Clinical morbidity associated with S. haematobium infection in preschool age children from an endemic district in Zimbabwe

Clinical Morbidity Associated with *S. haematobium* Infection in Pre-School Age Children from an Endemic District in Zimbabwe.

Tariro L. Mduluza-Jokonya[1,2], Thajasvarie Naicker[1], Maritha Kasambala[2], Luxwell Jokonya[3,1], Arthur Vengesai[1,3], Herald Midzi[2], Emilia Choto[2], Kempton Musonza[4], Simba Rusankaniko[4], Elopy Sibanda[5], Francisca Mutapi[6], Takafira Mduluza[2]

[1]Optics & Imaging, Doris Duke Medical Research Institute, College of Health Sciences, University of KwaZulu-Natal; KwaZulu-Natal, Durban, South Africa naickera@ukzn.ac.za
[2]Department of Biochemistry, University of Zimbabwe, P.O. Box MP 167, Mt Pleasant, Harare, Zimbabwe. mduluza@medic.uz.ac.zw ; tmduluza@yahoo.com
[3]Department of Surgery, College of Health Sciences, University of Zimbabwe, P.O. Box MP 167, Mt Pleasant, Harare, Zimbabwe. doclux@gmail.com
[4] Department of Community Medicine, College of Health Sciences, University of Zimbabwe, P.O. Box MP 167, Mt Pleasant, Harare, Zimbabwe. srusakaniko@gmail.com
[5] Twin Palms Medical Centre, 113 Kwame Nkrumah Avenue, Harare, Zimbabwe ensibanda@gmail.com
[6]Institute for Immunology and Infection Research and Centre for Immunity, Infection and Evolution, School of Biological Sciences, University of Edinburgh, Ashworth Laboratories, King's Buildings, Charlotte Auerbach Rd, EH9 3JT, Edinburgh f.mutapi@ed.ac.uk

Corresponding Author:
Tariro L Mduluza-Jokonya
Email: tljokonya@gmail.com

Abstract

Background: *Schistosoma haematobium* infection is associated with urogenital morbidity. There are limited studies reporting on *Schistosoma. haematobium* infected pre-school age children, particularly concerning the extent of morbidity. In this study we investigated *Schistosoma. haematobium* morbidity in infected pre-school age children and established their disease burden.

Methodology: Pre-school age children (1-5years) who were lifelong residents of the study area and had no other infections were included in the study. Participants underwent a physical examination with clinicians blinded from their infection status. Diagnosis of *Schistosoma. haematobium* was by urine filtration.

Results: The prevalence of *Schistosoma. haematobium* was 35.1%(146/416). The clinical features observed in patients with *Schistosoma. haematobium* were: wheezes (morbidity attributable factor (AF=93.9%), haematuria (AF=92.6%), ascites (AF=91.5%), atopy (AF=76.9%), inguinal lymphadenopathy(AF=68.4%), stunting (AF=38.2) , malnutrition (MUAC)(AF=20%) and weight for height scales (AF=5%). *Schistosoma. haematobium* infected children were at greater odds ratio of presenting with inguinal lymphadenopathy (AOR)=99.2(95% CI 24.2 to 854.5), wheezes in the chest (AOR=35.4 95% CI 15.3 to 94.2), Distended abdomen with ascites (AOR=23.9 95% CI 11.4 to 54), haematuria (AOR=12.6 95% CI 11.6 to 14.1), atopy history (AOR=5.6 95% CI 1.85 to 20.2), malnutrition (AOR=2.3 95% CI 1.4 to 3.2) and stunting (AOR= 1.9 95% CI 1.1 to2.7).

Conclusion: The study is novel as it demonstrates for the first time clinical morbidity markers associated with *Schistosoma. haematobium* infection in pre-school age children. Furthermore the study adds scientific evidence to the call for inclusion of pre-school age children in schistosomiasis control programs. These morbidity markers highlight the need for early diagnosis and screening for *S. haematobium* in preschool age children.

Key words: Urogenital Schistosomiasis, morbidity, diagnosis, Pre-school aged children, neglected, *Schistosoma haematobium*

Introduction

Schistosomiasis is a neglected tropical disease and the 2nd most important parasitic disease in sub-Saharan Africa (1). There are five species of the trematodes that affect humans. These are *Schistosoma intercalatum, Schistosoma mekongi, Schistosoma japonicum, Schistosoma haematobium* and S*chistosoma mansoni*. *S. mansoni* and *S. japonicum* are responsible for intestinal schistosomiasis, while *S. haematobium* causes urinary schistosomiasis (2). In Zimbabwe the common species are *S. haematobium* and *S. mansoni* (3) with former being highly prevalent is many areas. Schistosomiasis morbidity has been extensively studied in adults and school aged children, but very little has been done on preschool age children (PSAC) (4–8). It has been noted that morbidity is directly proportional to infection intensity(5). Whereas the frequency of infection in PSAC has been presumed to be low, it is apparent that this is the age when infection begins (3).

Unlike all the other neglected tropical diseases that had their disability-adjusted life years (DALYs) lowered during the period 1990 to 2010, DALY for schistosomiasis has increased by 55.7% (9). Schistosomiasis affects people residing in poverty-stricken areas for up to half of their lives . The new global interest to eliminate schistosomiasis as a public health problem by 2025 (65th WHA, 2012) advocates targeting school age children (SAC) (10), while neglecting preschool age children (PSAC), due to assumed lack of exposure to infection.

An estimated 50 million PSAC need treatment but fail to access it because they are excluded from national schistosomiasis control programs (11). PSAC are neglected because of difficulties in obtaining parasitology for diagnosis, difficulties in detecting light infections and inadequate knowledge about risk factors associated with the infection in this age group. It is usually assumed

84 that the impact of schistosomiasis on health and associated morbidities in this age group are
85 negligible (11). Another main reason for excluding the PSAC is because of the lack of a paediatric
86 dose formulation of praziquantel (12). The first encounter with schistosomiasis occurs during the
87 first five years of life (13). This infection then persists, leading to a natural immune system change
88 and increasing morbidity and risk of co-infections; as well as affecting cognition and growth (11). In
89 this article we focus on *S. haematobium* which is highly prevalent in Zimbabwe, and determine the
90 infection burden in a neglected group which is excluded in mass treatment campaigns.

91 Trapped eggs in the human body systems causes much of the morbidity (14). The life cycle of *S.*
92 *haematobium* involves an asexual reproduction phase which occurs in snails of the genus *Bulinus*,
93 and the sexual reproduction phase which occurs in human hosts (15). *S.haematobium* penetrates the
94 human skin as cercariae and loses its tail and becomes a schistosomulum (16). The schistosomula is
95 transported to the organs via the venous and lymphatic systems (17). The schistosomula then enter
96 the lung and pass through the heart on their way to the liver. In the liver, they mature into adult
97 worms and copulate (18). After copulation females then deposit eggs into the vesicular and pelvis
98 venous plexus of bladder (19). The eggs then move to lumen of bladder and ureters where they are
99 eliminated with urine (20).

100 *S. haematobium* is known to cause the following morbidity: haematuria, dysuria, hydronephrosis and
101 bladder wall pathology (1,7,21,22). Due to advances in diagnosis and clinical observation,
102 schistosomiasis has also been associated with genital morbidity, where in adults, it has been linked to
103 acquisition of HIV infection (10,16). Genital schistosomiasis manifests differently in males and in
104 females. In men it manifests as epididymitis which can simulate tuberculosis, hemospermia and
105 prostatitis (10). In women the symptoms are unspecific, but the most frequent are dyspareunia,
106 dysmenorrhea, leucorrhea, menstrual disorders, post coital bleeding, cervicitis, endometriosis and
107 salpingitis. These genital lesions can cause early miscarriages, ectopic pregnancy and infertility (10).
108 The advanced stage includes bladder calcifications, urinary tract fibrosis, obstructive uropathy and
109 bladder malignancies (11,17). Of note is that urogenital schistosomiasis has been associated with

increased HIV transmission as it affects the pelvic organs and may also result in abnormal inflammatory reactions to immunizations (17). *S. haematobium* has also been associated with debilitating generalized conditions including malnutrition, anemia, growth retardation, impaired cognition and developmental delays during childhood (23).

Morbidity is expected to be higher in individuals with high infection intensity (5,21,24–26). To be specific, children under the age of five have been reported to harbour low infection intensity which results in difficulties in diagnosis (5,7,8,27). Furthermore with schistosomiasis being prominent in tropical areas there are many other infectious diseases that schistosomiasis might mimic (1,28). In this study we demonstrate morbidity associated with *S. haematobium* in children under the age of five years old in an endemic district in Zimbabwe and identify clinical morbidity markers that may be useful in the early diagnosis of schistosomiasis in PSAC.

Methodology

Study site and design

The study was carried out in Shamva district (31°40’0” E longitude and 17°10’0” S latitude) in Mashonaland Central province, Zimbabwe (29). Shamva district has the highest prevalence of schistosomiasis in Zimbabwe at 62.4% (30). It lies 945 m above sea level, the climate is warm and temperament with an average temperature of 20.2 °C and an annual rainfall of 887 mm. Located in the Mazowe valley, Shamva district is an area with high farming activity due to its fertile soil. Residents get their water supply from Mazowe river which spans through the district and is a huge source of alluvial gold which the vast majority of population survives through panning (29). The study was a community cross-sectional survey, children were recruited from 19 different villages in Shamva district gathering at expanded program for immunisation(EPI) centres and Shamva district health centres and hospital.

Study inclusion criteria

The participants recruited in the study had to be aged between 1 to 5 years from the Shamva district and met the following inclusion criteria: 1. Be lifelong residents of the study area 2. Had no previous anti-helminthic treatment exposure 3. Parental/guardian consent to participate 4. Be negative for *Schistosoma mansoni* and geohelminths 5. Malaria negative 6. Be negative for the ToRCHeS (toxoplasmosis, rubella, cytomegalovirus, hepatitis and syphilis) screen 7. Be HIV negative 8. Have a widal TO ratio <1:160.

Sample size

The required sample size was calculated to be 363 participants using Dobson's formula as follows:

$$n = \frac{z^2 pq}{e^2}$$

Where Z is the Z value for the 95% confidence interval, that is alpha = 5% (z = 1.96)

p=proportion/prevalence of the outcome to be investigated (p = 0.62)

q=1-p=0.38

d = precision for the given confidence interval expected expressed as decimal (d=0.05)

n = 363

Data collection

A questionnaire was administered in the form of history taking done by clinicians to the caregivers/parents and participants medical records were assessed carefully. In Zimbabwe, children <5 years old report to health centres once every month for general growth monitoring which is recorded on growth cards.

Clinical examinations

The clinical examinations were conducted on PSAC (n=416) by three medical practitioners independent of each other who were blinded to the infection status of the participant. The

examination of the study participants was holistically done according to a standard protocol adopted from standard clinical practices summarized below(Figure 2) (31,32).

Anthropometry

Height and weight were measured with the participants in light/no clothing. Infantometer baby board was used to measure height and for weight we used a baby scale. Mid Upper Arm Circumference (MUAC) : measurement was done on the left arm mid-point between the shoulder and the elbow tip, with the arm relaxed and hanging down the body. Height and weight for age charts as well as the MUAC reading were used to assess nutritional status.

Developmental assessment

We used the childhood developmental charts from UNICEF to measure gross motor, fine motor, language and social development.

HEENT(Head, eye, ear, nose and throat) Examination

Head: Shape, size, masses, fontanelles; amount, colour, texture and distribution of hair; scar and cleanliness of scalp.

Ears: Tragus or mastoid tenderness, tophi, cerumen, light reflex, bulging, retraction and perforation of tympanic membrane.

Eye: periorbital oedema, ptosis, lid lag and conjunctival pallor.

Nose: Deformities, deviation and perforation of septum, polyps and unusual discharges .

Mouth and throat: Breath odour; colour, fissures and ulceration of lips; bleeding, ulceration, and lid line of gums; tooth caries; tongue colour, coating, fissure, papillae atrophy; colour, ulceration, tumour, monilial patches of buccal mucosa and soft palate; tonsillar inflammation and exudates.

Lymphatic system examination

Lymph nodes: Site, size, consistency, tenderness, fixation, discrete or matted, regional or generalized enlargement

Respiratory system

Inspection: Cyanosis of lips and nails, clubbing of fingers, rate, depth and character of respiration, symmetry of shape and expansion, use of accessory muscles, retractions.

Palpation: Tenderness, subcutaneous crepitation, position of trachea, degree of chest expansion (in cm with tape or hand grip), tactile fremitus.

Percussion: percussion notes (resonance, hyper-resonance, dull, flat), diaphragmatic excursion

Auscultation: Character of breath sounds (vesicular, bronco-vesicular, bronchial, tracheal), crackles, wheezing, friction rub, vocal resonance.

Cardiovascular system

Arteries: pulse rate, rhythm, volume, character, radio-femoral delay (Carotid, Brachial Radial, Femoral, Popliteal, Dorsalis pedis and Posterior tibialis).

Precordium (Heart) examination

Inspection: Presence of precordial bulging, active or quiet precordium, location of apical impulse (interspace, distance from left midclavicular line)

Palpation: Point of maximal impulse and its character, parasternal heave, thrill, shock Percussion: cardiac outline (not frequently performed)

Auscultation: 1^{st} and 2^{nd} heart sounds, 3^{rd} and 4^{th} heart sounds, other added heart sounds (gallop, ejection click, opening snap, pericardial 'knock'), murmur, friction rub

Abdominal Examination

Inspection: Abdominal symmetry, shape (round, flat, scaphoid), movement with respiration, flank fullness, everted or inverted umbilicus, dilated vessels, scars, visible peristalsis, presence of hernia at hernia sites.

Palpation: tenderness (superficial or deep, site), rebound tenderness, guarding and rigidity, enlarged liver (size in cm below right costal margin along right midclavicular line, consistency, surface, edge, tenderness), enlarged spleen (size in cm along splenic growth line below left costal margin, consistency, surface, edge, tenderness, splenic (medial) notch), abdominal mass (size, consistency, surface, edge, tenderness, fixation, mobility with respiration), and enlarged kidneys (size, consistency, surface, edge and tenderness by bimanual palpation).

Percussion: Total vertical liver span, liver and splenic dullness, shifting dullness, fluid thrill .

Auscultation: Bowel sounds, bruit over the liver, friction rub over the liver and the spleen, renal bruit.

Genitourinary system

Costovertebral angle and suprapubic tenderness. In male, scrotum (oedema, hydrocele and hernia), testes (size and descent), vas deferens (nodules, tenderness), varicocele, urethral orifice (reddening, discharge, ulcer, phimosis). In females urethral orifice (reddening, discharge), vaginal discharge, cystocele/rectocele.

Integumentary system

Skin: Texture, rashes, ulcers, urticaria, pigmentation. Hair: texture, Nails: colour, shape (clubbing and spooning), texture, splinter haemorrhages, capillary refill time.

Musculoskeletal system (Locomotor system)

Muscle: muscle tenderness, spasm. Spine: deformity (kyphosis, scoliosis, kyphoscoliosis), gibbus, tenderness on percussion or pressure, limitation of movement. Joints: Swelling, tenderness, heat and redness, crepitus, deformity, limitation of movement on active and passive motions. Bones: deformity, fracture, tenderness.

Nervous system

Level of consciousness (GCS), orientation in time, place and person; speech disturbance (dysphasia).

Cranial nerves (CN) one to twelve assessed.

Motor system

Position, bulk, fasciculation (spontaneous or provoked), strength (power), tone, reflex (deep and superficial)

Deep tendon reflexes

Biceps Triceps supinators Patellar Ankle.

Sensory system

Two point discrimination, Finger-to-nose test, heel-to-shin test, supination-to-pronation of forearm.

Sample collection

Urine samples were collected by giving the caregiver a wide open container to let the child urinate in, children 1 year and below used paediatric urine collector attached by a clinician. The caregivers then brought the samples which were examined.

Samples processing

Urine samples collected were examined for macrohematuria using the Uristix reagent strips (Uripath, Plasmatec, UK) dipped into fresh, well-mixed urine for 40 sec and the test area was compared with a standard colour chart as per manufacturer's instructions. The parasitology team conducted parasitology examination and results were recorded separately, not accessed by the clinical team. Approximately 50 ml of urine sample was collected from each participant on three consecutive days. The samples were collected between 10am and 2pm and processed within 2 hours of collection by urine filtration method and were examined using microscopy for *S. haematobium* eggs detection. The number of eggs were reported per 10ml of urine. Stool samples were collected on a single day and processed using the Kato Katz method with 2 slides prepared per sample, parasite eggs were enumerated under a light microscope for *S.mansoni* in duplicate per gram of stool. A formal ether sedimentation technique was used to test for geohelminths presence (33).

Plasma and sera were obtained from blood collected in well-labeled EDTA and coagulant-free blood collection tubes respectively. Samples from each child were processed and tested for toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus 1 and 2, HIV and hepatitis. The sera was processed using the Maglumi 4000 chemiluminescence immunoassay analyser (CLIA). Children noted to have infection were managed appropriately by the doctors in the study and the community nurse. Thick blood film slides were stained using the Geimsa stain and examined for malaria parasites using microscopy.

Ethical statement

Ethical approval was obtained from Medical Research Council of Zimbabwe (MRCZ/A/2435). Gatekeeper approval was obtained from the Provincial and District Medical Directors and Community Leaders. Informed consent was obtained from the parents or guardians of the children. All participants with confirmed infection were offered treatment.

Statistical method

Data analysis was performed using STATA version 15. The statistical methods applied included the descriptive statistics, bivariate analysis using odds ratio and multivariate logistic regression modelling. In this study we determined how much of the detected morbidity was attributable to *S. haematobium* infection by elucidating Prevalence Ratios (PRs). The morbidity markers were selected based on them having a PR>1, which shows a significant association with *S. haematobium* infection. The multivariate logistic regression models were fitted to adjust for potential confounding factors for the five manifestations with three explanatory variables; that is sex, age and schistosomiasis infection. The effect of different factors on the prevalence of schistosome infection and morbidity was determined using logistic regression and the results reported as adjusted ORs (AORs) and 95% confidence interval (CI), along with the test for significance, as previously described (34). Infection intensity for *S. haematobium* was defined as the arithmetic mean egg count/10ml of at least two urine samples collected on three consecutive days .

Results

Demographics

A total of 416 children from 19 villages in Shamva district, Mashonaland central in Zimbabwe were included into the study (Figure 1). The number of males was 214 (51.4%) and the difference in sex composition was not statistically significant (p=0.20). Age was normally distributed (Shapiro Wilk test, p=0.068) and the range [min-max] was [1-5] years with mean ± (SD) age of 3.39 ±1.08years.

Morbidity observed in the study participants

Clinical features observed in the study participants were as follows: 8% (36) had hematuria, 36% (149) had inguinal lymphadenopathy, 19% (81) had ascites, 19% (79) had wheezes, 11% (46) had shortness of breath, 4% (20) had an atopy history, 10% (43) had malnutrition and 18% (75) had stunting

(Table 1).

***S. haematobium* epidemiology**

The overall *S.haematobium* infection prevalence was 35.1% (146). When segregated by sex, schistosomiasis prevalence was higher in females 37.1% (75/212) were positive compared to males with a prevalence of 33.2% (71/214). A greater proportion of females were infected at the ages of 2, 3 and 4 years with more males being infected at 1 year and 5 years. The likelihood of developing schistosomiasis increased with age (Figure 3).

Characterizing Schistosomiasis Morbidity in Children under the Age of Five Years

Children with *S. haematobium* were at greater odds of presenting with the following: haematuria (Adjusted Odds Ratio (AOR) = 12.6 95%CI 11.6 to 14.1), inguinal lymphadenopathy (AOR = 99.2 (95%CI 24.2 to 854.5), Ascites (AOR=23.9 (95%CI 11.4 to 54), wheezes (AOR = 35.4 (1.72 (95%CI 15.3 to 94.2), shortness of breath (AOR = 1.72(95%CI 0.87 to 3.35), atopy history AOR = 5.6 (95%CI 1.85 to 20.2), malnutrition (using weight for age and height for age charts) AOR = 1.8(95%CI 1.3 to 3.2), malnutrition (using MUAC tape) AOR = 2.3 (95%CI 1.4 to 3.2) and stunting (AOR = 1.9 (95%CI 1.1 to 2.2) (Table 2).

Morbidity attributable to *S.haematobium* was noted to be high for Inguinal lymphadenopathy (Attributable Fraction (AF) = 68.4% (95%CI 65.9 to 70.2), haematuria (AF = 92.6% (90.5 to 95.3), ascites (AF = 91.5% (95%CI 88.5 to 94.9), wheezes (AF = 93.9% (95% CI 90.1 to 96.2), shortness of breath (AF = 35.9 (95%CI 31.2 to 36.8), Atopy history (AF = 76.9 (95%CI 75.2 to 78.5),

malnutrition(using MUAC tape) (AF = 20% 95%CI 10 to 40) malnutrition (using weight for age and height for age chats) AOF = 20% 95%CI 10 to 40), Stunting (AF = 38.2 (95%CI 16.7 to 61%)) (Table 3).

The inguinal lymph nodes observed were rubbery, immobile, non-tender and >2cm in size. A relationship indicating that an increase in schistosomiasis infection is associated with a corresponding increase in inguinal lymphadenopathy prevalence in children who were *S.haematobium* infected was observed at each area (site) (Figure 4). An association between the likelihood of lymphadenopathy and the likelihood of schistosomiasis infection was also proven (Figure 5).

Discussion

To our knowledge, this is the first study reporting on different morbidity markers associated with *S haematobium* infections in PSAC. We found a positive association between *S. haematobium* infection with the following: inguinal lymphadenopathy, wheezes and crackles, ascites, an atopy history, haematuria and nutritional status. Inguinal lymphadenopathy, wheezes, ascites and atopy history have not been previously noted as *S. haematobium* morbidity markers.

To our knowledge this is the first study to identify the strong association between schistosomiasis and inguinal lymphadenopathy. There was a five-fold higher odds of having Schistosomiases among those who presented with inguinal lymphadenopathy than among those without the infection. Most of the other common causes of lymphadenopathy (35) (including tuberculosis and HIV) in the population were excluded, strengthening confidence in our findings. In a study in Zimbabwe among the general population, 4% of the lymph node samples had non-tuberculous inflammatory changes. Most of the nodes were from patients aged one to fifteen years in rural hospitals. In literature, *S. haematobium* has not been linked to lymphadenopathy, though *S. mansoni* and *S. japonicum* have

been recorded to cause enlarged abdominal lymph nodes (36–38). We present novel findings to suggest that this may have been partly due to schistosomiasis (35). Involvement of regional lymph nodes in schistosomiasis infected mice have been noted in *S. mansoni* infection (36). The association of inguinal lymphadenopathy with *S. haematobium* requires further investigation on the immunopathological manifestation.

The lungs have not previously been understood to be an end organ of schistosomiasis morbidity manifestation (2,39,40). We found strong associations between *S. haematobium* infection and respiratory morbidity among PSAC. *S. haematobium* infected children had wheezes and crackles in the chest on auscultation, with a 35-fold higher odds of respiratory morbidity. Acute schistosomiasis is known to present as shortness of breath, wheezing, and a dry cough and is said to happen in *Schistosoma* naïve travellers (41) Similar findings in children from an endemic area suggest comparable immunological naivety. Chest X-rays of people with pulmonary schistosomiasis show a milliary mottling resembling milliary tuberculosis or midzone infiltrates and condensed basilar zones (28). In areas like Zimbabwe, where schistosomiasis is endemic, TB is also prevalent making a diagnosis of pulmonary schistosomiasis difficult as clinicians are more likely to diagnose TB than neglected tropical diseases (28). In our study TB was an exclusion criterion. Our finding makes it crucial for clinicians and policymakers to be alerted, as this has the capacity of reducing under-fives morbidity vastly thus improving their quality of life.

S.haematobium is not previously correlated to abdominal morbidity, in our study we found an attributable fraction of 91.5 % with a PR of 11.8 to ascites in schistosomiasis positive PSAC. The odds ratio of the positive children presenting with abdominal distension and ascites was noted to be 21.9 (95% CI 10.9 to 44) with a p-value of <0.001) For the first time we have demonstrated ascites in *S. haematobium* infected children without *S.mansoni* or geohelminths as co-infections, or any other possible causes of ascites after a thorough work up. Furthermore, the children were treated by a

single dose of praziquantel (at 20mg/kg) and on follow-up the ascites had resolved without any further intervention. The infected individuals started with what appeared like a pot belly as in Figure 6. Further follow up with an ultrasound scan would be beneficial and further bio-chemical evaluation of the ascitic fluid would be very valuable.

Contrary to previous reports of an inverse relationship between schistosomiasis and atopy, infected children had a 6-fold higher odds of presenting with atopy (6,42,43). It has been reported that schistosomiasis in PSAC is usually at low intensities and this might explain why we had a positive relation (5). Further immunological studies are necessary to understand the higher odds ratio we reported.

Our study provided additional evidence of the relationship between schistosomiasis and haematuria (7,16,18,20,34). The observed haematuria is secondary to eggs being lodged in the bladder wall. However, due to low intensity of infection in the PSAC, macrohematuria is not often detected by the caregiver that makes the health seeking habits due to *S. haematobium* in this age group very poor (34). We recommend that caregivers and medical professions in endemic areas be made aware of the other signs and symptoms to look out for in infected PSAC, in-order to avoid this bias.

Nutritional status has been shown to be affected by *S. haematobium* status in PSAC and even in SAC. The process starts in the womb during pregnancy, infected mothers expose their foetuses to chronic inflammation which may result in low birth weight babies (13). After birth the baby is still exposed to inflammatory markers and once the baby can sit they become exposed to contaminated water when the caregiver takes them to a water source whilst doing house chores (13,27). Chronic exposure to inflammatory markers has been associated with malnutrition (44). In this study we report that malnutrition and stunting had the lowest attributable factors even though they are the most frequently described in association with schistosomiasis morbidity (1,5,8,15,22,27,42).

The strength of this study included the fact that although the calculated sample size was 368, we managed to enrol 416 participants. We were also able to exclude other major endemic conditions from the area, increasing the likelihood that the morbidities were due to *S. haematobium*. While there is a small chance that some excluded conditions were actually false negatives, we followed study protocol, repeating all tests at least twice. Another limitation is that we only excluded the main known endemic conditions in the area, and there is a chance that some participants had other infection altogether. This is unlikely as the white cell count and C-reactive proteins in all *S.haematobium* negative enrolled participants were within the normal ranges.

Conclusion

To achieve the 2025 goal of eliminating schistosomiasis, there is an urgent need for early schistosomiasis diagnosis. The morbidity markers described in this paper can be used to increase the index of *S. haematobium* suspicion in PSAC within endemic areas. In this study it was found that *S. haematobium* in PSAC contrary to popular belief does not only affect the genitourinary system. For the first time it was noted that it also affects the respiratory, gastrointestinal and lymphatic system. An interesting relationship was noted between Schistosomiasis and atopy. It is important that clinicians in schistosomiasis endemic areas be alerted of these morbidity markers of *S. haematobium* in order to increase indices suspicion for schistosomiasis in pre-school age children.

Data Availability

The statistical data on the parasitology and clinical scores used to support the findings of this study are available from the corresponding author upon request.

Conflict of Interest

The authors declare that there is no conflict of interest.

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Author Contributions

TLMJ, FM TN and TM conceived and designed the study. TLMJ, LJ, MK, EC, HM, AV, SR, ENS, , KM, FM, TN and TM performed the clinical examination or parasitology and the data analysis. TLMJ wrote the first draft and all authors contributed to the manuscript and revised the final version**.**

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Table 1: Distribution of clinical morbidities in pre-school aged children(1-5 years old).

Clinical Features		**Schistosomiasis Infection (eggs in urine) Status**		**Totals % (n)**
		Infected	Not infected	
Haematuria	Positive	24	12	9% (36)
	Negative	122	258	91% (380)
Inguinal lymphadenopathy	Present	95	54	36% (149)
	Absent	52	215	64% (267)
Ascites	Present	71	10	19% (81)
	Absent	76	259	81% (335)
Sounds in the chest	wheezes	72	7	19% (79)
	Clear	75	262	81% (337)
Respiratory rate	Shortness of breath	22	24	11% (46)
	Normal	125	245	89% (370)
Atopy History	Yes	15	5	5% (20)

	No	132	264	95% (396)
Malnutrition (weight and height for age chats)	Yes	17	17	8% (34)
	No	123	259	92% (382)
Malnutrition (MUAC)	Yes	5	4	2% (9)
	No	174	233	98% (407)
Stunting	Yes	38	37	18% (75)
	No	71	270	82% (341)

***Significant at 5% level of significance (p=<0.05)**

Table 2: Adjusted Odds Ratio of clinical features associated with S. haematobium morbidity

Clinical features	**Adjusted odds ratio (AOR)**	**95% Confidence Interval**
Haematuria	21.8*	(11.7- 40.7)
Inguinal lymphadenopathy	4.63*	(2.21-5.96)
Ascites	23.9*	(11.4-54)
Wheezes and crackles	35.4*	(15.3- 94.2)
Tachypnoea with Shortness of breath	1.72*	(0.87-3.35)
Atopy History	5.6*	(1.85-20.2)
Malnutrition (weight and height for age chats)	1.8*	(1.3-3.2)
Malnutrition (MUAC)	2.3*	(1.4-3.2)
Stunting	1.9*	(1.1-2.7)

***Significant at 5% level of significance (p=<0.05)**

Table 3: Morbidity Attributable to *S. haematobium* infection

Morbidity	Diagnostic Method	PR (95%CI)	Attributable Fraction (Infected)95%CI
Inguinal lymphadenopathy	Palpation in the lymph nodes area	3.16 (2.34-4.56)	68.4 (65.9-70.2)
Haematuria	Urine dipsticks	12.6 (11.4-14.1)	92.6 (90.5-95.3)
Distended Abdomen with shifting dullness (ascites)	Gastrointestinal system clinical examination	11.8 (9.23-13.2)	91.5 (88.5-94.9)

Wheezes and crackles	Respiratory system clinical examination	16.4 (13.5-20)	93.9 (90.1-96.2)
Tachypnoea with shortness of breath	Observation and respiratory rate	1.56 (1.02-3.11)	35.9 (31.2-36.8)
Atopy History	Questionnaire	4.32 (3.67-6.89)	76.9 (75.2-78.5)
Malnutrition (MUAC)	MUAC tape	1.2 (0.7-1.9)	20 (10-40)
Malnutrition (WHZ)	Weight for height WHO child growth charts	1.0 (0.8-1.4)	5 (0.0-40)
Stunting	Height for age from WHO child growth charts	1,7 (1.1-2.7)	38.2 (16.7-61)

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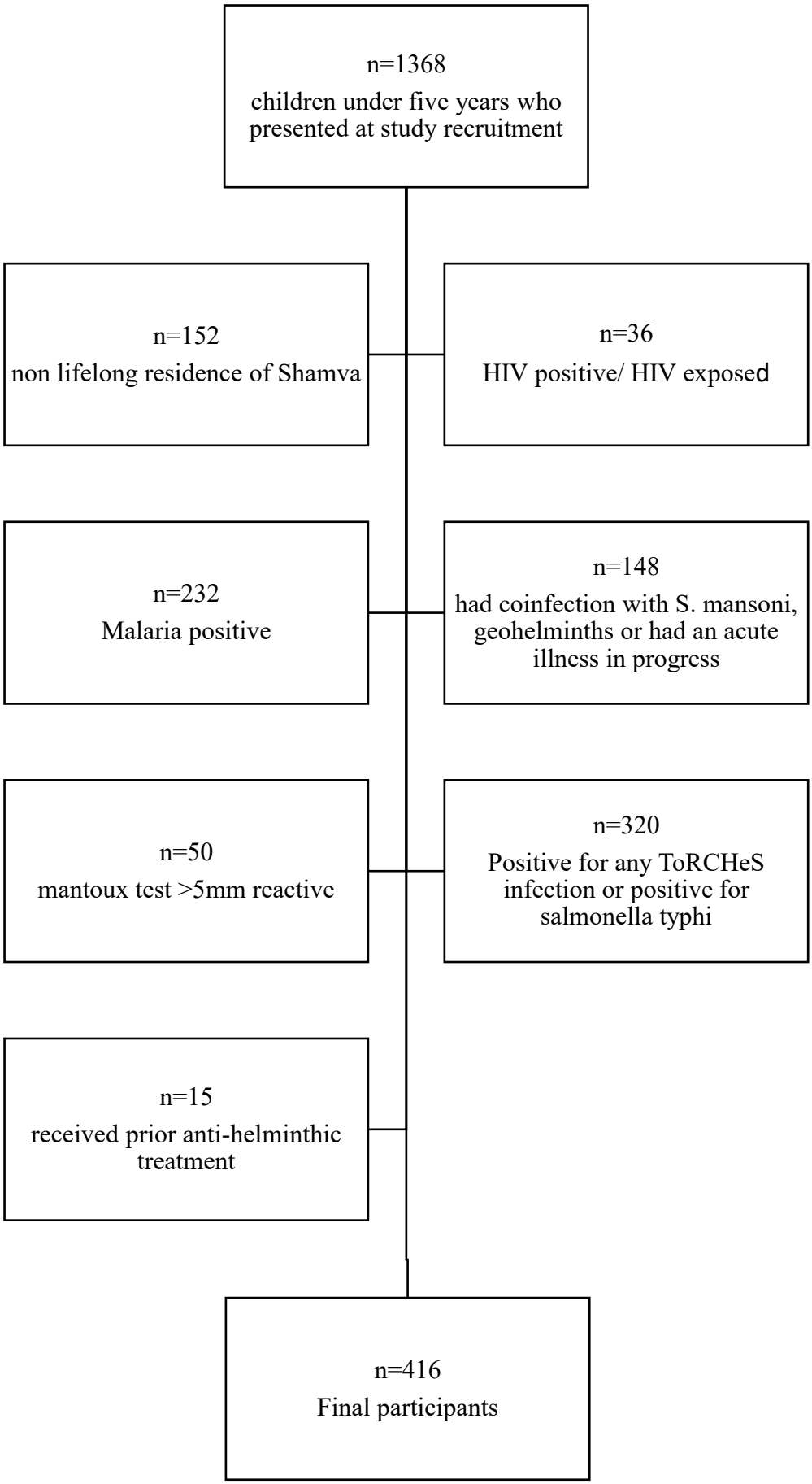


Figure 1: Flow diagram showing the selection steps of the study population and the exclusion criteria

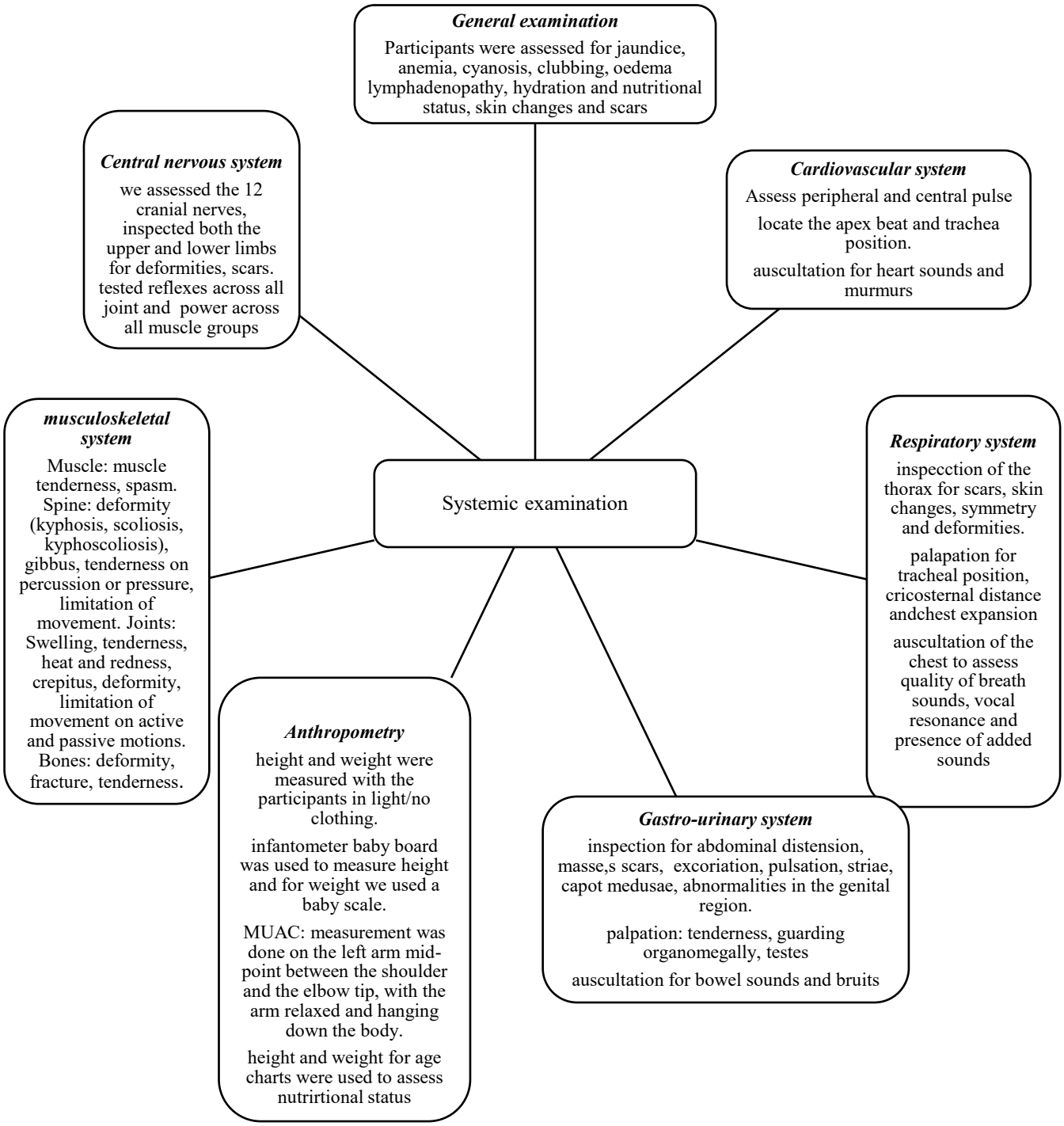


Figure 2: Showing the methodology protocol used for the systematic examinations conducted by the 3 clinical members independent of each other and without the knowledge of parasitology diagnostic outcome by urine filtration for *S. haematobium* ova.

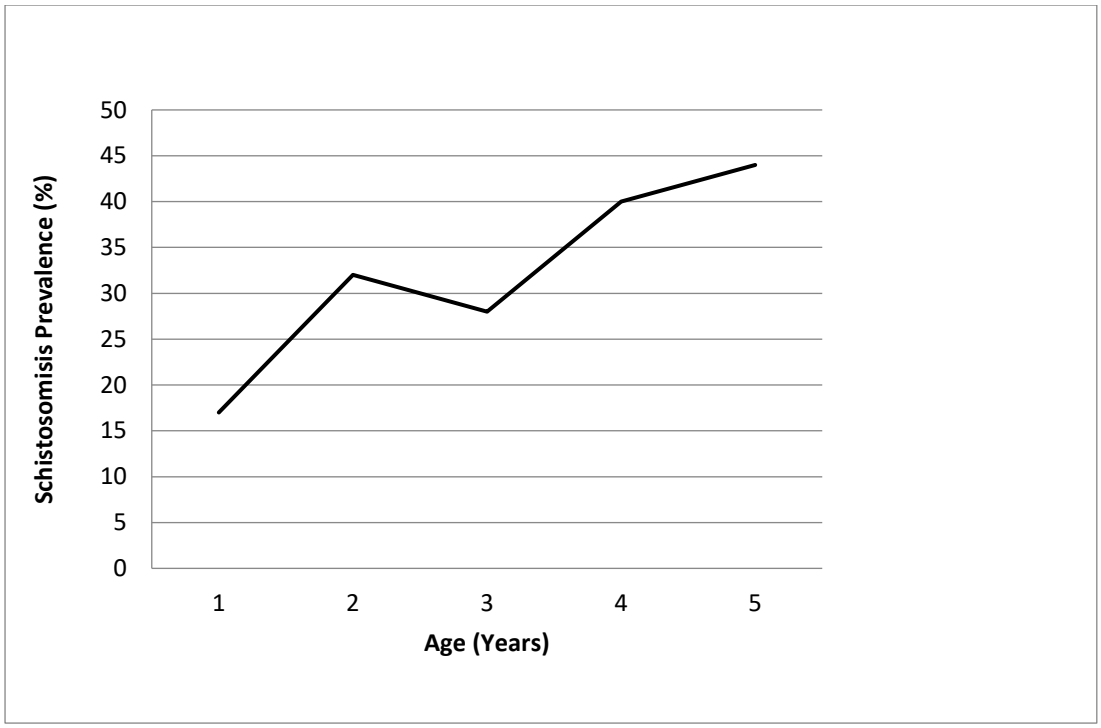


Figure 3: Schistosomiasis prevalence pattern according to the age of the child.

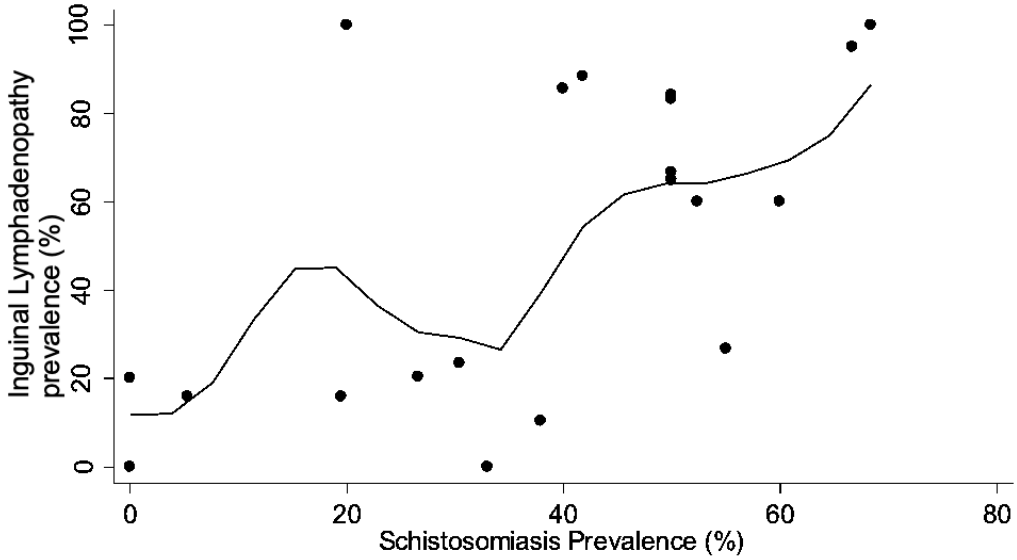
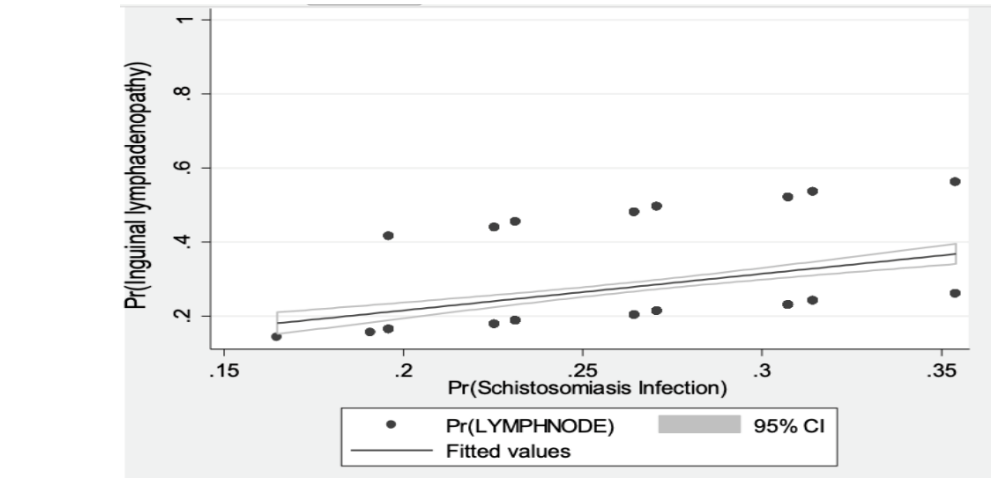


Figure 4: The association between schistosomiasis prevalence and inguinal lymphadenopathy prevalence observed at each area (site)



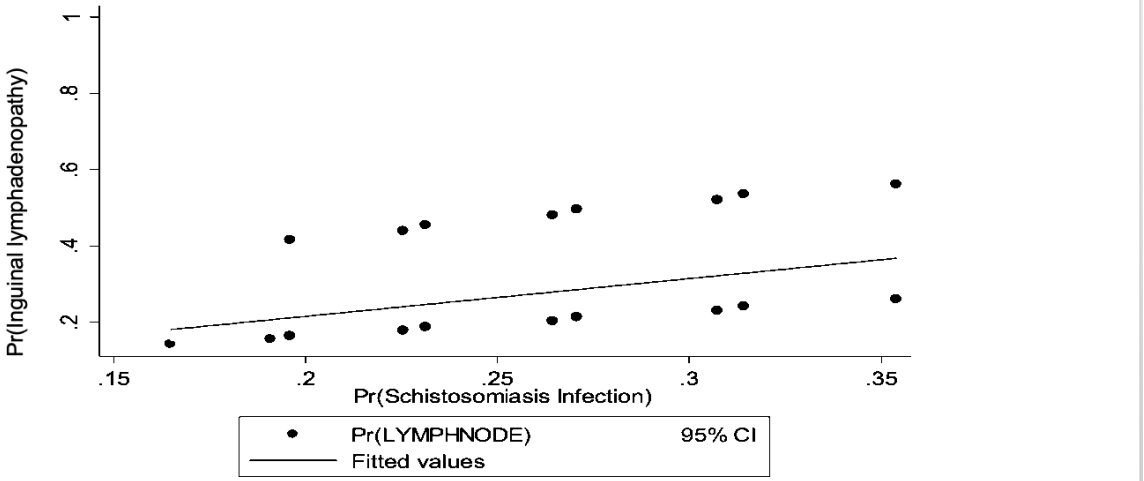


Figure 5: Probability(Pr) of Schistosomiasis Infection and inguinal lymphadenopathy Development

603 Figure 6: A 4 year old child with *S. haematobium* infection with no *S.mansoni* infestation.

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