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Context-Specific Procedures for the Diagnosis of Human Schistosomiasis – A Mini Review

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Schistosomiasis is a parasitic disease caused by trematode blood flukes of the genus *Schistosoma*, affecting over 250 million people mainly in the tropics. Clinically, the disease can present itself with acute symptoms, a stage which is relatively more common in naive travellers originating from non-endemic regions. It can also develop into chronic disease, with the outcome depending on the *Schistosoma* species involved, the duration and intensity of infection and several host-related factors. A range of diagnostic tests is available to determine *Schistosoma* infection, including microscopy, antibody detection, antigen detection using the Point-Of-Care Circulating Cathodic Antigen (POC-CCA) test and the Up-Converting Particle Lateral Flow Circulating Anodic Antigen (UCP-LF CAA) test, as well as Nucleic Acid Amplification Tests (NAATs) such as real-time PCR. In this mini review, we discuss these different diagnostic procedures and explore their most appropriate use in context-specific settings. With regard to endemic settings, diagnostic approaches are described based on their suitability for individual diagnosis, monitoring control programs, determining elimination as a public health problem and eventual interruption of transmission. For non-endemic settings, we summarize the most suitable diagnostic approaches for imported cases, either acute or chronic. Additionally, diagnostic options for disease-specific clinical presentations such as genital schistosomiasis and neuro-schistosomiasis are included. Finally, the specific role of diagnostic tests within research settings is described, including a controlled human schistosomiasis infection model and several clinical studies. In conclusion, context-specific settings have different requirements for a diagnostic test, stressing the importance of a well-considered decision of the most suitable diagnostic procedure.

Keywords: schistosomiasis, diagnosis, context-specific settings, disease control, imported infection

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INTRODUCTION

Schistosomiasis is a neglected tropical disease (NTD) caused by parasitic blood flukes of the *Schistosoma* genus, affecting over 250 million people of which the majority reside in sub-Saharan Africa (1, 2). The main species infecting humans are *S.mansoni*, *S.japonicum* (both causing intestinal schistosomiasis) and *S.haematobium* (causing urogenital schistosomiasis) (1, 2).

Furthermore, hybrid infections, resulting from interactions between human and animal schistosome species and potentially enhanced by zoonotic transmission, are increasingly being reported and may present a considerable risk of human pathology (3). Schistosomiasis can lead to significant morbidity and even mortality if not treated. The most effective and widely used drug is praziquantel (PZQ), which is safe and efficacious against the adult worm stages of all *Schistosoma* spp (4). It is commonly used for individual treatment as well as for mass drug administration (MDA), also known as preventive chemotherapy, to at-risk populations for control of schistosomiasis in endemic areas.

To successfully reduce the burden of disease and to eventually move towards elimination of schistosomiasis, the use of sensitive and specific diagnostic tests, to correctly identify those who are infected, is crucial. However, the diagnostic need is strongly related to its context-specific setting, each requiring its own distinctive approach. In this mini review, we will provide a summary of the current diagnostic procedures for human schistosomiasis (part 1) and discuss their appropriate use in context-specific settings (part 2).

1. DIAGNOSTIC PROCEDURES

Technically speaking, diagnostic laboratory tests include conventional microscopy, antibody detection methods, antigen detection methods, and Nucleic Acid Amplification Tests (NAATs). Additional clinical diagnostic methods such as clinical markers (e.g. haematuria), physical examinations and imaging techniques, including the recent developments in portable and affordable ultrasound machines, are beyond the scope of this review and have been described in detail elsewhere (2, 5–8).

The current reference standard for diagnosing schistosomiasis is based on the detection of eggs in stool (for intestinal schistosomiasis) or in urine (for urogenital schistosomiasis) by microscopy. For diagnosing individual cases the exact sample preparation can vary, e.g. from a direct stool smear to a glycerine sedimentation technique and information about clinical symptoms and possible exposure history is also often taken into account in the final diagnosis (5). However, for population based surveys or control programs in endemic settings the microscopy-based Kato-Katz (KK) technique and the urine filtration (UF) or urine sedimentation technique to quantitatively assess the intensity of *S.mansoni* and *S.haematobium* infections respectively, are most commonly used as a reference standard (9–13). Other available microscopy methods, including techniques such as FECT and FLOTAC, have been described and summarized extensively in Utzinger et al. (5). Even though microscopy techniques are highly specific and can accurately detect high intensity infections, they are not sensitive enough for low intensity infections or post-treatment monitoring (5). New developments in microscopy include optical devices combining digital image recognition with automated data analysis and reporting by using artificial intelligence. Although further technical improvement and validation in the field are needed, these smart and simplified optical diagnostic devices have the potential to identify moderate-to-high intensity infections in stool or urine at low costs (14, 15).

Schistosome-specific antibodies usually develop within a few weeks to months after infection, often before eggs are excreted (2, 5). Various serological methods can be used to detect these antibodies in human plasma or serum (5, 10, 13, 16). Most of these methods are reasonably specific, although a certain level of cross-reactivity with other helminthic diseases is generally accepted (5, 17). Sensitivities of antibody detection methods vary significantly depending on the test format used as well as the infecting species and targeted *Schistosoma* antigen(s), thereby also affecting the observed timepoint of seroconversion (17, 18). Generally, serology gives neither an indication of the intensity nor the status (past or present) of an infection (19). Still, antibody detection remains useful, especially in the case of travelers who often have not been exposed previously (5, 19). Furthermore, in settings where transmission is assumed to have been interrupted, highly sensitive antibody detection may play an important role to assess small pockets of ongoing risk of infection (20–24).

Living schistosomes release a number of antigens into the hosts' bloodstream and measurement of such schistosome-specific antigens allows accurate diagnosis of active infections. Most research has focused on Circulating Cathodic Antigen (CCA) and Circulating Anodic Antigen (CAA), two *Schistosoma* circulating antigens that were already identified in the 1970's at the Leiden University Medical Center (LUMC), the Netherlands (25, 26). Since then, CCA and CAA have been studied extensively, resulting in over 250 peer-reviewed publications. Both antigens are constantly regurgitated by live *Schistosoma* worms into the hosts' circulation, their presence indicating an active infection. Antigen-levels are generally associated with the number of worms present (27). Other unique characteristics of these antigens include the clearance from the blood circulation into the urine with little day-to-day variation (28, 29), and the decrease in levels within days or weeks after PZQ treatment (30–37), making antigen detection highly suitable for individual treatment monitoring.

Detection of CCA can be done *via* the Point-Of-Care (POC) CCA urine test, a cassette-based lateral flow format which has been evaluated extensively in endemic settings and is commercially available (Rapid Medical Diagnostics, Pretoria, South Africa) for diagnosing intestinal schistosomiasis (12, 38–41). To standardize semi-quantitative visual scoring, a graded and robust scale, called G-scores, became available (42). In combination with a set of reference standards, the G-scores are also useful in dealing with batch-to-batch differences. Furthermore, efforts are ongoing to develop a new test format to overcome observed specificity issues in pregnant women and newborn babies (43).

CAA can be detected in urine and serum *via* the Up-Converting reporter Particle technology based, Lateral Flow (UCP-LF) CAA test (44). The UCP-LF CAA test has been evaluated in various endemic and non-endemic settings and

has demonstrated high specificity and sensitivity for the detection of all human species including hybrids (31, 34, 35, 37, 44–52). Different formats of the UCP-LF CAA test have been developed, including a dry format which allows storage and worldwide shipment of reagents without a cold chain as well as a format applying larger sample volumes thereby increasing sensitivity (44). The most sensitive format requires a more advanced laboratory setting (i.e. sample pre-treatment as well as some centrifugation steps), but is particularly useful for quantifying extremely low worm burdens (32). Although the UCP-LF CAA test is not commercially available yet, efforts are ongoing to develop a more widely available and user-friendly test based on finger prick blood (CAA-RDT) (53).

For the detection and quantification of *Schistosoma*-specific DNA, several NAATs have been described for different types of clinical samples, including serum, stool and urine (54–61). In particular those that apply urine samples are of interest as this type of sample can be easily and non-invasively acquired (6, 56, 58, 59, 61). Although the described NAATs are mostly in-house assays, some are becoming commercially available (62, 63). The majority of these tests claim a specificity of 100%, while the sensitivity ranges from equal to significantly higher than standard microscopy (5). NAATs have also demonstrated to be very useful for detection and strain typing of hybrid schistosome infections (3). To overcome the need for expensive laboratory equipment and highly trained personnel, more field-friendly alternatives have been developed, such as for example loop-mediated isothermal amplification (LAMP) (64, 65) and recombinase polymerase amplification (RPA) (6, 66), although both need further validation.

Obviously, assay verification and validation are critical steps when implementing diagnostic tests. In particular for antibody detection methods and NAATs, both having a large diversity of assays available, successful participation in an external quality assessment scheme (EQAS) is essential to obtain the highest achievable diagnostic quality (67, 68). Overall, in-house tests require more quality control measurements than commercial tests and they suffer more from variation in test-performance, as well as lack of availability. Still, several non-commercial diagnostic tests for schistosomiasis have proven their diagnostic value in different settings and should therefore not be fully excluded (34, 57, 69). Recently, a list of all currently commercially available diagnostics for schistosomiasis has been made available by the Global Schistosomiasis Alliance Diagnostic Workstream and hopefully this list can be further extended in the near future (63).

2. DIAGNOSTIC APPROACHES FOR CONTEXT-SPECIFIC SETTINGS

We identified four different settings, namely endemic, non-endemic, disease-specific and research-specific, which can be further subdivided as shown in **Table 1**. For each situation, diagnostic requirements are discussed with a focus on non-microscopy procedures.

Endemic Settings

In schistosomiasis endemic regions more attention is generally given to diagnosis for public health purposes, than to the identification of infected individuals. The latter often being based on clinical symptoms only, sometimes combined with the detection of eggs in stool or urine. In these settings, the POC-CCA test should be further explored as a user-friendly tool for individual case detection of *S.mansoni* infections.

Control Programs

Schistosomiasis control in endemic countries relies mainly on transmission intervention measures combined with large-scale administration of PZQ. Programs are based on pilot surveys often performed on a limited number of school-aged children. For monitoring and evaluation of these programs and to determine whether MDA schemes should be adapted or even stopped, more accurate non-microscopy diagnostic procedures are needed (70). The POC-CCA is currently being recommended by the WHO for mapping prevalence of intestinal schistosomiasis as well as for surveillance purposes, as it is a more sensitive and easy-to-use alternative compared to KK (12, 38, 39, 41). As there is no direct rapid diagnostic test for diagnosing *S.haematobium* infections, an optional method for obtaining an indication of urogenital schistosomiasis prevalence would be hematuria dipsticks, which test for *S.haematobium* related microhematuria, as hematuria and proteinuria strongly correlate with urogenital schistosomiasis (71). However, even though these methods are not expensive and relatively easy to use, they only provide information on morbidity and do not provide a confirmed diagnosis of infection.

Elimination of Schistosomiasis as a Public Health Problem

In areas where morbidity has been significantly reduced, the next aim is elimination of schistosomiasis as a public health problem. This has been defined by the WHO as <1% of school-aged children with schistosomiasis being categorized as heavily infected (72). For intestinal schistosomiasis, this means >400 eggs per gram of feces and for *S.haematobium* >50 eggs per 10ml of urine (73), detected by KK or UF, respectively. One notes that these microscopy-based methods are still recommended for determining prevalence and intensity of infection, while their sensitivity is known to be limited (5, 74, 75). As the POC-CCA test has been shown to be a cost-effective alternative for determining *S.mansoni* prevalence, attempts have been made to estimate equivalent measures of prevalence between POC-CCA and KK (39, 76–79). Likewise, the definition of heavy intensity based on KK or UF should be redefined based on circulating antigen levels. Also, the diagnostic position of the user-friendly RPA assay, as an alternative for the POC-CCA test in case of *S.haematobium* infections, should be further explored (80).

Interruption of Transmission

Accurate diagnosis of schistosomiasis is also crucial for determining interruption of transmission and eventual elimination, especially in

TABLE 1 | Overview of proposed non-microscopy diagnostic methods for each context-specific setting.

	Essential characteristics				Proposed diagnostic method(s)[1]	
	Accuracy	**Sample type**	**Ease of use**	**Cost of tests**	**First choice**	**Optional/ Alternative**
Endemic settings						
Control programs/Monitoring & Evaluation	Moderate	Urine, Finger prick blood	Field applicable, rapid	High priority	POC-CCA	CAA-RDT[2] Haematuria dipsticks[3]
Elimination as a public health problem	Moderate	Urine	Field applicable, rapid	High priority	POC-CCA RPA[2]	
	High	Urine	Minimal labor (central laboratory facility)	Low to moderate priority	UCP-LF CAA	PCR[4]
Interruption of transmission	High	Urine, Serum	Minimal labor (central laboratory facility)	Low to moderate priority	UCP-LF CAA	PCR[4] Antibody detection[5]
Non-endemic settings						
Travelers	High	Serum	Suitable for routine diagnosis	Low priority	UCP-LF CAA Antibody detection[5] PCR[4]	
Migrants	High	Urine, Serum	Suitable for routine diagnosis	Low priority	UCP-LF CAA PCR[4]	POC-CCA Antibody detection[5]
Disease-specific clinical presentation[6]						
Genital schistosomiasis	High	Swap, Lavage, Semen	Suitable for routine diagnosis	Low priority	PCR[4]	
Neuro-schistosomiasis	High	CSF	Suitable for routine diagnosis	Low priority	Antibody detection[5] PCR[4]	
Research-specific settings						
Controlled Human Infection Model	High	Urine, Serum	Highly standardized	Low priority	UCP-LF CAA Antibody detection[5,8]	
Clinical studies[7]	Moderate	Urine, Finger prick blood	Field applicable	Moderate priority	POC-CCA	CAA-RDT[2]
	High	Urine	Minimal labor (central laboratory facility)	Moderate priority	UCP-LF CAA	PCR[4]

[1]Antibody detection (all Schistosoma spp.), PCR (all Schistosoma spp.), POC-CCA (S. mansoni), RPA (S. haematobium), UCP-LF CAA (all Schistosoma spp.), Hematuria dipsticks (morbidity marker for S. haematobium).

[2]Needs further validation.

[3]Hematuria dipsticks only provide information with regard to morbidity most likely related to S. haematobium infection.

[4]Depending on the DNA target and test format used, in addition might need collection of stool and/or urine samples.

[5]Depending on the antigen target, antibody type and test format used.

[6]Assuming that potential exposure took place and/or schistosomiasis in general has been diagnosed.

[7]Depending on the endemic situation, possible recourses and research question.

[8]Assuming infection of schistosomiasis naïve volunteers.

CSF, Cerebrospinal Fluid; PCR, Polymerase Chain Reaction; POC-CCA, Point-Of-Care Circulating Anodic Antigen; RPA, Recombinase Polymerase Amplification; UCP-LF CAA, Up-Converting Particle Lateral Flow Circulating Anodic Antigen.

regions where extensive control measures have reduced the prevalence and intensity of infection to very low levels. This is clearly recognized by the WHO and international stakeholders in the NTD Roadmap 2030 where they highlight the need for field-deployable, intelligent diagnostics and sampling strategies to evaluate pre-and post-intervention prevalence, especially for low endemic and near elimination areas (72). Recently, a strategy for the sustained, local interruption of transmission was presented in a viewpoint paper stressing the need for highly sensitive diagnostics (e.g. the UCP-LF CAA test) and intelligent testing procedures such as pooled sampling (81). Applying the UCP-LF CAA test on easily and non-invasively acquired urine samples makes the test an ideal candidate for field use and integration into national control programs. The high accuracy, quantitative outcome and reproducibility of the UCP-LF CAA test makes it amenable to pooled sample testing strategies through which information from whole communities can be obtained presumably in a more cost-effective way (82). Compared to exhaustive individual sampling and testing approaches, appropriate pooling strategies can significantly reduce logistical and laboratory costs of control programs, with minimal loss of sensitivity and specificity (81–83). To what extent NAATs might be suitable for defining interruption of transmission, needs more research (59, 84, 85). Eventually, in settings where transmission appears to have been interrupted, detection of specific antibodies will be useful for assessing exposure in young children (20, 75, 86, 87).

Non-Endemic Settings

In non-endemic settings, diagnosis is usually focused on identifying the infected individual with complete cure as the desired goal. Treatment success can be confirmed by follow-up testing, as there is no risk of re-infection. Distinctive populations can be identified, primarily short-term travelers (including tourists and expatriates) and migrants (including refugees). In general, travelers have not been exposed earlier in life and are therefore considered to be immune-naïve, whereas migrants, when originating from *Schistosoma* endemic areas, have often been exposed since childhood and are more likely to present with chronic infections. In exceptional cases, migrants originating from non-endemic schistosomiasis areas may have acquired an acute infection when passing through a schistosomiasis endemic area.

Travelers

Only 30-50% of infected travelers present with clinical symptoms (88, 89), but if they develop the so-called Katayama syndrome, it is generally seen several weeks before eggs can be detected. Travelers also often harbor a low worm burden, making appropriate diagnosis even more challenging, even when performed months after exposure (35, 45, 88, 90). Subsequently, schistosome-specific antibody detection plays a central role in the diagnosis of schistosomiasis in previously naïve individuals. Alternatively, detection of *Schistosoma* DNA in blood has shown to be highly sensitive and specific for early diagnosis of acute schistosomiasis, but also here the test remains positive for many months after treatment (91, 92). Contrary to these findings, there are strong indications that the clearance of *S.mansoni* DNA in stool or urine occurs within weeks to months following PZQ treatment, but this still needs further validation (93). The diagnostic value of the UCP-LF CAA test in travelers has recently been validated, demonstrating detectable CAA-levels within 4 weeks after exposure, with rapid reduction following appropriate treatment (34, 35).

Migrants

The increasing number of migrants, coming from or passing through *Schistosoma* endemic regions and arriving in Europe, augments the importance of timely and effective screening for *Schistosoma* infections (94–96). Detecting *Schistosoma*-specific antibodies remains the recommended and most used first-line test for screening migrants (97, 98), However, as these methods have their limitations both in sensitivity and specificity in this specific group of suspected infections, the detection of eggs in urine or stool is commonly used to confirm infection, even though its sensitivity is limited (5). A better alternative is the detection of *Schistosoma* DNA or circulating antigens in clinical samples, as both have demonstrated to be of clinical value when monitoring schistosomiasis in migrants after their arrival in Europe (37). The POC-CCA test can be a useful screening tool for *S.mansoni* infections when used in a standardized manner (99–101). However, detection of CAA as a routine procedure seems most efficient for migrants originating from different regions, as CAA is found in all *Schistosoma* species including hybrids and is also most suitable to diagnose low intensity infections (37).

Disease-Specific Clinical Presentation

Genital Schistosomiasis

Genital schistosomiasis, resulting from egg deposition in the genital tissue or fluids, occurs in both males (MGS) and females (FGS) (12, 102). Obviously the first step is to diagnose the presence of schistosomiasis, but there is also a need for diagnostic procedures which can reveal the cause of the organ-specific symptoms. Several studies have demonstrated that the detection of DNA in vaginal swabs, lavage and semen correlates well with the clinical presentation of genital schistosomiasis (103–105). In particular for FGS, this provides a sensitive and more standardized alternative to invasive diagnosis such as colposcopy examination (106, 107).

Neuro-Schistosomiasis

Early diagnosis and treatment of neuro-schistosomiasis, a rare but severe complication of schistosomiasis with spinal-cord involvement, is crucial. The reference standard for confirming neuro-schistosomiasis is the detection of eggs after pathological examination of a tissue biopsy, an invasive and often dangerous procedure. Detection of parasite-specific DNA in cerebrospinal fluid and the demonstration of intra-thecal antibody production seem the most promising diagnostic alternatives (108–110).

Research-Specific Settings

Controlled Human Schistosomiasis Infection Model

To accelerate and assist the development of novel medicines, vaccines and diagnostic tests, an experimental human *S.mansoni* infection model has been established recently where healthy volunteers were intentionally infected with male-only or female-only parasites. This model provided insight into the development of (acute) schistosomiasis in terms of symptoms, the related immune responses, and the performance of diagnostic tests over time. Following experimental infection, all previously schistosomiasis-naïve volunteers showed detectable antibodies against adult worm gut antigen within 4 to 6 weeks, including those exposed to 10 cercariae only, while the UCP-LF CAA test most accurately reflected worm burdens and appeared highly suitable for monitoring cure (32).

Clinical Studies

Diagnostic tests are also being used and/or evaluated in clinical studies. Currently, the freeBILy project evaluates the POC-CCA and UCP-LF CAA test for the diagnosis of *Schistosoma* infections in the still often neglected group of pregnant women and their newborn children (111). The project aims to assess the potential of integrating these diagnostics as a schistosomiasis control tool in test-and-treat strategies (111, 112). Another recent clinical trial is the RePST-study in which a panel of adult-worm and egg-related diagnostics were applied to compare standard versus intense treatment in school-aged children with a confirmed *S.mansoni* infection (113). Cure rates (CRs) based on worm detection (POC-CCA, UCP-LF CAA) were significantly lower than egg-based CRs

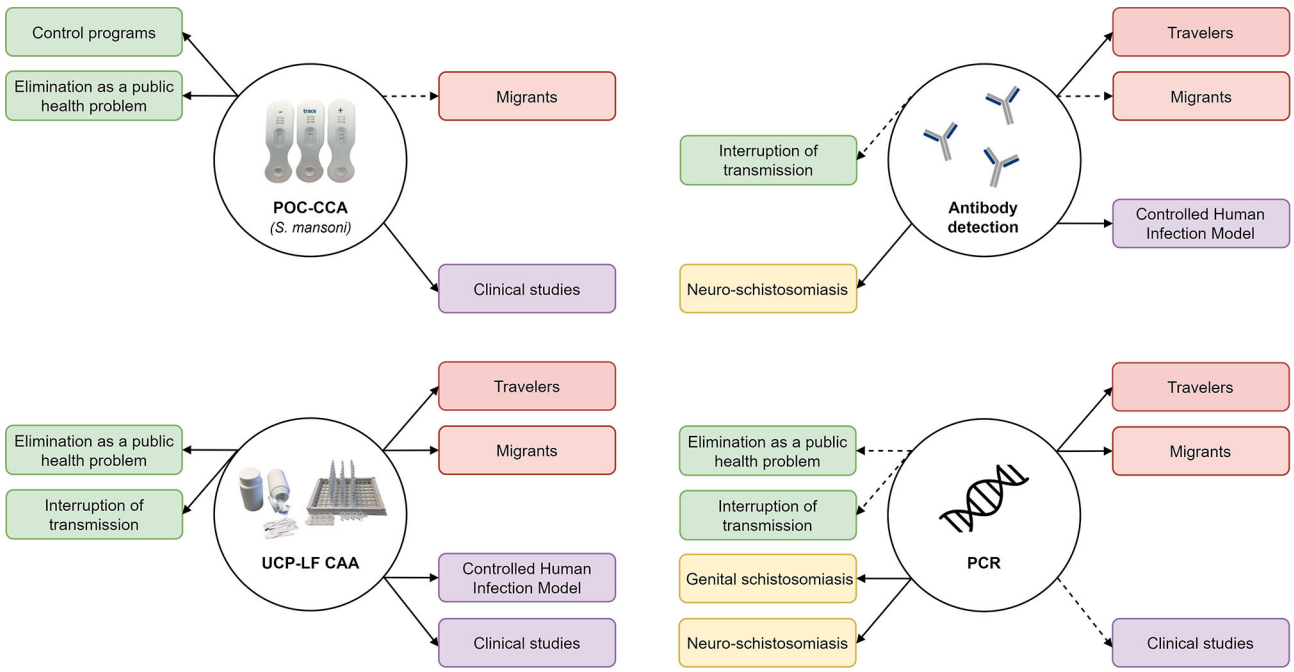

FIGURE 1 | Summary of the applicability of the POC-CCA, UCP-LF CAA, antibody detection and PCR in context-specific settings (solid lines represent first choice diagnostic, dashed lines represent optional or alternative diagnostics). PCR, Polymerase Chain Reaction; POC-CCA, Point-Of-Care Circulation Cathodic Antigen; UCP-LF CAA, Up-Converting Particle Lateral Flow Circulating Anodic Antigen.

(KK, PCR) (33, 114). To better understand and optimize treatment strategies, highly sensitive methods such as PCR and UCP-LF CAA should be used in conjunction to provide adequate insight into the host-parasite interaction and metabolic clearance of schistosome circulating antigens.

Other research studies to optimize schistosomiasis control efforts include the SCORE project where the POC-CCA test was evaluated in various endemic settings, contributing to the current WHO recommendation for using the POC-CCA test (38, 39). SCORE also supported further development of the UCP-LF CAA test into more sensitive as well as more user-friendly (dry) formats (44, 47). In addition, preliminary results from a study in Uganda investigating the dynamics of parasite clearance and re-infection based on egg- and antigen-methods, indicate that timing of post-treatment sampling is important, as well as the diagnostic test used to determine *Schistosoma* CRs and re-infection (115).

CONCLUSION

The current mini review provides a summary of diagnostic tests with a focus on the requirements for different context-specific settings. Although CAA detection seems the most favorable choice overall, alternative procedures such as antibody detection and NAATs will remain crucial for specific purposes. As 'no size fits all', diagnostic tests need to be carefully selected based on the data they provide in order to respond adequately to a specific situation (**Figure 1**). This is the first and most important step after which further choices will be guided by practicability and economics.

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