Target Product Profile

Schistosomiasis Surveillance Diagnostic

Use Case: Preventive chemotherapy reduction or stopping decision

Platform: Lateral flow test

Biomarker: CAA antigen
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Executive Summary

Neglected tropical diseases (NTD) affect the poorest populations. Several NTDs including schistosomiasis are controlled by preventive chemotherapy in the form of periodic mass drug administration (MDA). In areas with insufficient sanitation, schistosomes and soil-transmitted helminths 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 diagnostic tools including the Kato-Katz technique are thought to be sufficient for mapping disease distribution (see 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 diminish 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 an accurate stopping decision for MDA. 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 a *Schistosoma*-specific antigen.
# Overview of Target Product Profile

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Acceptable</th>
<th>Ideal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Context (Use Case)</strong></td>
<td>More sensitive than current microscopic methods, field-deployable, rapid diagnostic test to inform control programs.</td>
<td>More sensitive than current microscopic methods, field-deployable, rapid diagnostic test to inform control programs.</td>
</tr>
<tr>
<td>1.1 Clinical and/or surveillance need (value proposition)</td>
<td>Monitoring prevalence following mass drug administration (MDA) and informing the decision to adjust the treatment strategy to support elimination.</td>
<td>Monitoring prevalence following MDA and informing the decision to adjust the treatment strategy to support elimination.</td>
</tr>
<tr>
<td>1.2 Intended use (use case)</td>
<td>Primary school children 6 to 14 years old and other high-risk populations.</td>
<td>Primary school children 6 to 14 years old and other high-risk populations.</td>
</tr>
<tr>
<td>1.3 Target populations</td>
<td>Schistosomiasis-endemic countries.</td>
<td>Schistosomiasis-endemic countries.</td>
</tr>
<tr>
<td>1.4 Target countries/geographic coverage</td>
<td>Tier 2 facility, school setting at the community level, minimal or no infrastructure requirements.</td>
<td>Tier 2 facility, school setting at the community level, minimal or no infrastructure requirements.</td>
</tr>
<tr>
<td>1.5 Location of use (infrastructure level)</td>
<td>Surveillances teams made up of technicians from the regional level, such as community health workers, with minimal training.</td>
<td>Surveillances teams made up of technicians from the regional level, such as community health workers, with minimal training.</td>
</tr>
<tr>
<td>1.6 Target user</td>
<td>Inform schistosomiasis control programs by estimating community-wide prevalence.</td>
<td>Inform schistosomiasis control programs by estimating community-wide prevalence.</td>
</tr>
<tr>
<td>1.7 Fit with clinical workflow/linkage to action (process map)</td>
<td>45°C, 40% to 88% relative humidity, withstand daily temperature fluctuations from 25°C to 40°C, no cold chain required.</td>
<td>45°C, 40% to 88% relative humidity, withstand daily temperature fluctuations from 25°C to 40°C, no cold chain required.</td>
</tr>
<tr>
<td>1.8 Desired stability, storage, and cold chain requirements</td>
<td>Circulating anodic antigen (CAA).</td>
<td>CAA.</td>
</tr>
<tr>
<td>2. Design</td>
<td>Clean-catch urine (~4 mL) or finger stick blood &lt; 100 μL.</td>
<td>Urine (~4 mL) or finger stick blood &lt; 10 μL.</td>
</tr>
<tr>
<td>Attribute</td>
<td>Acceptable</td>
<td>Ideal</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>2.3 Sample preparation</td>
<td>Minimal collection or processing steps.</td>
<td>None.</td>
</tr>
<tr>
<td>2.4 Sample transport stability</td>
<td>(\geq 2 ) hours at ambient temperature, or time necessary to collect and analyze specimen.</td>
<td>(\geq 6 ) hours at ambient temperature, or time necessary to collect and analyze specimen.</td>
</tr>
<tr>
<td>2.5 Waste management (hazardous materials/chemicals)</td>
<td>Minimal or no hazardous materials, per World Health Organization (WHO) and country standards.</td>
<td>Minimal or no hazardous materials, per WHO and country standards.</td>
</tr>
<tr>
<td>2.6 Nature of result</td>
<td>Qualitative.</td>
<td>Qualitative and quantitative.</td>
</tr>
<tr>
<td>2.7 Time to result</td>
<td>Same-day result, (&lt; 24 ) hours.</td>
<td>Same-day result, (&lt; 15 ) minutes.</td>
</tr>
<tr>
<td>2.8 Throughput</td>
<td>(&gt; 50 ) samples per user per day.</td>
<td>(&gt; 100 ) samples per user per day.</td>
</tr>
<tr>
<td>2.9 Instrumentation format and complexity level</td>
<td>Field-based, rapid diagnostic test, few timed steps, no technically difficult techniques, CLIA-waived.</td>
<td>Field-based, rapid diagnostic test, no more than one timed step, automatic result reading, no technically difficult techniques, CLIA-waived.</td>
</tr>
<tr>
<td>2.10 Infrastructure requirements</td>
<td>Minimal, consistent with Tier 2 facility.</td>
<td>None.</td>
</tr>
<tr>
<td>2.11 Test-specific training requirements</td>
<td>Minimal, consistent with Tier 2 facility.</td>
<td>None.</td>
</tr>
<tr>
<td>2.12 Instrumentation size and weight</td>
<td>Small, easily deployable in the field.</td>
<td>No instrument.</td>
</tr>
<tr>
<td>2.13 Ancillary supplies</td>
<td>Minimal supplies to ensure optimal test performance, packaged as a kit.</td>
<td>None.</td>
</tr>
<tr>
<td>2.14 Mean time between failures</td>
<td>Minimal for instrument, not applicable for single use test.</td>
<td>No failures.</td>
</tr>
<tr>
<td>2.15 Quality control</td>
<td>Positive and negative control.</td>
<td>Positive and negative control.</td>
</tr>
<tr>
<td>2.16 Calibration</td>
<td>No run-to-run calibration required, instrument calibration not required in field.</td>
<td>None.</td>
</tr>
<tr>
<td>2.17 Product shelf life</td>
<td>12-month shelf life.</td>
<td>36-month shelf life, packaging should include thermal indicator.</td>
</tr>
<tr>
<td>3. Performance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attribute</td>
<td>Acceptable</td>
<td>Ideal</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>3.1 Analytical limit of detection (LOD)</td>
<td>Concentration of CAA corresponding to the number of worm pairs equivalent to the desired clinical sensitivity.</td>
<td>Concentration of CAA corresponding to a single worm pair.</td>
</tr>
<tr>
<td>3.2 Analytical specificity</td>
<td>Detects <em>S. mansoni</em> and <em>S. haematobium</em>, does not detect other helminths.</td>
<td>Detects <em>S. mansoni, S. haematobium, S. japonicum, S. mekongi, S. intercalatum</em>, and/or <em>S. guineensis</em>, does not detect other helminths.</td>
</tr>
<tr>
<td>3.3 Clinical sensitivity</td>
<td>&gt; 70%.</td>
<td>&gt; 95%.</td>
</tr>
<tr>
<td>3.4 Clinical specificity</td>
<td>&gt; 95%.</td>
<td>&gt; 99%</td>
</tr>
<tr>
<td>3.5 Reproducibility and robustness</td>
<td>Replicate determinations of weak positive and weak negative samples classify the same ≥ 95% of the time.</td>
<td>Replicate determinations of weak positive and weak negative samples classify the same ≥ 95% of the time.</td>
</tr>
<tr>
<td>3.6 Comparative reference method</td>
<td>Kato-Katz (multiple slides and multiple days) and/or urine filtration/egg counting.</td>
<td>An appropriate composite reference standard.</td>
</tr>
<tr>
<td>4. Commercialization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.1 Desired end-user price</td>
<td>To be determined.</td>
<td>To be determined.</td>
</tr>
<tr>
<td>4.2 Channels to market</td>
<td>To be determined.</td>
<td>To be determined.</td>
</tr>
<tr>
<td>4.3 Supply, service, and support</td>
<td>To be determined.</td>
<td>To be determined.</td>
</tr>
<tr>
<td>4.4 Product registration path and WHO prequalification</td>
<td>Not required for surveillance tests.</td>
<td>Not required for surveillance tests.</td>
</tr>
</tbody>
</table>
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 inform control programs.

Ideal: More sensitive than current microscopic methods, field-deployable, rapid diagnostic test to inform control programs.

Neglected tropical diseases (NTD) affect the poorest populations. Several NTDs including schistosomiasis are controlled by preventive chemotherapy 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 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. \(^2\)

Based on stakeholder opinions solicited at the Schistosomiasis Diagnostics Meeting (hosted by the Task Force for Global Health, Decatur, GA, August 2013), current diagnostic tools including the Kato-Katz technique are thought to be sufficient for mapping disease distribution (see 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 remote areas, a test that can function in the field with minimal infrastructure is necessary. It is anticipated that surveillance activities would be performed alongside control programs, which distribute praziquantel in the school setting through moderately trained school teachers or community health workers. \(^5\) Therefore, an acceptable test would be relatively simple and ready to use, requiring minimal training.
1.2 Intended use (use case)

Acceptable: Monitoring prevalence following MDA and informing the decision to adjust the treatment strategy to support elimination.

Ideal: Monitoring prevalence following MDA and informing the decision to adjust the treatment strategy to support elimination.

The surveillance needs for this diagnostic are to both monitor the impact MDA and inform the decision to reduce or discontinue MDA. The stopping decision in particular is a key part of program management—stopping too early can result in recurrence of transmission years later, while stopping too late wastes resources on unnecessary MDA. In the monitoring phase, the efficacy of the intervention also needs to be understood. The nature of these phases of elimination is that early monitoring is at relatively high prevalence, but as the stopping decision nears, the prevalence, and likely the intensity of infection, is low. The diagnostic test must be appropriate to both scenarios.4

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 guide ongoing MDA programs, as well as inform the decision to stop MDA. The target population will 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. As a surveillance test, individual patient follow-up will not be required, but 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.

Even though drug resistance to anthelminthic medicines have not been demonstrated in humans, the occurrence of resistance in livestock suggests it may be possible. Tools to identify and monitor drug resistance are important; however, more research is necessary.6

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 occur3:

- 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 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

By measuring the intensity of infection in treated areas over time, we expect to see reductions in intensity of infection and in the percentage of heavily infected individuals. Cohorts of 6- to 14-year-olds from sentinel primary schools are tested to assess their parasitological and clinical status.7 WHO guidelines suggest evaluating children in the third year class, while monitoring new cohorts of 6-year-olds may provide evidence of transmission levels within the community.1

Table 1: Recommended treatment strategy for schistosomiasis.8

<table>
<thead>
<tr>
<th>Category</th>
<th>Baseline prevalence among school-age children</th>
<th>Action to be taken</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk community</td>
<td>50% by parasitological methods* (intestinal and urogenital schistosomiasis) or 30% by questionnaire for history of haematuria</td>
<td>Treat all school-age children (enrolled and not enrolled) once a year</td>
<td>Also treat adults considered to be at risk (from special groups to entire communities living in endemic areas)</td>
</tr>
<tr>
<td>Moderate-risk community</td>
<td>10% but &lt;50% by parasitological methods (intestinal and urogenital schistosomiasis) or &lt;30% by questionnaire for history of haematuria</td>
<td>Treat all school-age children (enrolled and not enrolled) once every 2 years</td>
<td>Also treat adults considered to be at risk (special groups only)</td>
</tr>
<tr>
<td>Low-risk community</td>
<td>&lt;10% by parasitological methods (intestinal and urogenital schistosomiasis)</td>
<td>Treat all school-age children (enrolled and not enrolled) twice during their primary schooling age (e.g., once on entry and once on exit)</td>
<td>Praziquantel should be available in dispensaries and clinics for treatment of suspected cases</td>
</tr>
</tbody>
</table>

1 Equivalent to: high-risk community – all school-age children and adults require preventive chemotherapy annually; moderate-risk community – 50% of school-age children and 20% of adults require preventive chemotherapy annually; low-risk community – 33% of school-age children require preventive chemotherapy annually.
2 For urogenital schistosomiasis, detection of haematuria by chemical reagent strips gives results equivalent to those determined by urine filtration
3 Special groups: pregnant and lactating women; groups with occupations involving contact with infested water such as fishermen, farmers, irrigation workers or women in their domestic tasks, to entire communities living in endemic areas.

1.4 Target countries/geographic coverage

Acceptable: Schistosomiasis-endemic countries.

Ideal: Schistosomiasis-endemic countries.

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 2: Schistosomiasis-endemic countries in the WHO regions.\(^8\)

<table>
<thead>
<tr>
<th>Group</th>
<th>Countries and territories</th>
</tr>
</thead>
</table>
       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](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.\(^9\)
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.

It is anticipated that surveillance activities would be performed alongside control programs, which distribute praziquantel in the school setting through moderately trained school teachers or community health workers. The target user of the diagnostic would be surveillance teams composed of central or regional technicians, possibly community health workers. Therefore, an ideal test would be relatively simple and ready to use, requiring minimal training.

Stakeholder interviews and field observations provided additional data on the acceptable target user. The current tool, microscopy, requires an experienced microscopist to reliably generate accurate data. The availability of experienced microscopists at the national and regional level varies greatly from country to country. A diagnostic tool that required a less skilled technician would be useful. However, some stakeholders noted the importance of having the diagnostic test performed by a trained medical or laboratory technician rather than an unskilled worker.

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

Acceptable: Inform schistosomiasis control programs by estimating community-wide prevalence.

Ideal: Inform schistosomiasis control programs by estimating community-wide prevalence.

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

- 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.

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. Additionally, while the stopping decision may be based on diagnostic prevalence, other factors, such as vector populations and coverage surveys, also contribute. Guidelines on MDA stopping and post-elimination surveillance are currently in development, though comparisons to other control programs (such as lymphatic filariasis) may be of value.
Based on field observation in Kenya, an example process map was generated depicting the workflow of a helminth surveillance project (see Appendix B). Another field observation in the Philippines identified variation in where the specimen was produced. In the Philippines, collection cups are distributed to the students the day before to take home and bring back to school the next day with specimen. This variation was based on the cultural sensitivity of the community to giving stool specimens. Additionally, based on stakeholder interviews there was variation in whether specimens were processed at the school or at another location, such as a nearby health clinic or laboratory. Immediate actions were not associated with individual results; however, 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 has suggested that there are temperature fluctuations in the areas this test would serve, with results showing roughly 25°C to 40°C variations on a daily basis. This variability is unavoidable without cold chain support.

2. Design

2.1 Analyte (diagnostic marker)

Acceptable: Circulating anodic antigen (CAA).

Ideal: CAA.

The target analyte, CAA, is an adult worm gut-associated circulating antigen produced in all major human-disease causing species of Schistosoma, and several animal-disease causing species as well. These antigens are released into the circulation of the infected host at regular time intervals from the gut of adult schistosomes, and present oligosaccharide epitopes capable of inducing high affinity and very specific antibodies. CAA levels in serum and urine generally correlate well with worm burden (as determined by egg output); however the actual quantities produced by the worms and detected in the host circulation or excreta may depend on many factors, including host and parasite species, clearance rates, or duration and intensity of infection. CAA is extremely stable and unique (no biological background). It is also very specific to the genus, especially when the sample is pre-analytically precipitated by tri-chloroacteic acid.

2.2 Sample type and volume

Acceptable: Clean-catch urine (~4 mL) or finger stick blood < 100 μL.

Ideal: Urine (~4 mL) or finger stick blood < 10 μL.

The CAA antigen has been extensively studied in urine and serum samples, demonstrating less fluctuation in the day-to-day variations in the detection of CAA compared to fecal egg counts. The need to detect CAA with increasing sensitivity may require a greater volume of sample to be collected and processed. This has implications on the sample type used, as greater volumes of more invasive sample types may not be feasible.

Due to volume constraints and participant burden considerations, urine samples are currently considered the better sample choice. Urine samples are commonly obtained through a patient-controlled “clean catch” of the sample to avoid contamination of the sample by the early urine flow. This introduces an additional sampling burden on the patient, and compliance is variable; therefore, it would be ideal if the test is not impacted by potentially confounding substances in the early urine stream. Based on field experience and stakeholder feedback, 4 mL of urine is an easily obtained volume. Collecting greater volumes of urine may be possible to increase diagnostic sensitivity, more so than for other sample types.

From a participant burden perspective, it has been recommended that blood sampling > 100 μL is typically unreasonable as it would require venipuncture sampling (Schistosomiasis Diagnostics Meeting, August 2013). In the context of a large survey of children where the majority are expected to be
uninfected and will not receive treatment, the risks and discomfort associated with venipuncture sampling would outweigh the potential benefit afforded to them, making this method of sample collection unreasonable. Ten μL is a realistic volume of finger stick blood used for rapid diagnostic test assays and is therefore suggested as an ideal volume. However, it is unclear whether it is feasible to detect CAA with finger stick blood even though detection of CAA in serum is well studied.

Interviews with stakeholders involved in helminth surveillance mentioned that both urine and finger stick blood were acceptable sample types. If efforts are made to integrate multiple NTD surveillance programs, using one common sample type is ideal. Currently, lymphatic filariasis surveillance programs collect finger stick blood.

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. 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 concentration steps to meet limit of detection requirements and these necessary sample processing steps may be acceptable to reach higher limits of detection.

2.4 Sample transport stability

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

Ideal: ≥ 6 hours at ambient temperature, 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. The sample stability should allow flexibility in the workflow in a point-of-care setting. Acceptable sample stability would allow for a reasonable time for sample preparation/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.

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 in-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 and quantitative.

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 non-linearly 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.\textsuperscript{18}

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.\textsuperscript{19} CAA levels in serum and urine generally correlate well with worm burden (as determined by egg output); however, the actual quantities produced by the worms and detected in the host circulation or excreta may depend on many factors, including host and parasite species, clearance rates, or duration and intensity of infection.\textsuperscript{12}

Additionally, WHO-endorsed MDA guidelines are based on prevalence estimates (qualitative result); however, WHO targets for schistosomiasis control are based on intensity of infection (quantitative result).\textsuperscript{20} For the use case of MDA reduction or stopping decision, the accepted nature of result is qualitative, though the ideal nature of result is also quantitative.

\textit{Table 3: Categories of infection intensity.}\textsuperscript{5}

<table>
<thead>
<tr>
<th>Parasite</th>
<th>Light-intensity infections\textsuperscript{b}</th>
<th>Moderate-intensity infections\textsuperscript{b}</th>
<th>Heavy-intensity infections\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{A. lumbricoides}</td>
<td>1–4 999 epg</td>
<td>5 000–49 999 epg</td>
<td>≥50 000 epg</td>
</tr>
<tr>
<td>\textit{T. trichiura}</td>
<td>1–999 epg</td>
<td>1 000–9 999 epg</td>
<td>≥10 000 epg</td>
</tr>
<tr>
<td>Hookworms</td>
<td>1–1 999 epg</td>
<td>2 000–3 999 epg</td>
<td>≥4 000 epg</td>
</tr>
<tr>
<td>\textit{S. mansoni}</td>
<td>1–99 epg</td>
<td>100–399 epg</td>
<td>≥400 epg</td>
</tr>
<tr>
<td>\textit{S. haematobium}</td>
<td>1–50 eggs/10 ml of urine</td>
<td></td>
<td>&gt;50 eggs/10 ml of urine (or visible haematuria)</td>
</tr>
</tbody>
</table>

\textsuperscript{b} epg = eggs per gram of feces.
Table 4: Goals, interventions, and targets for schistosomiasis control and elimination

<table>
<thead>
<tr>
<th>Group</th>
<th>Countries eligible for control of mortality</th>
<th>Countries eligible for elimination as a public-health problem</th>
<th>Countries eligible for elimination (interruption of transmission)</th>
<th>Countries that have achieved elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goal</td>
<td>Control morbidity</td>
<td>Eliminate schistosomiasis as a public-health problem</td>
<td>Eliminate schistosomiasis (interrupt transmission)</td>
<td>Implement post-elimination surveillance</td>
</tr>
<tr>
<td>Recommended interventions</td>
<td>Preventive chemotherapy</td>
<td>Adjusted preventive chemotherapy</td>
<td>Intensified preventive chemotherapy in residual areas of transmission</td>
<td>Surveillance to detect and respond to resurgence of transmission and to prevent reintroduction</td>
</tr>
<tr>
<td></td>
<td>Complementary public-health interventions</td>
<td>Complementary public-health interventions strongly recommended</td>
<td>Complementary public-health interventions considered essential</td>
<td>To continue until all countries have interrupted transmission</td>
</tr>
<tr>
<td>Targets</td>
<td>100% geographical coverage and at least 5% national coverage</td>
<td>Prevalence of heavy-intensity infection &lt;1% in all sentinel sites</td>
<td>Reduce incidence of infection to zero</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Estimated time to progress from one group to the next</td>
<td>Up to 5–10 years from joining the group</td>
<td>Up to 3–6 years from joining the group</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Up to 5 years from joining the group</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 important related criteria 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
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 composed of 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 per day when using the Kato-Katz technique. Therefore, a throughput of 50 samples per user per day is acceptable, while 100 samples per user per 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, no technically difficult techniques, Clinical Laboratory Improvement Amendments (CLIA)-waived.

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

Data from stakeholder interviews support the need for a simple, field-based rapid diagnostic test. Stakeholders noted logistical challenges of conducting surveillance in remote communities. Namely, transporting supplies and specimens is labor and cost-intensive. This test format is further supported in the literature.\(^2\)

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 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 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.

“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."^21

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 must be needed. The test should 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. To attain an optimal sensitivity or a semi-quantitative result, the addition of a reader may be acceptable. Other supplies that may be acceptable are for specimen concentration or quality control checks, such as verification cartridges. If other supplies are needed, it is acceptable that they are provided as a kit. Ideally, no instruments or other supplies are required.
2.14 Mean time between failures

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

Ideal: No failures.

An acceptable time frame 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 CAA corresponding to the number of worm pairs equivalent to the desired clinical sensitivity.
**Ideal**: Concentration of CAA corresponding to a single worm pair ~1 pg/mL in serum, or ~0.1 pg/mL in urine.

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 Section 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,\textsuperscript{19,22} immunologic status of the host,\textsuperscript{23} as well as fecal sampling method and daily fluctuations in egg excretion.\textsuperscript{24,25} Additionally, the positive correlation between CAA and egg counts is affected by the same variability as the correlation between egg counts and worm burden. It has been suggested that CAA is a better proxy for worm burden than egg counts.\textsuperscript{26,27} A direct comparison of CAA levels and worm burden in primate models where direct measurement of worms is possible supports this assertion.\textsuperscript{28}

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.\textsuperscript{29} Greater sensitivity is a priority when prevalence levels and infection intensities are low, such as when deciding to reduce or stop MDA. The ideal case would detect the lowest unit of infection.

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 \textit{S. mansoni} and \textit{S. haematobium}, does not detect other helminths.

**Ideal**: Detects \textit{S. mansoni}, \textit{S. haematobium}, \textit{S. japonicum}, \textit{S. mekongi}, \textit{S. intercalatum}, and/or \textit{S. guineensis}, does not detect other helminths.

*Table 5: Geographic distribution of Schistosoma species.*\textsuperscript{20}

<table>
<thead>
<tr>
<th>Species</th>
<th>Geographical distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{mansoni}</td>
<td>Africa, the Middle East, the Caribbean, Brazil,</td>
</tr>
<tr>
<td></td>
<td>Venezuela, Suriname</td>
</tr>
<tr>
<td>\textit{japonicum}</td>
<td>China, Indonesia, the Philippines</td>
</tr>
<tr>
<td>\textit{mekongi}</td>
<td>Several districts of Cambodia and the Lao People’s</td>
</tr>
<tr>
<td></td>
<td>Democratic Republic</td>
</tr>
<tr>
<td>\textit{guineensis} and \textit{intercalatum}</td>
<td>Rain forest areas of central Africa</td>
</tr>
<tr>
<td>\textit{haematobium}</td>
<td>Africa, the Middle East</td>
</tr>
</tbody>
</table>
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*. Also of note is that many of the regions where *S. japonicum* is endemic are in China, where elimination programs are already well under way 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**: > 70%.

**Ideal**: > 95%.

The clinical sensitivity required will be related to prevalence levels. For the MDA monitoring scenario, 70% sensitivity may be sufficient as early MDA rounds will have higher prevalence. However, as the stopping decision approaches and prevalence is significantly reduced, presumably at or below 1%, sensitivity would need to be the highest attainable with a lateral flow test. Priority at the stopping decision is to identify as many cases as possible since there will be few, and each positive is of increased importance.

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 the stopping decision is approached, the level of false positives should be a minimal fraction of the prevalence level. It is presumed that at the stopping decision, with very low numbers of positives, all positives detected would be investigated and retested with the same or an alternative testing method. However, to avoid overburdening the surveillance program, samples requiring follow-up should be kept to a minimum.

Acceptable clinical specificity for the MDA monitoring and stopping-decision scenario should be at least > 95%, and ideally > 99% to minimize false positives at low prevalence.

### 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.\textsuperscript{30}

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, however, they are the most commonly used reference method. Studies have been conducted to quantify the shortcomings of these tests, or optimize them such as taking multiple samples over multiple days to improve sensitivity.\textsuperscript{31} While 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 6). Though there is no universally accepted method to adjust for the lack of a perfect gold standard,\textsuperscript{32} one option is to develop a CRS.\textsuperscript{33} A CRS combines more than one imperfect diagnostic test with the goal of increasing diagnostic accuracy (compared to truth—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.\textsuperscript{34,35} Future evaluations of new diagnostics for helminths may benefit from the use of a CRS as the reference test. Possible CRS 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.

Table 6: A sample of studies using methods to compensate for an imperfect gold standard test for helminth infection.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study purpose</th>
<th>Helminth species</th>
<th>Reference standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoffi, Z.; 2014; PLoS NTD\textsuperscript{37}</td>
<td>Evaluate the diagnostic accuracy of the 5 serologic assays for detecting <em>S. stercoralis</em> infection</td>
<td><em>S. stercoralis</em></td>
<td>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)</td>
</tr>
<tr>
<td>Study</td>
<td>Study purpose</td>
<td>Helminth species</td>
<td>Reference standard</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>---------------------------------------</td>
<td>------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Carvalho, G.L.X.; 2012; Mem Inst Oswaldo Cruz 38</td>
<td>Compare the diagnostic accuracy of TF-Test with results from 4 other copromicroscopic techniques</td>
<td><em>S. mansoni</em>, <em>A. lumbricoides</em>, hookworm, <em>S. stercoralis</em></td>
<td>Combined results from all 5 copromicroscopic techniques</td>
</tr>
<tr>
<td>Glinz, D.; 2010; PLoS NTD 39</td>
<td>Determine the diagnostic accuracy of 4 copromicroscopic techniques</td>
<td><em>S. mansoni</em>, <em>A. lumbricoides</em>, hookworm, <em>T. trichiura</em></td>
<td>Combined results of all 4 methods and at all time-points investigated</td>
</tr>
<tr>
<td>Verani, J.; 2011; AJTMH 40</td>
<td>Cross-sectional evaluation of <em>S. mansoni</em> prevalence in preschool age children compared to school age children in Kenya</td>
<td><em>S. mansoni</em></td>
<td>Stool positive (Kato-Katz, duplicate slides on 3 consecutive samples) or schistosome adult worm protein-specific ELISA positive</td>
</tr>
<tr>
<td>Utzinger, J.; 2008; Trans R Soc Trop Med Hyg 41</td>
<td>Evaluate FLOTAC as new technique to diagnosis hookworm infection</td>
<td>Hookworm</td>
<td>Combined results from Kato-Katz, FLOTAC, and ether concentration technique</td>
</tr>
<tr>
<td>Marti, H.; 1993; J Clin Epi 44</td>
<td>Obtain adjusted estimates of prevalence and sensitivity using a mathematical model</td>
<td><em>E. histolytica</em>, <em>G. lamblia</em>, <em>T. trichiura</em>, <em>A. lumbricoides</em>, hookworms</td>
<td>Mathematical model using multiple stool samples to estimate false negative rates and obtain estimates of prevalence and sensitivity</td>
</tr>
<tr>
<td>Nikolay, B.; 2014; Int J Parasitol 45</td>
<td>Conduct robust global assessment (meta-analysis) of relative performance of available diagnosis tools for STH</td>
<td><em>A. lumbricoides</em>, hookworm, <em>T. trichiura</em></td>
<td>Bayesian latent class model</td>
</tr>
<tr>
<td>Goncalves, A.Q.; 2014; Acta Tropica 46</td>
<td>Compare repeatability, concordance, and accuracy of 2 spontaneous sedimentation techniques</td>
<td><em>G. lamblia</em>, <em>E. histolytica</em>, <em>Blastocystis spp.</em>, <em>A. lumbricoides</em>, hookworm, <em>T. trichiura</em>, <em>C. hepaticum</em></td>
<td>Bayesian latent class model</td>
</tr>
<tr>
<td>Study</td>
<td>Study purpose</td>
<td>Helminth species</td>
<td>Reference standard</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>------------------------------</td>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>Booth, M.; 2003; Parasitology</td>
<td>Estimate single and dual-species infections based on raw egg count data and after latent class analysis</td>
<td>S. mansoni, hookworm</td>
<td>Bayesian latent class model</td>
</tr>
<tr>
<td>Steinmann, P.; 2008; Am J Trop Med Hyg</td>
<td>Evaluate the prevalence of multiparasitism in China examining multiple stool samples with 4 copromicroscopic techniques</td>
<td>8 helminth and 7 protozoa species</td>
<td>1) Combined results of all diagnostic methods</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2) Mathematical model by Marti et al. using multiple Kato-Katz measures</td>
</tr>
</tbody>
</table>

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 to $12, depending on school or community-based sampling.

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.
### Appendices

#### Appendix A: Common diagnostic tools for schistosomiasis

<table>
<thead>
<tr>
<th></th>
<th>Urine filtration</th>
<th>Kato-Katz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Technology</strong></td>
<td>Microscopy</td>
<td>Microscopy</td>
</tr>
<tr>
<td><strong>Description</strong></td>
<td>Urine sample is fixed, stained, and filtered using a low-pressure vacuum pump, then examined via microscopy$^{32}$</td>
<td>WHO-recommended technique that uses filtered stool of precise sample volume for microscopic egg detection$^{53}$</td>
</tr>
<tr>
<td><strong>Infrastructure required</strong></td>
<td>Laboratory</td>
<td>Laboratory</td>
</tr>
<tr>
<td><strong>User</strong></td>
<td>Well-trained microscopist</td>
<td>Well-trained microscopist (half day training)$^{54}$</td>
</tr>
<tr>
<td><strong>Diagnostic target</strong></td>
<td>Helminth egg</td>
<td>Helminth egg</td>
</tr>
<tr>
<td><strong>Species detected</strong></td>
<td>S. haematobium</td>
<td>S. mansoni, S. japonicum, S. haematobium</td>
</tr>
<tr>
<td><strong>Sample type</strong></td>
<td>Urine (collected 10am-2pm, last few drops of micturition to capture greatest egg burden)$^{55}$</td>
<td>Fresh stool</td>
</tr>
<tr>
<td><strong>Sample volume</strong></td>
<td>10mL</td>
<td>41.7mg</td>
</tr>
<tr>
<td><strong>Sample preparation</strong></td>
<td>Manual</td>
<td>Manual</td>
</tr>
<tr>
<td><strong>Limit of detection</strong></td>
<td>Unknown</td>
<td>24 epg (eggs per gram) $^{39}$</td>
</tr>
<tr>
<td><strong>Sensitivity reference$^{a}$</strong></td>
<td>Dazo 1974$^{52}$</td>
<td>Gold standard$^{b}$</td>
</tr>
<tr>
<td><strong>Result type</strong></td>
<td>Quantitative (egg count)</td>
<td>Quantitative (epg)</td>
</tr>
<tr>
<td><strong>Time to results (not including sample collection time)</strong></td>
<td>12 to 24 hours (to allow for staining)$^{52}$</td>
<td>~30 to 60 minutes (20 to 40 minutes clearing time required)$^{54}$</td>
</tr>
<tr>
<td><strong>Hardware / ancillary supplies</strong></td>
<td>Aseptic filtration system, filter papers, vacuum pump, microscope</td>
<td>Microscope, K-K kit$^{39}$</td>
</tr>
<tr>
<td><strong>Commercially available</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Stability, storage, and cold chain requirements</strong></td>
<td>No cold chain required</td>
<td>No cold chain required</td>
</tr>
<tr>
<td><strong>End user price (US$ per test)</strong></td>
<td>Variable, depends on filtration system, microscope $^{c}$</td>
<td>$0.03$ to $0.04$ (cost represents 2009 US$)$ $^{54}$</td>
</tr>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Multiple depending on supplies</td>
<td>Helm-Test Kit made by Labmaster Ltd, Belo Horizonte, MG Brazil$^{38}$, also provided by WHO (per 1998 WHO Geneva Supply Services document online)</td>
</tr>
</tbody>
</table>

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$^{a}$Paper cited includes latest test performance data.

$^{b}$The Kato-Katz method is typically used as the gold standard. WHO advises two Kato-Katz slides from a single stool to diagnose schistosomiasis.$^{53}$ See Enk 2008$^{56}$ for data on relationship between number of Kato-Katz slides and disease prevalence.

$^{c}$Price is an average of all supplies required for one stool test; for example, the Kato-Katz 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
References


52. Dazo BC, Biles JE. Two new field techniques for detection and counting of Schistosoma haematobium eggs in urine samples, with an evaluation of both methods. *Bull World Health Organ.* 1974;51(4):399–408.

