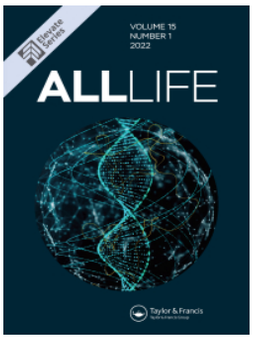

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REVIEW ARTICLE

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A critical review of the limitations of current diagnostic techniques for schistosomiasis

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ABSTRACT

Schistosomiasis is a parasitic disease that is endemic in tropical and subtropical areas. Its diagnosis is crucial for effective treatment and control, particularly in resource-limited settings where the disease burden is high. Various diagnostic methods are available. However, these methods are associated with low accuracy, efficiency or accessibility. This review summarizes the published literature on the diagnostics of schistosomiasis based on the techniques of microscopy, serology, molecular, antigen-based and aptamer-based assays. The limitations of each technique were summarized to encourage future research. Furthermore, we highlight the need for point-of-care diagnostics that are sensitive, specific, and easy to use in resource-limited settings may address the challenges associated with commonly used diagnostic techniques. The review concludes that further research and development are needed to improve the diagnosis of schistosomiasis and enable effective treatment and control of this debilitating disease.

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Diagnostics; schistosomiasis; accuracy; efficiency; limitation

Introduction

Schistosomiasis is a parasitic disease caused by blood flukes of the genus *Schistosoma*, which affects an estimated 240 million people worldwide (Exum et al. 2019). The disease is endemic in many tropical and subtropical regions, particularly in sub-Saharan Africa (Sacolo et al. 2018). Schistosomiasis is associated with significant morbidity and mortality, particularly in children and young adults (Vester et al. 1997; Mduluza-Jokonya et al. 2020). The impact of schistosomiasis is multifaceted, affecting both physical and economic aspects of the lives of those affected. The disease can cause chronic illness, leading to complications such as anemia, cognitive impairment, and hepatosplenomegaly (Cimini et al. 2021). In addition to its direct health impact, schistosomiasis is also linked to poverty and poor socioeconomic conditions. It is most prevalent in areas with poor sanitation and inadequate access to clean water (Mwanga et al. 2013; Nascimento et al. 2019). Early diagnosis and treatment are critical in preventing the progression of the disease and thus, the development of severe complications (Shiff et al. 2010; Wu et al. 2018). Several diagnostic methods are available for detecting schistosomiasis, each with its advantages and limitations. The gold standard is the microscopic examination of stool or urine samples which is the most widely used method (Katz and Chaves 1972). Microscopy involves identifying the presence of *Schistosoma* eggs in the patient's urine or excreta. The eggs can be visualized using various staining techniques.

Accurate and efficient diagnostics are essential for disease control and management (Amoah et al. 2020), as they play a critical role in identifying and treating diseases and in early diagnosis. Early and accurate diagnosis is key to improving patient outcomes, reducing transmission rates, and minimizing healthcare costs associated with delayed or misdiagnosed conditions (Shiff et al. 2010; Wu et al. 2018). Early diagnosis allows for prompt treatment, which can lead to better outcomes and a reduced risk of complications. Also, in the case of infectious diseases, early

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diagnosis can help prevent the spread of the disease to others. Accurate and efficient diagnostics are critical for disease surveillance and control (Weerakoon et al. 2018). In many cases, diseases can be asymptomatic or have non-specific symptoms, making diagnosis difficult. Accurate diagnostics can help identify cases that might otherwise go undetected, allowing for effective control measures to be implemented (Amoah et al. 2020). Efficient diagnostics help reduce healthcare costs associated with disease management (Krishnan 2016). Delayed or misdiagnosed conditions can result in unnecessary tests, treatments, and hospitalizations, leading to increased healthcare costs (Krishnan 2016; de Wilton et al. 2021). Accurate and efficient diagnostics ensure that patients receive appropriate care and treatment in a timely manner. Moreover, accurate and efficient diagnostics guide the development of new treatments and therapies (Fasogbon et al. 2023; Manciulli et al. 2023).

This review is aimed at discussing the diagnostic methods for schistosomiasis and identifying their limitations in terms of accuracy, efficiency and their field usability as point-of-care diagnostics especially in resource-limited centers. The data presented in the study were curated from Scopus, PubMed and Google Scholar databases. They were not systematically screened but studies were included based on relevance to our objective.

Challenges in accuracy and efficiency for schistosomiasis diagnostics

Microscopy methods

Microscopic examination of stool or urine samples is a common method for diagnosing schistosomiasis caused by many of the *Schistosoma* species. Kato-Katz technique is commonly associated with the diagnosis of *S. mansoni*, (Katz and Chaves 1972; Menezes et al. 2023), *S. japonicum* (Xu et al. 2023) and *S. mekongi* (Rahman et al. 2021). The technique is simple being that it provides quantitative data by counting the number of parasite eggs in a known volume of fecal sample. The technique involves filtering a portion of the stool through a mesh screen, placing the filtered material on a microscope slide, and examining it under low-power magnification for the presence of *Schistosoma* eggs. Similar to the Kato-Katz technique for stool samples urine filtration method is being used more specifically for the detection of *S. haematobium* in urine samples collected from individuals suspected of having *S. haematobium* infection (Deribew et al. 2022). Typically, the first-morning urine sample is preferred as it may contain higher concentrations of parasite eggs. The sensitivity of Kato-Katz and urine filtration varies depending on factors such as the number of stool/urine samples examined, the distribution of eggs in the sample, and the skill of the personnel (Assaré et al. 2021). The eggs of *Schistosoma* species can be identified based on their characteristic shape and the presence of a lateral spine (Boon et al. 2017; Gryseels 2020; Reguera-Gomez et al. 2021). While this method is widely used, its sensitivity is limited by factors such as low parasite burden and the presence of other helminth infections (Oliveira et al. 2018).

In a study that compared diagnostic methods in low burden infection, the prevalence rates of 8.5%, 43.0% and 56.2% were reported by Da Silva et al. (1998) for Kato-Katz, ELISA (detecting immunoglobulin G antibodies against adult worm antigens- IgG-ELISA), and immunofluorescence test (detecting immunoglobulin M antibodies to gut associated antigens- IgM-IFT), respectively. The results suggest that parasitological methods by Kato-Katz had very poor sensitivity for the detection of *S. mansoni* eggs in individuals with low worm burden, which is the situation commonly observed in low-endemic areas. The Kato-katz thick smear is the most recommended method for the epidemiological study of *S. mansoni*, yet it has lower sensitivity when compared with the Formol-Ether concentration methods used for the diagnosis of other intestinal helminthic infections according to a report among school children of Wonji Shoa town, Eastern Ethiopia (Taye 2014). The Kato-Katz technique was even reported to be less sensitive in evaluating *S. mansoni* infection, even in a high-prevalence setting in central Sudan (Ibrahim and Elbasheir 2016). A sensitivity of 41% and 66% was reported respectively for sedimentation and filtration methods to prepare fecal samples for microscopic examination of *Schistosoma* eggs (Giovanoli Evack et al. 2020). Also, Ferreira et al. (2017) reported a sensitivity and specificity of the Kato-Katz technique for diagnosing *S. mansoni* infection in Brazil at 25.6% and 94.6%, respectively.

The poor sensitivity of microscopic methods results in false positive or negative results, although Benjamin-Chung et al. (Benjamin-Chung et al. 2020) demonstrated that a double-slide Kato-Katz had relatively few

false positives compared to the conventional approach. While comparing the diagnostic performance of Kato-Katz with Real-Time PCR in urine samples from Kenyan children infected with *S. haematobium*, Vinkeles Melchers et al. (2014), suggested the day-to-day variation often associated with microscopic methods of schistosomiasis diagnosis as a major setback in this method. Given the very poor sensitivity of egg detection in non-schistosomiasis-endemic settings, most tropical and travel medicine clinics in Europe use conventional microscopy systematically combined with other diagnostic methods for schistosomiasis diagnosis (Gautret et al. 2016).

Recently, there has been interest in the use of digital microscopy for the diagnosis of schistosomiasis. Digital microscopy involves the capture of images of fecal or urine samples using a microscope and the analysis of these images using computer software, as shown in Figure 1 (reproduced after obtaining appropriate permission). A digital microscope, called Schistoscope has been shown to have higher sensitivity than traditional microscopy methods and can be used for the simultaneous detection of multiple parasites (Agbana et al. 2019; Diehl and Oyibo 2020; Meulah et al. 2022). Holmström et al. (2017) also provided evidence for the applicability of the digital microscope at the point-of-care settings.

Serology methods

Serological methods play an important role in the diagnosis of schistosomiasis by detecting specific

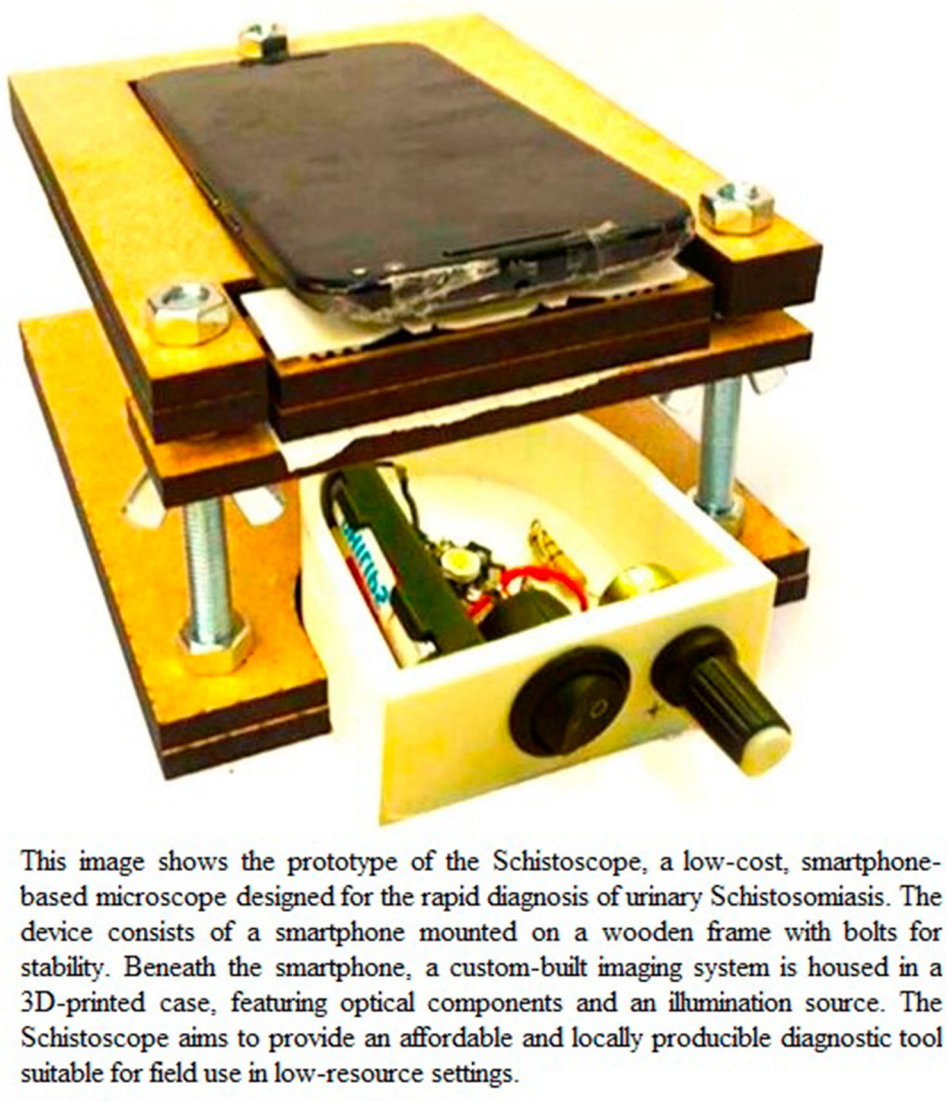

Figure 1. Components of a smartphone-based Schistoscope, a digital microscopic device for schistosomiasis diagnosis (Agbana et al. 2019).

antibodies or antigens produced in response to *Schistosoma* infection. ELISA is widely used to detect specific antibodies (IgG, IgA, IgM, or IgE) against *Schistosoma* antigens in serum or other body fluids (Beck et al. 2008). Many reports suggest that ELISA is the only reliable test for the measurement of IgG and IgM antibodies for both clinical diagnosis and epidemiological studies (Parker and Weber 1993; Hoermann et al. 2022). However, ELISA may produce false-negative results during the early stages of infection when antibody levels are low (Doenhoff et al. 2004; Xu et al. 2014). Cross-reactivity with other parasitic infections or exposure to unrelated antigens can also lead to false-positive results (Alarcón De Noya et al. 1996; Hamilton et al. 1999; Ishida et al. 2003; Lv et al. 2016), necessitating confirmatory tests. Other researchers have reported diverse approaches to reduce or eliminate cross-reactivity in ELISA assays. Examples include the use of sodium metaperiodate to successfully reduce the false reactivity of soluble egg antigen (SEA)-ELISA, with no decrease in sensitivity (Alarcón de Noya et al. 2000). The application of magnetic beads in ELISA assay in the form of immunomagnetic beads (IMB)-ELISA for diagnosing *S. mansoni* infection was also reported to reduce false positive results (Méabed and Hassan 2019). ELISA, like other serological assays, is often found challenging to distinguish between current or past infection (Hinz et al. 2017). However, the sandwich ELISA assays developed against *S. japanicum* protein (Sj29) were reported to have potential diagnostic capability that could distinguish between current or past infection and assess responses to drug treatment (Ren et al. 2017).

Indirect Hemagglutination Assay (IHA) is another serological assay that detects antibodies against *Schistosoma* antigens by causing red blood cell agglutination (Abdalla 2018; Suleiman et al. 2022). It is relatively simple and inexpensive, but its sensitivity and specificity may vary depending on the antigen used and geographical variations in *Schistosoma* species. False-positive results due to cross-reactivity with other helminthic infections also occur in IHA like ELISA and other serological assays (Malone et al. 2017). In general, serological methods primarily indicate exposure to *Schistosoma* parasites, rather than the current infection status or the worm burden so serological test may present positive results for many years ('serological scar') post infection, therefore the method is inappropriate to monitor the treatment efficacy.

Molecular methods

Molecular methods have become increasingly popular for the diagnosis of schistosomiasis, as they offer improved sensitivity and specificity compared to traditional microscopy-based methods. PCR, the most commonly used molecular method for the diagnosis of schistosomiasis, is a sensitive and specific technique that can detect small amounts of *Schistosoma* DNA in a variety of sample types, including stool, urine, blood, and tissue (Kato-Hayashi et al. 2010; Cai et al. 2019; Guegan et al. 2019), even when the sample has low parasite load (Magalhães et al. 2020). There have been various types of PCR assays developed to detect either the parasite nuclei DNA, ribosomal DNA or cell free DNA from the parasite in host samples. One of such novel technology is the development of a 18S rRNA gene (ribosomal DNA [rDNA])-specific PCR-based assay, to detect avian schistosomes in water samples, coupled with a follow-up 28S rDNA-specific PCR and sequencing to identify the schistosomes to the species or genus level (Jothikumar et al. 2015). Blin et al. (2023) also developed another rapid, reliable and cost-effective duplex tetra-primer amplification refractory mutation system (T-ARMS)-PCR assay to distinguish between three *S. haematobium* (human parasite), *S. bovis* and *S. curassoni* (animal parasites), and their hybrids. The technique has the advantage of amplifying multiple alleles in a single reaction with the inclusion of an internal molecular control. Hamburger et al. (Hamburger et al. 1991) reported a set of primers are used to amplify a 121-basepair highly repeated sequence specific to *S. mansoni*. These primers were designed to bind specifically to this repetitive sequence, allowing for the amplification of DNA fragments that can be further analyzed through techniques such as PCR to detect the presence of *S. mansoni* DNA in biological samples. Similarly, repetitive nuclear DNA sequences have been reported, that specifically identifies of *S. haematobium* (Abbasi et al. 2017).

Quantitative or real-time PCR provides an advantage in terms of its capability in multiplexed detection and ability to distinguish several intestinal parasites from Schistosome (Siqueira et al. 2021). However, PCR assays are not without limitations. Despite their high accuracy and sensitivity, a major challenge is the higher probability of the test generating false-positive or false-negative results (Kato-Hayashi et al. 2010; Keller et al. 2020), which may be due to contamination

or poor sample quality. Additionally, PCR requires specialized equipment and expertise, which may limit its availability in resource-limited settings (Jothikumar et al. 2015; Magalhães et al. 2020; Blin et al. 2023).

PCR assays based on the amplification of the Internal Transcribed Spacer (ITS) region of the ribosomal DNA (rDNA) of *Schistosoma* parasites have been reported to present improved specificity (Hoffmann et al. 2021), as PCR that utilize DraI, a restriction endonuclease enzyme, also increase sensitivity in the detection and amplification of *Schistosoma* DNA (Frickmann et al. 2021b). DraI digestion was reported to also allow for the detection of low parasite burdens and can be adapted for use with various sample types (Frickmann et al. 2021a, 2021b).

Both ITS1 and ITS2 regions are utilized in PCR for *Schistosoma* diagnosis, though they differ in their nucleotide sequences and primers used for amplification. However, ITS2 region is generally preferred for its higher variability among *Schistosoma* species, which aids in species identification and differentiation. (Meurs et al. 2015; Menezes et al. 2023). ITS1 region may also be used in conjunction with ITS2 for comprehensive analysis, particularly in epidemiological studies and genetic characterization of *Schistosoma* populations. The ITS region is highly conserved within *Schistosoma* species but differs significantly from other organisms, making it a suitable target for specific detection. ITS-based PCR diagnosis is useful for early diagnosis and monitoring treatment efficacy (Meurs et al. 2015).

Another molecular method that has been used for the diagnosis of schistosomiasis is loop-mediated isothermal amplification (LAMP). LAMP is a sensitive and specific nucleic acid amplification technique that can also detect *Schistosoma* DNA in stool, urine, and blood samples (Kumagai et al. 2022). LAMP was developed as an alternative to PCR to overcome the bottleneck of application in resource-limited settings and for field studies (García-Bernalt Diego et al. 2019; Diego et al. 2021). Mesquita et al. (2021) reported that the LAMP assay was effective as the parasitological examination for the detection of *S. mansoni* infection when performed in triplicate, and is more directly applicable in the field than other molecular techniques. Several LAMP-based assays have been developed for the diagnosis of different *Schistosoma* species, with high sensitivity and specificity; LAMP for detection of *S. mekongi* detection in human stools and even in the snails intermediate host (Kumagai et al. 2022). A report on the use of LAMP in the snail screening to characterize schistosomiasis transmission zones makes LAMP quite promising. The technique also gives useful information for surveillance services as it can detect *Schistosoma* species, even when snails are not shedding cercariae (Hamburger 2020; Mesquita et al. 2021); LAMP was also developed for rapid detection of *S. japanicum* (Xu et al. 2010), where the percentage sensitivity of LAMP was 96.7%, whereas that of PCR was only 60%, indicating that LAMP was more sensitive than conventional PCR for clinical diagnosis of schistosomiasis cases in endemic areas. Moreso, Crego-Vicente et al. (2021) reported a genus-Specific LAMP Assay that was used to detect *S. haematobium* and *S. bovis* hybrids that could be adapted for diagnosis in the field and also for surveillance in settings of hybrids endemicity. LAMP assays, however, often have a challenge of inconclusive results when LAMP products are run in gels for analysis. As an alternative to this, visual inspection of reaction tubes by the naked eye became prioritized, which also aided the field application of the LAMP assay (Mesquita et al. 2021). Also, there have been reports of non-specific amplification in LAMP assay, hence results presented are unreliable (Gandasegui et al. 2018; Mesquita et al. 2021).

Overall, molecular methods offer significant advantages over traditional microscopy-based methods for the diagnosis of schistosomiasis, including improved sensitivity and specificity. However, challenges exist with the accuracy and efficiency of these methods, which may limit their effectiveness in certain contexts. Further research is needed to address these challenges and improve the utility of molecular methods for the diagnosis of schistosomiasis.

Antigen detection methods

In recent years, antigen tests have emerged as a promising alternative for schistosomiasis diagnosis. The antigen test for schistosomiasis diagnosis is primarily based on the detection of schistosome antigens in infected individuals (Casacuberta-Partal et al. 2020). These antigens are glycoproteins released by adult schistosomes into the bloodstream of infected individuals. The most widely used antigen test is the point-of-care circulating cathodic antigen (POC-CCA) assay, which utilizes immunochromatographic techniques to

detect CCA in urine or stool samples (Neumayr et al. 2019). The test provides rapid results in about 20 min, enabling immediate diagnosis and initiation of treatment (de Sousa et al. 2020). This quick turnaround time is crucial for disease management, especially in endemic regions where laboratory facilities may be limited. The POC-CCA assay has demonstrated good sensitivity for detecting *Schistosoma* infections. Its simplicity makes it ideal for field settings and resource-limited areas (Ferreira et al. 2017; de Sousa et al. 2020; Hoekstra et al. 2020). However, its sensitivity has been reported to be lower in detecting early or low-intensity infections. False-negative results can occur, particularly in areas with low infection rates, potentially leading to missed diagnoses (Cai et al. 2021; Graeff-Teixeira et al. 2021). The results of POC-CCA assay are determined by visual reading, and the interpretation of a '*Trace*' reading as 'positive' or 'negative' is problematical (Colley et al. 2017). Also, the assay primarily detects *S. mansoni* infections, while its sensitivity for other *Schistosoma* species such as *S. haematobium* or *S. japonicum* may vary (Neumayr et al. 2019; de Sousa et al. 2020; Cai et al. 2021). In regions with mixed infections, complementary tests may be required for accurate species identification.

The varied sensitivity, specificity and inaccuracy of the currently available diagnostic methods of schistosomiasis led to the development of the up-converting phosphor lateral flow assay (UCP-LF) for circulating anodic antigen (CAA) quantification. The UCP-LF CAA assay presents high specificity, sensitivity and affinity for schistosomiasis diagnosis although, it is a laboratory-based assay requiring specialized equipment, protocol and skills that limit its application at the POC and in resource-limited settings (Corstjens et al. 2008, 2017; van Dam et al. 2012, 2015; Knopp et al. 2015; Fasogbon et al. 2023).

Aptamer-based diagnosis for schistosomiasis

Aptamers are synthetic nucleic acid molecules with precise target binding, facilitating the selective identification of the target (Molefe et al. 2018; Fasogbon et al. 2022). Aptamers are often generated from a synthetic random library with 10^{13}–10^{16} single-stranded DNA or RNA molecules by an *in vitro* iterative process known as systematic evolution of ligands by exponential enrichment (SELEX) (Long et al. 2016). Aptamer-based diagnostic presents an exciting approach in the schistosomiasis diagnosis, presenting high specificity, sensitivity, and potential for rapid detection of biomarkers associated with *Schistosoma* parasites. However, the translation of aptamer-based diagnostics for schistosomiasis encounters challenges and limitations like; the laborious task of identifying and validating aptamers with high specificity and affinity for *Schistosoma*-specific biomarkers (Long et al. 2016; Molefe et al. 2018) and the intricate nature of *Schistosoma* infections, encompassing diverse parasite species and distinct life cycle stages, poses a great challenge in selecting aptamers targeting diagnostic biomarkers (Colley et al. 2017). Hence, there are paucity of information on the development and application aptamers aptamers in schistosomiasis diagnosis.

However, Long et al. (2016) have reported two aptamers, namely, LC6 and LC15 exhibiting high specificity and affinity *S. japonicum* eggs. Although, this discovery advances knowledge regarding the potential of aptamer in the diagnosis of *S. japonicum* infection, however, the aptamer would not be applicable for early phase diagnosis (before shedding of egg), since it would only detect the parasite's egg. It would also be subject to variability in egg shedding. Fasogbon et al. (2023) recently proposed the development of aptamers that could specifically bind the genus-specific *Schistosoma* CAA as an alternative to monoclonal antibodies in the UCP-LF assay for early diagnosis of schistosomiasis.

Summary of the advantages and limitations of diagnostic methods

Each diagnostic method has its own strengths and weaknesses, and the choice of technique depends on factors such as the stage of infection, available resources, and specific requirements of the healthcare setting. Often, a combination of methods may be employed for accurate diagnosis and monitoring of schistosomiasis. The major advantages and limitations of the reviewed methods are summarized in Table 1.

Conclusion

The diagnosis of schistosomiasis, like other diseases, is crucial for effective treatment and control, particularly in resource-limited settings where the disease burden is high. Various methods are available for schistosomiasis diagnosis, and their selection depends

Table 1. Major advantages and limitations of reviewed methods.

S/N	Method	Advantages	Limitations
1.	Microscopy	• Widely available and cost-effective. • Can directly visualize parasite eggs in stool or urine samples. • Established method with well-defined diagnostic criteria.	• Requires trained personnel for accurate interpretation. • Sensitivity may vary depending on the experience of the personnel and the stage of infection.
2.	Serology	• Can detect antibodies produced in response to *Schistosoma* infection. • Useful for detecting chronic or past infections. • Less operator-dependent compared to microscopy.	• Cross-reactivity with other helminth infections may occur. • Cannot distinguish between current and past infections. • Sensitivity may be lower during the early stages of infection.
3.	Molecular Diagnostics	• Highly sensitive and specific. • Can detect *Schistosoma* DNA in various sample types (e.g. blood, stool, urine). • Useful for detecting low parasite burdens and early infections.	• Requires specialized equipment and trained personnel. • Generally more expensive than microscopy and serology. • Susceptible to contamination, which can lead to false-positive results if not carefully controlled.
4.	Antigen-Based Diagnostics	• Can detect circulating *Schistosoma* antigens in patient samples. • Generally more sensitive than microscopy and serology, especially in low-intensity infections. • Can be adapted for rapid diagnostic tests (RDTs) suitable for POC testing.	• Cross-reactivity with other helminth infections may occur. • The results of POC-CCA assay are determined by visual reading, and the interpretation of a 'Trace' reading as 'positive' or 'negative' is challenging.
5.	Aptamer-based Diagnostics	• Aptamers offer strong target specificity, sensitivity, enabling precise detection of biomarkers associated with schistosomiasis. • Aptamer-based diagnostic methods facilitates rapid detection that could be applicable in POC settings.	• Identifying aptamers with high specificity and affinity for target molecules can be challenging, requiring extensive screening processes.

on the prevalence of the disease in the population being tested, the availability of resources and personnel, and the sensitivity and specificity of the tests. However, they all have limitations in terms of accuracy, efficiency, and feasibility in resource-limited settings. Hence we recommend further research on point-of-care testing that would be applicable in resource-limited settings for schistosomiasis diagnosis.

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Data availability statement

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