ASSESSMENT OF IMPACT OF REPEATED ANNUAL MASS DRUG ADMISTRATION OF PRAZIQUANTEL ON SCHISTOSOMIASIS MORBIDITY IN SCHOOL CHILDREN IN ASEMBO BAY, WESTERN KENYA

BY

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A THESIS SUBMITTED IN FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN BIOMEDICAL SCIENCE AND TECHNOLOGY (MEDICAL PARASITOLOGY)

SCHOOL OF PUBLIC HEALTH AND COMMUNITY DEVELOPMENT

MASENO UNIVERSITY

DECLARATION

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

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ACKNOWLEDGEMENT

First and foremost, I wish to thank the Lord God Almighty for the gift of life and strength despite immense challenges during data collection, analysis and thesis write up. In addition, I wish to thank the National Institute of Health (NIH) in collaboration with the Kenya Medical Research Institute (KEMRI), Center for Global Health Research (CGHR) for funding, resulting into this thesis report. I also wish to express my sincere appreciation to the late Professor Ayub V. Ofulla whom we started this work with and also both Dr. Diana Karanja of KEMRI-CGHR and Dr. Bernard Guyah of Maseno University for their proper guidance during the course of this study. Special thanks also goes to Professor Daniel Colley of University of Georgia USA, who contributed immensiley to this work by helping get the funding for this work and for his academic input during study protocol development and publications. I would also like to thank the CGHR directors: the late Dr. John M.Vulule and Dr. Stephen Munga, for giving me the opportunity to work at KEMRI CGHR in Neglected Tropical Diseases (NTD) laboratory under the supervision of Dr. Diana Karanja. My thanks also goes to the NTD Branch Chief, Dr. Maurice Odiere and Dr. Pauline Mwinzi for providing good working environment in the branch.

I am hugely indebted to the entire schistosomiasis laboratory staff members who contributed to the success of this study both in the field during samples collections and in the laboratory. I also wish to thank Mr. Ireri for the ultrasound work conducted in the field and Dr. Dan Onguru for his immense support with citations.

I am equally grateful to Maseno University for granting me a chance to pursue this study in the Department of Biomedical Sciences and Technology and I acknowledge everyone in the department whose discussions and contributions greately contributed to the success of this study.

I appreciate both moral and financial support from my parents, Isaka Abudho and Suslia Abudho, my brothers and sister (George Abudho, Nicholas Onyango, David Odhiambo, Peter Okoth, Fred Ouma, Tobias Abudho and Grace Akinyi Abudho). Much thanks to my beloved wife Beatrice Omondi and our lovely children: Becky Amondi, Benjamin Jones Abudho and Bessie Amani (Nya Asao) for the peace of mind and encouragement during this work.

Lastly but not least, am highly indebted to the parents and school-going children in both Raliew and Kanyichudo primary schools and in Wera, Kokise and Rarieda high schools without whom, this study could not have been successful.

DEDICATION

This work is dedicated to my parents (Isaak Abudho and Suslia Abudho), my beloveth wife (Beatrice Omondi) and children: Becky Amondi Omondi, Benjamin Jones Abudho Omondi and Bessie Amani Omondi (Nya Asao) who supported me immensely during the course of this study despite the challenges faced.

ABSTRACT

Schistosomiasis remains a major public health problem in Kenya. The World Health Organization (WHO) recommends preventive chemotherapy with praziquantel (PZQ) through mass drug administration (MDA) to school age children to control morbidity due to schistosomiasis. Morbidity is considered linked to intensity of infection, which along with prevalence is used to determine the frequency of mass drug administration (MDA) to school-age children. Previous studies typically compared children who were uninfected after receiving MDA to their condition prior to treatment. This study hypothesized that multiple MDAs would result in decrease of worm burden and thus egg intensity and prevalence and in addition provide benefits such as decreased morbidity even if the children remained infected. The specific objectives were to determine schistosomiasis grade-intensity before and after successive rounds of annual MDA with PZQ, to assess morbidity measurements before and after successive rounds of annual MDA with PZQ and to determine if the measurements associated with morbidity change upon multiple rounds of annual MDA with PZQ. This study used a repeated cross-sectional study design to determine the impact of annual school-based MDA on children across all primary and high school years in five schools in Asembo Bay region near Lake Victoria in western Kenya, an area endemic for *S.mansoni*. At baseline and for the following four consecutive years, 897 and 1,440 school-going children in grades 1-12 were enrolled and stool samples evaluated by Kato-Katz for *S. mansoni* and soil transmitted helminths (STHs), blood samples for malaria diagnosis and anemia evaluation followed by annual MDA with PZQ and albendazole (ALB). For morbidity, to evaluate potential changes in morbidity, height, weight, mid-upper arm circumference, hemoglobin levels, abdominal ultrasound, and quality of life in children in these schools were measured. Morbidity component compared two cross-sectional samples of *Schistosoma mansoni* egg-positive children: one at baseline and one at year five, after four rounds of MDA. Data were analyzed for all ages (6-18 years old) and stratified by primary (6-12 years old) and secondary (13-18 years old) school groups. Four annual rounds of MDA with PZQ were associated with reduced *S. mansoni* prevalence in all school children (44.7–14.0%; $P<0.001$) and mean intensity of infection by 91% (90.4 to 8.1 eggs per gram [epg] of stool; $P < 0.001$). Prevalence of high-intensity infection (≥400 epg) decreased from 6.8% at baseline to 0.3% by the end of the study. A Chi square test for trend (Cochran-Armitage) was used to evaluate the association between annual treatments and changes in prevalence of *S. mansoni* and STH. Soil-transmitted helminth infections, already low (22.4%) at baseline, also decreased significantly (22.4%–10.1%; $P=0.029$) over the years. The prevalence of multiple potential morbidity markers did not differ significantly between the egg-positive participants at baseline and those at five years (13-18 years old–PedsQol-Physical; $P=0.599$, PedsQol-Emotional; $P=0.218$, PedsQol-Social; $P=0.821$, PedsQol-School; PedsQol-Total; $P=0.344$ and for organomegaly; 6-12 years old–Hepatosplenomegaly; $P=0.831$; Stunting; $P=0.585$ and wasting $P=0.999$; 13-18 years old–Hepatosplenomegaly; $P=0.463$; Stunting; $P=0.683$ and wasting; $P=0.077$) by Mann Whitney U nonparametric analysis and Fisher's exact test for continuous and categorical data, respectively. However, in all 13-18 years old and malaria negative 13-18 years old, there were significantly higher scores in school-related quality of life assessment by year five compared to baseline by Mann Whitney analysis ($P=0.021$* and $P= 0.048$*) respectively. Anemia registered a significant negative outcome and was not impacted positively by four rounds of MDA. In conclusion, annual school-based MDA with high coverage across all Grades (1–12) resulted in rapid and progressive declines in overall prevalence and intensity of infection in this high endemic area. This decrease was dramatic in regard to heavy infections in older school-attending children. For morbidity, there were no differences in the morbidity markers measured in a population of those infected or re-infected after multiple MDAs with praziquantel. These results are useful in informing policy on inclusion of high school children in MDA in schistosomiasis endemic areas. Further research is needed to identify and develop well-defined, easily quantifiable *S. mansoni* morbidity markers for this age group.

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LIST OF ABBREVIATIONS AND ACRONYMS

28GST	28-KDa glutathione S-transferase
ALB	Albendazoze
BMI	Body mass index
CAA	Circulating anodic antigen
CCA	Circulating cathodic antigen
CD4	Cluster of differentiation 4
CDC	Centers for Disease Control and Prevention
CNS	Central nervous system
DALYS	Disability -adjusted- life years
DNA	Deoxyribonucleic acid
DPD	Division of Parasitic Diseases
EF	Emotional functioning
EPG	Eggs per gram
GAHI	Global Atlas of Helminths Infection
HAZ	Height for age Z score
Hb	Haemoglobin
HIV	Human immunodeficiency virus
HRQoL	Health related quality of life
Ig4	Immunoglobulin 4
IgE	Immunoglobulin E
IRB	Institutional review board
KEMRI	Kenya Medical Reseach Institute
MDA	Mass drug administration

MUAC	Mid upper arm circumference
NTD	Neglected tropical diseases
P.R China	Peoples' Republic of China
PCR	Polymerase chain reaction
PedsQL	Pediatric Quality of life inventory
PET	Positron emission tomography
PF	Physical functioning
PZQ	Praziquantel
QoL	Quality of life
SchF	School functioning
SF	Social functioning
Sm	*Schistosoma mansoni*
SPSS	Statistical package for social sciences
STH	Soil transmitted helminths
Th-1	T helper 1
Th-2	T helper 2
USA	United States of America
WAZ	Weight for age Z score
WHA	World Health Assembly
WHO	World Health Organization

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CHAPTER ONE
GENERAL INTRODUCTION

1.1 Background Information

Human schistosomiasis is a snail–transmitted trematode infection caused by any of the five species in the genus *Schistosoma* (*Schistosoma japonicum, Schistosoma mekongi, Schistosoma haematobium, Schistosoma mansoni* and *Schistosoma intercalatum*. It is a water borne disease and infection is initiated when free swimming larval forms of the parasite released by specific freshwater intermediate hosts snails penetrate the skin of those who have contact with fresh water containing infected snails (King 2009). In schistosomiasis endemic regions, children and adolescents are reported to carry the heaviest burden of the infection (Fisher 1934; King *et al.,* 1988; DeStigter *et al.,* 1989; Odiere *et al.,* 2012; Onkanga *et al.,* 2016; Abudho *et al.,* 2018). Globally, approximately 700 million people are at risk of this infection (WHO 2012b; Colley *et al.,* 2014).

Schistosomes are estimated to infect more than 240 million people globally in 78 countries where schistosomiasis is endemic with over 90% of cases occurring in sub-Saharan Africa, where the infection is estimated to cause more than 200,000 deaths annually (WHO 2011; Sady *et al.,* 2013). In Kenya, it remains a serious public health concern with approximately 6 million people being infected and an additional 15 million being at high risk of the infection particularly in endemic areas of the country (GAHI 2010). *Schistosoma mansoni* infection is prevalent in western part of Kenya particularly in individuals living around Lake Victoria and can be hyperendemic in the communities along the shores including Asembo Bay region in Rarieda Sub-County in Siaya County, western part of Kenya. People living in schistosomiasis endemic areas may spend a third of their lives carrying Schistosoma parasitic worms because their

continuing environmental exposure leads to overlapping schistosome infections (King *et al.,* 2011; Colley 2014). Previous studies have shown that upto 33% of 1 year olds and more than 90% of children greater than 10 years of age can be infected (Stothard *et al.,* 2011; Verani *et al.,* 2011; Mwinzi *et al.,* 2012; Onkanga *et al.,* 2016).

In schistosomiasis endemic areas, initial infections often usually occurs in children as young as 1 or 2 years of age with the burden of infection increasing in intensity in the next decade of life as new worms colonize the body (Verani *et al.,* 2011; Colley *et al.,* 2014). Schistosomiasis infection age prevalence and intensity curves have been reported to typically peak in adolescents and young adults after which, the prevalence and intensity of the infection decrease in older age groups (Butterworth *et al.,* 1988; Woolhouse *et al.,* 1991; Gryseels *et al.,* 2006; Odiere *et al.,* 2012). This relationship is thought to be caused by age-specific changes in water contact and hygiene, and/or in combination with the gradual development of acquired protective immunity (Fulford *et al.,* 1991; Woolhouse *et al.,* 1991). For this reason and because of logistic advantages offered by school structures and the demography of population, WHO currently recommends mass drug administration (MDA) with praziquantel (PZQ) for the treatment of schistosomiasis in school aged children in endemic areas (WHO 2002; Albonico *et al.,* 2006) to reduce the disease burden in this high risk group and mortality (Richter 2003; Kabatereine *et al.,* 2007; Koukounari *et al.,* 2007; Mwinzi *et al.,* 2012). When initiated, this strategy usually involves yearly or biennial (MDA) with praziquantel (PZQ) to treat schistosomiasis and albendazole (ABL) to treat soil-transmitted helminths (STH) in schools (Kabatereine *et al.,* 1999). The MDA with praziquantel is usually carried out in primary school going children but not in secondary school children who are equally at risk in endemic areas. This study aimed to determine schistosomiasis infection grade-intensity before and after successive four rounds of annual praziquantel mass

drug administration in school-going children both in primary and secondary school children who are not normally included in school-based mass drug administration with paraziquantel for the control of schistosomiasis morbidity but who are equally at risk of the infection and usually carry the heaviest burden of infections and can contribute to continued transmission of the infection in the endemic areas if left untreated. In addition,in determination of schistosomiasis grade-intensity before and after successive rounds of annual praziquantel mass drug administration in both primary and secondary school children, school-based mass drug administration strategy can also benefit from already existing school structures in high school for mass drug administration with praziquantel. Intensity of infection, repeated infection and duration of infection are the major determinants of morbidity progression in schistosomiasis infection (King *et al.,* 2006), however, there is no systemic data on key indicators (prevalence and grade-intensity of infections) across all grades in both primary and secondary schools experiencing multiple annual rounds of high coverage MDA.

In endemic areas with typical transmission patterns, 60-80% of school age children and 20-40% of adults can remain actively infected (Colley *et al.,* 2014). Although approximately 20 million people have severe forms of the disease such as hepatosplenomegaly and pathologic changes and approximately 200,000 people die of schistosomiasis infection every year , majority of infected individuals suffer more from subtle or functional morbidities associated with chronic infection (Steinmann *et al.,* 2006; Network 2015). These subtle or functional morbidities include anaemia due to inflammation, malnutrition (on nutritional status for example height and weight), exercise intolerance and reduced work capacity, chronic inflammation and reduced cognitive functions (Ezeamama *et al.,* 2005; Friedman *et al.,* 2005a; King *et al.,* 2005; King and Dangerfield-Cha 2008; Bustinduy *et al.,* 2011). In addition, these subtle morbidities in school aged children

infected with schistosomes can contribute to lost days at school, pervasive learning disabilities and impaired childhood development (cognitive development) (Keita *et al.,* 2001; King *et al.,* 2005; King and Dangerfield-Cha 2008) making the infection a major cause of global disability (H. 2010). While severe disease likely develops in only 5% to 10% of those with substantial, untreated chronic infections (Steinmann *et al.,* 2006; Network 2015). The subtle morbidities are thought to have a broader public health impact on most of the over 240 million people with schistosomiasis (King *et al.,* 2005; H. 2010; King 2015). In 2001, a formal recognition of the global burden of schistosomiasis was given by World Health Assembly (WHA) Resolution 54.19 calling for the treatment of high risk groups to reduce morbidity and mortality associated with schistosomiasis (WHA 2001a). The effectiveness of this strategy is usually monitored by MDA coverage and by changes in prevalence and/or intensity of infection rather than determination of changes in morbidity indicators. Although a treatment directive was put in place, there is no systemic data on how multiple treatments impacts on multiple potential schistosomiasis morbidity indicators across all ages or grades in primary and secondary schools experiencing multiple annual rounds of high coverage MDA. This study aimed to assess morbididty measurements associated with *Schistosoma mansoni* before and after four multiple rounds of mass drug administration with praziquantel in school-going children in both primary and secondary schools in Asembo Bay, western part of Kenya. In addition, this study further aimed to determine if the measurements associated with morbidity due to *Schistosoma mansoni* change upon multiple rounds of annual drug administration with praziquantel in school-going children both in primary and secondary schools in Asembo Bay, western part of Kenya.

1.2 Statement of the Problem

Human schistosomiasis is still a major public health problem in developing countries despite numerous intense efforts directed at controlling it. In Kenya it poses a serious public health concern particularly in endemic areas such as Asembo bay area of Rarieda Sub-County, Siaya County. This is due to rapid re-infection as a result of continued exposure to contaminated water sources. World Health Assembly (WHA) Resolution 54.19 emphasizes on reduction of morbidity associated with schistosome infections and soil-transmitted helminthes (STH) in school aged children through mass drug administration but only primary school going children are normally included in school-based treatment programmes leaving out their counterparts in high schools who are equally at risk of the infection and development of schistosomiasis morbidity and can also contribute to continued transmission of the infection in endemic areas if left untreated. The effectiveness of this strategy is usually monitored by MDA coverage and by changes in prevalence and/or intensity of infection rather than schistosomiasis grade-intensity of infection before and after repeated annual multiple rounds of mass drug administration with praziquantel in school-going children both in primary and secondary schools. Furthermore, there are no systematic data on how annual preventive chemotherapy with praziquantel impacts on schistosomiasis related morbidity in all school-aged children in both primary and secondary schools or what impact this kind of treatment approach has on morbidity indicators among children in both primary and secondary schools living in endemic areas with ongoing transmission

1.3 Objectives of the Study

1.3.1 General Objective

To determine schistosomiasis morbidity in school children and impact of repeated mass drug administration of praziquantel in Asembo Bay, western Kenya.

1.3.2 Specific Objectives

a) To determine schistosomiasis infection grade-intensity before and after successive four rounds of annual praziquantel mass drug administration in school-going children both in primary and seconday schools in Asembo Bay, western Kenya.

b) To assess morbidity measurements associated with *Schistosoma mansoni* before and after four multiple rounds of mass drug administration (MDA) with praziquantel in school going children both in primary and seconday schools in Asembo Bay, western Kenya.

c) To determine if the measurements associated with morbidity due to *Schistosoma mansoni* change upon multiple rounds of annual drug administration (MDA) with praziquantel in school going children both in primary and secondary schools in Asembo Bay, western Kenya.

1.3.3 Research Questions

a) What are schistosomiasis grade intensity before and after successive rounds of annual mass drug administration rounds in school-going children both in primary and secondary schools in Asembo Bay, western Kenya?

b) What are morbidity measurements that are associated with morbidity due to *Schistosoma mansoni* in school-going children both in primary and secondary schools in Asembo Bay, western Kenya?

c) What are the changes in measurements associated with morbidity markers due to *Schistosoma mansoni* upon multiple rounds of annual mass drug administration (MDA) with

praziquantel in school-going children both in primary and secondary schools in Asembo Bay, western Kenya?

1.4 Significance of the Study

This study reported a rapid and progressive declines in overall prevalence and intensity of infection. This decrease was dramatic in regard to heavy infections in older school-attending children in secondary schools who are not normally included in the mass drug administration strategy for control of schistostosomiasis. Establishing the effictiveness and impact of yearly MDA with PZQ for schistosomiasis control on reduction of prevalence, intensity of infection and other morbidity associated with schistosomiasis infection in both primary and secondary school children who are not normally included in the mass drug administration strategy for control of schistostosomiasis adds systematic data to the understanding on how these key indicators (Intensity of the infection and prevalence, hepatomegaly hepatosplenomegaly, splenomegaly, wasting, stunting, MUAC, Peds Qol), and anaemia are impacted by yearly MDA. This information is useful in informing policy on MDA in schistosomiasis endemic areas.

CHAPTER TWO
LITERATURE REVIEW

2.1 Introduction

The main approach for schistosomiasis and its associated morbidity control recommended by the World Health Organization (WHO) is through mass drug administration (MDA) using the drug of choice praziquantel with the primary goal of preventing severe morbidity associated with high intensity of the infection in endemic areas where the infection is prevalent (WHO 2006; WHO 2013). The current WHO guideline for schistosomiasis MDA recommends annual mass drug administration with praziquantel in high risk communities with ≥50% prevalence of infection in school aged children (SAC) but only primary school going children are normally included in school-based treatment programmes leaving out their counterparts in high schools who are equally at risk of the infection and development of schistosomiasis morbidity in endemic areas.

Praziquantel has been used successfully over the past 30 years in many countries and is appropriate for MDA as it is well tolearated, safe for individuals who are not infected and inexpensive (Danso-Appiah *et al.,* 2008; Zwang and Olliaro 2014). Schistosome morbidity is mainly caused by eggs trapped in various parts of the human body, depending on the species of schistosome, hence the fundamental aim of morbidity control in endemic areas is to reduce prevalence and intensity of infection by drug treatment (Samuels *et al.,* 2012; Colley 2014). Several studies have demonstrated an association between schistosome infection and morbidity particularly among school aged children (Keita *et al.,* 2001; King *et al.,* 2005) and there is consensus among the various studies of resistance to schistosomiasis that children are generally more susceptible than adults. Morbidity associated with schistosomiasis include anaemia, chronic pain, diarrhea, and poor quality of life such as stunting, exercise intolerance and

cognitive impairment (Friedman *et al.,* 2005b; Samuels *et al.,* 2012). Several control programmes on schistosomiasis and soil-transmitted helminthiasis are now being implemented across sub-Saharan Africa with financial and technical support support from the schistosomiasis control initiative (Fenwick 2006; Garba *et al.,* 2006; Kabatereine *et al.,* 2006a; Samuels *et al.,* 2012; Onkanga *et al.,* 2016; Karanja *et al.,* 2017; Abudho *et al.,* 2018; Kittur *et al.,* 2019; Shen *et al.,* 2019). However, there are no systematic data on how annual preventive chemotherapy with PZQ impacts on schistosomiasis related morbidity in school-aged children in both primary and secondary schools or what impact this has on morbidity indicators of the children treated in this manner living in endemic areas with ongoing transmission.

2.1.1 Schistosomiasis Prevalence and Grade-intensity of Infection

The level of schistosomiasis infection in the human population is closely related to the proximity with local water bodies where daily water contact activities such as washing, bathing and fishing occur. Studies have shown that places with the highest prevalence and high infection intensities are closer to the source of infection (Handzel *et al.,* 2003; Kabatereine *et al.,* 2004b). Prevalence and intensity of infection are the key indicators currently used to measure the burden of schistosome infection in a given community. Prevalence of infection is the more easily collected indicator and is used by the World Health Organization (WHO) to provide guidelines for scope and frequency of mass treatment with PZQ (WHO 2013). The number of eggs per gram (EPG) of feces provides a relative measure of infection intensity and is a key indicator of transmission dynamics within communities as well as the risk of morbidity among individuals (Anderson and May 1985). Overall, the prevalence of schistosomiasis in endemic areas around Lake Victoria region western part of Kenya ranges from 5% to 100%, contributes to significant morbidity (Handzel *et al.,* 2003; Black *et al.,* 2010a; Odiere *et al.,* 2012; Samuels *et al.,* 2012; Onkanga *et*

al., 2016; Abudho *et al.,* 2018) and is very high along the shores of Lake Victoria (Handzel *et al.,* 2003; Standley *et al.,* 2010; Odiere *et al.,* 2012; Abudho *et al.,* 2018). Communities around the shores of Lake Victoria region in western Kenya are populated with individuals who suffer from significant morbidities associated with *Schistosoma mansoni* infection due to high prevalence and intensity of the infection in infected individuals (Handzel *et al.,* 2003; Odiere *et al.,* 2012; Abudho *et al.,* 2018). Schistosome eggs trapped in the host tissue are the major cause of schistosomiasis morbidity. Eggs trapped in the liver cause granulomatous reactions and lead to formation of fibrotic lesions with hepatosplenic enlargement which may in turn cause portal hypertension and hepatosplenic schistosomiasis (Vennervald *et al.,* 2004; Colley 2014).

The 54th World Health Assembly resolution 54.19 in 2001 endorsed to promote preventive measures, ensure treatment and mobilize resources for the control of schistosomiasis and soil-transmitted helminths (STHs) (WHA 2001a; Kabatereine *et al.,* 2006a). This resolution helped to increase interest from global sponsors and governments in endemic regions to control schistosomiasis and other neglected tropical diseases (NTDs) and to establish national action plans. Examples include Kenya, Uganda and Tanzania in 2003 (Guyatt *et al.,* 2001; Kabatereine *et al.,* 2006b; Kabatereine *et al.,* 2007; Samuels *et al.,* 2012; Karanja *et al.,* 2017; Abudho *et al.,* 2018; Kittur *et al.,* 2019; Shen *et al.,* 2019). In these countries, the main strategy for the delivery of anti-helminthics was through the school system, an approach that reduces both infection and morbidity in a cost-effective manner as well as enhances educational outcomes in the treatment areas (Guyatt *et al.,* 2001). However, treating only primary school going children in a school-based MDA approach leaves out other members in the community who are also at risk of morbidity from infection and who could contribute to continued transmission. This includes older children in secondary school who are also exposed to schistosomiasis infection in endemic

areas and who could be reached by utilizing school-based treatment approach. This study aimed to determine schistosomiasis infection grade-intensity before and after successive four rounds of annual praziquantel mass drug administration in school-going children both in primary and secondary schools in Asembo Bay, western part of Kenya an area endemic for *Schistosoma mansoni* infection. Mass drug administration studies determining schistosomiasis infection grade-intensity before and after annual repeated mass adrug administration comprising of both primary and secondary school-children in school settings in endemic areas have not been performed. Treatment data on prevalence and intensity of infection from high school children are needed to inform policy on the inclusion of secondary school children in school-based mass drug administration in endemic areas.

2.1.2 Morbidity Indicators Associated with Schistosomiasis

More than 90% of schistosome infections occur in sub-Saharan Africa (Ezeamama *et al.,* 2016), resulting in at least 3.3 million disability-adjusted life years because of associated morbidities (King 2015). In developing countries, chronic parasitic infections such as schistosomiasis are common, recurrent and have a role in the perpetuation of disability and long lasting health problems that represent an ongoing inflammatory challenge and a significant health threat particularly in the setting of rural populations who are at continuing daily risk for the infection as a result of repeated exposure to infectious cercariae (Engels and Savioli 2006; Utzinger *et al.,* 2009; Colley 2014; Colley *et al.,* 2014).

Despite the fact that there are highly effective anti-helminthics for treating worm infections, in most of the rural settings, access to treatments is severely limited (Danso-Appiah *et al.,* 2004; Ukwandu and Nmorsi 2004). Furthermore, even after successful therapy, environmental factors still strongly favour the process of re-infection and as a result, majority of the local residents in

endemic areas have long lasting worm infections such as schistosomiasis which persist for most of their lives (Satayathum *et al.,* 2006).

For several decades, researchers focused a lot on the advanced pathogen specific disease outcomes such as hepatoslpenomegaly, hepatic fibrosis, or for urinary schistosomiasis as bladder and kidney inflammation as the only signs of disease attributable to morbidity and leaving out more common non specific morbidities associated with schistosomiasis infections unacknowledged (Van der werf *et al.,* 2003). Nevertheless, there is an emerging appreciation of the negative impact of subtle morbidities associated with chronic schistosomiasis infection on human physical growth and development, which include malnutrition (on nutritional status for example, height and weight), impaired childhood development (cognitive development in childhood), haemoglobin (Hb) levels (anaemia) by increasing blood loss and decreasing food intake leading to iron deficiency anaemia, exercise intolerance and reduced work performance (Ezeamama *et al.,* 2005; Friedman *et al.,* 2005a; King *et al.,* 2005; King and Dangerfield-Cha 2008; Bustinduy *et al.,* 2011).

Anaemia has been acknowledged as a common problem throughout the world, and a greater public health concern in developing countries (WHO/CDC 2007), but its etiology is very complex, making the effect of any one factor difficult to assess. Malaria infection is among the key causative factors for most anaemia among young African children. In addition, heamoglobinopathies, poor nutritional status, micronutrients deficiencies and intestinal helminthic infections such as hookworm and schistosomiasis also play an important role as causative agents of anaemia (Crawley 2004; Koukounari *et al.,* 2006; Koukounari *et al.,* 2008; Butler *et al.,* 2012). Several studies have shown an association between schistosomiasis infection and anaemia (Friedman *et al.,* 2005b; Butler *et al.,* 2012) and most of anaemia observed in

schistosomiasis infected individuals is anaemia of inflammation, linked to blood loss due to high parasitic loads that eventually contributes to total body anaemia deficiency (Friedman *et al.,* 2005b; Butler *et al.,* 2012; Colley *et al.,* 2014). Schistosomiasis infection related pro-inflammatory cytokine interleukin-6 stimulates the release of hepatic hormone known as hepcidin (Nemeth *et al.,* 2004), a recently discovered peptide that is excreted in urine and plays a key role in mediation of iron trapping within the body leading to anaemia of inflammation (Nemeth *et al.,* 2003). Anaemia of inflammation is believed to be the leading cause of anaemia in schistosomiasis infection (Friedman *et al.,* 2005b). The effects of chronic anaemia include reduced aerobic capacity which impacts negatively on the physical work output in individuals infected in the regions endemic for schistosomiasis (King *et al.,* 2005; Colley *et al.,* 2014) resulting in decreased capital in human adults in affected populations (King and Dangerfield-Cha 2008; Victora *et al.,* 2008) with a related loss in years of healthy life. Anaemia of inflammation can be improved by curative therapy (Leenstra *et al.,* 2006).

Other subtle morbidities associated with schistosomiasis include reduced intelligence function scores and acute and chronic undernutritions in children but with treatments, the effects are reduced, highlighting the importance of effective control in improvement of nutritional status, prevention of cognitive and growth impairment before they become irreversible (Stephenson *et al.,* 1985; Coutinho *et al.,* 2006). Unexpected morbidities can also occur when eggs are deposited on ectopic sites such as central nervous system or migration of parasites to the CNS resulting in neuroschistosomiasis. Cerebral schistosomiasis mostly occurs during *S. japonicum* infection. Some of the clinical symptoms include headache, blurred vision, headache, vomiting and altered sensorium. Effects of eggs or parasite migration on the spinal cord can result in paralysis with muscle weakness, sensory loss and bladder incontinence (Colley *et al.,* 2014).

Health studies on potential schistosomiasis associated morbidity indicators across all ages or grades in primary and secondary schools experiencing multiple annual rounds of high mass drug administration coverage in school settings in endemic areas have not been performed. Secondary school children are not routinely included in most morbidity assessment studies (Kabatereine *et al.,* 2007; Verani *et al.*, 2011; Butler *et al.,* 2012; Samuels *et al.,* 2012; Won *et al.,* 2013; Davis *et al.,* 2015; Sircar *et al.,* 2018; Shen *et al.,* 2019) so there are limited data for this age group even though they tend to have the highest prevalence and intensity of schistosome infections which are the major indicators of morbidity development (Gryseels *et al.,* 2006). This study reported measures of morbidity that are associated with subtle morbidity due to *Schistosoma mansoni* across all ages or grades in both primary and secondary schools experiencing multiple annual rounds of high coverage MDA.

2.1.3 Changes of Morbidity Indicators Associated with Schistosomiasis upon Treatment

Currently, the WHO strategy for control of schistosomiasis relies on mass drug administration with Praziquantel (WHO 2006), which is effective in reducing disease associated morbidity based on the prevalence and intensity of infection in an area (WHA 2001a). Most commonly this translates to yearly or biennial MDA with PZQ in primary schools to treat schistosomiasis in addition to administration of albendazole (ALB) for soil-transmitted helminths (STHs) (Kabatereine *et al.,* 2007; Karanja *et al.,* 2017; Shen *et al.*, 2019). The effectiveness of this strategy is usually monitored by MDA coverage and by changes in prevalence and/or intensity of infection rather than determination of changes in morbidity upon treatments (Colley and Evan Secor 2004; Kabatereine *et al.,* 2007; Koukounari *et al.,* 2007; WHO 2012c).

While the goal of mass drug administration with praziquantel is to control morbidity, because many of the sequelae associated with schistosomiasis can have other causes, it has proven

challenging to easily measure morbidity specifically resulting from schistosomiasis. Nevertheless, some studies have reported a significant decrease in infection and morbidity among primary school-going children including improvement of haemoglobin concentration, lower prevalence of hepatomegaly, splenomegaly and lower prevalence in wasting after delivery of treatment. (Kabatereine *et al.,* 2007; Sircar *et al.,* 2018). However, some studies have also reported an increase in organomegaly despite delivering treatment (Davies *et al.,* 2015) while (Abudho *et al.,* 2020) did not observe any change in organomegaly after multiple rounds of treatment. These observations suggest that its difficult to identify schistosomiasis specific morbidity indicators and challenging to develop tools for assessing those indicators and that possibly explain varied reports from different studies. Pathology due to *S. mansoni* infection is caused largely by chronic deposition of parasite eggs in the liver and intestines, which results in egg-focused granuloma formation and focal and systemic inflammation (Colley and Evan Secor 2004; Colley *et al.,* 2014). Although a treatment directive was put in place and has mostly been carried out in primary school-going children in endemic areas, there is no systemic data on how measurements associated with morbidity due to *Schistosoma mansoni* change upon multiple rounds of repeated annual drug administration with praziquantel in school-going children across all grades in both primary and secondary schools experiencing multiple repeated annual rounds of high coverage MDA with praziquantel.

2.2 Schistosomiasis Epidemiology

Schistosomiasis is considered one of the widespread neglected tropical diseases (NTDs) (WHO 2012b). Globally, approximately 700 million people are at risk of this infection (WHO 2012b; Colley *et al.,* 2014). It is estimated to affect more than 240 million people globally in 78 countries where it is endemic with over 90% of cases occurring in sub-Saharan Africa, where

the infection is estimated to cause more than 200,000 deaths annually (WHO 2011; Sady *et al.*, 2013). In Kenya, it remains a serious public health concern with approximately 6 million people being infected and an additional 15 million being at high risk of the infection particularly in endemic areas of the country (GAHI 2010).

Five species of *Schistosoma* are known to infect human beings: *Schistosoma japonicum, Schistosoma mekongi, Schistosoma haematobium, Schistosoma mansoni* and *Schistosoma intercalatum*. Infections with *Schistosoma mansoni*, *Schistosoma japonicum Schistosoma mekongi,* and *Schistosoma intercalatum* are associated with chronic liver and intestinal fibrosis, whereas chronic *Schistosoma haematobium* infections lead to fibrosis, structuring and calcification of urinary tract. Based on prevalence, distribution and pathogenicity, the most important human schistosome species are *Schistosoma mansoni*, *Schistosoma japonicum* and *Schistosoma haematobium*. However, in Africa and middle East, the most predominant species are *Schistosma haematobium* that causes urogenital schistosomiasis and *Schistosoma mansoni* that causes intestinal schistosomiasis (Brooker *et al.,* 2009a), wheareas only *S. mansoni* is present in the Americas. *S. japonicum* is localized to Asia, especially in the Philippines and China. Other locally distribitued species that cause human disease are: *Schistosoma mekongi*, in the Mekong River basin, *Schistosoma guineensis* and *Schistosoma intercalatum* in west and central Africa (Figure 2.1). *Bulinus* and *Biomphalaria* specicies are the intermediate host snails for *Schistosoma haematobium* and *Schistosoma mansoni* respectively while S. *japonicum* uses amphibious freshwater Oncomelania spp snails as its intermediate host (Schimidt and Roberts 2009). In endemic areas, children, fishermen, women and farmers in irrigation areas often suffer from schistosomiasis.

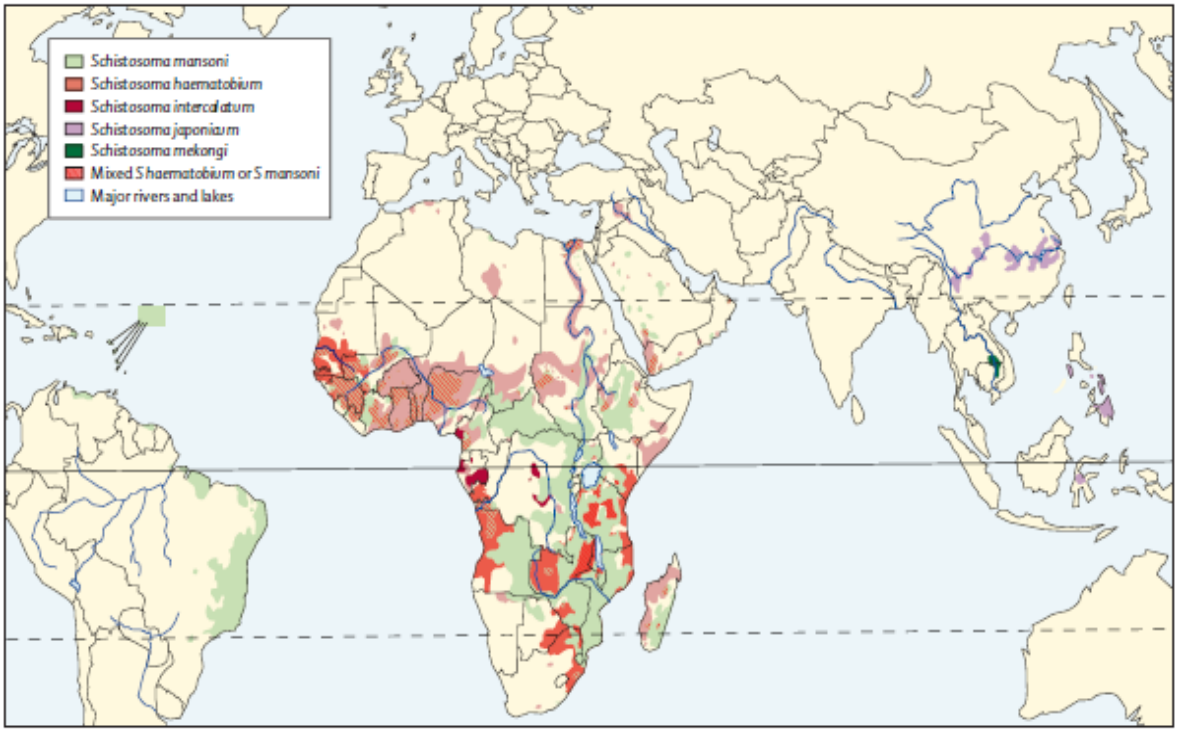

Figure 2.1: Global distribution of countries where human schistosomiasis is transmitted. Adapted from (Gryseels *et al.*, 2006).

Generally, the disease is characterized by a variety of symptoms including anaemia, abdominal pain, hepatoslenomegaly, diarrhea or bloody urine and in severe cases, Symmers peripotal fibrosis of the liver and its sequelae of portal hypertension and eosophageal varices may develop and finally death may occur due to haematemesis (King *et al.*, 2005). Intestinal clinical manifestations of *S. mansoni* infection include anaemia, abdominal pain, diarrhea, and blood in the stool. In severe cases, hepatosplenomegaly occurs and is repeatedly associated with ascites and other signs of portal hypertension (van der Werf *et al.*, 2003; Steinmann *et al.*, 2006). *S. haematobium* infection is characterized by haematuria and urogenital symptoms due to bladder and uretral fibrosis. Sandy patches in the bladder mucosa and hydronephrosis that are commonly seen in chronic cases. Female genital schistosomiasis has more recently been recognized as a serious problem and is considered a potential risk factor for human immunodeficiency virus

(HIV) acquisition. Bladder cancer is a possibility of a late stage complication of *S. haematobium* infection (Mostafa *et al.,* 1999). In affected populations, children carry the heaviest parasite burden (Fisher 1934; Verani *et al.,* 2011; Odiere *et al.,* 2012; Colley 2014) and while most infected individuals develop subtle or moderate morbidity (King *et al.,* 2005), a few develop severe pathology in the second decade of life or beyond. This form of its pathology may cause 200,000 deaths every year in Sub Saharan Africa (van der Werf and de Vlas 2002).

In schistosomiasis endemic areas, the most prevalent form of the disease is chronic schistosomiasis as a result of repeated exposure to infectious cercariae. In such endemic geographical regions, children and adolescents are reported to carry the heaviest burden of the infection (Fisher 1934; King *et al.,* 1988; DeStigter *et al.,* 1989; Odiere *et al.,* 2012). In endemic areas, initial infections usually occur in children as young as 1 or 2 years of age with the burden of infection increasing in intensity in the next decade of life as new worms colonize the body (Verani *et al.,* 2011; Colley *et al.,* 2014). In addition, others have reported infections in infants who are less than 3 months old (Odogwu *et al.,* 2006) and in Tanzania, a study reported a *S. mansoni* schistosomiasis infection of 32-64% among the school aged children in different geographical regions (Lwambo *et al.,* 1999; Mazigo *et al.,* 2010; Kinung'hi *et al.,* 2014). Schistosomiasis infection prevalence and intensity curves have been reported to typically peak in young adolescents after which prevalence and intensity of the infection decrease in adulthood (Woolhouse *et al.,* 1991; Odiere *et al.,* 2012). However, frequent contact with schistosome parasite infested water during activities such as laundry, swimming, bathing, sand harvesting, washing cars, fishing and others can still be linked to high prevalence of infection among subpopulations of adults in endemic areas (Colley *et al.,* 2014). Epidemiological surveys have reported that people living in schistosomiasis endemic regions are likely to be infected with

schistosomes at some point in their life. In geographical areas with typical transmission patterns, 60-80% of school age children and 20-40% of adults can remain actively infected (Colley *et al.,* 2014).

In Kenya, two most common species of *Schistosoma* are *Schistosoma mansoni* and *Schistosoma haematobium* which occur in the eastern, central, western and coastal regions of the country. In central and western Kenya, schistosomiasis is predominantly caused by *Schistosoma mansoni* while in the coastal region of Kenya; schistosomiasis is exclusively caused by *Schistosoma haematobium* (Brooker *et al.,* 2009b). In Nyanza region of western Kenya, studies strongly point to a high prevalence of *S. mansoni* particularly being confined along the shores of Lake Victoria, with the prevalence of the infection decreasing further away from the lake (Handzel *et al.,* 2003; Odiere *et al.,* 2012). Currently control of schistosomiasis is based on drug treatment, snail control, provision of clean water and improved sanitation, behavior change and health education but severe disease is largely controlled by treatment of infected people with praziquantel, the drug of choice due to its safety and efficacy (WHA 2001b).

2.3 Life Cycle of Schistosomiasis

Schistosomiasis is a chronic infection of the circulatory system caused by trematodes that inflame mainly the intestines, bladder, and liver. There are five types that affect humans: *S. haematobium*, which migrates to the perivesical and periureteral vessels, *S. mansoni* to the inferior mesenteric, *S. japonicum* to the superior mesenteric and the two others, *S. intercalatum* and *S. mekongi* to both mesenteric vessels (Goldsmid *et al.*, 1989).

Eggs produced by worm pairs are very critical in transmission of the parasite and approximately half of the parasite deposited eggs are released into the environment from infected individuals through faeces or urine and hatch on contact with fresh water to release the free-swimming

miracidium. The other half is said to be swept into circulation and be filtered out in the presinusidal capillaries of the liver and other human host tissues eliciting granulomatous inflammatory reactions that lead to severe forms of the disease such as portal hypertension, hepatosplenomegaly, esophageal and gastric varices among others if untreated (Hoffmann *et al.*, 2002). Egg production commences 5-7 weeks after infection when the infective larvae become adults (Colley *et al.*, 2014) and continues for 3-7 years which is usually the life of the worm (Fulford *et al.*, 1995). Eggs pass from the lumen of the blood vessels into adjacent tissues, and many then pass through the intestinal or bladder mucosa and are shed in the feaces (In case of *S. mansoni* and *S. japonicum*), or urine (in case of *S. haematobium*). The life cycle is completed when the eggs hatch, releasing miracidia that in turn infects fresh water snails (*S. mansoni* infects *Biomphalaria* species, *S. haematobium* infects *Bulinus* species and *S. japonicum* infects *Oncomelania* species). After two generations, primary and then daughter sporocysts within the snail, emerge infective schistosome cercariae which gain entry to the mammalian host via a percutaneous route and use a number of proteolytic enzymes to digest a route through the skin prior to their exit via blood capillaries or lymphatic vessels (MacDonald *et al.*, 2002; Mountford and Trottein 2004), and the life cycle continues (Jordan *et al.*, 1993; Waine and McManus 1997). It has also been reported that cercariae can remain infective in fresh water for 1-3 days but deplete their energy reserves greatly over a few hours (Lawson and Wilson 1980). Eggs excreted or retained in the body die within 1-2 weeks after being released by the female worm (Colley *et al.*, 2014).

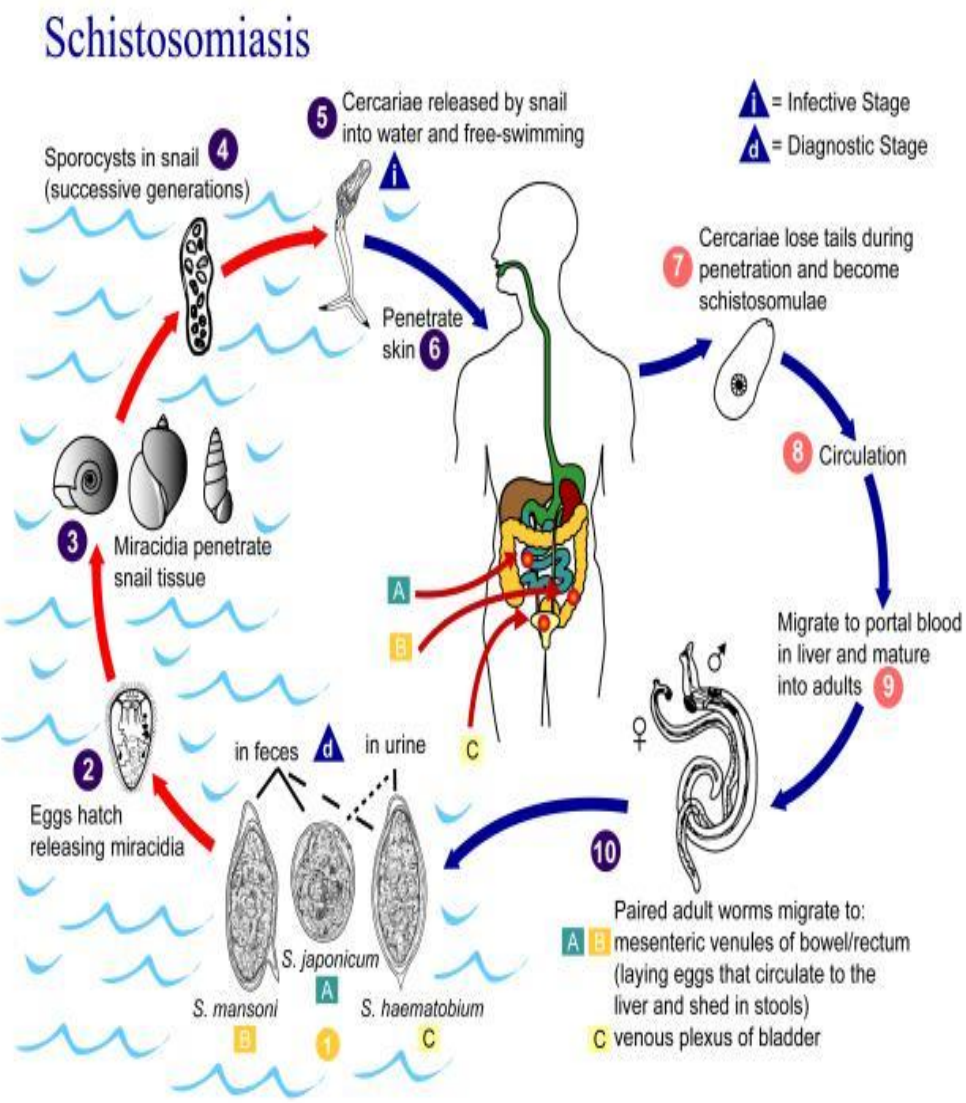

Figure 2.2 Schistosomiasis life cycle, from the DPDx website of CDC's Division of Parasitic Diseases: http://www.dpd.cdc.gov/dpdx

2.4 Pathogenesis of Schistosomiasis

The percutanous penetration of cercariae can provoke a temporary urticarial rash that sometimes persists for days as papulopruriginous lesions in newly exposed people such as travellers or immigrants to schistosome-endemic areas as a result of being exposed to schistosome antigens for the first time at an older age. Acute schistosomiasis (katayama fever) is a systemic

hypersensitivity reaction against the migrating schistosomulae, occurring few weeks to months after a primary infection as a consequence of worm maturation, egg production, release of egg antigen and the host's florid granulomatous and immune complex responses (Lambertucci 1993; Bottieau *et al.,* 2006; Colley *et al.,* 2014). It is characterized by sudden onset of fever, fatigue, myalgia, malaise, non productive cough and eosinophilia among others. Abdominal symptoms can develop later as a result of migration and positioning of the mature worms. Most of patients recover spontaneously after 2-10 weeks, but some develop persistent and more serious disease with weight loss, dyspnoea, diarrhea, diffuse abdominal pain, toxemia, and widespread rash (Ross *et al.,* 2007). Most individuals from schistosome endemic regions do not present with these syndromes most probably because of in-utero priming of T-lymphocyte and B-lymphocyte responses of babies born to mothers with helminthic infections (Eloi-Santos *et al.,* 1989; King *et al.,* 1998).

Schistosome-induced morbidity in established and chronic infection is due primarily to deposition of eggs that are trapped in the tissues of the human host during the perivesical or peri-intestinal migration in the liver, spleen, lungs or cerebrospinal system (Boros 1989). Eggs trapped in the tissues induce a granulomatous host immune response largely characterised by lymphocytes (which mainly produce T-helper-2 cytokine; eg interleukines 4, 5 and 13), eosinophils and alternatively, activated macrophages (Pearce and MacDonald 2002; Fairfax *et al.,* 2012). Down regulations of granulomatous response to eggs is done through several mechanisms in most individuals leading to progression of the infection to the chronic intestinal forms for *S. mansoni*, *S. japonicum* and *S. mekongi*. This form of disease presents as non-specific sporadic diarrhoea, abdominal pain and rectal bleeding with the frequency of the symptoms often related to intensity of infection (Mohamed *et al.,* 1990). In intestininal infection, eggs stimulate

the development of gastrointestinal features which are frequently focalized with isolated mucosal hyperplasia, pseudopolyposis, and polyposis interspersed with normal bowel (Cao *et al.,* 2010). Some individuals with the intestinal form of the disease only poorly immunoregulate their response to parasite egg antigens (Colley *et al.,* 1986) and as a result develop widespread fibrosis and consequently hepatosplenic disease with periportal fibrosis (Cheever 1968). Individuals with periportal fibrosis (Symmer's pipe stem fibrosis) still preserve hepatocellular funtions (Strauss 2002), thus differentiating this form of infection from other hepatic diseases such as cirrhosis. Clinical manifestations of this disease include upper abdominal discomfort with palpable nodular and hard hepatomegaly, frequently with splenomegaly. Death can rapidly occur as a consequence of the infection from ascites and haematemesis from oesophageal varices due to complication of portal hypertension (Richter *et al.,* 1998; King *et al.,* 2005). Early in infection, some of the tissue damage can be reversed by treatment but the longer it takes without treatment then, the more worse fibrosis will progress and the cumulative damage caused by the infection become irreversible (Smith and Christie 1986). Irreversible organ damage caused, can continue to affect the patients health status even when the disease is over, which may occur in as adults in their 30s or 40s (Smith and Christie 1986). The severity of the symptoms is thus related to both intensity of infection, time taken before chemotherapy is initiated and to individual immune responses. It is estimated that the time between initial infections to advanced fibrosis is usually 5-15 years (Gryseels 1992). However, periportal fibrosis can occur in children as young as 6 years, (Doehring-Schwerdtfeger *et al.,* 1990) showing that that the preschool aged children living in high endemicity areas are already infected with *Schistosoma* and hence, need for testing and treatment of preschool children (Odogwu *et al.,* 2006; Stothard *et al.,* 2011; Verani *et al.,* 2011; Navaratnam *et al.,* 2012).

2.5 Co-morbidities

Other infectious diseases are also prevalent in schistosomiasis endemic regions and hence, co-infections with multiple organisms are common features in individuals residing in such areas. Direct schistosomiasis health threats to individuals can lead to various morbidities and in addition, it can also affect immunological and physiological interactions between the human host and co-infecting organisms. In such regions improved control of schistosomiasis could provide additional benefits. A convincing example might be the effect of schistosomiasis infection on the susceptibility to HIV infection. The inflammation, friability and neovascularisation of the female genital epithelial tissue can lead to a compromised barrier to exposure to HIV infection among females with genital schistosomiasis during sexual intercourse. Recent studies have linked female genital schistosomiasis with more than double increased risk of HIV infection (Kjetland *et al.,* 2006; Mbabazi *et al.,* 2011; Downs *et al.,* 2012). Other findings have also reported an increased concentration of Cluster of differentiation 4 (CD4) positive cells in the semen of people who have high intensity of *S. haematobium* infection (Leutscher *et al.,* 2005), meaning increased coreceptors for HIV providing more targets for HIV infection (Secor *et al.,* 2003). Delayed praziquantel treatment for schistosomiasis in individuals co-infected with HIV results into more quick increase of HIV viral load and CD4 T cells loss as compared to those individuals who receive early treatment for the infection (Kallestrup *et al.,* 2005). However, so far, no paediatric schistosomiasis and HIV co-infection studies have been carried out to report on the interactions where HIV infection precedes schistosomiasis (Colley *et al.,* 2014). Upregulation of T-helper-2-type of immune responses in a schistosomiasis infection could alter immune responses to other co-infecting organisms, and in the process leading to downregulation of T-helper-1-type immune responses associated with control of viral or protozoan infections or interfere with the effectiveness of vaccines used for immunization.

Both *S. mansoni* and *P. falciparum* have overlapping distributions in many part of sub-Saharan Africa, where a significant proportion of the populations including school aged and preschool aged children are exposed to these infections (Mwangi *et al.,* 2006; Brooker *et al.,* 2007; Kinung'hi *et al.,* 2014). In those co-endemic areas, repeated and chronic infections with both parasites ensure that concurrent infections are common. Interactions between these two infections could provide some explanation for the widespread and uneven distribution of childhood schistosomiasis associated hepatosplenomegaly reported in those areas (Mwatha *et al.,* 2003). Different studies on schistosomiasis and malaria co-infections have however, reported conflicting outcomes. In some regions where both malaria and schistosomiasis are endemic, studies have shown that the prevalence of malaria, anaemia and pathological effects are higher in children co-infected with schistosomes than children who are not infected, whereas anti-malarial immune responses are decreased (Sokhna *et al.,* 2004; Wilson *et al.,* 2010; Wilson *et al.,* 2011). Rather than solely being a confounding factor, there is evidence from studies that chronic exposure to malaria and schistosomiasis infection may interact in childhood hepatosplenomegaly (Whittle *et al.,* 1969; Booth *et al.,* 2004), with a study done in eastern part of Kenya showing that *S. mansoni* associated hepatoslenomegaly being more more severe in Makueni District area where malaria infection is a greater public health concern than in high altitude areas of Machakos District (Fulford *et al.,* 1991) where malaria infection is less of a public health problem. Other studies have however, reported protective effects of schistosome infection on malaria infection accompanied by increased immune responses (Briand *et al.,* 2005), while other studies have not yet reported any effect (Lyke *et al.,* 2005). Cross-reaction of schistosome infection and malaria related antigens have been reported and this the situation more complicated (Pierrot *et al.,* 2006). Protective immune responses or susceptibility effects to malaria infection

could be influenced by a particular schistosome species responsible for the infection. *S. haematobium* is has been reported as promoting protection while *S. mansoni* increasing susceptibility to malaria infection (Sokhna *et al.,* 2004; Briand *et al.,* 2005). *S. mansoni* infection form granulomas in the liver of infected individuals and this could be the difference when malaria sporozoites pass through the liver immunologically affected by egg- induced granulomas (Colley *et al.,* 2014).

2.6 Health Related Quality of Life

Factors influencing its transmission mainly include environmental factors (getting into contact with infested water, proximity to infested water bodies), social economic factors (education and occupation) and one's characteristics (age, sex and treatment history) (El-Khoby *et al.,* 2000; Satayathum *et al.,* 2006; Matthys *et al.,* 2007; Kapito-Tembo *et al.,* 2009). Schistosomiasis mortality is low as compared to reported cases for such diseases as HIV and malaria and its burden is basically described in terms of morbidity which is always underreported. Measurements of the public health impact of schistosomiasis in control programs has focused on advanced quantifiable morbidities associated with schistosomiasis such as advanced hepatosplenomegaly or advanced hepatic fibrosis with portal hypertension (King *et al.,* 2005). However, most suffer from the less obvious or disabilities such as anaemia, impaired growth, undernutrion, abdominal pain, poor school performance and reduced work capacity (King *et al.,* 2005; King *et al.,* 2006; Bustinduy *et al.,* 2013). The non specificity of chronic schistosomiasis infection subtle morbidity markers are not always unique to the infection and so makes it difficult to correctly measure the burden due to the infection. Meta-analysis of the prevalence, time preference discounting and the weight of disability estimated that schistosomiasis accounted for at least 24-56 million disability-adjusted life- years (DALYs) lost in 2010 (H. 2010).

However, there is an ongoing debate of omission of the subtle morbidities, ignoring of co-morbidities, and addition of multiple parasitic infections in *Schistosoma* endemic areas by DALYS.

Evaluating the benefits of treating S. *mansoni* infection is presently monitored by assessing changes in infection prevalence in endemic areas. This is normally done by Kato-katz stool examination which has some disadvantages of being difficult to perform and may not accurately reflect the positive impact of treatment on health. Recently, attention is turning to the use of patient reported outcomes, such as health-related quality of life (HrQoL) (King *et al.,* 2005; Jia *et al.,* 2007; King and Dangerfield-Cha 2008) in health measurements in addition to commonly used morbidity and mortality indicators and the assessment of the impact of disease on perceived health. Many of the standardized instruments have been developed and explored as quality of life (QoL) assessment tools in evaluating infectious and chronic diseases in different settings (Sebit *et al.,* 2000; Jia *et al.,* 2007; Jia *et al.,* 2011; Alves *et al.,* 2012; Danansuriya and Rajapaksa 2012; Won *et al.,* 2013). However, limited studies have examined the perceived quality of life related to *S. mansoni* infection in individuals living in endemic areas despite the quality of life instruments being used widely in several settings (Won *et al.,* 2013). Measuring HrQoL of children is important because the medical field has experienced so many changes such as increase in the prevalence of chronic diseases such as schistosomiasis in endemic areas, resulting in the need for better HrQoL before and after treatment.

Health related Quality of life (HrQoL) has become a generally accepted concept in the fields of health care practice and research since the World Health Organization (WHO) defined health as 'not only the absence of diseases and infirmity but also the presence of physical, social and psychological well being of an individual (WHO 1946). Quality of Life hence is generally

considered as a multidimensional construct encompassing several domains such as physical, social and psychological which covers individual's perception of one's position in life in the context of culture, value systems, as well as in relation to one's goals, expectations, standards and concerns (WHOQOL 1995; Testa and Simonson 1996). Measuring HrQoL is crucial outcomes indicator in epidemiological studies and surveys, in evaluating health-care interventions and treatments, in identifying health inequalities, in understanding the burden of the disease and in allocating health resources (Eiser and Morse 2001). HrQoL tools have been mostly used to assess the burden of chronic diseases such as cancer and sickle cell diseases as opposed to assessing NTDs (Neglected Tropical Diseases), where they have only been utilised in estimating the burden of chronic schistosomiasis infection (Kamel *et al.,* 2001; Jia *et al.,* 2007) by either use of (EQ-5D plus or WHO QoL-bref questionnaire) (Kamel *et al.,* 2001; Jia *et al.,* 2011). Additionally, Previous studies on echinococcosis in P.R China (using SF 12) (Budke *et al.,* 2004), soil transmitted helminthes using both (EQ-5D and SF-12) (Ziegelbauer *et al.,* 2010) and the impact of acute schistosmiasis outbreak on the HrQoL of the travelers from Tanazania exposed to a fresh water pond suggest that the burden of schistosomiasis has been continuously underestimated (Budke *et al.,* 2004; Jia *et al.,* 2007). Furthermore, previous schistosomiasis studies in P.R China were all limited to general evaluation of the disabling sequelae of chronic schistosome infection or advanced schistosomiasis which made it not possible to contrast HrQoL outcomes among the schistosomiasis infected and non-infected people living in the same areas (Jia *et al.,* 2007; Jia *et al.,* 2011). All those studies utilized HrQoL instruments that do not take into account the different developmental stages of children which is the most vital stage for active schistosomiasis infection.

The number of available heath questionnaires has increased dramatically over the past decades but the choice of the HrQoL tool depends chiefly on the health condition being investigated and the group within the population being targeted such as the general population adults only or both adults and children (Terwee *et al.,* 2007). Although, HrQoL is generally self rated, this manner of measurement is challenging when applied in children because of the need of different instruments in different age groups, because children's cognitive skills differ with age. Even though studies have shown that children as young as 5 years can provide reliable reports on concrete health concepts (Tyler *et al.,* 1993; Rebok *et al.,* 2001) there is still considerable disparity between the evaluations made by the children and adolescents. Another challenge is the need to accommodate different cultures in different regional settings. To overcome these problems, a method for evaluating pediatric HrQoL was developed within the context of a structure that could be applied to all children of all ages who are of different cognitive development. Such systems can be used in longitudinal research study or clinical settings to monitor impact of treatments on HrQoL of different chronic infections such as schistosomiais. *Generic* and *condition- specific* types of instruments have been developed for measures of HrQoL. Generic instruments include general global health profiles summary ratings which have been validated in different settings with different populations. In contrast, disease specific or condition specific instruments are designed to focus or measure challenges associated with a specific illness such as cancer, individual diseases, patient groups or areas of function. Both instruments are multifactorial constructs and measure the individual's perception of physical, psychological and social functioning (Guyatt *et al.,* 1989; Guyatt *et al.,* 1993; Fumimoto *et al.,* 2001; Varni *et al.,* 2006; Danansuriya and Rajapaksa 2012).

The Pediatric Quality of life inventory (PedsQL) was chosen for this study because our population target were school going children aged 6-18 years both in primary and secondary schools selected in Asembo Bay, western Kenya. PedsQL is available in two generic instruments; The 23 item PedsQL^{TM} comprising of physical functioning (8 items), emotional functioning (5 items), social functioning (5 items) and school functioning (5 items) with forms for adults (over 26 years), young adults (18-25 years), adolescent (13-18 years), child (8-12 years), young child (5-7 years) and toddlers (2-4 years) and a shorter instrument with 15 items (PedsQL 4.0 SF 15) which has forms for adolescent, child, young child and toddler. The PedsQL^{TM} has been validated in different settings with different population with chronic illness in evaluation studies and in children with different debilitating conditions. Details are available at http://www.pedsql.org/about_pedsql.html.

2.7 Schistosomiasis Infection and Associated Risk Factors

Schistosomiasis is spread through human contact with water containing infective cercarie (Kloos *et al.,* 1997). Previous studies have reported a correlation between schistosomiasis transmission and numerous epidemiological and socio-economic factors such as sex, age, source of drinking water, latrine availability, sanitation hygiene (Barreto 1991; Raso *et al.*, 2005; Pullan *et al.*, 2008; Rudge *et al.,* 2008; Cundill *et al.*, 2011). In Kenya, *S. mansoni* infection continues to be one of the most important and widespread neglected tropical diseases (NTDs), especially in communities living around the shores of Lake Victoria in western Kenya (Handzel *et al.,* 2003; Black *et al.*, 2010b; Odiere *et al.*, 2012). The main determinant for the distribution and transmission of the disease is the absence or the presence of *Biomplaria* snail species intermediate host. High prevalence of this disease in western Kenya is closely correlated to contact with infested water bodies especially the Lake water during crossing with barefoot, car

washing in the lake, swimming, washing of clothes and utensils, playing in water, fishing and irrigation activity (Kabatereine *et al.,* 2004a; Black *et al.,* 2010b; Verani *et al.,* 2011; Mwinzi *et al.,* 2012). In schistosomiasis endemic areas, children are equally vulnerable to the infection due to high exposure to infested water bodies and are reported to carry the heaviest burden of the infection (Fisher 1934; Odiere *et al.,* 2012). Identification of risk factors of infection is important so as to understand factors affecting transmission in an endemic region. In addition, risk factors identification may inform possible intervention strategies or may facilitate disease control by targeting the high risk group.

2.8 Diagnosis of Schistosomiasis

Stool and urine samples can be examined microscopically for the schistosome parasite viable eggs (Stool samples for *S. mansoni* or *S. japonicum* viable eggs and urine samples for *S. haematobium* viable eggs). Tissue biopsies can also be examined for both S. *mansoni* and *S. japonicum* viable eggs. Currently, the presence of schistosomiasis infection cannot be ruled out completely because of the low sensitivity of stool and urine examination probably due to the tendency of eggs being passed out intermittently and in small amounts, resulting into some being not detected (De Vlas *et al.,* 1997). The WHO recommends Kato-Katz stool examination for schistosome eggs (Katz *et al.,* 1972) urine dipstick for heme (WHO 1991) or microscopic examination of polycarbonate filters for eggs in urine for field based control of schistosomiasis and mapping. Modern molecular techniques such as polymerase chain reaction (PCR) which are capable of detecting schistosome parasite deoxyribonucleic acid (DNA) in stool samples have greater sensitivity than microscopic examinations (ten Hove *et al.,* 2008; Meurs *et al.,* 2015), but are still disadvantaged by sampling limitations due to uneven distribution of eggs in the stool sample. For antibodies detection against schistosome antigens, serological assays have clinically

proven useful (Tsang and Wilkins 1997) but they also have the disadvantage of not being able to distinguish between current infection and past exposure because even after treatment, antibodies against the infection still persist for sometimes especially in individuals living in schistosomiasis endemic areas. Schistosome worms have no anus and cannot excrete waste products, so they regurgitate waste into the bloodstream. Some of these waste products are antigenic; circulating cathodic antigens (CCA) and circulating anodic antigens (CAA) are useful in blood- based and urine based assays. Detection of circulating schistosomal antigen is capable of discriminating between an active infection and past exposure. A point-of-contact circulating cathodic antigen assay is commercially available (Rapid Medical Diagnostics, Pretoria, South Africa). A Study conducted by our team showed that the lateral flow of urine in this cassette was more sensitive than the Kato-Katz technique (Shane *et al.,* 2010) and can be used for mapping of *S. mansoni* in endemic regions (Colley *et al.,* 2013).

New technologies are being studied for better diagnostic tools for testing schistome infections both in the field and in the clinical set ups and examples of these include positron emission tomography (PET) scans (Salem *et al.,* 2010) which have been tested to detect adult schistosome worms in vivo and another test called microfluidics results show potential to mimic both antibody and parasite antigen detection (Chen *et al.,* 2013). The potential benefits of these new advancement technologies in addition to improvement in clinical diagnosis of schistosomiasis include assessment of vaccines, improving the quality of schistosomiasis control and elimination programmes and drug development. Up to date, there is no gold standard for quantitative correlations to actual worm burden (Colley *et al.,* 2014).

2.9 Praziquantel Treatment

Adult worms are thought to possibly suppress schistosome specific immune responses so that the worm death following chemotherapy results in increased responsiveness to schistosome antigens (Ottesen *et al.,* 1978). In addition, drug treatment can damage the adult worm tegument as it kills the schistosomes (Andrews 1985) , thereby possibly releasing previously un-exposed antigens, making them accessible to the immune systems (Fallon and Doenhoff 1995). Furthermore, experimental report in mice has shown that praziquantel chemotherapy results into tegumental damage and release of antigens including 28-kDa glutathione S-transferase (28GST), the leading vaccine candidate (Dupre *et al.,* 1999), Sm23 antigens antibody responses to Sm23 are associated with resistance to infection, tubercle glycoprotein, alkaline phosphatase and actin (Redman et al.,1996). Worm death, either naturally or due to drug treatment has been shown to induce changes in cellular and humoral immune responses against schistosome parasites, and in recent times, studies have reported changes in the levels and types of antibody responses (Grzych *et al.,* 1993; Grogan *et al.,* 1996; Walter *et al.,* 2006) and cytokine responses following chemotherapy (Feldmeier *et al.,* 1988; Roberts *et al.,* 1993; Bourke *et al.,* 2013).

Praziquantel is an acylated quinoline-prazine compound that is active against all schistosome species, but whose mechanism of action is not well understood. Oxamniquine, a tetrahydroquinolone compound is effective against only *S. mansoni* and is no longer readily available in the market (Katz *et al.,* 1991). Since its discovery in mid 1970s (Thomas and Gonnert 1977), its safety and efficacy have ensured it widespread use. Since mid 1980s, morbidity control has been emphasized, with a reinforcement coming in the year 2001 when World Health Assembly (WHA) resolution 54.19 encouraged member states to regularly deworm 75% and up to 100% of school age children at risk of schistosome and helminthic

infections (WHO 2002; Savioli *et al.,* 2009). Praziquantel is the corner stone of schistosomiasis morbidity control with millions of people exposed and infected being treated every year (WHO 2002; Fenwick *et al.,* 2003; WHO 2012d). Praziquantel also forms a critical part in community-based schistosomiasis control programs (Colley 2014) with undoubtedly yielding health benefits to treated population. It is mostly marketed as 600mg tablets with a recommended standard regimen of 40mg/kg body weight in a single dose (WHO 2002) for treatment of *S. mansoni* and *S. haematobium*. For *S. mekongi* and *S. japonicum*, the recommended dosage is 60mg/kg. Praziquantel is well absorbed but undergoes extensive first pass hepatic clearance. The drug acts within one hour of ingestion by paralyzing the worm and damaging the tegument hence, causing the worm to detach from the wall of the vain and die. Common side effects of praziquantel are mild and occasionally include nausea, vomiting, malaise, headache, dizziness and abdominal pain. In heavy infections, acute colic with bloody diarrhea can occur shortly after treatment, probably provoked by massive worm shifts and antigen release (Stelma *et al.,* 1995; Colley *et al.,* 2014).

High risk of side effects correlates with high burden of infections which peaks about 2-4 hours after treatment and are self limiting (Colley *et al.,* 2014). The drug has a low toxicity in animals and no important long term safety difficulties have been documented in people (Dayan 2003). It is judged safe for treatment of young children (preschool children who are generally under the age of 5-6 years) and pregnant women after the first trimester (WHO 2002; Colley *et al.,* 2014). For children a dosepole is used to determine the number of tablets given (Montresor *et al.,* 2001) and for children who are younger than 5 years of age a new dosepole that extends below 94cm is used to determine the number of praziquantel tablets given (Sousa-Figueiredo *et al.,* 2012b). Praziquantel tablets are large and bitter in taste. Therefore, to use them for treatment of

schistosomiasis in preschool aged children, they get crushed and mixed with sweet drinks such as fruit juice before being administered orally to preschool aged children because there is no readily available paediatric formulation outside of Egypt (Epiquantel-praziquantel syrup) (Coulibaly *et al.,* 2012; Stothard *et al.,* 2013). Recent studies have reported that cure rates among preschool aged children are low when crushed praziquantel is used as compared to epiquantel in treatment of schistosomiasis (Navaratnam *et al.,* 2012; Sousa-Figueiredo *et al.,* 2012a), and this could possibly be attributed to extrapolation of adult dosage (Colley *et al.,* 2014).

Praziquantel has been shown to have little or no effect on eggs and immature worms. However, an interesting finding has been the recent demonstration that artemisinin based compounds such as artemether and artesunate that were developed primarily as antimalarial drugs are active against immature larva forms of the developing schsistosome worms which are relatively refractory to praziquantel (Utzinger *et al.,* 2000b; Utzinger *et al.,* 2007). The drug's use is limited because cercarial exposure and penetration time is usually unknown apart from exposure to sources that are well known as continuous transmission sites (Colley *et al.,* 2014). Artemisinin are currently critically important in treatment of malaria and are not being used in treatment of schistosomiasis. Double cure rates have been reported by meta-analysis when artemether and praziuantel drugs are used in combination for treatment of schistosomiasis as opposed to only using praziquantel (Perez del Villar *et al.,* 2012). For combination standard dosage, a lot of research is needed to understand the interactions and how to formulate the two drugs. In endemic areas for malaria, a lot of caution is necessary before such combination can be used to prevent introduction of resistance to artemisinin drugs in treatment of malaria infection (Colley *et al.,* 2014). Nevertheless, experimental studies on the possible use of artemisinin based compounds

alone or in combination with praziquantel could be undertaken should concern about selecting for artemisinin resistance in malaria reduce (Prichard *et al.,* 2012). Artemisinin or artemisinin-praziquantel combination could be developed as an arm of improved chemotherapy for schistosomiasis.

Tissue dwelling eggs can be excreted for several weeks after treatment and during the same period pre-patent or newly acquired infections can become productive because praziquantel is only effective against mature worm. The preferred timing of follow up is therefore 3-6 weeks after treatment (Renganathan and Cioli 1998; King *et al.,* 2011). After a single dose of 40mg/kg, 70-90% of patients cease to excrete eggs (Fenwick *et al.,* 2003; Utzinger and Keiser 2004). In most of those not cured, egg counts and antigen concentrations are nevertheless greatly reduced in number by 95% (Davis 1993; Stelma *et al.,* 1995; Utzinger *et al.,* 2000a). The efficacy of praziquantel has been shown to be unaltered in patients who are co-infected with HIV type 1 (Karanja *et al.,* 2002), and evidence has also shown that the *S. mansoni* treatment with praziquantel does not influence the viral load of HIV type 1 (Lawn *et al.,* 2000). The possibilities of resistance to praziquantel, the drug of choice for treating schistosomiasis continues to exist, but has not been reported yet even in the face of heavy use for over 30 years.

2.10 Immunity to Schistosomiasis

During chronic schistosomiasis infection, the adult worm continue to live in the bloodstream for decades by evading protective immune responses attack as a result of several mechanisms (Keating *et al.,* 2006). Eggs produced by the adult worm are supposed to be eliminated out of the body into the external environment by either faeces or urine. However, the flow of venous blood results into many schistosome eggs being carried to the opposite direction and getting trapped in the tissues (Colley *et al.,* 2014). Trapped eggs in the tissues contain proteolytic

enzymes and toxic substances which when released can lead to tissue necrosis (Buchanan *et al.*, 1973; Byram and von Lichtenberg 1977). Granulomas are therefore formed around tissues with trapped eggs as a response from the host to prevent proteolytic enzymes and toxic substances from causing more damage to the tissues (Colley and Secor 2014). However, egg induced granulomas formed can also be equally harmful to the host, and to prevent their negative impact on the tissues, studies have shown that anti-egg antigen responses develops successfully in the mice (Colley 1976) and the majority of individuals who have chronic schistosomiasis infections (Colley *et al.*, 1977; Barsoum *et al.*, 1982; Colley *et al.*, 1986).

Although intact adult worms evade immune responses attack, serodiagnostic assays are capable of detecting both anti-egg and anti-worm antibodies showing that adult worm antigens are easily recognized by the host immune system (Colley *et al.*, 2014). Morbidity associated with schistosome infection seems to be as a result of immunopathology against only the trapped eggs within the tissues (Andrade and Cheever 1971; Kamel *et al.*, 1978). Several studies have reported on the immunopathology and immunoregulation associated with morbidity of schistosome infection (Chiaramonte *et al.*, 2001; de Jesus *et al.*, 2004; Colley *et al.*, 2014; Colley and Secor 2014). The pathology in schistosomiasis infection has been shown to occur as a result of the parasite eggs being trapped in the host tissues and most of the schistosomiasis related pathology is induced by cellular immune responses (Cheever *et al.*, 2000). Evidence show that granulomatous reactions around the eggs are orchestrated by CD4-positive T cells and involves eosinophils, monocytes and lymphocytes (Cheever *et al.*, 2000; Colley and Secor 2014). In mice, a predominantly T-helper-1 reaction has been seen to occur in early stages of infection but shifts to an egg induced T-helper 2-biased profile later in the progression of the infection and evidence has it that an imbalance between these responses lead to severe lesions (Pearce 2005; Colley and

Secor 2014), and it is thought that these similar mechanisms could be the basis of fibrotic pathology in human beings (Abath *et al.,* 2006; Colley and Secor 2014).

Longstanding epidemiological and clinical evidence show that people living in endemic areas acquire some form of immune resistance after years of exposure (Butterworth 1993). Previous studies indicated that the intensity of infection peaks among older children (adolescents) and declines to lower levels in adults (King 2001), even in situations when adults have greater exposure to infection that the children in endemic areas (Kabatereine *et al.,* 1999). This pattern has been used to classify older individuals as partially resistant however, the decrease in infection rates after adolescence can also be explained by reduced water contact, and this makes it difficult to prove, the acquisition of effective immunity. Conversely, recent data from schistosomiasis endemic populations have shown that the observed decrease of schistosomiasis infection with age is associated with anti-worm immunity rather than reduced water contact (Mitchell *et al.,* 2011). Nonetheless, the changes which occur in the immune response of adolescents as they become older are considered very important in immunity to schistosomiasis (Hagan *et al.,* 1991; Grogan *et al.,* 1996). A previous study showed that the transition from a childlike to an adult like antibody repertoire occurs at younger age in populations subjected to higher levels of transmission (Mutapi *et al.,* 1997).

Debates in terms of whether protective resistance against schistosome infection exists is still ongoing (Warren 1973), but previous studies have suggested that resistance to schistosomiaisis infection does develop even though slowly (Karanja *et al.,* 2002; Fitzsimmons *et al.,* 2012; Mitchell *et al.,* 2012). Understanding the mechanism of protective immunity to schistosomiasis is a vital component of vaccine development. Debates in terms of whether protective mechanisms observed in experimental hosts are comparable to those observed in human

populations with a view to define the mechanisms of protective immunity to schistosomiasis have been extensive (Gryseels 2000; James and Colley 2001; Druilhe *et al.,* 2002). Even though adult worms are capable of evading immune responses, host protective immunity are possibly targeting other immature developmental stages of the worm such as skin stage and lung stage schistosomulae (Wilson 2009). The possibility of inducing protective immunity has been shown through immunization of different experimental hosts with irradiated cercariae (Hsu *et al.,* 1965; Yole *et al.,* 1996). However, the mechanism of protective immunity to schistosome infection related to resistance, to re-infection and responses to candidate vaccines are yet to be fully understood (Colley *et al.,* 2014).

Studies have indicated that populations with recent exposure to transmission have a strikingly similar age related infection pattern to those in long standing endemic conditions, and since slowly acquired immunity cannot be invoked in such circumstances, it is postulated that some form of age related innate resistance could also play an important part in epidemiology of schistosomiasis (Gryseels 1994; Naus *et al.,* 1998; Kabatereine *et al.,* 1999). Findings in both human and animals suggest that acquired immunity is mediated by IgE against antigens of larvae and adult worms which trigger blood eosinophils release of cytokines targeting schistosomulae (Butterworth 1993; Fitzsimmons *et al.,* 2012; Mitchell *et al.,* 2012). The slow development of acquired immunity is thought to be due to blockage of the IgE receptors by excess anti-schistosome IgG4 and possibly other blocking isotypes in the first year of infection, with some evidences indicating that protective immunity to schistosome infection is associated with a skewed Th-2 immune response with high levels of worm specific IgE and eosinophilia (Hagan *et al.,* 1985; Hagan *et al.,* 1987; Hagan *et al.,* 1991; Rihet *et al.,* 1991; Dunne *et al.,* 1992; Grogan *et al.,* 1996; Fitzsimmons *et al.,* 2012; Mitchell *et al.,* 2012). Correlates of resistance in

schistosomiasis infection include: Skewed Th2- immune response, IgE antibodies against worm antigens, low concentration of antidodies Ig4 which may serve as a blocking antibody inhibiting the action of IgE and high blood eosinophilia have been linked with repeated resistance to schistosomiasis infection in human in different epidemiologic regions (Jiz *et al.,* 2009; Fitzsimmons *et al.,* 2012; Mitchell *et al.,* 2012; Colley *et al.,* 2014; Colley and Secor 2014).

Sterile immunity to schistosomiaisis infection is rare or does not exist but partial immunity does develop (Mutapi *et al.,* 2013; Colley *et al.,* 2014; Colley and Secor 2014). Natural worm death or treatment results into release of ruptured worm tegument (Andrews 1985) which leads to exposure of hidden adult worm antigens (immunogens) (Fallon and Doenhoff 1995) that react with the protective immune responses which then react with the incoming immature suscesptible schistosomulae (Colley *et al.,* 2014). Repeated treatments increases the correlates of resistance to schistosome infection in response to worm antigens (Reimert *et al.,* 2006; Walter *et al.,* 2006; Bourke *et al.,* 2013) and repeated treatments to re-infections can lead to longer intervals before re-infection, even accounting for similar exposure patterns in individuals who are highly exposed (Karanja *et al.,* 2002). Much effort have been put towards the discovery and development of antischistosome vaccine and successful results have been observed in various experimental and reservoir host (McManus and Loukas 2008). However, no clinical trials for antischistosome vaccine for human have been successful (Colley *et al.,* 2014).

The pathology in schistosomiasis infection has been shown to occur as a result of the parasite eggs in the host tissues and most of schistosomiasis related pathology is induced by cellular immune responses (Cheever *et al.,* 2000). Evidence show that granulomatous reactions around the eggs are orchestrated by CD4-positive T cells and involves eosinophils, monocytes and lymphocytes (Cheever *et al.,* 2000). In mice, a predominantly T-helper-1 reaction has been seen

to occur in early stages of infection but shifts to an egg induced T-helper 2-biased profile later in the progression of the infection and evidence has it that an imbalance between these responses lead to severe lesions (Pearce 2005), and it is thought that these similar mechanisms could be the basis of fibrotic pathology in human beings (Abath *et al.,* 2006).

2.11 Control and Elimination of Schistosomiasis

Based on WHO recommendation, control of morbidity caused by schistosomiasis is done through preventive chemotherapy with praziquantel (WHO 1985; WHO 2006) with school aged children as a priority target group for treatment due to the focus on reducing morbidity from schistosomiasis infection. This is because of some of the following reasons: after a single dose of 40mg/kg, 70-90% of patients cease to excrete eggs (Fenwick *et al.,* 2003; Utzinger and Keiser 2004), ease of yearly distribution (or every other year) by trained school teachers or community health workers to attain adequate coverage to control morbidity in children and in cases of re-infections, it's used in prevention of severe hepatosplenic schistosomiasis or urogenital disease (Savioli *et al.,* 1990; WHO 2006; Colley 2014; Colley *et al.,* 2014). The WHO has recommended the inclusion of the preschool children in the preventive chemotherapy strategy (WHO 2010; Stothard *et al.,* 2011).

Snail control approaches are among the strategies which have been used in schistosomiasis control programmes and they include biological and chemical approaches. Biologically, the *Trematocranus placodon* fish of the family *Cichlidae* which feeds on *Bulinus* and *Biomphlaria* snail species has been studied and used to control snails on experimental basis, however, the results have not been remarkable (Evers *et al.,* 2006). Chemicals such as molluscide niclosamide which kills snails at low concentrations and are non-toxic to people are used to control snails. Although toxic to some fresh water fish and non target soft bodied aquatic organisms (Rocha-

Filho *et al.,* 2015), niclosamide is a licensed pesticide in the USA and it's widely used for snail control and has played an important role in schistosomiasis control campaigns (Zaki 1971; Yasuraoka *et al.,* 1989; WHO. 1993; Dai *et al.,* 2008).

In schistosomiasis endemic areas, health education and behavior change can also be used as a method for controlling schistosomiasis infection control in endemic areas however, challenging. With the participation of the community, behavior change can be useful in reducing exposure or contact with schistosome infested water and can possibly help reduce transmission of the infection in those areas (Colley *et al.,* 2014). Behavour change however, should also be supported by provision of safe water for bathing, washing which can be very expensive (Jordan 1985).

For elimination of schistosomiasis infection to be achieved, integrated application of some or all of the control methods are needed such as preventive chemotherapy, provision of clean water for bathing and washing, improvement of sanitation and drainage, health education and behavior changes to reduce contact with infective water, adequate disposal of solid waste and excreta, snail control to reduce contact with the intermediate hosts and to cercariae that have been shed by the snails , promoting health access for diagnosis and treatment and possibly use of a vaccine (Kolaczinski *et al.,* 2007; Utzinger *et al.,* 2009; Colley *et al.,* 2014). World Health Assembly (WHA) resolution 65.21 was adopted in May 2012 and it recommends to all member states and all international community to strengthen schistosomiasis integrated control interventions and also to intensify surveillance of schistosomiasis infection transmission (WHO 2012e). The ultimate vision of the resolution is a world free schistosomiasis, with the aim of controlling intermediate morbidity caused by schistosome infection by 2020, elimination of schistosome infection public health problems by 2025 and also interruption of transmission of schistosome

infections in many endemic areas including some few selected countries in Africa (WHO 2012c). Some of the critical issues that need to be addressed as elimination of schistosomiasis infection is sought include the following: understanding the lifecycle and the parasite movement between snail intermediate host and definitive mammalian host (Colley *et al.,* 2014), understanding the environmental changes that increase or decrease transmissions (Steinmann *et al.,* 2006; Wang *et al.,* 2009), effective treatment of people, elimination of snail intermediate host, prevention of people from coming into contact with schistosome infested water bodies (Colley *et al.,* 2014). It is also fundamental to understand how to detect the presence of parasites and active transmission when infection prevalence and intensity of infection are low, how to remove persistent low level of infection despite repeated treatment, when to ease MDA, when drug resistance could be suspected and for how long after evident elimination should monitoring and surveillance continue (Prichard *et al.,* 2012). Support from national governments, institutions and the local population coupled with intersectoral collaboration between the health, education section, water and sanitation are key features to achieve sustainable control and elimination of schistosomiasis (Gryseels *et al.,* 2006; Singer and de Castro 2007; Spiegel *et al.,* 2010; Freeman *et al.,* 2013).

CHAPTER THREE
MATERIAL AND METHODS

3.1 Study Area

This study was conducted in two primary (Raliew and Kanyichudo) and three secondary (Rarieda, Wera and Kokise) schools in fishing villages located within three kilometers on the shore of Lake Victoria in the Asembo Bay area of Rarieda Sub-County, Siaya County in western Kenya. The level of schistosomiasis infection in the human population is closely related to the proximity with local water bodies where daily water contact activities such as washing, bathing and fishing occur. Studies have shown that places with the highest prevalence and high infection intensities are closer to the source of infection (Handzel *et al.,* 2003; Kabatereine *et al.,* 2004a). Asembo bay area lies between Latitude 0º 12' 35" South and Longitude 34° 22' 43" East. The area is highly endemic for S. *mansoni* as reported by a survey conducted in primary schools in the area in 2001 which showed that the prevalence of *S. mansoni* ranges from 35-85% (Handzel *et al.,* 2003) and more recent findings (Mwinzi *et al.,* 2012; Foo *et al.,* 2015) also supported the high rate of schistosome infection in the region. Appendix 1 is a map of the Asembo Bay study area and the locations of the study schools in relationship to Lake Victoria.

3.2 Study Population

Approximately 96% of population in this area belongs to the Luo ethnic group and majorities are fishermen and also do subsistence farming (Phillips-Howard *et al.,* 2003). This study was conducted in two primary (Raliew and Kanyichudo) and three secondary (Rarieda, Wera and Kokise) schools in fishing villages located within three kilometers on the shore of Lake Victoria in the Asembo bay area of Rarieda Sub-County, Siaya County in western Kenya Study participants included pupils and students in primary and seconday schools (both boys and girls

from grades 1 to 12) attending 5 selected schools within the area. The inhabitants are predominantly fishermen which predidposes them to schistosomiasis infection**.**

3.3 Study Design

This study utilized a repeated cross sectional study design. A repeated cross sectional study is a study conducted in a new sample of participants at successive time points. For an annual study, this means that the participants in year one are different from the participants in year two who are different from participants in year three and so fourth and so on but from the same grades/standards every year of the study. The study involved baseline collection of parasitologic data (schistosomiasis prevalence and intensity of infections data) and morbidity assessment data in those who were *S. mansoni* egg positive and then providing annual MDA with PZQ and albendazole to all children attending the five selected schools. Both annual parasitologic survey and morbidity markers data collection on those who were *S. mansoni* egg positive were done by randomly selecting a sub-set of children from all grades (1-12) between the ages of 6-18 years old in each of the 5 schools prior to each annual MDA, utilizing a repeated cross sectional study design over a period of 5 years. Annual parasitologic surveys were performed inorder to determine the impact of annual MDA with PZQ on schistosomiasis prevalence and intensity of infections over a period of 5 years by utilizing a repeated cross sectional study design. Morbidity data from a cross section of children who were egg positive at year 5, one year after the last of four annual school-wide MDAs, were then compared to data from the cross section of children of similar age group at baseline to see the impact of four rounds of annual MDA with praziquantel on morbidity markers. It was hypothesized that when measures of morbidity were assessed after four rounds of MDA with praziquantel in year 5, they will decrease. It was also expected that overall prevalence and intensities of infection in each group would decrease.

One stool sample was taken upon enrollment from every child from grades (1-12) between the ages of 6-18 years old in all the five selected schools in this study. For morbidity assessment at baseline, thirty (30) *S. mansoni* positive children from each grade were then randomly selected totaling to 360 participants (that is from grades 1-12) according to sample size determination and calculation for morbidity component of this study. If there were more than 30 pupils per grade who were positive for schistosomiasis, then 30 children were selected randomly for inclusion per grade. On the 360 participants morbidity markers data were collected and these included measurements of height and weight and MUAC (mid upper arm circumference). Assessments for morbidity were also done by measuring heamoglobin levels (Hb), liver and/or spleen enlargement by palpation and fibrosis by ultrasound. Participants were further requested to give two more consecutive stool samples for egg quantification. In areas of high prevalence for schistosomiasis WHO recommends yearly mass drug administration of praziquantel to school-age children. These guidelines were followed for the next 4 years and annual MDA with PZQ and albendazole was provided to all children attending the five selected schools described above.

The participants in the selected grade in the 1st year were different from the children in that grade in the 2nd year, who were different again from the children in that grade in the 3rd year, and who were also different again from the children in that grade in the 4rd year and who were also different again from the children in that grade in the 5th year, (same grade but different individuals every year). This avoided the need to correct for non independent variables in our statistical analyses.

3.3.1 Sample Size Determination for Parasitologic and Morbidity Components of the Study

This study consisted of two components: parasitologic component (schistosomiasis prevalence and intensity of infections data) and morbidity assessment component conducted in those who

were *S. mansoni* egg positive and then providing annual MDA with PZQ and albendazole to all children attending the five selected schools. Parasitologic component addressed objective 1 evaluating the impact of four rounds of multiple MDA with praziquantel on *Schistosoma mansoni* prevalence and intensity of infection in the school children participants. This school wide component of the study involved providing annual MDA to all children attending the five selected schools and doing an annual parasitologic survey of a randomly selected subset of children from all grades in each of the five schools before each annual MDA, using a repeated cross-sectional study design.

Morbidity component of the study addressed study objectives 2. Based on schistosomiasis prevalence rate of 70% from the eligibility study carried out in the two primary and three secondary schools selected for this study and previous report of schistosomiasis prevalence in the area ranging between 35%-85% (Handzel *et al.,* 2003; Black *et al.,* 2010b) minimum sample size was determined according to the statistical Fisher's formula

$$N = \frac{Z^2P(1-P)}{D^2}$$

- Where:
- N= minimum sample size required
- Z= 1.96 standard error
- P= postulated prevalence rate of 70% (Eligibility survey)
- D= 0.05= the inverse of 95% confidence limit,
- 322 over 12 grades results into 27.0 per class. Assuming a 10% loss to follow up, the number was adjusted to 30 per standard.

3.3.2 Inclusion Criteria

Study participants were included in the study if:

1. They were residents of the study area,
2. They were school going pupils in primary or students in secondary schools within the study area,
3. They were between the ages of 6-18 years old,
4. The parents or guardians consented and the pupils and student assented to participate in the study,
5. They were *Schistosoma mansoni* positive by stool egg examination.

3.3.3 Exclusion Criteria

Participants were excluded from the study if:

1. They were anemic
2. They had just received praziquantel.
3. Not able to provide consent.

3.3.4 Participant Enrollment and Follow-up

Following identification of a village with appropriate population size and schistosomiasis prevalence after eligibility survey, school head teachers and village chiefs were asked for permission to conduct this study in the five selected schools. Once granted, the study team had a meeting with the teachers, parents, children to inform them on the study and to obtain consent from the parents and assents from the children in order to participate. Individuals from whom both consent and assent were obtained were screened for infection by stool (Kato-Katz) as well as checked for malaria and heamoglobin levels. For morbidity data collection, if more than 30 individuals were eligible, 30 individuals were randomly selected from all grades (1-12). Following these evaluations, the study team worked with the Ministry of Education and the

Ministry of Public Health and Sanitation to provide mass treatment of all children with PZQ for schistosomiasis and albendazole for soil transmitted helminthes. Children diagnosed with malaria were offered combination therapy with artemether-lumefantrine (Appendix II).

In year 1 after baseline data collection and first round of MDA with praziquantel, annual parasitologic evaluation using stool samples was done again on all children in grades (1-12) between the ages of 6-18 years old in the 5 selected schools in this study. Morbidity assessment was also performed in those who were *S. mansoni* egg positive by randomly selecting a sub-set of children from all grades (1-12) between the ages of 6-18 years old in each of the 5 schools prior annual MDA. This procedure was repeated in the successive years 2, 3 and 4 for all the children from all grades (1-12) between the ages of 6-18 years old in the 5 selected schools in this study. Consent and assent was again obtained from both parents and children, respectively, before evaluating the students for morbidity. It was also confirmed that they were in school the previous year and indeed received treatment for schistosomiasis. If there were more than 30 per class, 30 were randomly selected for morbidity assessments but all students whether or not positive for schistosomiasis infection and soil transmitted helminthes received PZQ and albendazole treatments respectively through mass drug administration program as recommended by WHO in areas with high prevalence. Malaria positive individuals were treated with artemether-lumefantrine. In year 3 4 and 5 the same plans were repeated. Children moved up one grade every year so it means that different individuals were evaluated in 5^{th} year than in baseline, years 1, 2, 3 and 4.

3.4 Methods of Data Collection

3.4.1 Stool Sample Collection and Screening

Students who agreed to participate in the study (with their parents' permission) were asked to provide stool samples, urine sample and finger prick blood to assess their malaria parasitologic and anaemia status. Quantitative evaluation of *Schistosoma mansoni* eggs was determined by the modified Kato/Katz feacal thick smear technique on duplicate slides of each of the three feacal specimen collected on consecutive days from each participant and the result expressed as mean eggs per gram of feaces (epg) (Katz *et al*., 1972). Using a wooden applicator stick, a small amount of the feacal material in a stool cup was placed on the newspaper and a piece of nylon screen (80 mesh) pressed on top so that some of the feacal material sieved through. The sieved feaces was collected by scrapping the flat-sided spatula across the upper surface then transferred to a slide with a template with a hole (pre-measured to hold 41.7mg of stool) placed on the center of the microscope slide until the hole completely got filled. The template was then passed over using the side of the spatula to remove excess feaces from the edge of the hole then carefully removed to leave a cylinder of feaces on the slide.

The feacal material was then coved with cellophane strip pre-soaked with 3% malachite green, 50% glycerol and 50% water, and the microscope slide inverted so that the feacal material pressed firmly against the hydrophilic cellophane strip on a smooth hard surface to allow the feacal material to spread evenly between the slide and the strip. The slide was then carefully pushed sideways to avoid separating the cellophane strip and the slide with the feaces placed on the bench facing upwards for water to evaporate and glycerol to clear. The smear was then read immediately for hookworm eggs as the egg clears first, then examined in a systematic way for *S. mansoni* infection and the scored number of eggs reported multiplied by 24 to obtain the total number of eggs per gram (epg) which is an estimation of the worm burden (WHO,1993). For

each sample, a duplicate set of slides were made and eggs counted by independent microscopist. Any discrepancy in the results was reconciled by comparing to results of the third independent quality control microscopist. From the same stool examinations, other soil transmitted helminthes present were noted. The presence of other helminthes eggs were recorded but quantitative counts of eggs was done only for *S. mansoni*. The intensity of infection was expressed as eggs per gram of feaces (epg) based on the arithmetic mean of the egg counts calculated from the total slides per child and categorized according to WHO guidelines as light (1-99 epg), moderate (100-399 epg) and heavy (≥ 400 epg) (Committee WHOE 2002.). STH infections were categorized as either positive or negative. Praziquantel and albendazole treatments were offered to all students as part of mass drug administration for schistosomiasis (40mg/kg of body weight) and Soil transmitted helminthes infections respectively (Appendix III).

3.4.2 Blood Collection and Processing

Approximately 100µl of blood was tested for heamoglobin levels using a portable, battery operated heamoglobinometer (Hemocue®, Angelholm, Sweden) and expressed in g/dl. Anaemia was defined according to Kenya National guidelines Normal (≥11.2), mild (8.2 to <11.2), moderate (5.2 to<8.2), and severe (<5.2) (Kimathi 2002.). Malaria infection status was determined by examining a Giemsa stained blood smear for malaria parasite numbers per 300 leukocytes and infection status defined by the presence of a single *Plasmodium falciparam* parasite. Malaria positive children were treated with artemether-lumefantrine.

3.4.3 Anthropometric Measurements

Anthropometric measurements were conducted for height, weight and mid-upper arm circumference. Height was measured with a seca stadiometer. Shoes and head covering were removed and children then asked to stand on the base of the stadiometer with both feet together

and head in contact with the vertical board then precise height was measured to the nearest 0.1cm. Weight was measured using an electronic Seca Scale 803. Children were also asked to remove shoes and excess clothing before body weight was measured to the nearest 0.1kg. Mid upper arm circumference (MUAC) was taken with a flexible MUAC tape and recorded to the nearest 0.1cm. Measurements for height, weight and MUAC were done twice for each child and the average values were used for the analysis. Body mass index (BMI) was calculated as weight in kilogrammes divided by the square of height in meters. To standardize anthropometric variables, data were entered into the WHO Anthro (version 3.2.2, January 2012 soft-ware and Z scores of weight-for age (WAZ) and height for age (HAZ) were computed (WHO 2012a). Values of BMI-for-age Z scores of <-2 defined wasting and stunting was defined by values of height- for age Z scores <-2. These measurements were performed by certified field workers who have received sufficient training and standardization on these measurements from qualified physicians and nutrition specialists.

3.4.4 Ultrasonography

Ultrasound machine was used to measure morbidity associated with liver abnormalities in schistosomiasis. Liver changes associated with schistosomiasis include periportal and/or diffuse fibrosis and enlargement of the liver. Spleen changes and enlargement associated with schistosomiasis infection were noted. The WHO Niamey protocol guideline was used (Richter *et al.,* 2001). A portable US ALOKA 900V ultrasound machine with a 3.5 MHz transducer was used in the field by trained technicians. Physical exam (palpation) was also performed by a trained physician (Appendix IV).

3.4.5 Health Related Quality of Life (HrQoL) Measurements

In this study, the PedsQ^{TM} 4.0 child self report was used (age 5-18) but did not collect parents proxy reports. The PedsQ^{TM} 4.0 Generic Core Scales consists of 23 items grouped into four

domains: Physical Functioning (PF), Emotional Functioning (EF), Social Functioning (SF) and School Functioning (SchF) comprising of 8, 5, 5 and 5 items respectively totaling to 23 items. The survey questions assessed how much of a problem each item has been during the past one month. A five point Likert-like response scale is used. The responses were made on a 5 point scale ranging 0 (never a problem), 1 (almost never), 2 (sometimes), 3(often) and 4 (almost always a problem). Responses were linearly transformed to 100, 75, 50, 25 and 0 respectively resulting to a 0-100 scale (0=100, 1=75, 2=50, 3=25, 4=0) with higher scores representing better level of functioning and better HrQoL.

According to the instructions given with The PedsQ^{TM}, overall and sub-scale scores were computed as the sum of the items divided by the number of items answered (accounting for the missing data). If more than 50% of the items in the sub scale were missing, the scale score was not computed. To be noted, the Physical health Summary score (8 items) is the same the Physical functioning subscale. The Psychosocial health summary score (15 items) is computed as the sum of the items divided by the number of the items answered in the emotional, social, and school functioning subscales. Total scores are also presented (Varni *et al.*, 2001).

Before the onset of the study, The PedsQ^{TM}, 4.0 was translated into Dholuo and back translated into English (DhoLuo-English). The approved Dholuo version was first pre-tested on randomly selected 30 children, 15 (6-10 years) and 15 (11-17years). These children never participated in QoL survey but they were in the same schools. All the PedsQ^{TM}, 4.0 questionnaires in this study were administered by well trained research assistants who are native DhoLuo speakers. The PedsQ^{TM}, 4.0 questionnaire is contained in (Appendix V). Details are available at http://www.pedsql.org/about_pedsql.html.

3.5 Data Analysis and Management

The latitude and longitude coordinates of each school were obtained using a Global Positioning System on Android phones and projected to UTM zone 36S. Maps were created with ArcGIS (version 10.3, ESRI, Inc., Redlands, CA). Each study participant was assigned a unique identification number. Data were entered using Microsoft Excel (Microsoft coporation, Redmond, Washington, USA) and kept confidential. For parasitology analyses, data were analyzed using IBM SPSS version 24 (IBM coporation, Armank, New York, USA) and GraphPad Prism version 6 (GraphPad Software, La Jolla, California, USA). Mann Whitney U nonparametric analysis was used for evaluating infection intensity between years. A Chi square test for trend (Cochran-Armitage) was used to evaluate the association between annual treatments and changes in prevalence of *S. mansoni* and STH and helped in addressing objective 1. Tests were considered statistically significant at $P \leq 0.05$. In addressing objectives 2 and 3 dealing with measures of morbidity associated with schistosomiasis infection, data were subsequently analyzed using IBM SPSS version 24 and GraphPad Prism version 6. Mann Whitney nonparametric analysis and Fisher's exact test were used for evaluating differences between years for continuous data and categorical data, respectively. Tests were considered statistically significant at $P \leq 0.05$.

3.6 Ethical Considerations

Approval of the study was obtained from the institutional review board (IRB) of the University of Georgia, the Department and Institutional Scientific steering committees of KEMRI and the National/KEMRI clearance committee. The Institutional Review Board of the CDC also reviewed the study and participation information was also reviewed by above mentioned boards and committees (Appendix VI).

3.7 Written Informed Consent

Informed consent for the study participation was obtained from parents or guardians and assents from pupils and students participants by signing the consent forms. All participants and their parents or guardians received adequate explanation of the study and their participation requested in the language they understood best. Recruitment was purely voluntary and participants and their parent or guardians were allowed to ask questions about their rights and the study as a whole before they were enrolled after providing written consent and assent. The process of obtaining blood samples by venipucture exposed participants to a minimal risk of discomfort and a slight chance of bruise at the site of venipucture. To minimize risk of infection, qualified KEMRI trained personnel carried out the process in a sterile manner. The other aspects of the study involved acquisition of stool and urine specimens for diagnosis and the use of noninvasive ultrasound imaging and abdominal palpation, the answering of a short questionnaire regarding the participant's lifestyle as it relates to potential contact likely to pose a risk of acquiring schistosomiasis, height and weight measurements, mid upper arm circumference (MUAC) measurements and a short quality of life questionnaire. None of these noninvasive determinations were associated with any potential risks.

All participants were treated for schistosomiasis and soil transmitted helminthes using Praziquantel and Albendazole respectively as provided by the Ministry of Health of Kenya and across Africa. Blood was screened for malaria parasites and participants found to be parasitaemic were treated with artemether-lumefantrine. Participants benefited by accessing free examination by the collaborating physician and prescription of drugs for other ailments other than those mentioned above.

3.8 Confidentiality

Participant confidentiality was strictly maintained among the staff members and the participants. All the samples collected from the study participants were allocated unique study identification code for purposes of sample tracking and identification for treatment. All information and medical records were made confidential. Data generated from this study have appeared in publication but the identity of the individuals were not revealed in publications or otherwise.

3.9 Summary of Measurements of Variables (Morbidity Markers)

Variable	Measurements of Morbidity Markers
Anemia	Approximately 100µl of blood was tested for eamoglobin levels using a portable, battery operated heamoglobinometer (Hemocue®, Angelholm, Sweden) and expressed in g/dl. Anaemia was graded according to the Kenya National guidelines: Normal (≥11.2), mild (8.2 to <11.2), moderate (5.2 to<8.2), and severe (<5.2)
Organomegalies **Hepatomegaly (Enlarged liver)** **Splenomegaly (Enlarged spleen)** **Hepatosplenomegaly(Enlarged spleen and liver)**	Ultrasound machine was used to measure morbidity associated with liver abnormalities in schistosomiasis. Liver changes associated with schistosomiasis include periportal and/or diffuse fibrosis and enlargement of the liver. Spleen changes and enlargement associated with schistosomiasis infection were noted. The WHO Niamey protocol guideline was used
Pediatrics Quality of Life (PedsQ™ 4.0)	PedsQ™ 4.0 child self report was used (age 6-18). The PedsQ™ 4.0 Generic Core Scales consists of 23 items grouped into four domains: Physical Functioning (PF), Emotional Functioning (EF), Social Functioning (SF) and School Functioning (SchF) comprising of 8, 5, 5 and 5 items respectively totaling to 23 items.The PedsQ™, 4.0 questionnaire is contained in Detail: http://www.pedsql.org/about_pedsql.html.
Anthropometric Measurements **Stunting** **Wasting** **Mid upper arm circumference (MUAC)**	Anthropometric measurements were: height, weight and mid-upper arm circumference. Height was measured with a seca stadiometer. Height was measured to the nearest 0.1cm. Weight was measured using an electronic Seca Scale 803. Weight was measured to the nearest

	0.1kg. Mid upper arm circumference (MUAC) was taken with a flexible MUAC tape and recorded to the nearest 0.1cm. Body mass index (BMI) was calculated as weight in kilogrammes divided by the square of height in meters. To standardize anthropometric variables, data were entered into the WHO Anthro (version 3.2.2, January 2012 soft-ware and Z scores of weight-for age (WAZ) and height for age (HAZ) were computed Values of BMI-for-age Z scores of <-2 defined wasting and stunting was defined by values of height- for age Z scores <-2.

CHAPTER FOUR

RESULTS

4.1 Total Number of Children Screened and Study Populations

Annual school-wide preventive chemotherapy with PZQ and ALB was provided in all 5 schools for 4. As a result of the extensive sensitization of the surrounding communities and the schools, treatment coverage exceeded 90% each year. At baseline, a total of 1,110 children from the two primary schools and three secondary schools were enrolled for the parasitologic study. In subsequent years, 897 (Year 1), 1,302 (Year 2), 1,327 (Year 3) and 1,440 (Year 4) children were evaluated for *S. mansoni* and STH infections. On average, 100 children (range = 31-202) were randomly enrolled from each grade (Grades 1-12) other than Year 1 when an error occurred and no first grade students were evaluated (Table 4.1). While many children in each Grade were evaluated each year, the proportion represented in each grade shifted somewhat, resulting in more students being evaluated in lower grades at baseline and more being evaluated in the upper grades by Years 2, 3 and 4. The proportion of male students varied from 49% to 57% over the years.

Table 4.1: Total number of children screened from each grade in all Years

Grade	Baseline N (%)	Year 1 N (%)	Year 2 N (%)	Year 3 N (%)	Year 4 N (%)
1	124 (12.3)	0 (0)	77 (5.9)	71 (5.4)	70 (4.9)
2	111 (11.0)	72 (8.0)	80 (6.1)	129 (9.7)	80 (5.6)
3	126 (12.5)	81 (9.0)	88 (6.8)	100 (7.5)	98 (6.8)
4	128 (12.7)	108 (12.0)	111 (8.5)	111 (8.4)	93 (6.5)
5	90 (8.9)	83 (9.3)	103 (7.9)	90 (6.8)	94 (6.5)
6	84 (8.3)	86 (9.6)	103 (7.9)	80 (6.0)	104 (7.2)
7	79 (7.8)	97 (10.8)	126 (9.7)	108 (8.1)	105 (7.3)
8	65 (6.4)	65 (7.2)	62 (4.8)	76 (5.7)	88 (6.1)
9	63 (6.2)	39 (4.3)	156 (12.0)	177 (13.3)	202 (14.0)
10	49 (4.8)	122 (13.6)	200 (15.4)	181 (13.6)	193 (13.4)
11	61 (6.0)	70 (7.8)	124 (9.5)	105 (7.9)	168 (11.7)
12	31 (3.1)	74 (8.2)	72 (5.5)	99 (7.5)	145 (10.1)
Total	1,011 (100)	897 (100)	1,302 (100.0)	1,327 (100.0)	1,440 (100.0)

Table 4.1. The overall number and grade by grade number of school-going children enrolled in each year for all the five study year

Annual school-wide preventive chemotherapy with PZQ and ALB was provided in all five schools for 4 years. As a result of the extensive sensitization of the surrounding communities and the schools, treatment coverage exceeded 90% each year. At baseline, a total of 1,110 children from the two primary schools and three secondary schools were enrolled for the parasitologic component of the study. In subsequent years, 897 (Year 1), 1,302 (Year 2), 1,327 (Year 3), and 1,440 (Year 4) children were evaluated for *S. mansoni* and STH infections. On average, 100 children (range = 31–202) were randomly enrolled from each grade (Grades 1–12) other than Year 1 when an error occurred and no first grade students were evaluated (Table 1). Although many children in each grade were evaluated each year, the proportion represented in each grade shifted somewhat, resulting in more students being evaluated in lower grades at baseline and more being evaluated in the upper grades by Years 2, 3, and 4.

4.2 Changes upon Mass Drug Administration on *Schistosoma mansoni* and Soil Transmitted Helminths Infections

The overall prevalence of S. *mansoni* was 44.7% at baseline and decreased after each round of MDA (Table 2). Generally, the overall prevalence of STH infections was very low in this area. At baseline, the overall prevalence of hookworms was 3.0% which was low but still decreased rapidly to 0.1%, 0.6%, 0.2% and eventually to <1% after 1, 2, 3 and 4 rounds of MDA with albendazole (Table 2). The overall prevalence of *A*scaris *lumbricoides* was 2.8% at baseline which was equally low but still decreased to 0% after 1 round of MDA with albendazole then slightly increased to 1.8% after 2 rounds of treatments then decreased to 1.1% and finally to 0.6 % after 3 and 4 rounds MDA with albendazole treatments (Table 4.2). At baseline, the

prevalence of *Trichuris trichiuria* was 5.3% but decreased more gradually to 4.3% after 1 round of MDA with albendazole and then increased a bit by 0.1% after 2 rounds of MDA with albendazole then decreased to 3.4% and finally to 1.3% after 3 and 4 rounds of MDA with albendazole (Table 4.2). Each of the 5 schools declined in *S. mansoni* prevalence by more than 60% following the 4 years of MDAs. Analyses of the yearly progression of the changes in prevalence for these helminths by the Cochran-Armitage test for trend indicates that prevalence of each infection changed significantly over the study years (*S. mansoni*, $X^2 = 311.2$, $p < 0.0001$; hookworm, $X^2 = 54.9$, $p < 0.0001$; Ascaris, $X^2 = 10.6$, $p < 0.0001$; Trichuris, $X^2 = 28.9$, $p < 0.0001$).

Table 4.2: Overall prevalence of *S. mansoni* and soil-transmitted helminths among screened primary and secondary students over 5 years

	Baseline (n=1011)	Year 1 (n= 897)	Year 2 (n=1302)	Year 3 (n=1327)	Year 4 (n=1440)
Schistosoma mansoni	44.7%	34.4%	25.7%	23.1%	14.0%
Hookworms	3.0%	0.1%	0.6%	0.2%	0%
Ascaris lumbricoides	2.8%	0%	1.8%	1.1%	0.6%
Trichuris trichiuria	5.3%	4.3%	4.4%	3.4%	1.3%

Prevalence of *S. mansoni* and soil-transmitted helminths over 5 study years. The prevalence of *S. mansoni* infection decreased from 44.7% to 14.0% after four rounds of mass drug administratio with praziquantel.

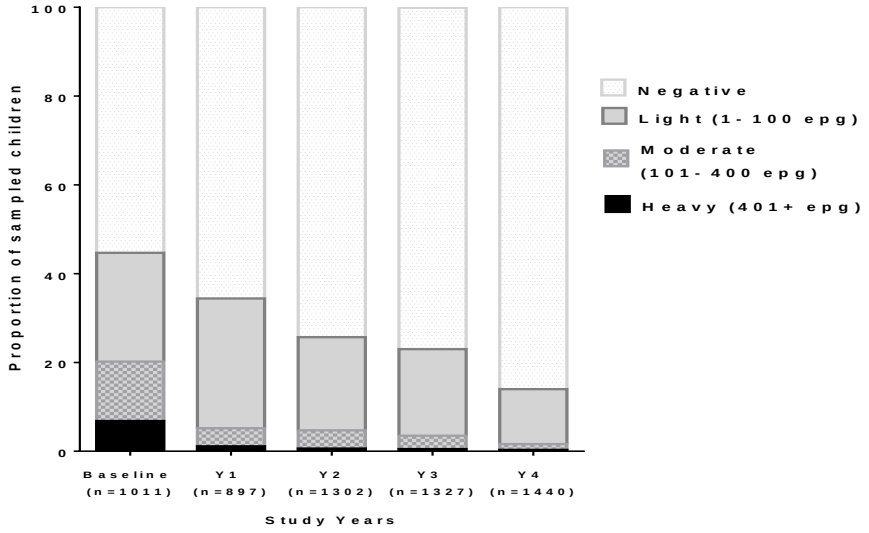

Figure 4.1: Overall prevalence and intensity (by WHO standard intensity categories) of *Schistosoma mansoni* infection for school children in the primary and secondary schools studied.

Figure 4.1 Demonstrates the yearly progressive decrease of both prevalence and intensity of *S. mansoni* infection for all students from grades 1-12, resulting in almost virtual elimination of heavy infections (from 6.8% to 0.3%) after four rounds of school-based MDA. The prevalence of infection also decreased from 44.7% to 14.0% after four of MDA with praziquantel.

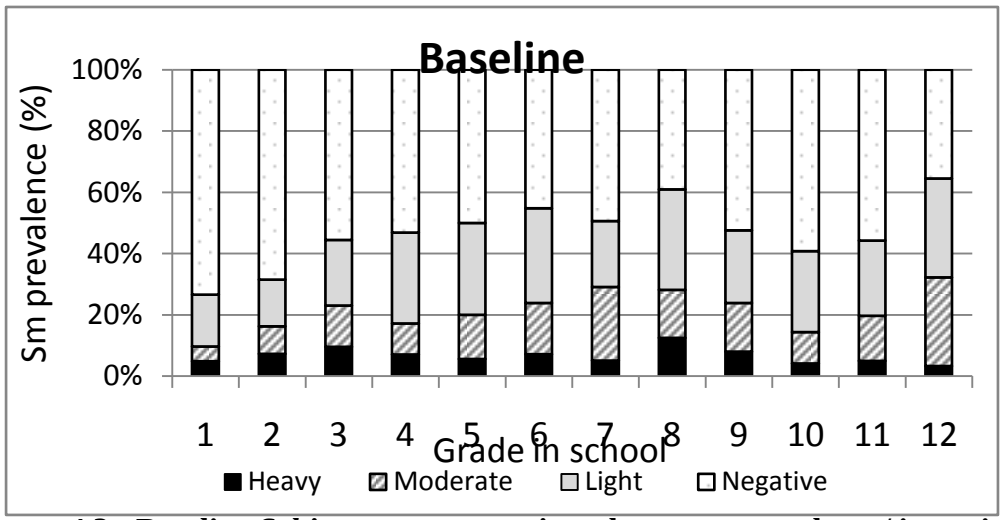

Figure 4.2: Baseline *Schistosoma mansoni* grade versus prevalence/ intensity curves

The overall schistosomiasis baseline infection data across grades (1-12) was consistent with typical schistosomiasis age/prevalence curves where prevalence increases with age (Figure 4.2). However, for heavy infections, the prevalence observed was not consistent with the typical schistosomiasis age/prevalence curve because it varied across all grades with no discernable pattern.

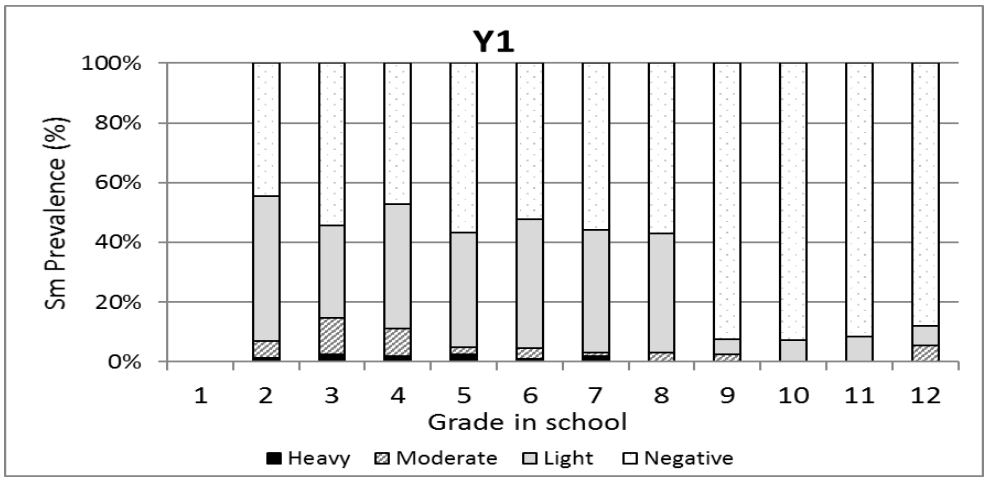

Figure 4.3: Year 1 *Schistosoma mansoni* grade versus prevalence/ intensity curves

One year after the first round of high coverage school-based mass drug administration, prevalence was decreased and infections levels were dramatically shifted from heavy or moderate to light, with very low prevalence of heavy intensity of infections in the lower grades (1 to 7) and no heavy intensity of infections in the older students (Grades 8 to 12; Figure 4.3).

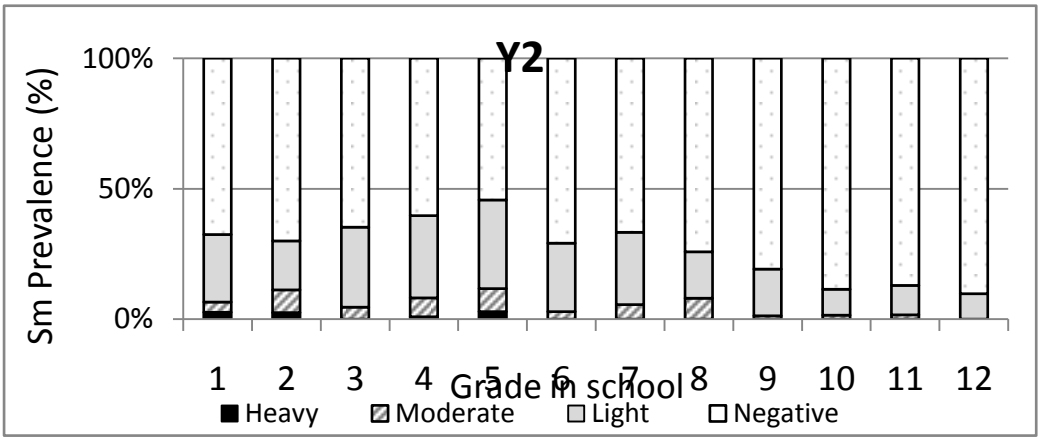

Figure 4.4: Year 2 *Schistosoma mansoni* grade versus prevalence/ intensity curves

The same pattern of decrease was essentially repeated in subsequent years. After 2 rounds of mass drug administration (Year 2, Figure 4.4).

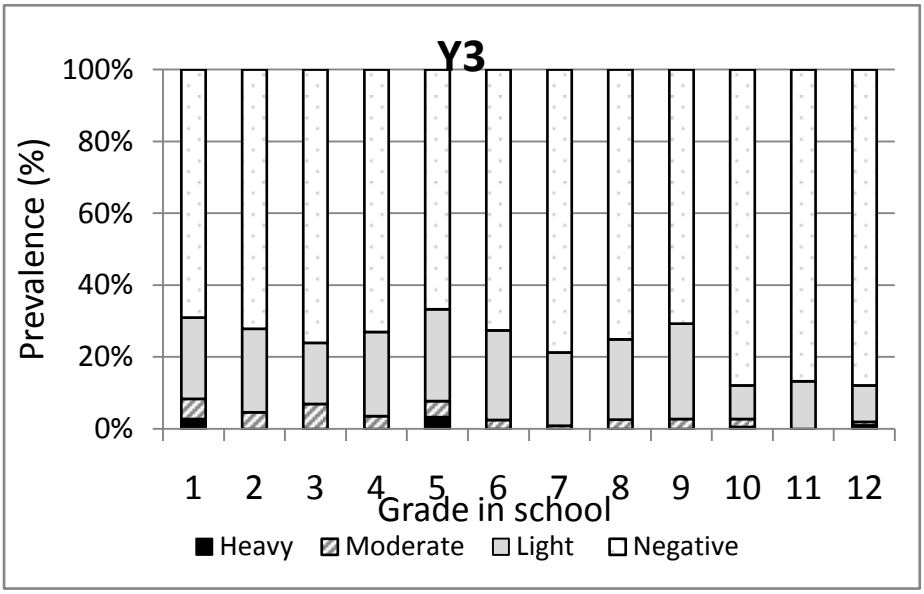

Figure 4.5: Year 3 *Schistosoma mansoni* grade versus prevalence/ intensity curves

The schistosomiasis age/prevalence pattern was shifted compared to baseline with high prevalence and heavy infections present only in the lower grades. This pattern was maintained after 3 rounds of MDA (Year 3, Figure 4.5).

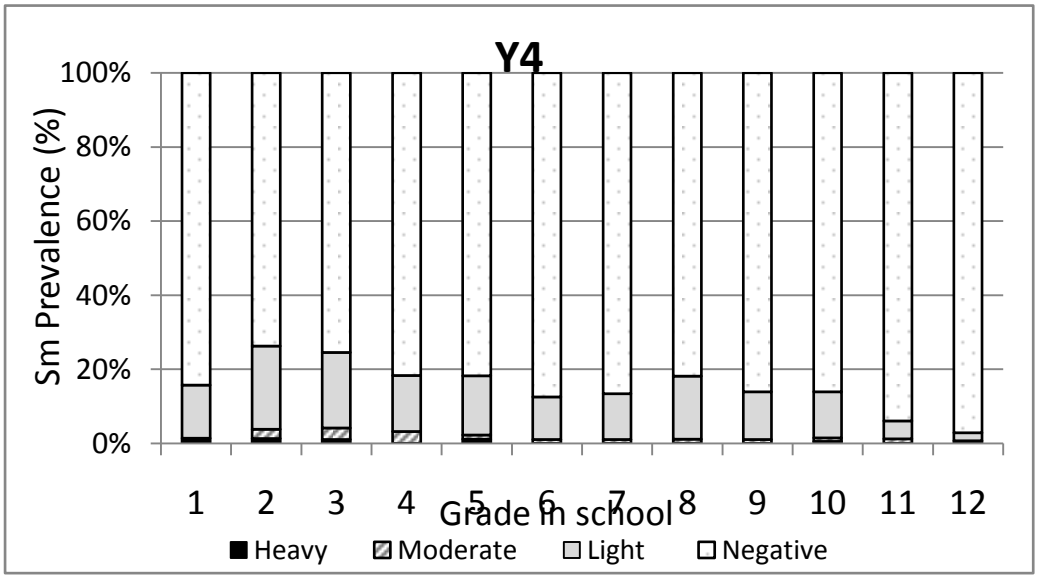

Figure 4.6: Year 4 *Schistosoma mansoni* grade versus prevalence/ intensity curves

The schistosomiasis age/prevalence pattern was shifted compared to baseline with high prevalence and heavy infections present only in the lower grades. This pattern became less obvious after the fourth round of MDA (Year 4, Figure 4.6) because prevalence and intensity were decreased in all grades (1-12) and the curves became essentially flat.

Table 4.3: Prevalence (%) of heavy infections (≥400 epg) among screened children over 5 years of study.

Grade	Baseline	Year 1	Year 2	Year 3	Year 4	P value for chi square test for trend
1	4.8	--	2.6	2.8	1.4	0.184
2	7.2	1.4	2.5	0	1.3	0.002*
3	9.5	2.5	0	0	1.0	<0.001*
4	7.0	1.9	0.9	0	0	<0.001*
5	5.6	2.4	2.9	3.3	1.1	0.149
6	7.1	1.2	0	0	0	<0.001*
7	5.1	2.1	0	0	0	0.0011*
8	12.5	0	0	0	0	<0.001*
9	7.9	0	0	0	0	<0.001*
10	4.1	0	0	0.6	0.5	0.239
11	4.9	0	0	0	0	0.002*
12	3.2	0	0	1.0	0	0.234

epg = eggs per gram. Grades/Years with ≥ 5% prevalence of heavy infection are highlighted in dark grey. Grades/Years with 1–5% prevalence of heavy infection are highlighted in light grey. *Indicates statistical significance.

Table 4.3 summarizes the proportions of heavy infections by Grade and Year following MDA. While nearly all grades were higher than the WHO threshold of 5% heavy infections at baseline, one round of MDA was sufficient to achieve no or extremely low proportions of heavy infections, especially in the older students. This decrease in heavy infections was reflective of the overall change in intensity, which at baseline was 90.4 epg, and after 4 rounds of MDA was 8.1 epg. This was a statistically significant ($p < 0.001$) 91% mean reduction in overall intensity.

4.3 Study Characteristics

4.3.1 Demographics of the S. Mansoni-positive Study Groups

A total of 295 *S. mansoni*-positive school-attending children were enrolled in the cross sectional baseline assessment; 51.9% were female. One year after four rounds of annual MDA, there were 69 individuals who were *S. mansoni* egg-positive and were therefore included in the year five cohort; 47.8% were female. The median age was 13 years both in the baseline group and in the year five group. There were 117 *S. mansoni* egg positive 6–12 years old in the baseline group and 32 in the year 5 group. For 13–18 years old, there were 178 *S. mansoni* egg positive13–18 years old in the baseline group and 37 in the year 5 group (Table 4). The smaller number of egg-positive participants available at year five and the lower intensities of infection among these participants compared to the baseline cohort (Table 4.4) reflect the impact of the four rounds of praziquantel MDA carried out in the schools.

4.3.2 Prevalence of *Schistosoma mansoni,* soil Transmitted Helminth, and Malaria Infections at Baseline and Year Five Groups

The overall S. *mansoni* prevalence in 6–18 years old at baseline and in the year five group was 100% and 18.75% respectively (Table 4). The median egg burden was 80 EPG in the baseline group and 12 EPG in the year 5 group ($P < 0.001$). The overall prevalence of any STH was 22.4% ($n = 66$) in the baseline survey group and 7% ($n = 10$) in the year five group ($P = 0.029$). With regard to individual STH infections, hookworm infection was 7.1% ($n = 21$) in the baseline group and 0% in the year five group ($P = 0.019$). The prevalence of *Trichuris trichiura* was10.9% (n = 32) in the baseline group and 7.3% ($n = 5$) in the year five group ($P = 0.508$) and *Ascaris lumbricoides* infection prevalence was 7.8% ($n = 23$) in the baseline group and 2.9% ($n = 2$) in the year five group ($P = 0.277$). The overall point prevalence of malaria was 40% ($n = 118$) and 44.9% ($n = 31$) in the baseline and year five groups respectively ($P = 0.494$)

Table 4.4: Demographics and prevalence of other parasitic diseases in *Schistosoma mansoni*-positive children by age group at baseline and year 5

	***Schistosoma mansoni* positive**		
	Baseline	**Year 5**	***P*-value**
All ages	***n* = 295**	***n* = 69**	
Schistosomiasis prevalence	295/295 (100%)	69/368 (18.8%)	0.000*
Median age (years)	13 (6–18)	13 (7–18)	0.180
Female *n* (%)	153 (51.9)	33 (47.8)	0.594
Malaria *n* (%)	118 (40.0)	31 (44.9)	0.494
EPG – Median (range)	80 (30–1746)	12 (4–366)	0.000*
Any STH	66 (22.4)	7 (10.1)	0.029*
Ascaris lumbricoides	23 (7.80)	2 (2.90)	0.277
Trichuris trichiura	32 (10.9)	5 (7.3)	0.508
Hookworm	21 (7.1)	0	0.019*
6–12 (Primary school)	***n* = 117**	***n* = 32**	
Median age (years)	11 (6–12)	10 (7–12)	0.502
Female *n* (%)	63 (53.9)	14 (43.8)	0.326
Malaria *n* (%)	60 (51.3)	18 (56.3)	0.691
EPG – Median (range)	96 (6–1746)	16 (4–132)	0.000*
Any STH	33 (28.1)	6 (18.8)	0.366
A. lumbricoides	11 (9.40)	2 (6.3)	0.735
T. trichiura	18 (15.4)	4 (12.5)	0.786
Hookworm	8 (6.84)	0	0.202
13–18 (Secondary school)	***n* = 178**	***n* = 37**	
Median age (years)	16 (13–18)	15 (13–18)	0.509
Female *n* (%)	90 (50.6)	19 (51.4)	0.999
Malaria *n* (%)	58 (32.6)	13 (35.1)	0.848
EPG – Median (range)	74 (4–1284)	8 (4–366)	0.000*
Any STH	33 (18.5)	1 (2.70)	0.013*
A. lumbricoides	12 (6.74)	0	0.228
T. trichiura	14 (7.87)	1 (2.70)	0.477
Hookworm	13 (7.30)	0	0.131

Differences among the study groups were evaluated using Mann-Whitney U test for continuous data and Fisher's exact test for categorical data; an asterisk (*) indicates statistical significance 1 year after four rounds of annual MDA with praziquantel.

List of the abbreviations

EPG: Eggs per gram of feces; STH: Soil transmitted helminths

4.3.3 Prevalence of anemia (schistosomiasis associated indicator) in *Schistosoma mansoni* positive children at baseline and year five groups

Anemia prevalence was significantly higher in *S. mansoni* positive children in the year five group than in baseline group prior to MDA ($P < 0.001$, Table 5). Statistical differences remained when age groups were separated into 6–12 years old and 13–18 years old. It did not appear to be a consequence of differences in malaria infections as the prevalence of anemia was similarly high in both malaria positive and malaria negative individuals in the five year group than in baseline group.

Table 4.5: Prevalence of anemia in *Schistosoma mansoni*-positive baseline and year 5 children

	Baseline		**Year 5**		
	n	**Anemic (%)**	***n***	**Anemic (%)**	***P*-value**
All ages	295	73 (24.8)	69	47 (68.1)	< 0.001
Malaria positive	118	36 (30.5)	31	19 (61.3)	0.003
Malaria negative	177	37 (20.9)	38	28 (73.7)	< 0.001
6–12 (Primary school)	117	38 (32.5)	32	18 (56.2)	0.022
Malaria positive	60	22 (36.7)	18	10 (55.6)	0.179
Malaria negative	57	16 (28.1)	14	8 (57.1)	0.058
13–18 (Secondary school)	178	35 (19.7)	37	29 (78.4)	< 0.001
Malaria positive	58	14 (24.1)	13	9 (69.2)	0.003
Malaria negative	120	21 (17.5)	24	20 (83.3)	< 0.001

Differences between cross-sectional groups were evaluated using Fisher's exact test.

4.3.4 Comparison of Quality of Life Scores (Schistosomiasis Associated Morbidity Indicator)

There were no differences in median scores for the physical (PedsQoL-physical), emotional (PedsQoL-emotional), social (PedsQoL-social) and total (PedsQoL-total) quality of life scores children in the overall group (6–18 years old) between the baseline and year five groups. There was a small but statistically significant ($P = 0.048$) increase (i.e., QoL improvement) in median scores for the school PedsQoL in the malaria negative secondary school (13–18 years old

groups) between baseline and year five (Table 6). None of the results for (6–12 years old groups) differed significantly (data not shown).

Table 4.6. PedsQoL data according to malaria infection in *Schistosoma mansoni*-positive secondary school children at baseline and year 5

	Baseline Median (range)	**Year 5 median (range)**	***P*-value**
All 13–18 year olds	***n* = 182**	***n* = 37**	
PedsQoL-Physical	81.3 (12.5–100)	78.1 (53.1–100)	0.599
PedsQoL- Emotional	67.5 (30.0–100)	70.0 (40.0–100)	0.218
PedsQoL- Social	80.0 (35.0–100)	80.0 (45.0–100)	0.821
PedsQoL-School	70.0 (10.0–100)	75.0 (55.0–100)	**0.021***
PedsQoL –Total	75.0 (39.1–96.7)	77.1 (55.4–98.9)	0.344
Malaria Positive 13–18 year olds	***n* = 58**	***n* = 13**	***P*-value**
PedsQoL-Physical	79.7 (68.8–90.6)	78.1 (78.1–84.4)	0.929
PedsQoL- Emotional	70.0 (55.0–80.0)	70.0 (60.0–75.0)	0.952
PedsQoL- Social	80.0 (70.0– 90.0)	85.0 (70.0–90.0)	0.875
PedsQoL-School	70.0 (60.0–90.0)	80.0 (70.0–85.0)	0.321
PedsQoL –Total	77.2 (65.2–85.9)	79.3 (68.5–84.8)	0.572
Malaria Negative 13–18 year olds	***n* = 124**	***n* = 24**	***P*-value**
PedsQoL-Physical	81.3 (67.2–90.6)	76.6 (68.8–84.4)	0.472
PedsQoL- Emotional	65.0 (55.0–80.0)	77.5 (57.5–85.0)	0.211
PedsQoL- Social	80.0 (70.0–90.0)	77.5 (65.0–92.5)	0.823
PedsQoL-School	70.0 (60.0–80.0)	75.0 (70.0–85.0)	**0.048***
PedsQoL –Total	73.9 (63.6–83.7)	74.5 (67.9–81.5)	0.491

Differences among the study groups were evaluated using Mann-Whitney U test; an asterisk (*) indicates statistical significance between the groups 1 year after four rounds of annual MDA with praziquantel.

4.3.5 Prevalence of (Schistosomiasis Associated Indicators) Organomegaly, Wasting and stunting

The overall prevalence of organomegaly, stunting and wasting was similar in the baseline and year five groups (Tables 4.7 and 4.8). A smaller proportion of children had hepatomegaly or hepatosplenomegaly in the year five group than in the baseline group but these differences were

not statistically significant. By contrast, there was a higher proportion of children with splenomegaly in the year five group compared to baseline group but it also was not a significant difference. Stratifying the groups based on malaria status, which can also affect liver and spleen pathology, did not reveal any statistically significant differences. No children in either age group had evidence of fibrosis (image pattern ≥ C) of schistosomiasis-associated fibrosis by ultrasound at either time point. Because fibrotic image pattern was rare in both groups, evaluating statistical significance was not warranted.

Table 4.7. Organomegaly, wasting and stunting prevalence in *Schistosoma mansoni*-positive primary school children at baseline and year 5

	***Schistosoma mansoni* positive, *n* (%)**		
	Baseline	**Year 5**	***P*-value**
All 6–12 years old	***n* = 117**	***n* = 32**	
Hepatomegaly alone	26 (22.2)	6 (18.8)	0.810
Hepatosplenomegaly	36 (30.8)	9 (28.1)	0.831
Splenomegaly alone	25 (21.4)	10 (31.3)	0.248
Normal	30 (25.6)	7 (21.9)	0.818
Stunting	5 (4.4)	0	0.585
Wasting	1 (0.9)	0	0.999
6–12 years old malaria positive	***n* = 60**	***n* = 18**	
Hepatomegaly	11 (18.3)	0	0.059
Hepatosplenomegaly	23 (38.3)	7 (38.9)	0.999
Splenomegaly	15 (25.0)	8 (44.4)	0.143
Normal	11 (18.3)	3 (16.7)	0.999
Stunting	3 (5.0)	0	0.999
Wasting	1 (1.7)	0 (0.0)	0.999
6–12 years old malaria negative	***n* = 57**	***n* = 14**	
Hepatomegaly	15 (26.3)	6 (42.9)	0.326
Hepatosplenomegaly	13 (22.8)	2 (14.3)	0.719
Splenomegaly	10 (17.5)	2 (14.3)	0.999
Normal	19 (33.3)	4 (28.6)	0.999
Stunting	2 (3.5)	0	0.999
Wasting	0	0	0.999

Differences among the two study groups were evaluated using Fisher's exact test.

Table 4.8. Organomegaly, wasting and stunting in older *Schistosoma mansoni*-positive secondary school children at baseline and year 5

All 13–18yearolds	**Baseline *n* = 178 (%)**	**Year 5 *n* = 37 (%)**	***P*-value**
Hepatomegaly alone	24 (13.5)	4 (10.8)	0.793
Hepatosplenomegaly	31 (17.4)	4 (10.8)	0.463
Splenomegaly alone	33 (18.5)	6 (16.2)	0.819
Normal	90 (50.6)	23 (62.2)	0.211
Stunting	8 (4.5)	2 (5.4)	0.683
Wasting	1 (0.6)	2 (5.4)	0.077
13–18 years old malaria positive	***n* = 58 (%)**	***n* = 13 (%)**	
Hepatomegaly	6 (10.3)	2 (15.4)	0.633
Hepatosplenomegaly	15 (25.9)	2 (15.4)	0.720
Splenomegaly	18 (31.0)	1 (7.7)	0.162
Normal	19 (32.8)	8 (61.5)	0.065
Stunting	3 (5.2)	1 (7.7)	0.563
Wasting	0 (0.0)	0 (0.0)	0.999
13–18 years old malaria negative	***n* = 120 (%)**	***n* = 24 (%)**	
Hepatomegaly	18 (15.0)	2 (8.33)	0.528
Hepatosplenomegaly	16 (13.3)	2 (8.3)	0.738
Splenomegaly	15 (12.5)	5 (20.8)	0.330
Normal	71 (59.2)	15 (62.5)	0.823
Stunting	5 (4.2)	1 (4.2)	0.999
Wasting	1 (0.8)	2 (8.3)	0.072

Differences among the two study groups were evaluated using Fisher's exact test.

CHAPTER FIVE

DISCUSSION

5.1 Schistosomiasis Grade-Intensity of Infection Before and After Repeated Annual Rounds of Mass Drug Administration with Praziquantel

Baseline data from the current study of primary and secondary school children indicated that *Schistosoma mansoni* infection was highly prevalent among untreated school children in the Asembo Bay area of western Kenya. This observation was in agreement with previous studies done around Lake Victoria region (Handzel *et al.,* 2003; Odogwu *et al.,* 2006; Kabatereine *et al.,* 2007; Verani *et al.,* 2011; Mwinzi *et al.,* 2012; Samuels *et al.,* 2012; Karanja *et al.,* 2017; Abudho *et al.,* 2018; Shen *et al.,* 2019), making this an area in need of schistosomiasis control. The baseline infection data across grades were consistent with the typical schistosomiasis age/prevalence curve where infection increases with age then decline gradually with an increased age (Odiere *et al.,* 2012; Colley 2014; Colley *et al.,* 2014; Mugono *et al.,* 2014). However, the same pattern was not observed for the prevalence of heavy intensity of infection across all grades which varied with no discernable pattern. This observation could be attributed to different water contact exposure levels and hygiene. At baseline, data from this study further showed that in the study area which is endemic for *S. mansoni*, infection starts at young age (Children in Grade 1). Similar observations had been made by previous reports which reported that in *S. mansoni* endemic areas, initial infection can be acquired at a young age (Verani *et al.,* 2011). In addition, a study conducted in Uganda around Lake Victoria reported *S. mansoni* infection in children less than 3 years of age (Odogwu *et al.,* 2006).

In terms of intensity of infection categorizations, almost half of the children infected with *S. mansoni* at baseline had light to moderate intensities of infection. Generally, in the present study, less than 10% were heavily infected (≥400 epg). These observations were in agreement with

previous studies (Odiere *et al.*, 2012; Samuels *et al.*, 2012) and supported the previous evidence that most individuals in endemic areas excrete low number of eggs (Butterworth *et al.*, 1991). Prevalence levels of STH infections were quite low at baseline compared to a 2003 report from western Kenya (Handzel *et al.*, 2003). In Kenya, a single round of albendazole MDA was conducted in Kenyan schools in 2009 and our data are consistent with more recent surveys of STH infection levels in this area (Opisa *et al.*, 2011; Odiere *et al.*, 2012; Sang *et al.*, 2014). This consistency in results could be attributed to Kenya National Deworming exercise conducted in the area prior to the start of this current study in which some of these schools participated.

Mass drug administration with PZQ and ALB was used in this school-based program to treat school children for schistosomiasis and STH infections, respectively. After one round of MDA with PZQ, prevalence of heavy infection was rapidly reduced in all the grades and driven to essentially zero in older children in grades 8-12. Two and three rounds of PZQ MDA also progressively continued to reduce both prevalence and intensities to lower levels, with most grades exhibiting low proportions of heavy infections. In this study, four rounds of annual PZQ MDA significantly reduced *S. mansoni* infection prevalence across all grades in both primary and secondary schools and virtually eliminated heavy infections as defined by WHO guidelines, supportive of the goal to prevent high intensity schistosome infections that are generally associated with morbidity in children (King *et al.*, 2005; King and Dangerfield-Cha 2008; WHO 2013). Findings from this study are in line with several studies suggesting that rounds of mass drug treatment with praziquantel is effective on *S. mansoni* infection even in highly endemic areas, resulting in dramatic reduction in the prevalence and intensity of *S. mansoni* infection (Kabatereine *et al.*, 2007; Toure *et al.*, 2008). However, a recent study (Sircar *et al.*, 2018) which combined the use of both community and school-based approaches of delivering mass

drug treatment did not observe a significant reduction in both prevalence and intensity of infection of *S. mansoni* infection over time in either cohort. This observation could be attributed to large variability in *S. mansoni* infection prevalence and intensity of infection in both community and school arms of treatment at baseline.

Currently, WHO guidelines recommend annual school-based MDA with PZQ in areas where prevalence of infection is ≥50%. Where the prevalence of infection is below 50% but at or above 10%, current recommendations call for school-based MDA every other year, while if prevalence is below 10% infection, MDA twice during primary school is considered sufficient (WHO 2013). In addition, the prevalence of heavy infection is recommended by WHO as a guide for when to move from morbidity control to elimination as a public health problem and then on to elimination of transmission. When the prevalence of heavy infection is ≥5% in sentinel sites, morbidity control is considered to be still in order, and countries would be eligible for elimination as a public health problem when heavy infection prevalence is below 1% in all sentinel sites (WHO 2013). The data presented here regarding heavy infections in school children may contribute to potential re-evaluations of some of these targets, guidelines and goals. This is because, even though mean epg counts decreased by more than 90% and heavy intensity infections were almost eliminated, four rounds of high coverage annual school-based MDA was not sufficient to eliminate schistosomiasis. For areas where elimination of transmission may be considered feasible, MDA will need to be complemented with other schistosomiasis integrated control programs such as provision of clean water, provision of improved sanitation, health education, and/or snail control as supported by previous study (Secor and Montgomery 2015).

Another observation made possible by this current study Grade-by-Grade study design and analysis indicated that by Year 4, on average, children in the lower grades had somewhat higher

levels of heavy infections than their counterparts in grades 6-12. There could be several explanations for this observation: 1) Because treatment is school-based, those in the lower, entering grades did not receive as many rounds of MDA as those in the upper grades; 2) Those in the higher grades do not frequent active transmission sites as often as the younger children, and would thus have a lower risk of re-infection; 3) Those in the higher grades, could have had more opportunities to experience dying (or PZQ-killed) adult worms as supported by earlier studies (Woolhouse and Hagan 1999; Karanja *et al.,* 2002) and had achieved some level of immune-mediated resistance to re-infection; and/or 4) Those in the higher grades perhaps benefited more from health education and behavioral change that may have accompanied the sensitization and education associated with MDA. These possibilities are not mutually exclusive and it could be any combination that led to lower levels of re-infection in the older children.

5.2 Assessment of Morbidity Markers Associated with Schistosomiasis and Changes Upon Mass Drug Administration with Praziquantel

Anemia one of the multiple markers evaluated in this study was not positively impacted by four rounds of MDA with praziquantel and registered a significant negative outcome. A more recent study evaluating the effect of MDA on morbidity in school children demonstrated an increase in anemia despite rounds of MDA with praziquantel (Sircar *et al.,* 2018). This could be an indication that this potential marker may not always be a reliable schistosomiasis morbidity indicator of decreasing prevalence and intensity due to MDA with praziquantel in a population of school children in endemic areas. Because the relationship between malaria and anemia in this area is well documented (Gimnig *et al.,* 2016; Valice *et al.,* 2018), the data was analyzed together as well as separating individuals based on malaria status but still did not find statistically significant differences in the proposed measures of morbidity following repeated MDA. It was proposed that the high prevalence of malaria seen to increase in this area during

this timeframe (Abudho *et al.,* 2018) could have also played a role in masking some of the benefits of MDA leading to a significant increase of anemia in year five despite four rounds of MDA. Furthermore, other factors mentioned above could have also impacted haemoglobin levels thus contributing/or maintaining high prevalence of anemia observed in this study despite multiple rounds of MDA.

Pediatric Quality of Life inventory tool (PedsQoL) for the four specific categories: Physical, emotional and social results from this study demonstrated that MDA with PZQ did not improve quality of life of the participants in various domains with the exception of school functioning domain. This observation was in contrary to a previous morbidity study conducted in both the community and schools (Sircar *et al.,* 2018) which demonstrated an improvement in quality of life of participants in both community and school-based treatment arms. The variability in the infection intensities in Sircar and others study conducted both in schools and communities could have contributed to more pronounced effects of treatments leading to improved quality of life after treatments. Nonetheless, school functioning results from this study demonstrated a higher score in school-related quality of life assessment by year five compared baseline in 13-18 years old malaria-negative children. This observation supported the concept that MDA can improve school performance and have a greater effect in endemic areas and was in line with a previous study evaluating the impact of MDA on schistosomiasis morbidity in school children (Musuva *et al.,* 2017; King *et al.,* 2020).

The overall prevalence of organomegaly, stunting and wasting was similar in the baseline and year five groups despite four rounds of MDA with praziquantel. In a recent western Kenya study of primary school children where malaria prevalence was lower (< 15%), significant decreases in wasting and ultrasound-detected organomegaly, along with significantly improved pediatric

quality-of-life scores were observed over a five year period in children that received either 2 or 4 rounds of MDA (Sircar *et al.,* 2018). However, some studies have also reported an increase in organomegaly despite delivering treatment (Davies *et al.,* 2015) while this current study (Abudho *et al.,* 2020) did not observe any change in organomegaly after multiple rounds of treatment. High prevalence of malaria seen in our study could have contributed to lack of differences in these schistosomiasis morbidity indicators following repeated MDA. In addition, low prevalence of stunting and wasting observed both at baseline and in year five could have led to lack of more pronounced effects of multiple MDA.

The inability to demonstrate benefits of MDA using the proposed morbidity markers studied could be attributed to many factors. The bleakest interpretation of morbidity data would be that multiple rounds of MDA did not appreciably reduce the morbidity in school age children who become re-infected. Although infection intensity was lower in the group surveyed after four years of MDA, infected individuals still harboured inflammation-inducing schistosome eggs in their tissues and tested positive by Kato-Katz. It might have been that it was necessary to be egg free to be morbidity free. Alternatively, there might have been other measures of morbidity that would have been able to demonstrate differences more clearly.

For morbidity component of this study, it was hypothesized that multiple annual rounds of MDA would result in less morbidity, even in children who have *S. mansoni* infection one year following the last MDA in year five. However, most of the measures evaluated were not significantly different between the two time points. This could be an indication that these potential schistosomiasis morbidity indicators may not always be a reliable indicator of decreasing prevalence and intensity in a population of school children. Furthermore, others factors such as malaria which was seen to increase in this area during this timeframe (Abudho *et*

al., 2018) could have played a role in the significant increase of anemia in year five despite four rounds of MDA.

5.3 Limitations of the Study

Limitations in the execution of the parasitologic component of this study which addressed objective 1 included screening of only one stool sample with two Kato-Katz slides at baseline as opposed to three consecutive stool samples of two slides each in the following years. While this is what is routinely done by control programs, in this study it may have underestimated the initial prevalence and intensities of infection at baseline as compared to the later time points. In Year 1, we had a protocol deviation that led to the failure to collect stool samples from first year, Grade 1 students.

The principal limitation of morbidity assessment component of this study which addressed both objectives 2 and 3 was that the characteristics of the year five group prior to MDA was not known. It was assumed that they had the similar characteristics to the baseline group but was not known. In addition, the five year time difference between morbidity measurements could have also reduced the ability to detect differences if events that affect health had occurred in the interim.

CHAPTER SIX

SUMMARY OF FINDINGS, CONCLUSIONS AND RECOMMENDATIONS

6.1 Summary of Findings

These results show that *S. mansoni* infection was prevalent among children in the 5 schools studied in the Asembo Bay region of western Kenya. Findings from this study also show that mass drug administration with PZQ had an overall positive impact on the levels of *S. mansoni* infection in both primary and secondary school children. Thus, when assiduously applied, preventive chemotherapy as supported by WHO guidelines offers a practical program to control *S. mansoni* infection and its associated morbidity in endemic areas. However, the findings from this study also indicate that additional schistosomiasis interventions will likely be needed to complement MDA in order to achieve the goal of elimination promoted by WHA resolution. For schistosomiasis morbidity outcomes after controling for *S. mansoni* infection, this study did not find an impact of four rounds of MDA on potential markers of morbidity in primary and secondary school children in western Kenya who were *S. mansoni*-positive at the end of the study. This may either be due to the tested measures not being sensitive markers for morbidity in children, confounding by malaria or other conditions, or the discouraging prospect that there is no lasting benefit of previous MDA for children with schistosome (re)infection.

6.2 Conclusions

1. *Schistosoma mansoni* grade-intensity and prevalence of infection among children in the five schools studied in the Asembo Bay region of western Kenya indicated that schistosomiasis infection was prevalent in Asembo Bay region and mass drug administration (MDA) with PZQ had an overall positive impact on the levels of *S. mansoni* infection in both primary and secondary school children.

2. School-related quality of life morbidity indicator assessment significantly improved after repeated rounds of MDA with Praziquantel for control of *Schistosoma mansoni* infection.
3. Most of the morbidity indicators associated with *Schistosoma mansoni* infection studied did not change upon annual repeated rounds of mass drug administration with praziquantel among children in the five schools studied in the Asembo Bay region of western Kenya.

6.3 Recommendations from this Study

1. The high level of improvement of schistosomiasis grade-intensity of infection in secondary school-aged children seen here argues that they should be included in MDA intervention programs and morbidity assessments.
2. School related quality of life morbidity indicator assessment can be can be used as assessment tool for morbidity indicator associated with *Schistosoma mansoni* infection in endemic areas after MDA programmes.
3. There is need for specific markers that can be able to differentiate schistosomiasis infection from other possible conditions in children living in Schistosoma endemic areas.

6.4 Recommendations for Future Studies

Additional research is needed to identify markers of schistosomiasis morbidity that can be used to monitor the effectiveness of control programs regardless of the underlying malaria prevalence and this could include measurement of inflammatory markers and others morbidity markers such as cognitive development, school attendance and behavior, shuttle run test and ascites in subsequent studies.

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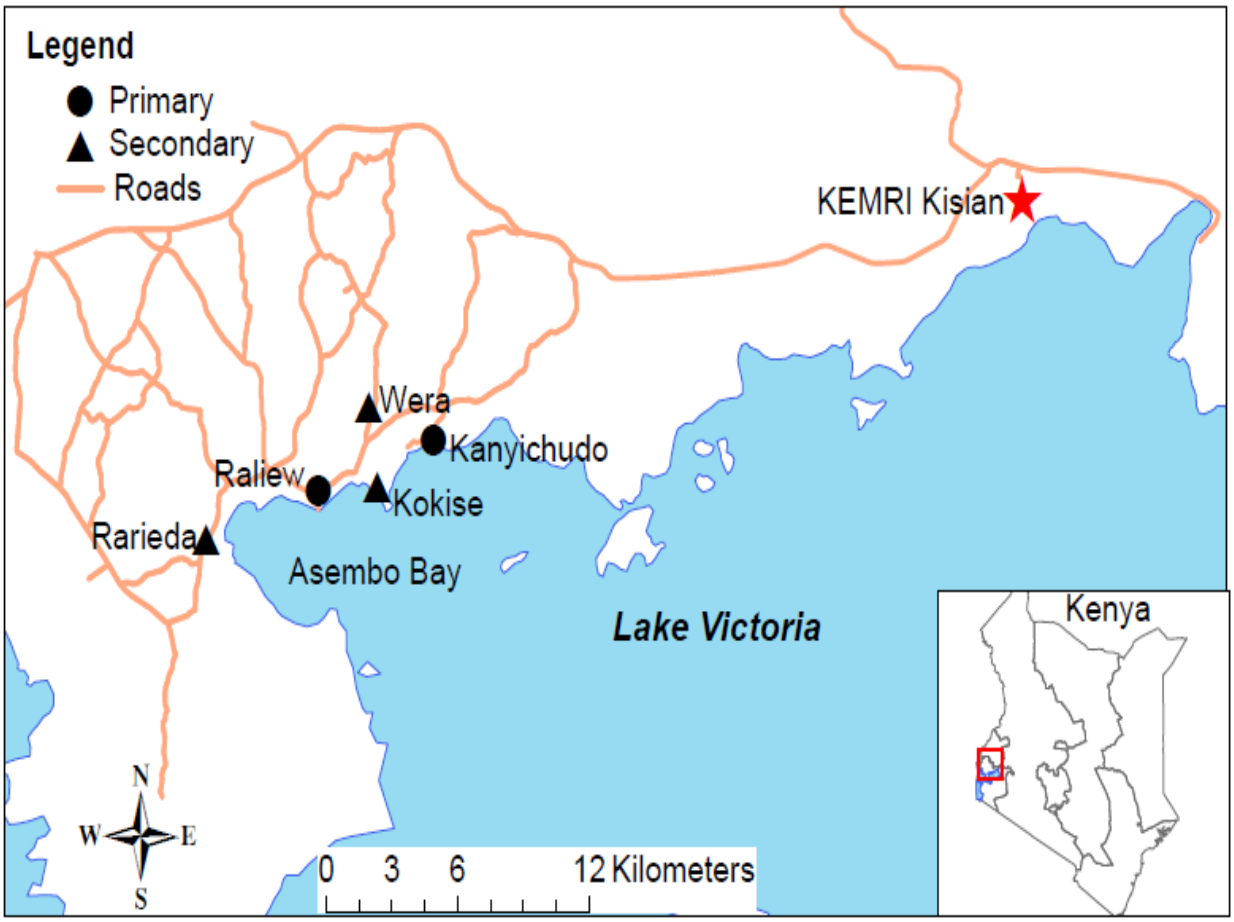
APPENDICES

APPENDIX 1: Map of the study site schools in the Asembo bay area of western Kenya



APPENDIX II: CONSENT FORM.

STUDY TITLE: Determinants of resistance in human schistosomiasis: School-based treatment, immune responses and outcome

INSTITUTIONS: Kenya Medical Research Institute, Centre for Global Health Research. (KEMRI-CGHR), University of Georgia (UGA) and Centers for Disease Control and Prevention, Division of Parasitic Diseases and Malaria (CDC/DPDM)

PRINCIPAL INVESTIGATORS: Diana M.S. Karanja (KEMRI-CGHR), Dan Colley (UGA), Evan Secor (CDC/DPDM)

CO-INVESTIGATORS:

KEMRI-CVBCR	CDC/DPDM	UGA
Pauline N.M. Mwinzi	Susan P. Montgomery	Sarah Nicholson
Bernard Abudho		Jennifer Carter
Liz Ochola		

Explanation of the purposes of the research

Your child is being asked to take part in a medical research study being performed by the Kenya Medical Research Institute (KEMRI), the University of Georgia, Athens, Georgia, and the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, USA. It is very important that you understand the following general principles that apply to all participants in our studies:

1) You and your child's participation is entirely voluntary;
2) You may withdraw from participation in this study or any part of this study at any time with no penalty, harm, or loss of access to treatment;
3) After you read about the study please ask any questions that will allow you to understand the study more clearly.

What is Bilharzia

Bilharzia, also known as schistosomiasis is a disease caused by worm parasites transmitted by snails. The snails live in different types of water including ponds, rivers and lakes. People whose activities cause them to come into contact with water where infected snails live and where there may be transmission going on are likely to suffer from the disease. Bilharzia worm parasites enter your body through the skin when you are in the water of a lake, river, stream, or pond. Bilharzia can sometimes be serious or even cause death if not diagnosed and treated properly. In our earlier study in the Asembo Bay area, we found that children in schools closer to Lake Victoria were more likely to have bilharzia than children in schools farther away from the Lake. The most common way to find out if someone has bilharzia is to check for the eggs of the parasite in the stool and urine.

Why do we want to conduct this study:

Although there is medicine available for the treatment of bilharzia, many people still are not able to get it, because they either do not know about it, or they live too far from the hospitals. The World Health Organization recommends that children who live in areas where there is a high prevalence of bilharzia should get the medicines. Scientists still do not know how often children should get the medicines to protect them from the effects of the disease. We are therefore interested to find out how often children who are at risk of getting bilharzia should get treated to keep them from being sick and if treating them a certain number of times will keep them from getting the disease again in the future. This will help scientists be able to develop methods of controlling the disease.

What is important for you to know.

To do this study, we will need to study some of your child's urine, feces and blood. We will first collect stool, urine, and a small amount of blood from a fingerstick. Some of the blood and urine will be tested at the school site. The stool and the rest of the blood and urine will be returned to the laboratory for preparation and other studies. While we are testing for bilharzia, we will also test for anaemia, intestinal worms (roundworms, whipworms and hookworms), and malaria. Your child will be assigned a study number, and the links between the name and number, and all data collected through use of stools, urine, and blood, will be kept confidential. None of the

information that we collect will be told to other people in your village. We will just use the information to find out about this disease, and the best way to protect people from suffering the effects of the disease.

If we find that your child has bilharzias, we will do additional tests on your child. These tests will include: 1) asking your child for 2 more stool samples; 2) using a machine that uses sound waves to find out if the bilharzias has caused any damage to your child's spleen or liver; 3) measuring your child's height, weight, and mid upper arm circumference; 4) measuring your child's physical fitness using a shuttle run test; 5) asking your child some questions about how healthy they feel; and 6) collecting 8ml (less than one tablespoon) of blood from your child's arm. If we find that your child has anaemia or malaria, they will be offered treatment whether or not they take part in this aspect of the study. All children will be offered treatment for bilharzias and intestinal worms.

We would like to investigate how the treatment of bilharzia can be conducted so as to reach all communities and community members who are at risk of getting the disease. You and your family may not get any direct benefits from being in this study but what you tell us will help us determine the best approach for controlling bilharzia in your community. Although you will receive treatment for bilharzia and other worms, this treatment is also available at the government hospital.

This study is expected to last about 5 years. You can decide if you want your child to take part in this study. Taking part in this study will not cost you or your family anything. Your child may also leave the study at any time. You can leave for any reason without any problems.

Who Can Participate In The Study:

We can include your child in the study only if you give permission for him/her to participate, and if your child agrees to participate. We shall include children over the age of 5 and up to age18.

Risk involved

The risks or hazards to your child if she/he takes part in this study are minimal. There is the minor discomfort while drawing blood. To minimize any risk, hazard or discomfort during our study, the blood will be obtained from your child's finger or arm in a sterile way by well trained staff.

Questions about research

If you have any questions about this study, you may contact Dr. Diana Karanja at the Kenya Medical Research Institute, Kisumu Tel; 057-2022929 during the study and in the future. If you have concerns about human rights, ethics and welfare issues you may contact Dr. Rashid of the National Ethical Review Board, Kenya Medical Research Instititute; Tel; 020-722541.

PARENTAL/GURDIAN PERMISSION

I, Mr./Mrs./Miss _____, being a person aged 18 years and over and being the lawful/legal guardian of: Mr/Miss (Child's name) _____ voluntarily agree that my child may be included in the study which I have read or has been read to me. I have been made to understand the implications and benefits of the tests and treatments I accept the tests and treatments to be carried out. I understand that I may withdraw him/her from the research at any time, for any reason, without any penalty or harm. All the above conditions have been explained to me in the _____ language in which I am fluent.

_____Age of child_____

School name _____Village_____

_____ Parent's/Guardian's signature

_____ Date

_____ Place

_____ Person Obtaining Consent

_____ Witness

Specimen Storage/Export

Some blood, urine or stool samples obtained from your child may be useful for further development of tests to detect schistosomiasis or see how it makes people sick. For this, we will need to store the blood or serum for a longer time and possibly send it to the United States. Your child's name will not accompany the specimen if it is stored or exported from Kenya. Is it okay to store and/or export your child's blood or stool samples? _____Yes _____No

Parent's/Guardian signature _____

Assent for children:

We are asking to measure your weight, height, mid upper arm circumference and to take a small amount of blood from your arm, some of your urine and stool and to treat you for bilharzia, malaria and intestinal worms if you have them. You do not have to do this if you do not want to, but there is no danger if you do. It might help you. Do you agree to these measurements on your body and to take the drugs? _____ Yes _____ No

Child's Name _____

Child's signature or thumbprint or mark: _____

Person Obtaining Consent _____

Signature _____ Date _____

Witness _____ Date _____

Witness Signature _____

OFFICIAL STAMP

APPENDIX III: KATO/KATZ STANDARD OPERATING PROCEDURE (SOP)

Introduction

This procedure is designed to determine the intensity of schistosomiasis mansoni infection in our study participants by estimating the number of eggs per gram of feaces as well as to determine the presence of Hookworm, Ascaris, Taenia, and Trichuris.

2) Materials and Reagents

2.1 <u>The kit: contents</u>.

A roll of nylon screen 80 mesh (20m)

400 plastic templates with a hole of 6 mm on a 1.5 mm thick template, delivering 41.7 mg feaces

400 plastic spatula

A roll of hydrophilic cellophane, 34 um thick-20m

2.2 <u>Other materials needed:</u>

Microscope slides (75 x 25 mm)

Toilet paper or absorbent tissue

Newspaper or scrap paper

Solution of 100 ml of glycerol and 100 ml of distilled water

Flat bottom jar

3% aqueous malachite green OR 3% methylene blue

Glycerol

Gloves

Disposal container (pail with polythene paper)

Operating Procedure

3.1 Pre-soaking of cellophane strips**.**

Glycerol-Malachite green or glycerol-methylene blue solution (1 ml of 3% aqueous malachite green or 3% methylene blue is added to 100 ml glycerol and 100 ml distilled water. This solution is mixed well and the cellophane strips of 2 cm square are soaked in this solution in a jar for at least 24 hrs prior to use.

3.2 Procedure

Person(s) responsible: Laboratory Technician

Place a small amount of faecal material on the newspaper or scrap paper and press a piece of nylon screen on top so that some of the faeces are sieved through the screen and accumulated on the top.

Scrap the flat-sided spatula across the upper surface of the screen to collect the sieved faeces

Place the template on the center of the microscope slide (labeled accordingly with Study ID.) and add faeces from the spatula so that the hole is completely filled.

Each hole is pre-measured to hold 41.7 mg. Of the sieved stool.

Pass over the template using the side of the spatula to remove excess faeces from the edge of the hole.

(The spatula and template may be discarded or reused if carefully washed)

Remove the template carefully so that the cylinder of faeces is left on the slide

Cover the faecal material with a pre-soaked cellophane strip. The strip must be very wet if the faeces are dry, and less so if the faeces are soft. If excess glycerol solution is present on the upper surface of the cellophane, wipe it with toilet paper. NOTE: In dry climates, excess glycerol will retard but not prevent drying.

Invert the microscope slide and press the faecal sample firmly against the cellophane strip on a smooth hard surface.

The faecal material should be spread evenly between microscope slide and the cellophane strip.

NOTE: It should be possible to read a newspaper print through the smear after clarification.

Carefully remove the slide by sliding sideways to avoid separating the cellophane strip or lifting it off.

Place the slide on the bench with the cellophane upwards. Water evaporates while the glycerol clears the faeces.

Examine immediately for hookworm eggs. Hookworm eggs will be cleared if kept for more than 20 minutes.

Then keep the slide for at least one or more hours at room temperature to clear the faecal material prior to examination for schistosomiasis and other parasites.

Notes:

Ascaris and trichuris eggs will remain visible and recognizable for many months in these preparations.

Hookworm eggs clear rapidly and will no longer be visible after 30-60 minutes.

Schistosome eggs may be recognizable for up to several months but it is preferable to examine the slide within 24 hours.

4) Examination of the smear.

Person responsible: Lab technologist and the lab technician.

The smear should be examined in a systematic manner and the number of eggs of each species reported.

This number is multiplied by 24 to obtain the number of eggs per gram of faeces (EPG)

The EPG gives an estimation of the worm burden and allows the identification of individuals likely to suffer from severe consequences of the infection.

5) Disposal of Faecal Samples

The faecal samples and all the disposable materials used in the procedure are placed in a waste polythene paper bag placed in a pail, closed and taken to the incinerator for safe disposal.

WHO-proposed thresholds for the classification of individuals

	Light intensity	Moderate intensity	Heavy intensity
A. lumbricoides	1-4999	5000-49,999	≥ 50,000
T. trichiura	1-999	1000-9,999	≥ 10,000
Hookworm	1-1999	2000-3,999	≥ 4,000
S. mansoni	1-99	100-399	≥ 400

5) Quality Control

Two well-trained microscopists (laboratory technicians) examine and record the egg counts independently. A microscopist from a different lab selects at random a few slides each day and examines them independently for quality control. The readings are reconciled by the Lab technologist before final recording.

APPENDIX IV: ULTRASOUND RECORD SHEET.

Place Cohort ID Label Here *Aliquot 7*

Date (DD/MM/YY): __ __/__ __/__ __

Name: _____

Date of Birth (DD/MM/YY) __ __/__ __/__ __

Examiner: _____

Machine: _____

Transducer: _____

TEST RESULTS

Liver

Left lobe: _____mm

Right lobe: _____mm

Abdominal swelling? (No / Yes)

If yes, is the cause unclear (e.g., not hepatomegaly, not ascites, etc.)? (No / Yes)

Spleen

Spleen length: _____mm

Splenic vein diameter: _____ mm

Echogenicity: _____ [0 = normal; 1 = hypoechoic; 2 = hyperechoic]

Texture: _____ [0 = homogenous; 1 = coarse; 2 = hyperechoic foci]

PSL: _____ mm

MCL: _____ mm

Shape: _____ [0 = convex-concave; 1 = biconvex]

Surface:_____ [0 = normal, 1 = irregular]

Tenderness: _____ [0 = no; 1 = yes]

Liver texture pattern [please put an "x" next to all that apply]

____ B = Feather streaks; ___ B1 = Flying saucers; ____ B2 = Spider thickening

____ C1 = More prominent peripheral rings; ____ C2 = More prominent pipe stems

____ D = Ruff ____ Dc

____ E = Patches ____ Ec

____ F = Birds claw _____ Fc

____Not classifiable [____Cirrhosis-like; _____Fatty liver-like; ____ Other]

Patterns immediate score _____

Gall bladder

Wall thickness: _____ mm; _____ Not measurable

Shape of gall bladder wall: _____ [0 = normal, 1 = irregular]

Segmental portal branch walls

Left portal branch	Right portal branch	
External:_____mm	External:_____mm	Mean: _____mm
Internal: _____ mm	Internal:_____ mm	Mean:_____mm

Segmental portal branch intermediate score: _____

1. **Portal vein diameter on deep inspiration:** _____mm

2. **Porto systemic collaterals:** _____ [0 = not detected; 1 = detected]

   If present specify type _____ Collateral score_____

3. **Ascites:** _____ [0 = not present; 1 = present]

   Ascites score _____

FINAL IMPRESSIONS

By patterns _____

By segmental branches _____

Comments:

Pictures taken? (Yes / No)

APPENDIX V: PEDIATRIC QUALITY OF LIFE INVENTORY

PedsQL ™
Pediatric Quality of Life

Inventory

Version 4.0

CHILD REPORT (ages **8-12**)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.

If you do not understand a question, please ask for help.

*In the past **ONE month**, how much of a **problem** has this been for you …*

About My Health and Activities ***(PROBLEMS WITH…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. It is hard for me to walk more than one	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by	0	1	2	3	4
6. It is hard for me to do chores around the	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

About My Feelings *(PROBLEMS WITH…)*	**Never**	**Almost Never**	**Some - times**	**Often**	**Almost Always**
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

How I Get Along with Others *(PROBLEMS WITH…)*	**Never**	**Almost Never**	**Some - times**	**Often**	**Almost Always**
1. I have trouble getting along with other	0	1	2	3	4
2. Other kids do not want to be my friend	0	1	2	3	4
3. Other kids tease me	0	1	2	3	4
4. I cannot do things that other kids my age	0	1	2	3	4
5. It is hard to keep up when I play with	0	1	2	3	4

About School *(PROBLEMS WITH…)*	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or	0	1	2	3	4

APPENDIX VI: ETHICAL APPROVAL

KENYA MEDICAL RESEARCH INSTITUTE

P.o. Box 54840-00200, NAIROBI, Kenya
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E-mail: director@kemri.org info@kemri.org Website:www.kemri.org

TO:DR. DIANA M. S. KARANJA (PRINCIPAL INVESTIGATOR)

THROUGH: DR. JOHN VULULE
THE DIRECTOR, CGHR,
KISUMU

Dear Madam,

RE: SSC PROTOCOL No. 2125 - 3 RD REVISION (RE-SUBMISSION): DETERMINANTS OF RESISTANCETO SCHISTOSOMIASIS IN THE HUMAN HOST: SCHOOL-BASED TREATMENT, IMMUNE RESPONSES AND OUTCOME

Reference is made to your letter dated February 2, 2012. We acknowledge receipt of the revised research proposal on February 6, 2012.

This is to inform you that the Committee determines that the issues raised at the initial review and on 28th January 2012 are adequately addressed. Consequently, the study is granted approval for implementation effective this 6th day of February 2012 for a period of one year.

Please note that authorization to conduct this study will automatically expire on February 4, 2013. If you plan to continue data collection or analysis beyond this date, please submit an application for continuation approval to the ERC Secretariat by December 21, 2012. The regulations require continuing review even though the research activity may not have begun until sometime after the ERC approval.

Please note that any unanticipated problems resulting from the implementation of this study should be brought to the attention of the ERC. You are required to submit any proposed changes to this study to the SSC and ERC for review and approval prior to initiation and advise the ERC when the study is completed or discontinued.

Work on this project may begin.
Sincerely,

CHRISTINE WASUNNA, FOR:
SECRETARY,
KEMRI ETHICS REVIEW COMMITTEE

APPENDIX VII: MANUSCRIPT 1

Am. J. Trop. Med. Hyg., 98(5), 2018, pp. 1397–1402
doi:10.4269/ajtmh.17-0908

Impact of Four Years of Annual Mass Drug Administration on Prevalence and Intensity of Schistosomiasis among Primary and High School Children in Western Kenya: A Repeated Cross-Sectional Study

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Abstract. Schistosomiasis remains a major public health problem in Kenya. The World Health Organization recommends preventive chemotherapy with praziquantel (PZQ) to control morbidity due to schistosomiasis. Morbidity is considered linked to intensity of infection, which along with prevalence is used to determine the frequency of mass drug administration (MDA) to school-age children. We determined the impact of annual school-based MDA on children across all primary and high school years using a repeated cross-sectional study design in five schools near Lake Victoria in western Kenya, an area endemic for *Schistosoma mansoni*. At baseline and for the following four consecutive years, between 897 and 1,440 school children in Grades 1–12 were enrolled and evaluated by Kato-Katz for *S. mansoni* and soil-transmitted helminths (STH), followed by annual MDA with PZQ and albendazole. Four annual rounds of MDA with PZQ were associated with reduced *S. mansoni* prevalence in all school children (44.7–14.0%; $P < 0.001$) and mean intensity of infection by 91% (90.4 to 8.1 eggs per gram [epg] of stool; $P < 0.001$). Prevalence of high-intensity infection (≥ 400 epg) decreased from 6.8% at baseline to 0.3% by the end of the study. Soil-transmitted helminth infections, already low at baseline, also decreased significantly over the years. In this high prevalence area, annual school-based MDA with high coverage across all Grades (1–12) resulted in rapid and progressive declines in overall prevalence and intensity of infection. This decrease was dramatic in regard to heavy infections in older school-attending children.

INTRODUCTION

Human schistosomiasis is a snail-transmitted trematode infection caused by any of five species in the genus *Schistosoma*. Globally, approximately 700 million people are at risk of this infection.[1,2] More than 240 million people in 78 countries are estimated to be infected with schistosomes. More than 90% of the cases occur in sub-Saharan Africa, where the infection is estimated to cause more than 200,000 deaths annually.[3,4] In Kenya, both *Schistosoma mansoni* and *Schistosoma haematobium* remain serious public health concerns with approximately 6 million people infected and an additional 15 million being at high risk of the infection in endemic areas of the country.[5] *Schistosoma mansoni* infection is common in the western part of Kenya and its prevalence shows an inverse relationship with the distance from Lake Victoria.[6,7]

Schistosomiasis-associated morbidity and mortality reduction through treatment of school-age children was emphasized in 2001 when the World Health Assembly (WHA) 54.14 formally recognized the global burden of the infection. Mass drug administration (MDA) with praziquantel (PZQ) is the strategy the World Health Organization (WHO) presently recommends[8] to reduce cumulative morbidity associated with schistosomiasis in endemic areas.[1,9–12] When initiated, this strategy usually involves yearly or biennial (MDA) with PZQ to treat schistosomiasis and albendazole (ALB) to treat soil-transmitted helminths (STHs) in primary schools.[9] The effectiveness of MDA programs for *S. mansoni* is mainly monitored by measuring changes in the prevalence of infection and drug treatment coverage, although WHO guidelines are also based on the prevalence of heavy infection (≥ 400 eggs per gram [epg] of feces).[13] The aim of this school-wide, repeated, cross-sectional study was to evaluate the impact of 4 years of high-coverage annual MDA on the prevalence and intensity of *S. mansoni* infection across all grades of primary and secondary school children. The information generated from this study will add systematic data to the understanding on how these key indicators are impacted by yearly MDA over a period of 5 years.

MATERIALS AND METHODS

Ethics statement and eligibility criteria. Ethical clearance was obtained from the Departmental and Institutional Scientific Steering Committees of Kenya Medical Research Institute (KEMRI) followed by the National KEMRI Scientific and Ethical Review Unit. The Institutional Review Board of the University of Georgia also reviewed and approved the study protocol (ID no. 00003501). On review of the protocol, the Centers for Disease Control and Prevention staff were not considered to be engaged with human subjects. Before the start of the study, informational meetings were held with the teachers, children, and parents of the children in the schools in the study. In these meetings, individual informed consent was first obtained from the parents or guardians of school-going children. Assent to participate in the study was also obtained from each participating child.

Study area and population. This study was conducted in two primary and three secondary schools in fishing villages located within 3 km of Lake Victoria in the Asembo Bay area of Rarieda Sub-county, Nyanza Region in western Kenya. The selected primary schools are the main feeder schools for those attending the selected secondary schools (Figure 1), and all were selected based on their expected prevalence of *S. mansoni* infection based on previous studies in the area.[6,11]

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APPENDIX VIII: MANUSCRIPT 2

Abudho *et al. Infectious Diseases of Poverty* (2020) 9:67
https://doi.org/10.1186/s40249-020-00690-7

Infectious Diseases of Poverty

RESEARCH ARTICLE Open Access

Evaluation of morbidity in *Schistosoma mansoni*-positive primary and secondary school children after four years of mass drug administration of praziquantel in western Kenya

Bernard O. Abudho[1,2*], Bernard Guyah[2], Bartholomew N. Ondigo[1,3,4], Eric M. Ndombi[1,5], Edmund Ireri[6], Jennifer M. Carter[7], Diana K. Riner[7], Nupur Kittur[7], Diana M. S. Karanja[1] and Daniel G. Colley[7,8]

Abstract

Background: World Health Organization guidelines recommend preventive chemotherapy with praziquantel to control morbidity due to schistosomiasis. The primary aim of this cross-sectional study was to determine if 4 years of annual mass drug administration (MDA) in primary and secondary schools lowered potential markers of morbidity in infected children 1 year after the final MDA compared to infected children prior to initial MDA intervention.

Methods: Between 2012 and 2016 all students in two primary and three secondary schools within three kilometers of Lake Victoria in western Kenya received annual mass praziquantel administration. To evaluate potential changes in morbidity we measured height, weight, mid-upper arm circumference, hemoglobin levels, abdominal ultrasound, and quality of life in children in these schools. This study compared two cross-sectional samples of *Schistosoma mansoni* egg-positive children: one at baseline and one at year five, 1 year after the fourth annual MDA. Data were analyzed for all ages (6–18 years old) and stratified by primary (6–12 years old) and secondary (12–18 years old) school groups.

Results: The prevalence of multiple potential morbidity markers did not differ significantly between the egg-positive participants at baseline and those at 5 years by Mann Whitney nonparametric analysis and Fisher's exact test for continuous and categorical data, respectively. There was a small but significantly higher score in school-related quality of life assessment by year five compared to baseline by Mann Whitney analysis ($P = 0.048$) in 13–18 year olds where malaria-negative. However, anemia was not positively impacted by four annual rounds of MDA, but registered a significant negative outcome.

(Continued on next page)

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(Continued from previous page)
Conclusions: We did not detect differences in morbidity markers measured in a population of those infected or re-infected after multiple MDA. This could have been due to their relative insensitivity or a failure of MDA to prevent morbidity among those who remain infected. High malaria transmission in this area and/or a lack of suitable methods to measure the more subtle functional morbidities caused by schistosomiasis could be a factor. Further research is needed to identify and develop well-defined, easily quantifiable *S. mansoni* morbidity markers for this age group.

Keywords: Schistosomiasis, Kenya, Mass drug administration, School-based, Morbidity, School pediatrics quality of life scores

Background

Human schistosomiasis caused by the trematode *Schistosoma mansoni* is endemic in western Kenya near Lake Victoria where its prevalence has an inverse relationship with the distance from the shore [1, 2]. The Passage of World Health Assembly (WHA) Resolution 54.19 in 2001 led to renewed emphasis on reducing the global burden of schistosomiasis. The current World Health Organization (WHO) strategy to reduce schistosomiasis-associated morbidity is mass drug administration (MDA) with praziquantel (PZQ) based on the prevalence and intensity of infection in an area [3]. Most commonly this translates to yearly or biennial MDA with PZQ in primary schools to treat schistosomiasis in addition to administration of albendazole (ALB) for soil-transmitted helminths (STHs) [4]. The effectiveness of this strategy is usually monitored by MDA coverage and by changes in prevalence and/or intensity of infection rather than determination of changes in morbidity [4–9].

While the goal of PZQ MDA is to control morbidity, because many of the sequelae associated with schistosomiasis can have other causes, it has proven challenging to easily measure morbidity specifically resulting from schistosomiasis. Pathology due to *S. mansoni* infection is caused largely by chronic deposition of parasite eggs in the liver and intestines, which results in egg-focused granuloma formation and focal and systemic inflammation [5, 10]. This, in turn leads to sequelae that can range from "subtle or functional morbidities" such as anemia, physical (growth stunting, wasting) and cognitive disabilities, which can impact a child's quality of life [11–13], to periportal fibrosis, portal hypertension, hematemesis, and death. While severe disease likely develops in only 5 to 10% of those with substantial, untreated chronic infections [14, 15], the subtle morbidities are thought to have a broader public health impact on most of the over 240 million people with schistosomiasis [12, 16, 17]. However, they are more difficult to assess for example specific morbidity assessment of anemia in *S. mansoni* infection is challenging because in many areas where individuals are at risk for schistosomiasis, they are also at risk for malaria and both infections cause anemia. The synergistic effect of co-infection and potential interaction outcome of schistosomiasis and malaria infections on anemia may affect the usefulness of anemia as a marker of schistosomiasis [18, 19].

Assessments of morbidity markers associated with *S. mansoni* infection were conducted in two populations; one group prior to MDA (at baseline) and a second group, all that were *S. mansoni* egg-positive 1 year after four rounds of high coverage, school based annual MDA in year five. The population in year five remained *S. mansoni* egg-positive either due to not being cured during the MDA or due to re-infection during the year following the last MDA. Secondary school children are not routinely included in most morbidity assessment studies, so there are limited data for this age group even though they tend to have the highest prevalence and intensity of schistosome infections [20]. Although rapid re-infection can occur after treatment, some data suggest that having received treatment in childhood can reduce morbidity associated with urinary schistosomiasis later in life [21]. The primary aim of this cross sectional study was to address whether 4 years of effective primary and secondary school MDA is enough to lower morbidity in individuals with infections a year after the final MDA compared to children who were *S. mansoni*-positive prior to the initial MDA intervention.

A secondary aim of this cross-sectional study was to evaluate the utility of several potential markers of morbidity to detect changes before and post-MDA in primary and secondary school children. This analysis was done in conjunction with our studies documenting the effectiveness of the four rounds of annual MDA in significantly lowering the prevalence and intensity of *S. mansoni* infection [22] and evaluating immunological outcomes in the same groups of children [23].

Methods

Ethics statement

Ethical approval to conduct the study was obtained from the Departmental and Institutional Scientific Steering Committees of Kenya Medical Research Institute (KEMRI) followed by the National KEMRI Scientific and Ethical Review Unit (SERU). The Institutional Review Board (IRB) of the University of Georgia also reviewed and approved the study protocol (ID#00003501). Before the start of the study, informational meetings were held