



The usefulness of indirect diagnostic tests for *Schistosoma haematobium* infection after repeated rounds of mass treatment with praziquantel in Mpwapwa and Chakechake districts in Tanzania

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ABSTRACT

Background: Indirect diagnostic tests are used to assess the disease burden and to monitor the impact of different interventions in areas endemic for urinary schistosomiasis. This study was performed to assess their accuracy in the diagnosis of urinary schistosomiasis among primary school children in low and moderate transmission areas in the districts of Mpwapwa and Chakechake, respectively.

Methods: School children were interviewed regarding their history of haematuria and participation in treatment campaigns. Urine samples were collected and inspected for macro-haematuria (visual haematuria) and tested for micro-haematuria using urine reagent strips and *Schistosoma haematobium* eggs by urine filtration method.

Results: The prevalence of *S. haematobium* was 6.8% in Mtera Dam area and 38.7% in Uwandani Shehia. In Mtera Dam area, a history of haematuria and visual haematuria had low sensitivity (<60%) with high specificity (>90%). The urine reagent strips had high sensitivity and specificity (≥75%). In Uwandani Shehia, a history of haematuria had high sensitivity and specificity (>60%). Visual haematuria had low sensitivity (<50%) but high specificity (>80%). The urine reagent strips maintained high performance in all parameters assessed.

Conclusions: The study findings suggest that urine reagent strips will continue to serve as a very useful adjunct test for monitoring the prevalence of urinary schistosomiasis in endemic areas.

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Introduction

Human schistosomiasis is highly endemic in Sub-Saharan Africa (SSA), including Tanzania, mainly due to limited access to potable water and adequate sanitation (Colley et al., 2014; Mazigo et al., 2012). It is estimated that at least 230 million people worldwide are infected with *Schistosoma* spp, and SSA accounts for 85% of the schistosomiasis burden (Colley et al., 2014; WHO, 2002). School-aged children bear most of the burden and contribute significantly to the transmission cycle of the disease in SSA (Atalabi and Adubi,

2019). The common species causing human schistosomiasis in SSA include *Schistosoma haematobium* (in urinary schistosomiasis) and *Schistosoma mansoni* (in intestinal schistosomiasis) (Colley et al., 2014).

The distribution of the disease is focal in character and depends on the availability of fresh water bodies with the intermediate snail hosts: *Bulinus* spp, which are suitable intermediate hosts for *S. haematobium*, and *Biomphalaria* spp, which are the intermediate host for *S. mansoni*. Infection in the human results from activities that lead to frequent contact with water bodies infested with cercariae, the infective larval stage, which mechanically penetrate the skin of the definitive human host. The cercariae then proceed through a series of development stages and mature into the adult form, which lay eggs; these eggs are responsible for the morbidity associated with the disease (Colley et al., 2014; Gryseels et al., 2006).

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The World Health Organization (WHO) approved a strategy for morbidity control that is mainly based on periodic mass drug administration (MDA) of a single dose of praziquantel (40 mg/kg body weight) to school-aged children (Savioli et al., 2009; WHO, 2002). Rapid assessment using the prevalence of haematuria along with egg count-based criteria are commonly used diagnostic methods to identify communities at high risk of schistosomiasis (Brooker et al., 2009; Lengeler et al., 2002).

As a result of the scale-up of morbidity control activities, there have been changes in the epidemiology of schistosomiasis, with high transmission areas becoming moderate or low transmission areas (Knopp et al., 2013b). Reduced prevalence and intensity of infections may pose challenges regarding the diagnostic performance of indirect screening tests such as history of haematuria, visual haematuria, and micro-haematuria using urine reagent strips (Knopp et al., 2018). This study was performed to assess the performance of indirect diagnostic tests for *S. haematobium* infection among school-aged children in low and moderate transmission settings in Mpwapwa District, Mainland Tanzania and Chakechake District, on Pemba Island, Zanzibar.

Materials and methods

Study areas

The study comprised two cross-sectional surveys. The first cross-sectional survey was conducted between March and June 2015 in four primary schools (Chungu, Chibwegele, Kisima, and Mtera) in the Mtera Dam area, Mpwapwa District. The second survey was conducted between April and May 2016 in Uwandani Shehia, Chakechake District, Pemba Island (Figure 1).

Mpwapwa District is one of the six districts in Dodoma Region. It is located 120 km from Dodoma Region Headquarters. Mtera Dam is a man-made reservoir that was created in 1975. The dam receives water from the Great Ruaha River. At full capacity, the

basin has a surface area of 620 m² and is 8.5 m deep; it is located 690 m above sea level. The reservoir stores about 125 million cubic meters of water. The basin lies within the Rift Valley on a high mountain range to the east of Mpwapwa District. Mpwapwa District has a total population of 345 568, and 78 519 are school-aged children. The main economic activities for inhabitants include farming, fishing, and small-scale trading. Several rounds of MDA of praziquantel (40 mg/kg) to school-aged children have been conducted by the National Neglected Disease Control Program.

Uwandani Shehia is one of the 29 shehias (administrative units in Zanzibar) of Chakechake District, Pemba Island. Recent studies have reported that a number of shehias on Pemba Island have a high prevalence and persistent transmission of *S. haematobium* infection, including Uwandani Shehia (Knopp et al., 2013b; He et al., 2019). The main economic activities include rice farming and fishing. MDA of praziquantel has been implemented by the Ministry of Health in Zanzibar and recently in collaboration with various implementing partners, with the aim of eliminating urinary schistosomiasis as a public health problem in Zanzibar (Knopp et al., 2013b).

Study population and sampling

The study population comprised primary school children attending selected primary schools. A multi-stage sampling technique was used to select the primary schools in the Mtera Dam area. First, four of the 12 villages in Mtera Ward were selected. Second, using the available list of schools in these villages, the simple random sampling technique (Barnett, 2002) was used to select one school from each village. Finally, according to the list of all standard I–VII school children in the respective schools, random sampling was then used to select school children for the study. Uwandani Shehia has only one primary school; all of the primary school children were invited to participate in the study.

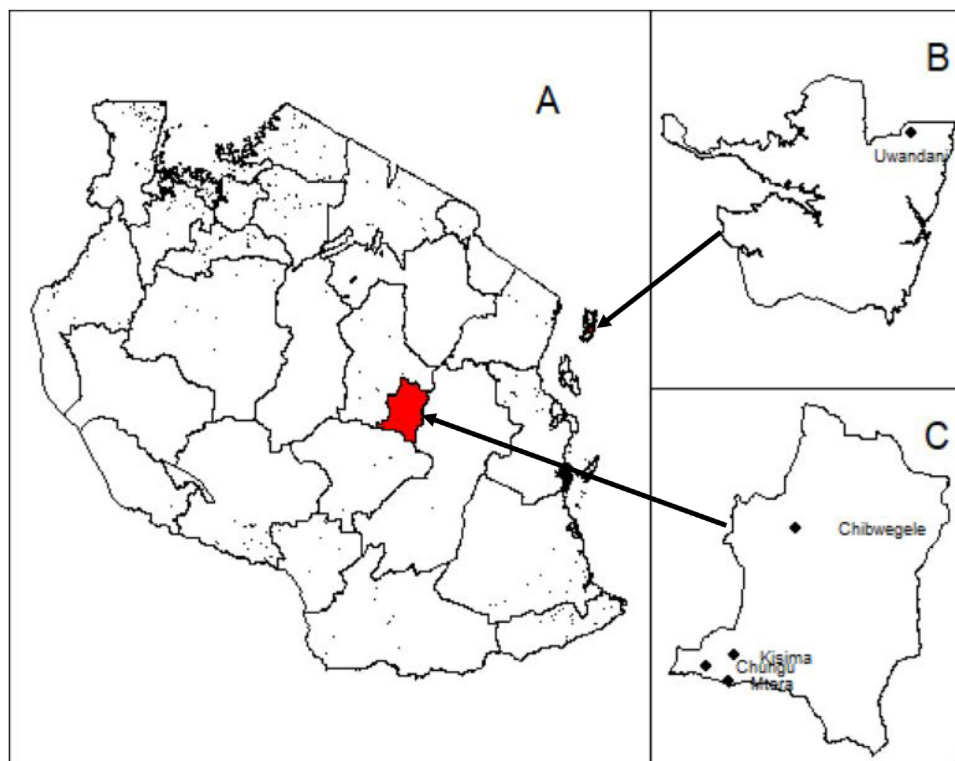


Figure 1. Map of Tanzania (A) Chakechake District (B), and Mpwapwa District C showing point locations of the surveyed primary schools.

Data collection

School children were interviewed individually by trained research assistants using a simple questionnaire designed to collect information on sociodemographic characteristics including age and sex, and their history of currently passing blood in urine, painful micturition (dysuria), their frequency of micturition, and participation in praziquantel MDA campaigns. Questions on urinary schistosomiasis symptoms were assessed using a dichotomous response of 'yes' or 'no'.

Laboratory analysis

Following interviews, the pupils were subjected to a parasitological procedure, which commenced with the collection of a terminal urine sample in a clean 20-ml clearly labelled, wide-mouthed sample container; urine collection was performed between 10.00 a.m. and 2.00 p.m. The urine samples were inspected for macro-haematuria (visual haematuria) using a colour chart. This was followed by screening for micro-haematuria using urine reagent strips (10-parameter urine test strips, Neotest Multistix, United Kingdom). The urine samples were then shaken vigorously and 10 ml drawn into a syringe and then discharged through a nucleopore filter membrane with a fine pore size of 8–30 µm. All urine filters were put on microscope slides, covered with cellophane, and examined by experienced laboratory technicians. A few drops of Lugol's iodine were added to stain the *S. haematobium* eggs after cellophane coverage. The egg count was recorded as the number of eggs per 10 ml of urine sample. The intensity of infection was categorized as light (<50 eggs/10 ml of urine) or heavy (≥50 eggs/10 ml of urine) according to the standard method (WHO, 2002).

For quality control, all slides were re-read by a senior experienced technician at Muhimbili University of Health and Allied Sciences at the end of the survey. The numbers of *S. haematobium* eggs were compared with the original egg counts. In the case of a discrepancy between the first and second readings (false-negatives, false-positives, egg counts resulting in a different infection intensity category), a third microscopist from Ifakara Health Institute re-examined the slides.

Data analysis

Data were double-entered into Microsoft Excel and analysed in Stata 15.0 (StataCorp, College Station, TX, USA). The estimates of prevalence were calculated overall and stratified by sex. The Chi-square test was used to compare the prevalence of *S. haematobium* between males and females (95% confidence interval (CI); $p < 0.05$ considered as significant). The sensitivity, specificity, and positive and negative predictive values (PPV and NPV) of the indirect methods were determined using egg microscopy as the gold standard technique and calculated using the Stata command `diagt`. Multiple logistic regression was performed to estimate the adjusted odds ratio (aOR) between the response variable (presence of *Schistosoma* eggs by urine filtration) and a set of explanatory variables to control for confounding. Associations were deemed significant if the p -values were below 0.05.

Results

Description of the study population

In the Mtera Dam area, a total of 353 school children attending the four primary schools participated in the study (Table 1). Their median age was 11 years (range 5–16 years) and 209 (59.2%) were male. In Chakechake District, 150 primary school children from Uwandani Shehia participated in the study (Table 1). The median age of school children from Uwandani Shehia was 10 years (range

Table 1

Prevalence by sex of *Schistosoma haematobium* infection, as detected by different diagnostic tests, in Mtera Dam area (Mpwapa District) and Uwandani Shehia (Chakechake District, Pemba), Tanzania.

Diagnostic tool	Male (n = 209)	Female (n = 144)	Test statistics
Mtera Dam area			
Egg microscopy	14 (6.7)	10 (6.9)	$\chi^2 = 0.008$ $p = 0.928$
History of haematuria	26 (12.4)	17 (11.1)	$\chi^2 = 0.032$ $p = 0.858$
Visual haematuria	30 (14.4)	22 (15.3)	$\chi^2 = 0.058$ $p = 0.810$
Micro-haematuria	59 (28.2)	39 (27.1)	$\chi^2 = 0.056$ $p = 0.813$
Uwandani Shehia			
Egg microscopy	30 (45.5%)	28 (33.3%)	$\chi^2 = 2.29$ $p = 0.130$
History of haematuria	34 (51.5)	39 (46.4)	$\chi^2 = 0.038$ $p = 0.536$
Visual haematuria	15 (22.7)	17 (20.2)	$\chi^2 = 0.14$ $p = 0.712$
Micro-haematuria	34 (51.5)	38 (45.2)	$\chi^2 = 0.58$ $p = 0.445$
Infection intensity			
Light	8 (4.3)	6 (4.2)	
Heavy	6 (2.9)	4 (2.8)	
Uwandani Shehia	(n = 66)	(n = 84)	
Egg microscopy	30 (45.5%)	28 (33.3%)	$\chi^2 = 2.29$ $p = 0.130$
History of haematuria	34 (51.5)	39 (46.4)	$\chi^2 = 0.038$ $p = 0.536$
Visual haematuria	15 (22.7)	17 (20.2)	$\chi^2 = 0.14$ $p = 0.712$
Micro-haematuria	34 (51.5)	38 (45.2)	$\chi^2 = 0.58$ $p = 0.445$
Infection intensity			
Light	11 (16.6)	11 (13.1)	
Heavy	19 (28.8)	17 (20.2)	

7–14 years) and 66 (44%) were male. Overall 244/353 (69.1%) school children in Mtera Dam area had participated in a MDA campaign in the year before the survey. In Uwandani Shehia, 129/150 (86%) school children had participated in a praziquantel MDA in the year before the survey.

Prevalence and intensity of *S. haematobium* infection

The results of microscopy (gold standard test) revealed that 24 school children (6.8%, 95% CI 4.6–9.9%) were infected with *S. haematobium* in Mtera Dam area. In Uwandani Shehia, the prevalence of *S. haematobium* by microscopy was 38.7% (95% CI 31.2–46.8%). At both study sites, there was no statistically significant difference in prevalence between males and females (Table 1). The results for the estimated prevalence by indirect methods are shown in Table 1. Urine reagent strip tests (micro-haematuria) at both sites had higher positive test rates compared to the other indirect tests (Table 1). In Uwandani Shehia, primary or higher parental education was associated with a reduced risk of schistosomiasis, while in Mtera Dam area, older age children (>10 years) had an increased risk of getting schistosomiasis. Proximity to the source of water was associated with an increased risk of schistosomiasis in both study areas (Table 2).

Table 3 summarizes the diagnostic performance of the indirect tests compared with microscopic examination (urine filtration) as the gold standard test. In Mtera Dam, an area with a low prevalence of urinary schistosomiasis (6.8%), both a history of haematuria and visual haematuria had low sensitivity, while specificity and NPV were high (>90%). The performance of the urine reagent strips had moderate to high sensitivity, specificity, and NPV. However, the PPV of all indirect tests was very low (<40%).

In Uwandani Shehia, an area with a moderate prevalence of *S. haematobium*, the performance of history of haematuria in terms of sensitivity, specificity, and predictive values was mainly moderate to high. On the other hand, visual haematuria had low sensitivity, but specificity, NPV, and PPV were moderate to high. The urine reagent strips maintained high performance in all parameters assessed (Table 3).

Table 2

Risk factors for schistosomiasis among school children in Mtera Dam area (Mpwapwa District) and Uwandani Shehia (Chakechake District, Pemba), Tanzania.

Variable	Mtera Dam area			Uwandani Shehia		
	aOR	95% CI	p-Value	aOR	95% CI	p-Value
Sex, male	1.823	0.638–5.238	0.262	1.748	0.709–4.307	0.225
Age group, ≤10 years	1					
Age group, >10 years	4.336	1.516–12.401	0.006	0.840	0.342–2.066	0.705
Parent education						
Informal	1			1		
Primary	1.029	0.339–3.127	0.959	0.160	0.056–0.453	0.001
Secondary and above	1.454	0.217–9.748	0.699	0.702	0.011–0.470	0.006
Distance to the water source						
<1000 m	1			1		
1000–2000 m	0.058	0.018–0.192	<0.001	0.233	0.083–0.655	0.006
>2000 m	0.059	0.012–0.290	0.001	0.024	0.006–0.093	<0.001

aOR, adjusted odds ratio; CI, confidence interval.

Table 3Diagnostic performance of indirect tests in detecting *Schistosoma haematobium* infection among school children in Mtera Dam area (Mpwapwa District) and Uwandani Shehia (Chakechake District, Pemba), Tanzania.

Mtera Dam area Prevalence (<i>n</i> = 353)	6.8%			
Indirect test	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
History of haematuria				
Overall	45.8 (25.6–67.2)	90.3 (86.5–93.3)	25.6 (13.5–41.2)	95.8 (92.9–97.7)
In boys	50.0 (23.0–77.0)	90.3 (85.2–94.0)	26.9 (11.6–47.8)	96.2 (92.3–98.4)
In girls	40.0 (12.2–73.8)	90.3 (84.0–94.7)	23.5 (6.8–49.9)	95.3 (90.0–98.2)
Visual haematuria				
Overall	50.0 (29.1–70.9)	87.8 (83.8–92.5)	23.1 (12.5–36.8)	94.8 (92.0–96.8)
In boys	64.3 (35.1–87.2)	89.2 (84.0–93.2)	30.0 (14.7–49.4)	97.2 (93.6–99.1)
In girls	30.0 (0.4–57.9)	85.8 (78.7–91.2)	13.6 (2.9–34.9)	94.3 (88.5–97.7)
Reagent strips				
Overall	75.0 (53.3–90.2)	75.7 (70.7–80.2)	18.4 (11.3–27.5)	97.6 (94.9–99.1)
In boys	78.6 (49.2–95.3)	75.4 (68.7–81.3)	18.6 (9.7–30.9)	98.0 (94.3–99.6)
In girls	70.0 (34.8–93.3)	76.1 (68.0–83.1)	17.9 (7.5–33.5)	97.1 (91.9–99.4)
Uwandani Shehia Prevalence (<i>n</i> = 150)	38.7%			
Indirect test	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
History of haematuria				
Overall	67.2 (53.7–79.0)	63.0 (52.3–72.9)	53.4 (41.4–65.2)	75.3 (64.2–84.4)
In boys	70.0 (50.6–85.3)	63.9 (46.2–79.2)	61.8 (43.6–77.8)	71.9 (53.3–86.3)
In girls	64.3 (44.1–81.4)	62.5 (48.5–75.1)	46.2 (30.1–62.8)	77.8 (62.9–88.8)
Visual haematuria				
Overall	44.8 (31.7–58.5)	93.5 (86.3–97.6)	81.2 (63.6–92.8)	72.9 (63.9–80.7)
In boys	36.7 (19.9–56.1)	88.9 (73.9–96.9)	73.3 (44.9–92.2)	62.7 (48.1–75.9)
In girls	53.6 (33.9–72.5)	96.4 (87.7–99.6)	88.2 (63.6–98.5)	80.6 (69.1–89.2)
Reagent strips				
Overall	96.6 (88.1–99.6)	82.6 (73.3–89.7)	77.8 (66.4–86.7)	97.4 (91.0–99.7)
In boys	96.7 (82.8–99.9)	86.1 (70.5–95.3)	85.3 (68.9–95.0)	96.9 (83.8–99.9)
In girls	96.4 (81.7–99.9)	80.4 (67.6–89.8)	71.1 (54.1–84.6)	97.8 (88.5–99.9)

CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

Discussion

The epidemiological transition from high to low urinary schistosomiasis transmission observed in various endemic areas, as a result of scale-up of praziquantel MDA in school-aged children, has implications for the accurate estimation of true urinary schistosomiasis prevalence in affected communities (Bogoch et al., 2012; King and Bertsch, 2013; Knopp et al., 2018; Krauth et al., 2015). Following scale-up of MDA activities, a cessation of symptoms is evidenced in the reduction of egg excretion, proteinuria, and haematuria (Emukah et al., 2012; Lwambo et al., 1997b). This study assessed the performance of indirect tests (history of haematuria, visual haematuria, and urine reagent strip tests) as markers for *S. haematobium* infection in areas with repeated rounds of praziquantel MDA. The results showed that in the low prevalence (<10%) Mtera Dam area in Mpwapwa District, both history of haematuria and visual haematuria had low to

moderate sensitivity and PPV, but high specificity and NPV. In Uwandani Shehia in Chakechake District, a 10–50% moderate transmission area, a history of haematuria had moderate to high specificity and predictive values, and visual haematuria had low sensitivity but moderate to high specificity and predictive values. However, the urine reagent strip tests maintained high performance in all diagnostic performance indices, with only lower PPV in Mtera Dam area compared to Uwandani Shehia.

The diagnostic performance of history of haematuria and visual haematuria, with low sensitivity and high specificity and NPV results, has been reported in areas with reduced transmission after scaled up praziquantel MDA in school-aged children (Knopp et al., 2018; Knopp et al., 2013a; Lwambo et al., 1997a). The low sensitivity of these tests has implications for their utility for rapid screening of infected individuals and individuals at risk of morbidities of *S. haematobium* infection in low prevalence areas (King and Bertsch, 2013; Knopp et al., 2018; Knopp et al., 2013a).

Other factors may also affect the performance of history of haematuria and visual haematuria, such as age, sex, and recall bias of the participants. In the current study, males were more likely to have higher sensitivity and PPV for these two indirect tests than females, similar to the results of previous studies (Ansell et al., 2001; Guyatt et al., 1999).

The high sensitivity of the urine reagent strips is comparable to findings of previous studies in different schistosomiasis transmission settings in SSA (Bocanegra et al., 2015; Brooker et al., 2009; King and Bertsch, 2013; Krauth et al., 2015; Ochodo et al., 2015; Robinson et al., 2009). The specificity and NPV were high, similar to previous studies (King and Bertsch, 2013; Ochodo et al., 2015). However, a low specificity of reagent strips has been reported in other low transmission settings (Ochodo et al., 2015). The PPV were very low in the low transmission area of Mtera Dam area and this increases the probability of identifying individuals with false-negative results. This finding is similar to those of previous studies in low transmission settings (Lwambo et al., 1997a; Robinson et al., 2009). However, the high PPV of urine reagent strips in Uwandani Shehia area is similar to other moderate transmission areas in SSA (Bocanegra et al., 2015; Okeke and Ubachukwu, 2014; Robinson et al., 2009). Hence, these variations in performance of the urine reagent strips in low transmission settings will require confirmation of positive results with more sensitive diagnostic tests.

Study limitations include the use of a single urine sample for indirect testing (visual haematuria and urine reagent strip) and for microscopy, the gold standard test. Previous studies have shown that the performance of microscopy varies with the intensity of infection, prevalence of disease, and circadian and day-to-day variations of egg production in urine (Knopp et al., 2013a; Utzinger et al., 2015). A study in a low transmission area among Ghanaian school children showed that repeated screening improved the detection of *S. haematobium* infection and the performance of indirect tests (Kosinski et al., 2011).

In conclusion, the findings of this study clearly show that urine reagent strips will continue to serve as very useful adjuncts for monitoring the community prevalence of *S. haematobium* following the implementation of MDA in urinary schistosomiasis areas. However, history of haematuria and visual haematuria as indirect tests have reduced performance in low transmission settings. It is therefore of paramount importance to search for highly accurate diagnostic tools for use in settings targeted for elimination of urinary schistosomiasis.

Author contributions

Billy Ngasala wrote the main manuscript and fully participated in all experiments. Hamza Juma and Richard Mwaiswelo participated in the acquisition of data. Billy Ngasala and Richard Mwaiswelo participated in the analysis and interpretation of data. Billy Ngasala designed the study. All authors made substantial contributions to writing and revising the manuscript.

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Ethical approval

Ethical clearance for the study protocols was provided by the Ethical Research and Publication Committee of Muhimbili University of Health and Allied Science. Written consent to participate in the interview and collect urine samples was obtained from the parents or guardians of the school children 1 week before

the survey; in addition, the school children assented to participate on the day of the survey.

Conflict of interest

The authors declare that they have no competing interests.

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