EFFICACY, ADVERSE EFFECTS AND ACCEPTABILITY OF PRAZIQUANTEL IN THE TREATMENT OF *SCHISTOSOMA HAEMATOBIUM* IN PRE-SCHOOL AGE CHILDREN: A STUDY OF SELECTED EARLY CHILDHOOD DEVELOPMENT CENTRES OF KWALE COUNTY KENYA.

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JOMO KENYATTA UNIVERSITY OF

AGRICULTURE AND TECHNOLOGY

2022

Efficacy, Adverse Effects and Acceptability of Praziquantel in the Treatment of *Schistosoma Haematobium*in Pre-School Age Children: A Study of Selected Early Childhood Development Centres of Kwale County Kenya

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A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of Master of Science in Public Health of the Jomo Kenyatta University of Agriculture and Technology

2022

DECLARATION

This thesis is my original work and has not been presented for a degree in any other University.

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DEDICATION

I dedicate this work to God Almighty my creator, my strong pillar, my source of inspiration, wisdom, knowledge and understanding. He has been the source of my strength throughout this journey and on His wings only have I soared. I also dedicate this work to my children who have been affected in every way possible by this quest. To my parents and siblings thank you for the prayers, support and encouragement during this period. My love for you all can never be quantified. God bless you.

ACKNOWLEDGEMENT

My deepest gratitude goes to God who has provided all that was needed to complete this project. There was never lack or want. Throughout this study, He took care of everything that would have stopped me in my tracks and strengthened me even through my most difficult times.

I would like to express my deep and sincere gratitude to my mentor and supervisor, Dr. Doris W. Njomo, for giving me the opportunity to carry out this study and providing invaluable guidance throughout this research. Your dynamism, vision, sincerity and motivation have deeply inspired me. I greatly appreciate the freedom you have given me to find my own path and the guidance and support you have offered when needed. You have created the invaluable space for me to do this research and to develop myself as a researcher in the best way possible. It has been a great honor and privilege to work and study under your guidance. I am extremely grateful for what you have offered me. I would also like to thank you for not only being a great mentor but also for your friendship and empathy.

I would also like to thank my supervisor Dr. Jimmy Kihara for his guidance and support throughout the project including, proposal development, facilitating my data collection with the materials and laboratory personnel and thesis writing.

I also thank my supervisor Dr. Amos Mbugua for his academic guidance and support throughout the project including, proposal development, manuscript publication and thesis writing.

I also wish to thank Ng'ang'a Murima for the statistical guidance from proposal development, data analysis, manuscript publication and thesis writing. Your invaluable advice and support is highly appreciated.

My utmost regard also goes to my parents, Joseph Kimani and (Mrs.) Mary Kimani who painstakingly laid the foundation for my education and prepared me for my future. I shall be forever grateful for your love, prayers, and sacrifices. I can never thank you enough. From the depth of my heart, I appreciate my children, Natalie, Nathan and Nolan who even at such a tender age have had to endure so much stress and discomfort just for me. This page cannot tell it all. I appreciate my siblings Catherine (nanny and assistant rolled into one), Moses (godfather) and Salome (best aunt). To my friend Zila Wakio, words cannot express my gratitude. Thank you for the immense support you have accorded me and your great sense of humor.

I am also grateful to the Director Kenya Medical Research Institute, Jomo Kenyatta University of Agriculture and Technology, Kwale County; Ministry of Health, Ministry of Education, Moses Machimbo (laboratory work), Community Health Extension Workers, the Early Childhood Development Education children for participating in this study, Parents and Early Childhood Development Education Teachers for their support.

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ABBREVIATION AND ACRONYMS

AIDS	Acquired Immunodeficiency Syndrome
CD	Compact Disc
CDC	Center for Disease Control
CHEWs	Community Health Extension Workers
CMR	Center for Microbiology
CR	Cure Rate
DALYs	Disability-adjusted life years
DOT	Direct Observed Treatment
DNA	Deoxyribonucleic Acid
DtWI	Deworm the World Initiative
ECD	Early Childhood Development
ELISA	Enzyme Linked Immunosorbent Assay
ERR	Egg Reduction Rate
GOK	Government of Kenya
HIV	Human Immunodeficiency Virus
ID	Identification
IRB	Institution Review Board

ITROMID	Institute of Tropical Medicine and Infectious Diseases
JKUAT	Jomo Kenyatta University of Agriculture and Technology
KDHS	Kenya Demographic Health Survey
KEMRI	Kenya Medical Research Institute
KSHs	Kenya Shillings
MDA	Mass Drug Administration
Mg	Milligrams
Mls	Milliliters
Mm	Millimeters
MOE	Ministry of Education
MOH	Ministry of Health
NCP	National Control Programme
NSBDP	National School-based Deworming Programme
NTDs	Neglected Tropical Diseases
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PSAC	Pre-schoolAge Children
PZQ	Praziquantel

SAE	Severe Adverse Event
SAC	School-age Children
SCC	Squamous Cell Carcinoma
SCI	Schistosomiasis Control Initiative
SPSS	Statistical Package for Social Sciences
SSA	Sub-Saharan Africa
STH`	Soil-Transmitted Helminthes
WHA	World Health Assembly
WHO	World Health Organization

OPERATIONAL DEFINITIONS

Acceptability	The number of children spitting and/or vomiting all or part of the PZQ dose, immediately after oral administration treatment
Adverse Effect	A symptom absent before treatment and experienced after treatment with crushed praziquantel mixed with fruit juice
Efficacy	Percentage of children positive at the pre-treatment cross-sectional survey who became egg negative 5 weeks after treatment

ABSTRACT

The recommended strategy for control of schistosomiasis is preventive chemotherapy with praziquantel (PZQ). Pre-school age children (PSAC) are excluded from population treatment programs. In high endemic areas, these children are also at risk, and require treatment with PZQ. The Government of Kenya initiated the National School-Based Deworming Programme (NSBDP) where PSAC in Early Childhood Development (ECD) Centres are only eligible for treatment with albendazole (ABZ) but not with PZQ. Four hundred PSAC were enrolled, from 10 randomly selected ECD Centers in Kwale County, Kenya where children were treated with crushed PZQ tablets mixed with fruit juice, at a single dose of 40 mg/kg. Treatment efficacy was assessed by examining urine samples for *Schistosoma haematobium* eggs in the 5 weeks' post-treatment follow-up. Children testing negative for *S. haematobium* during the follow-up were considered cured. Egg reduction rate (ERR) was calculated as the decrement in the infection intensity (group's geometric mean egg counts per 10 ml of urine) following treatment, expressed as a proportion of the pre-treatment infection intensity. Twenty-four hours' post-treatment, adverse effects were assessed through questionnaires administered to the parents or guardians.Treatment acceptability was determined by observing if the child spat and/ or vomited all or part of the PZQ dose immediately after treatment.Before treatment, 80 out of the 400 children enrolled in the study tested positive for *S. haematobium* (20.0% (95% confidence interval (CI) 16.4 - 24.2%). Of these, 41 (51.3%) had infections of heavy intensity while the rest (48.7%) were of light intensity. Five weeks' post-treatment, 10 children who had heavy intensity infection were diagnosed with *S. haematobium* (prevalence: 2.5% (95% CI 1.5 - 4. 9%). Infection intensities decreased significantly from 45.9% (95% CI: 31.0 - 68.0) eggs/ 10 ml urine to1.4% (95% CI: 1.1 - 1.7) eggs/ 10 ml urine during pre-and post-treatment respectively. The ERR was 96.9%. 330 out of the 400 children recruited inthe study were assessed for AEs 24 hours post treatment. One experienced dizziness, one experienced a headache, four had abdominal pain/discomfort, two had nausea and two experienced itching. None of the children vomited. While six respondents took no action when their child experienced an adverse event, one gave food, two gave milk and the other one made the child to rest. Treatment tolerability among the 400 children was high as none of the children spat and/ or vomited as observed in this study. The study revealed that crushed PZQ is safe and effective in the treatment of urogenital schistosomiasis in this age group. The study recommends the Government of Kenya to consider having the PSAC children treated with PZQ as they have a high *S. haematobium* burden.

CHAPTER ONE

INTRODUCTION

1.1 Background Information

Human schistosomiasis (bilharzia) is a major yet neglected public health problem. It is classified as one of the neglected tropical diseases (NTDs). These are a group of diseases found predominantly in tropical and subtropical areas that are associated with poor sanitation and poverty and which have historically received insufficient attention towards their control. It is a fresh-water snail transmitted intravascular debilitating disease resulting from infection by the parasitic dimorphic *Schistosoma* trematode worms, which live in the bloodstream of humans (Steinman *et al*., 2006, Gryseels *et al*., 2006).

Over 200 million people are infected globally, with 85% of these cases living in Sub-Saharan Africa (World Health Organization (WHO) 2010). It is estimated that at least 91.4% of those requiring treatment for schistosomiasis live in Africa.The majority of infections in sub-Saharan Africa are caused by *Schistosoma mansoni* and *Schistosoma haematobium* which reside in intestinal mesenteric veins and bladder respectively, leading to intestinal and urogenital schistosomiasis(WHO 2010).

In Kenya, nearly 6 million people are infected and an additional 15 million are at high risk of infection particularly in endemic areas (Garba *et al*., 2010, Ekpo *et al*., 2010). *S. haematobium* occurs mainly in areas around the upper and lower Coast region and some parts of the Lake Victoria and Kano plains in Western Kenya (Hotez *et al*., 2009). Children carry the heaviest burden of infection in affected populations (Danso *et al*., 2008, Gryseels *et al*., 1996).Symptoms of urogenital \schistosomiasis include haematuria, dysurea, nutritional deficiencies, anemia, growth retardation, decreased physical performance and impaired memory and cognition (WHO 2004).

Control of schistosome infections is through treatment of infected people with a single dose of the anti-helminth drug praziquantel (PZQ) which is safe, highly efficacious, cheap (costing less than US$0.50/dose) and can reverse schistosome-related morbidity particularly in the early stages of disease progression (Fenwick *et al*.,2009).

Studies point to a growing body of evidence that in many endemic communities, schistosomiasis infection – contrary to previous beliefs – starts in early childhood. The presence of infection, points to the fact that infants and pre-school aged children are also at risk of infection like their older school-aged counterparts. The growing concern here is that infection in infants and pre-school age children may persist until the child starts school if left untreated. In preventive chemotherapy control programmes infants and PSAC are not eligible for treatment until school-age (Stothard *et al*., 2007a, Sousa-Figueiredo *et al*., 2010a, Ekpo *et al*., 2011).

Current schistosome control programs advocated by the World Health Assembly in 2001 through resolution 54.19 recommend regular de-worming of school age children at risk of infection with anti-helminthes (WHO 2006). However, these programs exclude pre-school children due to the perception that these children are not sufficiently exposed to infective water to experience high infection rates (King *et al*., 2004). There are still concerns associated with treatment of preschoolers for schistosomiasis. They are believed to be at risk of choking, and there is a lack of prescribing information by the pharmaceutical companies on toxicity, method of administration, adverse effects and pharmacokinetics in this age group (King *et al*., 2006). This may result in clinical disease that is not managed and the lack of safety data on PZQ in this age group (Fenwick *et al*., 2009).

With international support (Stothard *et al*., 2009) several national control programmes (NCPs), including Kenya, are active in conducting MDA with PZQ. The Government of Kenya through the MOH and the MOE implemented the National School-based de-worming Programme (NSBDP) in 2009 and over 3.6 million out of more than 8 million

targeted school-age children living in endemic areas were treated for STH. As recommended by WHO, under the supervision of local health staff, trained teachers treated the children once with a single oral treatment of albendazole (for STH). The program's objective was to reduce STH infections to a level at which morbidity will no longer be a public health problem (<1% prevalence of heavy intensity infections). In 2012, the NSBDP was scaled up and albendazole and praziquantel were co-administered toschool children in Kwale County in 2013 and 2014. During the year 2015 only albendazole wasadministered in Kwale County due to logistical challenges experienced by NSBDP in the country (NSBDP 2013, 2014, 2015). However, during the 2009 treatment, only primary school-age children, (6-14 years) both enrolled and non-enrolled were covered by the programme leaving out the children in the age bracket of 2-6 years who attend the ECD Centers or pre-school.

Recent attention has focused upon documenting prevalence of infection in pre-school children PSAC and in so doing has defined a clear 'PZQ treatment gap', i.e., PSAC in need of treatment are generally excluded from MDA programmes (Stothard *et al*., 2011, Ekpo *et al*., 2012, Hodges *et al*., 2012).

The reasons behind this gap are complex but include the absence of a suitable PZQ pediatric formulation. The WHO is now recommending that young children living in endemic areas be considered for treatment with crushed or broken PZQ tablets, during child health campaigns at the standard dose of 40 mg/Kg (WHO 2013, WHO 2011), as a pragmatic stop-gap (Stothard *et al*., 2013, Sousa *et al*., 2012, Navaratnam *et al*., 2012, Sousa *et al* ., 2010), until an appropriate pediatric PZQ formulation becomes available (WHO 2011, Stothard *et al*., 2013, Sousa *et al*., 2012, Navaratnam *et al*., 2012, Sousa *et al*., 2010).

Previous studies have shown that, there have not been adverse reactions to PZQ treatment when given to young children due to the excellent safety and tolerability (Stothard *et al*., 2007). The common approach in high endemic areas is to use

praziquantel tablets (600 mg), crush them between two spoons, mix with water or fruit juice, and then administer orally to pre-school children at a dose of 40 mg/kg (Stothard *et al*., 2011, Garba *et al*., 2010, Sousa-Figueiredo *et al*., 2010). World Health Organization (WHO) is now recommending that young children living in endemic areas be considered for treatment with PZQ during child health campaigns at the standard dose of 40 mg/kg (WHO 2011). The PSAC require treatment as they also carry a heavy worm burden and pose a risk of re-infecting the treated school children while interacting and playing at the community level. A high percentage of infected children means that the environment becomes more heavily contaminated – which in turn increases the risk of infection for the whole community. By reducing the number of worms in children, everyone benefits (WHO, 2004).

Failure to reach a majority of the 2–6-year-olds in Early Childhood Development (ECD) Centers could result in higher prevalence of schistosomiasis and its negative health effects such as malnutrition and poor cognitive performance. In turn, these effects retard the child's growth and development (Drake *et al*., 2000). Treatment of children is also likely to be more successful in averting the development of subsequent, more serious disease sequelae because earlier stages of infection-induced pathology may be reversible if treated promptly (Botelho *et al*., 2010).

The goal of this study was to assess the acceptability, adverse effects and efficacy of treating pre-school age children with praziquantel for *S. haematobium* infection in selected ECD Centers of Kwale County, Kenya.

1.2 Statement of the Problem

Current schistosome control programs advocated by the World Health Assembly in 2001 through resolution 54.19 recommend regular de-worming of school age children at risk of infection with anti-helminthes (WHO 2006). However, these programs exclude pre-school children due to the perception that these children are not sufficiently exposed to infective water to experience high infection rates (King *et al*., 2004). There are still

concerns associated with treatment of preschoolers for schistosomiasis. They are believed to be at risk of choking, and there is a lack of prescribing information by the pharmaceutical companies on toxicity, method of administration, adverse effects and pharmacokinetics in this age group (King *et al*., 2006). This may result in clinical disease that is not managed and the lack of safety data on PZQ in this age group (Fenwick *et al*., 2009).Children have the highest prevalence and intensity of schistosomiasis infections, but the consequences of chronic infection, such as growth stunting, anaemia, hepatic/urinary fibrosis, and impaired cognitive development, continue to have an effect throughout adulthood (Brindley *et al*., 2013).The growing concern here is that infection in infants and pre-school age children may persist until the child starts school if left untreated.

1.3 Justification

In Kenya it is estimated that about 6 million people are infected with schistosomiasis and even more are at risk (Chitsulo *et al*., 2004). The prevalence is set to range from 5% to over 65% in various communities in Kenyaand contributes to significant morbidity (Ouma *et al*., 2001). In Kenya, the population of children enrolled in ECD Centers is 2.2 million (MOE, Kenya, 2012). Kwale County has a total enrollment of 43,874 pupils and a mean age of 4.5 years. The Government of Kenya through the Ministry of Health (MOH) and the Ministry of Education (MOE) implemented the National School-based Deworming Programme (NSBDP) in 2009 and over 3.6 million out of more than 8 million targeted school-age children living in endemic areas were treated for soil transmitted helminthes (STH). As recommended by WHO, under the supervision of local health staff, trained teachers treated the children once with a single oral treatment of albendazole (for STH). The program's objective was to reduce STH infections to a level at which morbidity will no longer be a public health problem (<1% prevalence of heavy intensity infections). In 2012, the NSBDP was scaled up and albendazole and praziquantel were co-administered toschool children in Kwale County in 2013 and 2014. During the year 2015 only albendazole wasadministered in Kwale County due to

logistical challenges experienced by NSBDP in the country (MOE 2013-2015). However, only SAC, both enrolled and non-enrolled were covered by the programme in the treatment of schistosomiasis, leaving out the children who attend the ECD Centers. The PSAC require treatment as they also carry a heavy worm burden and pose a risk of re-infecting the treated school children while interacting and playing at the community level. A high percentage of infected children means that the environment becomes more heavily contaminated – which in turn increases the risk of infection for the whole community. By reducing the number of worms in children, everyone benefits (WHO, 2004).

Failure to reach a majority of the preschoolers in ECD Centers could result in higher prevalence of schistosomiasis and its negative health effects such as malnutrition and poor cognitive performance. In turn, these effects retard the child's growth and development (Drake *et al*., 2000).Treatment of children is likely to be more successful in averting the development of subsequent, more serious disease sequelae because earlier stages of infection-induced pathology may be reversible if treated promptly (Botelho *et al*., 2010).The goal of this study was to assess the efficacy, adverse effects and acceptability, of treating pre-school age children with praziquantel for *S. haematobium* infection in selected ECD Centers of Kwale County, Kenya.

1.4 Research Questions

1. What is the prevalence and intensity of *Schistosoma haematobium* infection in pre-school age children of selected Early Childhood Development Centres of Kwale County pre and post treatment with crushed praziquantel?
2. Are there any adverse effects after administration of crushed praziquantel among pre-school age children?
3. How willing are the children in the uptake of the crushed praziquantel mixed with fruit juice?

1.5 Objectives

1.5.1 General Objective

To assess the efficacy, adverse effects andacceptability, of treating pre-school age children with praziquantel for *Schistosoma haematobium* infections in selected Early Childhood Development (ECD) Centers of Kwale County, Kenya

1.5.2 Specific Objectives

1. To determine the efficacy of crushed praziquantel against *S. haematobium* among ECD children.
2. To determine the adverse effects of crushed praziquantel in the treatment of urinary schistosomiasis among ECD children.
3. To assess how willing the children are in the uptake of the crushed praziquantel mixed with fruit juice.

1.6 Significance of the Study

Failure to reach a majority of the children in ECD Centers could result in higher prevalence of schistosomiasis and its negative health effects such as malnutrition and poor cognitive performance. In turn, these effects retard the child's growth and development. Treatment of children is also likely to be more successful in averting the development of subsequent, more serious disease sequelae because earlier stages of infection-induced pathology may be reversible if treated promptly. The current study was aimed at assessing the acceptability, adverse effects and efficacy of treating pre-school age children with PZQ for *Schistosoma haematobium* infection. The results of this study will be useful to policy makers involved in the control of the disease to include the PSAC in order to effectively control the disease

CHAPTER TWO

LITERATURE REVIEW

2.1 Epidemiology of Schistosomiasis

Schistosomiasis is the third most devastating tropical disease globally (after malaria and intestinal helminthiases) and is a major cause of morbidity and mortality for developing countries in Africa, South America, the Caribbean, the Middle East, and Asia (WHO 2013) Schistosomiasis also known as Bilharzia is caused by schistosomes, which are parasitic trematode worms of the genus *Schistosoma*. It is the most widespread water-borne parasitic disease and remains a public health problem where it occurs. In 74 countries where the disease is endemic, an estimated 250 million people are infected out of which 85% are from sub-Saharan Africa and approximately 700 million people are at risk of infection (Steinmann *et al*., 2006, Ross *et al*., 2002). Approximately 20% of the infected population is pre-school children (Mudza *et al*., 2017)

Schistosomiasis is a debilitating disease that mainly affects but not limited to the poor rural communities. It is prevalent in tropical and subtropical areas, especially in poor communities without access to safe drinking water and adequate sanitation. (Bruun *et al*., 2008, WHO 2014). There are several factors that contribute to the high rate of *S. haematobium* infection in developing countries. These include extreme poverty, inadequate or total lack of health facilities, lack of knowledge of the risks and poor sanitary conditions (Hotez and Kamathi, 2009; King, 2010). Approximately 76% of the population in Sub-Saharan Africa (SSA) lives near rivers, lakes, and other water bodies contaminated with snail intermediate hosts (Wu *et al*., 1992, Leenstra *et al*., 2006, Ezeamama *et al*., 2005, Ezeamama *et al*., 2008). Those living near dam reservoirs are at particular risk, and SSA has several examples where the infection has emerged or where there has been a dramatic rise in the prevalence of schistosomiasis as a result of irrigation project construction (Wu *et al*., 1992, Ezeamama *et al*., 2012)

Five species infect humans, namely: *Schistosoma mansoni, Schistosoma japonicum, Schistosoma mekongi, Schistosoma intercalatum, and Schistosoma haematobium*. The burden of disease, attributable to the three majors human schistosome species (*S. mansoni, S. haematobium,* and *S. japonicum*) is estimated to be between 24-29 million disability adjusted life years (WHO 2002, King *et al*., 2005).

In Africa the most common ones are *S. mansoni* and *S. haematobium* that cause intestinal and urinary schistosomiasis respectively. (Engels *et al*., 2002, WHO, 2002).

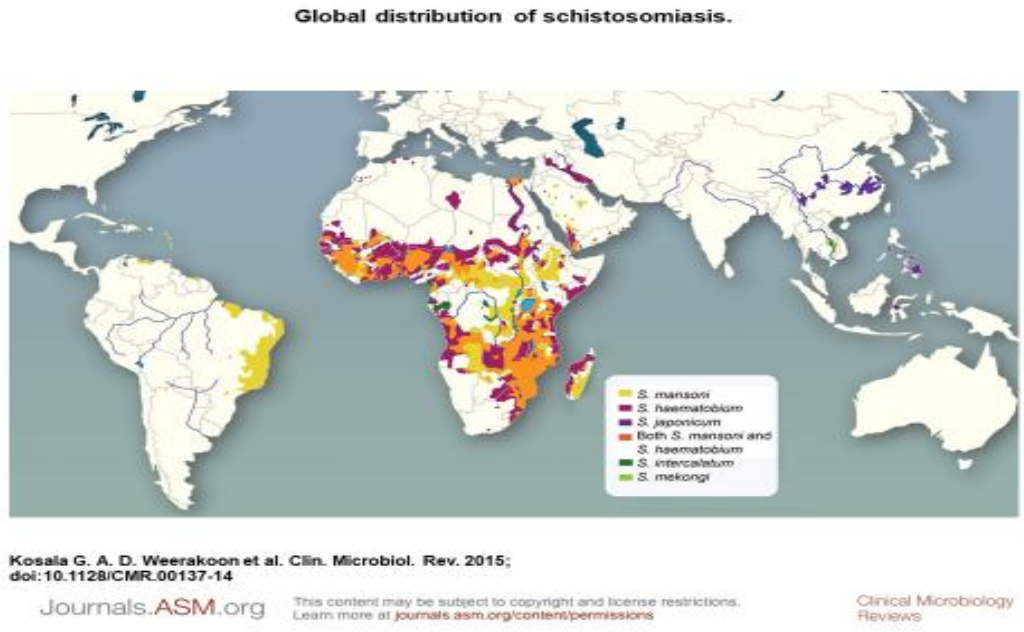

Figure 2.1: Map on the Global Distribution of Schistosomiasis

Schistosomiasis is a snail transmitted and dynamic infection spreading to new foci due to social dislocation or massive migrations caused by drought, war, famine, labor migration and effects of man-made ecological changes such ascultivation of rice in paddy fields and creation of dams such as Kariba dam in Sudan that produces expanses of water which are suitable breeding grounds for snails (Blank *et al*., 2006).Transmission requires contamination of surface water by excreta from infected

definitive hosts, specific fresh water snails as intermediate hosts which transmit the infective stage (cercariae) and human contact with contaminated water through activities such as farming, fishing, and domestic chores (WHO, 2014).

Distribution of schistosomiasis is very focal and is determined by the geographical distribution of snail intermediate hosts which differ in their habitat preferences for slow-flowing or still waters. Endemicity of the particular species of *Schistosoma* is determined by availability of suitable snail host, the potential of infected humans to contaminate the local water and human activities like flood irrigation of crops in the contaminated water. Schistosomiasis has a worldwide distribution as shown in Table 2.1

Table2.1: Parasite Species and Geographical Distribution of Schistosomiasis

	Species	**Geographical distribution**
Intestinal schistosomiasis	*Schistosoma mansoni*	Africa, the Middle East, the Caribbean, Brazil, Venezuela and Suriname
	Schistosoma japonicum	China, Indonesia, the Philippines
	Schistosoma mekongi	Several districts of Cambodia and the Lao People's Democratic Republic
	Schistosoma guineensis and related *S. intercalatum*	Rain forest areas of central Africa
Urogenital schistosomiasis	*Schistosoma haematobium*	Africa, the Middle East, Corsica (France)

Source: http://www.who.int/news-room/fact-sheets/detail/schistosomiasis2018

Approximately 120 million of the infected people are asymptomatic (Savioli *et al*., 1997; van der Werf *et al*., 2003), while 20 million have severe clinical symptoms. Mortality rate due to schistosomiasis is about 200,000 deaths per year worldwide (Conlon, 2005) but predictions based on standardized data from sub-Saharan Africa show that mortality rates due to urinary and intestinal schistosomiasis are 150,000 and

130,000 persons per year respectively (van der Werf *et al*., 2003). The disability-adjusted life years (DALYs) lost due to schistosomiasis are estimated at 4.5 million (WHO, 2002) but several authors have noted that this is underestimated since it excludes some morbidity parameters (van der Werf *et al*., 2003; King, 2005).

Classified among the neglected tropical diseases, urogenital schistosomiasis remains one of the most prevalent parasitic diseases in the tropical and subtropical countries, constituting a major public health problem. The disease is caused by the helminth parasite *Schistosoma haematobium* and is the most prevalent form of schistosomiasis in Africa and the Middle East affecting approximately 107 million people. Approximately two-thirds of the schistosomiasis cases are due to infection caused by *S. haematobium*, which represents an important cause of severe urinary tract disease. The classic sign of urogenital schistosomiasis is haematuria (blood in urine) (Ross *et al*., 2002).

Renal failure accounts for a large percentage of the estimated 150,000 deaths from urinary tract schistosomiasis in SSA, and there is also a significant association between major bladder wall pathology and squamous cell carcinoma (Xu *et al*., 2011). A significant percentage of women and men with urinary schistosomiasis acquire genital ulcers and other lesions (Chen *et al*., 1993). In the former, urogenital schistosomiasis is a significant cause of poor reproductive health, including sexual dysfunction and infertility (Kjetland*et al.,* 2012).Genital infection in males may result in damage to seminal vesicles, prostate and other related organs; this may lead to irreversible infertility (Ross *et al*.,2002). Urogenital schistosomiasis in both sexes is a significant risk factor for Human Immunodeficiency Virus (HIV) infection due to both local genital tract and systemic immunological effects. Schistosome co-infection may hasten HIV disease progression in individuals already infected with HIV, and facilitate viral transmission to sexual partners **(**Kjetland*et al*., 2006).

The link between *S. haematobium* and urinary bladder cancer has been documented. For example, squamous cell carcinoma of the urinary bladder has been associated with

Schistosoma haematobium infection in studies in many areas of Africa (Mbabadzi *et al*., 2011). In addition, studies from Africa have shown that the estimated incidence of urinary bladder cancer is higher in areas with a high prevalence of infection with *S. haematobium*, compared to areas with a low prevalence. Urinary bladder cancer as a proportion of all cancers appears to be 10 times more common among men in Egypt than among men in Algeria. Furthermore, the estimated incidence of urinary bladder cancer is related to the proportion of cancerous urinary bladder specimens containing *S. haematobium* eggs which is more common in men, who are more involved in agricultural work, than in women. A higher proportion of urinary bladder cancers are seen in areas where there is histological evidence of infection compared to areas without these characteristics (Kjetland*et al.*, 2012).

In Kenya, urinary schistosomiasis is estimated to affect roughly one-quarter of the Kenyan population (King *et al*., 2005). It occurs mainly in areas around the upper and lower Coast Province and some parts of the Lake Victoria and Kano plains in Western Kenya as shown in Fig 2.2

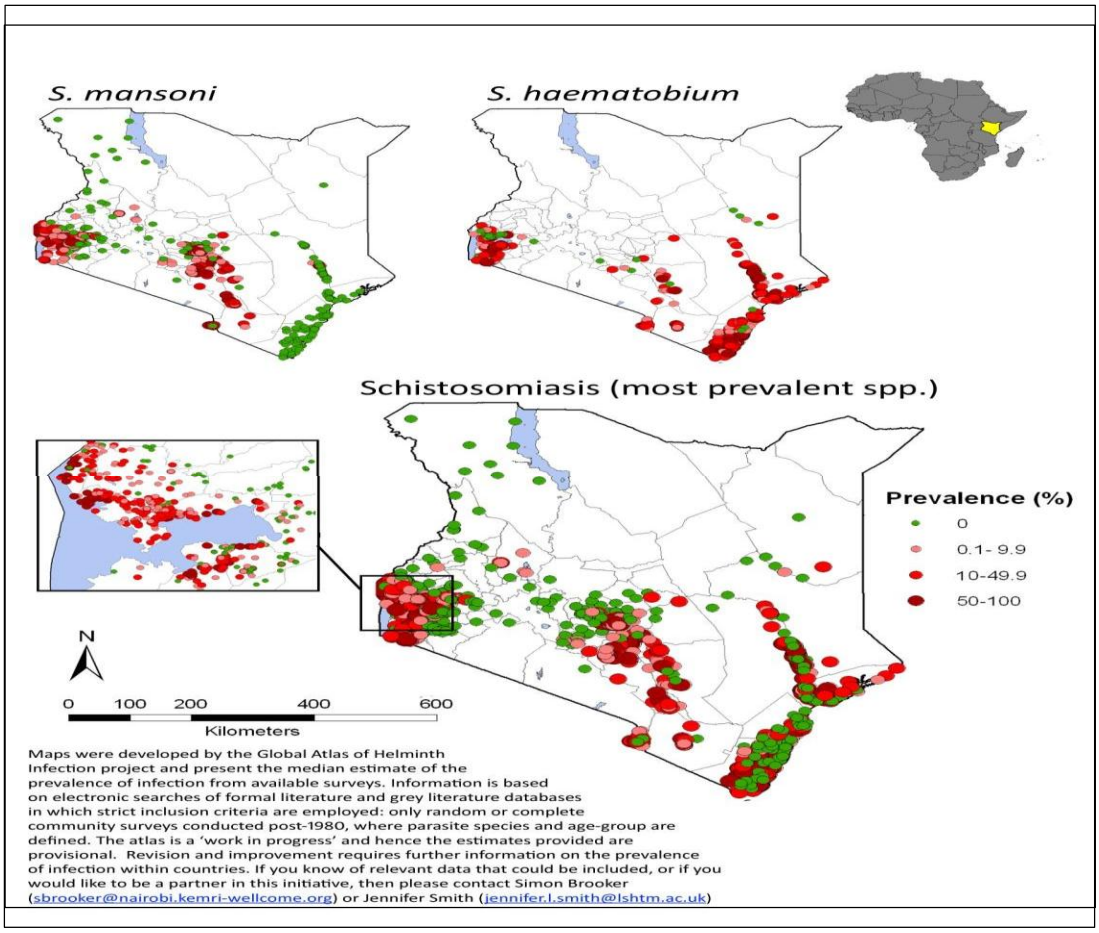

Figure 2.2: Prevalence of Schistosomiasis in Kenya (Courtesy of Brooker Simon, 2008)

In affected populations, children carry the heaviest burden of infection (Gryseels*et al*., 1996) and in young children, urogenital schistosomiasis causes hematuria, dysuria, nutritional deficiencies, anemia, growth retardation, decreased physical performance and impaired memory and cognition(Koukounari 2007, Jukes *et al*., 2002, Bhargava*et al*., 2003).

The prevalence and intensity of *Schistosoma* infections in humans follow a characteristic pattern of variation with age. Standard age prevalence curves for schistosomiasis, which are based on egg excretion, show that both prevalence and

intensity of infection peak between 10 and 15 years of age, after which prevalence declines gradually over years and infection intensity decreases more rapidly (Sleigh *et al*., 1986). The age distribution of infection rates and intensity is generally attributed to high levels of contact with cercariae-contaminated water among school-aged children and adolescents followed by less water contact and the development of an acquired protective immunity against infection in older adolescents and adults (Dalton *et al*., 1978, Butterworth *et al*., 1985, Wilkins *et al*., 1984). In contrast, younger children are often thought not to be infected with schistosomes or to have such low intensity infections that they do not suffer morbidity. Most mass treatment programs have not been designed to include them and younger children are often not even screened for the possibility of infection (Stothard *et al*., 2007). However, in areas endemic for schistosomiasis, very young children are also in regular contact with water in locations where infected snails are present and infants are bathed in water where transmission is occurring (Mafiana *et al*., 2003, Odogwu *et al*., 2006, Woolhouse *et al*., 2000, Sousa *et al*., 2010). Previous studies on human infection with *S. haematobium* suggest a role for the immune response in efficient egg excretion. It is possible that younger children have not developed the appropriate immune responses to excrete eggs, leading to false negative results when urine examinations are used for diagnosis (Karanja *et al*., 1997).

The frequency of schistosome infections among infants and young children is being increasingly recognized (Stothard *et al*.,2011) This situation was overlooked, partly, because of an emphasis on school-aged children, the low parasite egg output at this age, and the low sensitivity of standard diagnostics. Early childhood infection undoubtedly has a substantial role in host immunomodulation and the establishment of chronic antischistosome-egg inflammation that contributes to pathological effects in endemic pediatric populations (Bustinduy *et al*., 2013). Over 123 million children suffer from schistosomiasis worldwide, but only school aged children (SAC) are presently targeted for mass drug administration (MDA) with PZQ treatment in WHO-led preventive chemotherapy (PC) efforts (Colley *et al*., 2014). This is despite growing evidence that in some endemic foci a majority of PSAC become infected and can develop early disease

(Stothard *et al*., 2013, Sousa *et al*., 2012). The need to include the vulnerable PSAC group inMDA in order to prevent and avert early-onset morbidity is acknowledged by the WHO, and work is in progress to develop a workable pediatric PZQ formulation (WHO 2011). Nevertheless, ongoing MDA programs only cover 34.6% of SC with standard tablets (600 mg), meaning at least 79 million SC go untreated (WHO 2016), contributing to the existing double PZQ treatment gap (untreated PSAC and SC). There is commitment to scale up this figure in the next few years, as PZQ donation is soon to reach more than 100 million SC per year (WHO 2018).

2.2 Schistosome Biology

2.2.1 Species and Their Hosts

Schistosomiasis is a parasitic disease caused by infection with platyhelminth, trematode blood fluke worms of the genus Schistosoma. In addition to infecting man, the parasite infects a range of animals and birds. In human beings the disease is caused by mainly five species: *S. haematobium* in Africa and Middle East; *S. mansoni* in Africa and South America; *S. japonicum* in South East Asia, China and Philippines; *S. mekongi* in South East Asia and *S. intercalatum* in Africa (Gray *et al.,* 2011)). Specific parasites have different snail intermediate hosts, egg morphology and final location in the definitive hosts. *S. haematobium* and *S. intercalatum* develop in *Bulinus* species of snails; *S. mansoni*, in genus *Biomphalaria*; *S. japonicum* in genus *Onchomelania* and *S. mekongi* in *Tricula* species (Gray *et al.,* 2011). The most common parasites affecting man in Africa are *S. mansoni* and *S. haematobium*, whose adult worms reside in the blood vessels of the intestines and urinary tract respectively. The reservoir hosts play an important role in the epidemiology of the disease since they are a source of infection even after the human population has been cured of the disease (Cheng, 2007).

2.2.2 Life Cycle

Schistosomes are digenetic trematodes of the family Schistosomatidae. The adult worms are dioecious with separate sexes. Schistosome life cycle involves an intermediate host, usually a fresh water snail and a definitive host that can be humans, various animals or birds.

The schistosome life cycle undergoes an alteration of generations in two different hosts with the asexual, multiplying stage in the intermediate snail host and the sexual non-multiplying stage in the definitive host (human). Mature eggs hatch only in fresh water (with right temperature and light), releasing a ciliated free swimming larval stage known as miracidium, which remains infective for up to 48 hours and must find appropriate intermediate host to continue the life cycle. The miracidium penetrates the snail and transforms into primary sporocyst which intern develops into daughter sporocysts, migrate to the snail's digestive gland and mature and multiply (germ ball), eventually releasing many unisexual free swimming cercariae into water. When definitive host (man) is in contact with water, cercariae will penetrate the skin, shed its tail and transform into a schistosomulum, which then enters the blood stream. The schistosomulum is transported passively by the blood flow via the left side of the heart and lungs and to eventually reach the liver where the worms feed and attain maturity (male and female)(Brooker *et al.,* 2009a).

Depending on the species the paired worms either migrate to the mesenteric veins *S. mansoni, S. japonicum, S. intercalutum*) or to the veins of the vesicle plexus (*S. haematobium*). It is in this location that the female will lay their eggs whose number varies depending on the species. Many eggs are trapped in the tissues as they are transported in the blood stream and are the cause of the observed morbidity. About half of the eggs penetrate through the bladder or intestinal wall and are excreted to the external environment via the urine or faeces to continue the life cycle (Brooker *et al*., 2009a).

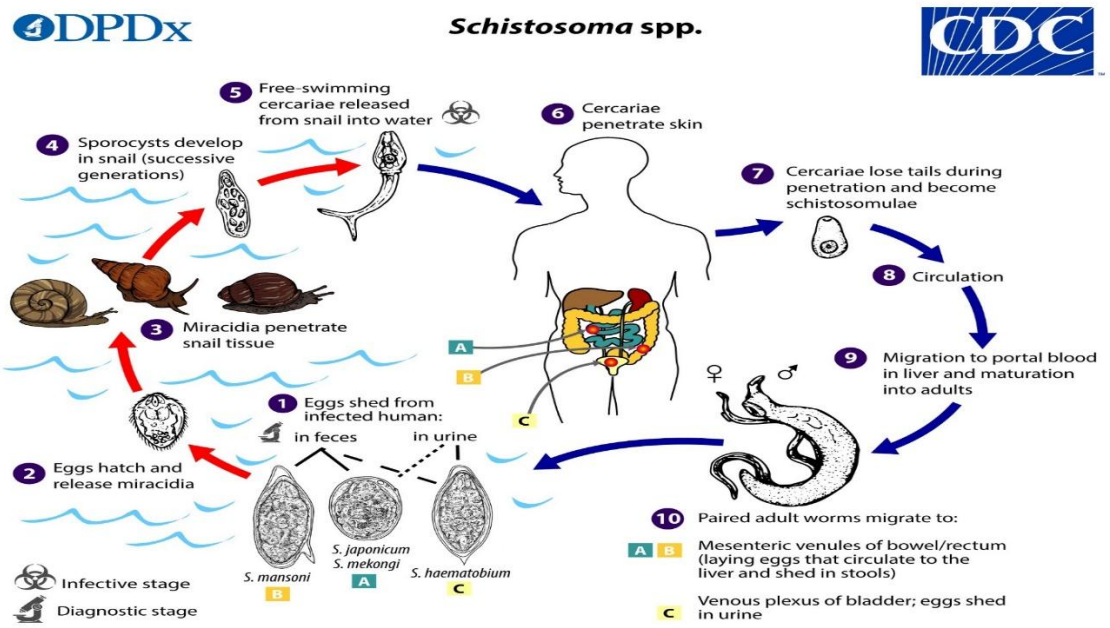

Figure 2.3: Life Cycle of Schistosomes, courtesy of CDC www.cdc.gov/parasites/.

2.3 Clinical Manifestations of *S. haematobium*

Eggs trapped in the host tissues are the major cause of pathology. Some infected individuals remain asymptomatic (Utzinger *et al*., 2001), while others may incur severe irreversible morbidity depending on immunological factors, age, gender and duration of exposure (Doehring-Schwerdtfeger *et al*., 1992; Booth *et al*., 2004). Clinical disease can be divided into three categories, as described in the following section, depending on the schistosome stage of infection.

2.3.1 Cercarial Dermatitis

When the cercaria penetrates the skin, an immediate reaction to cercarial antigens occurs that leads to cercarial dermatitis, commonly called, ‘swimmers itch’ and the patient scratches. The dermatitis presents as erythymatous lesions and after approximately 10-

15 hours they appear as a maculo papular rash that peaks 2-3 days after cercarial penetration. The lesions disappear spontaneously after 5-7 days (Gryseels *et al*., 2006; Leutscher &Magnussen, 2006). Due to scratching, a secondary infection may occur and result into vesicles or pustules (Leutscher & Magnussen, 2006). Cercarial dermatitis is rare in individuals living in endemic areas and may go unnoticed.

2.3.2 Acute Schistosomiasis

Acute schistosomiasis is a systemic hypersensitivity reaction against migrating schistosomulae and starts 3 to 9 weeks after cercarial penetration. Acute schistosomiasis can occur in both light and heavy infections. The schistosomulae grow into adult worms that lay eggs and the eggs pass through the bladder or intestinal walls but approximately 50% of them are trapped in the walls and mediate an immune reaction, that cause mucosal granulomatous inflammation and formation of pseudopolyps and scars around the trapped eggs (Vennervald & Dunne, 2004, Gryseels *et al*., 2006) leading to an inflammatory reaction and the response to this reaction causes a sudden feverish syndrome, with severe systemic illness referred to as Katayama fever (Gryseels *et al*., 2006). Individuals with acute schistosomiasis may have enlarged tender livers and on rare occasions a slightly enlarged spleen. Other symptoms associated with acute schistosomiasis include; intermittent abdominal pains, fever, high eosinophilia, headache, malaise, localised oedema, unproductive irritating cough, loss of appetite, weight loss, nausea, vomiting, bloody diarrhoea and muscular pains. The acute stage lasts 14-21 days. As with 'Swimmer's itch', Katayama fever mainly affects those from non-endemic areas who are exposed to the parasite for the first time, like tourists and immigrants (Cheever *et al*., 2000, Gryseels *et al*., 2006).

2.3.3 Early Manifestation of *S. haematobium*

Pathology of *S. haematobium* infected individuals most frequently occurs in the bladder. This is an early reaction triggered by some of the retained eggs that are carried to the liver via the portal circulation where they get trapped in the presinusoidal periportal

spaces in the liver. The eggs contain a developing miracidium, which releases proteolytic enzymes through minute pores in the egg shell. The released enzymes give rise to typical eosinophilic inflammatory and granulomatous reactions that result in granuloma formation (Gryseels *et al*., 2006). When the miracidium in the egg dies, usually after about 6-8 weeks, the antigen load decreases and the granuloma sometimes shrinks. Healing of the affected area leads to formation of fibrotic lesions around the portal venules. The granulomatous reactions and the fibrotic lesions may result in hepatosplenic schistosomiasis, which may be accompanied by increased portal pressure. The severity of these symptoms is associated with intensity of infection and related to the type of immune responses generated by the infected individual (Vennervald *et al*., 2004, Gryseels *et al*., 2006). Hepatosplenic schistosomiasis is more common in children and adolescents than in adults (Vennervald *et al*., 2004).

2.3.4 Late Manifestation of *S. haematobium*

The *S. haematobium* eggs deposited in the tissues of the ureters can cause obstructive uropathy, hydroureter and hydronephrosis, which can be visualized by ultrasonography. One study showed that presence of lesions was related to the intensity of infection both on individual and population level (Hatz, 2001). Calcification of the bladder has been suggested as a risk factor towards the development of bladder cancer. Obstructive uropathy can give rise to gradual compression of the kidney parenchyma eventually causing non-functioning kidney. The glomerular and proximal tubular function of the kidney may remain intact for a long time (Utzinger *et al*, 2011). Squamous cell bladder carcinoma may contribute to death attributed to *S. haematobium* infection.

Whereas the most typical symptoms of urinary schistosomiasis, namely, hematuria and proteinuria, are directly due to the emergence of eggs, symptoms of intestinal schistosomiasis are unspecific, including abdominal pain, diarrhea, and blood in stool. Eventually, a heavy and chronic *S. haematobium* infection can lead to bladder cancer and kidney failure, whereas chronic *S. mansoni* infections can lead to hematemesis, and

heavy *S. japonicum* infections to liver cirrhosis, which is a risk factor for colon and liver cancer (Utzinger *et al*, 2011).

2.4 Diagnosis of Schistosomiasis

2.4.1 Microscopy

Infections are conventionally diagnosed by the detection of fluke eggs in fecal or urine samples. Microscopic examination of stool or urine is the gold standard for diagnosis but requires the adult worms to be producing eggs (Gray, 2011). The eggs are sufficiently characteristic to facilitate specific diagnosis (Arora *et al.,* 2002).

The eggs of *Schistosoma haematobium* are large (110-170 µm long by 40-70 µm wide) and bear a conspicuous terminal spine as shown in figure 2.4.

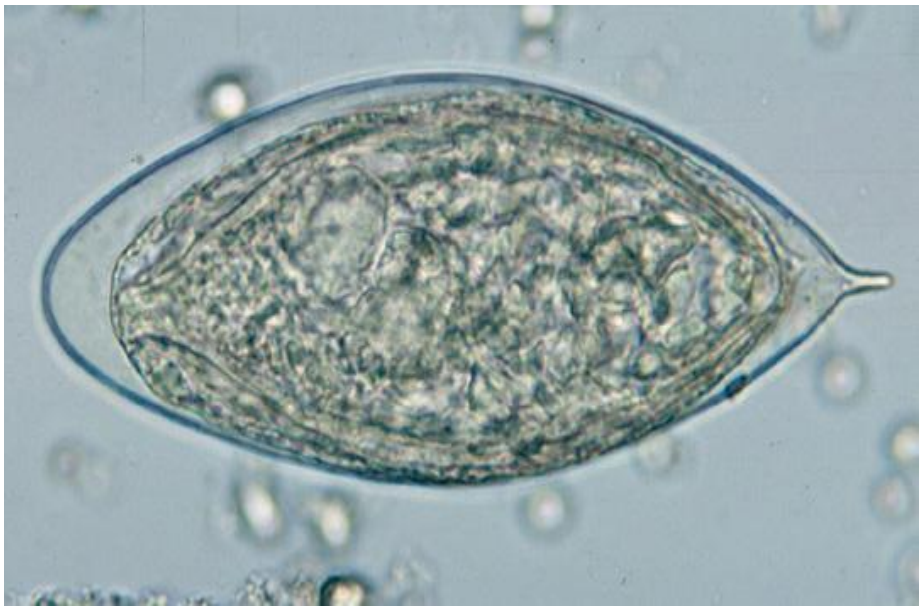

Figure 2.4: Egg of S. haematobium in wet mount of urine concentrates, showing the characteristic terminal spine. (Source: CDC, 2013)

2.4.2 Urine Filtration Method

Urine filtration is one of the methods recommended by the WHO for the detection of *Schistosoma haematobium* (WHO 2013). The filtration device is composed of a plastic filter holder that contains a nylon filter (pore size, 12 to 20 µm). Complete filtration of the urine is ensured by a rubber O-ring that prevents urine from bypassing the filter. For diagnostic purposes, a standard 10-ml quantity of the urine to be tested is forced through the device with a syringe. If eggs of *S. haematobium* are present (size 150 by 60 µm), they are unable to pass through the filters and can be observed and counted under a microscope with a 10x objective. It has a specificity of 94.6% and sensitivity of 100% (Koukounari *et al*., 2009)

The intensity of infection of *S. haematobium* is categorized as light, moderate or heavy based on the number of eggs per 10ml of urine (WHO, 2002). From population studies the mean egg burdens correlate with the severity of the disease (Ross *et al.,* 2002, Gryseels *et al*., 2006). Urine is collected between 10 a.m. and 2 p.m., to coincide with the peak production of eggs by the blood fluke *S. haematobium*(Omenesa*et al*., 2015)

2.4.3 Immunological Tests

Schistosoma infection is highly immunogenic and a wide range of immunodiagnostic techniques to detect anti-schistosome antibodies, which are present in serum and urine of infected individuals have been developed.These antigens are commonly referred to as Circulating Anodic Antigens (CAA) and Circulating Cathodic Antigens (CCA) according to their migratory behavior in immune electrophoresis. The enzyme-linked immunosorbent assay (ELISA) technique uses soluble egg antigens (SEA) as the target. Measurement of CAA in blood serum and urine ELISA based assays is sensitive, specific and much less variable than egg counts (Chand *et al.,* 2010).Detection of circulating adult worm and egg antigens is a promising technique that may supersede traditional diagnostic methods. There is recent development in immunoblot assay for the detection of adult worm antigens which reportedly has 95% sensitivity and 100% specificity. It is capable of detecting low levels of antigens from adult worms and eggs (Gray, 2011).

The tests are useful in patients who are not excreting eggs such as those with katayama syndrome. The tests are also useful in field studies for defining regions of low endemicity, where individual patients have low egg burdens and may also be beneficial in determining whether infection has re-emerged after an apparently successful control programme. However, they have several drawbacks common to antibody detection techniques such as difficulty in distinguishing active from past infection with parasite specific antibodies remaining for a long time after cure. They also have the inability to measure the intensity of the infection (Storthard *et al.*, 2006, Gryseels *et al.*, 2006).

2.4.4 Ultrasonography

Diagnosis can also be done using ultrasound which is a noninvasive, radiation free and inexpensive way to assess morbidity.Ultrasonography can detect hypertrophy of the bladder mucosa, thickening of the bladder wall and bladder calcification (Clive, 2012). In some patients, calcification of the ureters can be detected. Dilation of the renal collecting system can be detected very early and this represents significant uretic dysfunction. Ultrasonography should be repeated after treatment, about 70% of schistosomiasis bladder lesions regress in less than 12 months after treatment with praziquantel (Clive, 2012).

2.5 Treatment and Control of Schistosomiasis

Control of schistosomiasis is normally aimed at reducing infections and morbidity by interrupting the parasite life-cycle. This can be achieved through different methods directed on the hosts, parasites and the environment (CDC, 2012). Schistosomiasis control measures include regular chemotherapy, health education; good sanitation, avoiding contact with contaminated water and control of the vector snails (Gryseels, 1990, WHO, 2002). Integrating various measures is expected to yield better results.

2.5.1 Chemotherapy

Chemotherapy plays a major role in the control of schistosomiasis and represents the single most effective and practical strategy to control human schistosomiasis. The World

Health Organization changed the schistosomiasis control policy from interrupting the transmission by snail control to morbidity control by treating endemic populations with praziquantel once a year (WHO, 2002).

Praziquantel is still the only drug used for treatment of all schistosome species in Sub-Saharan Africa (Utzinger & Keiser, 2011). It is effective against all adult *Schistosoma* species and according to the WHO, it is considered safe in pregnancy, lactation and in children below the age of 24 months (Gryseels *et al*., 2006). It is administered at 40 mg/kg of body weight and it works by causing severe spasms and paralysis of the worm muscles, exposing worm antigens and allowing the body immune system to attack them. The drug achieves 60-90% cure rates with egg reduction of 90-95% in those not cured (WHO, 2012). However, the drug is not effective against eggs and juvenile schistosomes; therefore, follow-up at 4-6 weeks is recommended with a repeat of treatment in 6-12 weeks (CDC, 2013). It cannot be used for chemoprophylaxis because of its short half-life (1-1.5 hours) and it cannot kill schistosomula that are 3-21 days old. Furthermore, it can be administered by non-medical personnel and has tolerable mild adverse effects (Raso *et al*., 2004; Gryseels *et al*., 2006). However, Vinkeles*et al*., (2014) observed that some individuals with high pre-treatment schistosomiasis infection intensity may experience serious adverse effects.

Many countries have used it in their control programmes (N'Goran *et al*., 2003), among which Egypt treated 20 million people between 1997 and 1999 (Cioli, 2000; Doenhoff *et al*., 2000). Magnussen (2003), in his review of 10 years of experience with schistosomiasis control in different African, Asian and American endemic settings, proposed various treatment targets for schistosomiasis with regard to prevalence of infection. With a prevalence ≥ 50%, the school-age children should be mass treated once every year; with a prevalence in the range of 20 – 49.9%, all school-age children should be treated once in every 2 years and at a prevalence < 20%, only the infected individuals should be treated or enrolled school children should be treated twice in their school time, i.e. at the beginning and completion of primary school level.

In May, 2001 the WHO Assembly passed Resolution 54.19 which recommended regular treatment of high risk groups in endemic areas, particularly school age children, as the best means of reducing morbidity and mortality (WHO, 2002). The frequency of treatment is determined by the prevalence of the infection in school-age children. In high transmission areas, treatment may be repeated every year for a number of years with constant monitoring to determine the impact of the control measure (WHO, 2014). However, re-infections occur due to the cost of implementing the control measures. People of all ages can get re-infected following treatment, although older people re-acquire the infections at slower rates than younger ones (Kabatereine *et al*., 2007).

The government of Kenya launched the National School-Based Deworming Programme (NSBDP) in 2009.The programme's goal is to eradicate parasitic worms as a public health problem in Kenya. Through the NSBDP, the GOK seeks to improve the health and education status of its children and secure Kenya's future. Regularly providing deworming tablets to children through schools is a proven cost-effective treatment strategy due to the readily available, extensive and sustained educational infrastructure. The WHO has certified the safety of administering deworming tablets by teachers, with support from the local health system.

The NSBDP is implemented by the MOE in collaboration with the MOH with technical assistance from Deworm the World Initiative (DtWI) at Evidence Action.

2.5.2 Snail Intermediate Hosts Control

Snail control has been used with some success though a perfect molluscicide does not exist. A list of desirable characteristics for molluscicides includes; toxicity to snails in low concentrations, absence of toxicity to mammals, lack of adverse effects when it enters the food chain and are stable in storage for at least 18 months (WHO, 2002). In addition, proven efficacy, specificity to snails and a variety of formulations and easy measurement of concentration in breeding sites is desirable (De souza, 1999). Niclosamide is currently the preferred molluscicide but the high cost of importing it

limits the use. However, it has successfully been used in The People's Republic of China, Egypt, and Morocco (Yang *et al*., 2010). The berries of endod (*Phytolacca dodecandra*) have been shown to be natural molluscicide when they fall into the water (Hanelt *at al*., 2001) and its presence by the sides of the river in Ethiopia has been shown to be associated with reduction in local snail population (Sharma, 2009).

Biological control of snails using predators and competitor snails has had some success. Competitor snails such as *Marisa comuarietis* compete for food with the intermediate hosts and prey on snail eggs and has been used in Puerto Rico as a control agent. *Melanoides tubSERUulata* and *Thiara granifera* are also competitor snails. A cray fish *Procambarus clakii* feeds on *Biomphararia* species and can reduce snail population significantly. Snail eating fish have been cultured and released in the infected water with some success such as in The Peoples' Republic of China (Schimidt and Roberts, 2000; Zhou *et al*., 2010).

Environmental management has been practiced to control the snail vectors. This involves altering the rate of water flow by clearing the vegetation in the drainage canals, stream channelization, seepage control and canal lining. It makes the habitat unsuitable for snails which prefer stagnant shaded water. However, this method is not practical to apply since altering the environment may make it suitable for other disease vectors such as *Simulium* that prefer fast moving water (CDC, 2013).

2.5.3 Public Health Education

Public health education is a very effective way of controlling many infectious diseases. Educating communities on: proper disposal of human waste, wearing shoes while in the fields and dangers of bathing, swimming, washing clothes or fetching water in canals and slow moving streams is effective in controlling schistosomiasis (WHO, 2014). In endemic countries such as Kenya and Nigeria it helps minimize infections in human hosts, significantly reduce contact with the infected water as well as prevent the contamination of the environment with human waste from infected persons. However,

this has been hampered by high illiteracy levels of people living in infected environments such as irrigated land and lack of amenities such as toilets especially in the fields where they spend time working and also lack of piped water for domestic use (CDC, 2013; WHO, 2014). Behavioral change and public health education interventions should be tailored to children's understanding so that the goal of modifying the behavior to not urinating or defecating into open water, or being in contact with the open water while playing or washing to interrupt transmission can be met. Behavioral interventions should also target children's role models such as parents, older siblings and teachers so that they can exemplify adequate behavior change through their own life. Sensitizing children, parents and teachers on the importance and benefit of periodic deworming might increase the coverage of drug intake and this reduces worm burden in humans (Utzinger *et al.,* 2007).

2.5.4 Use of Vaccination

Vaccines confer effective protection against infections. A vaccine could reduce worm fecundity and/ or prevent *Schistosoma* infection and re-infection not only in humans but also reservoir hosts such as water buffaloes that significantly contribute to transmission of *Schistosoma japonicum* (McManus *et al*., 2008). Over the past 20-30 years, multiple vaccine candidates based on recombinant-derived schistosome proteins (Loukas *et al.,* 2007), radiation-attenuated schistosome larval stages (Bickle, 2009; Lin *et al*., 2011) or DNA- derived proteins have been identified (McManus *et al*., 2008). Although protection against various schistosome species was achieved in wide range of host reservoir animals, there are currently only very few vaccine candidates such as recombinant Sm 14/FABP antigen and rSh28GST antigen which are studied in clinical trials (Tendler *et al*., 2008; Webster *et al.,* 2010). However, there is no vaccine for schistosomiasis though a number of parasite derived antigens confer partial protection against re-infection when used on mice. Research is currently underway to develop a vaccine for schistosomiasis (WHO, 2014).

CHAPTER THREE

MATERIALS AND METHODS

3.1 Study Site

This study was conducted in Kwale County, which is situated in the Coast Region of Kenya. It has 4 sub-counties: Msambweni, Lunga-Lunga, Matuga and Kinango. The total population stands at 642,609 of which 137,262 are PSAC (Kenya National Bureau of Statistics 2019). Kwale County is mainly an inland county, but it has a coastline south of Mombasa. The area is hot and humid year-round with annual mean temperature range of 22°C - 34°C, average relative humidity range of 70% - 80%, and annual rainfall range of 900–1500 mm. Altitude ranges from 0 to 462 meters above sea level. The majority of the population 81.9% lives in the rural areas with poor road and transport network. Poverty which stands at 71% and lack of sanitation in this area contributes a lot to the high prevalence of soil-transmitted helminthes especially in infants and pre-school children. A large proportion of the population in the study area has no access to safe water and adequate sanitation (Kenya Demographic Health Survey 2019)

The current study was conducted in Matuga and Lunga-Lunga sub-counties.

3.2 Study Design

This study was a longitudinal, pre and post-test design conducted from May to July 2015. Detection of Schistosoma infections was conducted before and after treatment with crushed PZQ mixed with quencher orangefruit juice. The acceptability and safety of PZQ was also assessed. The experimental design entailed laboratory examination of urine samples from the children, where efficacy of the crushed praziquantel mixed with fruit juice was determined, by assessing the prevalence and intensity of the *Schistosoma haematobium* eggs pre and post treatment. The descriptive explanatory strategy assessed any adverse effects after treatment through researcher administered questionnaires to the parents/guardians of the ECD children 24 hours after treatment. Any adverse

effectsexperienced by the children one-hour post treatment were observed and recorded by the teachers of the ECD children and community health extension workers (CHEWs) who took part in the treatment of the children. It also assessed the acceptability of the crushed praziquantel mixed with fruit juice, by observing if the child spat and/ or vomited all or part of the PZQ dose immediately after treatment.

3.3 Target Population

This study was embedded in a larger study: Evaluating Different Drug Delivery Approaches for Treatment of STH and Schistosomiasis Infections in the NSBDP among Children Attending ECD Centers in Coast Province, Kenya. SC No. 2547. In this study, 28 ECD Centers were targeted for treatmentwith PZQ. In the above study, it was the first time that the PSAC from these ECD Centers were receiving MDA with PZQ.

In the present study, 10 schools were randomly selected in Matuga and Lunga-lunga sub-counties, from these 28 ECD Centers targeted for treatment with PZQ for the first time. The selected schools for this study were Bondeni A, Bondeni B, Bumbani Khairat, Kiduka, Mbegani, Miongoni, Mwananyahi, Mwauchi and Kindergarten in Diani. All the children $\leq$ 6 years of age were enrolled in this study. The total number of children enrolled in this study was 400 PSAC and excluded those who had an existing medical condition.

3.3.1 Inclusion Criteria

Eligibility for inclusion into this study included: 1) aged $\leq$ 6 years old at recruitment; 2) enrolled in ECD centers that were targeted for treatment with Praziquantel; 3) production of a urine sample; 4) Parental/guardian consent to participate in the study.

3.3.2 Exclusion Criteria

Children whose parents failed to give consent and those who had existing medical conditions were excluded from the study. These criteria were based on the WHO Manual of Preventive Chemotherapy (WHO 2006).

3. 4 Sample Size Determination

The minimum required sample size for the proposed study was determined using the formula by Cochran (1963). Since the prevalence of urogenital schistosomiasis in pre-school age children in Kwale County is unknown, a prevalence of 31.1%based on a similar study by Amin *et al* (2012) was used to calculate the sample size. Additionally, 95% confidence level was adoptedin the estimation of the sample size.

$$n = \frac{Z_{\alpha}^{2} pq}{d^{2}}$$

Where;

n = Minimum required sample size

Z_{α} = Normal standard deviate for the desired confidence level (95%)

p = Proportion of pre-school children with urogenital schistosomiasis (0.31)

q=1-p (0.69)

d=Desired level of precision (0.05)

$$n = \frac{0.95^{2}{}_{x}\, 0.31\, x\, 0.69}{0.05^{2}} = 329.4$$

Hence, the minimum required sample size for the survey was 330 children.

3.5 Specimen Collection during Pre and Post-treatment with Praziquantel

3.5.1 Pre-treatment

A fresh urine specimen was collected from each child in 120ml clean, labeled, plastic, wide mouthed urine containers with lids, between 10 a.m. and 2 p.m., to coincide with the peak production of eggs by the blood fluke *S. haematobium* (Odegaard *et al*., 2012). This was doneafter consenting by parents or guardians in English or Kiswahili, (See Appendix 1 and 2). The pupils were given clean, labeled urine containers in school to collect single terminal urine of at least 10 ml and return the containers immediately. The Principal Investigator and Laboratory Technician instructed and demonstrated to the children how to use the container to collect urine. For the very young ones less than 4 years, the Principal Investigator and Laboratory Technician together with the ECD teacher, assisted in urine collection. The urine samples were examined immediately by gross observation for presence of blood in urine (macro hematuria).

The labeled properly capped containers containing the urine samples were transported with a cooler box to the KEMRI Center for Microbiology Research, Kwale Laboratory for microscopic examination to determine the presence of Schistosome eggs (Darren *et al*., 2011) within the same day.

3.5.2 post-treatment

Five weeks post treatment; urine samples were collected from the children who had tested positive for ova of *S. haematobium*. The sample collection and processing procedures were the same as those pre-treatments. This was to assess cure and egg reduction rates (WHO 2013).In the present study, a child was considered to have been cured if no *S. haematobium* eggs were detected microscopically in urine samples collected 5 weeks' post-treatment.

The egg reduction rate was calculated as the decrease in geometric mean intensities of *S. haematobium* eggs divided by pre-treatment geometric mean intensity multiplied by a factor of 100 (WHO 2013).

$$\textbf{ERR (\%)= 100 x}\left(1 - \frac{\textbf{arithmetic mean egg counts at follow-up}}{\textbf{arithmetic mean egg counts at baseline}}\right)$$

3.6 Specimen Processing

This was done within the same day of collection at the KEMRI Center for Microbiology ResearchLaboratory, Kwale.

3.6.1 Urine Filtration

Nuclepore urine filtration method was used to determine prevalence and intensity of Schistosoma infection (Richard *et al* 2014). This filtration method involves passing 10 ml of thoroughly mixed urine through the microfilm of pore size 15 μm. *S. haematobium* eggs which are 120-150 μm in diameter are bigger than the pore size of the microfilm and hence get trapped on the surface of the film. The film was transferred on to the labelled microscope slide upside down.The film remained fixed on the slide as it was examined under a microscope at low magnification objective of X10 and X40. A drop of lugol's iodine was added to stain the eggs during examination as previously described by Odegaard and Hsier, 2014. This was done in duplicate.

3.6.2 Urine Examination-Observation and counting of the *S. haematobium* eggs

Schistosoma haematobium eggs from the two filters were each counted per filtrate from 10 ml of urine and recorded according to egg count categories. The mean counts of the two filters were recorded according to egg count categories which included;Egg counts ranging 1 to 49 per 10 ml of urine indicated light infection; 50 - 100 eggs per 10 ml indicated heavy infection and above 100 eggs per 10 ml indicated very heavy infection

(WHO, 2006).For quality control, 10% of the urine filter slides were re-examined by a senior laboratory technician as recommended by WHO 2013.

3.7 Treatment with Praziquantel

400 PSAC were enrolled, tested and treated for *S. haematobium*. Praziquantel tablets (Prazitel®, Cosmos Ltd) were used for treatment in this study. These were received as a donation from WHO for the NSBD Programme.Children were treated by trained community health workers (CHWs) supervised by a trained nurse or public health officer. They were assisted by the teachers of the ECD centers. This was done during the health break. The parents and ECD teachers of the children were requested to ensure that the children were well fed before treatment. This was coordinated by the ECD school teacher by having the parents provide porridge to their children in school for those ECD centers that do not normally provide porridge during the health break.Each child was weighed using a calibrated weighing scale and a single dose of 40mg/kg PZQ administered. Before administration, the orange fruit juice was dilluted in a ratio of 1:1 (1part water:1-part juice); the PZQ tablets after splitting were crushed with a mortar and pestle and the powder mixed with 300mls of diluted orange juice to decrease the bitter taste.

Drug administration was supervised using the modified Direct Observation Therapy (DOT). One-hour post-treatment observations for any adverse effects were made and recorded by the 10 ECD teachers and CHEWs who took part in the deworming exercise.

It is important to note that an appropriate pediatric formulation for treating pre-school aged children is currently not available outside of Egypt (i.e., PZQ syrup, Epiquantel, manufactured by the Egyptian International Pharmaceutical Industries Co. A.R.E., Cairo, Egypt). Recent studies using Epiquantel in PSAC revealed similar efficacy with crushed praziquantel tablets (Navaratnam *et al*., 2012, WHO (2010). Hence, the common approach in high endemic areas is to use PZQ tablets (600 mg), crush them between two spoons, mix with water or fruit juice, and then administer orally to pre-

school aged children at a dose of 40 mg/kg (Stothard *et al.*, 2011, Garba *et al*.,2010, Sousa-Figueiredo *et al.*, 2010b).

3.8 Adverse Effects

An adverse effect was defined as a symptom absent before treatment and experienced after treatment with crushed praziquantel mixed with orange juice.

One-hour post-treatment observations for any adverse effects were made and recorded by the ECD teachers and CHEWs who took part in the deworming exercise.

Parents or guardians of the treated children were also interviewed using structured questionnaires 24 hours' post-treatment for episodes of treatment-related adverse effects. The study clinician evaluated the following adverse effectsabdominal pain, dizziness, nausea, headache, vomiting, drowsiness, itching, as likely or unlikely associated with study drug. Other symptoms reported by parents or guardians were also recorded.

3.9 Treatment Efficacy Evaluation

Treatment efficacy was defined as the percentage of children positive at the pre-treatment cross-sectional survey who became egg negative 5 weeks after treatment.

Five weeks after PZQ administration, urine samples from the children who tested positive for *S. haematobium* were collected again, using the same procedures. The efficacy of praziquantel was assessed five weeks post treatment using the same diagnostic criteria as baseline. This was determined by means of cure rate (CR, percentage of children positive at the pretreatment cross-sectional survey who became egg-negative 5 weeks after treatment, as assessed by urine filtration for *S. haematobium*) and egg reduction rate (ERR, reduction in the group's geometric mean *S. haematobium* egg count in 10 ml of urine comparing the before and after treatment situation) (Sabah *et al*., 1986).

3.10 Treatment Acceptability Evaluation

Treatment acceptability was defined as the number of children spitting and/or vomiting all or part of the PZQ dose, immediately after treatment and it was assessed by DOT and recorded by the ECD teachers and CHWs who took part in the MDA. This was the first time that these children were being treated in school with praziquantel. This was done using the

3.11 Statistical Analysis

Data were double entered in Microsoft Excel spreadsheet. Statistical analyses were done with Statistical Package for Social Sciences (SPSSversion 17). PSAC who had at least one urine sample subjected to a filtration method for *S. haematobium* diagnosis before and after treatment were included in the final analysis. Continuous data (e.g., schistosome egg counts) are presented as geometric mean. Infection intensities were stratified according to the cut-offs defined by the WHO (2004).

Data collected through interviewer administered questionnaire, including data on acceptability of PZQ and adverse effects that were observed by parents and ECD teachers were analyzed descriptively using mean (standard deviation) for continuous variables such as age. Further categorical variables were described using absolute numbers and proportions

3.12 Ethical Considerations

Ethical clearance to conduct the current study, including review and approval was obtained from Kenya Medical Research Institute Scientific and Ethics Review Unit-KEMRI SSC No.2958 (See Appendix 5).Permission to conduct this study was also sought from the county education office, county health office, local leaders, teachers, children and parents/guardians were informed about the study in the area. Written

informed consent was obtained from a parent or guardian, for every child in the study. In addition, oral assent was obtained from the children. Research participants were informed of their right to participate or withdraw at any stage of the study and such decisions were respected. Confidentiality was upheld during the research (See Appendix 1)

CHAPTER FOUR

RESULTS

4. 1 Demographics of Enrolled Pre-school Age Children

The present study enrolled a total of 400 children of pre-school age (≤ 72 months). The mean age of the children was 4.8±1.1 years. Those aged three years or less constituting 11.2%, 4 years (26.3%), 5 years (27.5%) and 6 years (35%) of the study sample. Only one child was aged two years. Boys constituted 51.2% whereas girls were 48.8% of the enrolled children as shown in Table 4.1

Table 4.1: Characteristics of Enrolled Pre-school Age Children

Characteristic	Frequency (n=400)	%
Age (years)		
≤ 3	45	11.2
4	105	26.3
5	110	27.5
6	140	35.0
Sex		
Male	205	51.2
Female	195	48.8

4. 2 Efficacy of Praziquantel Treatment

Efficacy outcomes of PZQ 40mg/kg against *S. haematobium* was reported as cure rate and egg reduction rate. This was determined by means of cure rate (CR, percentage of children positive at the pre-treatment cross-sectional survey who became egg-negative 5 weeks after treatment, as assessed by urine filtration for *S. haematobium)* and egg reduction rate (ERR, reduction in the group's geometric mean *S. haematobium* egg

count in 10 ml of urine comparing the before and after treatment situation) (Sabah *et al*., 1986).

4.2.1 Parasitological Cure Rates

The overall pre-treatment prevalence of *S. haematobium* infections was 20.0% (16.4% - 24.2% 95% confidence interval (CI) and the post-treatment was 2.5% (1.5% - 4.9% 95% CI). The parasitological cure rate of praziquantel treatment was thus 87.5% (95% CI 77.0% - 92.1%). The cure rates of praziquantel treatment did not differ with the age or sex of the PSAC as shown in Table 4.2

Table 4.2: Parasitological Cure Rate of Praziquantel Treatment

Variable	Pretreatment infections		Post-treatment infections		Cure rate		P-value
	No.	% (95%CI)	No.	% (95%CI)	No.	% (95%CI)	
Overall (n=400)	80	20.0 (16.4 - 24.2)	10	2.5(1.5 - 4.9)	70	87.5 (77.0 - 92.1)	-
Sex							
Male (n=205)	47	22.9 (17.7 - 29.2)	8	3.9 (2.3 - 8.1)	39	82.9 (67.5-89.6)	0.087
Female (n=195)	33	16.9 (12.3 – 22.8)	2	1.0 (0.2 - 3.7)	31	93.9 (80.4 – 98.3)	
Age group							
≤ 4 years (n=150)	14	9.3(5.6 - 15.1)	0	0.0 (0.0 - 2.5)	14	100.0 (78.5 - 100.0)	0.102
5 years (n=110)	19	17.3 (11.4 - 25.4)	2	1.8 (0.5 - 6.4)	17	89.5 (68.6 - 97.1)	0.395
6 years (n=140)	47	33.6 (26.3 - 41.7)	8	5.7 (3.4 - 11.8)	39	83 (67.5 - 89.6)	REF

4.2.2 Effect of Praziquantel Treatment on Infection Intensities

Before treatment was conducted, 80 out of the 400 children (20%) were infected with *S. haematobium*. Forty-one of the 80 children (51.3 %) who were infected with *S. haematobium* had heavy intensity of infection (≥50 eggs/10 ml urine), whereas 39 children had light intensity of infection (1–49 eggs/10 ml urine). The number of boys infected (58,8%) were more than the girls (41. 2%).Children aged 6 years had the highest rate of infection 58.8% followed by 5 years, who had 23.8%, those aged 4 years had 11.2%, while those aged ≤3 years recorded the lowest infection rate of 6.2% (Table 4.3). Visible hematuria (gross hematuria) was observed in 7 children who had heavy intensity of infection. After treatment with Praziquantel, 10 children who were infected with *S. haematobium* were found to have an infection of light intensity (1–49 eggs/10 ml urine). These were the children who had heavy intensity of infection (≥50 eggs/10 ml urine) before treatment.

The overall geometric mean of *S. haematobium* eggs in the infected children before treatment was 45.9 (95% CI: 31.0 - 68.0) eggs/ 10 ml urine. Post-treatment geometrical mean intensity of *S. haematobium* eggs was 1.4 (95% CI: 1.1 - 1.7) eggs/ 10 ml urine. This variation between pre- and post-treatment geometrical mean intensity was statistically significant ($p<0.001$). The ERR was 96.9% following treatment. Pre-treatment and post-treatment arithmetic mean intensity of *S. haematobium* was 146 and 2.7 respectively. The reduction in the intensities of the infection was significant even when the analysis was stratified by sex and age ($p<0.001$ for sex and $p<0.05$ in all age categories) as shown in Table 4.3.

Table 4.3: S. haematobium Infection Intensities

Characteristic	N	Geometric mean (95% CI) *		P-value
		Before Treatment	After treatment	
Overall	80	45.9 (31.0 - 68.0)	1.4 (1.1 - 1.7)	<0.001
Sex				
Male	47	59.2 (36.6 – 101.5)	1.7 (1.2 - 2.5)	<0.001
Female	33	32.0 (16.8 – 61.0)	1.1 (0.9 - 1.5)	<0.001
Age group				
≤ 3 years (n=45)	5	11.0 (2.5 - 48.4)	1.0 (0.0 - 1.0)	0.034
4 years (n=105)	9	42.1 (13.7 - 129.2)	1.0 (0.0 - 1.0)	<0.001
5 years (n=110)	19	32.4 (13.4 -78.1)	1.4 (0.7 - 2.4)	<0.001
6 years (n=140)	47	62.6 (38.6 - 101.5)	1.5 (1.1 - 2.0)	<0.001

**eggs/10ml urine*

4.3 Adverse Effects

These were assessed 24 hours post treatment through researcher administered questionnaires to the parents or guardians and through observations made and recorded one-hour post treatment by the ECD teachers and CHEWs, who took part in the deworming exercise.

Three hundred and thirty out of the 400 children recruited in the study were assessed for AEs 24 hours post treatment. One experienced dizziness, one experienced a headache, four had abdominal pain/discomfort, two had nausea and two experienced itching. None of the children vomited. While six respondents took no action when their child experienced an adverse effect, one gave food, two gave milk and the other one made the child to rest as shown in Table 4.4

Table 4.4: Adverse Effects through Parent's Questionnaires 24 hours Post-Treatment

Characteristic	Number	%
Experienced any side effects after deworming (n=330)		
Yes	10	3.0
No	320	97.0
Adverse effects (n=10)		
Vomiting	0	0
Abdominal Pain/discomfort	4	40
Headaches	1	10
Nausea	2	20
Dizziness	1	10
Itching	2	20
Action taken (n=10)		
Given food	1	10
Given milk	2	20
None	6	60
Rested	1	10

4.4 Treatment Acceptability Evaluation

In this study treatment acceptability was defined as the number of children spitting and/or vomiting all or part of the crushed PZQ dosemixed with orange juice, immediately after treatment. This was assessed by DOT by the ECD teachers and CHEWS who took part in deworming. All the 400 ECD children enrolled in this study were treated with the crushed PZQ mixed with fruit juice.

The ECD teachers and CHEWS observed and recorded that none of the children spat and/or vomited the PZQ dose mixed with orange juice during treatment.

CHAPTER FIVE

DISCUSSION, CONCLUSION AND RECOMENDATIONS

5.1 Efficacy of praziquantel in crushed praziquantel against *S. haematobium* among ECD children of Kwale County.

Results of the current study showed that praziquantel achieved high cure rates of 86.2% against *S. haematobium* infections 5 weeks after treatment. This is in agreement with results of a Cochrane systematic review which showed that treatment with the standard dose of praziquantel (40 mg/kg) generally results in cure rates of 95% 1-2 months after treatment (Kramer *et al*.,2014). In this study, the results show that 10 children out of the 80, who had tested positive for *S. haematobium*, had an infection of light intensity (1–49 eggs/10 ml urine) after treatment. These were the children who had infections of heavy intensity of (≥50 eggs/10 ml urine), before treatment. The design of our study did not allow estimating the proportion of infections after treatment that was due to juvenile stages of the parasite, which are largely insensitive to praziquantel. This is in line with a study in Mali assessing urinary schistosomiasis in pre-school aged children showing that, the presence of *S. haematobium* eggs five weeks post-treatment could be explained by factors such as high pretreatment worm load that could not be completely cleared by the treatment that remained in the treated children and started producing eggs, and the presence of high numbers of immature worms less sensitive to praziquantel that escaped drug action and matured to egg producing worms during subsequent follow-ups (Dabo *et al* ., 2011); praziquantel is refractory against immature worms (Sabah *et al* ., 1986). The effect of treatment in terms of egg reduction rates which was 96.9% was high and supported by evidence of Cochrane systematic review (Danso *et al*., 2008). This is also in line with the reference drug efficacy of PZQ (600-mg tablet) against *S. haematobium* by WHO 2013.

The results of this study revealed that the prevalence of *S. haematobium* in PSAC from Kwale County was high (20%).This is in comparison to a study, that observed the same

prevalence among school aged in the same county (24.5%) (Hotez *et al*., 2009). The findings are consistent with emerging evidence that the burden of schistosomiasis is high in pre-school aged children. A similar study in Sudan investigating the safety, efficacy and acceptability of praziquantel in pre-school age children reported a prevalence of 31.1% (Amin *et al*., 2012), which is higher than what was found in this study (20%). In Ghana, a study investigating the extent of schistosomiasis in pre-school children and infants found prevalence of 11.2% for *S. haematobium*, with the highest egg count detected in a 4-month-old infant (Amni *et al*., 2012, Bosompem *et al*., 2004).

In a rural endemic area in Nigeria, a prevalence of 58.1% was reported for *S. haematobium*in children aged 1-6 years (Ekpo *et al*., 2010). Similar findings have emerged from Mali where prevalence of *S. haematobium* among pre-school children aged 1-4 years was found to be 51.2% (Dabo *et al*., 2011). In Uganda nearly 50% of children less than three years of age living along the northern shoreline of Lake Victoria had *S. mansoni* infections (Sousa *et al*., 2010a). A study from the shoreline villages of Lakes Albert and Victoria in Uganda found even higher prevalence of *S. mansoni* (62.3%) in pre-school children (Sousa *et al*., 2010b). The common feature associated with infection in these children from the various settings would be likely due to the fact that the children and their caregivers (parents or guardians) share the common risk factor of proximity to large water bodies known to harbor infectious cerceria. Schistosomiasis in infants and pre-school age children is of concern for at least two reasons. First, this younger age-group plays a hitherto unrealized role in maintaining local disease transmission; even though these infected children may be excreting fewer eggs, it is their regular water contact that leads to contamination of water. Moreover, rinsing and washing children's soiled clothes in environmental water bodies also contributes towards more cryptic contamination and disease transmission (King *et al*., 2004). Thus, this age-group will play an increasingly important role in environmental transmission likely to frustrate the attempts made by preventive chemotherapy campaigns striving towards more general reductions in environmental transmission (Sousa*et al*., 2012). Second, such regular water contact is also likely to result in frequent

(re)infection episodes, which lead to a progressive increase of individual worm burden. It is therefore likely that untreated infections acquired in early childhood contribute to worsening the longer-term clinical picture of disease in the individual. Lack of safe water supplies, inadequate sanitation, insufficient access to health care and prohibitive treatment costs all contribute to disease transmission and high morbidities, especially in infection with schistosomiasis. *S. haematobium* infection that is predominant in Coastal region of Kenya is found to cluster in a subset of school age children with suggestions of synergistic effects on anemia, cognitive performance and stunting (Kihara *et al*., 2011).Chronic anaemia during childhood is associated with impairment in physical growth, cognition, and school performance (Fenwick*et al*., 2009), whereas severe anemia accounts for up to one half of the deaths in children younger than 5 years of age (Kjetland*et al*., 2006).

In Kenya, during the 2009 treatment, only primary school-age children, both enrolled and non-enrolled were covered by the National School Based Deworming Programme, leaving out the children in the age bracket of 2-6 years who attend the ECD Centers or pre-school. This age bracket requires to be treated as they also carry a heavy worm burden and pose a risk of re-infecting the treated school-age children while interacting and playing at the community level. In Kenya, the population of children enrolled in ECD Centers is 2.2 million (Granthame*t al*.,2001). A high percentage of infected children means that the environment becomes more heavily contaminated, which in turn increases the risk of infection for the whole community. By reducing the number of worms in children, everyone benefits (WHO 2004).

5.2 Adverse effects of crushed PZQ among ECD children of Kwale County

Praziquantel at a single dose of 40mg/kg body weight continues to be a safe and tolerable drug among pre-school age children, as observed in this study. Only 10 out of the 330 children experienced treatment-associated adverse seffects within twenty-four hours of praziquantel administration. Furthermore, in this study, almost all of the

observed adverse effects among the pre-school aged children were mild and transient, similar to reports from a recent study by Coulibaly *et al*., 2017 and no serious adverse effects were reported. Previous studies have also shown that there have not been severe adverse reactions to PZQ treatment when given to young children due to the excellent safety and tolerability (Sousa *et al*., 2012).

Praziquantel is reported to be associated with gastrointestinal symptoms (such as abdominal pain, nausea, vomiting and diarrhea), neurological symptoms including (headache, muscle pain, drowsiness, dizziness and fainting), and dermatological symptoms (such as itching, skin rashes) Zwang *et al*., 2020. The type and severity of the adverse effects mainly depend on pre-treatment infection intensity and feeding status of the children before drug administration may help reduce the nauseating effect of the drug. As recommended by WHO 2013, the provision of meals before drug administration may help to reduce the nauseating effect of the drug and hence, also reduce the occurrence and severity of treatment-associated adverse effects of the drug. In this study the adverse effects experienced by the children were not severe and included nausea, dizziness, vomiting, abdominal pain/discomfort, itching, and headache which were largely self-limited. This is in line with other studies involving pre-school age children, where minor and transient side-effects 24 hours after treatment were reported in Uganda (Sousa *et al*., 2012), and in Mali (Dabo *et al*., 2011) in accordance with established evidence that praziquantel is associated with minor and transient adverse effects (Dabo *et al*.,2011, Korenromp *et al*., 2004).In a study in Sudan there were no drug-related adverse effects experienced after treatment with praziquantel (Amin *et al*., 2012). In studies carried out in Uganda and Mali, the adverse effects experienced were minor and transient 24 hours after treatment whereas in Sudan, no adverse effects were reported. In this study, abdominal pain was the most observed adverse event (40%) and this is in line to a similar finding as reported by Coulibaly *et al*., 2017.

5.3 Acceptability of crushed PZQ mixed with fruit juice among ECD children of Kwale County.

The taste of pharmaceuticals is of particular importance as it highly affects the compliance of patients, especially for patient groups like children. PZQ an affordable anthelmintic is the recommended gold-standard drug for the treatment of schistosomiasis. Treatment for PSAC has not been implemented due to several key obstacles that include difficulty in swallowing and risk of choking given the large-sized commercially available tablets and high rejection rates due to the bitter taste when pills are crushed and dispersed in liquids which could reduce treatment adherence (Jaison *et al*., 2018).

In this study PZQ was administered in crushed tablet form and mixed with orange-juice as previously piloted (WHO 2006).In our study none of the children spat and/or vomited during treatment.Previous studies have shown that the fruit flavor helped to mask the bitter taste of PZQ (Korenromp *et al*., 2004).

5.4 Conclusions

The objective of this study was to assess the efficacy, adverse effects and acceptability of treating pre-school age children with praziquantel for *Schistosoma haematobium* infection in selected ECD Centers of Kwale County, Kenya

i. The study concludes that the burden of*S. haematobium* among pre-school aged children is high, as indicated by a prevalence of 20%.Among the children who were infected with *S. haematobium* 51.3 % had heavy intensity of infection (≥50 eggs/10 ml urine), whereas 39 children had light intensity of infection (1–49 eggs/10 ml urine).
ii. The study findings showed that crushed praziquantel administered to pre-school aged children at a dose of 40 mg/kgis effective in the treatment of urogenital schistosomiasis. This is evident as praziquantel achieved high cure rates of 86.2% against *S. haematobium* infections 5 weeks after treatment.

iii. From the study it is evident that praziquantel at a single dose of 40mg/kg body weight continues to be a safe and tolerable drug among pre-school age children. Only 3% of the treated children experienced treatment-associated adverse effects within twenty-four hours of praziquantel administration. Furthermore, in this study, almost all of the observed adverse effects among the pre-school aged children were mild and transient

iv. Praziquantel administered in crushed tablet form and mixed with orange-juice is well tolerated by pre-school aged children. This is as observed in this study where none of the children spat and/or vomited during treatment.

5.5 Recommendations

i. The high prevalence rates of *S. haematobium* infections among the pre-school age children suggests that there is need for the ministry of health of Kwale County to carry out mass screening and treatment among these children and the community as a whole.

ii. Treatment for urinary schistosomiasis should be integrated within child health services such as child immunization programs in the county. Campaigns for urinary schistosomiasis should also be integrated into other public health interventions such as malaria, HIV/AIDS and tuberculosis in the county.

iii. There should be collaboration with health promotion and community strategy units to achieve behaviour change communication among the community members and the caregivers, in the control of schistosomiasis.

iv. The Kwale County Government should ensure provision of safe water, adequate sanitation and hygiene, among its residents.

v. This research has shown that the pre-school children are infected with *S. haematobium*. Further research is recommended among the caregivers. This would inform their inclusion in control strategies since they act as carriers, infecting the pre-school age children and the rest of the population.

vi. Continued research efforts should be made to identify and embark on the control of snail vectors in the county to generate data that can be used in integrated vector management control programs.

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APPENDICES

Appendix 1: Consent Form for Persons Below 18 Years of Age

Title of Study: Efficacy, Adverse Effects and Acceptability of Praziquantel in the treatment of *Schistosoma haematobium* in pre-school age children: a study of selected Early Childhood Development Centers of Kwale County, Kenya

Introduction

I am a MSc.Student at the Jomo Kenyatta University of Agriculture and Technology currently working on my research study for a master's degree course in Public Health.

Your child/dependent is asked to participate in a public health research project on a disease caused by worms known as urinary schistosomiasis (bilharziasis). This disease is common in most coastal areas due to prevailing environmental conditions that favor its transmission. The international body known as World Health Organization (WHO) has asked governments in regions where this disease occurs to undertake programmes to control and even eliminate it as a public health problem. One of the ways to control this disease caused by worms is by giving treatment to all persons living in areas where the infections occur. The purpose of this consent form is to give you information that might help you to decide whether to participate in the study or not. You are allowed to ask questions related to the study and implications on your part.

Purpose of the study

In Kwale County, children in selected early childhood education centers will receive treatment for urinary schistosomiasis (bilharziasis) in the ongoing National School Based Deworming Programme. The treatment consists of a drug known as, praziquantel (PZQ). The current project aims to determine the acceptability safety and efficacy of

praziquantel among the ECD children. The results of this study will provide the Ministry of Health with information that might become useful during administration of similar programmes in other parts of the country.

Procedures to be followed

A study technician will ask your child to give a small amount of urine, to find out if he/she has schistosomiasis. The specimen will be tested in the KEMRI laboratories for urinary schistosomiasis.

Risks

The risk from participation in this study is minimal. Urine collection does not involve any invasive procedure

Benefits

Your child's urine will be checked for urinary schistosomiasis. The children will be given treatment free of charge. The treatment also has benefits for improving blood quality (anaemia).

Results

Once the urine is examined for urinary schistosomiasis, the principle investigator will bring back the results to you. These results will be collected at a date that will be communicated to you by the principle investigator through your child's teacher before your child is treated.**Assurance of confidentiality**

Your child's name and other records will remain confidential and will not appear when we present this study or publish its results.

Right to refuse or withdraw

It is important that you understand the following general principles that will apply to all participants in the study:

1. Your child's participation is entirely voluntary.
2. You may withdraw your child from this study any time without penalty or loss of benefits.

Please feel free to ask any questions that you may have.

Do you agree to let your child/dependent to participate in the study? Yes [ ]
No [ ]

I acknowledge that this consent form has been fully explained to me in a language that I understand and I do agree to let my child/dependent to participate in the study.

Parents/Guardian's name: _____

Parents/Guardian's signature or thumb print: _____ Date: ___/___/____

Study Number: _____

Name of Child (Participant): _____

Name of Witness: _____

Signature or thumb print of Witness: _____ Date: ___/___/_____

Investigator's signature: _____ Date: ___/___/____

Contact

If you have questions in the future, please contact the Principal Investigator of this study, Bridget Kimani, Kenya Medical Research Institute (KEMRI), Centre for Microbiology Research (CMR), P.O. Box 19464-00200, Nairobi, telephone 020-2720794 or The Secretary, KEMRI Scientific Ethical Review Unit, P.O Box 54840-00200, Nairobi, telephone 020-2722541 or 020-2713349.

Appendix II: Kiswahili Version of Consent Form for Persons Below 18 Years of Age

Title of Study: **Efficacy, Adverse Effects and Acceptability of Praziquantel in the treatment of *Schistosoma haematobium* in pre-school age children: a study of selected Early Childhood Development Centers of Kwale County, Kenya**

Mimi ni mwanafunzi katika chuo kikuu cha Jomo Kenyatta University of Agriculture and Technology. Lengo la utafiti huu ni kuniwezesha kustahimili Shahada ya Uzamili.

Utangulizi

Mtoto wako anaulizwa kujihusisha kwenye mradi wa utafiti wa matibabu dhidi ya ugonjwaunaosababishwa na minyoo - ugonjwa wa kichocho. Ugonjwa huu hupatikana katika sehemu za mkoa wa pwani kwa sababu ya hali ya mazingira. Shirika la afya ulimwenguni (WHO), limehimiza mataifa ambapo ugonjwa huu unapatikana kuanzisha miradi ya kuzuia na hata kuuangamiza. Jinsi moja ya kuuzuia ugonjwa unaosababishwa na minyoo ni kuwapa dawa watoto wote wa maeneo yanayokumbwa na ugonjwa huu. Fomu hii ya makubaliano itakuelimisha kuhusu ugonjwa huu ili uweze kuamua kama utamruhusu mtoto wako kujihusisha au kutojihusisha kwenye utafiti huu. Unakubaliwa kuuliza maswali yanayohusiana na uchunguzi huu wakati wowote tunapoendelea kujadiliana.

Shabaha ya uchunguzi

Pengine unajua ya kwamba watoto wa wilaya ya Kwale watakuwa wakipata matibabu kutoka kwa wizara ya afya dhidi ya ugonjwa wa kichocho. Matibabu haya yanahusu dawa inayojulikana kama praziquantel. Utafiti huu mpya ambao nakuuliza kujihusisha nao unanuia kuchunguza matibabu dhidi ya ugonjwa wa kichocho, na pia kuweza kudhibitisha umuhimu wa kuwapa madawa wanafunzi

shuleni Matokeo ya uchunguzi huu yataiwezesha wizara ya afya kujua mambo yatakayotiliwa maanani wakati watakapokuwa wakitoa matibabu kama haya sehemu zingine nchini.

Yatakayofanyika

Mfanyi kazi wa afya atamuuliza mtoto wako kutoa vipimo vidogo vya mkojo. Kisha ataupima ili aweze kutambua kama mtoto wako ana ugonjwa wa kichocho. Hutajulishwa matokeo ya ugonjwa utakaopimwa usipouliza kuyajua.

Madhara

Madhara yapatikanayo kwa kujihusisha na uchunguzi huyu ni machache sana.Utoaji wa mkojo hauna uchungu wowote wala jeraha.

Manufaa

Manufaa utakayoyapata ni upimaji wa kichocho. Mtoto wako aatatibiwa bila malipo. Matibabu haya pia huzuia upungufu wa damu mwilini (anaemia).

Matokeo/Majibu

Baada ya mkojo wa mtoto wako kupimwa utaweza kupata matokeo iwapo mtoto wako ana kichocho au la. Mtafiti mkuu atawasiliana nawe kuhusu siku ya kupata majibu kupitia mwalimu wa mtoto wako. Hii itafanyika kabla ya mtoto wako kutibiwa.

Siri

Wakati tutakapowasilisha matokeo ya uchunguzi huu au kuchapisha nakala, jina la mtoto wako na stakabadhi zinazomhusu zitahifadhiwa kisiri.

Haki ya kukataa au kujiondoa

Ni muhimu uyaelewe yafuatayo:

1. Kujihusisha kwenye uchunguzi huu ni kwa hiari yako
2. Unaweza kumuondoa mtoto wako wakati wowote bila kuadhibiwa au kupoteza manufaa

Sasa unaweza kuuliza maswali yoyote yanayohusiana na uchunguzi huu.

Je,unakubali mtoto wako kuhusishwa katika uchunguzi huu? Ndio [ ]
La [ ]

Nakubali kuwa hii fomu imeelezwa vyema kwa lugha ninayoielewa na nimekubali mtoto wanguahusishwe katika uchunguzi.

Jina la mtoto: _____

Sahihi au alama ya kidole cha mzazi:_____ Tarehe:
____/____/____

Nambari ya mtoto: _____

Jina la shahidi: _____

Sahihi ya shahidi: _____ Tarehe:
___/___/___

Sahihi ya mchunguzi: _____ Tarehe:
___/___/___

Maelezo au maswali zaidi

Ukiwa na maswali baadaye, unaweza kuwasiliana na mkuu wa uchunguzi huu Bridget W. Kimani Kenya Medical Research Institute (KEMRI), Centre for Microbiology Research (CMR), SLP 19464-00202, Nairobi; simu 020-2720794au Karani, KEMRI – SERU, SLP 54840-00200 simu 020-2722541 au 020-2713349.

Appendix iii: English Version Parents Questionnaire

Title of Study: **Efficacy, Adverse Effects and Acceptabilityof Praziquantel in the treatment of *Schistosoma haematobium* in pre-school age children: a study of selected Early Childhood Development Centers of Kwale County, Kenya**

Socio demographic data for parents

Name of interviewee: _____

Age: _____

Sex: M [ ] F [ ]

1. Main occupation (Tick)
    a. Peasant farmer [ ]
    b. Small business (kiosk, kibanda) [ ]
    c. Bigger business (shop) [ ]
    d. Housewife [ ]
    e. Salaried worker (teacher, police, chief) [ ]
    f. Fisherman [ ]
    g. Casual laborer [ ]
2. Level of Education (Tick)
    a. Never attended school [ ]
    b. Did not complete primary school [ ]
    c. Completed primary school but did not complete secondary school [ ]
    d. Completed secondary school [ ]
    e. Others (specify) _____
3. Religion? (Tick)
    a. Christian [ ]

b. Islam [ ]

c. Others (specify)_____

4. Marital Status (Tick)

a. Single [ ]

b. Currently married [ ]

c. If married - Polygamous [ ] Monogamous [ ]

d. Divorced [ ]

e. Widow/widower [ ]

5. Was your child treated for urinary schistosomiasis?

a. Yes [ ] b. No [ ] c. Do not know [

6. If yes, where did your child receive treatment?

a) At home [ ]

b) In school [ ]

c) At the health center [ ]

d) In church [ ]

e) At the mosque [ ]

f) Other:_____

7. Did the children have any side effects after deworming? (Tick)

a. Yes [ ] b. No [ ] c. Do not know [ ]

8. If yes, which side effects did they suffer? (Tick all that apply)

a. Vomiting [ ]

b. Abdominal Pain/discomfort [ ]

c. Headaches [ ]

d. Nausea [ ]

e. Diarrhea [ ]
f. Dizziness [ ]
g. Fever [ ]
h. Allergic reaction [ ]
i. Other (Specify)_____

9. If yes what action did you take to manage the side effect?

10. Do you think that the side effects suffered are related to the deworming?

a. Yes [ ] b. No [ ] c. Do not know [ ]

Thank you for your participation in this exercise.

Appendix IV: Kiswahili Version Parents Questionnaire

Title of Study: Efficacy, Adverse Effects and Acceptabilityof Praziquantel in the treatment of *Schistosoma haematobium* in pre-school age children: a study of selected Early Childhood Development Centers of Kwale County, Kenya

Socio demographic data for parents

Jina la muhusika: _____

Umri: _____

Jinsia: Kike [ ] Kiume [ ]

1. Kazi (Tia alama ya kusahihisha)
    a. Mkulima [ ]
    b. Biashara ndogo (kiosk, kibanda) [ ]
    c. Biashara kuu (Duka) [ ]
    d. Mke nyumbani [ ]
    e. Mwajiriwa (mwalimu, polisi, chifu) [ ]
    f. Mvuvi [ ]
    g. Mfanyi kazi ya mikono [ ]
2. Kiwango cha Elimu (Tia alama ya kusahihisha)
    a. Sijawahi enda shuleni [ ]
    b. Sikumaliza shule ya msingi [ ]
    c. Nilimaliza shule ya msingi lakini sikumaliza shule ya upili [ ]
    d. Nilimaliza shule ya upili [ ]
    e. Nyinginezo (fafanua) _____
3. Dini? (Tia alama ya kusahihisha)

a. Mkristo [ ]
b. Muislamu [ ]
c. Ingine (fafanua) _____

4. Hali ya Ndoa (Tia alama ya kusahihisha)
   a. Hujaolewa [ ]
   b. Umeolewa [ ]
   c. Kama umeolewa-Wake wengi [ ] Mke mmoja [ ]
   d. Talaka [ ]
   e. Mjane [ ]
5. Je,mtoto wako alipata matibabu dhidi ya ugonjwa wa kichocho? (Tia alama ya kusahihisha)
   a. Ndio [ ] b. La [ ] c. Sina habari [ ]
6. Iwapo ndio, mtoto wako alipata matibabu wapi? (Tia alama ya kusahihisha)
   a. Kwa nyumba [ ]
   b. Shuleni [ ]
   c. Kituo cha afya [ ]
   d. Kanisani [ ]
   e. Mskitini [ ]
   f. Mahali pengine (Fafanua) _____
7. Je, Mtoto wako alipata madhara yoyote baada ya kumeza dawa za minyoo? (Tia alama ya kusahihisha)
   a. Ndio [ ] b. La [ ] c. Sina habari [ ]
8. Iwapo ndio,madhara gani yaliyowakumba? (Tia alama ya kusahihisha)
   a. Kutapika [ ]
   b. Maumivu ya tumbo [ ]
   c. Kuumwa na kichwa [ ]
   d. Kuhisi kutapika [ ]
   e. Kuhara [ ]
   f. Kizunguzungu [ ]

g. Kuhisi joto jingi mwilini [ ]
h. Uvimbe mwilini [ ]
i. Mengine (fafanua) [ ]

9. Iwapo mtoto wako alipata madhara yoyote, ulichukua hatua gani?
10. Je, kuna uhusiano wowote kati ya madhara yaliyomkumba mtoto wako na dawa za minyoo alizopewa?

Asante kwa kuwa mhusika katika zoezi hili.

Appendix V: Parasitology Data Form For Ecd Children

Title of Study: Efficacy, Adverse Effects and Acceptabilityof Praziquantel in the treatment of *Schistosoma haematobium* in pre-school age children: a study of selected Early Childhood Development Centers of Kwale County, Kenya

<table>
<tr><td colspan="5">SCHISTOSOMIASIS SCHOOL SURVEY - CHILD FORM

PARASITOLOGICAL DATA</td></tr>
<tr><td colspan="5">Personal data Date __/__/____

ID Number _____ School _____ Sub-county_____

Name _____ Age _____ Years _____ Sex M [ ] F[ ]</td></tr>
<tr><td colspan="5">Parasitological data</td></tr>
<tr><td colspan="3" rowspan="2">(a) Urine, visual examination</td><td colspan="2">Present</td></tr>
<tr><td>Yes</td><td>No</td></tr>
<tr><td colspan="3">Visible haematuria(Blood in urine)</td><td></td><td></td></tr>
<tr><td rowspan="2">(b) Urine, examination by microscopy</td><td rowspan="2">eggs/10 ml urine</td><td rowspan="2">Heavy-intensity threshold (>50eggs/ml)</td><td colspan="2">Heavy-intensity infection</td></tr>
<tr><td>Yes</td><td>No</td></tr>
<tr><td colspan="3"></td><td></td><td></td></tr>
</table>

Appendix VI: Acceptability Data Form for Ecd Children

Title of Study: Efficacy, Adverse Effects and Acceptabilityof Praziquantel in the treatment of *Schistosoma haematobium* in pre-school age children: a study of selected Early Childhood Development Centers of Kwale County, Kenya

SCHISTOSOMIASIS ECD SURVEY –CHILD ACCEPTABILITY

DATA

ID Number _____ School_____ Date __/__/__

No.	Name	Age	Sex	Spat	Vomited

Appendix VII: Ethical Clearance Letter

KENYA MEDICAL RESEARCH INSTITUTE

P.O. Box 54840-00200, NAIROBI, Kenya
Tel (254) (020) 2722541, 2713349, 0722-205901, 0733-400003; Fax: (254) (020) 2720030
E-mail: director@kemri.org info@kemri.org Website:www.kemri.org

KEMRI/RES/7/3/1 **March 26, 2015**

TO: **BRIDGET W. KIMANI,**
PRINCIPAL INVESTIGATOR

THROUGH: **DR. WILLIE SANG,**
ACTING DIRECTOR, CMR,
NAIROBI

forwarded 1/4/2015

Dear Madam,

RE: **SSC PROTOCOL NO. 2958 - (*RESUBMITTED-INITIAL SUBMISSION*): ACCEPTABILITY, ADVERSE EVENTS AND EFFICACY OF PRAZIQUANTEL IN THE TREATMENT OF SCHISTOSOMA HAEMATOBIUM IN PRE-SCHOOL AGE CHILDREN: A STUDY OF SELECTED EARLY CHILDREN DEVELOPMENT CENTRES OF KWALE COUNTY, KENYA-(*VERSION 5.0 DATED 3rd MARCH, 2015*)**

Reference is made to your letter dated 10th March, 2015 and the revised documents received at the KEMRI/Scientific and Ethics Review Unit (SERU) on 23rd March, 2015.

This is to inform you that the Committee notes that the issues raised at the 236th meeting of the KEMRI/Ethics and Review Committee (ERC) held on 17th February, 2015 have been adequately addressed.

Consequently, the study is granted approval for implementation effective this day, **26th March, 2015** for a period of one year. Please note that authorization to conduct this study will automatically expire on **March 25, 2016.** If you plan to continue data collection or analysis beyond this date, please submit an application for continuation approval to SERU by **February 12, 2016.**

You are required to submit any proposed changes to this study to SERU for review and the changes should not be initiated until written approval from SERU is received. Please note that any unanticipated problems resulting from the implementation of this study should be brought to the attention of SERU and you should advise SERU when the study is completed or discontinued.

You may embark on the study.

Yours faithfully,

EAB

PROF. ELIZABETH BUKUSI,
ACTING HEAD,
KEMRI/SCIENTIFIC AND ETHICS REVIEW UNIT

Appendix VIII: Publication and Dissemination of Results

PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Safety, efficacy and acceptability of praziquantel in the treatment of *Schistosoma haematobium* in pre-school children of Kwale County, Kenya

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OPEN ACCESS

Citation: Kimani BW, Mbugua AK, Kihara JH, Ng'ang'a M, Njomo DW (2018) Safety, efficacy and acceptability of praziquantel in the treatment of *Schistosoma haematobium* in pre-school children of Kwale County, Kenya. PLoS Negl Trop Dis 12 (10): e0006852. https://doi.org/10.1371/journal.pntd.0006852

Editor: Amaya Lopez Bustinduy, London School of Hygiene and Tropical Medicine, UNITED KINGDOM

Received: December 15, 2017

Accepted: September 17, 2018

Published: October 17, 2018

Data Availability Statement: All relevant data are within the paper.

Funding: The source of funding is from the Kenya Medical Research Institute-Internal Research Grants, grant number is: KEMRI/IRG/173/6. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Abstract

Background

The recommended strategy for control of schistosomiasis is preventive chemotherapy with praziquantel (PZQ). Pre-school children (PSC) are excluded from population treatment programs. In high endemic areas, these children are also at risk, and require treatment with PZQ. The Government of Kenya initiated the National School-Based Deworming Programme (NSBDP) where PSC in Early Childhood Development Education (ECDE) Centers are only eligible for treatment with albendazole (ABZ) but not with PZQ.

Methodology/Principal findings

400 PSC were enrolled, from 10 randomly selected ECDE Centers in Kwale County, Kenya where children were treated with crushed PZQ tablets mixed with orange juice, at a single dose of 40 mg/kg. Adverse events were assessed 24 hours post-treatment through questionnaires administered to the parents or guardians. Acceptability was determined by observing if the child spat and/ or vomited all or part of the PZQ dose immediately after treatment. Efficacy was assessed by examining urine samples for *Schistosoma haematobium* eggs in the 5 weeks post-treatment follow-up. Children testing negative for *S. haematobium* during the follow-up were considered cured. Egg reduction rate (ERR) was calculated as the decrement in the infection intensity (group's geometric mean egg counts per 10 ml of urine) following treatment expressed as a proportion of the pre-treatment infection intensity. Before treatment, 80 out of the 400 children enrolled in the study tested positive for *S. haematobium* (20.0% (95% confidence interval (CI) 16.4–24.2%). Of these, 41 had infections of heavy intensity (51.3%) while the rest (48.7%) were of light intensity. Five weeks post-treatment, 10 children who had heavy intensity infection were diagnosed with *S. haematobium* (prevalence: 2.5% (95% CI 1.5–4.9%). Infection intensities decreased significantly from 45.9 (95%

CI: 31.0–68.0) eggs/ 10 ml urine to1.4 (95% CI: 1.1–1.7) eggs/ 10 ml urine during pre-and post-treatment respectively. The ERR was 96.9%. There were no severe adverse events during follow up 24 hours post treatment. Treatment tolerability among the 400 children was high as none of the children spat and/ or vomited as observed in this study.

Conclusion/Significance

The study revealed that crushed PZQ is safe and effective in the treatment of urogenital schistosomiasis in this age group. It is therefore recommended that PZQ should be administered to the PSC in Kwale County.

Author summary

Control of schistosome infections is through treatment of infected people with a single dose of the anti-helminth drug praziquantel (PZQ) which is safe, highly efficacious, and can reverse schistosome-related morbidity particularly in the early stages of disease progression. However pre-school children are normally excluded due to the belief that these children are not sufficiently exposed to infective water to experience high infection rates. This could lead to clinical manifestation of the disease and the lack of safety data on praziquantel in this age group. Due to this we investigated the safety, efficacy and acceptability of praziquantel in Kwale County, Kenya. We examined urine samples from 400 preschool children. They were treated with crushed praziquantel (40mg/kg) mixed with orange juice and the efficacy of the treatment was determined 5 weeks after treatment. Acceptability was determined by whether the child spat and/ or vomited the treatment through the direct observed treatment (DOT).No child spat or vomited during treatment. Safety of the treatment was assessed by interviewing the parents of the treated children for adverse events (e.g., abdominal pain, dizziness, and headache). The treatment was well tolerated and most of the parasites were cleared by praziquantel.

Introduction

Human schistosomiasis is a major neglected public health problem caused by trematodes of the genus *Schistosoma*. Over 200 million people are infected globally, with 85% of these cases living in Sub-Saharan Africa [1]. In Kenya, nearly 6 million people are infected and an additional 15 million are at high risk of infection particularly in endemic areas [2, 3]. Schistosomiasis (Bilharzia) is classified as one of the neglected tropical diseases (NTDs). These are a group of diseases found predominantly in tropical areas that are associated with poor sanitation and poverty and which have historically received insufficient attention towards their control. The majority of infections in sub-Saharan Africa are caused by *S. mansoni* and *S. haematobium* which reside in intestinal mesenteric veins and bladder respectively, leading to intestinal and urogenital schistosomiasis. In Kenya, *S. haematobium* occurs mainly in areas around the upper and lower Coast region and some parts of the Lake Victoria and Kano plains in Western Kenya [4]. In affected populations, children carry the heaviest burden of infection [5], [6]. Symptoms of urogenital schistosomiasis include haematuria, dysurea, nutritional deficiencies, anemia, growth retardation, decreased physical performance and impaired memory and cognition [7–10, 1].

Control of schistosome infections is through treatment of infected people with a single dose of the anti-helminth drug praziquantel (PZQ) which is safe, highly efficacious, cheap (costing less than US$0.50/ dose) and can reverse schistosome-related morbidity particularly in the early stages of disease progression [11].

Studies point to a growing body of evidence that in many endemic communities, schistosomiasis infection–contrary to previous beliefs–starts in early childhood. The presence of infection, points to the fact that infants and pre-school aged children are also at risk of infection like their older school-aged counterparts. The growing concern here is that infection in infants and pre-school children (PSC) may persist until the child starts school if left untreated. In preventive chemotherapy control programmes infants and PSC are not eligible for treatment until school-age [12–14].

Failure to reach a majority of the 2–6 year olds in Early Childhood Education (ECDE) Centers could result in higher prevalence of schistosomiasis and its negative health effects such as malnutrition and poor cognitive performance. In turn, these effects retard the child's growth and development [15].

Treatment of children is also likely to be more successful in averting the development of subsequent, more serious disease sequelae because earlier stages of infection-induced pathology may be reversible if treated promptly [16].World Health Organization (WHO) recommends that young children living in endemic areas be considered for treatment with PZQ during child health campaigns at the standard dose of 40mg/kg [12].

Current schistosome control programmes advocated by the World Health Assembly in 2001 through resolution 54.19 recommend regular de-worming of school age children at risk of infection with anti-helminthes [17]. However, these programs exclude pre-school age children due to the perception that these children are not sufficiently exposed to infective water to experience high infection rates [18]. One of the concerns associated with treatment of preschoolers for schistosomiasis is that they are believed to be at risk of choking on whole tablets. The other one is that there is limited formal data with respect to prescribing information by the pharmaceutical companies on toxicity, method of administration, adverse effects and pharmacokinetics in this age group [19].This may result in clinical disease that is not managed and the lack of safety data on PZQ in this age group [11].

Previous studies have shown that, there have not been severe adverse reactions to PZQ treatment when given to young children due to the excellent safety and tolerability [17]. For administration of PZQ to children under 5 years, it is possible to break the tablet into small pieces or crush them in flavored syrup which would make the tablet palatable and acceptable [17].

The goal of this study was to assess the acceptability, adverse events and efficacy of treating pre-school children with praziquantel for *S. haematobium* infection in selected Early Childhood Development Education Centers of Kwale County, Kenya.

Methods

Ethical statement

Permission to conduct the current study, including review and approval was obtained from the Scientific Steering and Ethical Review Committees, Kenya Medical Research Institute (KEMRI) SSC No.2958. The county education office, county health office, local leaders, teachers, children and parents/guardians were informed about the study in the area. Written informed consent was obtained from a parent or guardian, for every child in the study. In addition, assent was obtained from the children.

Study site

This study was conducted in Kwale County, which is situated in the Coast Region of Kenya. It has 4 Constituencies: Msambweni, Lunga-Lunga, Matuga and Kinango. The total population stands at 649,931, of which 36,197 are PSC [20]· Kwale County is mainly an inland county, but it has a coastline south of Mombasa. The area is hot and humid year round with annual mean temperature range of 22˚C—34˚C, average relative humidity range of 70% - 80%, and annual rainfall range of 900–1500 mm. Altitude ranges from 0 to 462 meters above sea level. The majority of the population 81.9% live in the rural areas with poor road and transport network. Poverty which stands at 71% and lack of sanitation in this area contributes a lot to the high prevalence of soil-transmitted helminthes especially in infants and pre-school children. A large proportion of the population in the study area has no access to safe water and adequate sanitation [21–22]

The current study was conducted in Matuga and Lunga-Lunga constituencies.

Study design and population

Under the Kenya National School Based Deworming Programme (NSBDP), children in primary schools in the Coast region of Kenya were the first to receive treatment with albendazole and praziquantel. This was after results from a baseline survey in 2011 showed that the prevalence of soil transmitted helminthes and schistosomiasis was high [23].

This sub-study was embedded in a larger study Evaluating Different Drug Delivery Approaches for Treatment of Soil-transmitted Helminthiasis and Schistosomiasis Infections in the NSBDP among Children Attending ECDE Centers in Coast Province, Kenya. SC No. 2547. In the above study, 28 ECDE Centers were targeted for treatment with PZQ.

In the present study, 10 schools were randomly selected from these 28 ECDE Centers. All the children $\leq$ 6 years of age were enrolled in this study. The study sample was 400 PSC.

This study was a longitudinal, pre and post-test design. Detection of Schistosoma infections was conducted before and after treatment with crushed PZQ mixed with orange juice. The acceptability and safety of PZQ was also assessed. The experimental design entailed laboratory examination of urine samples from the children, where efficacy of the crushed praziquantel mixed with orange juice was determined, by assessing the prevalence and intensity of the *Schistosoma haematobium* eggs pre and post treatment. The descriptive explanatory strategy assessed the acceptability of the crushed praziquantel mixed with orange juice. It also assessed any adverse events after treatment through researcher administered questionnaires to the parents/guardians of the ECDE children 24 hours after treatment. Acceptability was determined by observing if the child spat and/ or vomited all or part of the PZQ dose immediately after treatment. Any adverse events experienced by the children one hour post treatment were observed and recorded by the teachers of the ECDE children and community health extension workers (CHEWs) who took part in the treatment of the children.

Inclusion and exclusion criteria

Eligibility for inclusion into this study included: 1) aged $\leq$ 6 years old at recruitment; 2) enrolled in ECDE centers that were targeted for treatment with Praziquantel; 3) production of a urine sample; 4) Parental/guardian consent to participate in the study.

Participants who had existing medical conditions were excluded from the study. These criteria were based on the World Health Organization (WHO) Manual of Preventive Chemotherapy [17]

Parasitological diagnosis of the infection

Urine samples were collected from all the 400 enrolled children in clean labeled wide mouthed urine containers with lids, between 10 a.m. and 2 p.m. Visible hematuria was recorded upon urine collection. The labeled properly capped containers containing the urine samples were transported with a cool box to the KEMRI Center for Microbiology, Kwale Laboratory for examination.

The urine was thoroughly mixed and a duplicate 10 ml aliquot of urine filtered through 15-mm polycarbonate filters (Nuclear pore R; Costar Europe Ltd., Badhoevedorp, the Netherlands).The filter paper was then placed on a labeled slide and a drop of Lugol's solution added. The slides were then examined under a microscope within 6 hours and the mean counts of the two filters recorded and expressed as eggs per 10ml urine [17]. The intensity of infection was categorized according to the WHO classification as negative for no detectable eggs; light for 1–49 eggs/10 ml urine; or heavy for > 50 eggs/10 ml urine.

5 weeks post treatment, urine samples were collected from the children who had tested positive for ova of *S. haematobium*. This was to assess cure and egg reduction rates [17]. In the present study, a child was considered to have been cured if no *S. haematobium* eggs were detected microscopically in urine samples collected 5 weeks post-treatment.

The egg reduction rate was calculated as the decrease in geometric mean intensities of *S. haematobium* eggs divided by pre-treatment geometric mean intensity multiplied by a factor of 100.

Treatment and adverse events

400 PSC were enrolled, tested and treated for *S. haematobium* pretreatment. Praziquantel tablets (Prazitel, Cosmos Ltd) were used for treatment in this study. Each child was weighed using a calibrated weighing scale and a single dose of 40mg/kg PZQ administered. Before administration, the PZQ tablets after splitting were crushed with a mortar and pestle and the powder mixed with fruit juice to decrease the bitter taste. This was done during the health break after the children had eaten. Drug administration was supervised using the modified Direct Observation Therapy (DOT). One hour post-treatment observations for any adverse events were made and recorded by the 10 ECDE teachers and CHEWs who took part in the deworming exercise.

Parents or guardians of the treated children were also interviewed using structured questionnaires 24 hours post-treatment for episodes of treatment-related adverse events. The study clinician evaluated the following adverse events abdominal pain, dizziness, nausea, headache, vomiting, drowsiness, itching, as likely or unlikely associated with study drug. Other symptoms reported by parents or guardians were also recorded.

Treatment efficacy evaluation

Five weeks after praziquantel administration, urine samples from the children who tested positive for *S. haematobium* were collected again, using the same procedures. The efficacy of praziquantel was assessed five weeks post treatment using the same diagnostic criteria as baseline. This was determined by means of cure rate (CR, percentage of children positive at the pretreatment cross-sectional survey who became egg-negative 5 weeks after treatment, as assessed by urine filtration for *S. haematobium*) and egg reduction rate (ERR, reduction in the group's geometric mean *S. haematobium* egg count in 10 ml of urine comparing the before and after treatment situation) [24].

Treatment acceptability evaluation

In this study treatment acceptability was defined as the number of children spitting and/or vomiting all or part of the PZQ dose, immediately after treatment and it was assessed by DOT. This was the first time that these children were being treated in school with praziquantel.

Statistical analysis

Data were double entered in Microsoft Excel spreadsheet. Statistical analyses were done with Statistical Package for Social Sciences (SPSS version 17). PSC who had at least one urine sample subjected to a filtration method for *S. haematobium* diagnosis before and after treatment were included in the final analysis. Continuous data (e.g., schistosome egg counts) are presented as geometric mean. Infection intensities were stratified according to the cut-offs defined by the WHO [25].

Results

Demographics of enrolled preschool children

The present study enrolled a total of 400 children of preschool age (≤ 72 months). The mean age of the children was 4.8±1.1 years. Those aged three years or less constituting 11.3%, 4 years (26.3%), 5 years (27.5%) and 6 years (35%) of the study sample. Only one child was aged two years. Boys constituted 51.2% whereas girls were 48.8% of the enrolled children.

Efficacy of praziquantel treatment

Parasitological cure rates. The overall pretreatment and post treatment prevalence of *S. haematobium* infections was 20.0% (16.4% - 24.2% 95% confidence interval (CI) and 2.8% (1.5% - 4.9% 95% CI) respectively. The parasitological cure rate of praziquantel treatment was thus 86.2% (95% CI 77.0% - 92.1%). The cure rates of praziquantel treatment did not differ with the age or sex of the PSC as shown in Table 1.

Effect of praziquantel treatment on infection intensities. Before treatment was conducted, 41 of the 80 children (48.8%) who were infected with *S. haematobium* had heavy intensity of infection (≥50 eggs/10 ml urine), whereas 39 children had light intensity of infection (1–49 eggs/10 ml urine). Visible hematuria was observed in 7 children who had heavy intensity of infection. After treatment with Praziquantel, 10 children who were infected with *S. haematobium* were found to have an infection of light intensity (1–49 eggs/10 ml urine). These were the children who had heavy intensity of infection (≥50 eggs/10 ml urine) before treatment.

The overall geometric mean of *S. haematobium* eggs in the infected children before treatment was 45.9 (95% CI: 31.0–68.0) eggs/ 10 ml urine. Post-treatment geometrical mean intensity of *S. haematobium* eggs was 1.4 (95% CI: 1.1–1.7) eggs/ 10 ml urine. The ERR was 96.9% following treatment. Pre-treatment and post-treatment arithmetic mean intensity of *S. haematobium* was 146 and 2.7 respectively. The reduction in the intensities of the infection was significant even when the analysis was stratified by sex and age as shown in Table 2.

Table 1. Parasitological cure rate of praziquantel treatment.

Variable	Pretreatment infections		Post-treatment infections		Cure rate		P-value
	No.	% (95%CI)	No.	% (95%CI)	No.	% (95%CI)	
Overall (n = 400)	80	20.0 (16.4–24.2)	10	2.5(1.5–4.9)	70	87.5 (77.0–92.1)	
Sex							
Male (n = 205)	47	22.9 (17.7–29.2)	8	3.9 (2.3–8.1)	39	82.9 (67.5–89.6)	0.087
Female (n = 195)	33	16.9 (12.3–22.8)	2	1.0 (0.2–3.7)	31	93.9 (80.4–98.3)	
Age group							
≤ 4 years (n = 150)	14	9.3(5.6–15.1)	0	0.0 (0.0–2.5)	14	100.0 (78.5–100.0)	0.102
5 years (n = 110)	19	17.3 (11.4–25.4)	2	1.8 (0.5–6.4)	17	89.5 (68.6–97.1)	0.395
6 years (n = 140)	47	33.6 (26.3–41.7)	8	5.7 (3.4–11.8)	39	83 (67.5–89.6)	REF

https://doi.org/10.1371/journal.pntd.0006852.t001

Table 2. *S. haematobium* infection intensities.

Characteristic	N	Geometric mean (95% CI) *		P-value
		Before Treatment	After treatment	
Overall	80	45.9 (31.0–68.0)	1.4 (1.1–1.7)	<0.001
Sex				
Male	47	59.2 (36.6–101.5)	1.7 (1.2–2.5)	<0.001
Female	33	32.0 (16.8–61.0)	1.1 (0.9–1.5)	<0.001
Age group				
≤ 3 years (n = 45)	5	11.0 (2.5–48.4)	1.0 (0.0–1.0)	0.034
4 years (n = 105)	9	42.1 (13.7–129.2)	1.0 (0.0–1.0)	<0.001
5 years (n = 110)	19	32.4 (13.4–78.1)	1.4 (0.7–2.4)	<0.001
6 years (n = 140)	47	62.6 (38.6–101.5)	1.5 (1.1–2.0)	<0.001

*eggs/ 10 ml urine

https://doi.org/10.1371/journal.pntd.0006852.t002

Adverse events

Adverse events were assessed 24 hours post treatment. This was through researcher administered questionnaires to the parents and through observations made one hour post treatment by the ECDE teachers and CHEWs, who took part in the deworming exercise.

330 out of the 400 children recruited in the study were assessed for AEs. One experienced dizziness, one experienced a headache, four had abdominal pain/discomfort, two had nausea and two experienced itching. None of the children vomited. While six respondents took no action when their child experienced an adverse event, one gave food, two gave milk and the other one made the child to rest as shown in Table 3.

Treatment acceptability evaluation

None of the 400 (100%) PSC spat and/ or vomited during treatment. This was assessed by DOT, by ECDE teachers and CHEWs present during deworming.

Table 3. Adverse events through parent's questionnaires 24 hours post treatment.

Characteristic	Number	%
Experienced any side effects after deworming (n = 330)		
Yes	10	3.0
No	320	97.0
Adverse events (n = 10)		
Vomiting	0	0
Abdominal Pain/discomfort	4	40
Headaches	1	10
Nausea	2	20
Dizziness	1	10
Itching	2	20
Action taken (n = 10)		
Given food	1	10
Given milk	2	20
None	6	60
Rested	1	10

https://doi.org/10.1371/journal.pntd.0006852.t003

Discussion

Results of the current study showed that praziquantel achieved high cure rates of 86.2% against *S. haematobium* infections 5 weeks after treatment. This is in agreement with results of recent Cochrane systematic review which showed that treatment with the standard dose of praziquantel (40 mg/kg) generally results in cure rates of 80% 1–3 months after treatment [24].

In this study, the results show that 10 children out of the 80, who had tested positive for *S. haematobium*, had an infection of light intensity (1–49 eggs/10 ml urine) after treatment. These were the children who had infections of heavy intensity of (≥50 eggs/10 ml urine), before treatment. The design of our study did not allow estimating the proportion of infections after treatment that were due to juvenile stages of the parasite, which are largely insensitive to praziquantel. This is in line with a study in Mali assessing urinary schistosomiasis in preschool aged children showing that, the presence of *S. haematobium* eggs five weeks post-treatment could be explained by factors such as high pretreatment worm load that could not be completely cleared by the treatment that remained in the treated children and started producing eggs, and the presence of high numbers of immature worms less sensitive to praziquantel that escaped drug action and matured to egg producing worms during subsequent follow-ups [26]; praziquantel is refractory against immature worms [24]. The effect of treatment in terms of egg reduction rates which was 96.9% was high and supported by evidence of Cochrane systematic review [5].

The results of this study revealed that the prevalence of *S. haematobium* in pre-school children from Kwale County was high (20%) compared to that observed among school aged in the same county (24.5%) [27]. The findings are consistent with emerging evidence that the burden of schistosomiasis is high in pre-school children. A similar study in Sudan investigating the safety, efficacy and acceptability of praziquantel in pre-school age children reported a prevalence of 31.1% [28], which is higher than what was found in this study (20%). In Ghana, a study investigating the extent of schistosomiasis in pre-school children and infants found prevalence of 11.2% for *S. haematobium*, with the highest egg count detected in a 4-month old infant [28], [29]. In a rural endemic area in Nigeria, prevalence of 58.1% was reported for *S. haematobium* in children aged 1–6 years [3]. Similar findings have emerged from Mali where prevalence of *S. haematobium* among pre-school children aged 1–4 years was found to be 51.2% [26]. In Uganda nearly 50% of children less than three years of age living along the northern shoreline of Lake Victoria had *S. mansoni* infections [13]. A recent study from the shoreline villages of Lakes Albert and Victoria in Uganda found even higher prevalence of *S. mansoni* (62.3%) in pre-school children [13]. In Sudan, an earlier study found high prevalence of schistosome infection (40%) among pre-school children in the Gezira Irrigation Scheme [30]. The common feature associated with infection in these children from the various settings would be likely due to the fact that the children and their caregivers (parents or guardians) share the common risk factor of proximity to large water bodies known to harbor infectious cerceria. Schistosomiasis in infants and pre-school age children is of concern for at least two reasons. First, this younger age-group plays a hitherto unrealized role in maintaining local disease transmission; even though these infected children may be excreting fewer eggs, it is their regular water contact that leads to contamination of water. Moreover, rinsing and washing children's soiled clothes in environmental water bodies also contributes towards more cryptic contamination and disease transmission [18]. Thus this age-group will play an increasingly important role in environmental transmission likely to frustrate the attempts made by preventive chemotherapy campaigns striving towards more general reductions in environmental transmission [31]. Second, such regular water contact is also likely to result in frequent (re) infection episodes, which lead to a progressive increase of individual worm burden. It is therefore likely that untreated infections acquired in early childhood contribute to worsening the

longer-term clinical picture of disease in the individual. Lack of safe water supplies, inadequate sanitation, insufficient access to health care and prohibitive treatment costs all contribute to disease transmission and high morbidities, especially in infection with schistosomiasis. *S. haematobium* infection that is predominant in Coastal region of Kenya is found to cluster in a subset of school age children with suggestions of synergistic effects on anemia, cognitive performance and stunting[32]. Chronic anaemia during childhood is associated with impairment in physical growth, cognition, and school performance [33], whereas severe anemia accounts for up to one half of the deaths in children younger than 5 years of age [34].

In Kenya, during the 2009 treatment, only primary school-age children, (6–14 years) both enrolled and non-enrolled were covered by the National School Based Deworming Programme, leaving out the children in the age bracket of 2–6 years who attend the ECDE Centers or pre-school. This age bracket requires to be treated as they also carry a heavy worm burden and pose a risk of re-infecting the treated school-age children while interacting and playing at the community level. In Kenya, the population of children enrolled in ECDE Centers is 2.2 million [35].A high percentage of infected children means that the environment becomes more heavily contaminated–which in turn increases the risk of infection for the whole community. By reducing the number of worms in children, everyone benefits [25].

Given the difficulties of younger children swallowing large PZQ tablets and an associated risk of choking, medications were administered in crushed tablet form and mixed with orange-juice as previously piloted [17].Previous studies have shown that the fruit flavor helped to mask the bitter taste of PZQ [36]. In our study none of the children spat and/or vomited during treatment.

Previous studies have shown that there have not been adverse reactions to PZQ treatment when given to young children due to the excellent safety and tolerability [37]. In this study the adverse events experienced by the children were not severe and included nausea, dizziness, vomiting, abdominal pain/discomfort, itching, and headache which were largely self-limited. This is in line with other studies involving pre-school children, where minor and transient side-effects 24 hours after treatment were reported in Uganda [30], and in Mali [26] in accordance with established evidence that praziquantel is associated with minor and transient adverse events [26, 36] In a study in Sudan there were no drug-related adverse events experienced after treatment with praziquantel [28]. In studies carried out in Uganda and Mali, the adverse events experienced were minor and transient 24 hours after treatment whereas in Sudan, no adverse events were reported.

Conclusion

In conclusion, the present study showed that crushed praziquantel administered to preschool children at a dose of 40 mg/kg is safe and effective in the treatment of urogenital schistosomiasis. The pre-school children experienced minor side effects which were temporal and most of them required resting under a shade until they subsided. The study also adds to the evidence base that, the prevalence of *S. haematobium* in preschool age children is high, and they should be regarded as high risk group in the area, and should be taken into consideration during treatment programs in Kwale County and other endemic regions. This will prevent long-term chronic ill-health or schistosomiasis-related complications later in life.

Acknowledgments

The authors are grateful to the Director KEMRI, JKUAT, Kwale County; MOH, MOE, Moses Machimbo (laboratory work), CHEWs, the pupils, parents and ECDE teachers for their support.

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