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Chapter 7

Schistosomiasis – Updating Technologies and Diagnostic Approaches in Surveillance Strategies and Clinical Management

Marta Guimarães Cavalcanti and José Mauro Peralta

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Abstract

Schistosoma infection is a poverty-related parasitic infection, being the second most important neglected tropical disease in the world after malaria. Schistosomiasis is caused by five distinct *Schistosoma* species distributed in tropical and subtropical areas. But, imported cases can also be seen in non - endemic areas. Human populations acquire infection after exposure to contaminated water collections. *Schistosoma* infection falls on a large spectrum of clinical manifestations that ranges from absence of signs and symptoms to severe forms of disease. Although morbidity and mortality have been reduced along the years after use of mass drug administration (MDA) in endemic areas, large populations are still at risk of disability-related outcomes on daily basis. Recently, a great deal of debate has been done over two main issues in schistosomiasis management in endemic and non-endemic areas: how to accurately diagnosis *Schistosoma* infections pre and post-therapy in addition to assess morbidity level. Adoption of promising new diagnostic tools and development of new markers of disease progression might change the current scenario by improving schistosomiasis clinical management in both community and institutional settings.

Keywords: schistosomiasis, diagnostic tests, markers of therapy response, morbidity, community settings, institutional settings

1. Introduction

Schistosoma infection is a poverty-related parasitic infection, being the second most important neglected tropical disease in the world after malaria. Schistosomiasis is a blood-fluke-induced infection, which may present with acute and chronic disease forms. Schistosomiasis is caused by five distinct *Schistosoma* species distributed in tropical and subtropical areas. However,

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imported cases can also been seen in nonendemic areas. Human populations acquire infection after exposure to contaminated fresh water sources like dams, rivers, canals, lakes, and streams. *Schistosoma* infection falls on a large spectrum of clinical manifestations that ranges from absence of signs and symptoms to severe forms of disease. Although morbidity and mortality have been reduced along the years after use of mass drug administration (MDA) in endemic areas, large populations are still at risk of disability-related outcomes on a daily basis. A broad spectrum of clinical manifestations and also asymptomatic infections are observed [1, 2]. Three major species, *Schistosoma haematobium*, *Schistosoma japonicum*, and *Schistosoma mansoni*, and another two minor species, *Schistosoma mekongi* and *Schistosoma intercalatum*, are recognized as the mainly pathogenic *Schistosoma* species that infect human populations [3, 4]. Parasite transmission occurs after contamination of water collections with *Schistosoma* eggs eliminated by infected individuals, which further develop in the infective form called cercariae in freshwater snails. The release of *Schistosoma* cercariae from snails is followed by skin penetration of the definitive hosts (human and nonhuman species like buffalos in the case of *S. japonicum* or rodents in the case of *S. mansoni* infection). In the latter, *Schistosoma* immature forms evolve to adults that lay eggs, which are spread in the definitive hosts and/or eliminated in the environment through excreta, like urine in the case of *S. haematobium* and stool for the other species. In some areas, nonhuman definitive hosts are also essential to maintain *Schistosoma* life cycle, such as buffalos for *S. japonicum* and rodents for *S. mansoni* [5, 6]. Schistosomiasis world distribution is essentially in tropical and subtropical areas, with more than 90% of infected individuals living in sub-Saharan Africa [7, 8]. However, imported cases of schistosomiasis are also becoming increasingly frequent in nonendemic areas such as Europe. Spotlights were thrown on schistosomiasis in the recent years since elimination is believed to be a reachable goal for some endemic regions on the globe. Education, sanitation policies, and hygiene awareness proved to promote a high impact on infection transmission [9]. Also, field work in different transmission areas shows that chemotherapy plays an evident role in decreasing prevalence, parasite burden, and late morbidity [10].

Recently, a great deal of debate has been done over two main issues in schistosomiasis management in endemic and nonendemic areas: how to accurately diagnosis *Schistosoma* infections before and after therapy in addition to assess morbidity level. The adoption of promising new diagnostic tools and the development of new markers of disease progression might change the current scenario by improving schistosomiasis clinical management in both community and institutional settings.

The diagnosis of active *Schistosoma* infection is based on the demonstration of egg excretion by parasitological methods such as Kato-Katz (K-K), which has a low cost and can be performed in field studies. Direct egg detection achieves 100% specificity and high sensitivities parallel with high parasite burden. However, in individuals with less than 100 eggs per gram (epg), parasitological method loses sensitivity. Non-egg excretors are usually underdiagnosed. Furthermore, the assessment of cure rate is unreliable postchemotherapy use [11, 12]. Moreover, the evaluation of the effectiveness of schistosomiasis control or eradication programs after (mass) chemotherapy is distorted. New approaches have been developed and proposed as complementary or in substitution to K-K. New approaches such as DNA detection assays

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and rapid tests have evolved in the last years [13]. The accurate assessment of schistosomiasis diagnosis, morbidity determination, and therapy response through new technologies became suitable for use in both institutional as well as community settings. The upgrade of diagnostic technology that encompasses the detection of active infection before chemotherapy and monitoring of treatment response will permit advances in public health policies as well as in individual clinical management [14, 15]. Moreover, the assessment of clinical presentation, the disease stage, and the prognosis have been the object of progresses that go side by side with the development of new image diagnostic apparatus. Also, biochemical, immunological, and molecular markers have been tested for the evaluation of fibrosis, vascular damage, and even cancer [16]. The present review aims to discuss the new surveillance strategies and their impact on schistosomiasis clinical management.

2. New diagnostic tools in both community and institutional settings

The laboratory investigation of *Schistosoma* infection consists of different techniques, including parasitological, immunological, and molecular biology methods [17-19]. Frequently, diagnostic approaches are also applied on the monitoring of drug response. In addition, the assessment of morbidity levels can be achieved by using image tests and biochemical markers [20-22]. However, the diagnosis of active *Schistosoma* infection and the monitoring of therapy response as well as the determination of morbidity levels are distinctively assessed at community and institutional settings (Figure 1). Furthermore, in community settings, conventional or investigational tools aim to assess the efficiency of national control programs in the morbidity control and/or elimination of transmission by measuring the prevalence and intensity of infection in intermediary and definitive hosts [23-25]. In contrast, in institutional settings, diagnostic approaches aim to improve clinical management of individual cases.

Traditionally, egg detection by microscopy is the major criteria for active *Schistosoma* infection [24, 26]. Egg excretion can be detected by parasitological methods such as urine filtration and centrifugation methods in the case of *S. haematobium*. Since *S. japonicum*, *S. mansoni*, *S. mekongi*, and *S. intercalatum* eggs are shed in the feces, egg patent infection is detected in fecal samples by parasitological methods such as Kato-Katz test (K-K). The principal characteristics of K-K are as follows: an easy-to-do technique, low cost, reliability, and accurate identification of eggs in the case of *Schistosoma* species. Also, parasitological methods are quantitative. As a result, parasite load can be estimated. Egg counts correlate with the intensity of being <100 eggs per gram (epg), >100-399 epg, and >400 epg designated as light, moderate, and severe infection, respectively, according to WHO guidelines. Furthermore, the assessment of morbidity levels can also be roughly determined. Based on findings in high endemic areas, the elevated number of eggs was associated with severe forms of disease. Both urine filtration and Kato-Katz test have been applied for diagnosis and monitoring therapy response and used in field studies in areas of transmission as well as in institutional settings. Although Kato-Katz are affordable and suitable for low-income areas with individuals presenting with heavy to moderate infections, *Schistosoma* infection diagnosis can be quite tricky to detect in individuals with acute schistosomiasis or light infection living in nonendemic and low-endemic areas when based

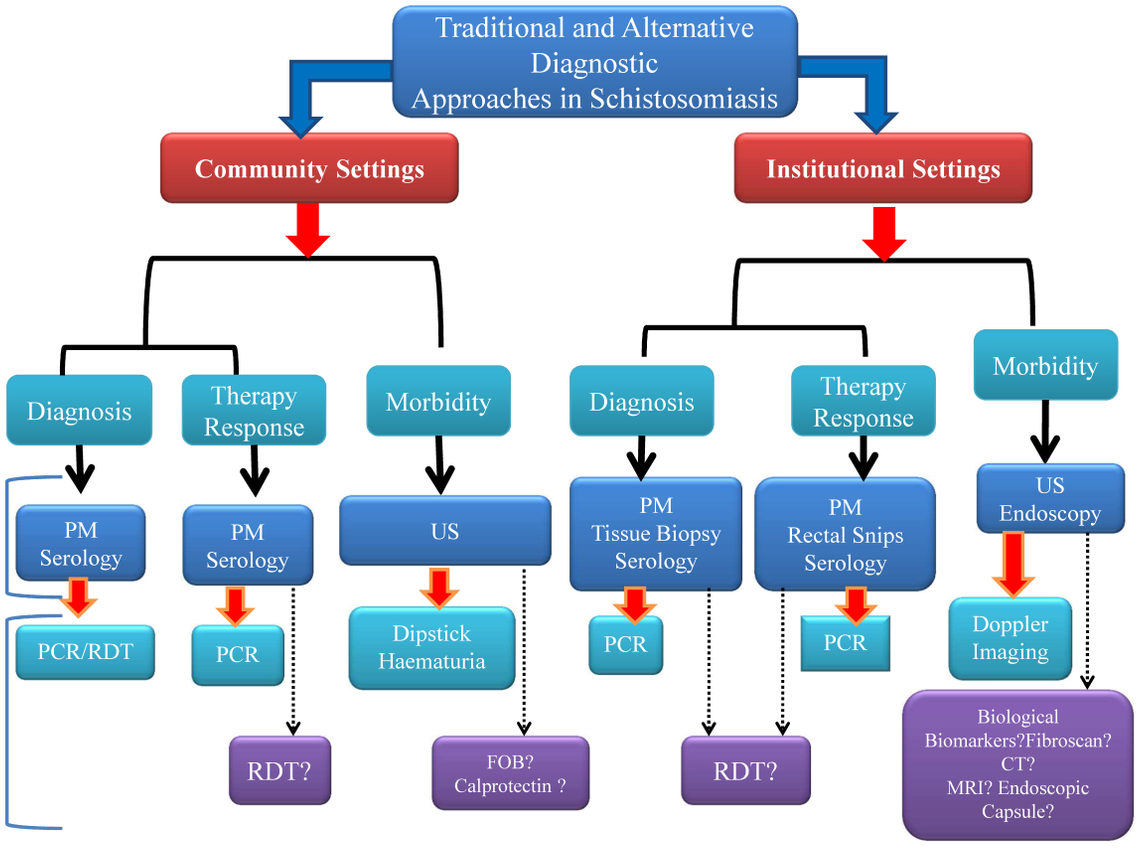


Figure 1. Schistosomiasis flowchart for clinical management in community and institutional settings. Conventional and new tools to diagnosis, determination of response to therapy, and morbidity assessment are indicated under community and institutional settings in hierarchic order. Bellow conventional tests, new tools were depicted according to the strength of literature evidence (red boxes). Approaches still under investigation and/or diagnostic platforms that show debatable results are inside the gray boxes. PM: parasitological method; US: ultrasonography; PCR: polymerase chain reaction; RDT: rapid test (POC-CCA /POC-CAA); FOB: fecal occult blood; CT: computed tomography; MRI: magnetic resonance imaging.

solely on microscopy [27]. Lack of egg shedding, one gender-induced infection, and daily variability are some of the causes that directly interfere with the sensitivity of microscopy, thus compromising the detection of *Schistosoma* infection and resulting in the underestimation of "real prevalence" [15, 28]. Moreover, the erratic elimination of *Schistosoma* eggs makes the determination of therapy response uncertain. In addition, some patients may present with severe forms of disease such as neuroschistosomiasis or genital schistosomiasis without any egg excretion detectable [13]. Strategies to overcome the lack of sensitivity of urine filtration and Kato-Katz test include testing replicate samples of urine or stool samples and/or augmenting the number of Kato-Katz slides/sample [29].

Other parasitological methods such as sedimentation, centrifugation, flotation techniques, and miracidium hatching were developed and had improved the diagnosis of light infections by increasing sensitivity [26, 32]. In institutional settings, tissue biopsy such as rectal snips and liver biopsy are largely used to diagnose active infection in non-egg excretors despite its invasiveness [31]. Eventually, surgical specimens reveal previously undiagnosed schistoso-

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miasis. Except for rectal snips, histological examination is not quantitative, lack of information on parasite burden does not preclude clinical assistance.

Albeit the availability of diverse parasitological methods and tissue biopsies as alternatives to the reference test (Kato-Katz), nonparasitological methods were also developed to overcome microscopy false-negative results. This is the case of immunological tests, which have become more useful for showing active infections in recently exposed individuals, such as travelers or chronically infected immigrants residing in nonendemic areas [32]. In areas of transmission, immunodiagnosis is a suitable tool for surveillance in low endemic areas [29]. Several immunodiagnostic tests were developed, but currently the ELISA-based assays using egg antigen, cercarial, or adult worm antigens have been extensively used [33]. In addition, recombinant proteins and peptides have been potential targets [34-36]. Despite its infrequent use in National Programs for Schistosomiasis Control, serology is a potent auxiliary diagnostic approach that permits the diagnosis of non-egg excretors. However, the presence of active infection may be undermined by persistent reactivity despite successful treatment [13, 29]. Although immunoreactivity does not correlate with the intensity of infection, data have demonstrated that isotypic immunoresponse may reflect morbidity levels [37, 38].

Moreover, rapid tests (RDT) for the detection of *Schistosoma* antigens like circulating cathodic (CCA) and anodic (CAA) antigens and DNA detection assays have proven to be an advanced and feasible strategy for diagnosing *Schistosoma* infection despite the absence of their use as routine diagnostic approaches [13, 39]. See detailed comments in Table 1. During active infection, gut-produced *Schistosoma* glycoproteins - POC-CCA and POC-CAA - are detectable in the blood, urine, and stool. At individual level, results revealed that both CAA and CCA ELISA-based assays can be quite sensitive to detect active infection early after exposure in travelers even in the cases of light infections. Also, the tests allow a quantitative assessment of antigen levels, which correlates with the intensity of infection [40]. Point-of-care platforms (POC) have been applied to estimate infection prevalence with high accuracy in field studies in high and moderate endemic areas [41, 42]. Although research groups claim that CCA and CAA might be a suitable substitute for Kato-Katz test, its performance is still debatable in low endemic areas [43, 44]. RDT for hematuria (urogenital schistosomiasis), fecal occult blood (FOB), and calprotectin detection (entero-schistosomiasis) are also point-of-care approaches, which have been shown to have fair association with egg-patent infections with dual use as diagnostic tools and markers of morbidity [25, 45]. Although strong evidences support the usage of hematuria detection by RDTs, larger studies are still necessary to establish the usefulness of FOB and/or calprotectin detection in cases of light infection commonly found in low endemic areas.

3. Assessment of morbidity and drug response in community and institutional settings

Sanitation and community health education in addition to chemotherapeutic intervention are measures that effectively contribute to the control and/or elimination of *Schistosoma* infection

in several endemic areas and the resolution or attenuation of progressive forms of disease at individual level [10, 46, 47]. However, the determination of the effects of these measures, in particular, drug intervention, still presents as a challenge (Table 1). Tests like microscopy have low sensitivity and underestimate cure rates especially in non-egg excretors. Day-to-day variations in egg excretion contribute to the misdiagnosis of schistosomiasis elimination after treatment [15]. The evaluation of drug response in individuals previously diagnosed by tissue biopsies is also troubled since the procedures might be invasive like brain or spinal cord biopsies in neuroschistosomiasis [48]. In immunoreactive egg and non-egg excretors submitted to PZQ treatment, it was shown that reactivity against several proteins mostly related to parasite musculature or glycolytic metabolism is enhanced after therapy [49]. Immunoreactivity might persist for long periods of time despite effective drug response, although seroconversion may occur in some individuals. Nonetheless, in low-endemic areas, immunodiagnosis has proven to be a valuable tool for schistosomiasis surveillance [50]. Changes in immunoreactivity in controlled areas can be used as an indicator of maintained transmission and/or active infection in community settings [51]. Therefore, the assessment of drug response is a hot topic in the schistosomiasis and development of new tools became an urgent matter (Table 1). Investigations have shown a potential role in drug response assessment with the use of rapid tests and DNA detection assays [14, 52].

	Traditional Tools		**Investigational Tools**	
Community Settings	**Tests**	**Characteristics/Observations**	**Tests**	**Characteristics / Observations**
Vector control	Light Exposure Test (Cercarial shedding detection)	For determination of transmission control, elimination or erradication. Inaccurate. no *species* identification; Test does not detect prepatent infections; no assessment of early post-control measures in snail infection rates.	Antigen Detection	Detection in 2nd week post-infection (pi); secretion by live larvae; group specific. Not commercially available assays.
			DNA- based assays	Detection in 1st week pi; quantitation of parasite load (real -time PCR; specie-specific identification. Mapping foci of vector snails and monitoring transmission. In house assays.
Non-human Hosts	Parasitological Methods (Egg detection)	Traditional methods which are simple, cheap and effective for *Schistosoma* detection.	CCA-dipsticks (urine lateral flow test) Serology (IgG/ IgM)	Detection of active infection independent of patent egg-excretion in primate non-humans. Only determination of genus but not species.

	Traditional Tools		Investigational Tools	
Community Settings	**Tests**	**Characteristics/Observations**	**Tests**	**Characteristics / Observations**
				Defines exposure to *Schistosoma*. In chimpanzee populations serology present high sensitivity but reactivity may persist for years after infection has been cleared. Comercial available test.
Humans Hosts Sanitation / Education	Questionaries Parasitological Methods (Egg detection) Serology	Questionnaries are applied to identify high - risk populations and permits assessment of *Schistosoma* infection Parasitological tests are quantitative methods. Low price per test. Used for Screening sentinel populations like school children.See more comments below.	DNA- based assays[1]	Identification and mapping of *Schistosoma* endemic areas. DNA based assays are powerful tools for detection of *Schistosoma* active infections. DNA detection show better performance even in light infection (low parasite loads) or despite absence of egg excretion. Mostly tested in "small" studies.
Chemotherapy	Parasitological Methods (Egg detection)	Microscopy is highly sensitive and specific to detect egg-patent infections. Day-to-day variations on egg excretion is a limitation. Absence of egg excretion post-treatment may not represent response to therapy. Cure rates determined in different *S. mansoni* and *S.haematobium* infections are variable (49.2 to 98.40%) [53, 54]. Understimates reinfection and also incomplete cure.	DNA-based assays[1]	DNA detection has higher sensitivity after use of chemotherapy. Persistent DNA amplification in both egg excretors and non-egg excretors strongly suggest no response to therapy. Presents good performance compared to parasitological methods to determine effect of MDA. Cure rates calculated by different DNA - based assays in distinct populations and by different Schistosoma species may varie from 21.1 - 30.7 to 75.6% [55, 15]. Persistence of DNA amplification until 6 months and post- 6 months after treatment might suggest incomplete infection and reinfection, respectively DNA-based assays for *Schistosoma* infection detection are not currently commercially available.
	Serology	Loss of sensitivity of microscopy has been replaced in	Rapid Test	POC-CCA maintains higher sensitivity than parasitological

	Traditional Tools		Investigational Tools	
Community Settings	**Tests**	**Characteristics/Observations**	**Tests**	**Characteristics / Observations**
		some control programs by serology which may remain reactive for extended periods post effective drug use. In areas submitted to several rounds of chemotherapy, low and/or absence of reactivity might represent control of infection.Long periods of obsevation are necessary to determine *Schistosoma* infection "real status". Reinfection or incomplete cure may not be assessed.		methods after PZQ use. However, specificity may be compromised by the presence of persistent low reactivity (trace positive samples) post-chemotherapy.Cure rates may vary from 23.3 - 26.1 to 40.7- 47.8% [42, 54]
Institutional Settings				
Chemotherapy	Parasitological Methods (Egg detection)	Assessment of post-therapy response by parasitological methods in clinical wards has similar advantages and limitations as in community settings. In immigrants (long gone from endemic areas) and recently exposed travelers, absence of egg excretion pre-therapy represent an obstacle. Ova detection is inappropriate to determine therapy response in these groups. See above other coments.	DNA-based assays[1]	DNA-based assays are a reliable tool to detect response to therapy in distinct clinical specimens. Absence of DNA amplification correlates with response to therapy in individuals treated in Travel Medicine Clinics [56].In case of therapy failure, maintained DNA amplification correlate with persistence of clinical signs, symptoms and pathological abnormalities associated to therapy failure [57]. Usefulness of DNA-based assays to detect past infection incomplete cure for non re-exposed individuals has to be established with large studies [58].
	Tissue Biopsy	No viable eggs in rectal snips show good correlation with response to therapy. However, tissue biopsy (rectal snips, liver biopsies) are invasive procedures. And, lack of ova		

	Traditional Tools		Investigational Tools	
Community Settings	**Tests**	**Characteristics/Observations**	**Tests**	**Characteristics / Observations**
		detection may not represent absence of active infection [59].		
	Serology	Immunoreactivity persistence for years after effective therapy is the major limitation. Negative seroconversion representes response to therapy and it is observed in some individuals [56]. But, assessment of therapy failure is mostly difficult [59].		
Transplant	Tissue Biopsy	Donnor and organ-recipients from endemic areas with / without transaminase alterations can be screened by tissue biopsy [60]. But, negative tissue samples do not rule out active infection.	DNA- based assays[1]	Further studies are necessary.

[1]**DNA based assay** - conventional PCR, real-time PCR and LAMP (Loop-mediated isothermal amplification)

Table 1. Effectiveness of interventions in surveillance programs and monitoring therapy response in clinical management: use of traditional and investigational tools.

RDTs for antigen detection have been largely used for population studies to evaluate post-therapy response and efficacy [42, 43]. In areas of moderate and high endemicity, therapy response represented by decrease or disappearance of antigen detection may represent cure. However, in light infections, rapid test accuracy is reduced with maintained antigen detection in individuals without infection. The use of antigen detection assays is a debatable matter to measure posttherapy response. In contrast, DNA assays seem to be a suitable marker of drug response. Cure is determined by the absence of DNA amplification postchemotherapy use, while persistent DNA amplification correlates with nonresponse to therapy [15].

Schistosomiasis presents as a large spectrum of manifestations and disease severity during acute and chronic phases. Usually, imaging tests and/or biological markers are required to confirm diagnosis, to assess morbidity, and to stage disease progression [21, 22]. Image tests such as ultrasonography became revolutionary to assess urogenital *S. haematobium* infection and *S. mansoni* liver disease [61]. In both community and institutional settings, conventional ultrasound (US) examination is a well-standardized test to assess bladder and liver fibrosis, which is the hallmark of disease progression in urinary and intestinal schistosomiasis, respectively [62-65]. US predicts disease prevalence rates and is a reliable noninvasive indicator of morbidity levels which aloud disease staging [64, 66]. However, morbidity measurement in a multivariate clinical manifestation infection like schistosomiasis is no easy

task. Targeting one compartment to measure schistosomiasis morbidity might not be enough since some clinical presentations can affect a single compartment like in neuroschistosomiasis and others. In intestinal *Schistosoma* infection, independent hepatosplenic forms are the most common clinical presentation after asymptomatic *S. mansoni* infection. However, in contrast to hepatic schistosomiasis, the study of disease progression by using image and/or biochemical markers is still poorly developed [21]. Promising new approaches such as capsule endoscopy have been introduced, but large-scale studies are still necessary to evaluate the usefulness of the method [67]. In hepatosplenic forms, vascular gastropathy and colopathy can be indicators of portal hypertension severity [68]. The assessment of vascular alterations in superior gastrointestinal tract are used to determine schistosomiasis levels of morbidity through the use of upper digestive endoscopy in association with conventional ultrasonography and Doppler imaging [66]. In institutional settings, transient elastography, magnetic resonance, and computerized tomography might give supplementary information regarding fibrosis progression and vascular status, although standardization is necessary especially for disease staging [22, 69]

4. Conclusion

In community settings, concerns have been increasing on the effectiveness of schistosomiasis control interventions like MDA over the years. The low accuracy of the reference test to detect active *Schistosoma* infection and the improper estimates of cure rates jeopardize the truthful analysis of drug intervention, which compromises the effectiveness of surveillance systems. In clinical settings, underdiagnosed schistosomiasis and inadequate morbidity assessment also increase the burden on public and private health systems. In order to change this scenario, new diagnostic tools, markers of treatment response, and morbidity assessment have been developed over the years showing promising results. Nonetheless, efforts still have to be made to find a single cheap and easy-to-do approach that is suitable and reliable for diagnosis, treatment evaluation, and disease staging in community and institutional settings.

Author details

Marta Guimarães Cavalcanti[1,2] and José Mauro Peralta[2*]

*Address all correspondence to: peralta@micro.ufrj.br

1 Serviço de Doenças Infecciosas e Parasitárias, Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

2 Departmento de Imunologia, Instituto de Microbiologia Paulo de Góes, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

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