Schistosoma haematobium infection and asymptomatic bacteriuria in young South African females

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ABSTRACT:

Schistosoma haematobium eggs can induce lesions in the urinary and genital tract epithelia, as eggs pass through or get trapped in the tissue. Local inflammatory reactions induced by *S. haematobium* eggs might affect the ability of bacteria to establish mucosal super-infection foci. *S. haematobium* infection and asymptomatic bacteriuria can both portray haematuria, proteinuria and leukocyturia. This shared set of proxy diagnostic markers could fuel routine misdiagnosis in *S. haematobium* endemic areas. Furthermore, *S. haematobium* infected individuals might be at a higher risk of contracting bacterial urinary tract infections, which could manifest either as symptomatic or asymptomatic bacteriuria.

The aim of the current study was to explore whether schistosomal lesions are susceptible to super-infection by bacteria measured as asymptomatic bacteriuria. *S. haematobium* infection was determined by microscopy of urine samples. Furthermore, urine samples were tested with dipslides for asymptomatic bacteriuria and with dipsticks for haematuria, proteinuria and leukocytes. We found no association between asymptomatic bacteriuria and *S. haematobium* infection in a sample of 1040 female primary and high school students from a schistosomiasis endemic area in KwaZulu-Natal, South Africa. Furthermore, it was demonstrated that asymptomatic bacteriuria is not a bias for use of micro-haematuria as a proxy diagnostic measure for *S. haematobium* infection in this population.

1 Keywords:

2 urogenital schistosomiasis, asymptomatic bacteriuria, haematuria, *Schistosoma haematobium*,
3 diagnostics
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9 1. INTRODUCTION:

10 Urogenital schistosomiasis caused by the blood-dwelling digenean trematode *Schistosoma*
11 *haematobium* remains a poverty related disease burden for an estimated 112 million people living
12 in Sub-Saharan Africa [1,2]. The associated morbidity poses diverse challenges and a heavy impact
13 on local public health services. *S. haematobium* associated morbidity range from subtle to severe
14 [3,4]. It can typically present with anaemia, stunted growth, and cognitive impairment in children,
15 as well as with organ specific manifestations such as genital and urinary tract lesions. In severe
16 cases it may lead to kidney damage and bladder cancer [5]. Furthermore, female genital
17 schistosomiasis has been hypothesised to be associated with HIV-transmission through genital
18 mucosal lesions [6].
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20 Tissue reactions induced by *S. haematobium* eggs migrating through or getting trapped in urinary
21 tract epithelial tissues frequently invoke symptoms and paraclinical signs such as dysuria,
22 pollakisuria, proteinuria, and haematuria [7]. Haematuria is generally accepted as a good
23 diagnostic measure for urogenital schistosomiasis in children, where micro-haematuria correlates
24 well with the number eggs shed in urine [8]. However, haematuria, proteinuria, dysuria and
25 pollakisuria are also common denominators for symptomatic urinary tract infections (UTI) [9],
26 making misdiagnosis possible. Asymptomatic bacteriuria and *S. haematobium* infection also share
27 a set of overlapping paraclinical signs such as haematuria, proteinuria and leukocyturia commonly
28 observed by urine dipstick measures as proxy diagnostic parameters [8,10].
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30 As uro-genital schistosomiasis can result in granuloma formation and hence epithelial
31 inflammation in the urinary and genital tracts, local conditions of importance to bacterial
32 colonisation may have changed [11]. Especially the early inflammatory phase of *S. haematobium*
33 egg induced immune reactions is poorly described in humans. In a mouse model Fu *et al.* (2012)
34 showed a distinct Th2 cytokine driven cell profile rich in activated macrophages, mixed eosinophil
35 and neutrophil infiltrates accompanied by IgE isotype switch associated with *S. haematobium* eggs
36 [12]. Furthermore, other aspects like increased urine voiding frequency, granuloma formation,
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urinary tract fibrosis and dysfunction also resembled human disease. Thus, schistosome eggs seem to be accompanied by an antibacterial cell arsenal as they reach the mucosal surfaces in the genitourinary tracts; potent phagocytes as macrophages, neutrophils and also eosinophils, which pack granule proteins with antibacterial properties like major basic protein and eosinophil cationic protein [13-15]. In contrast a recent mouse model demonstrates *S. haematobium* egg mediated IL-4 induction associated with an UTI susceptible phenotype [16]. Eggs penetrating the epithelial surface could also be creating entry points for bacteria before the local inflammatory response is sufficiently expanded and able to control the infection focus. Furthermore, calcification of trapped eggs in chronic infections can build up with repeated exposure to infection and result in alterations and obstructions in the urinary tract, which are known risk factors for UTI [17]. These scenarios underline that comprehensive understanding of the local immune dynamics elicited by *S. haematobium* eggs and potential bacterial superinfection is yet far from achieved. Successful establishment of bacterial infection possibly depends on a range of factors including *S. haematobium* egg infection intensity, re-infection rate and host immune status [18].

The aim of the study was to explore, whether urinary tract schistosomiasis alters susceptibility to superinfection with bacteria in schistosome infected individuals. Furthermore, the study investigates whether asymptomatic bacteriuria constitute a bias, due to overlapping paraclinical signs, for use of urine dipsticks to detect micro-haematuria as a proxy diagnostic measure for *S. haematobium* infection in primary and high school students from an endemic area with a highly focal infection distribution in rural South Africa [19].

2. METHODS AND MATERIALS:

2.1 Study design, area and population:

A cross-sectional study nested in a larger mass treatment dependent study in randomly selected schools was carried out from May – August 2012 in Ugu District, KwaZulu-Natal, South Africa. Schools, which had not yet undergone mass treatment for schistosomiasis, were included. Exclusion criteria were male gender, clinical illness assessed by local authority district nurses, and delivery of less than 20 ml urine. Figure 1 illustrates the participant recruitment process. Furthermore, samples from menstruating young women were excluded. However, occasionally it was not possible to enquire about period status due to spectators.

The majority of the Ugu population is of Zulu ethnicity and more than 80% live in rural settings, many without potable water, basic sanitation and electricity [20]. Many gorges and river systems traverse the poverty challenged rural inlands facilitating focal schistosomiasis epidemiology [19]. South African registered praziquantel is expensive and there is limited availability at local clinics, which render it unlikely, that but a few study participants could have received recent treatment prior to study enrolment.

<insert figure 1>

2.2 Urine collection: Participants were invited to give a urine sample in 400ml wide-mouthed screw capped plastic containers. Collection took place 10am – 2.30pm. The urines were immediately put into cooler boxes with icepacks to prevent egg hatching and sun exposure.

2.3 Parasitology: Egg preservation for standard microscopy of *S. haematobium* infection egg intensity was done in the field. 10ml swirled urine was poured directly into 15ml tubes containing 1ml 5% formalin solution (formaldehyde solution 38% w/v, Medicolab) and kept out of sunlight. At a later stage in the laboratory, the preserved urines were centrifuged (Beckman Coulter, Allegra X-22), the supernatant decanted and the entire residual was mounted onto glass slides for standard counting by light microscopy. One in ten urine samples was tested twice for quality control. Egg counts were done blinded to bacteriuria and dipstick results.

2.4 Dipstick parameters and bacteriuria: Urines were tested on site for haematuria (≥ 10 rbc/ μ l), leukocytes (≥ 20 -25 wbc/ μ l) and proteinuria (≥ 10 -15mg/dl) with dipsticks (Neotest 4, Occidem Biotech) as recommended by the manufacturer. Each urine sample was swirled before testing. Immediately after dipstick testing, Uricult dipslides (Orion Diagnostica) were used to sample for presence of significant, per definition, asymptomatic bacteriuria ($\geq 10^5$ CFU/ml) according to the manufacturer's recommendations. If doubt arose as to whether a slide was negative, dipslides were incubated for an additional 24 hours and re-read. Polymicrobial growth was considered as contamination. All dipstick and dipslide readings were carried out by the same investigator.

2.5 Ethical considerations: Girls below 16 years of age, whose guardians had provided informed written consent, and who themselves gave assent, were included. Females above the age of 16 years were encouraged to inform their parents and obtain their permission, but this was not a legal requirement. Only individuals who accepted praziquantel treatment on sample collection day was included. Any individual could at any time withdraw from participation without meeting objections or adversity. A research assistant, who was proficient in the local majority ethnic group language isiZulu, was present during urine collection to explain the procedure and to respond to questions from participants. Field testing of urine samples was carried out in a manner ensuring anonymity from spectators. Furthermore, privacy for the participants was prioritised over inquiries about menstrual status.

All participants testing positive for bacteriuria ($\geq 10^5$ CFU) and those who tested positive for glucose in urine were referred to a local clinic. Individuals with significant bacteriuria were informed that they did not have to go to a clinic, if they had no symptoms. Referral letters provided information both in isiZulu and in English.

2.6 Data analysis: Sample size calculation was done using Epi Info 7.1.1.0 (CDC). Parameters used were “cross-sectional study” with a power of 80%, two-sided confidence intervals of 95%, a ratio of exposed:unexposed of 1 and an estimated outcome in % exposed:unexposed of 5,5:2 giving a risk ratio of 2,75 and a sample size of 1034 (Fleiss w/CC). Data were analysed using SPSS 19.0 for Windows (IBM SPSS Inc.) and tested with Mann-Whitney U-test for significant differences.

Spearman’s correlation-coefficient was used to describe intensity related associations. In order to test independent variables for significant associations’ binary logistic regression models using *S. haematobium* eggs in urine and bacteriuria were run as dependent variables. Bivariate analyses were done for independent variables; age (Gaussian distributed), haematuria, proteinuria, leukocytes.

3. RESULTS:

A total of 1119 urine samples were obtained from girls from three primary (n=246) and nine high schools (n=873) (table 1). Age data was obtained from only 46.4% (n=519) of the participants giving a median age in the sample of 16 years of age. The median age in primary school students

was 11 (range 7-15yrs, 17.9% (n=44/246)) and in high school students 17 (range 13-24yrs, 54.2% (n=473/873), two outliers excluded).

The *Schistosoma haematobium* prevalence was 20.4% (n=218/1071) with a geometric mean intensity of 14 eggs/10ml urine (range 1-965 eggs/10ml). No significant differences in *S. haematobium* prevalence or infection intensity in primary compared to high school students were found. The prevalence found at each school ranged from 0% - 33.3%. Of the schistosomiasis positive 76.1% (166/218) had low intensity infection (<50 egg/10ml), and hence 23.9% (52/218) high intensity infection (≥50 eggs/10ml) as classified according to WHO standard categorisation, corresponding to 15.5% and 4.9% of the total sample (n=1071).

An overall prevalence of 10% (n=1080, range 0-20.6%) asymptomatic bacteriuria (≥10⁵CFU/ml) as per definition was observed. The prevalence of asymptomatic bacteriuria was significantly different (p=0.004) between primary and high schools, being 4.7% and 11.3%, respectively (table 1). Gram-negative bacteria were found in 79.6% (86/108) and gram-positive in 20.4% (22/108).

<INSERT TABLE 1>

Dipstick test results (n=1115) showed that 46.4% were positive for micro-haematuria (trace measures regarded positive), 7.3% were positive for leukocytes and 25.1% had proteinuria (table 1). No significant difference was found between the primary versus high school students in terms of prevalence of haematuria. However, significantly more high school students were leukocyte positive (p=0.002) or proteinuria positive (p=0.001) compared to the primary school students. Having *S. haematobium* eggs in urine was positively associated with both haematuria and proteinuria (p<0.001) (table 2). However, no association with leukocytes was found. *S. haematobium* infection intensity correlated with the degree of haematuria (p<0.01, r=0.469) also when asymptomatic bacteriuria positive were excluded (p<0.01, r=0.466). Not surprisingly, the degree of haematuria was significantly correlated to the degree of proteinuria (p<0.01, r=0.331, n=1115). In contrast, leukocytes as well as proteinuria were positively associated with asymptomatic bacteriuria (n=1076, p=0.002). Haematuria was not significantly associated with asymptomatic bacteriuria, however, a tendency was observed (p=0.054). No association between asymptomatic bacteriuria and *S. haematobium* positives was found (n=1040).

Bivariate binary logistic regression showed that having haematuria encompassed a ten-fold risk of being *S. haematobium* positive in terms of eggs in urine (OR=10.5; 95% CI[7.0-15.8], p<0.001) whereas proteinuria resulted in a 5-fold risk (OR=5.5; 95% CI[4.0-7.6], p<0.001) (table 2). Proteinuria was also associated with an increased risk of asymptomatic bacteriuria (OR=1.9; 95% CI[1.3-2.9], p=0.002) as were leukocytes (OR=2.5; 95% CI[1.4-4.4], p=0.003). Multivariate regression analysis controlling for asymptomatic bacteriuria and age show that having micro-haematuria gave a 12-fold risk of having *S. haematobium* eggs in urine (OR=12.5; 95% CI[6.62-23.7], p<0.001, n=499). Correspondingly, regression analysis controlling only for asymptomatic bacteriuria gave a 10-fold risk of being *S. haematobium* egg positive when presenting with micro-haematuria (OR=10.0; 95% CI[6.7-15.0], p<0.001, n=1036).

<INSERT TABLE 2>

4. DISCUSSION

In areas endemic for schistosomiasis, it is not surprising that a number of people present with concomitant asymptomatic bacteriuria or symptomatic urinary tract infections [21], but a key question is, whether an association exists in terms of increased or decreased ability of bacteria to establish infection foci. Propensity to bacterial infection is known to be related to mechanical obstruction or alteration of the urinary tract, where crevices or blockages hinder bacterial removal by micturition [11]. However, bacterial colonisation ability might also be affected by local inflammatory reactions induced by *S. haematobium* eggs lodged in the urogenital mucosal epithelia.

The results from this study indicate that urogenital schistosomiasis and asymptomatic bacteriuria are not associated in young females, but rather appear to be chance co-infections in individuals harbouring both infections. A study conducted in 2003 in Nigeria supports this conclusion and found asymptomatic bacteriuria ($\geq 10^5$ bacteriae) in 1.4% of 443 boys and girls (5-15 years old) [22]. However, with this very low prevalence the Nigerian study was not powered to detect a potential significant association between asymptomatic bacteriuria and urogenital schistosomiasis. Uneke *et al.* (2009) observe high prevalence of asymptomatic bacteriuria coinciding with high *S. haematobium* prevalence in another Nigerian study, but this study does not

1 demonstrate a significant association between uro-genital schistosomiasis and asymptomatic
2 bacteriuria either, despite using low cut-off for asymptomatic bacteriuria (10^4 CFU) [23]. Some
3 older studies have pointed towards an association though; a study done in Niger in 1985
4 demonstrated a higher prevalence of asymptomatic bacteriuria in women, girls and boys with high
5 intensity *S. haematobium* infections from an endemic village as compared to a village with low
6 endemicity of schistosomiasis [24]. Higher asymptomatic bacteriuria prevalences are reported
7 from schistosomiasis endemic compared to non-endemic regions [25-28]. However, it is possible,
8 that these results are not in jeopardy with findings from the current study as high intensity *S.*
9 *haematobium* infections increase the risk of alterations in the urinary tract potentially hindering
10 bacterial removal. Furthermore, chronic and early stage inflammatory schistosomal lesions might
11 affect bacterial infection establishment differently, possibly also depending on intensity of
12 infection [18].

13 The prevalence of asymptomatic bacteriuria was observed to be higher in the high school students
14 compared to primary school students, which was to be expected as both asymptomatic bacteriuria
15 and symptomatic urinary tract infections are commonly more prevalent after onset of puberty and
16 sexual debut [29]. Haematuria, proteinuria and leukocytes showed associations confirming
17 findings from previous studies [30,31]. Haematuria was the strongest predictor for *S.*
18 *haematobium* infection. Leukocyte positivity was related to asymptomatic bacteriuria and not *S.*
19 *haematobium* infection. The present dipsticks detect leukocyte esterase most likely of neutrophilic
20 origin with a sensitivity of ≥ 20 -25 wbc/ μ l. As expected, both haematuria and proteinuria showed
21 positive correlations with the intensity of *S. haematobium* infection.

22 This study confirmed the dipstick haematuria usefulness as a proxy diagnostic marker for *S.*
23 *haematobium* infection in rural KwaZulu-Natal. There are several inherent limitations to the study;
24 no data on potential urinary tract symptoms, recent intake of antibiotics or potential sexual debut
25 was obtained and exact participant age is largely unknown. Mid-stream urine collection is the gold
26 standard for determining degree of bacteriuria, but the urine samples in this study are likely to be
27 first-midstream catch and full urine samples. Furthermore, due to privacy concerns it was not
28 possible to enquire about menstrual status at all times, which might mean that the observed
29 prevalence of asymptomatic bacteriuria is slightly overestimated. However, menstruation is a
30 variable independent of *S. haematobium* infection status and it is reasonable to assume, that the

1 missing menstrual status data is as frequent in the *S. haematobium* negative group as it is in the
2 egg positive. Hence, not an impactful confounder on the main study scope as no association was
3 observed. This is supported by the fact that we did not observe an association between *S.*
4 *haematobium* and asymptomatic bacteriuria in the primary school subsample, where the vast
5 majority had most likely not entered puberty.

6
7 Spatial modelling based on a combination of micro-haematuria data, questionnaire information
8 and geographical data could be beneficial as a future approach for identifying *S. haematobium*
9 hotspots, hence addressing the highly focal epidemiology of schistosomiasis [32]. Asymptomatic
10 bacteriuria did not constitute a bias for use of micro-haematuria as a *S. haematobium* proxy
11 diagnostic marker in the investigated population. However, in certain subgroups blood in urine
12 should not per default lead to the diagnosis of urogenital schistosomiasis. For example pregnant
13 women, diabetic women, multiple sclerosis patients and HIV/AIDS-positive individuals are possibly
14 more prone to development of symptomatic UTI [33-37]. Furthermore, genetic blood group
15 predisposition, physical displacement of bacteria towards the urethra (eg. associated with sexual
16 activities), behavioural factors, and anatomical or functional abnormalities are associated with
17 higher risk of symptomatic UTI. Interactions between bacterial and host factors determine
18 whether asymptomatic bacterial colonisation will lead to symptomatic UTI [17]. It remains to be
19 elucidated whether causal relations between symptomatic UTI and uro-genital schistosomiasis
20 exist in particular in areas with high transmission potentials.

21
22 In conclusion, no association between as per definition asymptomatic bacteriuria and *S.*
23 *haematobium* infection was observed in a sample from schistosomiasis endemic localities in rural
24 KwaZulu-Natal, South Africa. Despite the investigated schools being focally low-endemic localities
25 and more than 75% of the enrolled student having low-intensity infections, asymptomatic
26 bacteriuria did not constitute a bias for micro-haematuria as a proxy diagnostic marker. Hence, the
27 urine dipstick is consolidated as a useful tool for mapping prevalence and generating information
28 for intervention and prevention strategies even in uro-genital schistosomiasis low-endemic
29 regions.

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6. REFERENCES:

1. Hotez PJ, Kamath A (2009) Neglected tropical diseases in sub-saharan Africa: review of their prevalence, distribution, and disease burden. *PLoS Negl Trop Dis* 3: e412.
2. WHO (2013) Report of an informal consultation on schistosomiasis control, 30 March – 1 April 2011.
3. Vennervald BJ, Dunne DW (2004) Morbidity in schistosomiasis: an update. *Curr Opin Infect Dis* 17: 439-447.
4. Khalaf I, Shokeir A, Shalaby M (2012) Urologic complications of genitourinary schistosomiasis. *World J Urol* 30: 31-38.
5. Gryseels B, Polman K, Clerinx J, Kestens L (2006) Human schistosomiasis. *Lancet* 368: 1106-1118.
6. Kjetland EF, Ndhlovu PD, Gomo E, Mduluzi T, Midzi N, et al. (2006) Association between genital schistosomiasis and HIV in rural Zimbabwean women. *AIDS* 20: 593-600.
7. Gryseels B (2012) Schistosomiasis. *Infect Dis Clin North Am* 26: 383-397.
8. King CH and Bertsch D (2013) Meta-analysis of Urine Heme Dipstick Diagnosis of *Schistosoma haematobium* Infection, Including Low-prevalence and Previously-Treated Populations. *PLoS Negl Trop Dis* 7: e2431.
9. Wang A, Nizra, P., Malone, MA, Riley, T (2013) Urinary tract infections. Primary care: *Clinics in Office Practice* 40: 687-706.
10. Deville WL, Yzermans JC, van Duijn NP, Bezemer PD, van der Windt DA, et al. (2004) The urine dipstick test useful to rule out infections. A meta-analysis of the accuracy. *BMC Urol* 4: 4.
11. Foxman B (2010) The epidemiology of urinary tract infection. *Nat Rev Urol*: 653–660.
12. Fu CL, Odegaard JI, Herbert DR, Hsieh MH (2012) A novel mouse model of *Schistosoma haematobium* egg-induced immunopathology. *PLoS Pathog* 8: e1002605.
13. Malik A, Batra JK (2012) Antimicrobial activity of human eosinophil granule proteins: involvement in host defence against pathogens. *Crit Rev Microbiol* 38: 168-181.
14. Persson T, Andersson P, Bodelsson M, Laurell M, Malm J, et al. (2001) Bactericidal activity of human eosinophilic granulocytes against *Escherichia coli*. *Infect Immun* 69: 3591-3596.
15. Ramarokoto CE, Kildemoes AO, Randrianasolo BS, Ravoniarimbina P, Ravaoalimalala VE, et al. (2014) Eosinophil Granule Proteins ECP and EPX as Markers for a Potential Early-Stage Inflammatory Lesion in Female Genital Schistosomiasis (FGS). *PLoS Negl Trop Dis* 8: e2974.
16. Hsieh YJ, Fu CL, Hsieh MH (2014) Helminth-induced interleukin-4 abrogates invariant natural killer T cell activation-associated clearance of bacterial infection. *Infect Immun* 82: 2087-2097.
17. Lee JBL and Neild GH (2007) Urinary tract infection. *Medicine* 35: 423-428.

18. Mduluza T, Ndhlovu PD, Midzi N, Scott JT, Mutapi F, et al. (2003) Contrasting cellular responses in *Schistosoma haematobium* infected and exposed individuals from areas of high and low transmission in Zimbabwe. *Immunol Lett* 88: 249-256.
19. Pillay P, Taylor M, Zulu SG, Gundersen SG, Verweij JJ, et al. (2014) Real-Time Polymerase Chain Reaction for Detection of *Schistosoma* DNA in Small-Volume Urine Samples Reflects Focal Distribution of Urogenital Schistosomiasis in Primary School Girls in KwaZulu Natal, South Africa. *The American Journal of Tropical Medicine and Hygiene*.
20. Khumalo D, Mqadi N, Luthuli W, Potter A, Zybrands W (2008) Ugu Case Study. The water dialogues, South Africa
21. Adeyeba OA, Ojeaga SGT (2002) Urinary schistosomiasis and concomitant urinary tract pathogens among school children in metropolitan Ibadan, Nigeria. *AJBR* 5: 103 - 107.
22. Eyong M, Ikepeme EE, Ekanem E (2008) Relationship between *Schistosoma haematobium* infection and urinary tract infection among children in South Eastern, Nigeria. *Niger Postgrad Med J* 15: 89-93.
23. Uneke CJ, Ugwuoke-Adibuah S, Nwakpu KO, Ngwu BAF (2009) An Assessment of *Schistosoma haematobium* infection and urinary tract bacterial infection amongst school children in rural eastern Nigeria. *Internet Journal of Laboratory Medicine* 4: 5-5.
24. Bretagne S, Rey JL, Sellin B, Mouchet F, Roussin S (1985) *Schistosoma haematobium* bilharziosis and urinary infections. Study of their relationship in 2 villages of Niger. *Bull Soc Pathol Exot Filiales* 78: 79-88.
25. Laughlin LW, Farid Z, Mansour N, Edman DC, Higashi GI (1978) Bacteriuria in urinary schistosomiasis in Egypt a prevalence survey. *Am J Trop Med Hyg* 27: 916-918.
26. Kassim OO (1989) Proteinuria and haematuria as predictors of schistosomiasis in children. *Ann Trop Paediatr* 9: 156-160.
27. Pugh RN, Gilles HM (1979) Malumfashi Endemic Diseases Research Project, X. *Schistosoma haematobium* and. *Ann Trop Med Parasitol* 73: 349-354.
28. Wilkins HA (1977) *Schistosoma haematobium* in a Gambian community. III. The prevalence of bacteriuria and of hypertension. *Ann Trop Med Parasitol* 71: 179-186.
29. Nicolle LE (2008) Uncomplicated urinary tract infection in adults including uncomplicated pyelonephritis. *Urol Clin North Am. United States*. pp. 1-12, v.
30. Brouwer KC, Munatsi A, Ndhlovu PD, Wagatsuma Y, Shiff CJ (2004) Urinary schistosomiasis in Zimbabwean school children: predictors of morbidity. *Afr Health Sci* 4: 115-118.
31. Doehring E, Ehrich JHH, Vester U, Feldmeier H, Poggensee U, et al. (1985) Proteinuria, hematuria, and leukocyturia in children with mixed urinary and intestinal schistosomiasis. *Kidney Int* 28: 520-525.
32. Sturrock HJ, Pullan RL, Kihara JH, Mwandawiro C, Brooker SJ (2013) The use of bivariate spatial modeling of questionnaire and parasitology data to predict the distribution of *Schistosoma haematobium* in Coastal Kenya. *PLoS Negl Trop Dis* 7: e2016.
33. Hochreiter WW, Bushman W (1999) Urinary tract infection: a moving target. *World J Urol* 17: 364-371.
34. Metz LM, McGuinness SD, Harris C (1998) Urinary tract infections may trigger relapse in multiple sclerosis. *Axone* 19: 67-70.
35. Law H, Fiadjoe P (2012) Urogynaecological problems in pregnancy. *J Obstet Gynaecol* 32: 109-112.
36. Zhanell GG, Harding GK, Nicolle LE (1991) Asymptomatic bacteriuria in patients with diabetes mellitus. *Rev Infect Dis* 13: 150-154.
37. Ronald A, Ludwig E (2001) Urinary tract infections in adults with diabetes. *International Journal of Antimicrobial Agents*, 2001, Vol17(4), pp287-292 17: 287-292.

Figure 1: Flow-chart showing sample selection

Table 1: Prevalence data from the twelve schools in Ugu District.

Prevalence of *Schistosoma haematobium* infection (eggs/10ml urine), asymptomatic bacteriuria ($\geq 10 \sim 5$ CFU/ml) and dipstick parameters haematuria (≥ 10 rbc/ μ l), leukocytes (≥ 20 -25 wbc/ μ l) and proteinuria (≥ 10 -15mg/dl). n denotes the number of urine samples (number of participants) data was obtained from for a given test. Significant differences in prevalence in high schools versus primary schools are marked with an asterisk.

School phase ^a	Urine samples total (n)	Egg counts: <i>S. haematobium</i>		Dipslides: Bacteriuria		Dipsticks: Haematuria		Leukocytes	Proteinuria
		total (n)	prevalence (%)	total (n)	prevalence (%)	total (n)	prevalence (%)	prevalence (%)	prevalence (%)
A Primary	47	46	6,5	16	12,5	47	31,9	8,5	2,1
B Primary	105	98	27,6	104	4,8	105	54,3	1,9	26,7
C Primary	94	92	18,5	94	3,2	94	30,9	1,1	13,8
D High	138	136	20,6	138	10,1	138	48,6	5,1	23,9
E High	132	127	6,3	131	20,6	131	22,1	0,0	17,6
F High	122	117	25,6	121	9,9	122	57,4	1,6	37,7
G High	93	92	15,1	93	6,5	93	46,2	19,4	22,6
H High	126	112	33,0	123	8,1	126	69,0	22,2	31,0
I High	117	108	26,9	117	15,4	114	54,4	4,4	33,3
J High	21	18	0,0	19	10,5	21	33,3	9,5	14,3
K High	24	24	33,3	24	0,0	24	45,8	16,7	66,7
L High	100	100	17,0	100	9,0	100	40,0	8,0	19,0
TOTAL	1119	1071	20,4	1080	10,0	1115	46,4	7,3	25,1
Primary schools	246	236	19,9	214	*4,7	246	41,1	*2,8	*17,1
High schools	873	835	20,5	866	*11,3	869	47,9	*8,5	*27,4

^aPrimary school grades R-7 (aged 7-15), high school grades 8-12 (aged 13-24)

Table 2: Age and urine parameters as predictors for *S. haematobium* infection and asymptomatic bacteriuria (bivariate logistic regression).

Parameter	<i>S. haematobium</i> eggs in urine	N	Asymptomatic bacteriuria	n
Haematuria	p<0.001 OR=10.5; 95% CI[7.0-15.8]	1067	p=0.055 OR=1.5; 95% CI[1.0-2.2]	1076
Proteinuria	p<0.001 OR=5.5; 95% CI[4.0-7.6]	1067	p=0.002 OR=1.9; 95% CI[1.3-2.9]	1076
Leukocytes	p=0.141 OR=1.5; 95% CI[0.9-2.6]	1067	p=0.003 OR=2.5; 95% CI[1.4-4.4]	1076
Age	p=0.765 OR=1.0; 95% CI[1.0-1.0]	499	P=0.794 OR=1.0;95% CI[1.0-1.0]	516
Bacteriuria	p=0.314 OR=1.3; 95% CI[0.8-2.0]	1040	n/a	

Schistosoma haematobium infection and asymptomatic bacteriuria in young South African females

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Schistosoma haematobium infection and asymptomatic bacteriuria share symptoms, however, no association was observed among >1000 young females. Haematuria was a strong predictor of SH infection in low endemic localities.