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Short Communication

Is it Time to Reconsider Serological Approaches for the Diagnoses and Surveillance of Schistosomiasis in Endemic Areas under Control? Contributions of a Field Research in a Brazilian Low Endemic Area

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Abstract

We conducted this study for assessing the field diagnostic accuracy and usefulness of Kato-Katz coprological test, the enzyme-linked immunosorbent assay with soluble egg antigen of *Schistosoma mansoni* modified by sodium metaperiodate (SMP-ELISA) and the circumoval precipitin test (COPT), for the detection of schistosomiasis infection in a low endemic area of Brazil.

Methods: Survey was conducted in northwest Brazil and was done using as reference standard a single Kato-Katz slide, similar to the used routinely in endemic areas in previous studies. The accuracy of SMP-ELISA and the COPT, used simultaneously or in a sequential (two-stage) form was evaluated.

Results: With a single Kato-Katz smear the schistosomiasis prevalence was 1.8%, by SMP-ELISA prevalence was31% and COPT 27.4%. SMP-ELISA showed high sensitivity (95.2%) and COPT best specificity (75.2%). When we use simultaneous SMP-ELISA and COPT, there was a net gain in sensitivity but a net loss in specificity. When SMP-ELISA was used as initial screening test and positives were re-tested with COPT there was a net loss in sensitivity but a net gain in specificity.

Conclusion: For epidemiological surveys we suggest the use of an easy, fast and cost-effective test as SMP-ELISA as initial screening method; the positives should be tested again with a specific confirmatory technique such as the COPT to identify real positives. Maybe, in those COPT positive persons, it might be useful to emphasize the search of *S. mansoni* eggs.

INTRODUCTION

When specific schistosomiasis control measures are applied in endemic areas, the true prevalence of remaining cases is difficult to assess through coprological studies [1,2] because the intensity of *Schistosoma mansoni* infection decreases; however these infected people with very low parasitic loads, are able to keep the transmission [3,4]. The method recommended by the World Health Organization (WHO) for the diagnosis of *S. mansoni* infection [5] is the Kato-Katz coprological test, which is

reasonably sensitive in high endemic areas, relatively simple and inexpensive, even under field conditions [6]. However, it loses sensitivity when used in low endemic areas where patients have few numbers of eggs in stools [7-11]; especially when only one sample stoolis done. In consequence, the results and impact of intervention measures are difficult to assess and interpret [3].

Priorities of control measures vary according to endemicity and program development [12]. In highly endemic areas the priority is the reduction of morbidity and mortality [13,14]. In low endemic areas, where infected individuals with low egg loads predominate, the interruption of the transmission is the most important goal. Therefore, sensitivity of the diagnostic method is crucial [9,15] and precise diagnosis of schistosome infections will play a pivotal role in achieving these goals [16]. Moreover, Brazilian researches emphasize the need of the study of new or combined methodology to evaluate if there is successful disease elimination and its surveillance in endemic countries [17].

An alternative way to diagnose schistosomiasis is through the detection of antigens or antibodies against *S. mansoni*. However, the study of antigenemy has not proven to be sensitive enough in low transmission areas [18].

Under these circumstances of low endemicity and limited sensitivity of both parasitologic and antigen determination, immunological techniques for detection of antibodies may be the best available methods for diagnosis. Several studies suggest that in areas of low intensity of infection, the sensitivity and specificity of methods such as the enzyme-linked immunosorbent assay with soluble egg antigen of *S. mansoni* modified by sodium metaperiodate (SMP-ELISA) and the circumoval precipitin test (COPT), appear to be satisfactory [19-24]. Moreover, researchers from Brazil and China use COPT as a gold standard in the diagnosis of *S. mansoni*-infection in low endemicity areas due to its high sensitivity and specificity[25,26].

When patients eliminate large quantities of *S. mansoni* eggs and they are easily found by performing one fecal examination, it was not necessary to assess the serologic tool. Such is the case of Brejo do Espírito Santo in the interior of Bahia (Brazil) where initial studies in 1976 found a prevalence of infection of 75.4% with an arithmetic mean of 802.5 (24-21360) eggs per gram of feces [27]. After the introduction of control measures of schistosomiasis, between 1980-1997, preliminary observations made between 2002-2003 suggest that there has been a significant reduction in both the prevalence (1.8%) and intensity of infection (a mean of 45.6 eggs per gram of stool) [27]. It is possible that the true prevalence of schistosomiasis in Brejo do Espírito Santo would be greater if serology was used. It is the case of Venezuela and China, where control programs have been successfully implemented and its assessment is based on coprologic and serologic tests [22,28,29].

We conducted this study with the goal of assessing the field diagnostic accuracy and usefulness of Kato-Katz coprological test, and SMP-ELISA and COPT serological tests, for the detection of schistosomiasis infection in a low endemic area of Brazil.

MATERIALS AND METHODS

Study area. The study setting was Brejo do Espírito Santo, a rural area in the municipality of Santa Maria da Vitória, located at the southwest of the State of Bahia (Brazil), approximately 580 km away from Brasília.

Field work and laboratory procedures

a. In this work all of the 3,164 residents of Brejo do Espírito Santo were interview. Forty five percent of the interviewees (1,428) provided a single stool sample, from which one smear was prepared and evaluated at site by the Kato-Katz method [30]. The arithmetic mean of egg output was calculated and expressed as eggs per gram of feces. Parasitological tests were performed by the staff of the Regional Direction of Health of Santa Maria da Vitória within 24-48 hours after collection.

b. We collected also an additional 5 ml blood sample for serologic assays from 1,325 people. Serum samples were kept in ice and then frozen to -80ºC until processing at the *Sección de Biohelmintiasis* of the Institute of Tropical Medicine (Venezuela) where the immunological diagnosis of schistosomiasis was blindly made by means of enzyme-linked immunosorbent assays with soluble egg antigen of *S. mansoni*, modified by sodium metaperiodate (SMP-ELISA), as described by Alarcón de Noya et al., [31]. In those positive samples and in a subset of negative for SMP-ELISA, the circumoval precipitin test (COPT) was carried out [32]. Paired examinations of feces and blood samples were available in 521 participants and were classified in four patterns of combined serological results (Groups A, B, C and D) (Figure 1).

c. The parasitological history of this population obtained in earlier surveys conducted between 1976-1989 was available and reviewed in order to identify previous infection.

Data analysis

For the statistical analysis, SPSS 19 for Windows (Version 19.0; Copyright SPSS Inc., 2010) was used. All variables under study (except the parasitic load) were expressed as categorical variables and grouped in contingency tables:

a. Prevalence measurement. We calculated the prevalence of *S. mansoni* infection for: one stool examination and immunological serological tests.

b. Measures of diagnostic accuracy. The following measures of diagnostic accuracy were estimated: sensitivity, defined as the proportion of *S. mansoni* egg carriers who were correctly identified by the serological tests; specificity, defined as the proportion of negative participants to *S. mansoni* eggs correctly identified by the tests; positive and negative predictive values (PPV, NPV), defined as proportion of participants who tested positive and were true carriers and proportion of participants who tested negative and were true non carriers, respectively. Positive and negative likelihood ratios (PLR, NLR) for dichotomous variables were also estimated as: PLR = sensitivity/ (1–specificity) and NLR = (1–sensitivity)/specificity for each test [33]. For each measure the 95% Confidence Interval (95%CI) was calculated.

c. Reference standards. In this study, we evaluated the immunodiagnostic accuracy using as reference one stool sample (as routinely done in the field) and similar to Prata *et al.,* in the past 29 years [27].

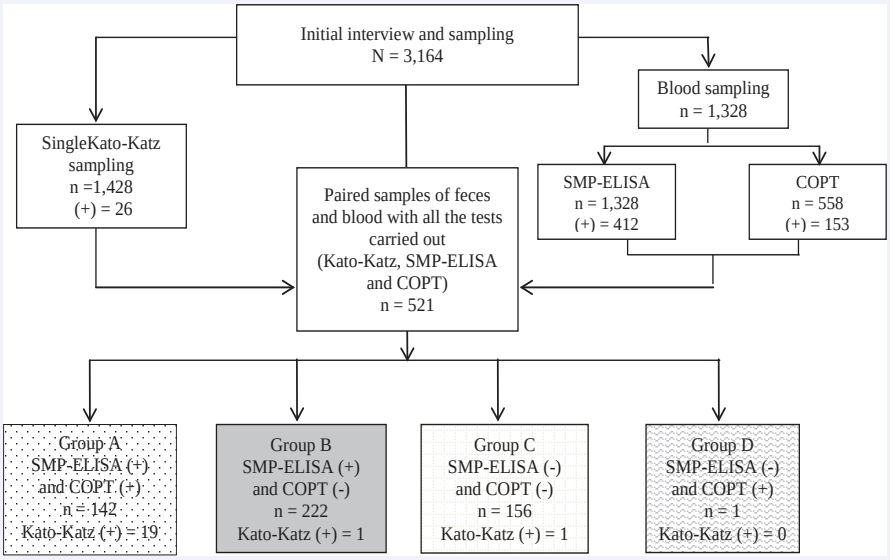

Figure 1 Flowchart and overall results of the work carried out in Brejo do Espírito Santo, Bahia State, Brazil, 2002.

d. Multiple testing. Based on results of sensitivity and specificity of serological proves for the reference standard, we calculated the diagnostic accuracy parameters for the multiple uses of the immunodiagnostic tests, as follows:

i. For the simultaneous use of ELISA and COPT, net sensitivity was calculated as, Sensitivity test 1 + Sensitivity test 2 - (Sensitivity test 1 x Sensitivity test 2), and, the net specificity as, Specificity test 1 x Specificity test 2. PLR and NLR were calculated using net sensitivity and net specificity results.

ii. For the sequential (two-stage) use of ELISA and COPT, the test with best sensitivity was chosen as initial screening test followed by the test with best specificity. Net sensitivity was calculated as, Sensitivity test 1 x Sensitivity test 2, and, net specificity as, Specificity test 1 + Specificity test 2 – (Specificity test 1 x Specificity test 2). PLR and NLR were calculated using net sensitivity and net specificity results.

Ethical considerations

This study protocol was approved by the Ethics Committee in Research in the Faculty of Medicine of TriânguloMineiro (FMTM), Scientific Ethics Committee of the Institute of Tropical Medicine of the UCV, and the National Council of Ethics in Research (CONEP) in Brasilia. Each patient or legal representative signed, after reading the term of free and informed consent, as for to collect the coprological and the serological samples. All results were delivered house by house.

RESULTS

Study population and results of laboratory procedures

The demographic characteristics of population are described in Table (1), as well as their previous status of schistosomiasis infection and sickness. Among the 3,164 initially interviewed, 1,428 made the coprological study which showed *S. mansoni* eggs in 26 (1.8%) of them (arithmetic mean 45.6 ± 54.9 eggs per gram of feces). SMP-ELISA was positive in 412 out of 1,328 (31%) collected samples; the COPT performed in 558 individuals resulted positive in 153 (27.4%) (Figure 1).

Outcomes of paired samples (n = 521) were classified according to their results in four groups: 142 (27.3%) had positive SMP-ELISA and positive COPT (Group A); other 222 (42.3%) had positive SMP-ELISA and negative COPT (Group B) and 156 (29.9%) were negative for both serological tests. Only one person (0.2%) had negative SMP-ELISA and positive COPT (Figure 1).

Stool examination performed was positive almost on the same frequency in women (47.6%) than in men (52.4%). Significant differences regarding gender and age were not observed.

Immunodiagnostic accuracy

The comparison between SMP-ELISA and the presence of *S. mansoni* eggs in stools is shown in Table (2) and validity parameters results are summarized in Table (3). It was found that SMP-ELISA had 95.2% sensitivity, and 31.2% specificity. From the 378 persons with negative COPT only two (0.5%) had *S. mansoni* eggs (Table 2). The sensitivity of COPT was 90.5%, the specificity 75.2% (Table 3). PPV was low both for SMP-ELISA and COPT (5.5% and 13.3%, respectively) although NPV was high (above 99.0%) (Table 3). Positive likelihood ratios were quite low although they were higher for COPT (Table 3).

From the 364 people with positive SMP-ELISA (data not shown), 142 (39.0%) had simultaneously positive COPT and, from 157 persons with negative SMP-ELISA, only one (0.6%) had positive COPT (Figure 1). When simultaneous SMP-ELISA and COPT were used, net sensitivity was 99.6% and net specificity 23.2%. When sequential (two-stage) tests were achieved, net sensitivity was 86.2% and net specificity 82.2%.

Among 344 individuals with positive SMP-ELISA and without *S. mansoni* eggs, 203 (59.0%) had evidence of schistosomiasis in previous parasitological survey registers (1976-1989).

Table 1: Demographic characteristic and previous status of schistosomiasis infection and sickness of study population, Brejo do Espírito Santo, Bahia State, Brazil, 2002-2003.

Study population	Participants (n)	Gender		Age (median and range)	Previous schistosomiasis (1976-1989)	Hepatic or hepatosplenic pathology attributable to *S. mansoni*
		Male	Female			
General census	3164	1594 (50.4%)	1570 (46.6%)	28 (1-90)	1522 (41.1%)	354 (11.2%)
Sampling	521	268 (51.4%)	253 (48.6%)	28 (2-90)	284 (54.5%)	85 (16.3%)

Table 2: Comparison of serological tests for schistosomiasis and stool examination by the Kato-Katz method at Brejo do Espírito Santo, Bahia State, Brazil, 2002-2003.

Serological test (n)		Kato-Katz method (n)		
		Positive	Negative	Total
SMP-ELISA	Positive	20	344	364
	Negative	1	156	157
	Total	21	500	521
COPT	Positive	19	124	143
	Negative	2	376	378
	Total	21	500	521

Table 3: Field validity parameters of the comparisons between SMP-ELISA, COPT with the Kato-Katz method as gold standard at Brejo do Espírito Santo, Bahia State, Brazil, 2002-2003.

Serological tests under study	Validity parameter					
	Sensitivity% (95%CI)	Specificity% (95%CI)	% (95%CI)	NPV% (95%CI)	PLR Ratio(95%CI)	NLR Ratio(95%CI)
SMP-ELISA	95.2(74.1-99.8)	31.2(27.2-35.5)	5.5(3.5-8.5)	99.4(96.0-100)	1.4(1.2-1.6)	0.2(0-1.0)
COPT	90.5(68.1-98.3)	75.2(71.1-78.9)	13.3(8.4-20.2)	99.5(97.9-99.9)	3.7(3.0-4.5)	0.1(0-0.5)

Abbreviations: PPN: Positive Predictive Value; NPV: Negative Predictive Value; PLR: Positive Likelihood Ratio; NLR: Negative Likelihood Ratio: 95%CI: 95% Confidence Interval

DISCUSSION

When we performed this study, the situation of schistosomiasis in Brejo do Espírito Santo was of low endemicity, a condition diametrically opposed to that observed in 1976, when it was characterized as hiperendemic area before the implementation of control measures based on health education [27]. In the present study, the prevalence of schistosomiasis based on coprology was 1.8% and 31% by SMP-ELISA.

SMP-ELISA showed high sensitivity compared to a single stool examination which is the most common situation at endemic areas subject to control programs. SMP-ELISA was positive in 31% of the individuals surveyed, especially adults. However, it is likely that many of them were old cases of schistosomiasis that existed in the community when there was elevated transmission and which retain antibodies despite the parasitological cure. In fact, 59% of positive SMP-ELISA without *S. mansoni* eggs in stools had eggs of this helminth sometime during the period 1976-1989. In spite of the high sensitivity, PPV was poor indicating the effect of low prevalence.

Likelihood ratios are estimated on sensitivity and specificity values and do not depend on the prevalence of the disease [34]. The low value of PLR does not qualify SMP-ELISA as an adequate technique to diagnose schistosomiasis. In contrast, its low NLR makes SMP-ELISA an excellent test to rule out the infection.

In spite of the high sensitivity and specificity demonstrated in other studies [32], COPT is a laborious exam to be performed as the routine test in surveillance and control programs, even with the necessary personnel and resources. COPT is specific to genus, since antibodies present in the patient's serum react with homologous eggs and has no cross reactions with other intestinal parasites [32,35]. This fact explains the low rates of false positives (2.4%) and false negatives (11.0%) in sera of persons untreated for schistosomiasis found by Mott & Dixon [35]. Another advantage of COPT is that, after specific treatment against schistosomiasis, the test becomes negative [32]. For this reason in Puerto Rico and Venezuela, COPT has been used to evaluate the impact of control measures [36-38]. Our study did not achieve as high levels of specificity as reported by other authors. Nevertheless, low NLR for COPT makes it an excellent test to discard infection [34].

In this survey we confirmed that COPT hardly gives positive results when SMP-ELISA is negative; maybe, if we emphasize the search of *S. mansoni* eggs in those COPT positive persons we could recognize more people eliminating eggs in stools. In 124 individuals with positive COPT we cannot identify *S. mansoni* eggs (false negatives?). It is possible to explain these by method failure, or because the majority of eggs have been retained in the tissues, as suggested by Pugh [39], by the presence of fibrosis, which hinder the passage of eggs to the gut lumen. We must also

consider the possibility that these patients might have long-standing infections with adult worms, with low fertility and decreased deposition of eggs [40]. The low intensity of infection may affect the sensitivity and specificity of serology [35] although Ruiz-Tiben et al. [41], disagree with this theory. The probability of unisexual infection does not explain this fact because in these circumstances COPT would also be negative [42].

Other possible explanations for false-negative results should be considered. It is more likely that operational conditions such as eventual failures in the storage and transportation of serum samples from the endemic area to Uberaba, and later to the reference laboratory in Venezuela may be responsible for these results. Lambertucci *et al*. [43], have described the possibility of false negatives of COPT due to loss of antibodies because of improper sample storage. Therefore, we propose a similar study using tests such as SMP-ELISA and COPT and increasing the number of Kato-Katz samples to assess the proportion of false negative in serology in schistosomiasis low transmission areas.

We found 0.4% (2/521) of patients with *S. mansoni*-eggs in stools with negative COPT, a finding similar to that obtained by Espírito Santo *et al.* [25], (0.2%); they also found that 1-1.8% of patients had negative ELISA-IgM or ELISA-IgG with positive COPT, we observed only 1 from 521 persons (0.2%) with negative SMP-ELISA and positive COPT, possibly explained by the use of SMP which reduces, but not eliminated cross reactivity with other trematodes and soil-transmitted helminths [31].

As a single, simple, sensitive, and specific assay for field diagnosis of schistosomiasis is not yet available [44], immunodiagnostic tests could be an alternative. However, the use of SMP-ELISA and COPT should be carefully weighted. The ideal situation would be the use of both serological tests simultaneously which increases the sensitivity as demonstrated by Ibrahim & Ibrahim [45] which also used combination use several test for diagnosis schistosomiasis in Central Sudan; in this case, they used, as well as the Kato-Katz method, ELISA and IHA and found good sensitivity (93.3%) and increased specificity to 85.8% and PPV to 55.1% with the simultaneous use of both serological techniques. Authors found at least 3/125 positive patients with positive Kato-Katz with negative ELISA and IHA. In thestudyconducted in Rio de Janeiro, Brazil, Espírito Santo *et al.* [25], suggest that the combination of these diagnostic tools could be useful for the diagnosis of schistosomiasis in epidemiological studies in areas of low endemicity.

Despite the fact that combined approaches have been successful in diagnostic screening, whereby individuals are initially tested for the presence of anti-schistosomal antibodies and then those with positive results confirmed by copro-microscopy techniques [29], the approach can be logistically demanding and time-consuming. On the other hand, if serodiagnosis is used alone, there is the likelihood of underestimating the true prevalence of infection because the majority of methods for determining anti-schistosomal antibodies tend to remain positive for several years and it is difficult to differentiate between an active infection and previous exposure to an infection that has been cleared [16], in addition, there is variable rates of cross-reactivity with other trematodes and soil-transmitted helminths, leading to lower test reproducibility and reduced specificity, and therefore to the impossibility to determine the intensity of infection [16].

As mentioned before, COPT is laborious and expensive to be performed limiting its use in the field at the present moment. On the other hand, the use of sequential tests would increase specificity decreasing the probability of false positives but it has the disadvantage of decreasing the capability of identifying true positives. In the present study, the probability of false-negative results with sequential tests was approximately 14%. In face of these results, the decision of using sequential or simultaneous testing should be based on the objective [46]. In this case, the goal is the screening of population for control purposes. Therefore, COPT is unfeasible due to the high laboratory requirements. The ideal situation would be the use of simultaneous testing alternative for surveillance and control as well as for epidemiological studies in low endemic areas in which the whole community would be screened using SMP-ELISA and only those individuals who were positive, would be retested using COPT. SMP-ELISA is highly sensitive, easier, faster, and more economic. Confirmatory test (COPT) would increase the net specificity ruling out false positives. Often, treating those positive SMP-ELISA would result more cost-effective than repeating stool examination because of the low costs of praziquantel, although at endemic areas of cysticercosis it might be used with caution. Frota *et al*. [47], proposed to use ELISA with eggs antigens for screening populations, with subsequent diagnostic confirmation with Kato-Katz, In this study, the initial prevalence by the Kato-Katz method (3.8%) increased to 8.7% when the feces exam was repeated oriented by positive results of ELISA; similarly, in a low endemic area in Ceará (Brazil), Pinheiro et al. [48], pre-selected individuals through the use of a serological technique like ELISA with adult worm antigen and, thereafter performed three combined parasitological methods for schistosomiasis diagnosis. Using Kato-Katz, 9.1% of fecal samples were positive for *S. mansoni* eggs, while the saline gradient method resulted in a detection of 18.2%, and 42.4% using the Helmintex® 48].

When prevalence of schistosomiasis and parasitic load are very low, the Kato-Katz method loses sensitivity. In this circumstances, even when the stool exam or slides are repeated several times (until 25 slides according to Ferrari et al. [49], the probability to find one *S. mansoni* egg is very low. Under field conditions, for control and sureillance purposes, health workers of the Brazilian Control Program routinely make only one slide per patient. In previous approaches since the 70´s in this hiper endemic community Prata *et al*. [50], and Ruiz-Guevara [27] estimated the prevalence using only one Kato-Katz slide and we considered appropriate to determine the prevalence in the same conditions after massive interventions. On the other hand, in low endemic areas the preparation of multiple slides and samples for each individual results in logistical difficulties, thus neutralizing the operational advantages of the technique [51]. Therefore, in schistosomiasis low endemic areas, it is important to use first techniques with elevated sensitivity as SMP-ELISA and then confirmation with more specific and laborious test as COPT.

As with other infectious diseases such as Chagas disease, AIDS, toxoplasmosis, where a sensitive laboratory test is used first, and afterward, another technique, more specific to define individuals who are actually infected, in areas of low prevalence

of schistosomiasis, as is now the Brejo do Espírito Santo, it is fully justified the use of sequential tests to identify those people who require specific treatment. This can be a solution for evaluating schistosomiasis control programmes in Brazil. The difficulties or limitations of antibody persistence inherent to serology after cure, and the high proportion of false positives widely referred to in the literature [14], would be solved with the use of sequential testing, and would make the rapid immunodiagnostic methods, a useful tool to monitor the effects of treatment and other control measures. A new era in the diagnosis of schistosomiasis comes with the fall of parasitological detection as the gold-standard test in low transmission areas [52].

CONCLUSION

For epidemiological surveys we suggest the use of an easy, fast and cost-effective test as SMP-ELISA as initial screening method; the positives should be tested again with a specific confirmatory technique such as the COPT to identify real positives. Moreover, in those COPT positive persons, it might be useful to emphasize the search of *S. mansoni* eggs.

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