

Association of *Schistosoma haematobium* Infection Morbidity and Severity on Co-infections status in Pre-school Age Children Living in a Rural Endemic Area in Zimbabwe

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Abstract

Background: Individuals living in *Schistosoma haematobium* endemic areas are often at risk of having other communicable diseases, simultaneously. This usually creates diagnostic difficulties leading to misdiagnosis and overlooking schistosomiasis infection. In this study we investigated the prevalence and effects of coinfections in pre-school age children and further investigated association between *S. haematobium* prevalence and under 5 mortality.

Methods: Four hundred and sixty five Preschool age children (1-5 years old) with 51% being male were clinically examined for the following top morbidity causing conditions: respiratory tract infections, dermatophytosis, malaria and fever of unknown origin. The conditions were diagnosed as per approved WHO standards. *S. haematobium* infection was diagnosed by urine filtration and the children were screened for conditions common in the study area which included HIV, tuberculosis, malnutrition and typhoid.

Results: Prevalence of *S. haematobium* was 35% (145). The clinical conditions assessed had the following prevalence in the study population: upper respiratory tract infection 40% (229), fever of unknown origin 45% (189), dermatophytosis and malaria both had 18% (75), The odds of co-infections observed with *S. haematobium* infection were: upper respiratory tract infection AOR = 1.22 (95% CI 0.80 to 1.87), dermatophytosis AOR = 4.79 (95% CI 2.78 to 8.25), fever of unknown origin AOR = 10.63 (95% CI 6.48-17.45) and malaria AOR = 0.91 (95% CI 0.51 to 1.58). Relative risks of the severe sequels when coinfecting were: Severe pneumonia RR=7.5 (95% CI 2.92-19.23), $p < 0.0001$, complicated malaria RR=12 (95% CI 11.53-94.53), $p = 0.02$, severe dermatophytosis RR=8.5 (95% CI 1.2-60.2): $p = 0.03$, and fever of unknown origin RR=2.32 (95% CI 1.12-4.80), $p = 0.02$.

Conclusion: This study is novel as it identifies a possible association relationship between *S. haematobium* infection and top morbidity conditions in children under five years. There is need to alert policy makers so as to initiate early treatment of schistosomiasis in pre-school age children.

Background

Human schistosomiasis is a parasitic disease caused by blood flukes called trematode worms of the genus *Schistosoma*, predominantly affecting people in low- and middle-income countries (1). An estimated 206.4 million people in 78 countries required treatment for schistosomiasis in 2016 (2,3). In sub-Saharan Africa alone, about 52 endemic countries reported moderate to high prevalence (4). Individuals living in schistosomiasis-endemic areas are often at risk to several pathogens simultaneously (5). These coinfections could arise due to chance because of host susceptibility or co-circulation of various disease agents (6). Alternatively, schistosomiasis may increase or decrease the risk for another infection (7). Studies on co-infection in adults have shown that schistosomiasis co-infection hinders diagnosis and treatment of other communicable diseases (8,10). To date, however, little focus has been given to pre-school age children (PSAC), who were regarded as a low risk group. However, recent studies

suggest that they may have similar risk to adults (11). The prevalence and relationship of schistosomiasis to co-infections in PSAC has not yet been described.

The World Health Organization (WHO) Sustainable Developmental Goal (SDG) 3 aims to reduce under-5 mortality to at least as low as 25 per 1,000 live births in every country by 2030 (4). In Zimbabwe, the top causes of morbidity and mortality in PSAC include acute respiratory tract infections (ARI), malaria, diarrhoea, fever and skin diseases (12,13). In this study we investigated the prevalence and extent of morbidity associated with *S. haematobium* coinfections in children under the age of five years in an endemic district of Zimbabwe. Furthermore we investigated the relationship between the selected conditions severe sequel and under-5 mortality rate.

Methods

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 (14). Shamva has the highest prevalence of schistosomiasis in Zimbabwe at 62.3% (15). It lies 945 m above sea level, the climate is warm and temperamental 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 the main source of alluvial gold which the vast majority of population survives through panning (14). The study was a community cross-sectional survey, children were recruited from 19 different villages in Shamva district gathering at expanded program of immunisation (EPI) centers and Shamva district rural health centres.

Study inclusion criteria

Participants recruited into the study were residents of the Shamva district in Zimbabwe. The PSAC were aged between 1 to 5 years 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. Be negative for the ToRCHeS (toxoplasmosis, rubella, cytomegalovirus, hepatitis and syphilis) screen 6. Be HIV negative and have no exposure to HIV 8. Have a widal TO ratio <1:160 9. Mantoux test reaction <5mm, and 10. Have a normal nutrition status based on clinical examination, mid upper arm circumference measurement and weight-for-age as well as height-for-age measurements.

Sample size

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

$$n = z^2 pq / e^2$$

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 ($d = 0.05$)

$n = 363$

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. Written informed consent was obtained from the parents or guardians of the children. All participants with confirmed infections were offered treatment.

Data collection

A questionnaire was administered to the caregivers/parents and medical records assessed for those who were admitted. The coinfections were selected from top morbidity causes in children under-five years old in Zimbabwe (12). Information was extracted from the demographic and health survey, Zimbabwe and Zimbabwe provincial and district census statistics (13,14,16 - 22). The data captured on under-5 mortality was then compared with the prevalence of the top mortality conditions in children which included HIV, malaria, diarrhea and schistosomiasis (23,24).

Clinical examinations

The clinical examinations were conducted at the nearest health facilities and at EPI allocated facilities on PSAC ($n = 415$) by **two** medical practitioners independent of each other according to a protocol (Figure 1).

***S. haematobium* infection diagnosis**

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 as follows:

Haematuria check

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.

Parasitology examination

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, as previously described (25). The number of eggs were reported per 10ml of urine. The parasitology team recorded the results separately, not accessed by the clinical team.

Blood processing and analysis

Plasma and sera were obtained from blood collected in well-labeled EDTA and plain blood tubes, respectively. Serum and plasma obtained from each child were processed and tested for Toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus 1 and 2, HIV, typhoid 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.

Co-infections diagnosis

Upper respiratory tract infection (URTI)

URTI was diagnosed on clinical signs and symptoms after excluding allergy and influenza and as per IMCI guidelines (26–29).

- Severe pneumonia was defined as per WHO guidelines (30,31).

Fever of unknown origin (FUO)

FUO was defined as children who within the past six months had been admitted with a temperature of 38.5°C and no other diagnosis found after blood, urine and stool cultures as represented from their medical records (32).

- Seizures were described as change in movement, attention or loss of consciousness in a child diagnosed with FUO, with no family history of febrile seizures (33).

Malaria

Parasitology examination

A few drops of anticoagulated participants blood specimen with EDTA were used for parasite identification and count. Briefly, about two drops of the blood sample were collected on glass slide for preparation of thin and thick blood smears in duplicate. The smears were stained with 10% Geimsa working solution for 10mins, thin smears were fixed in 100% methanol before geimsa staining. Malarial parasites were identified under a microscope and parasite load was calculated after counting asexual parasites per 200 white blood cells using the formula assuming that the mean WBC in children 1-5 years old is 11 000/ μ L (34):

Parasite count/ μ L= number of observed asexual parasite x 11000 WCC/ μ L all divided by 200 WCC (35).

Complicated malaria was described as per WHO guideline for severe malaria: hyperparasitemia (parasite load > 100,000 parasites/ μ L), persistent vomiting, respiratory distress, convulsion (more than two in 24 hours), posturing, comma, discoloration of urine, unable to walk, sit, and stand or unable to feed and drink in infants, hyperpyrexia and hypoglycemia (31,36)

Dermatophytosis

Skin scraps were collected from individuals with signs of dermatophytosis, examined on a warmed potassium hydroxide treated slide for microscopy (37).

- Severe dermatophytosis was described as ringworms covering greater than 20% surface area using the paediatric burns chart (38).

Statistical method

Initial analysis was to determine a relationship between the top clinical conditions which paediatrics presented with at health facilities and their *S. haematobium* infection status. This was performed using STATA version 15. The statistical methods applied was descriptive statistics providing the risk and odds ratios. Secondly multinomial regression analysis was done adjusted for sex, age and *S. haematobium* infection. Results were reported as adjusted odds ratios (AORs) and risk ratios (RR) with 95% confidence interval (CI), along with the test for significance, as previously described (39).

Secondly a relationship was determined of being *S. haematobium* infected and the clinical conditions advancing to severe sequels, this was done by multinomial regression analysis which gave adjusted odds ratio. Relative risk ratio was calculated by dividing the cumulative incidence in *S. haematobium* infected group by the cumulative incidence in the uninfected group. 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

Screening involved 465 PSAC, aged one to five years from the Shamva district, 415 who met the eligibility criteria and consented to be part of the study (Figure 2). The sex ratio was equal and the mean age was 3.39 years. Those with malaria had *P. falciparum* as the parasite.

Infection prevalence in the study population

The prevalence of *S. haematobium* was 35.1% (145) by urine filtration. While among study participants, 40% (229) presented with a URTI, 45% (188) with FUO and 18% (75) with dermatophytosis and 18% with malaria (Table 1). The prevalence of co-infections with *S. haematobium* was: URTI 35% (80), malaria 33.3% (25), FUO 55% (91) and dermatophytosis 67% (50).

Regression analysis of the co-infections

In univariate analysis, the following associations with schistosomiasis infection had significant odds ratio (OR): URTI OR = 1.98 (95% CI 1.657 to 2.48), dermatophytosis OR = 5.10 (95% CI 2.99 to 8.72) and FUO OR = 9.07 (95% CI 5.70 to 14.44)(Table 2). In multivariable analysis, after adjusting for age, sex and infection status, the following were independently associated adjusted odds ratio (AOR): dermatophytosis AOR = 4.79 (95% CI 2.78 to 8.25) and FUO AOR = 10.63 (95% CI 6.48 to 17.45).

Association between under-5 mortality rate and schistosomiasis in Zimbabwe

We demonstrated a positive relationship between *S. haematobium* infection with child mortality and under-5 mortality in Zimbabwean Provinces (Figure 2). Provinces with an increased schistosomiasis prevalence (Manicaland, Mashonaland East, West and Central) all showed an increased under-five and child mortality rate. Whereas Matebeleland North and Bulawayo had both a decrease in *S. haematobium* infection prevalence and mortality ratios.

Severity of morbidity associated with co-infections

PSAC with schistosomiasis and URTI had an eight-fold higher odds of pneumonia than children with URTI alone AOR = 7.90 (95% CI 2.76 to 27.5), $p = 0.008$ (Table 2). Children with schistosomiasis and malaria had a 7-times greater odds of complicated malaria AOR = 7.09 (95% CI 1.51 to 33.39), $p = 0.005$. Children with dermatophytosis had a 20-fold higher odds of severe dermatophytosis AOR = 20.3 (95% CI 4.78 to 83.2; $p < 0.001$) compared with children who did not have schistosomiasis. Among children with FUO, those who also had schistosomiasis coinfection had twice the chance of seizures AOR = 1.62 (95% CI 1.56 to 4.73).

Relative risk of acquiring pneumonia after an acute respiratory infection was RR = 7.5 (95%CI 2.92-19.23), $P < 0.0001$ in children with *S. haematobium* co-infection; Severe and persistent dermatophytosis on *S. haematobium* coinfection was RR = 8.5 (95%CI 1.2-60.27), $p = 0.03$; seizures following FUO diagnosis was RR = 2.32 (95%CI 1.12-4.80), $P = 0.02$ and relative risk for malaria advancing into complicated malaria on *S. haematobium* infection was RR = 12 (95%CI 11.53-94.53), $p = 0.02$ (Figure 2).

Discussion

Children growing up in resource limited rural areas have high exposure to schistosomiasis infection and a high likelihood of associated coinfections with diseases prevalent in poor communities. Considering URTI, dermatophytosis and FUO; a strong positive association between schistosomiasis and URTI; dermatophytosis and FUO were observed. The trends revealed an association between schistosomiasis and under-5 mortality rate from the national data provided by the Ministry of Health in Zimbabwe. There was a negative association between schistosomiasis and malaria, though participants with the two as co-infections had a greater likelihood of presenting with complicated malaria. Similarly, participants with URTI, FUO and dermatophytosis as coinfections had a higher likelihood of having severe sequelae of the diseases.

A positive association on comparing schistosomiasis prevalence with under-5 and child mortality rate in the district mirrored the trends in different provinces of Zimbabwe was demonstrated. The provinces that had a high schistosomiasis rate also had high mortality rate (12,13). This made us wonder if schistosomiasis co-infections were possibly worsening the disease courses as we also found that in co-infections there was a greater chance of the disease course turning out to be severe (12). It is necessary to explore the effects of schistosomiasis and other diseases co-infections in all the top morbidity and mortality causes in PSAC. Early schistosomiasis treatment in PSAC has the potential to lower the under-five mortality rate, by reducing the incidence of severe sequelae of the top morbidity conditions in this age group which are also top causes for mortality in this age group. This should be shared with policy makers in low and middle income countries.

Children infected with *S. haematobium* had a 20-fold higher odds of severe dermatophytosis, after adjusting for other clinical conditions. *S. haematobium* infection had a 38% increased risk of getting dermatophytosis. There is no previous documentation between *S. haematobium* and dermatophytosis. In literature, extensive dermatophytosis was noted in a case report involving *S. mansoni* (40). It is postulated that *S. mansoni* exacerbated dermatophytosis by lowering immunity due to the liver involvement or by suppression of the T-helper 1 system which is involved in suppressing fungal infections (41,42). Dermatophytosis cause great morbidity in PSAC in Zimbabwe (13). Since it is a skin condition, it is associated with psychological trauma via discrimination in its severe form. It is necessary to notify clinicians in schistosomiasis endemic areas of this finding in-order to decrease the morbidity rate associated with dermatophytosis. Further studies on this association and immunological profiling is recommended.

Children with schistosomiasis had risk reduction associated with malarial plasmodium coinfection. It is documented that malaria infection is exacerbated/ameliorated by schistosomiasis co-infection (19 - 21). The enhanced T-helper 1 system and an increase in anti-interferon-gamma antibody causes a protective effect against the malarial parasite (46). Of note is; though schistosomiasis was demonstrated to have a protective effect with malaria in the event of co-infection malaria infection had 7-fold chance of exacerbating to complicated malaria requiring hospital admission in these PSAC. This makes it crucial for PSAC to be included in national schistosomiasis control programs, as there is capacity of improving the morbidity and mortality rate in children under the age of five. However, the dilemma in PSAC infections and diseases require urgent attention, as this is the age of growth and development during which the immune system is developing. Further studies are required to understand co-infection in PSAC inclusive of malaria infection outcome.

There was a 10-fold chance of finding FUO and schistosomiasis as a coinfection, children with schistosomiasis had 138% risk of FUO. Despite advances in medicine, the proportion of patients discharged with undiagnosed FUO after systematic examination has not improved (47). The cause of febrile illness is not identified in approximately 9 - 51% of patients, this is even higher in resource limited areas endemic for childhood illnesses (48). Of the children who had FOU and schistosomiasis there was a 2-folded chance of them having serious sequelae such as seizures. Most clinician tend to think of other

conditions in contrast to neglected tropical diseases when a patient presents with a fever (31). It might be necessary to make it a priority to screen for schistosomiasis when a child from an endemic area presents with a fever. However further immunological investigations are necessary in-order to find if the fever is due to schistosomiasis infection itself or exacerbation of a co-infection, during the early immunological responses to diseases manifestation.

In our study the odds of having URTI was 2% higher in schistosomiasis infected children with a 1% increased risk of *S. haematobium* infected children acquiring a URTI. Furthermore, in the coinfecting cohort odds of ending up with severe pneumonia was 7-fold compared to schistosomiasis negative population. This is a very significant finding as ARIs are the leading cause of morbidity and mortality in children under the age of five in Zimbabwe (13). Thus tackling schistosomiasis crisis in this age group will have enormous contribution in reducing the mortality and morbidity rate.

The strength of this study included that although the calculated sample was 363, we managed to enrol 415 participants. We focused on the major morbidity and mortality causes in this age group from our study area which also fit into most of the low income countries where schistosomiasis is endemic. The main limitation of this study is there is a possibility that the children may have had more than two infections as co-infections which might make our data biased, however we did thorough clinical examinations and laboratory tests in all the participants to rule this out. We also considered socioeconomic status as a confounding factor by focusing on children with a similar background and in the same villages with similar lifestyles.

Conclusion

This study is novel as it demonstrates an association between schistosomiasis and top morbidity conditions in a schistosomiasis endemic area namely: URTI, dermatophytosis, malaria and FUO in PSAC living in a schistosomiasis endemic district. Furthermore, we demonstrated a detrimental effect where coinfection led to severe sequelae of these clinical conditions. The clinical conditions described in this paper have a high impact on morbidity and mortality in children under the age of five. This brings out the importance of including PSAC in national schistosomiasis control programs. It is of paramount importance that clinician and policy makers in endemic areas are alerted of these associations in order to reach the WHO sustainable developmental goal (SDG) 3 by 2030.

Abbreviations

AOR – adjusted odds ratios

ARI – Acute respiratory tract infection

CI – confidence interval

EPI – expanded program on immunization

FUO – fever of unknown origin

HIV – Human Immunodeficiency Virus

MRCZ – Medical Research Council of Zimbabwe

PSAC – Preschool age children

RR – risk ratio/relative risk

SDG – Sustainable Development Goals

ToRCHeS – toxoplasmosis, rubella, cytomegalovirus, hepatitis and syphilis

URTI – upper respiratory tract infection

WBC – white blood cells

WCC – white cell counts

WHO - World Health Organization

Declarations

Ethics approval and consent to participate

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. Written informed consent was obtained from the parents or guardians of the children.

Consent for Publication

None required

Availability of data and material

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.

Competing interests

The authors declare that there is no conflict of interest.

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Authors' contributions

TLMJ, TN, FM and TM conceived and designed the study. TLMJ, HM, AV, MK, EC, SR, ES, LJ 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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Tables

Table 1: Clinical conditions among children aged 1-5 years in a schistosomiasis-endemic district of Zimbabwe

Clinical Conditions		Schistosomiasis infection Status		Total prevalence of the condition in the study population
		negative	positive	
Upper Respiratory Tract Infection (URI)	Negative	121	66	40%
	positive	149	80	
Matophtytosis	Negative	244	96	18%
	Positive	25	50	
Fever of Unknown Origin (FUO)	Negative	172	55	45%
	Positive	97	91	
Malaria	Negative	220	121	18%
	Positive	50	25	

Table 2: Crude and adjusted odds ratio of the association between Schistosomiasis infection and other clinical conditions.

Other Clinical Conditions	Crude Odds Ratio	Adjusted Odds Ratio	Risk ratio
Upper Respiratory Tract Infection	1.98* (1.66-2.48)	1.22 (0.80-1.87)	1.01 (0.84-1.2)
Matophtytosis	5.10 *(2.99-8.716)	4.79* (2.78-8.252)	1.38*(1.22-1.56)
Fever of Unknown origin	9.07 *(5.70-14.44)	10.63* (6.48-17.45)	2.38* (1.90-2.983)
Malaria	0.91 (0.54-1.54)	0.91(95% CI 0.51 to 1.58)	0.98 (0.90-1.08)

*significant at 5% level of significance

Table 3: Odds ratio of having severe sequelae from co-infections with schistosomiasis in PSAC from an endemic district.

Co-infected with schistosomiasis	Sequelae experienced	AOR	95% Confidence interval
Upper Respiratory Tract Infections	Severe Pneumonia	8.41*	3.09 to 22.93
Malaria	Severe malaria	7.09*	1.51 to 33.39
Dermatophytosis	Severe dermatophytosis	20.3*	4.78 to 83.2
Fever of Unknown Origin	Seizures	1.62*	1.56 to 4.73

***significant at 5% level of significance**

Figures

<p style="text-align: center;">General examination</p> <p>Participants were assessed for jaundice, anemia, cyanosis, clubbing, oedema lymphadenopathy, hydration and nutritional status, skin changes and scars</p>	<p style="text-align: center;">Cardiovascular system</p> <p>Assess peripheral and central pulse locate the apex beat and trachea position. auscultation for heart sounds and murmurs</p>
<p style="text-align: center;">Respiratory system</p> <p>inspection of the thorax for scars, skin changes, symmetry and deformities. palpation for tracheal position, cricosternal distance and chest expansion auscultation of the chest to assess quality of breath sounds, vocal resonance and presence of added sounds</p>	<p style="text-align: center;">Gastro-urinary system</p> <p>inspection for abdominal distension, masses, scars, excoriation, pulsation, striae, caput medusae, abnormalities in the genital region. palpation: tenderness, guarding organomegally, testes auscultation for bowel sounds and bruits</p>
<p style="text-align: center;">Anthropometry</p> <p>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. 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 were used to assess nutritional status</p>	<p style="text-align: center;">musculoskeletal system</p> <p>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.</p>
<p style="text-align: center;">Developmental assessment</p> <p>we used the childhood developmental charts from UNICEF to measure gross motor, fine motor, language and social development</p>	<p style="text-align: center;">Central nervous system</p> <p>we assessed the 12 cranial nerves, inspected both the upper and lower limbs for deformities, scars. tested reflexes across all joint and power across all muscle groups</p>

Figure 1

Clinical examinations protocol listing the details of physical examinations conducted on each participant as adopted from standard clinical practices (49,50).

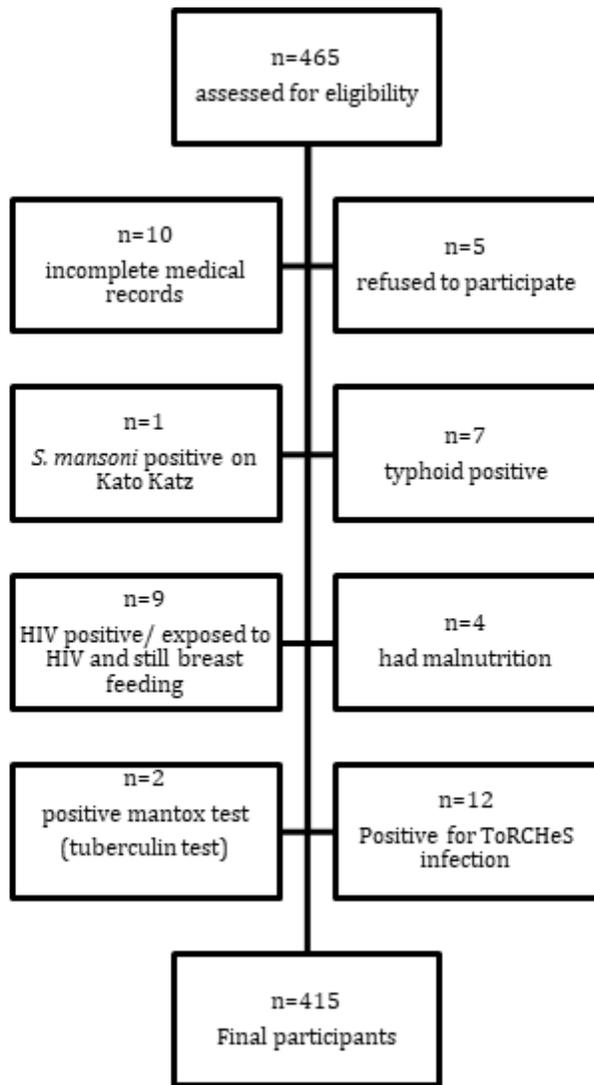


Figure 2

Screening profile showing the participants who were excluded from the study and the type of conditions they had at time of recruitment.

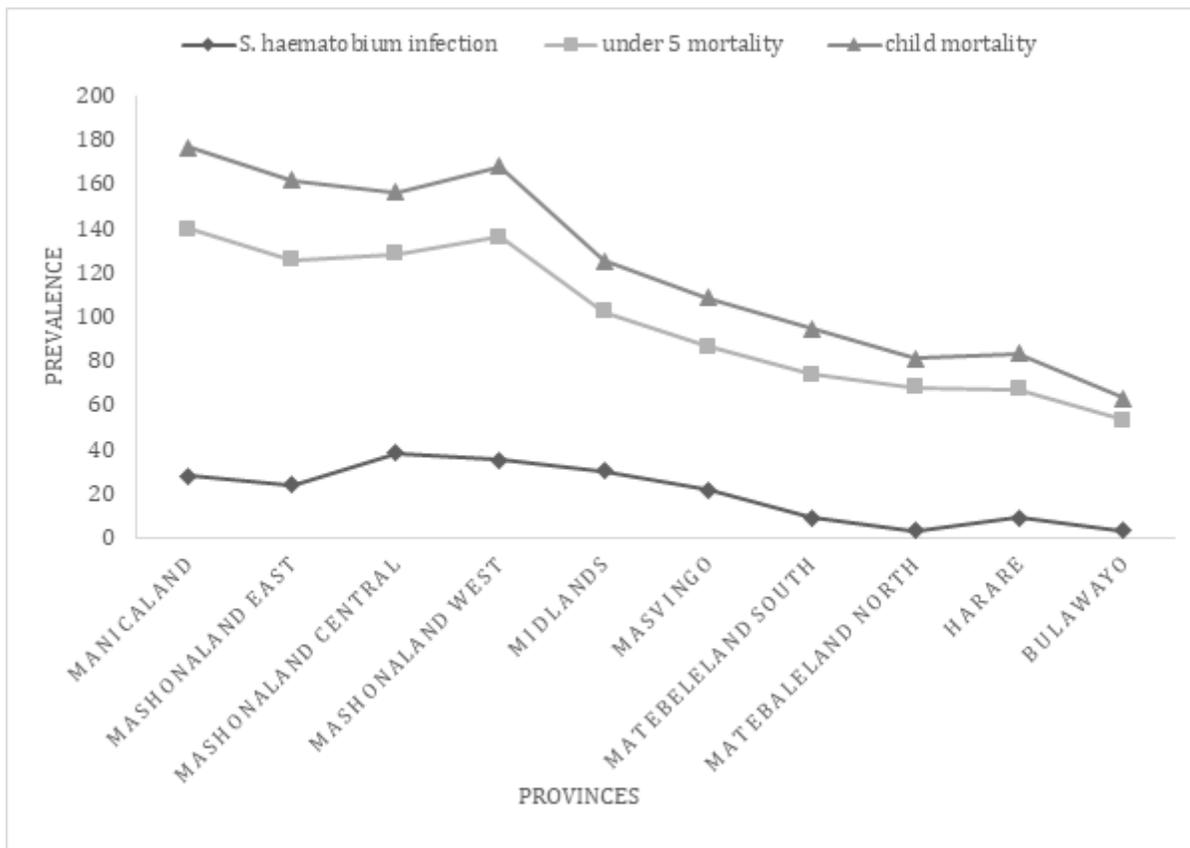


Figure 3

Trends showing schistosomiasis prevalence in comparison to child and under 5 mortality per 1000 live births from Zimbabwe provinces. The data was extracted from the national demographic and health survey, Zimbabwe and Zimbabwe provincial and district census statistics (13,14,16 - 22).