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A simple new screening tool for diagnosing imported schistosomiasis

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ABSTRACT

Objectives: We sought to test the sensitivity and feasibility of a *Schistosoma* infection screening process consisting of a scored patient consultation questionnaire and a serological diagnostic test.
Study design: Prospective cross-sectional study.
Methods: We collected from Schistosoma-exposed individuals a 14-point check list of clinical and laboratory data related to *Schistosoma* infection, alongside a serological test to detect *Schistosoma* spp infection. A check list score was created and compared with the risk of infection and clinical recovery through an agreement analysis.
Results: Two-hundred and fifty individuals were enrolled, of whom 220 (88%) were male and 30 (12%) female. The median age was 39 (range 18–78). One hundred-fifty (60%, 95% CI 54.9%–65.1%) had a check-list score ≥2. Serology test results were positive for 142 (56.8%, 95% CI 51.6%–62%). Chronic complications compatible with long-term *Schistosoma* infection were detected in 29 out of these 142 (20.4%, 95% CI 13.8%–27%).,. The median score value was 3, the area under the receiver operating characteristic (ROC) curve against serology results was 0.85 and the estimated intercept check-list questionnaire score value was 1.72 (95%, CI: 1.3–2.2). Participants with a positive serological test had a substantially higher check-list score (Cohen's kappa coefficient: 0.62, 95% CI: 0.54–0.70). Ninety four percent patients empirically treated showed a subsequent improvement in clinical and laboratory parameters.
Conclusions: A two-component process consisting of a scored patient consultation questionnaire followed by serological assay can be a suitable strategy for screening populations at high risk of schistosomiasis infection.

Conflicts of interest

The authors of this study have no conflicts of interest to declare.

1. Introduction

Schistosomiasis, a water-borne human helminthiasis, is regarded as the third most serious endemic tropical parasitic disease in the world, after malaria and amoebiasis. It affects over 258 million people in 78 countries, most of them in sub-Saharan Africa, where 90% of cases occur, and causes an estimated 200,000 deaths annually [1]. Morbidity and mortality attributable to advanced stages of the disease have been estimated at around 3.3 million disability-adjusted life-years [2,3].

The disease is caused by worms of the *Schistosoma* genus, most

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frequently S*chistosoma mansoni* and *Schistosoma haematobium* species, which use certain types of freshwater snails (*Bulinus* spp. for *S. haematobium* and *Biomphalaria* spp. for *S. mansoni*) as intermediary hosts from which the human-invasive *cercaria* form asymptomatically penetrates exposed skin. Thereafter, *Schistosoma* flukes may remain clinically silent for decades (30%–50% of cases) or cause relatively mild and non-specific symptoms before eventually evolving into severe and irreparable organ damage such as fibrosis leading to portal hypertension (*S. mansoni)* or obstructive uropathy and hydronephrosis (*S. haematobium)*, which in turn may lead to squamous cell carcinoma of the bladder [4]. Consequently, schistosomiasis should never be considered a benign asymptomatic infection [5]. A highly cost-effective, safe and well-tolerated short course treatment (praziquantel) is widely available [6], and in areas with moderate to high transmission rates of schistosomiasis, mass-preventive periodic chemotherapy among school children has proved to be an effective control strategy [7,8].

Direct examinations of biological samples (faeces or urine) are the gold standard for diagnosis, but show low sensitivity in non-endemic countries. Serological assay, the most widely available laboratory test, shows an 80% sensitivity [9,10]. Therefore, both direct and indirect diagnostic methods show drawbacks.

The prevalence of *Schistosoma* infection among migrants living in the North Metropolitan Health District of Barcelona, Spain, is estimated to be high but remains largely underdiagnosed. The underlying reasons for these underdiagnoses are the lack of infection suspicion due to the silent nature of the infection until late-stage complications and the unavailability of rapid screening tools at the primary care level, compounded by the steady increase in the number of migrants from schistosomiasis-endemic regions [11–14].

The aim of this study was to assess the sensitivity of a screening methodology consisting of a check-list questionnaire eliciting patient sociodemographic background information and identifying symptoms and signs of *Schistosoma* infection, combined with a serological assay. If effective and feasible, such a relatively simple screening process could help to increase the treatment coverage of this largely preventable life-threatening disease in Europe.

2. Methods

2.1. Study population

The North Metropolitan International Health Unit serves a population of approximately 1,300,000, of whom about 15% are immigrants from non-EU countries, most of them living in the northern crown of the greater metropolitan area of Barcelona, Spain. The medical facilities run by this service are publicly accessible and free of charge.

2.2. Study design

This prospective cross-sectional study involved a sample from a cohort of sub-Saharan African migrants aged 18 or older who were attended at the Unit facilities for pre-travel health advice between June 2015 and February 2020. Those attended at the Unit who met inclusion criteria were randomly invited to participate in the study. However, any candidates with known positive *Schistosoma* serology who reported previous treatment with praziquantel were excluded. Given that the prevalence of infection is 24% among migrants from schistosomiasis-endemic countries who are now living in non-endemic countries [15], a sample size of 200 was estimated to be representative within the usual confidence parameters.

2.3. Sign and symptom check-list questionnaire

A clinician completed a detailed questionnaire for each participant which included questions to obtain basic sociodemographic information including age, gender, country of origin, years of residence in the EU and known prior history of schistosomiasis and a 14-item checklist to determine the presence or absence of the most commonly recognized signs and symptoms of previous or current *Schistosoma* infection [16], listed in Table 1 below. The checklist included retrospective data from clinical records of the patients, such eosinophil, creatinine, glomerular filtrate and transaminase counts. A score of 1 was awarded for every affirmative answer of each of the questions or clinically demonstrated presence of a symptom.

2.4. Serological assay

In parallel, a venous blood sample (5 mL) was collected and tested for *Schistosoma* spp. with the SCHISTO-96 test kit (Scimedx Corporation, Dover, USA). A spectrophotometer absorbance reading (450–620 nm) greater than 0.3 optical density (OD) units was a regarded as a positive result for *Schistosoma* infection.

2.5. Treatment protocol

Patients who had either a total check-list questionnaire score ≥ 2 or positive serological test results were treated with praziquantel in accordance with standard protocols. Patients with one or more positive checklist items but negative serology were clinically rechecked and treated with praziquantel if necessary, given the limited 80% sensitivity of the serological test[9,10].

Six months after treatment, patients were reassessed by means of complete blood count and blood chemistry tests and abdominal ultrasonography. Patients who presented eosinophilia also underwent *Strongyloides stercoralis* serology testing and were treated according to the results.

2.6. Data management and statistical analysis

An electronic case report form was created *ad hoc* in Access® format and sociodemographic baseline data for each patient were introduced alongside data obtained from the sign and symptom questionnaire (see Table 1), serological results for schistosomiasis, presumptive *Schistosoma* species if any were identified based on clinical data, eosinophil count and comorbidities. Data was obtained from electronic clinical records (i.e. previous ultrasound study or laboratory results), and current or past signs and symptoms referred by the patient at enrolment.

Qualitative variables were displayed as proportions with corresponding 95% Confidence Intervals (95% CI). Continuous variables were displayed as median and 25–75 Interquartile Range (IQR). For association analysis, the Chi-Square test was used to compare two qualitative variables and Student's *t*-test was used for quantitative variables after testing for normality (skewness and kurtosis tests) or their

Table 1
Areas covered by signs and symptoms checklist for the diagnosis of schistosomiasis.

Laboratory criteria	
Eosinophilia (>500 cells/μL or absolute count >8%)	Yes = 1/No = 0
Transaminitis of unknown origin	Yes = 1/No = 0
Abnormal dipstick test result	Yes = 1/No = 0
Renal failure (creatinine >1.3 mg/mL)	Yes = 1/No = 0
Clinical criteria	
Adult or childhood haematuria	Yes = 1/No = 0
Dysuria	Yes = 1/No = 0
Recurring urinary tract infections	Yes = 1/No = 0
Chronic abdominal pain	Yes = 1/No = 0
Rectal bleeding	Yes = 1/No = 0
Diarrhoea of unknown origin	Yes = 1/No = 0
Chronic liver disease	Yes = 1/No = 0
Sterility	Yes = 1/No = 0
Ictus/myelitis	Yes = 1/No = 0
Image criteria	
Abnormal ultrasound findings (urogenital and/or hepatosplenic)	Yes = 1/No = 0

non-parametric counterparts when necessary (Fisher test or Wilcoxon test, respectively). To ascertain the sensitivity/specificity of the check-list questionnaire score against serology results, we performed a ROC analysis. Area Under the Curve (AUC) and the intercept of plotted score values with the ROC curve were estimated. The estimated score intercept was considered a cut-off and tested for sensitivity and specificity against the outcome of interest (i.e. positive serology).

A p-value ≤ 0.05 was considered statistically significant. Data analysis was carried out using R (R Core Team, Vienna, Austria, 2015) [17, 18] and the Stata© 14.0 statistical package (Stata Corp., College Station, Texas, 2015).

3. Results

3.1. Baseline patient characteristics and check-list questionnaire results

Of a total of 2076 sub-Saharan African migrants who attended the pre-travel service during the study period and met the inclusion criteria, 252 (12.1% of the eligible population) were randomly invited to participate. Two of those invited declined to be included in the study (0.8%). The final study sample consisted of 250 individuals. The screening process as applied to the study sample is illustrated in the flow chart in Fig. 1 below.

The top rows of Table 2 below show the participants' baseline characteristics. Briefly, 220 were males (88.0%) and the mean age was 39.5 years (SD = 9.8, range 18–78). The most frequent country of origin was Senegal ($n = 73$, 29.6%). The subsequent rows show the results of the results of the 14-item questionnaire-checklist for signs and symptoms of schistosomiasis, followed by data regarding coinfection by hepatitis B or *Strongyloides stercolaris*.

The median checklist score for signs and symptoms was 3 (IQR 2–5, range 0–10). Chronic Abdominal pain (43.0%) and dysuria (22.0%) were the most prevalent symptoms; with referred background of haematuria (35.3%) the most frequently cited sign. Among the serious comorbidities, chronic renal insufficiency ($n = 37$, 15.0% CI 10.8–20.1) was the most frequent. Two participants (0.8%, CI 0.1–2.9) had previously undergone kidney transplantation and one (0.4%, CI 0.01–2.2) had suffered an ischemic cerebrovascular stroke. Overall, 142 (56.2%) had a positive serology test results.

Based on organ involvement, suspected schistosomiasis infection was classified as urogenital ($n = 58$, 41%, 95% CI 32.2%–48.2%), intestinal and hepatosplenic ($n = 26$, 18%, 95% CI 11.4%–23.9%) or indeterminate ($n = 58$, 41%, 95% CI 33.1%–49.2%).

Concomitant active Hepatitis B infection (HBsAg+) was detected in 26 cases out of 136 tested (19.1%) and *Strongyloides stercolaris* infection was detected in 47 of the 129 tested (36.4%), of whom 25 (53.2%, $p = 0.27$) had a positive *Schistosoma* spp serology test. The presence of *Strongyloides* infection was significantly associated with eosinophilia in blood tests ($p < 0.001$). Bivariate analysis showed that individuals with *Strongyloides* infection tended to report higher eosinophilia than those with schistosomiasis infection (mean 14.3% (SD 7.2) vs mean 9.2% (SD 6.73), $p < 0.001$).

3.2. Agreement and accuracy between checklist score and serological test

The AUC was 0.85 (see Fig. 2), and the intercept of the check-list questionnaire score value was estimated at 1.72 (95% CI 1.26–2.18). Therefore, we set the cut-off score value at ≥ 2 for testing against sensitivity and specificity. Considering this cut-off, we observed a sensitivity of 87% (95% CI 81.5%–92.5%), and specificity of 75% (95%

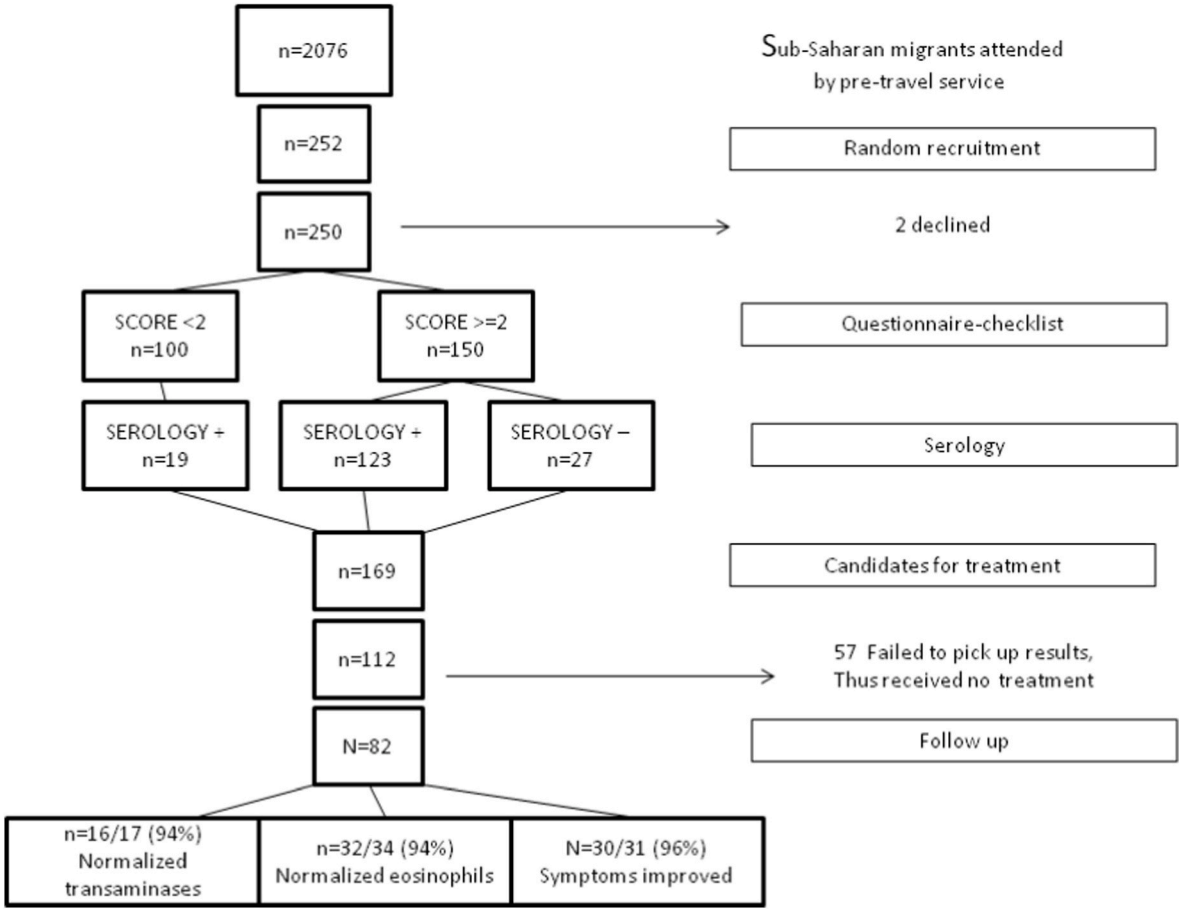

Fig. 1. Flow-chart of the screening and treatment procedure, showing number of participants ants at each step.

Table 2
Results of schistosomiasis screening questionnaire, showing sociodemographic information, signs and symptoms of schistosomiasis identified and serological assay results for the 250 study participants (significant *p*-values in boldface).

[n (%)]	N	Total	serology		*p*-value
			positive n = 142	negative n = 108	
Gender	249	219	127	92 (42.1)	0.4
Male		(88.0)	(56.0)	15 (50.0)	
Female		30	15		
		(12.0)	(50.0)		
Age (mean, SD)	250	39.5	38.5	40.8	0.05
		(9.8)	(8.7)	(10.9)	
<10 years in the EU	170	63	43	20	0.5
		(37.4)	(68.3)	(31.83)	
Country of origin	245				
Senegal		73	39	32(45.1)	0.6
Mali		(29.6)	(54.9.)	18(34.6)	0.2
Gambia		52	34	22(44.0)	0.8
Other		(21.3)	(65.4)	32(44.4)	0.5
		50(20.2)	28		
		72(29.1)	(56.0)		
			40		
			(55.6)		
Laboratory criteria					
Eosinophilia[a]	238	123	82	41 (40.2)	**0.002**
		(51.7)	(60.3)		
Transaminitis of unknown origin	234	33	27	6 (18.2)	**0.001**
		(14.1)	(81.9)		
Abnormal dipstick test result	101	35	28	7 (20.0)	0.2
		(34.7)	(80.0)		
Chronic Renal failure[b]	246	37	26	11 (29.7)	0.08
		(15.0)	(70.3)		
Clinical criteria					
Background of haematuria	247	88	71	16 (18.4)	<
		(35.3)	(81.6)		**0.001**
Dysuria	250	55	43	12 (21.8)	<
		(22.0)	(78.2)		**0.001**
Recurring urinary tract infections[c]	248	38	29	9 (23.7)	**0.007**
		(15.3)	(76.3)		
Chronic abdominal pain	249	107	77	29 (27.4)	<
		(43.0)	(72.6)		**0.001**
Rectal bleeding	249	21 (8.4)	17	4 (19.1)	**0.02**
			(81.0)		
Diarrhoea of unknown origin	249	27	21	3 (19.2)	**0.009**
		(10.8)	(80.8)		
Sterility[d]	175	13 (7.4)	9 (69.2)	4 (30.8)	0.9
Ictus/myelitis	248	1 (0.4)	1 (100)	0 (0.0)	0.6
Schistosoma during childhood	166	13 (7.8)	11	1 (8.3)	0.2
			(91.7)		
Image criteria					
Abnormal ultrasound finding (urogenital and/or hepatosplenic)	91	31	27	4 (12.9)	**0.04**
		(34.1).4	(87.1)		
Coinfections					
Hepatitis B (HBsAg+)	136	26	13	13 (50.0)	0.2
		(19.1)	(50.0)		
Strongyloides stercolaris	129	47	25	22 (46.8)	0.4
		(36.4)	(53.2)		

[a] Eosinophilia (>500 cells/μL or absolute count >8%).
[b] Renal insufficiency was defined as decreased estimated glomerular filtration rate (<60 mL/min/1.73 m^2) or elevated blood creatinine (>1.3 mg/mL).
[c] Recurrent urinary tract infections were defined as >2 urinary tract infections (urinalysis either by microscopy or by dipstick and/or urine culture with susceptibility data) as recorded in the patient's medical file.
[d] Sterility was defined as inability of a couple to conceive after 12 months of regular intercourse without use of contraception.

CI 69.7%–82.1%), with a predictive positive value of 82% (95% CI 75.7%–88.3%) and predictive negative value of 81% (95% CI 74.5%–87.5%) against serology positivity.

3.3. Clinical management

The screening process selected a total of 169 participants to be candidates for specific treatment for *Schistosoma* infection, of which 123 had a checklist score ≥2 and positive serology, 27 had a checklist score ≥2 and negative serology (after a clinical recheck), and 19 had a checklist score <2 and positive serology. Fifty-seven of these 169 (33%) did not return to pick up the results of the screening procedure and thus did not receive treatment. Overall, a total of 112 (45%) participants with presumptive *Schistosoma* infection successfully completed the treatment. Of these 112, 82 (73.2%) had a complete follow-up with laboratory and clinical final results.

Based on the baseline data at enrolment, after treatment, levels of transaminases normalized in 16 out of 17 cases (94%), eosinophilic count normalized in 32 out of 34 (94%) and symptoms improved in 30 out of 31 (96%).

4. Discussion

Our results support the contention that a two-component screening strategy, a checklist-type questionnaire followed by a serological test, could be a valuable tool to detect active schistosomiasis, with any screened individual scoring ≥2 on the questionnaire for schistosomiasis being offered treatment and those with score <2 and serology test positive. Such a screening procedure would help to prevent chronic complications resulting from schistosomiasis among a growing at-risk population in Europe. The fact that almost 20% of serological positive test had a score <2, supports the necessity of including the serological test, which is considered the most effective screening test for detection schistosomiasis in low-endemicity settings [19]. Otherwise, in support of a stand-alone questionnaire-checklist methodology is that the questionnaire-based screening process may show higher specificity regarding active infection than serological testing, which cannot distinguish between current and past infection. This may be the case of this mentioned subgroup of patients with score <2 and positive serological test. Furthermore, stand-alone use of a serology test could not be considered sufficient. Serological tests do have higher, but still limited sensitivity compared to conventional parasitological methods in scenarios of scarce egg density samples or in non-endemic countries [9,14,15,19]. In addition, available serological tests have sub-optimal specificity, which may differ depending on *Schistosoma* species.

Notwithstanding, we cannot rule out that a simple drug distribution strategy using as unique criteria the background of coming from an endemic country, as set up elsewhere, may be the most cost-effective and efficient strategy [20]. This is supported by the estimated high prevalence of Schistosoma infection among this population and the inclusion of previous laboratory results in the questionnaire (eosinophil and transaminase blood count), which may not be available for most of patients.

In this sense, it will be noted that the estimated prevalence of *Schistosoma* infection in our sample is higher than the previously reported estimates of 24% in Europe [15] though our figures are in line with those obtained by Beltrame et al. based on a comparable population of West African immigrants in Italy [13,14]. Even assuming the lower estimate, considering that over 73,000 individuals from hyperendemic areas of sub-Saharan Africa are legally registered residents of Catalonia [21], roughly 17,000 schistosomiasis-infected people could remain largely undiagnosed. Of note, these numbers are much higher than estimates for other infectious diseases already included in systematic screening programs such as those targeting the Zika virus or using serological assays to detect Chagas disease among exposed pregnant women.

Overall, the epidemiological data and our study results, strongly supports that whether a systematic *Schistosoma* screening or a mass drug distribution of high-risk populations is an urgent need among migrant populations in Europe, as screening programs applied in non-endemic countries are demonstrably able to reduce the morbidity and mortality attributable to this chronic disease [19,22,23]. This assertion is supported by the fact that 92% of our study-patients treated for previous

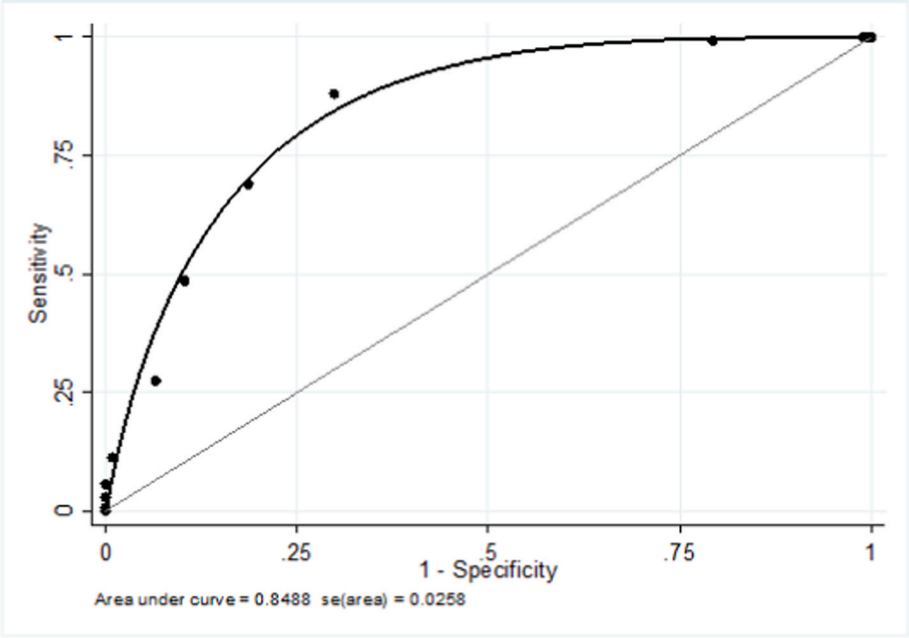

Fig. 2. ROC curve and estimated AUC of checklist score against serology test results.

analytical alterations (eosinophilia and/or transaminase elevation) showed a good response to treatment (i.e. resolution of these alterations). This reinforces the idea that the observed alterations were actually mainly attributable to previously undetected schistosomiasis infections. We should underscore that a substantial number of our patients already have long-term complications of Schistosoma infection (i.e. renal insufficiency) with more than 10 years of residence in Europe (60% of our study sample), which denotes a high rate of delayed diagnosis.

We would like to outline the underrepresentation of women in our study sample ($n = 12$; 5%), which deserves a separate comment. Women account for 30% of non-EU individuals living in our study area, and the prevalence of *Schistosoma* infection is uniform across gender [24]. This indicates that any test-and-treat strategy should be pro-active and community-based with the goal of reaching underdiagnosed sub-Saharan women and other hard-to-reach high-risk populations. In addition, our data suggest that women have specific signs and symptoms, like more urinary infections than men (26.7% (8/30) vs 13.8% (30/217), $p = 0.07$), which suggests that any check-list questionnaire should be gender-adapted Women may also show more gynaecological-related symptomatology [25–27] (i.e. dyspareunia, pelvic pain, discharge and bleeding, sterility).

Of note, given the high rates of lost of follow-up, a test and treat strategy is even most necessary [22]. Therefore, more sensible and specific, feasible point-of-care screening methodologies should be developed. For instance, besides improving sensitivity and specificity of serological tests, an obvious way to improve the availability and cost-effectiveness is to develop new devices that could be used as point-of-care tests, incorporating them at the primary care level [28,29]. These new devices should overcome the mentioned limitation of lack specificity towards past infection and variable specificity/sensitivity. The questionnaire may include proven biomarkers and prognostic factors in the chronically infected population living in non-endemic countries and more gender orientated questions focused on female genital manifestations. An adequate strategy could be the implementation of such screening programs in sexual and reproductive primary health centres to improve the accessibility of women to the schistosomiasis screening programs.

Our study is subject to several limitations. First, the population studied here was taken from a very specific European metropolitan area, and the generalizability of our results may therefore be questionable. Secondly, we cannot rule out the presence of a selection bias among individuals who agreed to participate in the study. Participants who agreed to participate may have done so because they considered themselves to be high-risk. This may in turn have produced a certain overestimation of *Schistosoma* prevalence in our results. Finally, it would be of interest to validate our results with further studies using a proper control group and comparing the relative cost-benefit ratios of empirical and non-empirical treatment strategies when applied in non-endemic countries.

In short, the prevalence of schistosomiasis infection and its complications among sub-Saharan African immigrants living in non-endemic countries may be largely underestimated. In order to determine the true prevalence of what tends to be regarded as a “benign” tropical disease in these high-risk populations a two-component screening approach such involving a questionnaire-checklist could prove quick to perform and effective at detecting schistosomiasis infection, besides the consideration of unspecific drug distribution strategy, allowing rapid treatment to avoid chronic disease and complications.

Ethical approval

The study protocol was approved by the local IRB (ethics committee of the Germans Trias i Pujol University Hospital) with the reference number PI-17-136.

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Declaration of competing interests

None to declare.

Declaration of competing interest

The authors of this study have no conflicts of interest to declare.

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