Association of *S. 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 *S. 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.

Methodology : About 465 Preschool age children were clinically examined for the following top morbidity conditions: respiratory tract infections, dermatophytosis, malaria and fever of unknown origin. *S. haematobium* infection was diagnosed by urine filtration and the children were screened for other communicable infections common in rural areas.

Results : Prevalence of *S. haematobium* was 35% (145). A positive relationship between *S. haematobium* prevalence and under-5 mortality rate in Zimbabwean provinces was demonstrated. The odds of co-infections observed for *S. haematobium* were: upper respiratory tract infection AOR = 1.98 (95% CI 1.657 to 2.48), dermatophytosis AOR = 5.10 (95% CI 2.99 to 8.72), fever of unknown origin AOR = 9.07 (95% CI 5.70 to 14.44) and malaria AOR = 0.91 (95% CI 0.54 to 1.54). The risk ratio of having *S. haematobium* and co-infections in children who had fever of unknown origin 138%, dermatophytosis 38%, Upper respiratory tract infection 1% increase risk and malaria had a 2% reduced risk. Odds of having severe sequelae following the above conditions were: severe pneumonia AOR = 8.41(95%CI 3.09-22.93), complicated malaria AOR = 7.09 (95% CI 1.51-33.39), severe and persistent dermatophytosis AOR=20.3 (95% CI 4.78-83.2) and seizures AOR=1.62 (95%CI 1.56-4.73).

Conclusion : This study is novel as it identifies a possible causal 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.

Introduction

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.

Methodology

Study site and design

The study was conducted in Shamva District in Mashonaland Central Province of Zimbabwe, with the highest prevalence of schistosomiasis in Zimbabwe at 62.3%. Children were recruited from 19 different villages in Shamva district and Shamva district hospital. All children were assessed for schistosomiasis, upper respiratory tract infections, dermatophytosis and malaria. Clinical screening was done by experienced clinician and laboratory work was done by experienced laboratory scientist.

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 8. Have a widal TO ratio <1:160 9. Mantoux test reaction <5mm 10. Had a normal nutrition status

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 and medical records assessed for those who were admitted. Information was extracted from the demographic and health survey- Zimbabwe statistics (13). The coinfections were selected from top morbidity causes in children under-five years old in Zimbabwe (12).

Clinical examinations

The clinical examinations were conducted on PSAC (n = 415) by **two** medical practitioners independent of each other according to a protocol (Figure 1)

S. haematobium infection diagnosis

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.

Diagnosis of other infections

Upper Respiratory Tract Infection

URTI was diagnosed on clinical signs and symptoms after excluding allergy and influenza (14–16). Severe pneumonia was defined as per WHO guidelines (17,18).

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 (19). 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 (20).

Malaria

Thick and thin blood film slides were stained using the geimsa stain and examined for malaria parasites using microscopy, as previously described(21). Complicated malaria was described as per WHO guideline for severe malaria (18,22).

Dermatophytosis

Skin scraps were collected from individuals with signs of dermatophytosis, examined on a warmed potassium hydroxide treated slide for microscopy(23). Severe dermatophytosis was described as ringworms covering greater than 20% surface area using the paediatric burns chart (24).

Statistical method

Data analysis was performed using STATA version 15. The statistical methods applied were descriptive statistics providing relative risk and regression analysis for odds ratio. Results were reported as adjusted ORs (AORs) and risk ratios (RR) with 95% confidence interval (CI), along with the test for significance, as previously described (25). 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 of whom met the eligibility criteria and consented to be part of the study. The sex ratio was equal, and the mean age was 3.39 years. Those with malaria had *P. falciparum* as the parasite.

The prevalence of *S. haematobium* was 35.1% (145) While among study participants, 40% (229) presented with a URTI , 45% (188) with FUO and 18% (75) with dermatophytosis and malaria as well (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).

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 urine 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).

We demonstrated a positive relationship between *S. haematobium* infection with child mortality and under-5 mortality in Zimbabwean Provinces (Figure2). 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 3). 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).

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 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* (26). 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 (27,28). 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 (32). 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. 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 agent 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 (33). 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 (34). Of the children who had FUO 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 (18). 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% increases 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 368, 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. 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.

Declarations

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, TN, ES and TM conceived and designed the study. TLMJ, TM, HM, AV, MK, EC and LJ 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
		No	Yes	35.1%
Upper Respiratory Tract Infection (URTI)	Negative	121	66	40%
	positive	149	80	
Dermatophytosis	Negative	244	96	18%
	Positive	25	50	
Fever of Unknown Origin (FOU)	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

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)
Dermatophytosis	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

Figure 1

Clinical examinations protocol

Figure 2

Trends showing schistosomiasis prevalence and under 5 child mortality per 1000 live births from Zimbabwe provinces.