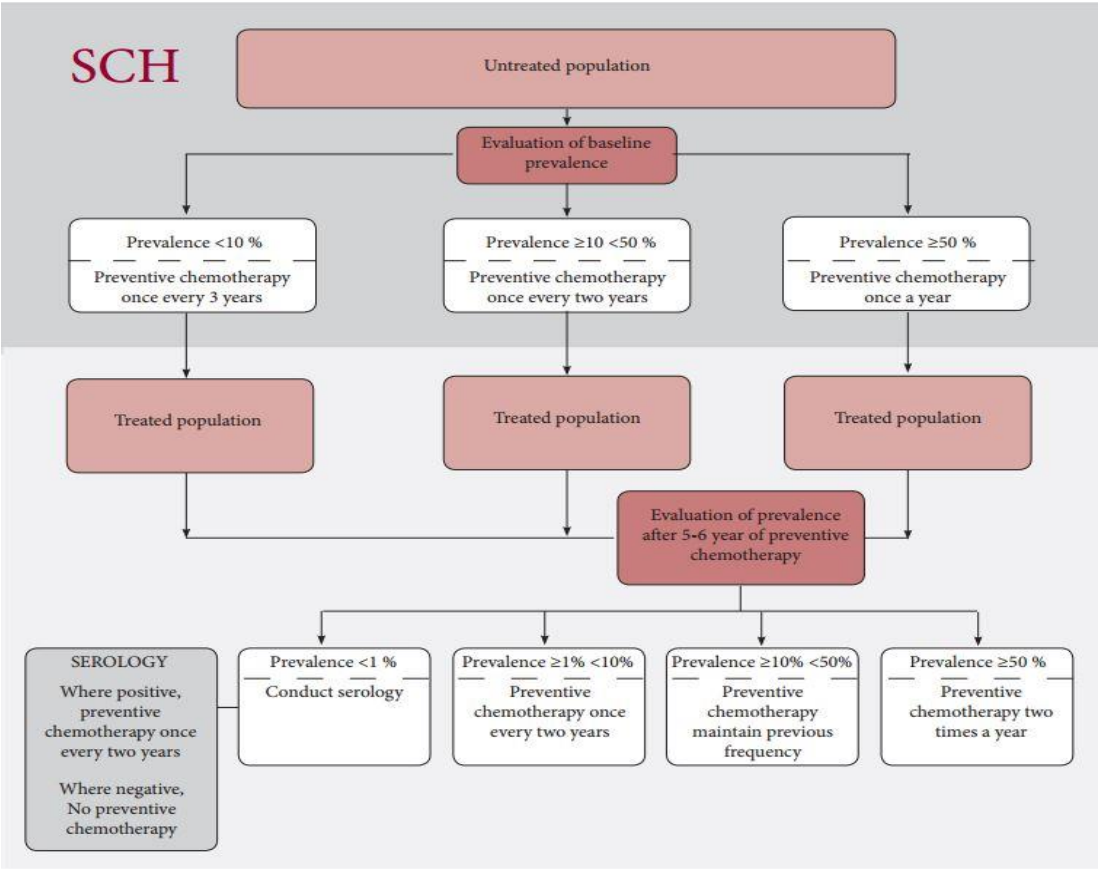
Control strategy

Schistosomiasis control programs in many countries use an effective preventative chemotherapy (PC) called praziquantel (PZQ; sold under a variety of brand names and dosages for human and veterinary use) for school-based deworming campaigns targeting children in endemic communities and districts. Administration of PZQ can reverse up to 90% of organ damage in schistosomiasis-affected individuals and has been responsible for a decline in both prevalence and morbidity in more than 50 endemic countries. Programs based on PZQ have been so successful that as many as 19 endemic countries may have interrupted transmission (yet to be certified). Burkina Faso, Cambodia, China, Egypt, Mauritius, and Morocco are notable examples.

PZQ for these programs is primarily donated by the UK Department for International Development, US Agency for International Development, and Merck KGaA—with a recent increase in commitment to 250 million tablets/year. Although this amount is sufficient to meet current requirements, it is not likely to cover projected increases in need. PZQ administration is expected to peak at about 660 million doses in 2017 and then decline again as countries are certified as having eliminated the disease. Given the scale of these treatments and the significance of the resources involved, correct targeting and timing of treatment administration are paramount.

Accurate surveillance to inform decisions by schistosomiasis control programs is critical to the success of the interventions outlined in the PHASE strategy, especially given the leading role of the PC component. Currently, decisions on where and when to administer PZQ are based on prevalence estimates as determined by diagnostic testing performed on the same school-age children (SAC) being targeted by school deworming programs (Figure 4).

Figure 4. Frequency of mass drug administration (MDA) based on prevalence estimates and prior community-based treatment (WHO guidelines, report of informal consultation, 2009).[24]



At a country level, the WHO defines four "groups" based on surveillance data, and progression through the classification is based on both prevalence of heavily infected sentinel sites and time spent within the group**.** In the first group, where morbidity control is the primary aim, PC is continued for at least 5 to 10 years after the prevalence of heavily infected sentinel sites drops below 5% before advancement to the next group is considered. The second group is focused on elimination of schistosomiasis as a public health problem and is characterized by a prevalence of heavily infected sentinel sites below 1%, for 3 to 6 years. The third group contains countries that are near elimination of transmission, defined as a vanishing incidence of infection for up to 5 years. These countries are then verified as "schistosomiasis eliminated" and advanced to the fourth group, where PC can be discontinued and surveillance is focused on detecting and responding to resurgence in transmission to prevent reintroduction. It is worth highlighting that as PC treatment reduces the prevalence of heavily infected sites, the individual worm burden falls in concert. Thus, it is now recognized that highly sensitive diagnostic tests are required to establish prevalence in the low-worm-burden settings created by PC, to establish vanishing incidence and to detect resurgence.

Any attempts to continue the use of current diagnostic tests past the mapping and impact-monitoring phases of a control program will result in inaccurate estimation of prevalence, possible errors in group advancement, and

ultimately poorly targeted PHASE interventions that may be costly to donors and control programs. Also, the inaccurate results may negatively affect the morale of frontline health care workers and affected populations. Thus, a diagnostic tool capable of more accurately informing late-stage decisions by control programs will potentially add value by more effectively targeting PHASE interventions and use of limited resources. Globally, as more countries move toward reaching elimination goals, the enhanced ability to more accurately identify and target remaining reservoirs of infections that either persist or reemerge could accelerate achievement of global elimination goals, wind down massive drug donations, and control program costs.

Diagnostics to detect schistosomiasis

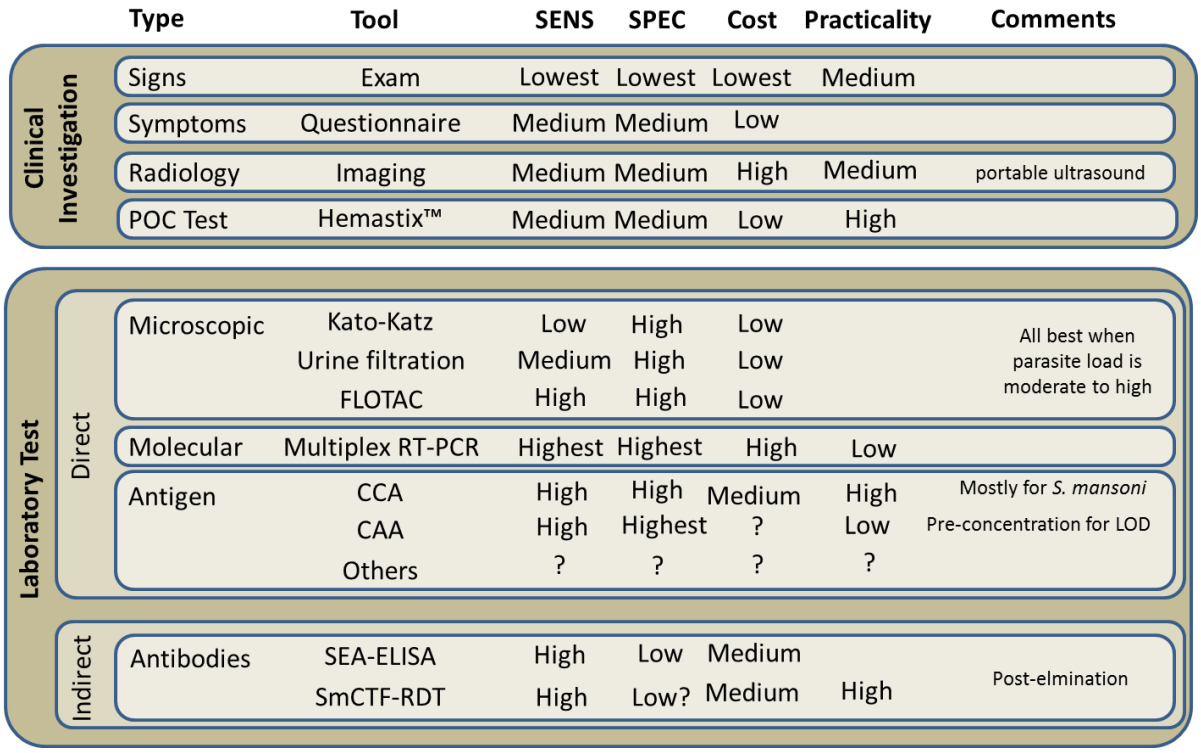
Current diagnostic tools and their shortcomings

Currently, microscopic examinations of stool and urine samples to determine the presence of *Schistosoma* parasite eggs are the "gold standard" methods for informing control program decisions regarding use of MDA.[2] The Kato-Katz (K-K) method is the most common coproscopy (stool microscopy) preparation, and urine filtration (UF) is done prior to uroscopy (urine microscopy). However, coproscopy and uroscopy are not sensitive to the low-intensity infections that characterize populations that have been treated with PZQ, especially over a number of years as detailed in WHO recommendations.[3-8] In addition, while the presence of eggs in excreta is a good proxy for morbidity at high worm burdens, it is *not* the best proxy for future transmission risk with lower worm burdens.[9] Thus, there has been increasing recognition within the international schistosomiasis community of the need for improved diagnostic tools to support late-stage control program decisions, such as when to stop MDA.[1,2]

Diagnostic tests for schistosomiasis can be classified in various ways. One useful taxonomy starts by classifying tests as *clinical* or *laboratory* (Figure 5). The clinical investigations are useful for individual diagnosis in highly endemic areas with high worm burden but become less accurate as prevalence and burden fall.[4,26] Given the diversity of applications, the operational constraints around training and interpretations, and the inherent low sensitivity of these tests in elimination settings, these clinical tests do not appear to fit the surveillance use cases of interest and were deemed out of scope for this landscape.

Figure 5. Existing schistosomiasis diagnostic tests classified by a useful taxonomy.

(SENS = sensitivity, SPEC = specificity, POC= point of care, FLOTAC = proprietary device name, RT-PCR = Reverse



Transcriptase – Polymerase Chain Reaction, CCA = Circulating Cathodic Antigen, SEA-ELISA = Soluble Egg Antigen ELISA, SmCTF-RDT = Schistosoma Mansoni Cercarial Transformation Fluid Rapid Diagnostic Test;, LOD = Limit of Detection)

Laboratory tests for schistosomiasis can be subdivided into *direct* (detecting the presence of the parasite; i.e., active infection) and *indirect* (detecting the host response to the parasite, which may be better correlated to exposure rather than active infection). Direct tests include microscopic tests, molecular tests (as nucleic acid levels decline rapidly once the parasite is cleared), and antigen tests. Indirect tests are typically antibody tests that interrogate the immune response of the host. In general, direct tests are more appropriate for informing MDA decisions as prevalence and infection intensity fall and incidence approaches nil, whereas indirect tests are most useful in post-elimination use cases.[4] Existing laboratory tests have recently been reviewed.[27]

Understanding the tests that are available or under development is important, but it is also important to understand the intrinsic properties of the biomarkers they are targeting. Many biomarkers may be applied to multiple platforms (e.g., antigens can be applied to both enzyme-linked immunosorbent assay [ELISA] and immunochromatographic rapid diagnostic tests [RDTs]). Thus, biomarker properties such as genus or species specificity, biological uniqueness, and abundance and persistence in accessible (and acceptable) sample types should be considered.

Diagnostic tests for schistosomiasis are typically targeted at biomarkers that are either genus or species specific. A test should be able to adequately discriminate against common bacterial pathogens that may be

found in surveillance samples. In the case of antibody tests, it should able to exclude immune responses to other closely related parasites. Some biomarkers are denoted as species specific because the methods for isolating and characterizing them have been confined to a single species, but subsequent use in field settings may later establish sufficient cross-reaction with other *Schistosoma* species to make them useful for detecting other members of the genus. Species differentiation is an important consideration for epidemiology research and in determining the autochthony of infection in a resurgence of incidence; however, the effectiveness of PZQ against all *Schistosoma* species makes species differentiation less important for informing the frequency and cessation of MDA and as an initial "red flag" that a resurgence in incidence has occurred in a particular geographic area.

The intrinsic specificity of a biomarker frequently arises from its biological or biochemical uniqueness. Ova targeted in egg-counting methods are distinct for each of the *Schistosoma* species when a properly trained microscopist performs the count. Antigens that present epitopes that are unique to the genus or species elicit immune responses that do not cross-react with other antigens—important when the antigen is an analytical target and when it is used as a reagent for an antibody test. Thus, antigen and antibody tests may be either genus or species specific but often are not well enough characterized with a diverse set of clinical samples to understand the specificity clearly.

The abundance and persistence of the biomarker in an accessible sample is also a key attribute to consider.[b] As illustrated by the coproscopic and uroscopic "gold standard" methods, diagnostic accuracy is poor when there is insufficient analyte in the sample to enable meaningfully low limits of detection—a problem exacerbated by the declining infection intensities that accompany the approach to elimination. Persistence of the analyte becomes important as both a sampling constraint and when the biomarker is not well correlated with the actual infection or transmission risk. The Shannon-Nyquist theorem dictates that sampling frequency must be at least twice as often as the frequency of a periodic signal if the true magnitude and frequency of the signal is of interest. Thus, if the biomarker rises and falls with a daily pattern, sampling should be done twice daily to avoid information "drop-out." This sampling constraint is also illustrated by the known shortcomings of the egg-counting methods, where repeated sampling over several days is required to achieve acceptable sensitivity in a background of shedding periodicity. Antibody tests illustrate the problems with persistence when the marker is not correlated with the desired endpoint—antibody levels often persist for months or years after the parasite has been cleared, making it a much better measure of exposure than patent infection. Circulating antigens constitutively excreted from adult worm pairs as part of normal metabolism appear unaffected by both abundance and persistence artifacts (at least in serum and urine samples). Antigen tests targeting egg surface

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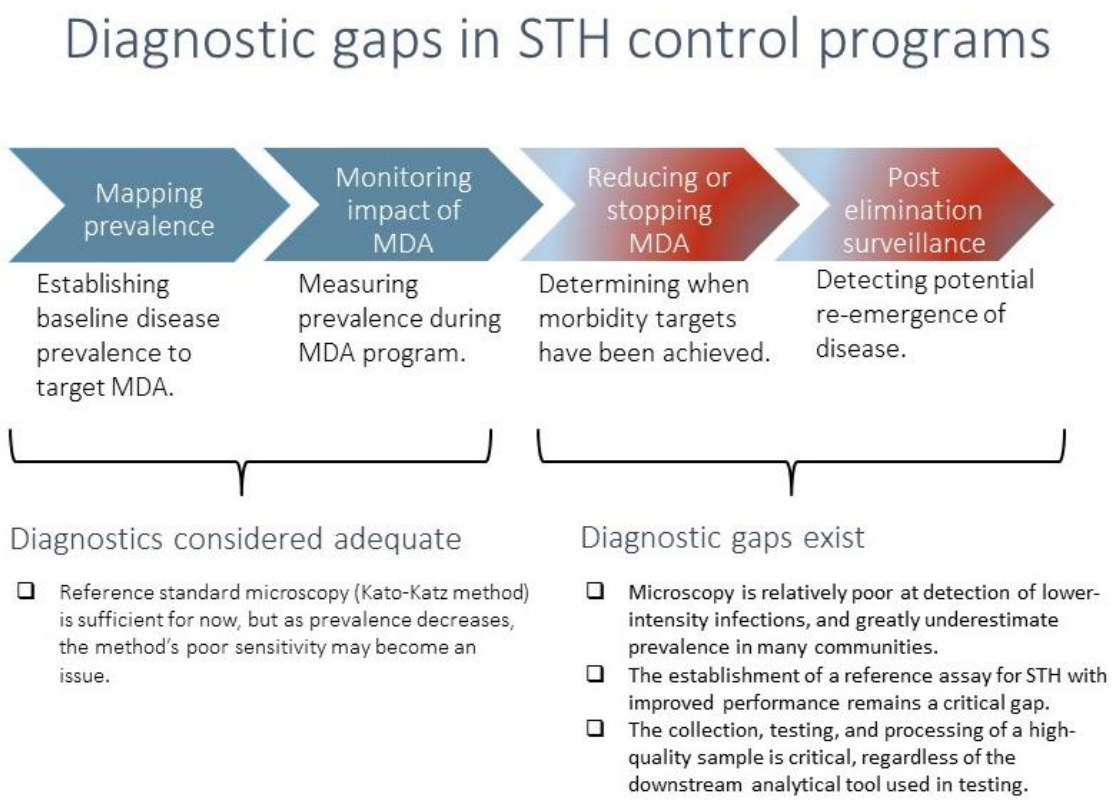
[b] Operational characteristics should also be respected when considering sample type—e.g., while a stool sample is certainly accessible, it is less acceptable in many settings. There is frequently a stigma around stool collection, and the unpleasantness of working with stool forces some deworming programs to decouple the collection at the school from the testing, which is done at a location removed enough to mitigate odors. These concerns apply less to other sample types.

antigens have the same issues as the eggs themselves, although these antigens may be expressed in other life stages as well, and definitive characterization does not appear to have been done. Molecular targets are more flexible and may fall into either of these categories, depending on the choice of target.

Prioritized uses for new, improved diagnostics

Based on information generated during our landscaping exercise, the greatest need is for new diagnostics to support elimination of schistosomiasis and post-elimination surveillance (Figure 6). This is based on the observation that existing diagnostic methods, while not optimally sensitive, are sufficient to identify intense infections and the initial effect of MDA on them. The need for greater sensitivity is primarily to detect lower intensity infections that can still be transmitted after MDA.

Figure 6. Uses for which current diagnostics are adequate or deficient.



Preferred product characteristics and promising solutions

The preferred diagnostic test solution for the later stages of the control-to-elimination continuum is a highly sensitive rapid diagnostic test (RDT) for a circulating anodic antigen (CAA), most likely coupled with a reader at first and eventually with some form of sample preconcentration to reach the lowest limit of detection

required (one fecund worm pair). This preference is due to the advanced state of CAA characterization, the current availability of commercialized platforms onto which CAA can be applied, and strong advocacy among key stakeholders within the schistosomiasis community. If tests other than a CAA test are developed, priorities would include development of an antibody test using *S. mansoni* cercarial transformation fluid as an antigen, especially if that test could be multiplexed with the highly sensitive CAA test. However, because of current product development barriers, including a lack of WHO guidelines, there is currently significant risk that newly developed schistosomiasis diagnostic products would not achieve intended impact for elimination efforts.

Based on PATH landscape and program analyses, the schistosomiasis diagnostic should have the attributes outlined below.

The analyte should be a CAA. A CAA is a polysaccharide waste product of adult worm pairs that is always present in several accessible sample types (blood and urine), very stable, and genus specific (one product could guide MDA in all endemic countries, regardless of the geographic distribution of *Schistosoma* species). Considerable work has already been done to establish this biomarker as the preferred analytical target.[c]

RDTs based on lateral flow immunochromatographic strips using highly sensitive labels and, ostensibly, a reader to increase signal-to-noise ratios are recommended to enable sensitivity for low-intensity infections while retaining desired ease of use. Proof-of-concept demonstrations have already been accomplished for several systems. The schistosomiasis community has indicated that readers are acceptable methods for linking to deworming programs to achieve additional diagnostic sensitivity.

Field-deployable, point-of-care (POC) CAA preconcentration methods are required for the lowest worm burden use cases (elimination certification and post-MDA surveillance). Proof of concept has already been demonstrated for an ultra-centrifugal filter method that demonstrates a theoretical worm-equivalent limit of detection of less than one worm pair (one breeding worm pair is the lowest infection intensity that corresponds to future transmission risk); however, this method is not as field deployable as the RDT it was developed to complement. Concepts for both an off-strip and an on-strip method have been proposed; to mitigate risk, both should be pursued in parallel until a clear "winner" emerges.

Table 2 shows recently reported results of the testing with a highly promising Up Converting Phosphor - Lateral Flow (UCP-LF) CAA assay, side-by-side with Kato-Katz analysis. The CAA assay shows vast superior results.

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[c] A rapid diagnostic test for a related, but inferior, circulating antigen (circulating cathodic antigen, or CCA) is already on the market and may replace coproscopy and uroscopy in *S. mansoni* prevalence mapping programs in Africa due to its ease of use and accuracy. It is not sensitive enough for low-worm-burden populations and is only sensitive for *S. mansoni*, not the other human-infecting *Schistosoma* species. It is also more prone to cross-reaction with other parasites and some human cancers.

Table 2. Diagnostic characteristics of various assays used for the detection of *S. japonicum* against a standard of infection-positivity by either Kato-Katz or UCP-LF CAA assay[28]*

Assay	True (+)	False (+)	False (-)	True (-)	Sens (%)	Spec (%)	Neg pred value (%)	Pos pred value (%)
Kato-Katz	4	0	26	136	13	bd**	84	bd
IHA	16	71	14	65	53	48	82	18
Urine CAA	28	0	2	136	93	bd	99	bd
Serum CAA	23	0	7	136	77	bd	95	bf
CAA†	30	0	0	136	100	bd	100	bd

*** Combined "gold standard: assuming 100% specificity of the egg detection and CAA results (n=30 positives).**

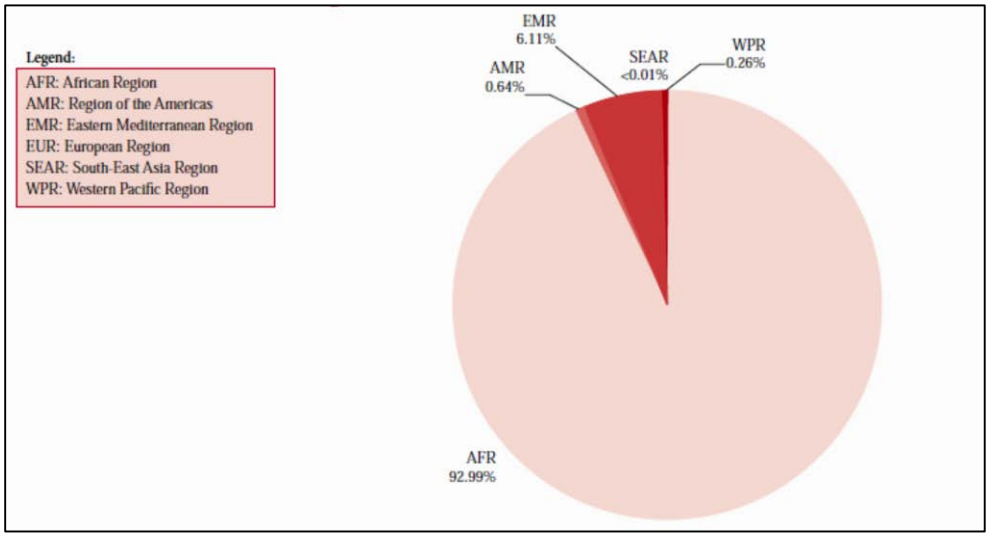
**** bd = by definition; specificity and positive predictive values are 100%.**

† CAA in urine and/or serum.

Potential markets for improved diagnostic tools

People who require PC for schistosomiasis are concentrated heavily in two of WHO's six regions, with 93% and 6% living in the African and Eastern Mediterranean regions, respectively (Figure 7).

Figure 7. Proportion of people requiring treatment for schistosomiasis who live in each WHO region, 2010.[2]



Among the 42 countries categorized as endemic in the **African Region**, 40 have populations requiring PC, and 2 (Algeria, Mauritius) are in a state of undetermined disease transmission (Table 3). The 40 PC-requiring countries can be divided into three groups as follows: fully mapped, 100% coverage of implementation (8 countries); mapping begun or completed, PC initiated, <100% geographical coverage (18 countries); and not yet mapped (14 countries). Given the consolidation of these countries and distributed states of implementation, this region represents the most likely place for optimized success of new diagnostic technologies, apart from being the largest market. As each group of countries is brought forward through the stages of implementation,

they may enter states of lower infection intensity sequentially following cycles of MDA. This could allow the deployment of more sensitive diagnostics to the first wave, observation of influence on resurgence of disease, and the thereby-informed application of diagnostics and MDA to neighboring countries.

Table 3. Status of schistosomiasis-endemic countries in the WHO African Region[2]

Group	Countries and territories
Countries requiring preventative chemotherapy	Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Liberia, Madagascar, Malawi, Mali, Mauritania, Mozambique, Namibia, Niger, Nigeria, Rwanda, Sao Tome and Principe, Senegal, Sierra Leone, South Africa, Swaziland, Togo, Uganda, United Republic of Tanzania, Zambia, Zimbabwe
Countries requiring updating for planning and implementation purposes	-
Countries requiring evaluation in order to verify if interruption of transmission has been achieved	Algeria, Mauritius

Table 4 provides detailed information on morbidity and mortality attributed to schistosomiasis in sub-Saharan Africa.

Table 4. Current estimated total number of individuals with morbidity and mortality due to S. haematobium and S. mansoni infection in sub-Saharan Africa[28]*

Schistosome species	Estimated morbidity and mortality, in millions**
S. haematobium	
At risk of infection	436
Infected	112
Haematuria during previous 2 weeks	71 (52–89)
Dysuria during previous 2 weeks	32 (17–55)
Minor bladder morbidity (detected by ultrasound)	76 (67–92)
Major bladder morbidity (detected by ultrasound)	24 (15–31)
Moderate hydronephrosis	9.6
Major hydronephrosis	9.6
Nonfunctioning kidney	[1.7]
Nonfunctioning kidney (deaths/year)	[0.15]
Bladder cancer (deaths/year)	
Males	[0.011]
Females	[0.0023]
S. mansoni	
At risk of infection	393
Infected	54
Diarrhea during previous 2 weeks	0.78 (0.0–7.8)
Blood in stool during previous 2 weeks	4.4 (3.0–8.3)
Hepatomegaly (mid-sternal line)	8.5
Splenomegaly	[6.3]
Ascites	[0.29]
Hematemesis (ever)	[0.93]
Hematemesis (deaths/year)	[0.13]

*** Source: MJ Vander Werf and SJ De Vlas (personal communication). Figures in square brackets should be interpreted with caution.**

**** 90% confidence interval in parentheses.**

The **Eastern Mediterranean Region** presents an interesting opportunity for "case study" approaches because Egypt has a very well-established control program and could serve as a control center for the three majority populations in Yemen, Sudan, and Somalia requiring PC (accounting for 57.8%, 38.4%, and 3.4% of regional PC need, respectively).

Most people requiring PC in the **Region of the Americas** are in Brazil, which accounts for 95.8% of regional need. The other country requiring PC in this region is Venezuela. Both Venezuela and Brazil have essentially had individual treatment by positive parasitological diagnosis, as opposed to MDA. The remaining countries of the region are in undetermined states of schistosomiasis infection. Thus, this region does not appear to have a population that is likely to benefit in the near term from enhanced diagnostics, since as a population it has not been synchronized by a coordinated campaign of treatment.

In the **European Region**, only Turkey has reported schistosomiasis cases since 1959. There appears to be little or no opportunity to observe the advantages of enhanced diagnostics in this region.

The **Southeast Asia** and **Western Pacific Regions** represent less than 0.3% of the worldwide population requiring PC and therefore may not constitute attractive markets. They are, however, important regions in which to test improved, strain-specific diagnostics given the geographical restriction of some strains to these areas. Indeed, some of the best data supporting the need for improved diagnostics of schistosomiasis (here, *S. japonicum*) have been generated in China. Ultimately, the accuracy and sensitivity of a diagnostic can only be established with confidence in the field.

Projected health and economic impacts of new diagnostics

Previous underestimation of the health impact of schistosomiasis

There is increasing evidence that the true impact of intense schistosomiasis infections on health and quality of life has been underestimated. Michaud CM et al. suspected this when reporting global disability-adjusted life year (DALY) and disease burden scores in 2003.[30]

King et al. performed a meta-analysis of reported data on disability-associated outcomes for all forms of schistosomiasis and reported a 2% to 15% disability weight associated with differential functional health domains—much higher than the previously reported 0.5%. Some of the functional health domains that associated significantly with schistosomiasis were anemia, chronic pain, diarrhea, exercise intolerance, and undernutrition—a more comprehensive panel than was previously assessed. In Tables 5 and 6, standardized mean differences less than zero indicate a morbidity or disability that is associated with infection, greater infection intensity, or nontreatment; odds ratios greater than 1 indicate the same.

Table 5. Summary estimates of the effect of schistosomiasis or heavy schistosomiasis in terms of disability-related continuous outcomes[31]

	How measured	Observational		Interventional
		Infected *vs* uninfected	Heavy *vs* light infection	RCT: placebo *vs* active schistosomicidal agent
Anaemia	Haemoglobin	−0·26 (−0·40 to −0·11) (n=20)	−0·65 (−1·26 to −0·05) (n=11)	−0·25 (−0·36 to −0·15) (n=5)
Undernutrition	Weight	−0·03 (−0·17 to 0·11) (n=16)	−0·19 (−0·45 to 0·07) (n=6)	−0·64 (−1·08 to −0·20) (n=5)
	Height	−0·05 (−0·31 to 0·22) (n=8)	0·05 (−0·24 to 0·35) (n=5)	−0·11 (−0·23 to 0·01) (n=4)
	Weight for height	−0·36 (−0·66 to −0·06) (n=5)	−0·17 (−0·65 to 0·31) (n=2)	−0·63 (−1·37 to 0·12) (n=3)
	Skin fold thickness	−0·22 (−0·84 to 0·39) (n=7)	−1·36 (−2·59 to −0·13) (n=5)	−0·66 (−1·22 to −0·10) (n=5)
Reduced fitness	Exercise duration	−1·09 (−1·27 to −0·92) (n=2)	..	..
	VO2 max	−0·03 (−0·24 to 0·17) (n=4)	−2·25 (−5·37 to 0·87) (n=2)	..
Educational	School performance	−0·73 (−2·52 to 1·05) (n=2)	..	..

Data are standardised mean difference (95% CI) and number of studies. *Meta-analysis of religious activity, personal care, healthcare needs, cognition, housework deficit, and work yield deficit was restricted because of small sample size (ie, number of available studies for inclusion), or because of inconsistent measures used to assess morbidity outcomes.

Table 6. Summary estimates of the effect of schistosomiasis or heavy schistosomiasis by disability-related outcomes[31]

	How measured	Infected *vs* uninfected subjects	Heavy *vs* light infection
Chronic symptoms	Diarrhoea history	1·59 (1·23–2·06) (n=27)	1·41 (1·06–1·87) (n=17)
	Pain history	1·50 (1·26–1·78) (n=30)	1·22 (0·94–1·60) (n=16)
Reduced fitness	Exercise intolerance	2·25 (1·31–3·85) (n=13)	1·18 (0·79–1·77) (n=11)
Education	Poor school performance	1·18 (0·72–1·92) (n=4)	..
Infertility	Obstetric history	1·45 (0·96–2·19) (n=3)	..

Data are odds ratios (95% CI) and number of studies.

Although the current Global Burden of Disease DALY estimates suggest that the population-level impact of schistosomiasis infections is negligible, these estimates are based on diagnosis and monitoring programs that are less than optimally sensitive and that underestimate the prevalence of infection. To better articulate the discrepancy between past and current evaluations of disease burden due to schistosomiasis, work has been carried out to analyze disability weights of a single strain, *S. japonicum*. Parsing stochastic and probabilistic analyses among age strata demonstrated that, in this context, Global Burden of Disease disability weights underestimate the burden by as much as 46-fold (Table 7). Specifically, the average disability weight calculated was 0.132, with age-specific weights calculated to be 0.098 among those less than 15 years of age and 0.186 for those 15 or more years old.

Table 7. Disability weight estimates from review studies of schistosome strains and schistosomiasis japonica[32]

	< 15 years	≥ 15 years	Overall	Strains	Ratio vs. GBD
Global Burden of Disease [23]	0.005	0.006	-	All	-
King *et al.,* 2005 [19]	-	-	0.020-0.150	All	4-30 : 1
Jia *et al.,* 2007 [16]	0.095[1]	0.159-0.246[2]	0.191	S. japonicum	19-27 : 1
Current analysis	0.098	0.186	0.130	S. japonicum	20-33 : 1[3]

[1]This study excluded individuals <5 years (5-14 y)
[2]This refers to the estimated disability weights for three age groups, namely: 15-44 y (0.159), 45-59 y (0.207), and ≥60 y (0.246).
[3]Considering the lower and upper bounds of the confidence intervals for these estimates, the ratio vs. GBD estimates ranges from 7 to 46.
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Effectiveness of enhanced diagnostics depends on initial level of infection prevalence

Modeling both the intensity of infection following rounds of MDA (Figure 9) and the probability of disease elimination with increasing true prevalence at the beginning of a given period as a function of diagnostic sensitivity (Figure 10) illuminates specific populations where enhanced diagnostics may have impact.

Each panel shows a different situation. They are shown in groups of four, each one demonstrating the impact of one of the four modeled diagnostics, which are (1) worst, or most realistic, (2) fitted, (3) better, and (4) best or ideal. There are several groups of four panels, each of the groups corresponding to the true prevalence range of communities at the start of the simulation.

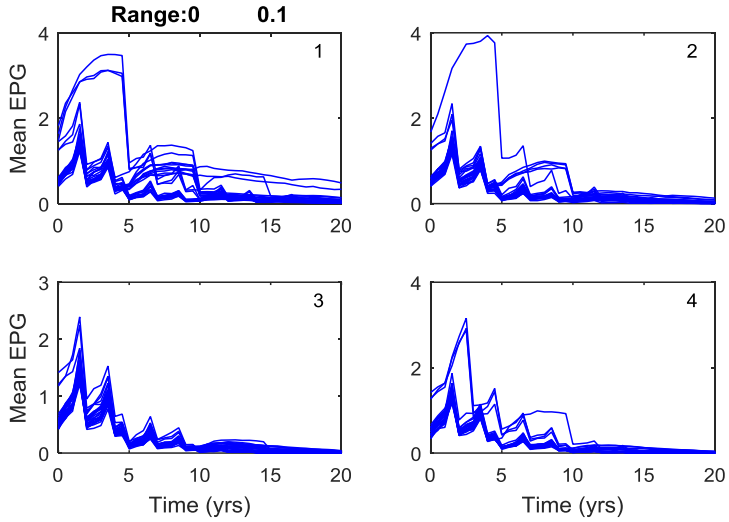
These results are drawn as mean EPG rather than prevalence, although the communities are defined in terms of prevalence of infection. The lowest true prevalence communities (0-10%) benefit relatively little from improved diagnostics, as MDA is able to control and eliminate. The intermediate true prevalence range 30-40% also shows relatively limited impact. The highest true prevalence communities (>50%) show a higher proportion of communities receiving more frequent MDA with more sensitivity diagnostics. However, targeting SAC alone is not able to eliminate infection from these communities, so the outcome is a reduction in the intensity of infection, but with the continued requirement for frequent MDA.

In essence, this modeling reveals that with insufficiently sensitive diagnostics, there will persist a number of infected people in the population that escape detection in the current schema of MDA. Since guidelines for making MDA decisions are made directly using these diagnostics, it is also reasonable to view the established MDA guidelines as actually generating a persistent population of infected people. It may appear to be a treatment-refractory population, but in fact it is simply insufficiently treated due to incomplete diagnosis. Thus, in addition to deploying the better diagnostic to accurately identify the prevalence of infection, there needs to be a corresponding standard MDA protocol that is titrated to treat the actual prevalence of infection.

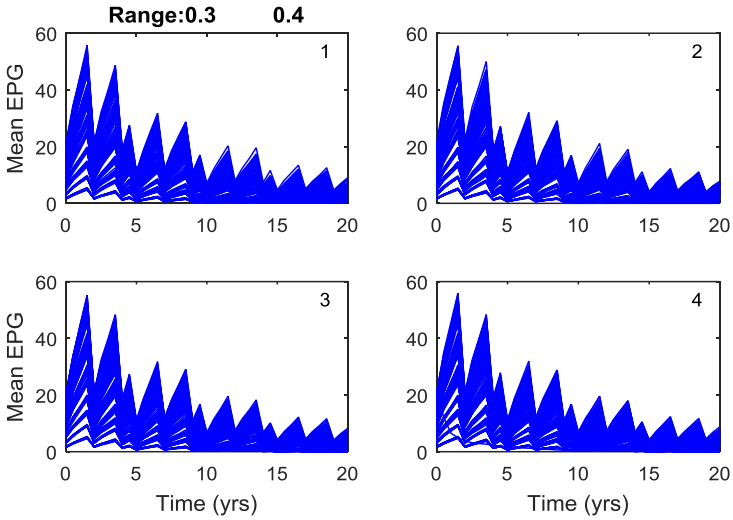
The guidelines for MDA should be adjusted to synergize with better diagnostics, and eliminate the disease completely.

Figure 8. The predicted mean intensity of *Schistosoma mansoni* infection in school-aged children over time. The top four panels are for initial true prevalence of 0%–10%, the second group 30%–40%, and the final group >50%. EPG = eggs per gram. Figure is PATH modelers-generated.

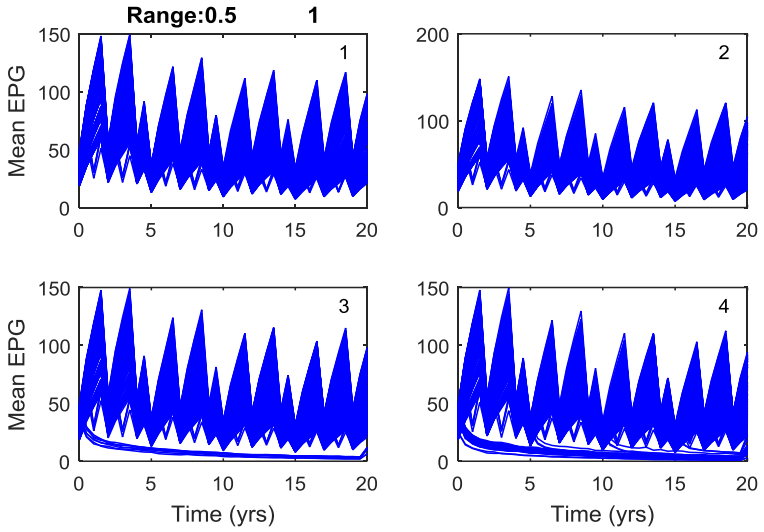
Lowest initial prevalence



Medium initial prevalence

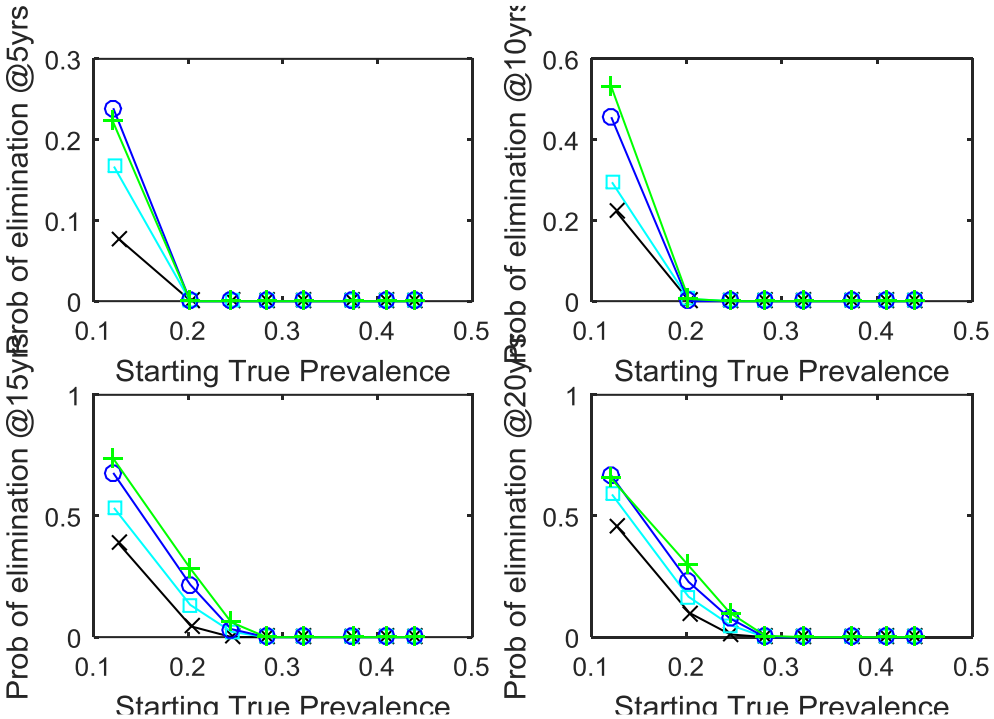


Highest initial prevalence



These results are drawn as mean eggs per gram (EPG) rather than prevalence, although the communities are defined in terms of prevalence of infection. The lowest true prevalence communities (0%–10%) benefit relatively little from improved diagnostics because MDA can control and eliminate infection. The intermediate true prevalence range (30%-40%) also shows relatively limited impact. The highest true prevalence communities (>50%) show a higher proportion of communities receiving more frequent MDA with more highly sensitive diagnostics. However, targeting SAC alone is not able to eliminate infection from these communities, so the outcome is a reduction in the intensity of infection but with the continued requirement for frequent MDA.

Figure 9. The proportion of communities in which infection is eliminated (defined as true prevalence <1%) as a function of the starting true prevalence for each of the four species considered. The four panels show results at 5, 10, 15, and 20 years. The four diagnostics (worst, fitted, better, best) are shown as black, cyan, blue, and green, in order of increasing sensitivity. Note that some panels have different vertical scales. Figure is PATH modelers-generated.



Investment and value proposition

PATH is developing new diagnostic tests to detect schistosomiasis infection as part of its pioneering role in global health innovation. Based on input from experts and modeling simulations, we believe that new diagnostics with greater sensitivity than previously used tests can substantially improve programmatic control and monitoring efforts. Although our modeling revealed that highly sensitive diagnostics will not always lead to substantial improvements in disease control and reductions in disability in every community, there are many communities where highly sensitive diagnostics can dramatically improve control efforts by identifying low-burden infections and thus the true prevalence of infection. These low-burden infections may over time appear to as treatment-refractory population, but in fact they are simply insufficiently treated due to incomplete diagnosis. Poor detection sensitivity leads to execution of a MDA protocol that is not calibrated to treat the actual degree of prevalence and the treatment guidelines appear to contribute to the resulting effect. Thus, in addition to deploying the better diagnostic to accurately identify the prevalence of infection, there needs to be a corresponding shift of guidelines for a standard MDA protocol that is titrated to treat the actual prevalence of infection. Knowing the true prevalence,

especially after repeated rounds of MDA, will lead to appropriate frequency of treatment and optimization of resource use.

There is abundant evidence that the gold standard Kato-Katz diagnostic method systematically underestimates the prevalence of schistosomiasis due to its lack of sensitivity. This inadequacy was reflected in an increased need to replicate smears for reliable detection of low-intensity infections of *S. japonicum* in samples from a Chinese population. Lin et al. found that the rate of underestimation of *S. japonicum* infection using two and three Kato-Katz thick smears (typical assay) was about 36.0% (28.4%–48.9%) and 25.0% (15.9%–40.7%), respectively.[33] The number of smears required to detect an infection varied with the infection intensity level. Thus, low-sensitivity diagnostic approaches will return false negatives when MDA-induced infection levels fall below detectable levels, though they may remain at transmissible levels.

Below a certain threshold sensitivity, the gold standard diagnostic for schistosomiasis provides no information on the prevalence of infection in a population. Specifically, in the context of post-MDA low- intensity infections, MDA re-initiation or discontinuation decisions are being made blindly. As a consequence, it is likely that adherence to WHO criteria when prevalence is incorrectly assessed to be below 1% leads to populations being taken off the MDA cycle prematurely.

Several features of the current schistosomiasis control plan present key areas for improvement:

- The "gold standard" diagnostic measures the wrong variable: egg counts. This is primarily a measure of morbidity and not transmissibility, and it is particularly irrelevant with post-MDA, low-intensity infections. A direct measure of persisting worms (i.e., single mating pair) is the most relevant indicator, as well as the built-in normalization factor for diagnostic sensitivity.

- The "gold standard" diagnostic lacks sensitivity. The sensitivity of the measure varies greatly with infection intensity, and it is fundamentally low compared to immune assays. The results are an underestimation of prevalence following MDA and misinform next-step decisions per WHO criteria.

  WHO standards for frequency of MDA are outdated and misaligned with inputs. Erroneous determination of prevalence (e.g., <1% as determined by insensitive diagnostic tests) directs populations into follow-up treatment schemes that may perpetuate transmission and cyclic resurgence. In essence, there may be systematic under-treatment of populations with MDA that creates worm populations cycling out of phase with the predetermined treatment scheme. Though PZQ resistance has not yet been documented, low cure rates in sub-Saharan Africa are being reported, and the repeated under-administration of a direct-acting drug to a population is a dangerously effective way to generate resistance. WHO criteria that properly guide MDA decisions based on accurate diagnosis could help to preserve the drug life cycle of PZQ.

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