Target Product Profile

Schistosomiasis Surveillance Diagnostic

Use case: Post-Elimination Surveillance

Platform: Lateral flow test

Biomarker: *Schistosoma* genus-specific antibody

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Table of Contents

Executive Summary

Neglected tropical diseases (NTD) affect the poorest populations. Several NTDs including schistosomiasis are controlled by preventive chemotherapy (PC) in the form of periodic mass drug administration (MDA). In areas with insufficient sanitation, schistosomes and soil-transmitted helminth (STH) are transmitted by eggs excreted in human stool and/or urine that contaminates the environment. Around 200 million individuals are infected with schistosomiasis, resulting in an estimated 1.7 to 4.5 million disability-adjusted life years (DALYs) lost, and 14,000 to 280,000 deaths per year.[1]

Control programs based on MDA have four designated stages: mapping disease distribution, impact monitoring of MDA interventions, stopping decisions for MDA, and post-elimination surveillance.[2] Current diagnostics including the Kato-Katz technique are thought to be sufficient for mapping disease distribution (Appendix A: Common diagnostic tools). As the most commonly used method for schistosomiasis detection, its main strength is its extensive validation and familiarity all over the world. Requiring nothing more than a microscope and a good light source or power, the simplistic technology allows easier use at lower infrastructure levels. However, the major limitations of the Kato-Katz technique are its need for a trained microscopist and low sensitivity for detecting light intensity infections, which diminishes its utility in later disease control stages. To support Schistosomiasis control programs to continue to move toward elimination, a more sensitive, field deployable diagnostic is needed.

This report proposes a target product profile (TPP) for the development of a new diagnostic technology that facilitates accurate **post-elimination surveillance**. Each attribute has an "acceptable" standard that must be met and an "ideal" standard that if met would maximize the target product's value. This TPP focuses on the development of a lateral flow rapid diagnostic test that detects *Schistosoma* antibody. Important to note, there are limited guidelines for post-elimination surveillance of NTDs, especially schistosomiasis, as few if any locations have reached this goal. Attributes were informed based on current knowledge and would benefit from further refinement as new guidelines are created.

Overview of Target Product Profile

Attribute	Acceptable	Ideal
1. Context (Use Case)		
1.1 Clinical and/or surveillance need (value proposition)	More sensitive than current microscopic methods, field deployable, rapid diagnostic test to monitor elimination.	More sensitive than current microscopic methods, field deployable, rapid diagnostic test to monitor elimination.
1.2 Intended use (use case)	Post-elimination surveillance after stopping mass drug administration (MDA).	Post-elimination surveillance after stopping MDA.
1.3 Target populations	Primary school children 6 to 14 years old and other high-risk populations.	Primary school children 6 to 14 years old and other high-risk populations.
1.4 Target countries/ geographic coverage	Countries where MDA for schistosomiasis has recently stopped.	Countries where MDA for schistosomiasis has recently stopped.
1.5 Location of use (infrastructure level)	Tier 2 facility, school setting at the community level, minimal or no infrastructure requirements.	Tier 2 facility, school setting at the community level, minimal or no infrastructure requirements.
1.6 Target user	Surveillance teams made up of technicians from the regional level, such as community health workers, with minimal training.	Surveillance teams made up of technicians from the regional level, such as community health workers, with minimal training.
1.7 Fit with clinical workflow/linkage to action (process map)	Identify recrudescence of infection by estimating community-wide seroprevalence.	Identify recrudescence of infection by estimating community-wide seroprevalence.
1.8 Desired stability, storage, and cold chain requirements	45°C, 40% to 88% relative humidity, withstand daily temperature fluctuations from 25°C to 40°C, no cold chain required.	45°C, 40% to 88% relative humidity, withstand daily temperature fluctuations from 25°C to 40°C, no cold chain required.
2. Design		
2.1 Analyte (diagnostic marker)	*Schistosoma* genus-specific antibody.	*Schistosoma* genus-specific antibody.

Attribute	Acceptable	Ideal
2.2 Sample type and volume	Serum or finger stick blood < 100 μL.	Finger stick blood < 10 μL.
2.3 Sample preparation	Minimal collection or processing steps.	None.
2.4 Sample transport stability	≥ 2 hours at ambient temp, or time necessary to collect and analyze specimen.	≥ 6 hours at ambient temp, or time necessary to collect and analyze specimen.
2.5 Waste management (hazardous materials/chemicals)	Minimal or no hazardous materials, per World Health Organization (WHO) and country standards.	Minimal or no hazardous materials, per WHO and country standards.
2.6 Nature of result	Qualitative.	Qualitative.
2.7 Time to result	Same day result, < 24 hours.	Same day result, < 15 min.
2.8 Throughput	> 50 samples per user per day.	> 100 samples per user per day.
2.9 Instrumentation format and complexity level	Field-based, rapid diagnostic test, few timed steps, no technically difficult techniques, CLIA-waived.	Field-based, rapid diagnostic test, no more than one timed step, automatic result reading, no technically difficult techniques, CLIA-waived.
2.10 Infrastructure requirements	Minimal, consistent with Tier 2 facility.	None.
2.11 Test-specific training requirements	Minimal, consistent with Tier 2 facility.	None.
2.12 Instrumentation size and weight	Small, easily deployable in the field.	No instrument.
2.13 Ancillary supplies	Minimal supplies to ensure optimal test performance, packaged as a kit.	None.
2.14 Mean time between failures	Minimal for instrument, not applicable for single-use test.	No failures.
2.15 Quality control	Positive and negative control.	Positive and negative control.
2.16 Calibration	No run-to-run calibration required, instrument calibration not required in field.	None.

Attribute	Acceptable	Ideal
2.17 Product shelf life	12-month shelf life.	36-month shelf life; packaging should include thermal indicator.
3. Performance		
3.1 Analytical limit of detection (LOD)	Concentration of antibody corresponding to recent infection.	Concentration of antibody corresponding to recent infection.
3.2 Analytical specificity	Detects *Schistosoma (S.) mansoni* and *S. haematobium*; does not detect other helminths.	Detects *S. mansoni*, *S. haematobium*, *S. japonicum*, *S. mekongi*, *S. intercalatum*, and/or *S. guineensis*, and no other helminths.
3.3 Clinical sensitivity	> 75%.	> 90%.
3.4 Clinical specificity	> 95%.	> 99%.
3.5 Reproducibility and robustness	Replicate determinations of weak positive and weak negative samples classify the same ≥ 95% of the time.	Replicate determinations of weak positive and weak negative samples classify the same ≥ 95% of the time.
3.6 Comparative reference method	Kato-Katz (multiple slides and multiple days) and/or urine filtration/egg counting.	An appropriate composite reference standard.
4. Commercialization		
4.1 Desired end-user price	To be determined.	To be determined.
4.2 Channels to market	To be determined.	To be determined.
4.3 Supply, service, and support	To be determined.	To be determined.
4.4 Product registration path and WHO prequalification	Not required for surveillance tests.	Not required for surveillance tests.

Rationale

1. Context (Use Case)

1.1 Clinical and/or surveillance need (value proposition)

Acceptable: More sensitive than current microscopic methods, field deployable, rapid diagnostic test to monitor elimination.

Ideal: More sensitive than current microscopic methods, field deployable, rapid diagnostic test to monitor elimination.

Neglected tropical diseases (NTD) affect the poorest populations. Several NTDs including schistosomiasis are controlled by preventive chemotherapy (PC) in the form of periodic mass drug administration (MDA). In areas with insufficient sanitation, schistosomes and soil-transmitted helminth (STH) are transmitted by eggs excreted in human stool and/or urine that contaminates soil and water sources. For schistosomiasis as well as STH control, the school infrastructure is essential to administer MDA, as school-aged children have the greatest burden of infection and morbidity.[3] Around 200 million individuals are infected with schistosomiasis, resulting in an estimated 1.7 to 4.5 million disability-adjusted life years (DALYs) lost, and 14-280 thousand deaths per year.[1]

Control programs based on MDA have four designated stages: mapping disease distribution, impact monitoring of MDA interventions, stopping decisions for MDA, and post-elimination surveillance.[2] Based on stakeholder opinions solicited at the Schistosomiasis Diagnostics Meeting (hosted by the Task Force for Global Health, Decatur, GA, August 2013), current diagnostics including the Kato-Katz technique are thought to be sufficient for mapping disease distribution (Appendix A: Common diagnostic tools). However, as disease prevalence decreases through effective control strategies, a more sensitive diagnostic will be necessary to inform control programs.[4]

User needs assessments in the form of stakeholder interviews and field observations examined the strengths and limitations of the Kato-Katz technique. As the most commonly used method for schistosomiasis detection, its main strength is its extensive validation and familiarity all over the world. Requiring nothing more than a microscope and a good light source or power, the simplistic technology allows easy use at lower infrastructure levels. Major limitations are the need for a trained microscopist and its low sensitivity for detecting light intensity infections, diminishing its utility in later disease-control stages. Additional challenges include the need to collect, process, and read fresh stool specimens within a limited time frame, which adds logistical constraints such as transport of equipment and technicians.

Since schistosomiasis is endemic in some very remote areas, a test that can function in the field with very minimal infrastructure is necessary. Surveillance activities may continue in the school setting even after MDA has stopped.[5] Therefore, an acceptable test would be relatively simple and ready to use, requiring minimal training.

1.2 Intended use (use case)

Acceptable: Post-elimination surveillance after stopping MDA.

Ideal: Post-elimination surveillance after stopping MDA.

The purpose of this diagnostic is during post-elimination surveillance, to rapidly identify if recrudescence of infection occurs. The use case can be described as a field-based test being performed by surveillance teams, with involvement of school teachers or community health workers. These teams may be of varied training and technical expertise, and the conditions where they perform the testing may be without basic infrastructure. The data collected will be used to support elimination efforts. The target population may primarily be school-aged children, both as a population of convenience in schools, as well as a population with potentially high relative prevalence. Delivery will be through high-level elimination programs. Current guidelines and information suggest a need for a surveillance test, which would not require individual patient follow-up. A mechanism to store and transfer surveillance data will be needed. The introduction of portable instrumented readers as well as low-cost tools would facilitate accurate results and reliable data handling.

1.3 Target populations

Acceptable: Primary school children 6 to 14 years old and other high-risk populations.

Ideal: Primary school children 6 to 14 years old and other high-risk populations.

Schistosomiasis can affect all age groups, but the highest prevalence and intensities of infection are typically found in younger people. Additionally, primary school-age children are an important high-risk group for schistosomiasis and STH infections because the infections occur[3]:

- During a period of intense physical growth and rapid metabolism resulting in increased nutritional needs; when these needs are not adequately met, growth is impaired and children are more susceptible to infection.
- During a period of intense learning; when children are infected, learning capacities are significantly diminished.
- In a setting of continuous exposure to contaminated soil and water; children generally lack awareness of the need for good personal hygiene and like to play with soil and water.

As a result, current World Health Organization (WHO) guidelines for helminth control involve school-based surveillance. School-based treatment is efficient because school infrastructure reduces distribution costs and provides the opportunity to reach both enrolled and non-enrolled school-age children.[3]

Current guidelines are unclear if target populations for MDA would differ from target populations for post-MDA surveillance. We assume cohorts of 6- to14-year-olds from sentinel primary schools will continue to be tested to assess their parasitological status.[2] WHO guidelines suggest monitoring new cohorts of 6-year-olds may provide evidence of transmission levels within the community. [1]

1.4 Target countries/geographic coverage

Acceptable: Countries where MDA for schistosomiasis has recently stopped.

Ideal: Countries where MDA for schistosomiasis has recently stopped.

Schistosomiasis is endemic in 76 countries and territories. Of these countries, 54 are endemic for *S. mansoni*, 55 are endemic for *S. haematobium*, and Philippines, China, and parts of Indonesia are endemic for *S. japonicum*.[1]

Table 1: Schistosomiasis endemic countries in the WHO regions.[6]

Group	Countries and territories
Countries requiring preventive chemotherapy	African Region: 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 Region of the Americas: Brazil, Venezuela (Bolivarian Republic of) Eastern Mediterranean Region: Egypt, Somalia, South Sudan, Sudan, Yemen South-East Asia Region: Indonesia Western Pacific Region: Cambodia, China, Lao People's Democratic Republic, Philippines
Countries requiring updating for planning and implementation purposes	Region of the Americas: Saint Lucia, Suriname Eastern Mediterranean Region: Iraq, Libya, Oman, Saudi Arabia, Syrian Arab Republic
Countries requiring evaluation in order to verify if interruption of transmission has been achieved	African Region: Algeria, Mauritius Region of the Americas: Antigua, Dominican Republic, Guadeloupe, Martinique, Montserrat, Puerto Rico Eastern Mediterranean Region: Djibouti, Iran (Islamic Republic of), Jordan, Lebanon, Morocco, Tunisia European Region: Turkey South-East Asia Region: India, Thailand Western Pacific Region: Japan, Malaysia

Source: http://www.who.int/neglected_diseases/ntddata/sch/sch.html

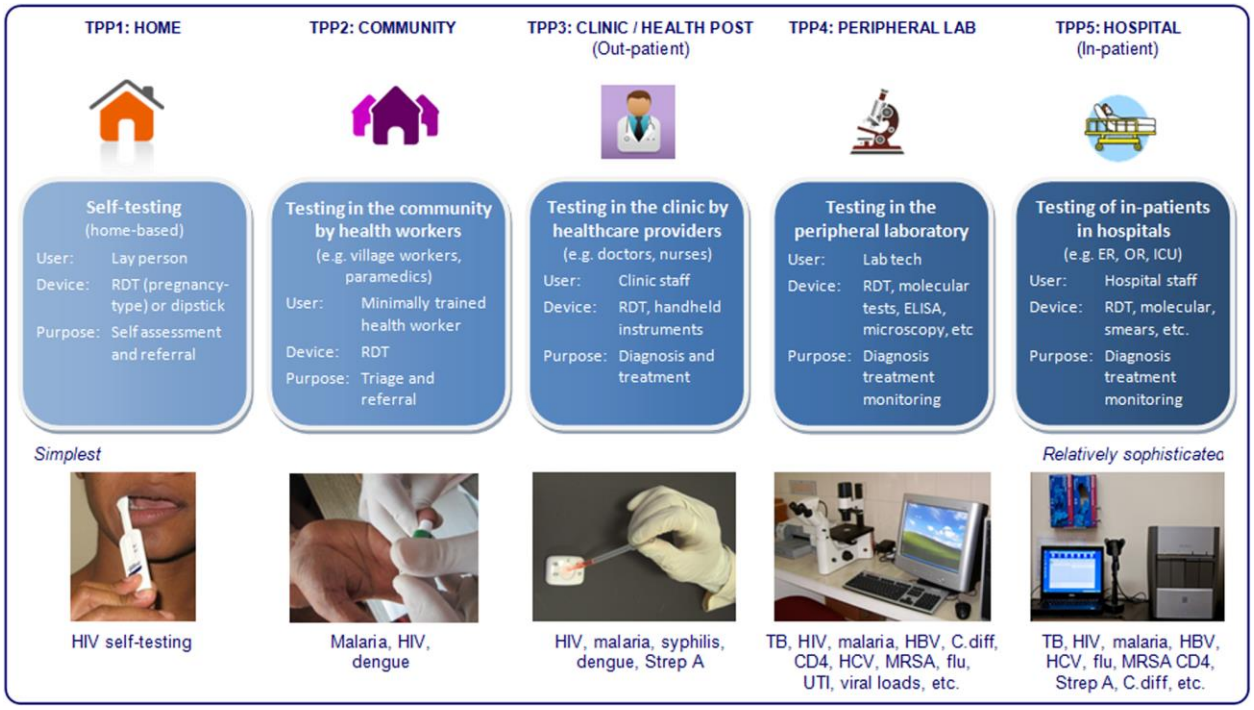
1.5 Location of use (infrastructure level)

Acceptable: Tier 2 facility, school setting at the community level, minimal or no infrastructure requirements.

Ideal: Tier 2 facility, school setting at the community level, minimal or no infrastructure requirements.

WHO guidelines emphasize school-based surveillance, and school settings in areas where schistosomiasis is endemic may have minimal or no infrastructure.

Figure 1: The spectrum of point-of-care testing for target product profiles.[7]



1.6 Target user

Acceptable: Surveillance teams made up of technicians from the regional level, such as community health workers, with minimal training.

Ideal: Surveillance teams made up of technicians from the regional level, such as community health workers, with minimal training.

Surveillance activities may continue in the school setting even after MDA has stopped. The target user of the diagnostic would be surveillance teams composed of central or regional technicians, possibly community health workers.[3] Therefore, an ideal test would be relatively simple and ready to use, requiring minimal training.

1.7 Fit with clinical workflow/ linkage to action (process map)

Acceptable: Identify recrudescence of infection by estimating community-wide seroprevalence.

Ideal: Identify recrudescence of infection by estimating community-wide seroprevalence.

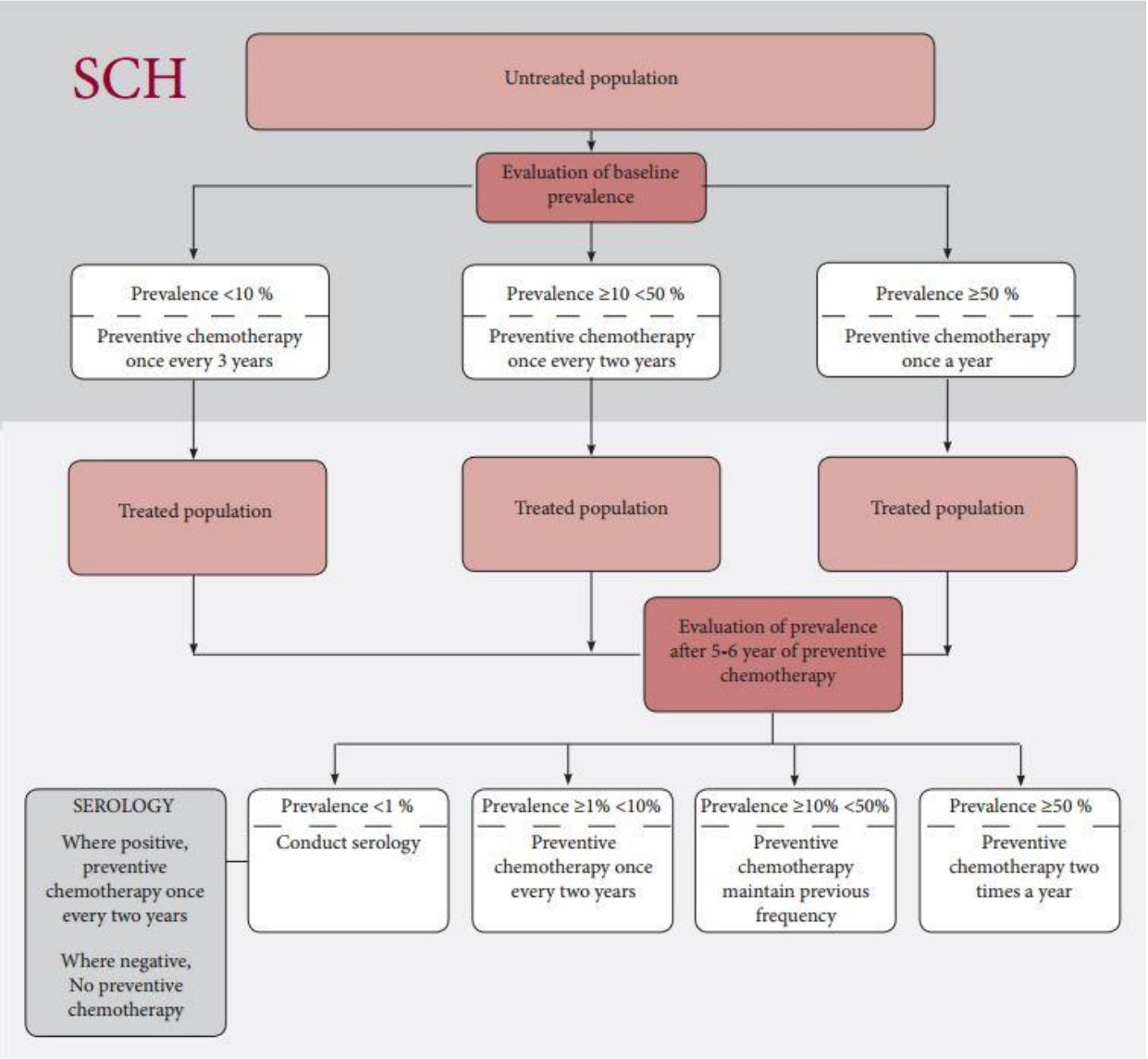
The following points are of interest to the structure and outcomes of a schistosomiasis control program[5]:

- Praziquantel treatment can cure infection in a single dose; however, reinfection from local water sources is common.
- Occasionally praziquantel is not 100% effective, and remaining worms may alter egg excretion, muddling measurements of treatment efficacy and prevalence.

- Praziquantel treatment is not considered an elimination strategy, but contributes to reduced morbidity.
- The PHASE approach to schistosomiasis control includes preventive chemotherapy, health education, access to clean water, sanitation improvements, and environmental vector control.[6]

Treatment for schistosomiasis is most often empiric, rather than by a test-and-treat paradigm. Periodic treatment for schistosomiasis is performed at the population level, with the frequency of treatment determined by the community-wide prevalence estimate. Decisions to reduce MDA use are also based on the estimated prevalence of infection at time intervals following MDA.[3] After MDA is stopped, frequent monitoring of prevalence estimates will be important to ensure recrudescence of infection has not occurred. Recrudescence would necessitate reengagement of the control program in the community.

Figure 2: Frequency of mass drug administration based on prevalence estimates and prior community-based treatment.[3]



Based on field observation in Kenya, an example process map was generated depicting the current workflow of a helminth surveillance project (Appendix B: Process map). Most stakeholders involved in helminth surveillance commented on the logistical challenges of using stool as a specimen. Post-elimination surveillance would use some form of blood as the specimen, varying the ideal workflow. Immediate actions still would not be associated with individual results, but stakeholder interviews noted the importance of providing quick feedback to the community to continue community engagement and high participation.

1.8 Desired stability, storage, and cold chain requirements

Acceptable: 45°C, 40% to 88% relative humidity, withstand daily temperature fluctuations from 25°C to 40°C, no cold chain required.

Ideal: 45°C, 40% to 88% relative humidity, withstand daily temperature fluctuations from 25°C to 40°C, no cold chain required.

Internal PATH data have suggested that there are temperature fluctuations in the areas this test would serve, with results showing roughly 25–40°C variations on a daily basis. This variability is unavoidable without cold chain support.

2. Design

2.1 Analyte (diagnostic marker)

Acceptable: *Schistosoma* genus-specific antibody.

Ideal: *Schistosoma* genus-specific antibody.

Antibodies specific to the *Schistosoma* genus will be used to allow detection of all *Schistosoma* species infecting humans. Previous research will be utilized to identify promising targets.

Additional data are not currently available.

2.2 Sample type and volume

Acceptable: Serum or finger stick blood < 100 μL.

Ideal: Finger stick blood < 10 μL.

Due to the life cycle of *Schistosoma* parasites in the host, stool and urine have been the necessary sample for diagnosis. Interviews with stakeholders involved in helminth surveillance mentioned that finger stick blood, as well as urine, were acceptable sample types. If efforts are made to integrate multiple NTD surveillance programs, using one common sample type is preferred and blood will be the ideal sample type.

From a participant burden perspective, it has been recommended that blood sampling > 100 μL is typically unreasonable as it would require venipuncture sampling (Schistosomiasis and STH Diagnostics

Meeting, August 2013). In the context of a large survey of children where the majority are expected to be uninfected and treatment is delivered irrespective of infection status, the risks and discomfort associated with venipuncture sampling may outweigh the benefit afforded to them, potentially making this method of sample collection unreasonable. If multiple assays could be evaluated from a single blood draw, either in a multiplex test or parallel tests, the risks of venipuncture sampling may be outweighed by the benefits. Ten µL is a realistic volume of finger stick blood used for rapid diagnostic test (RDT) assays and is therefore suggested as an ideal volume.[8]

2.3 Sample preparation

Acceptable: Minimal collection or processing steps.

Ideal: None.

The more commonly used diagnostics, such as urine filtration or the Kato-Katz technique, require significant sample preparation using urine or stool.[9] An improvement over this diagnostic would be acceptable. Since the location of use is community-based school settings, minimal to no sample preparation is ideal. However, technical constraints may require additional steps to meet limit-of-detection (LOD) requirements and these necessary sample processing steps may be acceptable to reach better diagnostic performance.

2.4 Sample transport stability

Acceptable: ≥ 2 hours at ambient temp, or time necessary to collect and analyze specimen.

Ideal: ≥ 6 hours at ambient temp, or time necessary to collect and analyze specimen.

A limitation of the current diagnostic, the Kato-Katz technique, is the rapid degradation of some helminth eggs in the stool sample.[10] The sample stability should allow flexibility in the workflow in a point-of-care (POC) setting. Acceptable sample stability would allow for a reasonable time for sample preparation and analysis (~2 hours), or the time necessary to transport the specimen from collection to analysis site. An ideal time would allow for stability of the sample for most of the day (~6 hours) prior to analysis, which could facilitate batching. Sample transport is not applicable for finger stick blood.

2.5 Waste management (hazardous materials/chemicals)

Acceptable: Minimal or no hazardous materials, per WHO and country standards.

Ideal: Minimal or no hazardous materials, per WHO and country standards.

The test should not contain hazardous reagents per WHO and country safety, environmental, and transport requirements. Any hazardous waste in the form of biologic specimens should be contained on the diagnostic device and disposed of appropriately.

2.6 Nature of result

Acceptable: Qualitative.

Ideal: Qualitative.

The goal of helminth control programs is to reduce morbidity due to helminths, which is not related to the presence or absence of infection (qualitative result) but rather the intensity of infection (quantitative result), determined by the number of worms infecting the human host (worm burden). While greater morbidity is due to higher worm burdens, the precise number of worms necessary to cause morbidity may vary from person to person. A study looking at how prevalence of infection may relate to prevalence of morbidity found that population risk of morbidity increases nonlinearly with prevalence of infection. Until the prevalence of infection is around 60%, the predicted morbidity is thought to be low, but after 60% the predicted morbidity increases rapidly.[11]

Determining the number of worms infecting a host is done by direct assessment at post-mortem examination or an indirect assessment by counting worms expelled after drug treatment. Quantifying the number of eggs excreted by the adult female worms and shed by the human host in stool is more feasible and as a result, the accepted method to determine prevalence and intensity of infection.[12] Additionally, the WHO-endorsed MDA guidelines are based on prevalence estimates (qualitative result), but the WHO targets for schistosomiasis control are based on intensity of infection (quantitative result).[13]

For the use case of post-elimination surveillance, a qualitative test based on antibody detection would be sufficient to determine if recrudescence of infection has occurred.

Table 2: Goals, interventions, and targets for schistosomiasis control and elimination.[13]

Group	Countries eligible for control of morbidity	Countries eligible for elimination as a public-health problem	Countries eligible for elimination (interruption of transmission)	VERIFICATION	Countries that have achieved elimination
Goal	Control morbidity	Eliminate schistosomiasis as a public-health problem	Eliminate schistosomiasis (nterrupt transmission)		Implement post-elimination surveillance
Recommended interventions	Preventive chemotherapy Complementary public-health interventions where possible	Adjusted preventive chemotherapy Complementary public-health interventions strongly recommended	Intensified preventive chemotherapy in residual areas of transmission Complementary public-health interventions considered essential		Surveillance to detect and respond to resurgence of transmission and to prevent reintroduction
Targets	100% geographical coverage and ≥75% national coverage Prevalence of heavy-intensity infection <5% across sentinel sites	Prevalence of heavy-intensity infection <1% in all sentinel sites	Reduce incidence of infection to zero		Incidence of infection remains zero (no cases)
Estimated time to progress from one group to the next	Up to 5–10 years from joining the group	Up to 3–6 years from joining the group	Up to 5 years from joining the group		To continue until all countries have interrupted transmission

2.7 Time to result

Acceptable: Same day result, < 24 hours.

Ideal: Same day result, < 15 minutes.

Results should be same day to expedite surveillance team workflow and travel, but could take hours if throughput is still reasonable. Since this test is primarily focused on surveillance rather than clinical case management, time to result is not necessarily bound to the logistics of the clinical intervention.

The most important related criterion is the overall throughput, where it is presumed that time to result should fit into the surveillance team's workflow such that they are able to meet the daily testing goals. Therefore, while contributions to time to result related to direct labor of the test administrator (hands-on time) are important, contributions based on wait times for results to develop are less important. Additionally, test batching may help reach hands-on and wait time goals while maintaining throughput needs. Ideally, however, there is some value to the workflow in obtaining results quickly, which is reflected in the ideal case.

Interviews with stakeholders involved in helminth surveillance programs mentioned the importance of having results quickly, regardless of clinical management. The results are more likely to reach the communities in a timely manner if rapid tests are used, and the more immediately the result is generated, the easier it is to provide to the participant. It was considered ethically necessary to provide results to the communities, as well as to the participants. Additionally, returning results quickly was important for continued community engagement.

2.8 Throughput

Acceptable: > 50 samples per user per day.

Ideal: > 100 samples per user per day.

WHO recommendations for monitoring and evaluation of helminth control programs suggest a sentinel site method.[3] Sentinel sites (schools) should be in each ecological zone and proportional to the number of school-age children in that zone. Roughly one sentinel site per 200,000 to 300,000 targeted children and a cluster sampling of approximately 50 children per school is suggested. The number of sentinel sites evaluated per day may depend on their distance from each other. The recommendation states that the surveillance team "should be able to collect and analyze specimens from at least 50 children in a sentinel site in one or two days," though possibly two sentinel sites per day may be ideal.[3] Recent discussions with stakeholders involved in helminth surveillance programs also specified that they expect a throughput of 50 samples/day when using the Kato-Katz technique. Therefore, a throughput of 50 samples/user/day is acceptable, while 100 samples/user/day may be ideal.

A balance would need to be found between available personnel resources, number of surveillance sites, and level of throughput. A semi-batch strategy, where samples are prepared quickly and then analyzed in parallel, may be recommended to reach higher throughput needs and potentially allow for resource savings.

2.9 Instrumentation format and complexity level

Acceptable: Field-based, rapid diagnostic test, few timed steps, and no technically difficult techniques, CLIA-waived.

Ideal: Field-based, rapid diagnostic test, no more than one timed step, automatic result reading, and no technically difficult techniques, CLIA-waived.

The test would ideally be in a rapid diagnostic format, particularly when using surveillance teams in the community. In this case, the test should be POC and field deployable, which experts also have stated is the ideal format.[2]

The level of complexity should be consistent with the site where it is used (point-of-care in the community) and the end-user (surveillance lab technician, community health worker). It should consist of only a few timed steps, ideally one, and not require technical steps such as precision pipetting. Results would ideally be automatic and simple to interpret. Any necessary training should be very minimal for a surveillance lab technician. Using the US Food and Drug Administration's (FDA) categories for complexity of diagnostic tests as a reference, the assay should be CLIA-waived (Clinical Laboratory Improvement Amendments).

> "The FDA categorizes diagnostic tests by their complexity—from the least to the most complex: waived tests, moderate complexity tests, and high complexity tests. Diagnostic tests are categorized as waived based on the premise that they are simple to use, and there is little chance the test will provide wrong information or cause harm if it is done incorrectly. Tests that are cleared by the FDA for home or over-the-counter use are automatically assigned a waived categorization."[14]

2.10 Infrastructure requirements

Acceptable: Minimal, consistent with Tier 2 facility.

Ideal: None.

Schistosoma infections are due to a lack of efficient sanitation infrastructure. Lack of efficient sanitation infrastructure is often seen in areas where there is lack of general health infrastructure. Therefore, if the product format is a field-deployable rapid diagnostic test, minimal infrastructure requirements are needed. Ideally, the test would not require any external power sources, only a self-contained portable source if necessary. There is no guarantee of usable water in the field environments where this would be used; therefore the test should not have water requirements.

2.11 Test-specific training requirements

Acceptable: Minimal, consistent with Tier 2 facility.

Ideal: None.

Based on the target user and location of use, any necessary test-specific training needs to be minimal and not technical in nature.

2.12 Instrumentation size and weight

Acceptable: Small, easily deployable in the field.

Ideal: No instrument.

For a field-deployable test, the instrument must be small enough to be carried into potentially remote communities. Ideally there would be no additional instrumentation or equipment.

Additional data are not currently available for this attribute.

2.13 Ancillary supplies

Acceptable: Minimal supplies to ensure optimal test performance, packaged as a kit.

Ideal: None.

A testing platform that is field deployable requires that ancillary supplies must be minimal. If supplies are necessary to ensure optimal sensitivity (such as specimen concentration) or quality control (such as verification cartridges), this may be acceptable. If other supplies are needed, it is acceptable that they are provided as a kit. Ideally, no instruments or other supplies are required.

Additional data are not currently available for this attribute.

2.14 Mean time between failures

Acceptable: Minimal for instrument, not applicable for single-use test.

Ideal: No failures.

An acceptable timeframe for failures would be minimal, though an instrument that has no failures would be ideal.

Additional data are not currently available for this attribute.

2.15 Quality control

Acceptable: Positive and negative control.

Ideal: Positive and negative control.

The manufacturer should maintain appropriate industry quality standards. Positive and negative controls are necessary for each test or batch of tests.

Additional data are not currently available for this attribute.

2.16 Calibration

Acceptable: No run-to-run calibration required; instrument calibration not required in field.

Ideal: None.

Ideally no calibration would be required, particularly in a field scenario. If required for a portable field instrument, the interval between calibrations should be sufficiently long to not burden surveillance teams.

Additional data are not currently available for this attribute.

2.17 Product shelf life

Acceptable: 12-month shelf life.

Ideal: 36-month shelf life; packaging should include thermal indicator.

Based on PATH experience, it is suggested that a shelf life less than 12 months is insufficient, as the time from manufacturing to delivering a test to the user in country is often a minimum of 12 months. It is suggested that a shelf life of 1 year is acceptable, and as many as 3 years would be closer to ideal. Additionally, it would be ideal for the test or kit to have an on-board temperature indicator to alert to extreme conditions exposure.

3. Performance

3.1 Analytical limit of detection

Acceptable: Concentration of antibody corresponding to recent infection.

Ideal: Concentration of antibody corresponding to recent infection.

The unit of measurement of current direct microscopy tests is the number of parasite eggs per gram (epg) of stool, which is a proxy for number of worms infecting the individual (see 2.6 Nature of Result). Though the correlation between egg counts and worm burden is acceptable, several factors cause variability in this correlation such as density-dependent fecundity and recent deworming treatment,[12,15] immunologic status of the host,[16] as well as fecal sampling method and daily fluctuations in egg excretion.[17,18]

A single worm pair is the smallest discrete unit of infection. When diagnosing a symptomatic case, or determining prevalence in high transmission regions, a higher limit of detection is acceptable. However, if true *infection detection* is desired, an analytical limit of detection of one worm pair is necessary. Worm pairs live on average 3 to 5 years and as long as 30 years in some cases. With a theoretical reproductive potential of 600 billion, the persistence of even a single egg-laying worm pair constitutes a significant risk for future transmission.[19] Greater sensitivity is a priority when prevalence levels and infection intensities are low, such as when stopping MDA.

A diagnostic test to identify recrudescence of infection would need to detect the lowest unit of infection. However, antibodies are markers of exposure, rather than infection. Understanding how immune responses correlate with infection over time will be integral to using seroprevalence as a marker of recrudescence.

Acceptable performance depends on the correlation between analytical limit of detection and clinical sensitivity, which would be specific to the test design. Acceptable levels, therefore, would achieve the desired clinical sensitivity.

3.2 Analytical specificity

Acceptable: Detects *S. mansoni* and *S. haematobium*; does not detect other helminths.

Ideal: Detects *S. mansoni*, *S. haematobium*, *S. japonicum*, *S. mekongi*, *S. intercalatum*, and/or *S. guineensis*, and no other helminths.

Table 3: Geographic distribution of Schistosoma species.[13]

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

According to WHO, it is estimated that at least 90% of those requiring treatment live in Africa. The most prevalent and clinically important species are *S. mansoni* and *S. haematobium*, with *S. japonicum* and others contributing to < 10% of the disease burden. Based on this information, acceptable diagnostics would be specific for *S. mansoni* and *S. haematobium*, and an ideal test would also detect *S. japonicum*, *S, mekongi*, *S. intercalatum*, and/or *S. guineensis*. Of note is that many of the regions where *S. japonicum* is endemic are in China, where elimination programs are already well underway and there is less relative need for intervention. Additionally, it is critical that the tests do not cross-react with other helminth infections.

3.3 Clinical sensitivity

Acceptable: > 75%.

Ideal: > 95%.

Technology platforms may have upper limits in terms of attainable sensitivity. The attainable, and therefore acceptable, clinical sensitivity for a test detecting antibodies may be 75%, depending on additional equipment such as a reader.

Additional data are not currently available for this attribute.

3.4 Clinical specificity

Acceptable: > 95%.

Ideal: > 99%.

Clinical specificity becomes increasingly important as prevalence is reduced. At high prevalence, a 5% false-positive level is not a barrier, but as MDA is stopped, the level of false positives should be minimal. Acceptable clinical specificity for post-elimination surveillance should be > 95%, and ideally > 99% to minimize false positives at low prevalence.

Additional data are not currently available for this attribute.

3.5 Reproducibility and robustness

Acceptable: Replicate determinations of weak positive and weak negative samples classify the same ≥ 95% of the time.

Ideal: Replicate determinations of weak positive and weak negative samples classify the same ≥ 95% of the time.

As a preliminary target, replicate determinations of weak positive and weak negative samples (close to the presumptive cutoff) should classify the same ≥ 95% of the time.[20]

Additional data are not currently available for this attribute.

3.6 Comparative reference method

Acceptable: Kato-Katz (multiple slides and multiple days) and/or urine filtration/egg counting.

Ideal: An appropriate composite reference standard (CRS).

Direct microscopy such as Kato-Katz and/or urine filtration (egg counting) have significant limitations as diagnostics for schistosomiasis, but they are the most commonly used reference method. Studies have been conducted to quantify the shortcomings of these tests or optimize them (for example, by taking multiple samples over multiple days to improve sensitivity).[21] While it is impractical to base aggressive elimination programs on such techniques, egg-counting data are necessary as part of any reference standard until new tests are fully validated.

Numerous studies have noted the absence of a "gold standard" for the detection of helminths. Studies evaluating Kato-Katz, as well as newer diagnostic technologies, have used a range of techniques to compensate including combining multiple tests as a reference and using mathematical models such as latent class analysis (see Table 4). Though there is no universally accepted method to adjust for the lack of a perfect gold standard,[22] one option is to develop a composite reference standard (CRS).[23] A CRS combines more than one imperfect diagnostic test with the goal of increasing diagnostic accuracy (compared to perfection—the true presence of infection). An important consideration is that the index test under evaluation is not included in the CRS, as this leads to biased diagnostic accuracy estimates.[24,25] Future evaluations of new diagnostics for helminths may benefit from the use of a CRS as the reference test. Possible CRSs may include: multiple microscopy techniques performed on one stool sample,

multiple microscopy techniques performed on stool samples collected over multiple consecutive days, and a microscopy technique and PCR technique performed on the same stool samples. Mathematical models may also be utilized to further explore the diagnostic accuracy of new tests under evaluation.

Moving from a measure of active infection to a measure of recent infection will also present challenges. A second immunoassay developed in parallel may be useful as part of a reference standard. More research is needed for this attribute.

Table 4: A sample of studies using methods to compensate for an imperfect 'gold standard' test for helminth infection.

Study	Study purpose	Helminth species	Reference standard
Knopp S, 2014, *Am J Trop Med Hyg* [26]	Evaluate the diagnostic accuracy of Kato-Katz, FLOTAC, Baermann, and PCR	Hookworm, *S. stercoralis,*	3 methods: direct comparison, composite reference, Bayesian method
Bisoffi Z, 2014, *PLoS NTD* [27]	Evaluate the diagnostic accuracy of the 5 serologic assays for detecting *S. stercoralis* infection	*S. stercoralis*	Stool positive (formol-ether concentration, Baermann, or agar/charcoal culture, 3 samples) or at least 3 positive results out of 5 serologic tests (3 non-commercial tests and 2 commercial tests)
Carvalho GLX, 2012, *Mem Inst Oswaldo Cruz* [28]	Compare the diagnostic accuracy of TF-Test with results from 4 other copromicroscopic techniques	*S. mansoni, A. lumbricoides,* hookworm, *S. stercoralis*	Combined results from all 5 copromicroscopic techniques
Glinz D, 2010, *PLoS NTD* [29]	Determine the diagnostic accuracy of 4 copromicroscopic techniques	*S. mansoni, A. lumbricoides,* hookworm, *T. trichiura*	Combined results of all 4 methods and at all time-points investigated
Verani J, 2011, *Am J Trop Med Hyg* [30]	Cross-sectional evaluation of *S. mansoni* prevalence in pre-school age children compared to school age children in Kenya	*S. mansoni*	Stool positive (Kato-Katz, duplicate slides on 3 consecutive samples) or schistosome adult worm protein-specific ELISA positive
Utzinger J, 2008, *Trans R Soc Trop Med Hyg* [31]	Evaluate FLOTAC as new technique to diagnosis hookworm infection	Hookworm	Combined results from Kato-Katz, FLOTAC, and ether concentration technique
Goodman D, 2007, *Am J Trop Med Hyg* [32]	Compared multiple methods for the detection of STH eggs in infants	*T. trichiura,* hookworm, *A. lumbricoides*	Combined results from all copromicroscopic methods evaluated
Knopp S, 2008, *PLoS NTD* [33]	Elucidate the effect of repeated stool sampling and the use of different	*T. trichiura,* hookworm, *A. lumbricoides, S. stercoralis*	Mathematical model by Marti, et al.[34]

Study	Study purpose	Helminth species	Reference standard
	diagnostic methods for STH		
Marti H, 1993, *J Clin Epi* [34]	To obtain adjusted estimates of prevalence and sensitivity using a mathematical model	*E. histolytica, G. lamblia, T. trichiura, A. lumbricoides,* hookworm	Mathematical model using multiple stool samples to estimate false negative rates and obtain estimates of prevalence and sensitivity
Nikolay B, 2014, *Int J Parasitol* [35]	Robust global assessment (meta-analysis) of relative performance of available diagnosis tools for STH	*A. lumbricoides,* hookworm, *T. trichiura*	Bayesian latent class model
Goncalves AQ, 2014, *Acta Tropica* [36]	Comparing repeatability, concordance, and accuracy of 2 spontaneous sedimentation techniques	*G. lamblia, E. histolytica, Blastocystis spp., A. lumbricoides,* hookworm*, T. trichiura, C. hepaticum*	Bayesian latent class model
Tarafder MR, 2010, *Int J Parasitol* [37]	Estimate the sensitivity and specificity of Kato-Katz using a Bayesian approach in the absence of a 'gold standard'	*A. lumbricoides,* hookworm*, T. trichiura*	Bayesian latent class model
Booth M, 2003, *Parasitology* [38]	Estimate single and dual-species infections base on raw egg count data and after latent class analysis	*S. mansoni,* hookworm	Bayesian latent class model
Steinmann P, 2008, *Am J Trop Med Hyg* [39]	Evaluate the prevalence of multiparasitism in China examining multiple stool samples with 4 copromicroscopic techniques	8 helminth and 7 protozoa species	1) Combined results of all diagnostic methods 2) Mathematical model by Marti, et al.[34] using multiple Kato-Katz measures

4. Commercialization

Research on the commercialization attributes is ongoing. Further detail will be added as it is available.

4.1 Desired end user price

Acceptable: To be determined.

Ideal: To be determined.

The cost per child tested using a single Kato-Katz test was $10–12, depending on school or community-based sampling.[40]

Additional data are not currently available for this attribute.

4.2 Channels to market

Acceptable: To be determined.

Ideal: To be determined.

No data currently available.

4.3 Supply, service, and support

Acceptable: To be determined.

Ideal: To be determined.

No data currently available.

4.4 Product registration path and WHO prequalification

Acceptable: Not required for surveillance tests.

Ideal: Not required for surveillance tests.

Note: If WHO wants to use the test in low risk areas where there is < 20% prevalence in school children to do "case by case treatment," then this would need to be revisited as it would be case management.[41]

Appendices

Appendix A: Common diagnostic tools for schistosomiasis

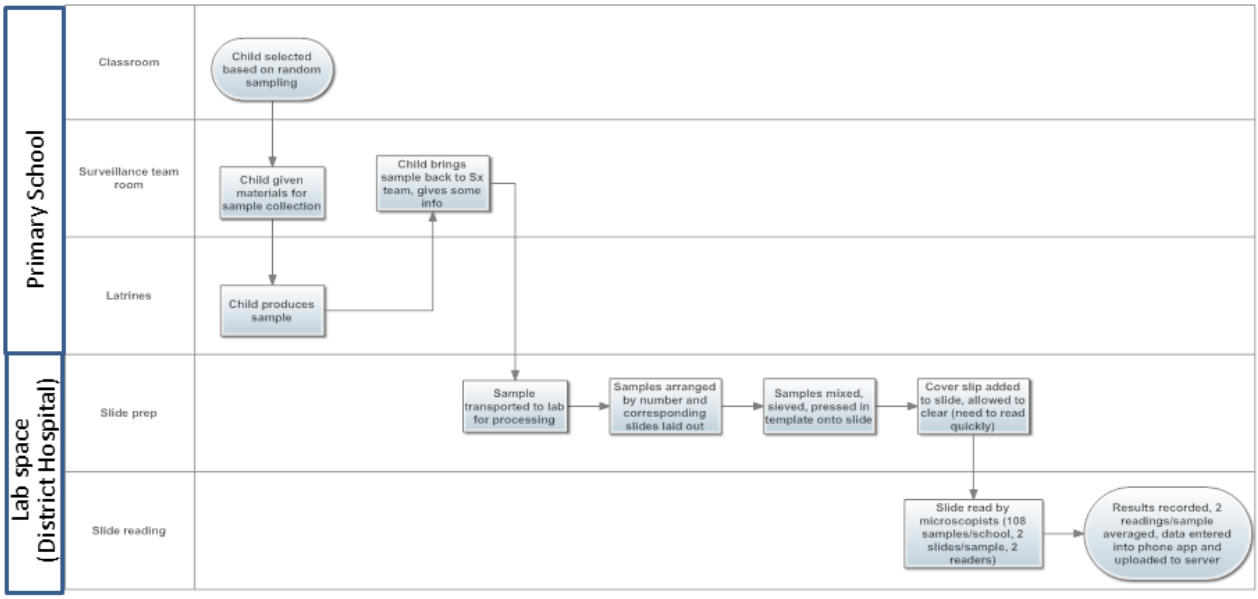
	Urine filtration	Kato-Katz
Technology	Microscopy	Microscopy
Description	Urine sample is fixed, stained, and filtered using a low-pressure vacuum pump, then examined via microscopy[42]	WHO-recommended technique that uses filtered stool of precise sample volume for microscopic egg detection[43]
Infrastructure required	Laboratory	Laboratory
User	Well-trained microscopist	Well-trained microscopist (half day training)[44]
Diagnostic target	Helminth egg	Helminth egg
Species detected	*S. haematobium*	*S. mansoni, S. japonicum, S. haematobium*
Sample type	Urine (collected 10 am to 2 pm, last few drops of micturition to capture greatest egg burden)[45]	Fresh stool
Sample volume	10 mL	41.7 mg
Sample preparation	Manual	Manual
Limit of detection	Unknown	24 eggs per gram (epg)[29]
Sensitivity reference[a]	Dazo 1974[42]	Gold standard[b]
Result type	Quantitative (egg count)	Quantitative (epg)
Time to results (not including sample collection time)	12–24 hours (to allow for staining)[42]	~30–60 minutes (20–40 minutes clearing time required)[44]
Hardware/ancillary supplies	Aseptic filtration system, filter papers, vacuum pump, microscope	Microscope, Kato-Katz kit[29]
Commercially available	Yes	Yes
Stability, storage, and cold chain requirements	No cold chain required	No cold chain required
End user price (USD per test)	Variable, depends on filtration system, microscope	$0.03–$0.04[c] (cost represents 2009 USD)[44]
Manufacturer	Multiple depending on supplies	Helm-Test Kit made by Labmaster Ltd, Belo Horizonte, MG Brazil;[28] also provided by WHO (per 1998 WHO Geneva Supply Services document online)

[a] Paper cited includes latest test performance data.

[b] The Kato-Katz (KK) method is typically used as the gold standard; WHO advises 2 KK slides from a single stool to diagnose schistosomiasis.[43] See Enk 2008[46] for data on relationship between number of KK slides and disease prevalence.

[c] Price is an average of all supplies required for one stool test—for example, the KK kit, microscope (based on assumed life expectancy and use), gloves, etc. It does not include staff salaries or infrastructure costs.

Appendix B: Process map of helminth surveillance (Sx) project in Kenya



1) Child selected in classroom based on random number generation
2) Child sent to classroom where Sx team is set up, given materials for sample collection
3) Child sent to latrine to make sample
4) Child brings sample back to Sx team
   - Child gives some data and sample to Sx team
5) Samples taken from school to clinic lab space
6) Samples sorted and materials arranged
7) Sample mixed, sieved, pressed in template on slide
8) Coverslip added to sample on slide, pressed, allowed to clear at least 10 min (not too long though)
9) Slide read by microscopist, 2 slides/sample, 216 slides per school
10) Results written down by microscopist
11) Written down data entered into phone app, saved on server

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