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Evaluation of a novel rapid diagnostic test for *Schistosoma haematobium* based on the detection of human immunoglobulins bound to filtered *Schistosoma haematobium* eggs

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Abstract

OBJECTIVES To determine whether the detection of human IgG bound to *Schistosoma haematobium* eggs from filtered urine could be used as a rapid diagnostic test (RDT-Sh).

METHODS We filtered 160 urine samples from children in the Kwale District of Kenya to isolate *S. haematobium* eggs and used anti-human IgG antibody conjugated to horseradish peroxidase to bind to the human IgG attached to the eggs. We then added 3,3',5,5'-tetramethylbenzidine base (TMB), which turns blue in the presence of horseradish peroxidase to detect the *S. haematobium* eggs. The RDT-Sh was compared in a blinded manner to urine microscopy.

RESULTS The RDT-Sh was positive in 89% of urine samples containing >1 egg/10 ml (58/65 samples) and 97% of urine samples containing >11 eggs/10 ml urine (35/36 samples) seen by microscopy. The RDT-Sh was negative 79% of the time when no eggs were seen on urine microscopy, but because up to three times more urine was used for the RDT-Sh, there were likely cases in which eggs were on the RDT-Sh filter but not detected by microscopy. We used latent class analysis incorporating urine microscopy, haematuria, proteinuria and RDT-Sh results to determine an overall 97% sensitivity and 78% specificity for RDT-Sh, 96% and 81% for urine microscopy, 71% and 98% for microscopic haematuria and 46% and 89% for proteinuria, respectively.

CONCLUSIONS The RDT-Sh is quick, inexpensive and easy to perform in the field for the diagnosis of *S. haematobium*.

keywords schistosomiasis haematobium, schistosomiasis, rapid diagnostic test, haematuria, schistosoma, sensitivity and specificity

Introduction

Schistosoma haematobium is the most prevalent of the six *Schistosoma* species that infect humans. The other five *Schistosoma* species — *S. mansoni*, *S. japonicum*, *S. mekongi*, *S. guineensis* and *S. intercalatum* — generally cause gastrointestinal pathology, whereas *S. haematobium* causes genitourinary disease (WHO 2012). Schistosomiasis is endemic in Africa with hundreds of millions of people at risk for disease and millions affected (Gryseels *et al.* 2006; Utzinger *et al.* 2009). Among human parasitic diseases, schistosomiasis is second only to malaria in terms of socioeconomic and public health consequences (Gryseels *et al.* 2006). *S. haematobium* eggs are highly immunogenic and cause the majority of the disease's morbidity and mortality (Gryseels *et al.* 2006).

The eggs can cause haematuria, calcified bladder, fibrosis of the neck of the bladder, hydroureter, hydronephrosis and bladder cancer (Gryseels *et al.* 2006). *S. haematobium* eggs can be found in both the human male and female reproductive organs, and people with mild worm burdens can have minimal or no symptoms (Gryseels *et al.* 2006). According to the European Association of Urology (EAU), a light *S. haematobium* infection is defined as <100 eggs/10 ml urine, while a severe infection is >400 eggs/10 ml (Bichler *et al.* 2006). WHO classifies a light infection as <50 eggs/10 ml urine and a heavy infection as 50 or more eggs/10 ml (WHO 2010).

Schistosoma haematobium eggs are excreted in the urine covered in human IgM and IgG (Koech *et al.* 1984). Urine from people infected with *S. haematobium* have protein precipitates containing IgG, IgM, IgA, IgE

and complement C3 (Bosompem *et al.* 1996). Humans initially generate an IgM immune response to adult *S. haematobium* worms and eggs, followed by IgA, IgG and IgE (Mutapi *et al.* 1998; Woolhouse *et al.* 2000; Osada *et al.* 2003). Human IgG and IgE levels correlate with egg burden (Mutapi *et al.* 1998; Woolhouse *et al.* 2000; Osada *et al.* 2003). IgG levels rise dramatically after children are reinfected with *S. haematobium* (Mutapi *et al.* 1998).

The 'gold-standard' test for diagnosing *S. haematobium* is by the visualisation of eggs under the microscope, typically by centrifuging or filtering urine to concentrate the eggs (Gryseels *et al.* 2006). Urine microscopy is highly specific if eggs are identified; however, intermittent egg shedding and a low egg count can negatively affect the sensitivity. Because urine microscopy requires a microscope, a trained technician and the time and resources to read the slides, it poses challenges, especially in the field and during large-scale screenings of urine for *S. haematobium*.

Haematuria, and to a lesser extent proteinuria, is associated with *S. haematobium* infection (Houmsou *et al.* 2011). Urine dipsticks for microscopic haematuria and proteinuria are being used to guide treatment and public health interventions for *S. haematobium* (Houmsou *et al.* 2011). Urine dipsticks are cheap, and haematuria in a *S. haematobium* endemic area is highly specific for infection (Houmsou *et al.* 2011). However, haematuria has only modest sensitivity for diagnosing the disease and will miss light infections.

The societal costs and benefits of presumptive treatment of at-risk people for possible schistosomiasis have been compared with treatment based on the results of a potential rapid diagnostic test (RDT) (Stothard 2009). It was determined that a RDT costing less than US \$ 3 would provide financial incentive to make treatment decisions based on the results of the RDT and one costing US \$ 5 would be cost-neutral (Stothard 2009). The purpose of our study was to determine whether the detection of human IgG in filtered urine could be useful as a RDT for the detection of *S. haematobium* eggs in an endemic area.

Materials and methods

Ethical considerations

The study received institutional review board (IRB) approval by Eastern Virginia Medical School (PR-149-INT) and the Kenya Medical Research Institute (KEMRI/RES/7/3/1) and was conducted in Kwale District on the coast of Kenya in September 2011. Study investigators met with parents, school administrators, teachers and

government administrators prior to data collection for discussion and to obtain verbal consent. Written informed consent was given on the day of the study. After obtaining written consent, urine was collected between 10:00 am and 2:00 pm from 177 schoolchildren that stated they had seen blood in their urine recently. 160 schoolchildren were between the ages of 8 and 17 years and qualified for use in data analysis. Of the 17 study subjects who were not included in the analysis, 16 had incomplete data and one person turned out not to fulfil the age criterion. All study subjects received 40 mg/kg of praziquantel at the conclusion of the study regardless of the urine microscopy or rapid diagnostic test for *Schistosoma haematobium* (RDT-Sh) results as directed by the Kenyan Ministry of Health. There were no adverse events during the study.

Field procedures

Urine from each participant was noted to be yellow/clear, turbid or grossly bloody. The urine was then analysed for protein and blood using Rapid Response urine dipsticks (BTNX Inc., Markham, On, Canada). From each urine sample, two 10-ml aliquots were removed and each filtered using Nuclepore™ polycarbonate 12-micron filter paper (Whatman Ltd., Maidstone, Kent, UK) and examined with a microscope to determine the number of *S. haematobium* eggs in each sample. Egg counts ranged from 0.5 egg/10 ml (one egg was seen on one aliquot and no eggs on the other aliquot from the same urine sample) to more than 1000 eggs/10 ml urine. The remainder of the urine sample was analysed by the RDT-Sh in the field. Urine microscopy was completed within 48 h of slide preparation in the laboratory.

Rapid diagnostic test for *Schistosoma haematobium* preparation

To prepare the antibody used in the RDT-Sh, we diluted anti-human IgG conjugated to horseradish peroxidase (Promega Corp., Madison, WI, USA) to 400 ng/ml using unsterile commercially available bottled drinking water. The antibody was diluted on the day of the experiment and kept at room temperature. We mixed 0.25 ml of the diluted anti-human IgG antibody into each urine sample.

The RDT-Sh filters were prepared in advance. A standard sized hole-punch was used to create paper discs of Whatman GE Healthcare Life Sciences grade 113 wet strengthened cellulose paper with a 30 micron pore size (Whatman GE Healthcare Life Sciences, Piscataway, NJ, USA). The paper discs were glued to one end of a Cole-Parmer polycarbonate female–female luer lock coupling device (Cole-Parmer, Vernon Hills, IL, USA) (Figure 1).



Figure 1 Rapid diagnostic test for *Schistosoma haematobium* (RDT-Sh) filters.

Up to 60 ml of urine (containing the anti-human IgG-conjugated antibody) was drawn up into a syringe and attached to the open end of the female luer lock coupling device (opposite to the end containing the glued filter paper) and the urine filtered (Figure 2). *S. haematobium* eggs remained trapped on the inner aspect of the filter paper. The empty 60-ml syringe was then removed. A syringe containing 3,3',5,5'-tetramethylbenzidine base (TMB) was then attached to the open female luer lock coupling device and approximately 0.25 ml of TMB was pushed through the filter. TMB turns from a pale yellow liquid to blue in the presence of horseradish peroxidase; therefore, the RDT-Sh was negative if the filter paper remained white and was considered positive if the filter paper turned blue (Figure 3). RDT-Sh filters that turned blue within 60 s were considered to be positive.

Data management

JMS and SB performed the RDT-Sh and were blinded to the urine microscopy results but not to the colour of the urine or the urine dipstick results. Urine microscopy was performed in the laboratory without knowledge of the urine colour, urine dipstick results or RDT-Sh results. Urine microscopy results were compared with RDT-Sh results after all data collection was completed.

Results

Within 60 s, most of the samples having *S. haematobium* eggs on microscopy were positive by the RDT-Sh and, for heavy infections, the RDT-Sh was usually instantly positive. The results are summarised in Table 1. The RDT-Sh was positive in 46% (6/13) of urine samples



Figure 2 Filtering urine using the rapid diagnostic test for *Schistosoma haematobium* (RDT-Sh).

containing 0.5–1 egg/10 ml urine, in 89% of urine samples containing >1 egg/10 ml (58/65 samples) and in 97% of urine samples containing >11 eggs/10 ml urine (35/36 samples). The RDT-Sh was negative in 79% of cases where no eggs were seen on urine microscopy. However, up to three times more urine was used for the RDT-Sh so there may have been eggs on the RDT-Sh filter but not seen by microscopy.

We estimated the number of eggs present on the RDT-Sh filter by taking the number of eggs per ml of urine seen on urine microscopy and multiplying it by the volume of urine filtered for the RDT-Sh; these results are summarised in Table 2. The RDT-Sh was less likely to be positive when very few eggs were found in the filter.

The RDT-Sh filter was not directly evaluated microscopically for the presence of eggs, so we could only assume that the average number of eggs seen on microscopy approximated the number of eggs that were on the RDT-Sh filter. However, different volumes of urine were used for the RDT-Sh and microscopy, so when few eggs were seen by microscopy, it is possible that no eggs were present on the RDT-Sh filter. The corollary is also possible that when no eggs were seen on microscopy, there were still eggs present on the RDT-Sh filter. Latent class analysis (LCA) was employed utilising microscopy, microscopic haematuria, proteinuria and RDT-Sh results in the analysis. LCA gives the RDT-Sh an overall 97% (95% confidence interval (CI): 91–100%) sensitivity and



Figure 3 Rapid diagnostic test for *Schistosoma haematobium* (RDT-Sh) filters. Top filter is positive and bottom filter is negative.

78% (95% CI: 67–89%) specificity when the RDT-Sh is read at 1 min. The LCA reports sensitivities and specificities for urine microscopy, microscopic haematuria and proteinuria as 96% and 81%, 71% and 98%, and 46% and 89%, respectively (Table 3).

A few of the urine samples contained visible sediment and obvious foreign bodies such as dirt and grass, clog-

ging the RDT-Sh filter 39 of 160 times (24%). In some cases, this reduced the amount of urine that could be filtered. The filter broke during the filtering process 15 of 160 times (9%), although this did not necessarily affect the results. In general, gross blood or cloudy urine resulted in lower RDT-Sh filtration volumes.

The ability of microscopic haematuria, proteinuria and the RDT-Sh to detect *S. haematobium* infection compared to urine microscopy is summarised in Table 4. Three study subjects had microscopic haematuria on urine dipstick and no *S. haematobium* eggs seen on microscopy; one subject was a 10-year-old girl who also had a negative RDT-Sh. The other two subjects were 9- and 16-year-old boys who both had positive RDT-Sh results within 1 min. The presence of glucose, nitrates, ketones, bilirubin, leucocyte esterase, urobilinogen, or a certain pH or specific gravity on the urine dipstick was not correlated with the presence of *S. haematobium* eggs seen on microscopy. We retrospectively analysed our data using the following algorithm summarised in Figure 4:

- All grossly bloody urine samples were considered positive for *S. haematobium*;
- All urine samples negative for gross haematuria were evaluated for microscopic haematuria;
- Those who were positive for microscopic haematuria were considered positive for *S. haematobium*.;
- Those negative for microscopic haematuria were evaluated using the RDT-Sh; and
- Those positive by the RDT-Sh were considered infected with *S. haematobium* and those negative by RDT-Sh were considered uninfected.

This algorithm would correctly identify as positive 85% (66 of 78 children) who had eggs (0.5 to >1000 eggs/10 ml) seen on urine microscopy, and identify as negative 78% (64 of 82 children) who did not have eggs seen on microscopy. If all samples with no haematuria and a negative RDT-Sh had the RDT-Sh filter examined

Table 1 The comparison of urine microscopy egg counts (# eggs/10 ml urine) to when the rapid diagnostic test for *Schistosoma haematobium* (RDT-Sh) turned positive

Urine microscopy (number of subjects)	RDT-Sh test					Total
	Negative (at 20 min)	1–20 min positive	30–60 s positive	<30 s positive	Instant positive	
0 eggs/10 ml (82)	44	21	6	3	8	51% (82/160)
0.5–1 eggs/10 ml (13)	3	4	1	3	2	8% (13/160)
1.5–5 eggs/10 ml (17)	4	1	3	2	7	11% (17/160)
5.5–10.5 eggs/10 ml (12)	1	0	1	1	9	7.5% (12/160)
11 to >1000 eggs/10 ml (36)	0	1	1	4	30	22.5% (36/160)
Total (160)	52	27	12	13	56	160

Table 2 The ability of the rapid diagnostic test for *Schistosoma haematobium* (RDT-Sh) to detect *S. haematobium* eggs when varying numbers of eggs are estimated to have been present on the RDT-Sh filter

Estimated number of eggs on the RDT-Sh filter (2.5 to >5500 eggs)	Percentage of RDT-Sh positive in 60 s	Total number of samples analysed
2.5–7.5 eggs*	46% (6/13)*	13
8–20 eggs	69% (9/13)	13
21–99 eggs	92% (21/23)	23
100 to >1000 eggs	96% (24/25)	25

Five samples with incomplete data not analysed.

*represents urine samples with very few eggs/10 ml urine on microscopy and therefore direct comparison to RDT-Sh may not be accurate.

microscopically for the presence of eggs, and those filters with eggs on microscopy treated as positive, the algorithm would have 100% sensitivity and 84% specificity. It would require that 76 filters be examined microscopically (to identify the 12 samples in our data set with no haematuria, a negative RDT-Sh and eggs seen on urine microscopy) compared with 320 filters needing urine microscopy if each of the original 160 urine specimens needed two 10-ml urine aliquots filtered and examined. This algorithm could be especially helpful in field settings where all but the lightest *S. haematobium* infections would be quickly and easily detected and treated. All samples negative for both haematuria and the RDT-Sh could have their RDT-Sh filter examined microscopically at a later time.

Discussion

Human IgG coats *S. haematobium* eggs in the urine (Koech *et al.* 1984). These immune complexes have complicated the past use of enzyme-linked immunosorbent assay (ELISA) tests that attempted to detect egg antigens (Uga *et al.* 1989). Anti-human IgG-conjugated

Table 3 Latent class analysis (LCA) utilising rapid diagnostic test for *Schistosoma haematobium* (RDT-Sh), urine microscopy, microscopic haematuria and proteinuria results to calculate sensitivity and specificity for each test

	Sensitivity (95% CI)	Specificity (95% CI)
RDT-Sh	97% (91–100)	78% (67–89)
Urine microscopy	96% (90–100)	81% (70–92)
Microscopic haematuria	71% (55–87)	98% (94–100)
Proteinuria	46% (31–60)	89% (83–95)

antibodies are cheap, easy to find and commercially available, whereas specific antibodies to *S. haematobium* egg antigens are not. This preliminary study was designed to determine whether the detection of human IgG in filtered urine was able to diagnose *S. haematobium* infection in an endemic area.

Limitations

As the RDT-Sh detects the immunoglobulin attached to the *S. haematobium* eggs in the urine, the RDT-Sh will not correctly diagnose an infection when there are no eggs present in the urine. The number of *S. haematobium* eggs excreted into the urine in *S. haematobium* infected children varies throughout the day as well as day-to-day (Doehring *et al.* 1983).

It is theoretically possible that concurrent genitourinary tract infections, cystitis, casts in the urine, *Enterobius vermicularis* and protein complexes in the urine could cause false positives with the RDT-Sh. The ammonia, salts, water, proteins, carbohydrates, red blood cells (6–8 mm), white blood cells (10 mm), trichomoniasis (10 mm), crystals, yeast (10–20 mm) and bacteria (<3 mm) found in some urine samples should all pass through the RDT-Sh 30-mm filter. Theoretical potential RDT-Sh false-negative results could occur from the filter breaking or leaking, a low volume of urine being filtered, few eggs on the RDT filter or eggs bursting under the pressure of filtration. It is also possible that some eggs are excreted with little or no IgG attached or that the

Table 4 The ability of gross haematuria, microscopic haematuria, proteinuria and rapid diagnostic test for *Schistosoma haematobium* (RDT-Sh) to detect *S. haematobium* eggs by microscopy

	Gross haematuria present (number of study subjects)	Positive for microscopic haematuria (number of study subjects)	Positive for proteinuria (number of study subjects)	RDT-Sh positive in 1 min (number of study subjects)
0 eggs on microscopy	0% (0/82)	4% (3/82)	23% (19/82)	21% (17/82)
0.5–10.5 eggs on microscopy	5% (2/42)	31% (13/42)	37% (15/41)	69% (29/42)
11 to >1000 eggs on microscopy	28% (10/36)	81% (29/39)	69% (27/39)	97% (35/36)

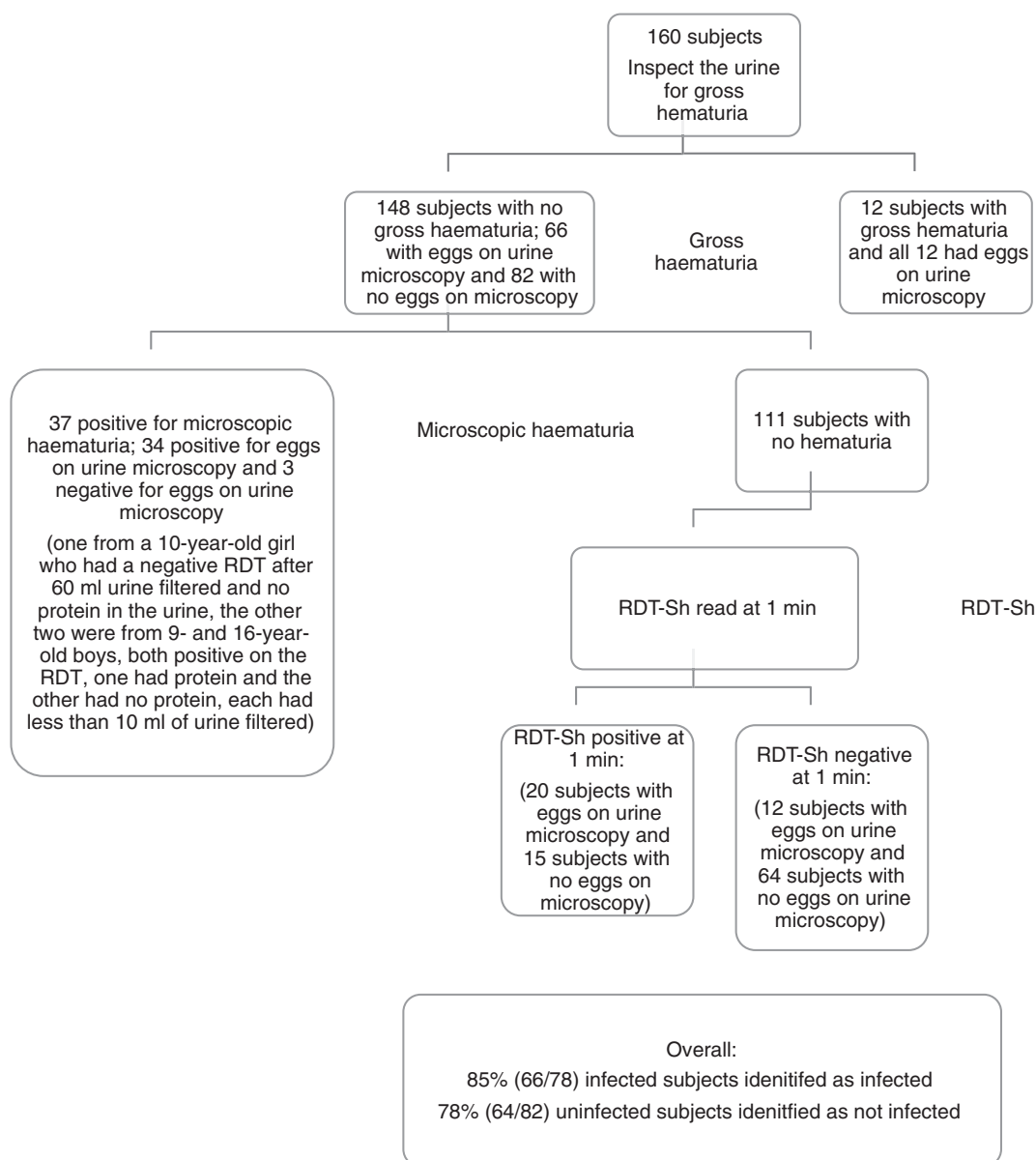


Figure 4 Algorithm to rapidly identify individuals with *Schistosoma haematobium* infection.

amount of anti-human IgG–conjugated antibody bound to the IgG on the eggs on the filter is not sufficient to cause a colour change when exposed to TMB.

Future directions

Basic modifications to the RDT-Sh may further improve the test. The addition of a 30-mm filter inside of a commercially available filtering device will allow for micro-

scopic counting of the eggs. Adding a synthetic larger pore pre-filter will remove sediment and debris. Some synthetic filters also bind non-specific proteins, and this could reduce the number of false-positive results with the RDT-Sh. Adding a water wash after the urine is filtered onto the RDT-Sh filter, but before the addition of TMB, may also reduce the number of false-positive RDT-Sh results, because it will remove anti-human IgG–conjugated antibody not bound to *S. haematobium*

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eggs. Adding more anti-human IgG-conjugated antibody to urine samples may help the filter turn positive faster when fewer eggs are present and improve the sensitivity of the RDT-Sh in light infections. Lastly, and most importantly, using an entire urine sample for the RDT-Sh will add as many eggs as possible onto the filter and should further improve the sensitivity of the test, especially in light infections.

Implications

Various methods for the diagnosis of *S. haematobium* have been recently evaluated using latent class analysis, including urine antigen detection of *S. haematobium* complexed to C3 (98% sensitive and 35% specific), the detection of anti-schistosome IgG from dried blood spots (48% sensitive and 57% specific), ultrasound examination (74% sensitive and 65% specific) and urine microscopy (93% sensitive and 98% specific) (Koukounari *et al.* 2009). There have been conflicting reports on the sensitivity and specificity of schistosome circulating cathodic antigen (CCA), but it is thought to be relatively insensitive for detecting *S. haematobium* (Stothard 2009). The test characteristics of the RDT-Sh compare favourably with these other methods of diagnosing *S. haematobium*, with the additional benefit that the test is rapid, cheap and easy to perform in the field.

The RDT-Sh was created with commercially available products and only costs approximately US \$ 0.45 per reaction. This estimates the costs for the antibody, TMB, filter paper and luer coupling devices, but does not include the syringes that were reused during the experiment. The urine dipsticks cost approximately US \$ 0.15 per strip.

Children living in *S. haematobium* endemic areas receive praziquantel for the treatment of schistosomiasis as part of organised large-scale drug administration campaigns. A cheap and easy-to-use RDT with sufficient sensitivity for diagnosing *S. haematobium* infection would be useful for targeting drug treatment only towards infected individuals; monitoring *S. haematobium* resistance to praziquantel; improving epidemiological mapping and monitoring of disease prevalence; and help guide public health interventions and prevention strategies. Current successful *S. haematobium* epidemiological mapping strategies include school-based questionnaires about self-reported haematuria as well as teacher-initiated testing of student's urine for blood (Brooker *et al.* 2009). The WHO currently advocates repeated stool and/or urine examinations of at least 50 people within a defined ecological zone to quantify the severity and types of infecting *Schistosoma* species (Brooker *et al.* 2009).

The mapping and treatment of neglected tropical diseases (NTDs) is being facilitated by the use of accurate rapid diagnostic tests that exist for malaria, onchocerciasis, visceral leishmaniasis and lymphatic filariasis (Brooker *et al.* 2009). There exists a urine antibody test to detect CCA, a protein regurgitated by adult *Schistosoma* worms. The CCA has good sensitivity and specificity for *S. mansoni*, but not for *S. haematobium* (Brooker *et al.* 2009). Concurrent use of CCA and the RDT-Sh on a single urine sample may allow for non-invasive, accurate and rapid mapping of schistosomiasis throughout Africa where *S. mansoni* and *S. haematobium* frequently co-exist. Additionally, after successful treatment with praziquantel, both the CCA and RDT-Sh should both become negative. This will allow for monitoring of praziquantel efficacy, an increasing public health concern especially because there are few acceptable treatment alternatives for schistosomiasis.

Haematuria has good specificity but only modest sensitivity for diagnosing *S. haematobium* infection in endemic areas, especially in people with light infections. The RDT-Sh has superior sensitivity to haematuria for detecting *S. haematobium* infection. Performing the RDT-Sh only on those samples negative for haematuria would be an additional strategy useful for rapidly detecting more *S. haematobium* infected individuals in a non-clinical setting than microscopic haematuria alone. Additionally, if only filters negative for both haematuria and the RDT-Sh are examined microscopically for the presence of *S. haematobium* eggs, it could substantially reduce the overall number of filters that would need to be evaluated microscopically and allow for the detection of nearly 100% of those infected individuals with eggs in the urine.

We have shown that the RDT-Sh can detect *S. haematobium* eggs by detecting the presence of human IgG on filtered urine. The RDT is inexpensive, quick, easy to perform and can be performed in the field. The RDT-Sh has excellent sensitivity, especially with larger numbers of eggs in the urine.

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