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Validation of innovative digital microscopes for the diagnosis of schistosomiasis and other helminthiases

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Current status of schistosomiasis in school-aged children in Mwanga district Tanzania; impact of two decades of annual Mass Drug Administration programme

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Abstract

Schistosomiasis is a neglected tropical disease with significant health implications, particularly among children. A cross-sectional study was conducted among school-aged children (SAC) in Mwanga district, Tanzania, a region known to be co-endemic for *S. haematobium* and *S. mansoni* infection and where annual mass drug administration (MDA) has been conducted for 20 years. In total, 576 SAC from five schools provided a urine sample for the detection of *Schistosoma* circulating anodic antigen using the upconverting particle-based lateral flow (UCP-LF CAA) test. Additionally, the potential of the point-of-care circulating cathodic antigen (POC-CCA) and microhaematuria dipstick test as field-applicable diagnostic alternatives for schistosomiasis were assessed and the prevalence outcome compared to UCP-LF CAA. Risk factors associated with schistosomiasis was assessed based on UCP-LF CAA. The UCP-LF CAA test revealed an overall schistosomiasis prevalence of 20.3%, compared to 65.6% based on a combination of POC-CCA and microhaematuria dipstick. No agreement was observed between the combined POC tests and UCP-LF CAA. Factors associated with schistosomiasis included age (5-10 years), involvement in fishing, farming, swimming activities and attending two of the five primary schools. Our findings suggest a significant progress in infection control in Mwanga district due to annual MDA, although not enough to interrupt transmission. Accurate diagnostics play a crucial role in monitoring intervention measures to effectively combat schistosomiasis.

Keywords: schistosomiasis, UCP-LF CAA, POC-CCA, microhaematuria dipstick, school-aged children, diagnosis, microscopy, Mwanga, Tanzania.

Introduction

Schistosomiasis is a major neglected tropical disease disproportionately affecting sub-Saharan African countries, with 90.0% of the global disease burden occurring in this region [1]. In Tanzania, the overall prevalence of schistosomiasis is 51.5% [2], and among school-aged children (SAC) it is reported to be 53.5% [3], reaching up to about 80.0% in the northwestern zone around Lake Victoria[4, 5]. However, current prevalence estimates do not include the northern region of Tanzania, including Mwanga district in the Kilimanjaro region. This district has been known to be endemic for both *Schistosoma haematobium* and *Schistosoma mansoni* [6]. The population is at high risk of schistosomiasis possibly due to the presence of the intermediate snail host (Bulinus and Biomphalaria) as well as irrigation schemes, which are the conducive environment for the transmission the *Schistosoma* spp. The presence of the hydroelectric dam known as "Nyumba ya Mungu" (Figure 1) which ensures a constant water supply to the surrounding villages for irrigation contributes to the continues transmission of schistosomiasis in Mwanga district [6].

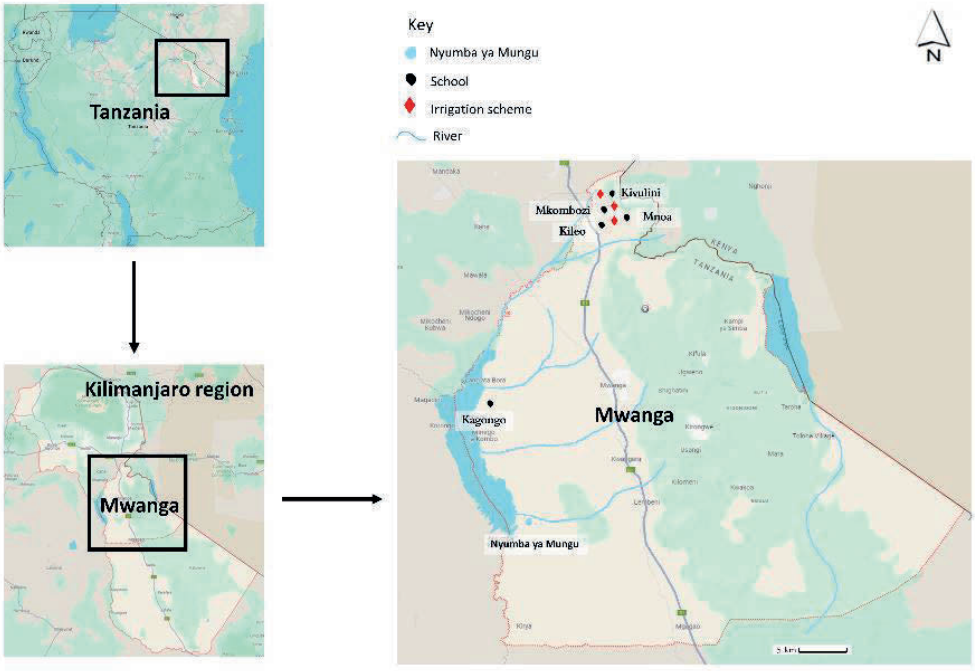

Figure 1. Map of Mwanga district Tanzania showing water sources, five primary schools and irrigation schemes

In Tanzania, including the Kilimanjaro region, mass drug administration (MDA) of praziquantel has been the major strategy to reduce the burden of schistosomiasis and has been organized annually since 2004 among SAC who are at the highest risk of infection[7]. The need to assess the success of MDA has

been highlighted by the World Health Organization and tools to enhance strategic guidance for schistosomiasis control programme in Tanzania have equally been reported [8, 9]. The most recent data on the prevalence status of schistosomiasis among SAC in Mwanga district are from 2005, indicating a prevalence ranging from 33.5 to 70.0% [6]. Conventional microscopy is the reference method to diagnose schistosomiasis in endemic settings and involves the detection of *Schistosoma eggs* in faeces or urine, depending on the species. However, microscopy requires experienced, well-trained technical personnel, is considered a time-consuming, laborious method and has limited sensitivity in low-intensity infection settings [10]. Furthermore, the availability and access to microscopy is challenging in many rural areas in Tanzania due to a lack of trained personnel and appropriate infrastructure.

Low-cost, user-friendly rapid tests could overcome such issues, but the accuracy of available point-of-care (POC) tests to determine the prevalence of schistosomiasis in regions co-endemic for *S. haematobium* and *S. mansoni* needs to be determined. The POC test for detecting *Schistosoma* Circulating Cathodic Antigen (POC-CCA) in urine has been endorsed by the WHO as an alternative to conventional microscopy, in particular for the diagnosis of *S. mansoni* infections[9]. It requires minimal training and has been validated in several field settings endemic for intestinal schistosomiasis [11, 12]. Another easy-to-use rapid test is the microhaematuria dipstick test for the detection of haematuria, which has been shown to be strongly associated with urogenital schistosomiasis, although it is considered nonspecific [13]. A quantitative Up-Converting reporter Particle Lateral Flow (UCP-LF) test detecting the genus-specific *Schistosoma* Circulating Anodic Antigen (CAA) is a highly accurate test to detect active infection of all *Schistosoma* species in urine or serum[14]. Although it requires a more advanced laboratory infrastructure, it has been shown to be 100% specific and can reach a sensitivity to detect single-worm infections [14-16].

This study aimed to determine the current prevalence of schistosomiasis in the Mwanga district Tanzania after approximately twenty years of MDA using the UCP-LF CAA test and to explore the potential of using the POC-CCA and microhaematuria dipstick as a combined POC test for diagnosing schistosomiasis in co-endemic settings in comparison to the laboratory-based UCP-LF CAA test. Furthermore, we investigated *Schistosoma* infection risk factors and associated parameters.

Materials and methods

Ethical considerations

Ethical approval for this study was obtained from Kilimanjaro Christian Medical University College (KCMUCo) research and ethical committee board (reference number: 2588). Administrative authorization was obtained from the district education officer and Mwanga District Medical Officer. Children were enrolled based on their availability, and those willing to participate were given a consent form to be signed by guardians and/or parents. Immediately after sample collection all children, including those who participated in our study, were provided with praziquantel under the yearly MDA programme at school at the recommended dose in the presence of a local clinician.

Study area and population

The study was conducted in Mwanga district, one of the seven districts of Kilimanjaro region in Tanzania. Farming, fishing, sand collection, pebble making, soil bricking and animal keeping are the major economic activities. The study was conducted in five schools, of which two were selected based on a previous study [6]. MDA of praziquantel had occurred in these schools more than 6 months prior to our study.

Sample/data collection and processing

Enrolled study participants provided consent forms from parents and were given sterile containers with unique identifiers to provide fresh urine samples. For each sample, POC-CCA and microhaematuria dipstick was done in the field for the diagnosis of *S. mansoni* and *S. haematobium*, respectively. An aliquot of 2 mL of urine was conserved (at -20 °C) per participant and was shipped on ice to Leiden University Medical Center in the Netherlands for retrospective UCP-LF CAA analysis. Following urine sample collection, a face-to-face interview using a closed-ended questionnaire in English and Swahili was conducted.

Field and Laboratory analysis

The POC-CCA test (batch 180817091) was obtained from Rapid Medical Diagnostics, South Africa (SA), and analysis was done according to the manufacturer's instructions. Briefly, two drops of urine were transferred into the sample window of the test cassette. The readout of the cassette was done in 20 minutes. Results were scored as negative, trace or positive. Microhaematuria dipstick (Mission Urinalysis, Lot no: URS8090018) test was performed by placing the strip on a flat surface and a drop of urine applied to the reagent pad. Readouts were done in 1 minute as either negative or positive according to the manufacturer's instructions.

The *Schistosoma* genus-specific UCP-LF CAA test was employed to detect CAA in urine samples and to confirm active infection with *Schistosoma* spp [14]. All urine samples were subjected to the UCAA*hT*417 wet format of the test. Briefly, 500µL of each urine sample was mixed with 100µL of 12% trichloroacetic acid, then incubated at room temperature for 5 minutes and centrifuged. The clear supernatant was then concentrated to 20µL using a 0.5 mL centrifugal device (Amicon Ultra-0.5, Millipore, Merck Chemicals B.V., Amsterdam, The Netherlands). The resulting concentrate was then applied to the lateral flow test strip. To quantify CAA concentrations and to validate the assay cutoff (0.6 pg/mL), reference standards with known CAA-levels were included. A CAA concentration above 0.6 pg/mL was considered positive. Infection intensity was categorized as low positive (>0.6-10 pg/mL), moderate positive (>10-100 pg/mL) and high positive (>100 pg/mL).

Statistical analysis

The agreement between the combination of POC-CCA an microhaematuria dipstick (combined POC test) and UCP-LF CAA was performed using Kappa (K) statistics. For POC-CCA, trace results were considered negative. Furthermore, the association between socio-demographic characteristics and risk factors associated with *Schistosoma* infection, based on the UCP-LF CAA test, was performed using chi-square statistics, binary and multiple logistic regression analyses. Statistical analysis was performed using IBM Statistical Package for Social Sciences version 29 (SPSS Inc., Chicago, United States of America). For generation of plots, GraphPad Prism version 9.3.1 for Windows (GraphPad Software, San Diego, California USA, www.graphpad.com) was used.

Results

Socio-demographic characteristics

A total of 576 children provided informed consent and subsequently provided a urine sample and were therefore included in the final analysis. In Table 1 socio-demographic characteristics of the study population are given. The children's age ranged from 5 to 16 years, with a mean age of 9.8 years (SD 2.4) and 50.7% were females. Furthermore, the majority of the children were in class range 1 to 3 (50.3%). Farming was the most common father's profession (46.7%) followed by fishing (23.4%). The most common mother's profession was farming (44.8%), followed by small businesses (34.2%).

Table 1. The prevalence of schistosomiasis across all five schools based on UCP-LF CAA, POC-CCA, microhaematuria dipstick and a combination of the POC-CCA and microhaematuria dipstick.

			Diagnostic test			
		Number of children	**UCP-LF CAA**	**POC-CCA**	**Microheamaturia dipstick**	**Combined Test***
			Positive (%)	Positive (%)	Positive (%)	Positive (%)
School	Kagongo	279	35 (12.5)	174 (62.4)	84 (30.1)	209 (74.9)
	Kileo	59	14 (23.7)	37 (62.7)	12 (20.3)	41 (69.5)
	Kivulini	57	19 (33.3)	30 (52.6)	12 (21.1)	36 (63.2)
	Mkombozi	106	31 (22.2)	35 (33.1)	23 (21.6)	43 (40.6)
	Mnoa	75	18 (24.0)	38 (50.6)	17 (22.7)	47 (62.7)
Total		**576**	**117 (20.3)**	**314 (54.5)**	**148 (25.7)**	**376 (65.3)**
	*combination of POC-CCA and/or microheamaturia dipstick positive outcome					

Prevalence and intensity of Schistosoma infection

In total 117 (20.3%) of children were found to be CAA positive (Table 1). The highest proportion of positives was observed among children attending Kivulini primary school (33.3%), followed by Mkombozi primary school (29.2%). The lowest proportion was 12.5% and was found among school children at Kagongo primary school. The majority of moderate to high intensity infections based on CAA-levels was observed in the schools in Kivulini and Mkombozi (Figure 2a). Furthermore, SAC within the age category 5-10 years were found to be more often CAA positive than those aged 11-16 years (Figure 2b). The outcome of the point-of-care tests are also summarized in Table 1. Based on POC-CCA and microhaematuria dipstick tests the prevalence of schistosomiasis were, 54.5% and 25.7% respectively. Assuming that the combination of two tests will give more clearer prevalence, combining POC-CCA and microhaematuria dipstick, the prevalence was 65.3%.

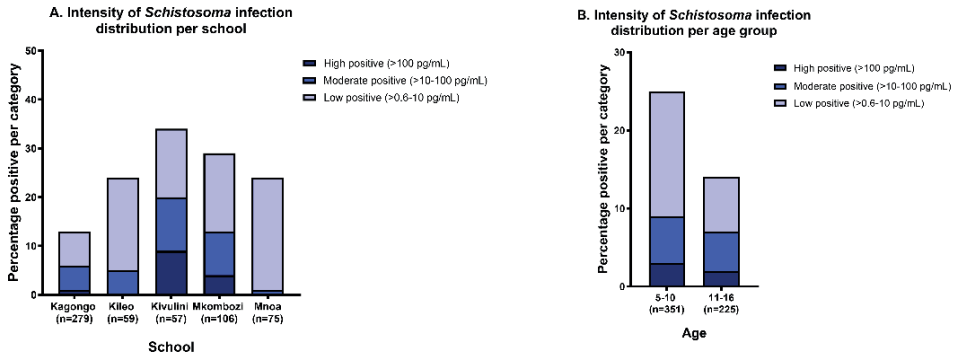

Figure 2. Prevalence and intensity of *Schistosoma* infection based on UCP-LF CAA amongst (A), five selected schools (B) the age categories.

The agreement between the combination of POC-CCA and microhaematuria dipstick and the reference test UCP-LF CAA.

The combination of POC-CCA and microhaematuria dipstick showed no agreement with the UCP-LF CAA test (Table 2). Furthermore the p-value indicates that this lack of agreement is not statistically significant, suggesting that the disagreement between tests is likely due to chance at significance level of 0.05. Analysis of the individual POC-CCA and microhaematuria dipstick tests also showed no agreement with the UCP-LF CAA test.

Table 2. The level of agreement between point-of-care circulating cathodic antigen (POC-CCA) test, microhaematuria dipstick and upconverting particle lateral flow circulating anodic antigen (UCP-LF CAA) urine test by Cohen's kappa coefficient in 576 school-aged children from Mwanga Tanzania.

Test		**UCP-LF CAA**				
		Positive	Negative	K-value	P-Value	Interpretation
POC-CCA	Positive	86	367	0.011	0.128	Poor
	Negative	31	92			
Microhaematuria dipstick	Positive	37	110	0.013	0.090	Poor
	Negative	80	349			
Combined (Microhaematuria and POC-CCA)	Positive	79	297	0.015	0.569	Poor
	Negative	38	162			

Risk factors associated with schistosomiasis

Using multivariate logistic regression analysis (adjusted odd ratio), the potential risk factors associated with *Schistosoma* infection, based on the presence of CAA, showed that children in class level 1-3 had two times higher odds of having schistosomiasis than children in higher classes. Children involved in farming and swimming activities had respectively 5.6 and 3.6 odds of being infected than those who did not farm nor swim. Furthermore, children attending Kileo, Kivulini, Mkombozi and Mnoa primary schools had 2.2, 2.6, 2.4 and 2.7 times higher odds of

CAA positive results respectively, when compared to those attending Kagongo primary school. More details can be found in Supplementary Table 1.

Discussion

Using a highly accurate diagnostic approach (UCP-LF CAA), this study indicated that after nearly two decades of MDA schistosomiasis remains highly prevalent (20%) among school-aged children in Mwanga district, Tanzania. Although POC-CCA and microhaematuria dipstick test showed an even higher prevalence than the UCP-LF CAA test, no agreement was found between these tests and the UCP-LF CAA results nor any association was observed between these tests and known risk factors for schistosomiasis, highlighting the limitation of these currently available rapid diagnostics tests (POC-CCA and microhaematuria) in accurately determining the true prevalence in this specific setting that is known to be co-endemic for *S. mansoni* and *S. haematobium*.

Different prevalence's have been observed throughout Tanzania[17-21]. As commonly known as well as shown in the current study, measurement of prevalence highly depends on the diagnostic method used. Since we have used a highly accurate diagnostic method in our study, i.e. the UCP-LF CAA test, it is difficult to directly compare our results to previously published results based on microscopy and/or POC-CCA as these methods have limited sensitivity/specificity. Our data confirm regional variation in the burden of schistosomiasis in Mwanga district, which would, extrapolated to Tanzania as a whole, argue for a more focally oriented schistosomiasis control approach.

A significant difference in infection rates among different age groups was identified. Younger children (5-10 years) exhibited a higher prevalence of schistosomiasis than the older age group (11-16 years), indicating early exposure to the infection[21]. The possible reason for older children having low prevalence is through acquired immunity due repeated infections as indicated by other previous studies for example possible presence of IgE antibodies [22, 23]. A significant association was found between schistosomiasis and children who swim in water bodies, which may be attributed to playful behavioral activities common among children [4]. The children involved in swimming activities had 3.6 times more risk of being infected, in line with recent systematic review demonstrated by Reitzug and colleagues [24]. Children's involvement in farming was found to be associated with an increased risk of being infected with schistosomiasis. Finally, children attending Kileo, Kivulini, Mkombozi and Mnoa primary schools were identified to have higher rates of *Schistosoma* infection compared to those attending Kagongo primary school. These findings are likely due to the proximity of irrigation schemes/rivers to these schools, which are perceived as safer water sources for young children and so most likely to visit compared to larger water bodies like the dams located closer to Kagongo, where parents have concerns about the risk of children drowning and so cautioned not to go there for water.

Despite of providing crucial updates on the prevalence of schistosomiasis among school children in the area, the study has several limitations. Firstly, the laboratory UCP-LF CAA test

detects all *Schistosoma* species, but it does not provide any species-specific information [14]. In control settings, where species information would be relevant, other measures can provide this, e.g. determining the presence of specific snail species, or performing egg microscopy or species-specific PCR. For treatment, species information as such is not needed, and CAA has been demonstrated to be an excellent marker for monitoring treatment efficacy [15, 25-27]. Although POC-CCA and microhaematuria rapid tests are user-friendly, kappa statistics revealed a poor agreement between these tests and the UCP-LF CAA. It was expected that the combined positivity rates of POC-CCA and microhaematuria dipstick test would reflect the UCP-LF CAA results, however this was not the case (Table 1). The poor agreement may be due to production batch differences, sexually transmitted infections (STIs), low-intensity infections, and subjectivity to test readouts, which might also affect results [28]. Furthermore, more accurate result with both tests might have been possible if the test was scored in a more quantitative manner. For example, following the recently described G-score scoring method for POC-CCA, an inclusion of control samples as a way to standardize the readout and to determine the cut-off for positivity. The microhaematuria test can be scored semi-quantitatively based on color intensity linked to the level of red blood cells. However, registering of more quantitative results was not foreseen in this study.

In conclusion, this study demonstrates a moderate prevalence of schistosomiasis in Mwanga district Tanzania, implicating that the ~ 20 years annual MDA of praziquantel in this region may have had an effect on reducing the schistosomiasis burden, but transmission is still ongoing. To improve the efficacy of MDA strategies, diagnosis at acute stages of the disease in combination with treatment could be extended not only to higher risk groups but also to all persons above two years of age as recommended by WHO [9, 29]. Apart from that, integrated approaches including improved access to WASH infrastructure, political willingness, and production of reliable data are important for controlling schistosomiasis in Tanzania [30]. The presence of persistent hotspots in countries like Tanzania where provision of MDA programme failed to provide long terms solution in some villages shows the need for such an integrated approach[31]. Furthermore, a combination of the POC-CCA and microhaematuria dipstick did not prove to be useful as a screening tool for schistosomiasis in this *S. haematobium* and *S. mansoni* co-endemic setting. However, efforts are ongoing to make CAA detection generally available, with a recent initiative focusing on the development of a more easy-to-use, accurate, affordable and visually scored CAA-RDT [32, 33]. The CAA-RDT could be of great potential in resource-poor endemic settings and assist in the development of targeted control measures and interventions to effectively combat schistosomiasis.

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Supplementary information

Supplementary Table 1. Socio-demographic characteristics associated to *Schistosoma* infection, as determined by UCP-LF CAA, among 576 school children in Mwanga

Variables	Frequency (%)	N° CAA Positive (%)	X^2	P-Value
Total (N=576)		**117 (20.3)**		
Age (years)				
5-10	351(60.9)	86(24.5)	9.7	0.002
11-16	225(39.1)	31(13.8)		
Sex				
Male	284(49.0)	58(20.4)	1.0	0.948
Female	292(50.7)	59(20.2)		
School enrolled				
Kagongo	279(48.4)	35(12.5)	4	<0.001
Kileo	59(10.2)	14(23.7)		
Kivulini	57(9.9)	19(33.3)		
Mkombozi	106(18.4)	31(29.2)		
Mnoa	75(13.0)	18(24.0)		
Class				
1-3	290(50.3)	76(26.2)	2	0.002
4-5	166(28.8)	22(13.3)		
6-7	120(20.8)	19(15.8)		
Mother's occupation				
Farming	258(44.8)	62(24.0)	4	0.067
Fishing	4(0.7)	0(0.0)		
House wife	88(15.3)	19(21.6)		
Small business	197(34.2)	28(14.2)		
Employed	29(5.0)	8(27.6)		
Father's occupation (n=575)				
Farming	269(46.7)	69(25.7)	3	0.006
Fishing	135(23.4)	17(12.6)		
Small business	119(20.7)	18(15.1)		
Employed	52(9.0)	13(25.0)		

Supplementary Table 2. Factors associated with *Schistosoma* infection among school children in Mwanga.

Variable	N	COR	95% CI	P-Value	AOR	95% CI	P-Value
Age							
5 – 10	351	1			1		
11 – 15	225	0.5	0.31-077	0.002	0.7	0.33-1.6	0.44
Class							
1– 3	290	1			1		
4 – 5	166	0.4	0.26-0.72	0.001	0.4	0.19-0.75	0.006
6 – 7	120	0.5	0.30-0.923	0.025	0.3	0.13-0.90	0.030
Farming Involvement							
No	330	1			1		
Yes	246	5.2	3.3-8.2	<0.001	5.6	3.3-9.4	<0.001
Fishing Involvement							
No	431	1			1		
Yes	145	1.7	1.1-2.6	0.024	0.8	0.50-1.42	0.525
Father occupation							
Farming	269	1			1		
Fishing	135	0.42	0.23-0.74	0.003	1.1	0.52-2.47	0.755
Small business	119	0.52	0.29-0.92	0.023	0.9	0.32-2.24	0.745
Employed	52	0.96	0.49-1.92	0.992	0.5	0.20-1.22	0.130
Swimming							
No	147	1			1		
Yes	429	2.0	1.2-3.4	0.011	3.6	1.85-6.95	<0.001
School							
Kagongo	279	1			1		
Kileo	59	2.2	1.1-4.4	0.029	2.2	0.89-5.26	0.087
Kivulini	57	3.5	1.8-6.7	<0.001	2.6	1.13-5.85	0.025
Mkombozi	106	2.9	1.7-5.0	<0.001	2.4	1.21-4.94	0.013
Mnoa	75	2.2	1.2-4.2	0.015	2.7	1.17-6.43	0.021

COR:Crue odds ratio; AOR: Adjusted odds ratio