

S. Haematobium Infection and Chemotherapy-Induced Changes in Interleukin-6 and Acute Phase Proteins Associated with Inflammation in School Children in a Schistosomiasis-Endemic Area

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Abstract

Objective: There is an increased risk of cases of direct and indirect morbidities as a result of stimulation of tissue-destructive inflammation caused by *Schistosoma haematobium* infection, hence the need to determine the levels of inflammatory markers in *Schistosoma haematobium* infected children and also determine the effect of repeated annual mass treatment on levels of interleukin-6 and acute phase proteins.

Methodology: Urine specimens from 212 school children were collected and examined to determine prevalence of *Schistosoma haematobium* at baseline and 2 years following annual rounds of praziquantel treatment. Levels of 4 acute phase proteins were measured from serum samples from the participants using the magnetic bead-based immuno-assays at baseline and 2 years following praziquantel treatment. Sandwich enzyme-linked immunosorbent assay was used to determine levels of interleukin-6.

Results: The overall pre-treatment prevalence of *Schistosoma haematobium* infection was 23.1% at baseline and 0.47% after 2 years of annual treatments. *Schistosoma haematobium* infected children had marginally higher levels of procalcitonin and tissue plasminogen activator before treatment though the difference of all three was not significant $p>0.05$ using Mann-Whitney non-parametric U test. Levels of ferritin and fibrinogen were lower in *Schistosoma haematobium* infected children before treatment, however the difference was also not significant $p>0.05$ using Mann-Whitney test. There was no association between infection status or interleukin-6 and the levels acute phase proteins $p>0.05$ for all acute phase proteins using the Mann-Whitney U test.

Discussion and Conclusion: Findings from this study suggest no bearing of *Schistosoma haematobium* infection status on level of acute phase proteins before and after annual treatment with praziquantel. The extent of inflammation cannot be determined using ferritin, tissue plasminogen activator and fibrinogen. Levels of interleukin-6 did not have any bearing on levels of acute phase proteins. There is a need to explore other acute phase proteins as inflammatory markers in *Schistosoma haematobium* infection.

Keywords: *Schistosoma haematobium*; Procalcitonin; Tissue plasminogen activator; Ferritin; Interleukin-6

Abbreviations:

TPA: Tissue Plasminogen Activator;

WHO: World Health Organization;

MDA: Mass Drug Administration;

PZQ: Praziquantel;

APPs: Acute Phase Proteins

Introduction

Schistosomiasis is a water-borne parasitic disease with a global disease burden calculated at 24-56 million disability-adjusted life-years

lost [1]. Chronic inflammation subsequent to infection with *S. mansoni* and *S. japonicum*, and *S. haematobium* appears to be the major source of burden in individuals with schistosomiasis. Subtle morbidities such as anaemia, growth deficiencies, physical fatigue and diminished cognitive development occur as a result of the inflammation [2-6]. There is an increased risk of direct and indirect cases of morbidities as a result of stimulation of tissue-destructive inflammatory and granulomatous reactions from *S. haematobium* infection. In children of school going age infected with *S. haematobium* anaemia associated with chronic inflammation is worsened by blood loss seen as gross and micro haematuria. In addition to this example of direct morbidity, the *Schistosoma*-infected host can be indirectly predisposed to greater susceptibility to other pathogens. For example, there is an increased risk to HIV acquisition in individuals with friable sandy patches that are common in female genital schistosomiasis caused by *S. haematobium* infections [5-7].

In the control of parasitic diseases, immune responses and consequently the inflammatory processes are meant to eliminate the harmful agent and restrict tissue damage but in some situations it may end up triggering pathological repercussions that can also affect injury and illness itself. In some instances inflammation can persevere even after the harmful agent has been eliminated, giving rise to chronic inflammation [8]. It is evident that immune responses and cytokine responses generated during the various stages of the life cycle of the parasite account for most of the morbidities culminating in chronic inflammation against schistosome antigens that are released from eggs trapped in tissues [9,10]. The location and number of eggs lodged in the tissues initially determine the magnitude of inflammation and with time the pathology associated with fibrosis and organ damage [11]. In *S. haematobium* endemic areas, children are exposed to the parasite through water related activities such as swimming and those infected continuously have eggs being deposited in their tissues and consequently the immunopathological reactions against these eggs trapped leads to an increase in acute phase proteins and inflammation. When the agent triggering inflammation occurs repeatedly the acute phase response and may be continuously activated and become chronic as the case in *S. haematobium*-endemic areas where there is constant exposure of worms and egg burden. Immune reactions to *Schistosoma* eggs trapped in the tissues in chronically infected cases ultimately result in inflammation in affected tissues followed by granuloma formation [11].

Praziquantel has become the drug of choice in the treatment of schistosomiasis and it is dispensed through mass drug administration programmes around Africa. The drug is effective against all schistosome species with minimal detrimental effects to the host and it is also effective against other trematode and cestode infections [12]. The mechanism of action is not yet fully understood though there is evidence suggesting that it increases the permeability of schistosome membranes to calcium thereby promoting tegument damage and worm paralysis [13]. The dying parasites are then removed from the host and destroyed by circulating immune cells. There is unequivocal evidence that praziquantel treatment minimizes worm burden thereby reducing the amount of deposited eggs culminating in an overall decline in inflammation related to the immunopathological reactions to the eggs and therefore praziquantel should be able to reduce chronic inflammation especially if administered regularly.

Knowledge of inflammation markers is necessary in assessing and identifying children who are likely to develop chronic pathologies later on in life. Chronic inflammation can be seen as a continuous series of distinct and consistent inflammatory stimuli. In such conditions, increased serum concentrations of acute phase proteins and proinflammatory cytokines are generally observed [14].

Acute phase proteins are a group of plasma proteins derived primarily from the liver and they are involved in inhibition of infection, mediating systemic effects like fever, leucocytosis, increased cortisol, decreased serum iron, and many others [15]. The extent of inflammatory tissue damage as well as diagnostic and prognostic information in some human diseases can be resolved by measurement of acute phase proteins [16,17]. Bacterial infections [18], neoplasia, [19] and inflammatory bowel diseases (IBD) have employed measurements of acute phase proteins in their prognosis [20]. However there is inadequate information regarding the use of acute phase proteins in parasitic infections like in human *Schistosoma* infection [21,22]. This is unusual considering the fact that parasitic infections elicit considerable inflammation.

Circulating microbial products are well known inducers of acute phase proteins [23], thus, in *S. haematobium* infected children the microbial products from the natural death of the schistosomes and those released following praziquantel treatment might induce overproduction of acute phase proteins. In this study, fibrinogen, ferritin and tissue plasminogen activator are going to be evaluated before and after treatment with praziquantel. Acute phase proteins have varying half-lives, rising and falling at different times, which limit the use of only one biomarker in determining inflammation. Thus the simultaneous measurements could be most effective in identifying individuals prone to chronic inflammation.

Traditional biomarkers such as C-reactive protein, serum amyloid A and haptoglobin have produced conflicting results in terms of correlation between inflammation and schistosomiasis and insufficiently sensitive or specific enough to guide treatment decisions in infectious diseases. Some studies have reported a direct relationship between schistosomiasis and presence of the acute phase proteins [24-26] whilst other researchers have found no link between the two. To our knowledge the combination of tissue plasminogen activator, fibrinogen, ferritin and procalcitonin has not been evaluated in individuals living in schistosomiasis endemic areas. Recently, there has been interest in the potential use of procalcitonin and ferritin as inflammatory markers in various infectious diseases as a result of the increase of both retrospective and prospective studies that consistently have documented elevated serum concentrations of procalcitonin and ferritin in various parasitic infection.

Acute phase proteins are released as a result of the action of cytokines such as IL-1, IL-6, and TNF- α produced by T-lymphocytes, macrophages, monocytes, endothelial cells, and fibroblasts at the site of inflammatory lesions. Although it is evident that a number of proinflammatory and anti-inflammatory cytokines are involved in the inflammatory response [27], available data indicates that IL-6 is the supreme stimulator [21,28]. Acute inflammation turns into chronic inflammation if the activity of IL-6 perseveres. However, in knockout mice incapable of expressing IL-6, the role of IL-6 in triggering the production of acute-phase proteins depends on the nature or site of the inflammatory stimulus; the response is largely inhibited in IL-6 knockout mice injected with turpentine but is normal when bacterial lipo-polysaccharide is the inflammatory stimulus [22]. Unrestrained and sustained action of cytokines is potentially harmful. Anti-cytokine therapies are thus useful in light of the role of proinflammatory cytokines in inflammation-related pathologies and this may have far reaching consequences in schistosomiasis vaccine development which has been elusive [29].

Identifying individuals at an early stage who are vulnerable to inflammation allows better prognosis and prevents the use of invasive, costly and time consuming procedures to determine those suffering from pathological complications of chronic inflammation conditions. It has been demonstrated that biomarkers C-reactive protein and faecal calprotectin can be used to evaluate disease status in patients with inflammatory bowel disease (IBD) though endoscopic evaluation which is expensive and invasive is the gold standard [30]. The goal of disease monitoring is to identify individuals at risk in order to treat earlier.

Although perpetual and continuous inflammation is presumed to be a hallmark of schistosomiasis, very few studies have actually examined the acute phase proteins simultaneously with the proinflammatory cytokine IL-6 in *S. haematobium* infections. In this study *S. haematobium* infections was first determined then determined ferritin,

fibrinogen, tissue plasminogen activator, procalcitonin and IL-6 at baseline to assess inflammation in both *S. haematobium*-infected and *S. haematobium* uninfected school children. Secondly we established if repeated rounds of praziquantel treatment for 2 years results in changes in the acute phase proteins and IL-6.

Methodology

Study population and study area

The study was carried out in Bandanyenje primary school located in a schistosomiasis endemic setting in the Manicaland Province of Zimbabwe. It is located approximately 217 km south of the capital city Harare with latitude and longitude of 7°1'N 38°35'E. In Bandanyenje, safe water and sanitation coverage are poor and school children depend on perennial rivers as their water source thus exposing the majority of their population to infection. The study population comprised of 212 (105 boys and 107 girls) aged between 7-13 years, who were permanent residents of the area. Serum samples from the participants were taken and measurement of acute phase proteins and IL-6 before and after praziquantel treatment.

Parasitology and blood sampling

A school-based longitudinal intervention study was conducted and involved examination and treatment of the study population at baseline, 6 weeks and at 2 year follow up surveys. Stool and urine samples were collected from 212 schoolchildren at baseline and follow up on three consecutive days and were processed for schistosomiasis using the Kato Katz, Formol-ether concentration method as modified by Peters et al. [31] and the filtration technique Mott et al. [32] respectively. Blood samples were collected from the 212 children at baseline and 2 years post-treatment and their serum was used to determine acute phase proteins and IL-6.

Praziquantel treatment

All 212 schoolchildren were given praziquantel (40 mg/kg body weight) at baseline regardless of the infection status. Praziquantel was administered at the same dose in all the children annually for 2 years.

Acute phase proteins and IL-6 determination

Serum levels of ferritin, fibrinogen, tissue plasminogen activator and procalcitonin, were determined by the magnetic bead-based immuno-assays using the Bio-Plex Pro™ human acute phase 4-plex immunoassay complete commercial kits. The Bio-plex manager software was used for running the assay, data acquisition and analysis. The analysis of IL-6 in the serum samples was done by sandwich ELISA.

Statistical Analysis

Data was analyzed using SPSS statistical software v16. Levels of serum levels of ferritin, fibrinogen, tissue plasminogen activator, procalcitonin and IL-6 at baseline and 2 years post-treatment in the schoolchildren were compared using student t test to determine the effect of praziquantel treatment on acute phase proteins and IL-6. The Mann-Whitney non parametric U-test was used to determine the effect of *S. haematobium* infection on the levels of ferritin, fibrinogen, tissue plasminogen activator, procalcitonin and IL-6. A value of $p < 0.05$

was considered to indicate a significant difference in statistical analyses.

Ethical Approval

Ethical approval and clearance of the study was obtained from the Biomedical Research Ethics Committee (BREC-UKZN), approval code, BE 467/16 as well as the Medical Research Council of Zimbabwe (MRCZ), approval code, MRCZ/A/1958. The aims, objectives and procedures of the study were explained to the parents/guardians of the recruited children in the local language (Shona), when they were invited to participate. Written informed consent was obtained from all the guardians of the school children in Shona and English. Participation was voluntary and the parents/guardians had the right to withdraw their child/children at any time point from the study. Treatment was administered by trained medical personnel and the children were closely monitored. Written consent to transport participants' specimens to UKZN for acute phase protein determination was also obtained from parents/guardians.

Results

212 (105 boys and 107 girls) aged between 7-13 were recruited from Bandanyenje primary school located in a schistosomiasis endemic area and were successfully traced and re-examined at both follow-ups with complete sets of longitudinal parasitological data on *S. haematobium* infection. The overall pre-treatment prevalence of *S. haematobium* infection was 49(23.1%) with 20(19%) boys and 29(27.2%) girls as determined using the urine filtration technique (Table 1). There was an overall decline in *S. haematobium* prevalence from 23.1% at baseline to 0.47% at 6 weeks post-treatment and, 0.47% 2 years post-treatment, an overall 87.1% reduction over 2 years ($p < 0.05$). A total of 211(99.5%) children were egg negative after treatment.

Variable	Baseline	6 Weeks post treatment	2 Years post treatment
Prevalence	49(23.1%)	1(0.47%)	1(0.47%)
Cure rate		98%	97.80%
Boys	20(19%)	1(0.47%)	1(0.47%)
Cure rate		95%	94.70%
Girls	29(27.1%)	0	0
Cure rate		100%	100%

Table 1: Overall prevalence of *S. haematobium* infection in the study population according to gender at baseline and 2 years post praziquantel treatment.

No significant changes were observed in ferritin, tissue plasminogen activator and procalcitonin among the *S. haematobium* positive and negative children ($p > 0.05$), Mann-Whitney non parametric test at baseline. Following repeated rounds of annual treatment changes occurred in the levels of the acute phase proteins though they were all insignificant with respect to infection status $p > 0.05$ Mann-Whitney non parametric test (Figure 3). Tissue plasminogen activator and procalcitonin levels increased slightly following treatment. In *S. haematobium*-uninfected children, levels of procalcitonin decreased following treatment though it was insignificant ($p > 0.05$) whilst the

ferritin and tissue plasminogen activator marginally increased following treatment.

The Mann-Whitney test was also used to determine the effect of *S. haematobium* infection on the levels of acute phase proteins. *S. haematobium*-infected children had slightly higher levels of procalcitonin and tissue plasminogen activator before treatment though the difference of the two was not significant, $p > 0.05$ (Figure 1).

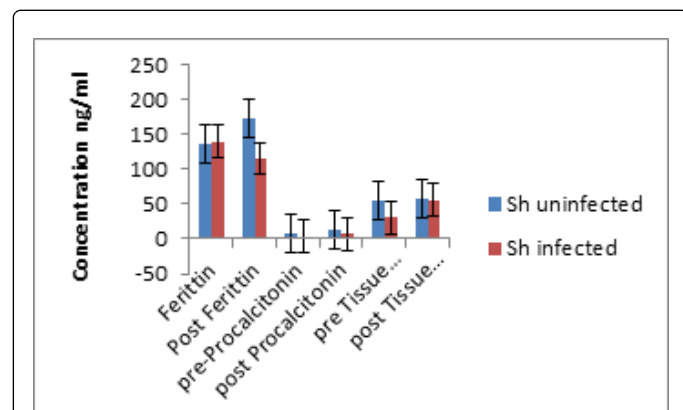


Figure 1: Mean concentration of acute phase proteins in *S. haematobium*-infected and uninfected children at baseline.

Levels of ferritin and fibrinogen were lower in *S. haematobium* positive children before treatment, however the difference was also not significant $p > 0.05$ (Figure 1 and Figure 2). Infection status had no bearing on the levels acute phase proteins, using the Mann-Whitney non parametric test, ferritin levels ($p > 0.05$), tissue plasminogen activator ($p > 0.05$), procalcitonin ($p > 0.05$) were shown to be unrelated to *S. haematobium* infection. Fibrinogen levels were within normal ranges for both *S. haematobium* positive and negative children and there the Mann-Whitney test could not be performed because there was only one group (Figure 2).

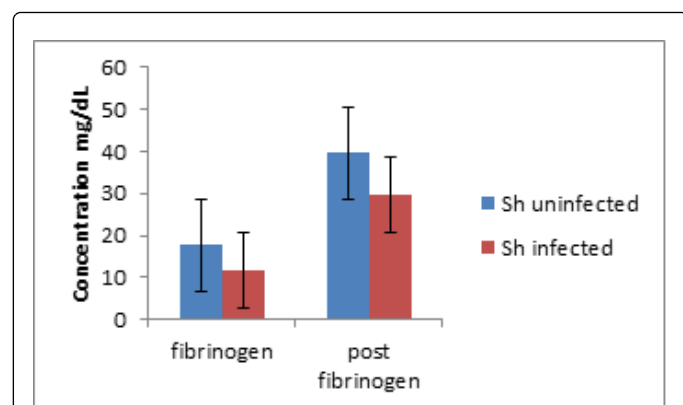


Figure 2: Mean concentration of fibrinogen in *S. haematobium* infected and uninfected children at baseline.

In order to determine the effect of treatment on the acute phase proteins the student t test was performed. In *S. haematobium* positive children there was a decrease in ferritin levels following treatment though it was insignificant $p > 0.05$, however in *S. haematobium* negative children there was a slight increase which was also no

significant ($p > 0.05$). There was an insignificant increase in procalcitonin and tissue plasminogen ($p > 0.05$ and $p > 0.05$ respectively) following praziquantel treatment in both *S. haematobium* and positive and negative children (Figure 3).

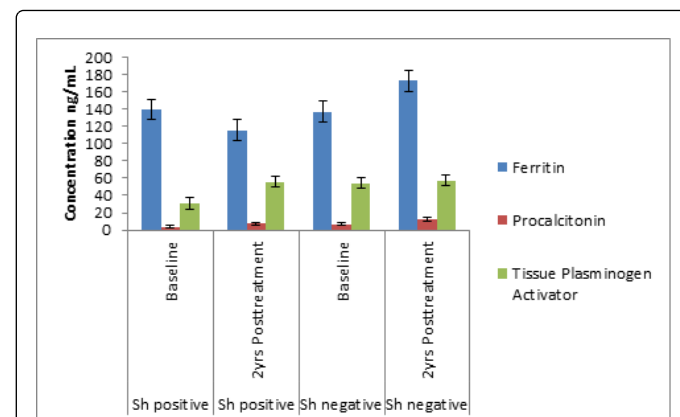


Figure 3: Mean concentration of acute phase proteins in *S. haematobium* infected and uninfected children at baseline and 2 years post praziquantel treatment.

At baseline level of IL-6 was higher in *S. haematobium* infected children than in *S. haematobium* uninfected children though the difference was insignificant ($p < 0.05$) (Figure 4). Following treatment there was an increase in IL-6 in *S. haematobium* uninfected children and a decrease in IL-6 in *S. haematobium* uninfected children, however the changes were insignificant $p < 0.05$ in both cases. The Mann Whitney test was used to determine the effect of IL-6 on the levels of the acute phase proteins. IL-6 levels did not have an effect on the levels of ferritin, procalcitonin and tissue plasminogen activator ($p = 0.334$, $p = 0.134$ and $p = 0.847$, respectively using Mann-Whitney test). Effect of IL-6 on fibrinogen levels could not be determined by the Mann-Whitney test because fibrinogen levels were within normal ranges for all the children.

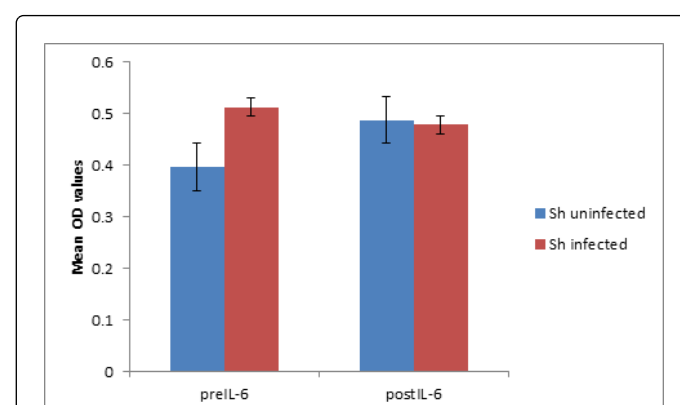


Figure 4: Mean OD values for IL 6 in *S. haematobium* infected and uninfected children before and after treatment with praziquantel.

Discussion

The *S. haematobium* prevalence was 23.1% which is slightly lower than 23.8% recorded in the province by Midzi et al. [33]. The

prevalence of *S. haematobium* infection declined from 23.1% to 0.47% following repeated rounds of annual praziquantel treatments (Table 1). This decline in prevalence resulted in a decline in the *S. haematobium* worms laying the eggs because of worm damage caused by praziquantel. The eggs are responsible for invoking and determining the magnitude of inflammation within tissues [34]. The low levels of acute phase proteins post treatment reflect the low prevalence of infection 2 years following repeated rounds of annual praziquantel treatment. If less children are infected (less exposure of *S. haematobium* eggs in tissues), the extent of inflammation will be reduced since the tissue-trapped eggs are responsible for inflammation.

The current study is the first in reporting the relationship between fibrinogen, ferritin, procalcitonin and tissue plasminogen activator and *S. haematobium* infection in school-going children. The effect of IL-6 on the circulating four acute phase proteins is also reported for the first time in this study. This study was motivated in part by the limited information regarding relationships between biomarkers of inflammation and *S. haematobium* infection. Contrary to what was expected, we observed no association between *S. haematobium* infection status and the inflammatory markers (Figure 1); fibrinogen, ferritin, tissue plasminogen activator and procalcitonin before treatment with praziquantel. Using the Mann-Whitney non parametric test all four acute phase proteins did not show any association with *S. haematobium* infection status. Repeated exposure to inflammatory agents, common in schistosomiasis endemic settings where there is frequent exposure to cercariae infested water is expected to result in constant elevations in acute-phase proteins and other inflammatory markers. Previous studies had reported relationships between *S. haematobium* and other acute phase proteins albeit with conflicting results. It is against this background that we evaluated the levels of the four acute phase proteins. Positive associations between levels of acute phase proteins such as C-reactive protein and hepcidin and schistosoma infections have been reported [24,25]. Ferritin has also been reported to be raised in inflammatory diseases [26] but such an association was not evident in our study though in the reported case the prevalence of *S. haematobium* was high. Our observation can be attributed to the moderate prevalence in our study group or simply just that other markers like C-reactive protein are better markers than the markers we evaluated. The expectation that a combination of more than one measure would perform substantially better than any single one was not supported by our observations.

Serum concentration of acute phase proteins typically peak within 24 to 48 h after the initiation with a decline coinciding with the recovery from the infection. It has been noted that acute phase proteins decline within 4-7 days after the initial stimulus if no further stimulus occurs and that repeated exposure to the agent stimulating inflammation results in chronic inflammation with levels of acute phase proteins being continuously elevated [35]. Circulating acute phase levels are felt to be a reflection of the response to pro-inflammatory cytokines such as IL-6 [15,28]. There were no significant differences in circulating IL-6 between *S. haematobium* infected and uninfected school children and the levels in both groups were not high (Figure 4). Inflammation with T-cell activation is a distinct characteristic of *S. haematobium* infection and as such, markers of inflammation are expected to be in circulation [36,37]. A Th2 immune response is induced by schistosomes through Th1 down-regulation via increased IL-6 production. Host macrophages recognize the larvae of schistosomes which induces secretion of IL-6. In children who are *S. haematobium* positive induction of the Th2 response would be expected resulting in increased production of IL 6 [38].

Following treatment there were no significant changes in the level of IL-6 (Figure 4). This was unexpected especially considering the fact that studies have shown that treatment of schistosomiasis with praziquantel induces noticeable changes in cytokine levels [39,40]. Marked changes in cytokines such as IL-6, IL-4, IL-5 and IL-10 occur following treatment of schistosomiasis induces marked changes in cytokine levels resulting in a shift to Th2 responses which have been associated with resistance to reinfection [41]. Exploring other cytokines not included in this study (i.e., IL-4, IL-5, and IL-13) is important in understanding the immune response to multiple parasitic infections and should be integrated in future research efforts.

Our study reveals novel insights in the use of the four acute phase proteins in evaluating inflammation in *S. haematobium*, albeit with some minor limitations such as sample size and availability of resources. General limitations of assessing serum levels of inflammatory markers such as acute phase proteins and cytokines are the relatively non-specificity, short half-life, nonspecific induction, and serum levels not reflecting biologic activity. Notwithstanding these limitations, serum levels of some of these biomarkers have yielded important insights in the level of inflammation in parasitic diseases.

Conclusion

The central question in this study was whether IL-6, ferritin, fibrinogen, tissue plasminogen activator and procalcitonin are suitable as identifiers for inflammation in *S. haematobium* infection and whether their levels would change following repeated rounds of annual praziquantel treatments. Our results show no significant association between *S. haematobium* infection status and level of the four acute phase proteins ferritin, fibrinogen, tissue plasminogen activator and procalcitonin. However, marginal increases were observed in levels of procalcitonin and tissue plasminogen activator in *S. haematobium* infected children. Treatment using praziquantel did not significantly affect the levels of the four acute phase proteins. There is a need to identify and select of the most appropriate biomarkers of inflammation in children since identifying individuals who are vulnerable early stages of inflammation allows better prognosis and prevents the use of invasive, costly and time consuming procedures to determine those suffering from pathological complications of chronic inflammation conditions in future.

Authors' Contribution

TJC, BN and TM developed the field study design, acute phase proteins and IL 6 immunoassays and analyzed the data. While AV, AFN, EPS, DZ and TM conducted field and sampling work. TJC, AV, AFN and BM conducted the laboratory assays. TJC and TM conducted the initial statistical analyses. All authors contributed to the manuscript.

Competing Interests

The authors declare that they have no competing interests.

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Ethics Approval

This manuscript draws from our work which received ethical approval from The Medical Research Council of Zimbabwe (MRCZ/A/1958) and BREC (BE467/16). All information pertaining to the discussion was obtained prior to written consent by the parents/guardian of the children participating in the study.

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