DIAGNOSTIC TARGET PRODUCT PROFILES

for monitoring, evaluation and surveillance of schistosomiasis control programmes

World Health Organization

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1. Introduction

Schistosomiasis is a parasitic disease of 240 million people globally (*1*). Infection occurs when people come into contact with contaminated water populated with the appropriate intermediate host snail. Larval parasites penetrate the skin and enter the body where they mature into adult male and female worms, mate and produce eggs. Some eggs released by adult females exit the body to continue the parasite's life cycle; other eggs become trapped in host tissues where they stimulate immunological responses that cause the morbidity associated with schistosomiasis.

2. Epidemiology

Human schistosomiasis, also known as bilharzia or "snail fever", is caused by five main species of trematodes of the genus *Schistosoma*. Approximately 90% of infections and the vast majority of morbidity occur in sub-Saharan Africa, where the two primary species responsible for human disease are *S. mansoni* and *S. haematobium*. Adult *S. mansoni* worms live in the mesenteric veins surrounding the intestines. To complete the life cycle, eggs must make their way to the lumen of the gut where they are excreted in host faeces. However, many eggs are washed by the portal circulation to the liver where they become trapped and stimulate granulomatous responses. Over time, untreated schistosomiasis can stimulate fibrosis of the liver and increased portal pressure, resulting in liver and spleen enlargement. In the most severe cases, ascites and oesophageal varices develop and can lead to haematemesis and death. Asian schistosomiasis caused by *S. japonicum* and *S. mekongi* has clinical manifestations like those of *S. mansoni* infections (*2*).

S. haematobium adult worms live in the blood vessels surrounding the bladder; eggs are excreted in the urine, resulting in haematuria which can be microscopic or visual. Chronic infection can result in bladder fibrosis with obstructive uropathy and is associated with increased risk of squamous cell carcinoma of the bladder. Worms in the venous plexus can also result in egg deposition in genital tissues, causing female and male genital schistosomiasis, which is associated with greater risk of HIV transmission (*3*). These severe morbidities tend to affect older individuals who have been infected for several years. However, the bulk of the more than 1.6 million disability-adjusted life years (*4*) caused by schistosomiasis worldwide affect children, who have the highest prevalence and intensity of infections. Morbidities in children include anaemia, delays in physical and cognitive development, and reduced tolerance to exercise (*2*).

3. Public health response

Because the prevalence and intensity of infection peaks at 7–15 years of age, the main strategy for control of schistosomiasis focuses on mass drug administration (MDA) of praziquantel, in priority to primary school-aged children. Praziquantel is safe for people who do not have infections, and it is more cost-effective to treat all school-aged children in a community above a certain prevalence threshold than to test and treat each individual. MDA is typically administered by control programmes in areas endemic for schistosomiasis once each year. However, MDA is not enough to interrupt transmission without additional measures such as increased access to clean water and sanitation, control of intermediate host snails, or education and behavioural change. As a result, WHO guidelines for most countries target control and then elimination of morbidity.

In general, higher intensities of infection are associated with higher levels of morbidity, but these relationships are poorly defined, and most control programmes monitor only prevalence of infection and not intensity (*5*). Research is under way to better define the relationship between prevalence, intensity of infection and various manifestations of morbidity; for the time being, the working guidance for control programmes is to administer MDA annually in communities with ≥ 10% prevalence among primary school-aged children (*6*). Because distribution of schistosomiasis is highly focal, implementation decisions are applied at the subdistrict level. Operational research is required to determine the frequency and design of epidemiological assessments to measure the impact of schistosomiasis programmes and support decision-making aligned to the focality of infection as well as determining persistent hotspots of transmission where community levels of infection are not responding to current MDA intervention.

4. Available diagnostic tools

Traditionally, schistosomiasis has been diagnosed by detecting parasite eggs in host stool (*S. mansoni S. mekongi, S. japonicum*) or urine (*S. haematobium*) (*7*). These methods have the advantage of providing information on both prevalence and intensity of infection and, theoretically, they can distinguish active infection from successful cure and/or subsequent reinfection. However, it is sometimes difficult to obtain samples for egg detection methods, their sensitivity for low intensity infections is poor, and they require access to microscopes and trained personnel. Usually, samples are processed in a laboratory distant from the site.

Circulating cathodic antigen (CCA) is regurgitated from the blind gut of schistosomes, cleared by the patient's kidneys and excreted in the urine. Like eggs, urinary CCA disappears after successful cure and resumes after reinfection. It also provides a relative intensity of infection and is considered much more sensitive than egg detection. A point-of-care CCA test is commercially available. Unfortunately, current formulations of the test are reliable only in high-prevalence areas and the false-positivity rate is too high to accurately determine prevalence < 10% (*8*). Furthermore, recent manufacturing issues have yielded product lots of variable performance and very high false-positive rates (*9, 10*). Even when working well, the point-of-care CCA test is much more effective at detecting *S. mansoni* infections than other schistosomiasis species infections (*11, 12*).

Like CCA, circulating anodic antigen is also detectable in an infected host's blood or urine, is a marker for active infection, provides information on relative intensity of infection and has the added advantage of being produced in detectable amounts by both *S. mansoni* and *S. haematobium* (*13*). However, it is not available as a commercial test, and current developmental tests require laboratory equipment for sample concentration and final test readout. Polymerase chain reaction to detect parasite DNA in stool or urine is anticipated to be more sensitive than egg detection methods but similarly requires laboratory equipment and relatively expensive reagents to perform; it is not available as a commercial test (*14*).

Current schistosome-specific antibody detection tests are not useful in ongoing control programmes because they are unable to distinguish active from former infections (*15*). In addition, the magnitude of antibody response is less reflective of intensity of infection than other methods. However, as prevalence approaches 0%, they can be useful for both deciding when to stop MDA and in conducting surveillance because there are fewer "former" infections, especially in younger age groups. Antibody detection is highly sensitive and can have high throughput on a variety of platforms at a modest cost. It is also easily multiplexed with other serological assays such that serum or plasma collected for a different purpose can be used to provide information about potential schistosome infections, thus reducing survey costs.

Although current antibody tests are not useful for monitoring and evaluation programmes because the antibodies to the currently used antigens remain long after successful treatment, there may be certain antigens to which antibodies, especially those of a certain isotype subclass (e.g. IgG4), disappear more rapidly. The Diagnostic Workstream of the Global Schistosomiasis Alliance has created a list of available tests: (www.eliminateschisto.org/resources/communication-piece-commercially-available-diagnostic-tests).

5. Diagnostic Technical Advisory Group

The WHO Department of Control of Neglected Tropical Diseases manages a diverse portfolio of 20 diseases and disease groups, each with its own unique epidemiological and diagnostic challenges. The Strategic and Technical Advisory Group, the principal advisory group to WHO for the control of NTDs, decided that a single WHO working group would help ensure a unified approach to identifying and prioritizing diagnostic needs, and to informing WHO strategies and guidance on the subject.

Thus, the Diagnostic Technical Advisory Group was formed as an advisory group to the Department. At its first meeting (Geneva, 30–31 October 2019), members discussed priorities for the year ahead as well as how to manage the complexity of supporting the diagnostics agenda across the entirety of the NTD portfolio. All NTDs had diagnostic needs which would have to be addressed in due course. The recommended diagnostic TPPs for *S. mansoni* and *S. haematobium* were:

- monitoring and evaluation of schistosomiasis control programmes; and
- determining if transmission has been interrupted and when to conduct post-MDA surveillance.

6. Purpose of the target product profiles

6.1 TPP for monitoring and evaluation

Health ministries currently lack effective tools for monitoring and evaluation of schistosomiasis control programmes. Egg detection can be used, but the cost, challenges of obtaining samples, and the need for trained personnel and equipment limit the frequency of monitoring. The purpose of this TPP is to guide the development of new diagnostic tools to reliably measure when prevalence is above or below a cut-off of 10% in school-aged children (**Table 1**). Communities remaining above 10% require annual MDA, while communities below 10% can reduce MDA frequency as long as < 10% prevalence can be maintained. However, the lack of a reliable test has hindered the development of maintenance strategies. The test is also needed to track changes of prevalence > 10% to ensure that annual MDA is reducing overall prevalence.

Use of the test in a survey should be less expensive that 2–3 rounds of MDA, the number of treatments expected to demonstrate a meaningful difference in prevalence. Field workers should be able to perform and interpret the test with only a single day of training, and any equipment used for reading the test should be highly portable and battery powered if it needs electricity at all. The amount of time for collecting samples, performing the test, interpreting the data and making a treatment decision should be less than one working day so that only a single field visit would be required for each community.

6.2 TPP for transmission interruption and surveillance

Programmes currently lack effective tools for conducting surveillance and for determining when schistosomiasis transmission has been interrupted. Traditional egg detection methods have the high specificity necessary for successful elimination programmes but lack sensitivity, especially in infections of low intensity that are most likely encountered in interruption of transmission scenarios.

The purpose of this TPP is to guide the development of new diagnostic tools to reliably detect 3% infection prevalence (**Table 2**). While this cut-off may seem relatively high, realistically, it can be achieved by using an economical lot quality assurance sampling approach (LQAS) by which any confirmed positive would trigger additional intervention measures. Even using the 3% cut-off, a combined, two-step test approach will be necessary to achieve the required survey testing specificity. By this approach, an initial (lower cost) screening test with higher sensitivity would be coupled with a secondary test with higher specificity that might be more expensive, but would be utilized with a more limited sample size (and would have the option of being centralized). To attain the required survey specificity, a positive result in both tests would be needed to confirm an active infection.

In a limited prevalence or "post-elimination" surveillance situation, tests otherwise unable to distinguish active from former infections (e.g. current antibody tests) could be used in children younger than the number of years transmission is thought to have been interrupted, as all such individuals should be negative. Antibody responses that linger after treatment could also be used for initial screening purposes in older individuals if followed by a test confirming if there is an active infection. Antibodies to antigens that clear after treatment could be used for all age groups.

7. Characteristics of a needed diagnostic test for Schistosomiasis to support Monitoring and Evaluation

Table 1. TPP for schistosomiasis monitoring and evaluation

1. Product use summary	Minimum	Ideal	Background, annotation re requirement risk, etc.
1.1 Intended use	An in vitro point-of-care test for the detection of analyte specific to *S. mansoni* **or** *S. haemotobium* to aid in monitoring and evaluation of schistosomiasis (SCH) control efforts.	An in vitro point-of-care test for the detection of analyte specific to *S. mansoni* **and** *S. haemotobium* to aid in monitoring and evaluation of schistosomiasis (SCH) control efforts.	The "ideal" test would be able to detect all species of schistosome infections so that one test could be used in all control programmes as praziquantel is the treatment for all schistosome infections. However, some analytes work better for one species (e.g. CCA detection for *S. mansoni)*. If a test only detected *S. mansoni* or *S. haematobium* but fulfilled the other M&E TPP requirements, it would still be useful for those specific programs, and therefore acceptable as a "minimum".
1.2 Targeted population	School-aged children resident in the defined geographical area and other high-risk groups.	Same.	Examples of high-risk groups may include fisherfolk, car washers, agricultural workers, an women doing household chores.
1.3 Lowest infrastructure level	The test will be performed under "zero-infrastructure" conditions including but not limited to schools, community health centres, households and outdoor conditions.	Same.	
1.4 Lowest level user	This test will be performed by health personnel, community health workers, and community volunteers.	Same.	
1.5 Training requirements	≤ 1 day for health personnel, community volunteers and lay people; testing job aid/instructions for use should be made available via the Internet for download (i.e. are publicly available) in addition to the instructions included with the test.	Same.	

2. Design	Minimum	Ideal	Annotation
2.1 Portability	Highly portable with no specialized transport needs.	Same.	"Portability" implies those characteristics described in 2.2-2.4 as well as no locational limitations to where the test can be performed.
2.2 Instrument/ power requirement	Self-contained kit operates independent of any mains power.	Self-contained kit operates independent of any power source, including battery or generator power.	
2.3 Water requirement	Self-contained kit operates independent of any water supply.	Same.	
2.4 Maintenance and calibration	For point-of-care tests, no maintenance is required and no calibration required.	Same.	
2.5 Sample type/ collection	Urine or whole blood from finger stick.	Same.	The desire is to avoid testing reliant on stool or venous blood. The most obvious candidates are urine or finger-stick blood; however, other non-stool, non-venous blood samples (e.g. saliva, breath) would also be acceptable if they meet test performance criteria.
2.6 Sample preparation/transfer device	· Sample preparation for whole-blood finger-stick should not exceed transfer of sample to the testing device, either directly or by use of a predefined and provided device (e.g. inverted cup, disposable fixed-volume transfer pipet, etc.) · Sample preparation for urine should not exceed 3 steps prior to adding the sample to the testing device; all necessary supplies for sample preparation should be provided in the kit.	Sample preparation should not exceed transfer of sample to the testing device, either directly or by use of a predefined and provided device (e.g. inverted cup, disposable fixed-volume transfer pipet, etc.)	
2.7 Sample volume	1-100 uL	1-10 µL	"Sample volume" represents that volume which is introduced to the test device itself. The volume of specimen available may be larger than this, particularly in the case of urine specimens. For this reason the volume of specimen from the patient could be: · 1-100 µL for capillary blood · 1-10 mL for urine"
2.8 Target analyte	**Biomarker(s) specific for current active infection from/viability of *Schistosoma mansoni* (*S.m*) or *Schistosoma haematobium* (*S.h*)**	**Biomarker(s) specific for current active infection from/viability of *Schistosoma mansoni* (*S.m*) and *Schistosoma haematobium* (*S.h*)**	Biomarkers based on antigens or other types (e.g. some nucleic acid-based markers) will presumably provide more favourable half-life kinetics and thus enable more accurate determination of current active infection from/viability of *S.m* or *S.h* in all age groups. However, a mainstream antigen-based biomarker such as CCA is not adequate outside of *S.m*, and existing antigens for IgG-based serology biomarkers possess half-life kinetics that enable determination of *prior* infection from *S.m* or *S.h*, but their half-life precludes their use as markers of active infection/viable parasite. Even though other markers have been proposed (e.g. CAA, miRNA markers, with suitable seroconversion, etc.) qualification and validation of these will require significant time and effort going forward. For this reason, this is a **high-risk** requirement.

2.9 Type of analysis	Qualitative	Semi-quantitative	Detection of active schistosome infections for monitoring and evaluation shall be independent of infection intensity, i.e. light, moderate and heavy intensity infections are all detectable. However, it may be desirable/"nice to have" the ability to gain some degree of information regarding intensity of infection.
2.10 Detection	High contrast, clear result for naked eye; indoor or outdoor reading of a signal that provides a definitive "yes/no" result without the need for color discrimination	Provides some indication of infection intensity	Same as above.
2.11 Quality control	Internal process control indicator	· Internal process control indicator · Stable signal for independent evaluation · Colourimetric or other indicator to identify excessive heat/humidity exposure"	For further consideration (i.e. beyond TPP scope): definition of how endogenous positive controls should/would be used if they are to be included with a test, e.g. will there be a community-wide quality panel, centralized reporting of results.
2.12 Supplies needed	All reagents and supplies included in test kit, with minimal import restrictions (e.g. animal-free)	Same	Assumed that all materials are included, but does not include sample collection devices.
2.13 Safety	Normal use of the test does not create any additional hazards to the operator when observing universal blood safety/body fluid precautions	Same	

3. Performance	Minimum	Ideal	Annotation
3.1 Species differentiation/detection	*S.m and/or S.h*	*S.m and S.h*	· There should be no interference from other trematode parasites, nor other co-endemic helminths (e.g. nematodes/soil-transmitted helminths, cestodes) · Tests for one species (minimal) need only be validated for that species; tests for both species need to be validated for both species. · Current test formats that meet other TPP characteristics are meant only for S.m so development of S.h detection is not a readily available capability. For this reason it is considered a high-risk requirement.
3.2 Diagnostic/clinical sensitivity[1]	**For a sample of 50 individuals: > 80%[2]** **For a sample of 100 individuals: > 60%**	**For a sample of 50 individuals: > 78%[3]** **For a sample of 100 individuals: > 75%**	**Assumptions made for diagnostic performance modelling** · Null hypothesis: community prevalence is ≥ 10 % (or, we reject null hypothesis when prevalence is < 10%) · This requirement is based on regional target for monitoring and evaluation and the known focality of schistosomiasis transmission, with a wide coefficient of variation between villages. · [1] Verification of sensitivity and specificity must be conducted in a manner where suitable reference tests (which may include composite reference tests), specimens and performance assessment protocols are demonstrated as being appropriate for the purpose. Additional operational research will be required to determine how to use results for area-wide decisions. · [2] **For minimum, risk of Type II error (i.e. mistakenly conclude that treatment must continue as before) should be < 30% minimum and risk of Type I error (i.e. mistakenly reduce treatment to a lower level of intervention when, in fact, MDA should continue) should be < 10%. Ideally, risk of Type II error should be < 20%, and risk of Type I error should be < 5%. Sensitivity and specificity targets are determined by size of LQAS sample, % confidence in survey cut-off, acceptable Type I error and acceptable Type II error. The effects of changes in these parameters on desired TPP sensitivity and specificity are demonstrated in the embedded "M&E options" file**. · [3] Current test formats such as Kato-Katz and urine filtration that meet other TPP characteristics (particularly when combined with specificity) do not consistently achieve this sensitivity across S.m and S.h. For this reason it is considered a **high-risk** requirement.
3.3 Diagnostic/clinical specificity	**For a sample of 50 individuals: > 97%[4]** **For a sample of 100 individuals: > 95%**	**For a sample of 50 individuals: > 98.5%[5]** **For a sample of 100 individuals: > 96.5%**	See description above for 3.2 Diagnostic/clinical sensitivity, including the assignment of this as a **high-risk** requirement. · [4] The "minimum" specificity requirement of > 97% for a sample of 50 individuals and > 95% for a sample of 100 individuals permits accurate rejection of the null hypothesis (i.e. < 10% prevalence) at least 70% of the time by providing < 3 positive test results within a 50-person sample or < 6 postive test results within a 100-person sample at a *single* site, i.e. for screening individual communities. · [5] The "ideal" specificity requirement of > 98.5% for a sample of 50 individuals and > 96.5% for a sample of 100 individuals permits accurate rejection of the null hypothesis (i.e. < 10% prevalence) at least 80% of the time by providing < 2 positive test results within a 50-person sample or < 6 positive test results within a 100-person sample.

3.4 Time to results	< 2 h to developed test result	< 0.5 h to developed test result	
3.5 Result stability	Developed test result remains stable for 0.5 h	Developed test result remains stable for 24 h	Ability to interpret final test results in a manner not constrained by timed steps helps greatly in resource-constrained settings.
3.6 Throughput	≥ 7 individuals tested/h per tester	≥ 10 individual tested/h per tester	"Throughput" represents how many tests can be run in parallel within an hour and is *separate from* the time to results.
3.7 Target shelf life/ stability	≥ 18 months, 2-40 °C, 75% RH (no cold chain required); temperature excursion/ prolonged deviation of 50 °C for 2 weeks acceptable.	≥24 months, 2 C - 40 C, 75% RH (no cold chain required); temperature excursion/ prolonged deviation of 50 C for two weeks acceptable.	
3.8 Ease of use	≤ 3 timed steps; ≤ 10 user steps, instructions for use should include diagram of method and results interpretation. Must be able to use in an unprotected external environment.	≤ 1 timed step; ≤ 5 user steps, instructions for use should include diagram of method and results interpretation. Must be able to use in an unprotected external environment.	This is in relation to the test operation *only*.
3.9 Ease of results interpretation	Refer to Requirement 2.10	Same	
3.10 Operating temperature	15-40 °C, 75% RH	Same	

4. Product configuration	Minimum	Ideal	Annotation
4.1 Shipping conditions	Conformance to applicable requirements of ASTM D4169-05 and ISO 11607-1:2006 (or equivalent); no cold-chain shipping required.	Same	
4.2 Storage conditions	Ambient storage conditions, 2-40 °C; no cold storage required	Same	
4.3 Service and support	None required.	Same	
4.4 Waste disposal	Does not include material that cannot be disposed of in normal laboratory biohazard waste streams.	· Does not include material that cannot be disposed of in normal laboratory biohazard waste streams. · Daily throughput needs are considered in the packaging so as to minimize waste, including use of biodegradable or recyclable materials in test and packaging."	
4.5 Labeling and instructions for use (IFUs)	Compliance required per in vitro diagnostic regulation (IVDR) and WHO prequalification (PQ) guidance; product Insert shall be available in multiple language(s) and shall include written and pictoral instructions for use (IFUs) for the test. Must provide accurate MSDS information on components that are potentially toxic.	Same	WHO PQ label/IFU guidance should be applied, regardless of whether test is prequalified by WHO or not.

5. Product cost and channels	Minimum	Ideal	Annotation
5.1 Target pricing per test	< US$ 3	< US$ 1	Actual price details to be captured if it can be estimated reasonably, as it will depend on various factors. "Minimum" based on meeting current Kato-Katz-level pricing, "ideal" based on key opinion leader feedback. **NOTE**: pricing does NOT include shipping and handling/distribution costs, which may be highly variable.
5.2 Capital cost	No capital costs	Same	
5.3 Product lead times	< 6 weeks	< 4 weeks	"Lead time" includes fulfillment *and* delivery of ordered tests to procurer. **NOTE**: May be adjusted to longer lead times provided shelf life is of sufficient duration, e.g. 2 years. Purpose for information is to address design decisions that can impact line/process design for production, and hence impact lead times.
5.4 Product registration (i.e. substantiation to regulatory body of product claims)	· IVDR (or other stringent regulatory authority) · Any registration required for export from country of origin (e.g. Korean Ministry of Food and Drug Safety, etc.) · WHO PQ (if required/applicable) · Country-level registration (if required/applicable for target countries)	Same	Need to confirm that WHO PQ will process neglected tropical disease diagnostic dossiers

8. Characteristics of a needed diagnostic test for Schistosomiasis to support decisions for transmission interruption and subsequent surveillance

Table 2. TPP for transmission interruption and surveillance

1. Product use summary	Minimum	Ideal	Background, annotation re requirement risk, etc.
1.1 Intended use[1]	A combination of two in vitro tests (first test is point-of-care, second test can be laboratory-based) for the detection of analyte specific to *S. mansoni* or *S. haematobium* to aid in determining whether transmission has been interrupted in a population.[2]	A combination of two in vitro point-of-care tests for the detection of analyte specific to *S. mansoni*, *S. haematobium* and other schistosome species to aid in determining whether transmission has been interrupted in a population.[3]	· **A two-step/two-test strategy is assumed**: Initial positive results are retested with an independent, second (i.e. higher specificity) test to confirm and provide the specificity required. (**NOTE**: a single-test approach would requires performance for both sensitivity and specificity that are highly onerous, and at best would require detection of a threshold that is three times higher than that currently used.) · [1]These requirements are based on testing of *individuals*. Pooling would require reexamination of impacted requirements re sensitivity, specificity, and potentially others. · [2]The "minimum" requirements assume two tests, one of which is a point of-care test, but the other may be laboratory-based, that when used together fulfill the overall testing requirements (such as sensitivity and specificity). Other test characteristics (e.g. infrastructure requirements, end user, training) should be consistent with point-of-care tests for at least one test but the other test may have characteristics consistent with a laboratory-based test (e.g. storage and equipment requirements that need a source of electricity). · [3]The "ideal" requirements assume the both tests are point-of-care tests, that when used together fulfill the overall testing requirements (such as sensitivity and specificity). Other test characteristics (e.g. infrastructure requirements, end user, training) should be consistent with for point-of-care tests for both tests.
1.2 Targeted population	All ages > 1 year	Same	Testing algorithm will be addressed programatically. For example, if transmission is thought to have been interrupted 10 years ago, all children aged < 10 years should be negative. However, because the worms can live for decades, there could be older individuals who still have active infections and may need to be tested.
1.3 Lowest infra-structure level	For laboratory-based tests, tests can be performed in a centralized (e.g. regional or national) diagnostic testing laboratory.	For point-of-care tests, the test will be performed under "zero-infrastructure" conditions including but not limited to schools, community health centres, households and outdoor conditions.	
1.4 Lowest level user	For laboratory-based tests, the test will be performed by trained laboratory personnel.	For point-of-care tests, this test will be performed by health personnel, community health workers, and community volunteers.	
1.5 Training requirements	For laboratory-based tests, < 1 week for trained laboratory technicians; testing job aids/instructions for use should be made available via the Internet for download (i.e. are publicly available) in addition to the instructions included with the test.	For point-of-care tests, ≤ 1 day for health personnel, community health workers, community volunteers and lay people; testing job aid/instructions for use should be made available via the Internet for download (i.e. are publicly available).	

2. Design	Minimum	Ideal	Annotation
2.1 Portability	For laboratory-based tests, there are no special requirements regarding portability of the test itself.	For point-of-care tests, the test will be highly portable with no specialized transport needs.	For "minimum", the laboratory-based test will need to function with samples that have been collected up to 1 day before. For "ideal", "portability" implies those characteristics described in 2.2-2.4 as well as no locational limitations to where the test can be performed.
2.2 Instrument/ power requirement	For laboratory-based tests, access to plug-in power (mains or generator) is acceptable.	Self-contained kit operates independent of any power source, including battery or generator power.	
2.3 Water requirement	For laboratory-based tests, access to a source of laboratory grade water is acceptable.	For point-of-care tests, the self-contained kit operates independent of any water supply.	
2.4 Maintenance and calibration	For laboratory-based tests, periodic maintenance and calibration of any instrumentation must be available in the countries and should not be needed more frequently than once a year.	For point-of-care tests, no maintenance is required and no calibration required.	
2.5 Sample type/ collection	Urine or whole blood from finger-stick; samples may be different types for each test used.	Urine or whole blood from finger-stick; samples should be the same type for each test used.	The desire is to avoid testing reliant on stool or venous blood. The most obvious candidates are urine or finger-stick blood; however, other non-stool, non-venous blood samples (e.g. saliva, breath) would also be acceptable if they meet test performance criteria.
2.6 Sample preparation/transfer device	For laboratory-based tests, sample preparation should not exceed transfer of specimen to a suitably designed sample transport device, either directly or by use of a predefined and provided device (e.g. inverted cup, transfer loop, etc; may provide their own validated transfer device) for final processing at a laboratory. (See comments in 2.1.)	For point-of-care tests, sample preparation should not exceed transfer of sample to the testing device, either directly or by use of a predefined and provided device (e.g. inverted cup, disposable fixed-volume transfer pipet, etc.).	See comments in 2.1.
2.7 Sample volume	1-100 uL	1-10 µL	"Sample volume" represents that volume which is introduced to the test device itself.

2.8 Target analyte	**Biomarker(s) specific for current active infection from/viability of *Schistosoma mansoni* (*S.m.*) or *Schistosoma haematobium* (*S.h.*).**	**Biomarker(s) specific for current active infection from/viability of *Schistosoma mansoni* (*S.m.*) and *Schistosoma haematobium* (*S.h.*), and other schistosome species.**	· Biomarkers based on antigens or other types (e.g. some nucleic acid-based markers) will presumably provide more favourable half-life kinetics and thus enable more accurate determination of current active infection from/viability of *S.m* or *S.h* in all age groups. However, a mainstream antigen-based biomarker such as CCA is not adequate outside of S.m, and existing antigens for IgG-based serology biomarkers possess half-life kinetics that enable determination of prior infection from *S.m* or *S.h*, but their half-life precludes their use as markers of active infection/viable parasite. Even though other markers have been proposed (e.g. CAA, miRNA markers, Abs with suitable seroconversion) qualification and validation of these will require significant time and effort going forward. For this reason, this is a **high-risk** requirement. · **NOTE**: In areas with low enough infection levels to warrant interruption of transmission/surveillance testing, infection levels are expected to be low. Therefore, incorporation of a sensitive first test that does not necessarily distinguish current from former infections with a secondary test highly specific for active infection could be a viable strategy. Only individuals who are positive for both tests are considered positive for active infection.
2.9 Type of analysis	Qualitative	Semi-quantitative	Detection of active schistosome infections for surveillance shall be independent of infection intensity, i.e. light, moderate and heavy intensity infections are all detectable. However, it may be desirable/"nice to have" the ability to gain some degree of information re infection intensity.
2.10 Detection	For laboratory-based tests, may include instrument-based detection of a signal that provides unambiguous determination of a qualitative or semi-quantitative measure.	For point-of-care tests, results shall be a high-contrast and clear result for the naked eye; indoor and outdoor reading of a signal that provides a definitive "yes/no" result. Signal interpretation may be qualitative or semi-quantitative.	Same as above.
2.11 Quality control	· Internal process control indicator	· Internal process control indicator · Colorimetric or other indicator to identify excessive heat/humidity exposure"	For further consideration (i.e. beyond TPP scope): definition of how endogenous positive controls should/would be used if they are to be included with a test, e.g. will there be a community-wide quality panel, centralized reporting of results.
2.12 Supplies needed	All reagents and supplies included in test kit, with minimal import restrictions (e.g., animal-free)	Same	Assumed that all materials are included, but does not include sample collection devices.
2.13 Safety	Normal use does not create any additional hazards to the operator when observing universal blood safety/body fluid precautions.	Same	

3. Performance	Minimum	Ideal	Annotation
3.1 Species differentiation/ detection	***S.m.* or *S.h.***	***S.m.* and *S.h.* and other species**	· There should be no interference from other trematode parasites, nor other co-endemic helminths (e.g. nematodes/soil-transmitted helminths, cestodes) · Current test formats that meet other TPP characteristics are are not a readily available capability for *S.m, S.h* and/or other species. For this reason it is considered a **high-risk** requirement.
3.2 Diagnostic/ clinical sensitivity[1]	**Initial/"screen"" test 1: >99%[2]** **AND** **Confirmation test 2: >90% (for test 1 positives) "**	**Initial/"screen"" test 1: >95%** **AND** **Confirmation test 2: >93% (for test 1 positives)[3]**	**Assumptions made for diagnostic performance modelling:** · Null hypothesis: local prevalence is ≥ 3 % (or, we reject null hypothesis when prevalence is < 3%). NOTE: 3% was selected as the threshold since there is no level of test sensitivity that can assure Type I error of < 5% for thresholds lower than this with a sample of 300 people/site at the levels of specificity required, and detection of > 2% prevalence can only be achieved if accepted Type I error is < 10% rather than < 5%. · Surveying 300 people in 10 randomly selected villages, where *all* communities must test "negative" to reject null hypothesis. This requirement is based on the known focality of schistosomiasis transmission with a wide coefficient of variation between villages. · Risk of Type II error (i.e. mistakenly conclude that treatment must continue as before) to be < 20%, and our risk of Type I error (i.e. mistakenly reduce treatment to a lower level of intervention when, in fact, MDA should continue) to be < 10%. · **NOTE**: An acceptable *single-test* approach requires 88% sensitivity and 99.5% specificity for a 3% prevalence threshold. Because specificity is the more critical factor for testing in very low prevalence areas, reaching a combined 99.5% specificity for the two-test system is key to optimal test performance. Therefore, a TWO-STEP testing strategy is proposed: initial positives are retested with an independent second (i.e. higher specificity and possibly lower sensitivity) test to confirm and provide the specificity required. · [1]Verification of sensitivity and specificity must be conducted in a manner where suitable reference tests (which may include composite reference tests), specimens and performance assessment protocols are demonstrated as being appropriate for the purpose. · [2]"Minimum" requirements represent a significant reduction of sensitivity needed for the confirmation screening test, and hence greater stringency is needed for the initial test. · [3]The "ideal" requirements represent a more "shared burden" of sensitivity between the initial screening test and the confirmation test.

3.3 Diagnostic/ clinical specificity[1]	**"Initial/"screen" test 1: >60% AND Confirmation test 2: >99% (for test 1 positives)[2]**	**"Initial/"Screen" test 1: > 80% AND Confirmation test 2: >98% (for test 1 positives)[3]**	See description above for 3.2 Diagnostic/clinical sensitivity, including the assignment of this as a **high-risk** requirement. **Assumptions made for Dx performance modelling**: · The combined specificity requirement of > 99.5% permits accurate rejection of the null hypothesis (i.e. <3% prevalence) at least 80% of the time by providing <6 false positive test result within a 300-people/site sample in a 10-site cluster, i.e.. EACH SITE would need < 6 positive results to reject 3% null hypothesis. · [1]Verification of sensitivity and specificity must be conducted in a manner where suitable reference tests (which may include composite reference tests), specimens and performance assessment protocols are demonstrated as being appropriate for the purpose. · [2]The "minimum" requirements represent a significant reduction of specificity needed for the initial screening test, and hence greater stringency needed for the confirmation test. · [3]The "ideal" requirements represent a more "shared burden" of specificity between the initial screening test and the confirmation test, while still yielding a combined specificity of 99.5% (and sensitivity of 88%).
3.4 Time to results	For laboratory-based tests, < 2 h to developed test result	For point-of-care tests, < 0.5 h to developed test result	
3.5 Result stability	For laboratory-based tests, developed test results can be stored for future reference, transfer, etc.	For point-of-care tests, developed test result remains stable for ≥ 0.5 h	Ability to interpret final test results in a manner not constrained by timed steps helps greatly in resource-constrained settings.
3.6 Throughput	For laboratory-based tests, [3] 100 tests/day per tester	For point-of-care tests, ≥ 10 tests/h per tester	"Throughput" represents how many tests can be run in parallel within an hour and is *separate from* the time to results.
3.7 Target shelf-life/ stability	≥ 18 months, 4–40 °C, 75% RH; temperature excursion/prolonged deviation of 50 °C for 2 weeks acceptable.	≥ 24 months, 4-40 °C, 75% RH; temperature excursion/prolonged deviation of 50 °C for 2 weeks acceptable.	Requirements relate to test kits (i.e. consumables, whether point-of-care tests or specimen collection kits for laboratory-based testing) that are used in the field. **NOTE**: Those consumables used in a laboratory for laboratory-based testing and do not require cold chain should meet these same stability requirements; those that DO require cold chain should meet the same stability duration for either "minimum" or "ideal", but at 4 ± 2 °C.
3.8 Ease of use	For laboratory-based tests, ≤ 5 timed steps; ≤ 15 user steps, instructions for use should include diagram of method and results interpretation.	≤ 1 timed step; ≤ 5 user steps, instructions for use should include diagram of method and results interpretation. For field-based test, must be able to use in an unprotected external environment.	This is in relation to the test operation only.
3.9 Ease of results interpretation	For laboratory-based tests, results can be interpreted by a suitable instrument.	For point-of-care tests, refer to Requirement 2.10 "Ideal".	
3.10 Operating temperature	20-40 °C	15-40 °C	

4. Product configuration	Minimum	Ideal	Annotation
4.1 Shipping conditions	For laboratory-based tests, conformance to applicable requirements of ASTM D4169-05 and ISO 11607-1:2006 (or equivalent); cold-chain shipping (e.g. 0-4 °C) is acceptable for any test components/ consumables.	For point-of-care tests, conformance to applicable requirements of ASTM D4169-05 and ISO 11607-1:2006 (or equivalent); no cold-chain shipping required.	
4.2 Storage conditions	For laboratory-based tests, cold storage is acceptable for any *laboratory-based* testing components/consumables.	For point-of-care tests, ambient storage conditions which may range from 4-40 °C; no cold storage required	
4.3 Service and support	For laboratory-based tests, support must be available from manufacturer for any laboratory-based equipment and/or procedures.	For point-of-care tests, none required.	
4.4 Waste disposal	Does not include material that cannot be disposed of in normal laboratory biohazard waste streams.	· Does not include material that cannot be disposed of in normal laboratory biohazard waste streams. · Daily throughput needs are considered in the packaging so as to minimize waste, including biodegradable or recyclable materials in test and packaging.	
4.5 Labelling and instructions for use	Compliance required per in vitro diagnostic regulation (IVDR) and WHO prequalification (PQ) guidance; product Insert shall be available in multiple language(s) and shall include written and pictoral instructions for use (IFUs) for the test. Must provide accurate MSDS information on components that are potentially toxic.	Same.	WHO prequalification label/IFU guidance should be applied, regardless of whether test is prequalified by WHO or not.

5. Product cost and channels	Minimum	Ideal	Annotation
5.1 Target pricing per test	< US$ 3	< US$ 1	Actual price details to be captured if it can be estimated reasonably, as it will depend on various factors. "Minimum" based on meeting current Kato-Katz-level pricing, "ideal" based on key opinion leader feedback. NOTE: Pricing does NOT include shipping and handling/distribution costs, which may be highly variable.
5.2 Capital cost	For laboratory-based tests, capital costs may vary but should not exceed US$ 10 000.	For point-of-care tests, none required.	
5.3 Product lead times	< 6 weeks	< 4 weeks	"Lead time" includes fulfillment and delivery of ordered tests to procurer. **NOTE**: May be adjusted to longer lead times provided shelf life is of sufficient duration, e.g. 2 years. Purpose of information is to address design decisions that can impact line/process design for production, and hence impact lead times.
5.4 Product registration (i.e. substantiation to regulatory body of product claims)	· IVDR (or other stringent regulatory authority) · Any registration required for export from country of origin (e.g. Korean Ministry of Food and Drug Safety) · WHO PQ (if required/applicable) · Country-level registration (if required/applicable for target countries)"	Same	Need to confirm that WHO PQ will process neglected tropical disease diagnostic dossiers.

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