SCHISTOSOMIASIS: Analysis of diagnostic gaps and a proposed path forward
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1. Executive summary

In recent years, great strides have been made in the control and approach to elimination of schistosomiasis through deworming programs in school-aged children that employ the antischistosomal drug praziquantel (PZQ). These programs are made possible by the large-scale donation of PZQ by the UK Department for International Development, the United States Agency for International Development, and Merck KGaA.\(^1\)\(^2\) Surveillance for *Schistosoma* infection is done as part of these mass drug administration (MDA) programs using World Health Organization (WHO)-approved diagnostic tools. Currently, microscopic examination of stool and urine samples to determine the presence of *Schistosoma* parasite eggs are the “gold standard” methods for informing control program decisions regarding MDA.\(^1\)\(^2\) 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, 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.\(^1\)\(^2\) Because of the way programs are managed, failure to adequately address new diagnostics could jeopardize achievement of the 2010 London Declaration goals.

In this report, we assess diagnostic needs, landscape potential solutions, and determine an appropriate strategy to support improvement of diagnostic testing for support of schistosomiasis elimination efforts. Based upon previous input from the schistosomiasis expert community, including input obtained during the 2013 Task Force for Global Health meeting (Decatur, GA, USA August 7–8, 2013), two diagnostic use cases for schistosomiasis were prioritized for further exploration, informing MDA stopping decisions and post-MDA surveillance. To this end, PATH has refined target product profiles (TPPs) for schistosomiasis diagnostics that are applicable to these use cases.\(^10\) Based on the findings in this report, and additional feedback from the community, we recommend further investment in new diagnostic tests with the following attributes:

- **The analyte should be a circulating anodic antigen (CAA).** 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 can guide MDA in all endemic countries, regardless of the geographic distribution of *Schistosoma* species). Considerable work has already been done that establishes this biomarker as the preferred analytical target.\(^ii\)

- **Rapid diagnostic tests (RDT) based on lateral flow immunochromatographic strips utilizing highly sensitive labels and a cognate reader** to increase signal-to-noise ratios are recommended to

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\(^1\) The Kato-Katz method is the most common coproscopy (stool microscopy) preparation, and urine filtration is done prior to uroscopy (urine microscopy). The schistosomiasis community frequently uses “Kato-Katz” and “urine filtration” as a short-hand identifier for these methods.

\(^ii\) 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 also is only sensitive for *S. mansoni*, not the other human-infecting *Schistosoma* species.\(^11\) It is also more prone to cross-reaction with other parasites and some human cancers.
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 pre-concentration 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 on-strip method have been proposed, and to mitigate risk, both should be pursued in parallel until a clear “winner” emerges.

We acknowledge that tests based on detecting host antibody responses and cell-free DNA have been demonstrated and may be feasible options in the future. Additional research on these methods are not a priority investment at this time given the advanced state of development of direct tests based on CAA antigen testing. Antibody testing may eventually prove a valuable adjunct to CAA testing in the lowest worm burden use cases.iii There are some antibody RDT already in development; progress on these tests should be monitored and encouraged. New molecular diagnostic tests targeting cell-free DNA appear to have high potential but have not been adapted to the POC. The emergence of new POC molecular platforms, and the potential for multiplexing with other neglected tropical disease (NTD) tests (most notably soil-transmitted helminthiasis), may create a need to reevaluate molecular test development in the future.

### 2. Disease overview

Schistosomiasis is a potentially debilitating disease resulting from infection by sexually reproducing trematode worms (genus *Schistosoma*).12,13 WHO estimates that worldwide approximately 700 million people are at risk of schistosomiasis, with 240 million actually affected, several million of whom have severe morbidity. In sub-Saharan Africa, 250,000 deaths are attributed to schistosomiasis every 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, WHO has recommended an overall control strategy abbreviated as PHASE (Preventative chemotherapy, Health education, Access to clean water, Sanitation improvement, Environmental vector control).2

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iii Antibody tests are indirect tests and are, in general, poor at distinguishing past exposure from current infection. An antibody negative is an excellent proxy for a true negative, however, and makes a good confirmatory test in low-prevalence, low-burden situations where the infrequency of true positive results makes false positives especially undesirable.
There are seven species of schistosomes that infect humans, but the majority of morbidity is cause by *S. haematobium* (Africa), *S. mansoni* (Africa and South America), and *S. japonicum* (Asia). The mature adult worms of all *Schistosoma spp.* 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 intestine and the liver.\textsuperscript{12,13}

It is the parasite eggs that are the primary source of chronic human morbidity, as large numbers are produced and most are not shed quickly into the excreta; residual eggs cause inflammation, hyperaemia, abnormal growths, and internal hemorrhage progressing to fibrosis and thickening of the tissues. *S. haematobium* infection can cause bladder cancer, and the other *Schistosoma spp.* induce embolization of

\textsuperscript{iv} *S. haematobium*, *S. japonicum*, *S. mansoni*, *S. intercalatum*, *S. mekongi*, *S. malayensis* (public health significance undetermined), and *S. guineensis* (recently separated from *S. intercalatum*).
eggs in the intestine to the liver through the portal system (responsible for progressive liver fibrosis, portal hypertension and ascites). However, it is the fecund adult worm pair that is the best indicator of future transmission risk—a single worm pair may generate ~300 eggs/day and live for decades—potentially representing many millions of future infections (although, this potential is rarely achieved). 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, e.g., after chemotherapy treatments. Thus, egg counts may be the best proxy for morbidity in high-burden populations, but direct indicators of worm burden are the best proxy for transmission risk and for informing MDA decisions.

An effective preventative chemotherapy (PC), praziquantel (PZQ, sold under a variety of brand names and dosages for human and veterinary use), is used by schistosomiasis control programs in many countries to target children in endemic communities and districts through school-based deworming campaigns. Administration of PZQ can reverse up to 90% of organ damage in schistosomiasis-affected individuals and has been responsible for the decline in both prevalence and morbidity in over 50 endemic countries around the globe. Programs based on PZQ have been successful enough that as many as 19 endemic countries may have interrupted transmission (yet to be certified) with Burkina Faso, Cambodia, China, Egypt, Mauritius, and Morocco as notable examples. PZQ is primarily donated by the UK Department for International Development, the United States Agency for International Development, and Merck KGaA for these programs—with a recent increase in commitment to 250 million tablets/year—sufficient for current needs but likely not covering projected increases in needs. PZQ administration is expected to peak at about 660 million doses in 2017 and then decline again as countries are certified as eliminated. Given the scale of these treatments and 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 in communities are made based on diagnostic testing performed on the same school children being targeted in the school deworming programs. 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 (Figure 2). In the first group, where morbidity control is still the primary aim, when the prevalence of heavily infected sentinel sites drops below < 5%, PC is continued for at least 5–10 years 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 prevalence of heavily infected sentinel sites below < 1%, for 3–6 years. The third group contains those 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 here that as PC treatment reduces the prevalence of heavily infected sites, the individual worm burden falls in concert. Considering these criteria, it is now accepted 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.
Currently, microscopic examination of stool and urine samples to determine the presence of *Schistosoma* parasite eggs are the “gold standard” methods for informing control program decisions regarding 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).\(^3\) 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 the 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.\(^1\),\(^2\)

The goal of this report is to identify candidate diagnostic options for schistosomiasis, determine what gaps may exist, and make recommendations for next steps related to product development of new diagnostics for schistosomiasis. The following considerations were important in this diagnostic landscape evaluation:

- **The intended use is for population-based surveillance.** For schistosomiasis surveillance, diagnostic tools will be used primarily to inform decisions by control programs on whether to treat entire populations with PZQ and not for individual diagnosis and patient management. Thus operational requirements such as the ability to perform the test at the POC and provide a rapid result may take on lesser importance IF specimens can be transported effectively to allow for testing within an external

\(^v\) The schistosomiasis community frequently uses “Kato-Katz” and “urine filtration” as a generalized identifier for these methods.
location. Conversely, the capacity to easily batch test large numbers of samples collected during surveys may increase the value of a specific option.\textsuperscript{27} Interestingly, the key opinion leaders in schistosomiasis surveyed for this work unequivocally stated a preference for a field-deployable, easy-to-use test—an observation reflected in our TPPs.

- **Targeted use cases.** Currently available methods\textsuperscript{vi} are considered by stakeholders to be adequate for monitoring schistosomiasis when prevalence is high, such as determining baseline prevalence (mapping) and the assessment of effects of early rounds of MDA in reducing burden (impact monitoring). Thus the early control stages of schistosomiasis control and elimination strategies are not the targeted used cases for new diagnostic tools (Figure 2)—informing late-stage decisions on when to stop MDA and then monitor for possible reemergence after MDA has been halted are prioritized.\textsuperscript{27} Additionally, it is desirable that the measure (infection or exposure) used in tools for informing both these late-stage use cases will need to be the same or extremely well correlated since data will be utilized longitudinally in these stages.

- **New diagnostic tools for schistosomiasis must be able to offer substantial improvement over current methods.** If new diagnostic tools do not provide substantial benefit over current methods for informing decisions by control programs, justifying their approval by WHO and use by control programs for surveillance will be difficult. Ideally, a new diagnostic test will offer improvement in terms of accuracy and operational characteristics to justify the transition costs from accepted microscopic methods. Care must be exercised in evaluating accuracy of a new method since the current “gold standard” microscopic tests are not sensitive to the desired endpoint, transmission risk from fecund adult worm pairs. Diagnostic accuracy analysis has been interpreted in the light of known shortcomings in the typical reference methods, and studies using composite references tests or statistical methods such as latent class analysis\textsuperscript{28-32} have been granted greater credence because of this. A direct assay for a relatively abundant analyte that is constitutively produced by a fecund worm pair, rather than one that is tied to egg production, appears to be a fundamental requirement for achieving a substantial improvement. Low limit of detection requirements can be addressed through improvement of signal to noise ratio (S/N) by several routes. Several common and popular solutions that have been used for schistosomiasis tests: 1) pre-analytical concentration of analyte from a large sample volume, 2) pre-analytical enzymatic amplification of analyte (e.g., PCR), 3) enzymatic amplification of raw signal during analysis (e.g., many ELISA systems), 4) use of high S/N labels (fluophores or up-converting phosphors [UCP]), or 5) noise reduction through automation and optoelectronics (e.g., lateral flow strip [LFS] readers).\textsuperscript{33-47} Several of these methods may need to be combined to meet TPP requirements.\textsuperscript{35,36,43-45} Note that some older, outdated methodologies and technologies that have been used in prior schistosomiasis research, such as those based on classic coproscopic and uroscopic methods and crude immunoprecipitation, were deemed beyond the scope of this landscape report and were omitted in detailed analysis. Their cost, complexity, and in many cases inferior performance compared to newer tests make them unlikely to be viable solutions for late-stage uses. A comprehensive review of these methods is also already publically available.\textsuperscript{38}

\textsuperscript{vi} These methods include the microscopic methods recognized by WHO as gold standards, as well as other accessory methods that are not universally applied, e.g., urine microhematuria dipsticks (for \textit{S. hematobium}) and an RDT for CCA (for \textit{S. mansoni})
3. Research gaps

It is a well-documented and accepted fact that the standard microscopic egg-counting methods lack sensitivity as worm burden falls, especially with single sample schemes that are easiest to perform in the school deworming programs. Numerous studies have shown that multiple samples over multiple days are a much better diagnostic accuracy criteria, but given the stigma surrounding sampling and testing excreta, this is far from an acceptable solution for most surveillance programs.5,20,38,48,49

“Unfortunately, the technological development of new assays has evolved slowly… partially due to the perceived lack of financial return to the diagnostic companies that contributes to making the investments insufficient and discontinuous. Nonetheless, as result of public, mostly academic investments, a number of diagnostic tests have been developed... few of these methods survived the critical non-industrial tactical approach generated by the classic academia-industry disconnect. Consequently, a number of great opportunities may have been buried or left put aside by universities and research institutes. In the same way, hard won resources may have been spent on attempts to develop less robust assays.” (quoted from Gomes, Enk, and Robello; 2014)38

In an attempt to answer strategic questions about schistosomiasis control and elimination, including developing and evaluating new tools for program managers to use, the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) was established in December 2008 with funding by the Bill & Melinda Gates Foundation. SCORE accomplishes its objectives through “funding investigators from around the world to conduct the needed research and evaluation activities.”50

The key opinion leaders in SCORE concluded that a sensitive rapid test for a circulating antigen constitutively produced by a fecund adult worm pair was the most promising tool – a conclusion with which PATH concurs for all the reasons outlined above. Suitable antigens had already been identified by a research group at Leiden University Medical Center (LUMC),35,37,46,51-54 and an RDT for one of them, circulating cathodic antigen or CCA, has been successfully commercialized by Rapid Medical Diagnostics (Pretoria, South Africa). To date, several large field studies have concluded that this CCA RDT when used to detect S. mansoni provides similar sensitivity to the best coproscopic gold standard methods (K-K on multiple samples), albeit with apparently lower specificity.11 It appears that CCA tests are not adequately sensitive to the other Schistosoma spp., presumably due to species-specific variation in the quantity of CCA excreted, a conclusion recently captured in a Cochrane Review.11 In its current format, the CCA RDT is not sensitive enough for low worm burden use cases. In addition, CCA has a higher potential for cross-reaction with other parasite antigens and some human cancers because of its repeated “Lewis X” polysaccharide epitopes.56,57 It would also be advantageous to control programs around the world to have a single test that would recognize all the globally important Schistosoma spp.

Fortunately, CCA is not the only circulating antigen associated with fecund adult worms identified by LUMC. A second antigen, circulating anodic antigen (CAA) has been the subject of extensive academic

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vii These results illustrate the danger of misinterpretation of diagnostic accuracy studies on imperfect references, however. The apparent false positives with the CCA RDT, most likely due to a superior limit of detection of the CCA test relative to egg counting, were viewed negatively because they impacted the calculated specificity versus egg counting. The manufacturer responded to this perception by making an experimental product which had been tuned to be “less sensitive.” This product performed even worse, perhaps not surprisingly.55
development and field demonstrations. CAA production does not appear to vary in abundance across species as much as CCA,\textsuperscript{44} and it has a biochemically unique structure.\textsuperscript{58} SCORE funded the LUMC group to reduce the limit of detection of a CAA test to “as low as possible” (Dan Colley, SCORE, personal conversation), preferably to analyte levels that correspond to a single worm pair.\textsuperscript{viii} LUMC accomplished this low limit of detection through use of a high S/N label (UCP) on an RDT, a cognate reader, a sample pretreatment step to release the antigen from immune complexes, and—for the most sensitive embodiment—a sample pre-concentration step. While this combination has proven to be an excellent performer so far,\textsuperscript{36,43,44} it is not meeting TPP requirements for ease of use and throughput (primarily due to the format of the pre-concentration step). The UCP label has also created manufacturing concerns in the past due to uncertain particle supply and the need for a custom reader. Further development of a CAA RDT on a commercially available reader with more conventional particles and retaining the sample pretreatment step should result in a field-deployable, easy-to-use test that is a significant improvement over other available tests for near-term use. We consider this the path of least resistance to move forward with this analyte of choice. Additional development of better integrated sample pre-concentration and the UCP and UCP-reader would then yield a second-generation test that fully met all ideal TPP attributes.

We acknowledge that tests based on detecting host antibody responses and DNA have been demonstrated and may be feasible options in the future. Additional research on these methods are not a priority investment at this time given the advanced state of development of direct tests based on CAA antigen testing. However, a research and development gap analysis for these methods are logical additions to this report.

Antibody testing may eventually prove a valuable adjunct to CAA testing in the post-elimination use cases. Antibody tests are indirect tests and are, in general, poor at distinguishing past exposure from current infection. This they are of questionable utility in the impact monitoring and stopping decision use cases. An antibody negative is an excellent proxy for a true negative, however, and makes a good confirmatory test in low-prevalence, low-burden situations where the infrequency of true positive results makes false positives especially undesirable; as well as being a good mapping tool to find areas of endemnicity. Most antibody tests in current use are older technologies that are used for mapping\textsuperscript{38} and are considered beyond the scope of this report. In addition, there is a plethora of research-only and “home brewed” ELISA tests that have not been qualified for human diagnostic use and are not emphasized here. There are second-generation antibody RDT already in development (Appendix 1), and encouraging field data have been gathered.\textsuperscript{38,60-64} Progress on these tests should be monitored and encouraged. Perhaps the most interesting potential application of antibody test is in a multiplex with CAA on a reader. The confirmatory value of the antibody test would be exploited without the added complexity of running a second test, and the use of a reader would enable the facile user interpretation of the result though the automation of an interpretation algorithm. An additional benefit would be the gathering of important population-wide data that could inform post-MDA surveillance test-type selection and possible transition. The biggest problem that remains unsolved in the multiplex approach is in sample introduction —it is

\textsuperscript{viii} Another advantage of the antigens identified by LUMC is that they have been able to characterize them with an experimental primate model that allows correlation to actual adult worm burden and, therefore, good estimation of how serum or urine concentration of the antigen relates to the parameter of most interest to elimination programs (low number of fecund worm pairs).\textsuperscript{59} To our knowledge, none of the other newer biomarkers are thus characterized.
likely that different samples, or sample pretreatments, may be required for a CAA test and an antibody test. More work is required on solving the practical aspects of sample preparation for a multiplexed assay.

New molecular diagnostic tests targeting *Schistosoma* DNA appear to have high potential but have not been developed into commercial human-diagnostic products or fully adapted to the POC (Appendix 1). In a very recent review of schistosomiasis diagnostics, 25 publications on molecular methods were identified, 10 of which were “in-house” methods to support research, 13 of which had progressed to “limited field studies,” and only 2 of which had been evaluated in “large-scale field testing.” The majority of demonstrations have involved PCR assays (both traditional or RT-PCR), however, two were of loop-mediated amplification, an isothermal method with better potential for application to POC. Most of the molecular tests use stool as a sample, although there has been some work with urine and plasma (including cell-free detection). Some researchers have investigated RDT detection of amplicons. A genus-specific 121 base-pair tandem repeat within the DRA1 gene (DNA) has been the target in most of these investigations; however, some recent work has focused on species differentiation using a variety of different targets (SSU rRNA gene, ITS-2, 28S ribosomal RNA gene, *cox1* gene and others). The lack of progression of these molecular assays from lab-based research tools into mature commercialized products is probably reflective of both the newness of the effort (most publications have appeared in the last decade) and the market dynamics discussed in the first paragraph of this section. The presence of strong direct-assay competitors in the CCAs and CAA that do not require the infrastructure and complexity of molecular assays undoubtedly has suppressed enthusiasm for further development of these molecular assays somewhat. Additional research is required for molecular assays that detect *Schistosoma* infection to “catch up” to the state of development of the circulating antigen assays, and may not be required if highly sensitive CAA RDT come to fruition. The emergence of new POC molecular platforms and the potential for multiplexing with other NTD tests may create a need to reevaluate molecular test development in the future.

4. Risks and mitigation

1. A newly developed CAA RDT may not be implemented and used by national schistosomiasis control programs to support elimination efforts.

   a. **Problem:** Current barriers that limit the potential application of newly developed diagnostic tools to support schistosomiasis elimination efforts:

   i. **WHO guidelines have not been amended:** It is unlikely for any new diagnostic tool to be widely implemented and used outside of research unless there is a recommendation from WHO. This approval has not yet occurred, and there is currently no assured timeline for when the necessary evidence and support by key stakeholders will be obtained.

   ii. **The CAA RDT developed may not be well accepted by a majority of stakeholders:** While the schistosomiasis community appears to be largely in agreement with what is needed right now, there is always a risk of misinterpreting that opinion or finding that it has drifted in the time...
that products are being developed. Any lack of consensus in the schistosomiasis community could hinder the amendment of the WHO guideline.

b. **Mitigation:** Postpone down-selection of new product development efforts until clarity is obtained on timeline and likelihood of success in amending WHO recommendations. Maintain engagement with schistosomiasis stakeholders to assess the status of current opinion regarding a change in guidelines. Remain up to date on the results of ongoing research to build evidence to support changes, including the outcomes of the current multi-site study led by the Task Force for Global Health[89]. If and when support for amending WHO guidelines is obtained, PATH will work with stakeholders to assess if gaps remain that warrant the initiation of new product development efforts. For instance, if antibody or molecular testing becomes a preferred option, then PATH can play a translational role supporting the commercialization of these assays.

2. **A newly developed schistosomiasis diagnostic will not have the proper characteristics to meet the needs of control programs.**

a. **Problem:** Research in the following areas are still needed to fully delineate optimal test characteristics for new diagnostics intended for use by schistosomiasis control programs in different endemic settings:

i. **Operational characteristics:** An RDT for a circulating antigen is the option strongly advocated for by SCORE and other key stakeholders within the schistosomiasis community. This is due in part to the combination of adequate analytical performance, combined with perceived ease of use, and the current wide-spread use of RDTs in many schistosomiasis-endemic countries due their use for other diseases. However, questions remain about the ability of these test to meet the needs of country programs in terms of throughput, costs, and robustness.

1. **Throughput:** RDTs seem best suited to use cases where a test result will be immediately used to inform the treatment of an individual—either clinical management or a “test and treat” surveillance strategy. However, test and treat is not the model currently being employed by most school deworming programs where these tests are administered—if testing is done on the same visit, PZQ is administered to all who get diagnostics, and the test results used are to evaluate previous treatment efficacy and guide future treatment. This suggests that a higher throughput method may be more efficient; however, the logistics of transporting samples back from the collection site to a laboratory can be problematic if there are any sample stability issues. In addition, a large part of the RDT time-to-result budget is consumed by linking the test to an individual, which may not be required in these programs.

2. **Test cost:** Although RDTs are usually not as expensive as some of the other options considered here (especially molecular tests), there is a perception among many key opinion leaders that the current CCA test is cost prohibitive.[55,90] While it remains to be seen what the final cost per test of a CAA RDT (with or without a reader, or an exotic reporter reagent) may end up, it seems unlikely that it will be significantly less than the
CCA RDT already on the market. There is a growing awareness, however, that microscopy—on the surface an inexpensive technique due to cheap supplies—has additional overhead that may make it even more expensive that the CCA RDT, especially if “gold standard” rigor is applied. A “true cost” analysis (including all personnel required and the actual time it takes to administer the program) suggests the overall cost per school using the K-K method is US$102 and the CCA RDT assay is US$23, and that the cost differential is even greater if multiple K-K are performed.35

3. Ensuring quality testing. Recent external quality control programs applied to malaria and HIV RDT have demonstrated that even the relatively simple RDT platform can be misused and mishandled91 to yield substandard performance.[Unpublished PATH data] It remains to be seen if a highly sensitive RDT can be engineered to be adequately robust in the difference endemic settings, especially if a reader or a sample pretreatment step is required.

ii. Performance characteristics: Better characterization of the test performance thresholds that are needed to properly inform public health decisions will be important to inform the development of new products and will accrue naturally as they are validated in field settings. As discussed above, high clinical sensitivity to infection, in the form of a low analytical limit of detection, will be required as worm burden falls, however there has been some debate on how low that must be. A limit of detection of one fecund worm pair is desirable based on first principles—fecundity and lifespan of the worm. However, the real target for transmission risk should be $R_0 < 1$. This may be achievable by reducing worm burden to something greater than one worm pair. The exact worm burden associated with $R_0 < 1$ is not well characterized, however. One worm pair limit of detection is a conservative value that should ensure vanishing incidence. Excellent specificity will be a requirement once true prevalence (and infection intensity) has reached low levels given the need to limit the impact of false positives on decisions to either prolong MDA or restart MDA (if resurgence is detected). Other performance parameters will most likely be subservient to the accuracy of the test.

b. Mitigation: Considerable work has already been done by PATH, SCORE, and others that have resulted in several iterations of TPPs for schistosomiasis tests for different use cases. In-depth user needs assessment research for soil-transmitted helminthiasis recently completed at PATH has also informed the schistosomiasis TPP. A recently completed survey of key opinion leaders has also vetted our current thinking. TPPs are living documents, and PATH will continue to inquire, test assumptions, and revise our TPPs to ensure that whatever product development we are involved in results in diagnostics that meet the need.

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ix $R_0$ is the basic transmission rate. $R_0 < 1$ corresponds to eventual extinction.


5. Diagnostic landscape

Diagnostics tests for schistosomiasis can be classified in various ways. One useful taxonomy starts by classifying tests as clinical or laboratory (Figure 3). 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. 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 3: Existing schistosomiasis diagnostic tests classified by a useful taxonomy. (Adapted from Motumbo, et al, unpublished data, in press).

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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 which interrogate the immune response of the host. In general, direct tests are more appropriate for informing MDA administration as prevalence and infection intensity fall and incidence approaches nil, while the indirect tests are most useful in post-elimination use cases. Existing laboratory tests have recently been reviewed. Except where noted in Section 3, those tests are summarized here, along with additional tests that were not captured in the review but that are known to PATH (Appendix 2).
While understanding the tests that are available and under development is important, it is also important to understand the intrinsic properties of the biomarkers to which they are targeted. Many biomarkers may be applied to multiple platforms (e.g., antigens can be applied to both ELISA and immunochromatographic RDT), but some possible combinations may not be represented in the list of tests in Appendix 2. Thus, biomarker properties like genus or species specificity, biological uniqueness, and abundance and persistence in accessible (and acceptable) samples types should be considered. In the table of identified biomarkers (Appendix 1), those intrinsic properties most important to the low-prevalence/worm-burden and post-elimination use cases are highlighted. No amount of heroic engineering of a platform or technology can correct for selecting the wrong biomarker to target for the use case.

Diagnostic tests used for schistosomiasis detection are typically targeted at biomarkers that are either genus or species specific. A test should be able to adequately discriminate against other common bacterial pathogens that may be found in surveillance samples and especially in the case of antibody tests 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 spp. 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 spp. 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 spp. (Figure 4) 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 are often not well enough characterized with a diverse set of clinical samples to understand the specificity well. Examples of two antigens that are well characterized are the circulating antigens CCA and CAA, introduced in Section 3. As discussed in that section, CCA has a repeated Lewis X structure that can be found in the proteome of other related parasites and even some human cancers, making it potentially cross-reactive to common comorbid conditions. However, the carbohydrate repeats that are antigenic in CAA are more unique to Schistosoma spp., making them less susceptible to nonspecific reactions on first principles. Crude preparations of antigens, such as soluble egg antigen, adult worm antigen, and Schistosoma mansoni cercarial transformation fluid contain a plurality of native epitopes which elicit complex immune responses. This is an advantage for creating a test that most closely mimic the actual biological milieu but presents problems for standardization, consistent manufacturing, and commutability of results across population. Molecular assay targets can also be either genus or species specific, and as long as targets are sufficiently long, biochemical uniqueness of the target is exquisite. The growing database of sequence data usually enables the determination of specificity a priori.
Figure 4: Distinguishing characteristics of schistome eggs that enable trained microscopists to distinguish different species. Even though S. intercalatum and S. haematobium both have terminal spines, they are distinguishable because they appear in different samples. (S. intercalatum in stool only, and S. haematobium in urine only.). Reproduced from the University of Cambridge, http://www.path.cam.ac.uk/~schisto/helminth_eggs/index.html.

Abundance and persistence of the biomarker in an accessible sample is also a key attribute to consider. As illustrated by the coproscopic and uroscopic “gold standard” methods, diagnostic accuracy is poor when there is not sufficient 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 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 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.

The two appendices to this report summarize the tests and biomarkers that we have identified. Emphasis has been given to those biomarkers and technologies that show the most potential for meeting the TPP

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*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 an location removed enough to mitigate odors. These concerns apply less to other sample types.*
with a commercial product before the 2020 London Declaration goal. As with all landscaping activities, they represent a snapshot in time—new candidates could emerge at any time in the future. We have, nevertheless, attempted to be as comprehensive as possible for the use cases defined above.

6. Use case statement

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 in communities are made based on diagnostic testing performed on the same school children being targeted in the school deworming programs. At a country level, 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 (Figure 2). In the first group, where morbidity control is still the primary aim, when the prevalence of heavily infected sentinel sites drops below < 5%, PC is continued for at least 5–10 years 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 prevalence of heavily infected sentinel sites below < 1%, for 3–6 years. The third group contains those 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 here that as PC treatment reduces the prevalence of heavily infected sites, the individual worm burden falls in concert. Considering these criteria, is now accepted 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 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 to poorly targeted PHASE interventions that may be costly to donors, control programs, and the morale of the frontline health care workers and the affected populations. Thus, a diagnostic tool capable of more accurately informing late-stage decisions by control programs has potential value by more effectively targeting PHASE interventions and their attendant limited resources. Globally, as more countries move towards reaching elimination goals, the enhanced ability to more accurately identify and target remaining reservoirs of infections that either persist or reemerge could further expedite global elimination goals and with them the winding down and conclusion of the massive drug donation and control programs costs.

7. Conclusion

Microscopic methods to count schistome eggs will remain the WHO-recommended method for schistosomiasis surveillance until required evidence is generated that clearly demonstrates how diagnostic tools measuring alternative indicators—infestation and exposure—will significantly improve decision-making by control programs. Currently, the continued use of microscopy remains preferred by key WHO
scientific advisors due in part to its low cost; demonstrated efficacy in high-prevalence, high-worm-burden settings; and its longstanding use by control programs.

The preferred diagnostic test solution for the later stages of the control to elimination continuum is a highly sensitive RDT for CAA, most likely coupled with a reader at first and eventually with some form of sample pre-concentration to reach the lowest limit of detection required (one fecund worm pair). This preference is due to the advanced state of CAA characterization, current availability of commercialized platforms onto which CAA can be applied, and the strong advocacy amongst key stakeholders within the schistosomiasis community. If other tests than a CAA test are developed, prioritized biomarkers would include an antibody test using Schistosoma mansoni cercarial transformation fluid as an antigen, especially if that test could be multiplexed with the highly sensitive CAA test. However, as current barriers, including lack of WHO guidelines, currently exist there is currently significant risk that newly developed schistosomiasis diagnostic products would not achieve intended impact for elimination efforts.

Thus PATH recommends the following at this time:

1. Continue and expand product development collaborations around the CAA test.
   a. Use TPPs, impact models, recent user-needs research, and landscaping to support current and future efforts.
   b. Identify and evaluate promising new/pipeline POC CAA tests for potential schistosomiasis CAA diagnostic applications.
      i. Define next phase of work with Becton Dickenson on the Veritor platform and obtain funding for same.
      ii. Expand the relationship with bioMeriuex and Alere to identify how they can bring new value to our product development partnerships.
      iii. Support LUMC in scale up of monoclonal antibody production and early identification of potential bottlenecks to future technology transfer activities.
   c. Assess opportunities for integrating schistosomiasis tests with diagnostics for other priority end-game diseases (multiplexing on immunoassay tests or platforms, evaluating schistosomiasis assays on POC molecular platforms evaluated for other end-game diseases)

2. Remain informed and involved in policy changes at WHO on the use of new schistosomiasis diagnostics.
   a. Support field studies with the results of development efforts to build evidence base.
   b. Ensure dissemination, understanding, and consensus-building around results.

3. Remain informed of the status and findings of key schistosomiasis research.
   a. Evidence generated for correlating antibody testing with prevalence and incidence (University of Nottingham/BioGlab/Omega Diagnostics collaboration).
b. Future test candidates (if needed).
   i. Omega Diagnostics antibody RDT.
   ii. Bilharz Institute antigen RDT.
   iii. Commercialization of molecular tests (PCR, LAMP).
   iv. Development of research methods (PCR, Luminex, mass spectrometry).

   c. Continue to monitor the landscape of literature and new products for emerging biomarkers and platforms that may modify the finding of this report.

4. Remain informed of the status and findings of diagnostic development of the other 2010 London Declaration diseases, especially soil-transmitted helminthiasis.

   a. Leverage learnings from biologically similar diseases and solutions to similar technical problems.

   b. Reevaluate the findings of this report to include multiplexing across diseases to support integrated NTD surveillance and operational efficiencies.

5. Continue engagements with schistosomiasis stakeholders.

   a. Assess evolving opinions, needs, and potential diagnostic solutions for use in schistosomiasis via SCORE, the Schistosomiasis Control Initiative, and others.

   b. Status of new test candidates; many of the past advances have come from academia, not companies.

   c. Maintain network of support for resources to support future product development (if needed).
8. References


### Appendix 1: Biomarker Landscape for Schistosomiasis

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Surveillance Measure</th>
<th>Description of Priority Candidates</th>
<th>Sample Type</th>
<th>Format</th>
<th>Use Within Schistosomiasis Diagnostics</th>
<th>Stage of Product Development</th>
<th>Prioritized Use Case</th>
<th>Recommendations</th>
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<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Out of scope (see report text)</td>
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<tr>
<td><strong>Schistosome Nucleic Acid</strong></td>
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| • Infection | DNA | • Dra1 121-bp tandem repeat: genus specific, highly repeated (abundant), both parasite associated (stool, urine) and cell free (plasma, urine) • SSU rRNA gene, ITS-2, 28S rRNA gene, cox1 gene: species specific, cell-free abundance uncharacterized RNA • Micro RNA (miRNA223): murine data only, human applications unproven, persistence low, sample type unclear | • Stool, urine, blood | • Lab- or field-based molecular test | • Any research-grade PCR system • Targeted applications have not been qualified. • POC applications have not been qualified | • No commercial diagnostic products available • Limited field demonstrations of research tools • A few RT-PCR reagent kits have been introduced for research only and veterinary use | • MDA stopping • Post-MDA surveillance | **NOT PRIORITIZED AT THIS TIME**
  • Near Term: No action needed at this time. Nucleic acid amplification tests (NAATs) are judged to be too far upstream in the product development process at this time to prioritize over circulating antigen tests.
  • Long term: Track progress and landscape of new commercial test options. Development of evaluation of NAATs with lower cost and complexity may be considered if circulating antigen test development stalls. Dra1 121-bp tandem repeats is probably best probe candidate if further development becomes a priority. Multiplexing of NAATs with other neglected tropical diseases (most notably STH) may become a priority as tools for those diseases are developed, and that may be easier with a NAAT than with an antigen detection immunoassay |
| **Schistosome Antigens** | | | | | | | | |
| • Infection | • CAA: highly genus specific, suitable for all 3 major human *Schistoma* spp., moderately abundant in blood and urine (independent of ova and parasites), very stable • CCA: fairly genus specific, sensitive for *S. mansoni*, moderately abundant in blood and urine (independent of ova and parasites) • SEA: complex, unpurified antigen preparation associated with presence of ova in sample • PGM, RAD23: newly discovered (2015) by proteomics, relatively uncharacterized | • Blood, urine, stool, saliva | • Antigen detection immunoassay (RDT, ELISA, etc.) | • Any ELISA platform (research or commercial) • Any RDT (for best limit of detection, a reader may be required): CCA commercialized by Rapid Medical Diagnostics (Pretoria, RSA), CAA-UCP in development by IMS/LUMC, Veritor CAA in development by Becton Dickenson (BD) (San Diego, USA) •SEA used in elimination in Egypt from TBI research product | • Commercial products available (CCA-RDT) • New products in development (CAA RDTs) • Research “home-brews” common • Recent discovery of new Ag • Field demonstrations of newly developed CAA UCP RDT | • MDA stopping • Post-MDA surveillance | **PRIORITIZED**
  • Near term: Continue to work with BD and IMS/LUMC to develop a high-sensitivity CAA RDT that meets minimal TPP attributes. Continue to support SCORE and others in field evaluation of CCA in *S. mansoni* endemic regions.
  • Long term: Support further improvements of LOD down to the ideal TPP target through development of pre-concentration technologies (on or off strip) for CAA RDTs. Support multiplexing of CAA with schistosome antibodies (for the post-elimination use case) or with other neglected tropical diseases (especially STH) |
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</tr>
</thead>
</table>
| Host Antibody | Exposure             | • α-SmCTF: detected with complex and relatively uncharacterized Ag reagent, SmCTF Ag is cheaper and easier to obtain than ova- and parasite-derived material, not capable of differentiating active infection from past exposure  
• α-AWA, α-SEA, α-CEF6, α-SBgA (and others): detected with complex and relatively uncharacterized Ag reagent, Ag are obtained from homogenized parasites and snails with little or no purification, not capable of differentiating active infection from past exposure  
• Blood | Antibody detection immunoassay (RDT, ELISA, etc.)  
• Note: IHA, COPT, DDIA, and other older techniques are out of scope (see text) | Any ELISA platform (research or commercial)  
Any RDT; SmCTF is under active development at Omega Diagnostics with BioGlab (both UK). Previous development at Vision Diagnostics with BioGlab | New products in development (α-SmCTF RDT)  
Research “home brews” are common  
Limited field demonstrations of α-SmCTF RDT | Post-MDA surveillance  
NOT PRIORITIZED AT THIS TIME  
• Near term: Track progress and maintain communication with Omega and BioGlab. Support (without investment) development of α-SmCTF RDT and field studies that establish utility.  
• Long term: Track progress and landscape of new commercial test options. If α-SmCTF proves to be a useful analyte, a biplex with CAA on an RDT could be useful to create the most-accurate post-elimination tool. |

Abbreviations: IHA = indirect hemagglutination assay; COPT = circumoval precipitin test; DDIA = dipstick dye immunoassay; SmCTF = *S. mansoni* cercarial transformation fluid
### Appendix 2: Diagnostic Landscape for Schistosomiasis

<table>
<thead>
<tr>
<th>Company</th>
<th>Diagnostic</th>
<th>Biomarker</th>
<th>Surveillance Measure</th>
<th>Availability</th>
<th>Description</th>
<th>Current Status for Use in Schistosome Surveillance</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Suppliers</td>
<td>Clinical and older microscopic and serological tests</td>
<td></td>
<td></td>
<td></td>
<td>Out of Scope (obsolete or inaccurate, see text)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Multiple Research Laboratories</td>
<td>Many types</td>
<td>Many types</td>
<td></td>
<td></td>
<td>Many academic research projects have created “home brew” tests for all biomarker and sample types. These are not called out in this technology landscape unless they display a high potential for advancement into a commercial product in the next five years. See text and bibliography for further reference.</td>
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</tbody>
</table>
| Becton Dickinson               | Veritor ICS RDT             | CAA       | Infection            | In development (awaiting funding) | * Multiplexed ICS and POC reader  
* Enhanced gold detector conjugate  
* On strip positive and negative controls used for quantitative signal correction algorithms  
* Uses LUMC’s very high affinity antibody reagents | * In development  
* Feasibility studies complete |                                |                                                                           |                                                                           |
| Intellligent Material Solutions| ICS RDT                     | CAA       | Infection            | In development | * UCP detector conjugates — made by Intelligent Material Solutions  
* Cognate reader  
* Uses LUMC’s very high affinity antibody reagents | In development | UCP detection system is part of LUMC demonstration of the only tests that has ever reached TPP ideal targets  
Inventors of CAA test are involved |                                                                           |                                                                           |
| Rapid Medical Diagnostics      | ICS RDT                     | CCA       | Infection            | Commercialized | * Visually read ICS  
* Gold detector conjugate |                          | Extensive field validation studies  
Findings recently summarized in Cochrane Review (see text) | Easy and familiar to perform  
Uses urine sample instead of stool  
Good performance for S. mansoni  
May supplant Kato-Katz for mapping | Not sensitive for other Schistoma spp.  
Low worm burdens give trace results that are hard to score  
Perceived as too expensive by some key opinion leaders |
| Omega                          | ICS RDT                     | α-SmCTF   | Exposure             | In development | * Based on BioGlab’s SmCTF antigen reagent  
* Visually read  
* SmCTF appears useful for some use cases, but validation is ongoing | * In development  
* Limited field studies | Antigen reagent is relatively cheap/ fast/easy to produce  
Limited field studies are positive to date | Ability to scale up is still undemonstrated  
Antibody tests are generally only useful for a post-elimination use case |
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<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Ng-Biotech                   | ICS RDT             | Antibody to Proprietary Ag                    | Exposure             | In development | • Unique Multiplex capability  
• Can be quantitative (using multiplex)  
• Read visually or with cloud enabled reader. | In development | Proprietary—performance and ability to meet product claims still unknown |• Proprietary—performance and ability to meet product claims still unknown  
• Antibody tests are generally only useful for a post-elimination use case |
| Shanghai ZJ Bio-Tech Co      | Liferiver RT-PCR reagent kit for use with many common RT-PCR machines | Target not specified in package insert         | Infection           | Commercialized | • Chinese-made research only RT-PCR kit for *S. japonicum* only  
• Typical RT-PCR kit components  
• FAM™ channel detection  
• Claimed LOD: 5×10³ copies/ml | Research only       | Little information available                   |• Research only, for *S. japonicum* only  
• Requires extraction  
• Diagnostic value not established  
• Not POC |
| Vacunek                      | RT-PCR reagent kit  | ?                                             | Infection           | Commercialized | • Veterinary product  
• Little information available             | Veterinary product; not qualified for human use | Little information available            |• Veterinary product—not clear if it is sensitive to human-infecting *Schistoma spp.*  
• Requires extraction  
• Diagnostic value not established  
• Not POC |
| Abcam, Genway, Bordier Affinity Products, etc. | ELISA kit           | Antibody to Proprietary Ag                    | Exposure             | Commercialized | • Typical research-only indirect ELISA kit  
• HRP-TMB detection  
• Ag from *S. mansoni* | Research only       | Little information available                   |• Little information available                                |
| DiagnostiC Automation/ Cortez Diagnostics, etc. | ELISA kit           | Antibody to Proprietary Ag                    | Exposure             | Commercialized | • Typical research-only sandwich ELISA kit  
• HRP-TMB detection  
• “Recombinant schistosome Ag”  
• Qualitative test with stop solution | Research only       | Little information available                   |• Little information available                                |
| IVD Research, etc.           | ELISA kit           | Antibody to Proprietary Ag                    | Exposure             | Commercialized | • Little information available             | Research only                                  | Little information available            |• Little information available                                |