# DIAGNOSTIC PERFORMANCE OF KATO KATZ AND POINT OF CARE CIRCULATING CATHODIC ANTIGEN ASSAYS FOR DETECTION OF *SCHISTOSOMA MANSONI* AND THEIR UTILITY IN MONITORING PREVENTIVE CHEMOTHERAPY IN SIAYA COUNTY, WESTERN KENYA

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**A Thesis Submitted in Partial Fulfillment of the Requirements for the Award of the Degree of Master of Science in Epidemiology and Biostatistics of Jaramogi Oginga Odinga University of Science and Technology**

## DECLARATION

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

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**H153/4201/16**

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**ABSTRACT**

Schistosomiasis pauses a serious public health concern, causing significant morbidity and mortality in tropical countries, despite there being affordable, effective, and safe drugs for its treatment. Accuracy in detection of the disease in endemic and at-risk populations is important to achieve elimination goals in line with WHO NTD 2030 roadmap. Kato-Katz assay has historically remained reliable assay for the diagnosis of schistosomiasis and most intestinal parasites, but it has major drawbacks, including low sensitivity and the need to promptly process stool samples upon collection. The novel point of care circulating cathodic antigen (POC-CCA) test using urine has shown promise for the detection of *S. mansoni* in different settings, and thus a growing need for its validation and utility in monitoring and evaluation of control programs for *S. mansoni*. This study evaluated the diagnostic performance of Kato Katz and POC-CCA in the detection of *S. mansoni* infections in low and high prevalence areas and to determine their effectiveness in monitoring of preventive chemotherapy, using a repeated cross-sectional approach, where 329 school-aged children (9-12 years) were enrolled each year and provided single stool and urine samples. Eight schools (4 in low-risk and 4 in high-risk strata) were purposively selected. Four thick smear slides were analyzed by KK while urine samples were analyzed by POC-CCA for detection of *S. mansoni*. Data was entered using CommCare®® and analyzed using Stata version 14 software. The mean age of the 329 enrolled SAC was 10.6-10.7 while the median age was 10 years. Both POC-CCA and Kato-Katz were able to report a decrease in prevalence over time [2019 (KK= 29.5%, POC-CCA=70.3%) 2021(KK= 28%, CCA=475)]. Notably, only the POC-CCA was able to monitor the decrease for both high and low prevalence areas [Low-risk stratum <10% (2019= 63.0%, 2020= 42.4%, 2021=28.5%). High-Risk Stratum (>20%) (2019= 77.8%, 2021= 65.6%)]. Generally, the POC-CCA assay was more sensitive (<90%) and accurate than Kato-Katz, and concordance between the two tools was low, while in low prevalence areas, the strength of agreement between the two tools was poor (2019, K=0.0360, 2020, K=0.0449, 2021, K= 0.1872). Moderate agreement was recoded in high-risk stratum in 2021 (K= 0.5557, P<0.0001). Moreover, the frequency of false negatives and false positives reported by the POC-CCA tool was of great concern. In conclusion, the POC-CCA tool was able to monitor the decrease in prevalence of *S. mansoni* following annual rounds of MDA using praziquantel drug. However, it is still unclear if this tool can be utilized for monitoring schistosomiasis control programs due to reportedly higher number of false negatives/positives.

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## ABBREVIATIONS

| | |
|---|---|
| **CDC** | Centers for Disease Control and Prevention |
| **CGHR** | Center for Global Health Research |
| **DALYs** | Disability Adjusted Life Years |
| **ERC** | Ethics Review Committee |
| **GAHI** | Global Atlas of Helminth Infections |
| **HIV** | Human Immune-Deficiency virus |
| **JRSM** | Joint Requisition for Special Medicines |
| **KEMRI** | Kenya Medical Research Institute |
| **K-K** | Kato-Katz |
| **MDA** | Mass Drug Administration |
| **NTDs** | Neglected Tropical Diseases |
| **POC-CCA** | Point of care circulating cathodic antigen |
| **SAC** | School-Aged Children |
| **SBT** | School-Based Treatment |
| **SSA** | Sub-Saharan Africa |
| **SSC** | Scientific Steering Committee |
| **STH** | Soil-Transmitted Helminth |
| **SWAP** | Safe Water and AIDS Project |
| **WHA** | World Health Assembly |
| **WHO** | World Health Organization |

# CHAPTER ONE: INTRODUCTION

## 1.1. Background Information

Schistosomiasis, also known as bilharzia, or snail fever, is among the neglected tropical diseases (NTDs), commonly known as "diseases of poverty", as they affect almost everyone in the "bottom billion" of the poorest populations of the world, with serious social and economic consequences, adversely impacting on the health and well-being of those infected and, thus, exacerbate poverty (Adenowo *et al.*, 2015; Sokolow *et al.*, 2016). The disease results from chronic infection with blood flukes belonging to the genus *Schistosoma*, speciated into *S. haematobium, S. mansoni, S. japonium, S. mekongi*, *S guinensis,* and *S. intercalatum* (Obonyo *et al.*, 2019; Utzinger *et al.*, 2015). Infections occur when people get into contact with freshwater bodies infested with infective schistosome forms called cercariae, which are transmitted by snails of the genus *Biomphalaria*, as intermediate hosts (Colley *et al.*, 2014), causing schistosomiasis, which is considered one of the most important water-related diseases (Utzinger *et al.*, 2015).

Considered a poverty associated disease, schistosomiasis is related to poor sanitation, contact with unprotected open cercariae infested fresh water sources where transmission takes place (Grimes *et al.*, 2014). Disease severity remains dependent on the species of the schistosome, period of infection, worm burden, immunity of the host, gender and age (Colley *et al.*, 2014). Most recent global estimates project about 250 million persons infected with the disease, and approximately 800 million being at risk of infection (Sokolow *et al.*, 2016). A huge proportion of 90% of the infection was found to be centralized in sub-Saharan Africa (WHO, 2015). Clinically, chronic infection with schistosomiasis results in painful passage of bloody urine, bloody diarrhea, liver enlargement (hepatomegaly), spleen enlargement (splenomegaly), and liver cancer (Skolnik & Ahmed, 2010). Estimates point to NTDs including schistosomiasis to be resulting in as many disability adjusted life years (DALYs) lost annually compared to malaria, largely because of their chronic nature and the long-lasting disabilities (Skolnik & Ahmed, 2010). According to (Hotez & Kamath, 2009) infection with schistosomes account for approximately 70 million annual DALYs every year globally.

Tropical Sub-Saharan Africa (SSA) bears the heaviest burden (over 500 million people) of many of the NTDs, and the number of people suffering from each or several of these diseases is simply breathtaking (Hotez & Kamath, 2009). Reports from the World bank and findings from recent studies point to poverty-stricken SSA, to have schistosomiasis alone significantly associated with extreme poverty and greatly affecting rural and deprived urban slum dwellers (Shah, 2013). The rate of transmission is more widespread among the majority poor leading to adverse effects such as agricultural productivity, pregnancy outcome, and child growth and development (Adenowo *et al.*, 2015). Within Kenya, schistosomiasis prevalence ranges widely between 5% to over 65% in different settings, and contributes significantly to morbidity in those endemic areas (Colley *et al.*, 2013). The disease remains of major public health interest in western Kenya, with previous studies reporting intestinal schistosomiasis as a great cause of morbidity among people living along Lake Victoria (Nagi *et al.*, 2014) and especially among school-aged children (Mwinzi *et al.*, 2015b).

Existing guidelines by World Health Organization (WHO) and recommendations for the control and elimination of the disease point at baseline prevalence evaluations in order to inform on programmatic decision making on the target populations and the treatment frequency within endemic areas (Mwinzi *et al.*, 2015b). This recommendation requires application of very accurate and reliable diagnostic tools that can also be used to map and determine local parasite prevalence and incidence (Kittur *et al.*, 2016).

There has been substantial success in the control of schistosomiasis as widely recorded in many countries, with significant decrease in both prevalence and infection levels (Assaré *et al.*, 2016). The level of endemicity in a setting determines how drugs will be administered. WHO clearly advises that if the prevalence is $\geq$ 50%, all adults and school aged children in the endemic setting should be treated yearly. Recent guidance by the WHO has focused on the possibility of attaining local elimination of schistosomiasis in some areas (Kittur *et al.*, 2016). Convectional stool thick smear Kato-Katz assay is used for diagnosis of intestinal schistosomiasis and other intestinal parasites, including soil transmitted helminths (STHs) in large scale epidemiological studies and for monitoring effectiveness of mass drug

administrations because the diagnostic tool has high specificity assumed to be 100%, its relative simplicity under field conditions, and low cost compared to other available diagnostic tools (Nikolay *et al.*, 2014). However, the assay has documented known limitations of low sensitivity in areas with light infection intensities, intra- and inter-specimen variation of helminth egg distribution, and aggregation in feces and the fact that the Kato-Katz procedure is quite time-consuming, requires well-trained laboratory technicians with ardent microscopy skills, the need for heavy functional equipment including the microscopes, and the need to process stool specimens promptly after collection (Shane *et al.*, 2011; Speich *et al.*, 2010). Furthermore, there is a growing concern that Kato-Katz assay will continue to miss *S. mansoni* infections in proportions of people living in low prevalence and low intensity regions (Allam *et al.*, 2009) which has important implications, especially when it is utilized to monitor the effectiveness of preventive chemotherapy. This is because the undetected light infections create a potential source of continued infection. It might therefore be possible to address some of the challenges facing the existing control programs if an alternative diagnostic assay to Kato-Katz can be identified and adopted or integrated with other diagnostic tools.

The novel single urine point of care circulating cathodic antigen (POC-CCA) assay has higher sensitivity, and rapidly detects *S. mansoni* infection than Kato Katz (Coulibaly *et al.*, 2011b) and correlates with infection presence and intensity. It has thus been suggested to become an alternative to Kato-Katz (Casacuberta *et al.*, 2016) and should therefore be factored in for subsequent post-treatment programmatic decision making (Mwinzi *et al.*, 2015b). However, due to the paucity of relevant published data in regions recording low prevalence, the need to validate the tool even in high prevalent settings, and the fact that there are not robust enough findings to firmly equate what a given prevalence by POC-CCA translates to Kato Katz calls for additional evaluations before it can be adopted (Colley *et al.*, 2013). This study therefore sought to address the urgent need to evaluate the diagnostic performance of these tools in the detection of *S. mansoni* infections in both low and high prevalence areas and also determine their effectiveness for monitoring preventive chemotherapy in Siaya county, western Kenya.

Population based distribution of praziquantel to endemic populations remains the current global control strategy for schistosomiasis. The WHO recommends effective target coverage rate of at least 75% for school-aged children for progress towards achieving control and elimination goals or simply to suppress the disease.

### 1.2 Statement of the Problem

Schistosomiasis remains a key global public health problem, and planning for preventive chemotherapy geared towards control and eventually achieve the WHO elimination targets in all schistosomiasis endemic populations requires a very accurate and reliable diagnostic tool that can determine local parasite prevalence and still be useful for effective monitoring and evaluation (M&E) of control programs (Aemiro *et al.*, 2022)**.** Currently, treatment efficacy for *S. mansoni* is primarily monitored by assessing changes in infection prevalence, commonly done by stool examinations using the conventional thick smear Kato-Katz stool assay. This method has several known drawbacks including the growing appreciation that its sensitivity continues to decline, especially as more MDA interventions are scaled up and progressively lower egg densities are recorded, the day-to-day variability in egg excretion, non-homogenous distribution of eggs in stool, its poor reproducibility and unnecessarily high risk of exposure to infection, and the need to perform stool sample examination soon after they are collected. Kato Katz assay often requires sending skilled teams and microscopists to remote areas to perform the assessments and in many cases is very costly.

Whereas the novel POC-CCA assay is proposed to be an alternative to Kato-Katz with some supporting studies from high *S. mansoni* prevalence areas (≥50%), more studies are still needed to validate the findings and the fact that there is limited data in low prevalence regions and on its utility for monitoring and evaluation of the benefits of preventive chemotherapy. Therefore, the continued application of Kato-Katz as a confirmatory test will greatly increase the misdiagnosis of parasitic intestinal helminth infections. The strategic plan for schistosomiasis control for the years 2012–2020, published by the WHO in 2013 were intended to control schistosomiasis morbidity by 2020 and eliminate the disease by 2025 (WHO, 2013). In the plan, the WHO appreciated that diagnostic tools employed in monitoring and evaluation of control programs, like the Kato-Katz technique, are outdated

and thus stated that there is a need to improve and validate the circulating cathodic antigen assay for *S. mansoni* (WHO, 2013). Therefore, there is a dire need to investigate the diagnostic performance of this tool and its effectiveness in monitoring preventive chemotherapy in a bid to reduce the limitations faced by national and other control programs.

## 1.3. Objectives

### 1.3.1. Main Objective

To evaluate the diagnostic performance of Kato-Katz and Circulating Cathodic Antigen for the detection of *Schistosoma mansoni* in low and high prevalence areas, and their utility in monitoring preventive chemotherapy in Siaya county, western Kenya

### 1.3.1. Specific Objectives

i. To determine the prevalence of *S. mansoni* by Kato-Katz and POC-CCA assays in low and high prevalence areas in Siaya county.
ii. To compare the sensitivity, specificity, and degree of agreement of Kato-Katz and POC-CCA assays in low and high prevalence areas in Siaya county.
iii. To determine the effectiveness of Kato-Katz and POC-CCA assays in monitoring of preventive chemotherapy.

## 1.4. Research Questions

i. What is the prevalence of *S. mansoni* by Kato Katz and POC-CCA assays in low and high prevalence areas in Siaya county?
ii. What is the sensitivity, specificity, and degree of agreement of Kato-Katz and POC-CCA assays in low and high prevalence areas in Siaya county?
iii. What is the effectiveness of Kato-Katz and POC-CCA assays in monitoring of preventive chemotherapy?

### 1.5. Justification of the Study

In the Lake Victoria region of western Kenya, *S. mansoni* infections are due to contact with lake water and contaminated environment (Mwinzi *et al.*, 2015b; Utzinger *et al.*, 2015). Various occupation-related hazards associated with the lake, like fishing, farming on swampy areas, sand harvesting, and household chores, including washing of clothing, utensils, and bathing, expose individuals living near the lake to schistosomal infections. In addition to severe disease, schistosomiasis can cause degrees of morbidity that could in turn contribute significantly to poor health outcomes in those infected, especially children (Mwinzi *et al.*, 2012). For decades, schistosomiasis burden was believed to be heavier mainly in older children and adults, but recent studies have informed that high rates of *S. mansoni* infections are as well found among preschool-age children (Verani *et al.*, 2011). Lack of accurate diagnostic tools remains among the key factors that hamper the estimation of the prevalence and burden of intestinal parasitic infections (Gelaw *et al.*, 2013). Therefore, reliable diagnosis of intestinal helminth infections requires rapid, easy to use, and highly sensitive tools that can also be used to monitor the effectiveness of mass treatment campaigns. This is especially important considering that critical public health decisions are dependent on the accuracy of diagnostic tests and more so as many national control programs align to achieve elimination targets of the disease.

### 1.6 Significance of the Study

The findings of this study are useful as they inform those involved in policy making and implementation, including the National NTD Control Program, and county governments on the utility of both Kato-Katz and POC-CCA diagnostic tools in diagnosis of *S. mansoni*, and their effectiveness in monitoring of preventive chemotherapy. This is critical as many countries align to WHO 2030 road map with clear elimination targets for PCT-NTDs. Moreover, the results add to the body of existing knowledge on disease specific NTDs.

### 1.7. Scope of the Study

This study was conducted in Siaya County, along Lake Victoria basin in Western Kenya. It compared the diagnostic performances of Kato-Katz and POC-CCA for the diagnosis of *Schistosoma mansoni* in both low and high prevalence areas and their utility in monitoring

preventive chemotherapy. The study involved 329 school-aged children (9-12 years) drawn from 8 primary schools in Siaya County; four schools were located close to Lake Victoria and with known high prevalence of schistosomiasis >20%, and four other schools 5 km away from the lake with known low prevalence <10% of schistosomiasis were selected. The 8 schools received three annual rounds of MDA. The eligible study participants, randomly selected in a school provided one stool sample and urine sample once per year for three years and only when the children were in school between the months of January and March of each year.

### 1.8 Limitations of the Study

This study used a repeat cross-sectional survey design, and new participants were enrolled each year so it remained unknown whether a participant tested in a given year actually received MDA during the previous year or would be present for the study in the following year, or could have been a new immigrant from an area with different schistosomiasis endemicity. The study area had been subjected to continuous annual rounds of MDA through the KEMRI-led SCORE project and the national deworming program by the Ministry of Health Mwinzi *et al.*, 2015b; Onkanga *et al.*, 2016).

# CHAPTER TWO: LITERATURE REVIEW

## 2.1 Introduction

This chapter presents reports from previous studies, which compare the diagnostic performance of Kato-Katz and circulating cathodic antigen (CCA) assays for the detection of *Schistosoma mansoni* in in different settings, including low and high prevalence areas. It also presents a review of the relevant existing literature on the research subject.

## 2.2 Epidemiology of Schistosomiasis

Schistosomiasis (snail fever) or bilharzia, caused by a blood trematode of the genus *Schistosoma*, is the main cause of morbidity among rural populations in endemic regions, where the five principal species causing human infections include *S. mansoni* (intestinal), *S. haematobium* (urinary), *S. japonicum* (intestinal), *S. mekongi,* and *S. intercalatum* (Obonyo *et al.*, 2019; Utzinger *et al.*, 2015). Estimates show that 207 million people globally are infected with schistosomes, about 799 million being at risk of infection, and 93% of all infections occurring in sub-Saharan Africa (Lo *et al.*, 2017). The disease is most prevalent in the communities of the developing world with limited resources, and is associated with poverty and underdevelopment, seen in nearly all countries of sub-Saharan Africa (Becker *et al.*, 2018; Savioli *et al.*, 2018).

It is estimated that over 6 million people are infected with schistosomiasis in Kenya, with many more at risk of infection (Oswald *et al.*, 2020; Pullan *et al.*, 2019). Different studies have shown that adolescents aged 10-19 years harbour the highest infection rates, although adults who are occupationally exposed through activities associated with water contact, mainly in rural areas, are also significantly infected (Ajjampur *et al.*, 2021; Sartorius *et al.*, 2021). In the western region of Kenya, schistosomiasis is mainly associated with Lake Victoria (Handzel *et al.*, 2003). At least 610 million children of school-going age are at risk of schistosomiasis or soil-transmitted helminthiases (WHO, 2011), and the prevalence among the school children along the Kenyan shores of Lake Victoria ranges between 29-94% (Mwinzi *et al.*, 2012; Straily *et al.*, 2021).

Even given the importance of soil-transmitted helminthes and schistosomiasis in Kenya, the national control program is not well instituted. In 2009, the government launched a national program that aimed at deworming school children in 254 districts. Currently, the school-based mass deworming is conducted as a preventive measure for schistosomiasis and intestinal helminths. Effective control of the infections has not been well established since the rest of the family members are not included in the program.

### 2.2.1 Biology and Life Cycle of Schistosomes

Human schistosomiasis results following infection with blood flukes belonging to the genus *Schistosoma*, the major species being *S. haematobium* (causative agent of urinary schistosomiasis), *S. mansoni,* and *S. japonicum,* (which cause the intestinal, hepatic, or hepatosplenic forms of human schistosomiasis), *S. mekongi,* and *S. intercalatum* (Obonyo *et al.,* 2019). The life cycle of these schistosomes includes humans and, in the case of *S. japonicum,* the animal becomes the end host and different intermediate host snails. The amphibious *Oncomelania* snail (*O. hupensis*) is the only intermediate host for *S. japonicum,* while *S. mansoni* and *S. haematobium* rely on the aquatic *Biomphalaria* and *Bulinus* snails, respectively (Alzaylaee *et al.,* 2020). The blood-dwelling schistosome pairs constantly release eggs, which reach the environment through fecal or urinary excretion (Ogongo *et al.*, 2018). The eggs hatch in freshwater and the miracidia released infect suitable intermediate host snails, where they develop into free-swimming cercariae, the infective stages that swim in infested waters. Upon contact with a potential end-host, the cercariae actively penetrate the skin, reach the liver via the bloodstream and develop into schistosomula (juvenile worms), which migrate further to reach their final peri-intestinal or peri-vesical locations (Alghanmi, 2014). Occupational activities involving direct contact with infected waters predispose humans to infections.

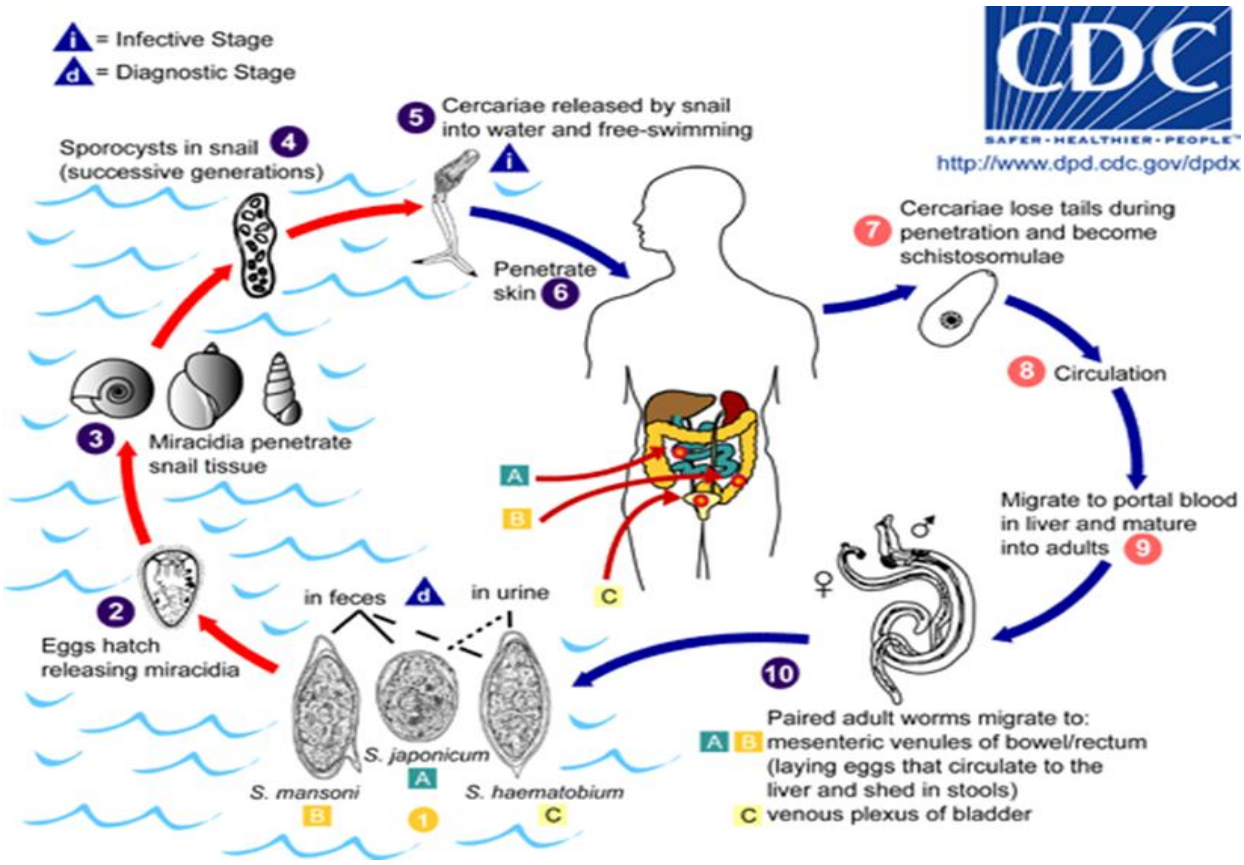


**Figure 2.1: The life cycle of *Schistosoma* spp**

(Source: https://www.cdc.gov/parasites/schistosomiasis/biology.html)

### 2.3 Diagnostic techniques for schistosomiasis

Normally, routine diagnosis of intestinal helminth infections, including schistosomiasis, is based on the detection of the helminth eggs and/or larvae in stool samples examined using different parasitological methods (Tay *et al.*, 2011). However, these microscopic approaches carry significant drawbacks, including low sensitivity for the detection of light infections (Bergquist *et al.*, 2015).

#### 2.3.1 Kato-Katz

Convectional Kato-Katz has remained in common use as a reliable diagnostic procedure for most intestinal parasite infections despite the availability of other diagnostic techniques. The WHO has recommended its use for epidemiological surveys and surveillance of intestinal schistosomiasis and STH control programs owing to its relatively low cost and simplicity

(Jeandron *et al.*, 2010; Mwinzi *et al.*, 2015b). Moreover, the Kato-Katz technique requires minimal, mostly reusable equipment, and laboratory workers can be effectively trained within hours (Speich *et al.*, 2010). However, it has variously been reported that single Kato-Katz examinations usually underestimate the prevalence of *S. mansoni* and *S. japonicum* (Barenbold *et al.*, 2018; Colley *et al.*, 2020b; Mazigo & Heukelbach, 2018).

Although Kato-Katz has a high specificity (assumed to be 100%), its sensitivity using a single stool sample examination is reduced by the daily variations in egg excretion, which itself depends a lot on the host's physiologic and immunologic profiles. This leads to inaccuracy in estimating the burden of infection, especially in places with high proportions of light infections (de Sousa *et al.*, 2019). In addition, the amount of stool analyzed is small (about 41.7mg), so may not adequately represent fecal contents, and explains the low sensitivity of Kato-Katz technique when eggs are present at low densities, or appear highly clustered (Glinz *et al.*, 2010). To boost diagnostic sensitivity, the use of multiple methods on the same stool sample, and examination of duplicate thick smears per stool sample has yielded reliable results in many settings (Utzinger *et al.*, 2011).

### 2.3.2 Point of care circulating cathodic antigen (POC-CCA) assay

The urine-CCA (circulating cathodic antigen) test is used for the qualitative presumptive detection of active schistosome infections, particularly *S. mansoni* (Pieri *et al.*, 2023). In areas endemic for *S. mansoni*, a single CCA urine test demonstrates a nearly accurate prevalence, based on multiple egg count determinations. The urine-based test is a fast and easy to perform procedure for the presumptive detection of schistosomes in persons with an active infection (Casacuberta-Partal *et al.*, 2021; Favre *et al.*, 2022; Graeff-Teixeira *et al.*, 2021b).

### 2.3.3 Immunodiagnosis

Although immunodiagnosis normally requires more highly equipped laboratories than those just using microscopy, they also tend to give higher sensitivities, especially for antibody detection (Chernet *et al.*, 2017; Neumayr *et al.*, 2019; Sousa-Figueiredo *et al.*, 2013). Because antibody detection is only qualitative in this test, it is difficult to differentiate

between light and heavy infections (Colley *et al.*, 2020b), which is at times important in modelling interventions. Moreover, following successful chemotherapy, antibody levels usually remain high for long periods, presenting a diagnostic dilemma that is the failure to differentiate active from cured infection (Bezerra *et al.*, 2021; Bezerra *et al.*, 2018; Mazigo & Heukelbach, 2018; Neumayr *et al.*, 2019). Detection of schistosome antigens, such as circulating anodic antigens (CAA) and circulating cathodic antigens (CCA), or soluble egg antigen (SEA) in blood or urine, using ELISA have several known advantages over antibody detection. Typically, active infections can be readily demonstrated, and because of their high specificity, are useful for drug efficacy trials and program monitoring. However, classical ELISA procedures are generally slow, require properly equipped laboratories and highly qualified personnel (Bezerra *et al.*, 2021; Bezerra *et al.*, 2018; Cai *et al.*, 2021).

For accurate and reliable assessment of the epidemiology and estimation of disease burden, and for monitoring drug efficacy and pharmacovigilance, diagnosis is critical (Straily *et al.*, 2021; Viana *et al.*, 2019a). Furthermore, increasing observation of polyparasitism, especially in the developing countries, signals the need to develop sensitive, simple to use diagnostic tools which are able to detect multiple intestinal parasite species in the same stool sample concurrently (Bezerra *et al.*, 2021).

### 2.4 Control of schistosomiasis

Schistosome and helminthic infections are known to mainly affect the poorest populations, and are more abundant among communities living in rural or underserved urban settings with low socio-economic status, lack basic amenities, including clean water, and proper sanitation (Dahal *et al.*, 2019; Lo *et al.*, 2017; Oswald *et al.*, 2020). Together with other neglected tropical diseases (NTDs), efforts towards the control schistosomiasis and STHs were for a long time overridden by other health priorities, like HIV/AIDS, tuberculosis, and malaria (Ajjampur *et al.*, 2021; Becker *et al.*, 2018; Freeman *et al.*, 2019). In last two decades, different programs have been instituted worldwide to provide appropriate treatment to millions of people, and the WHO has played a central role in this respect, whereby all WHO member states (over 200 countries) in May 2001 endorsed a resolution to provide regular treatment of at least 75% of all school-aged children at risk of schistosomiasis by

2010. This strategy encouraged many countries to establish national plans and programs to control NTDs (Molyneux *et al.*, 2021). Although a national control program for the community has not been set up, a national deworming program targeting school-aged children was launched in 2009. This is currently the primary approach being used for the mass treatment of schistosomiasis and STHs with support, mostly by local and international non-governmental organizations (Legge *et al.*, 2020; Oswald *et al.*, 2019; Pullan *et al.*, 2019). A five-year National Control Strategic plan for NTDs (2011-2015) was also launched in 2011, with priority given to 5 PCT-NTDs, namely schistosomiasis, STHs, leishmaniasis lymphatic filariasis, and trachoma.

Deworming of children have been shown to have the potential to significantly reduce the burden of malaria since children infected with *Ascaris* spp are twice as likely to get severe malaria (Hotez *et al.*, 2006). The drugs recommended by WHO for reducing morbidity due to STHs include albendazole, levamisole, mebendazole, and pyrantel, while for schistosomiasis is praziquantel (effective across all schistosome species), and oxamniquine (effective only against *S. mansoni*) as a second choice (WHO, 2002). Mass drug administration (MDA), which involves the mass treatment of populations with anthelminthic drugs has been widely adopted, especially in the developing countries (Hotez *et al.*, 2008; Pullan *et al.*, 2019; Werkman *et al.*, 2020). Since schistosomiasis occurs together with many of the other NTDs, especially STHs, an integration of their control with other helminth control programs would be of great benefit (Lo *et al.*, 2017). Other control strategies include health education and awareness, improved sanitation, and the provision of safe water. Besides, focal snail control for schistosomiasis is being implemented in other settings. The snail population can be reduced with molluscicides or by lining and covering water channels (Asbjornsdottir *et al.*, 2018; Molyneux *et al.*, 2021).

### 2.5 Conceptual Framework

In this framework, the diagnostic performance and monitoring utility of POCCA and KK assays are weighed against each other, with the primary variables being aligned to local *S. mansoni* prevalence (high vs low), the individual sensitivity and specificity of the two tests,

and their performance and reliability for field applications, especially in the phase of mass drug administration (Figure 2.5.1.).

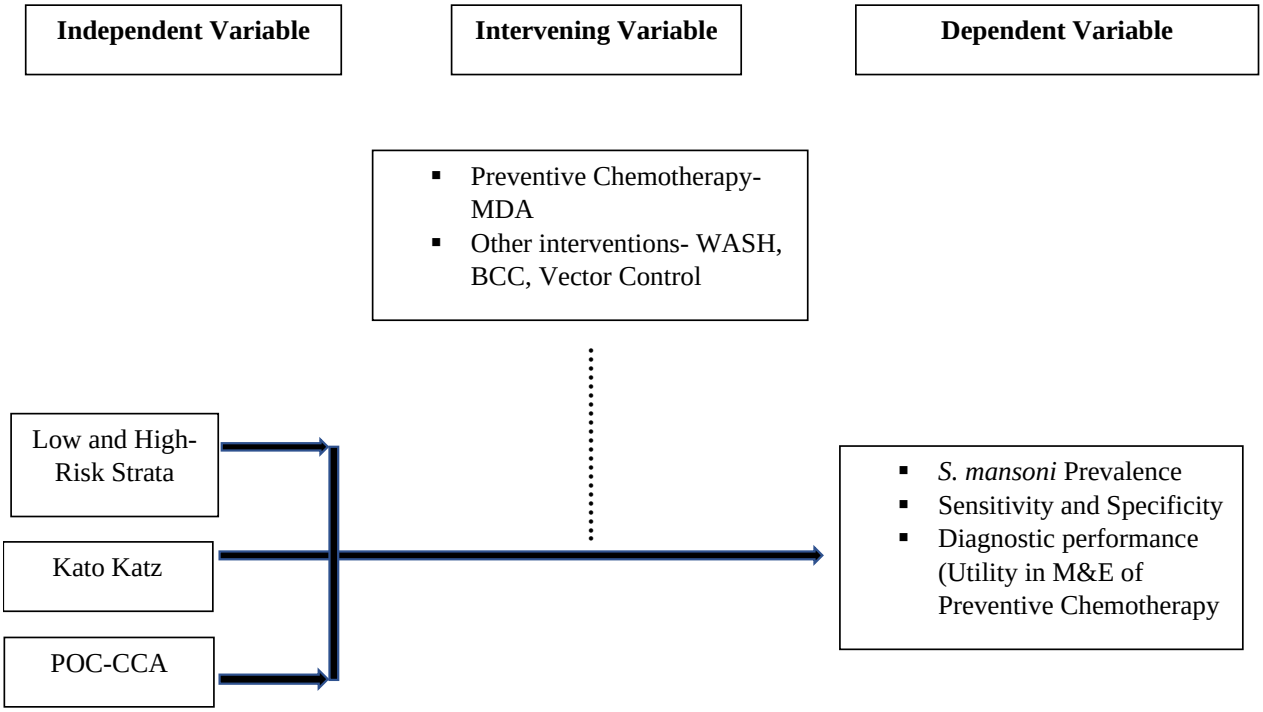


**Figure 2.1. Conceptual Framework (***source: author)*

# CHAPTER THREE: METHODOLOGY

## 3.1 Introduction

The chapter consists of the design and the methods that were applied in this study. It focuses on the study site, design, sample size and sampling procedure, laboratory procedures, data entry and analysis, and ethical considerations.

## 3.2 Research Setting

This study was conducted in Siaya County (Bondo and Rarieda sub-counties), western Kenya, which borders Lake Victoria to the South and West. The Kenya population and housing census of 2019 indicated estimates of 993,183 people (Kenya National Bureau of Statistics) residing in the county. In the county, the WHO_JRSM_2019 indicate 307, 942 School Aged Children (SAC), of which 57,383 and 49,250 SACs are in Bando and Rarieda sub-counties respectively. The major economic activities for Siaya county include subsistence farming, livestock rearing, fishing, and small-scale trading. The research setting was selected because of its endemicity for intestinal schistosomiasis. The area has subsequently been subjected to continuous annual rounds of MDA through the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) project and the government-driven national school-based deworming program. Earlier research in the region have illustrated an inverse relationship between schistosomiasis prevalence and distance of residence from the lake (Mwinzi *et al.*, 2015b; Onkanga *et al.*, 2016), which allowed the selection of schools based on the estimated baseline prevalence. The study area was categorized into low (<10%) and high (>20%) prevalence risk areas as obtained from previous studies conducted in the area.

## 3.3 Research Design

This analytic study was nested on a five-year SWAP Kenya/KEMRI-CDC. The nested study equally applied a repeat cross-sectional (3-years) study design that involved eight primary schools in Bondo and Rarieda sub-counties of Siaya county.

### 3.4. Study Population

School-age children, SAC (9-12 years) were considered ideal participants for this study, because, among other things, including ease of their access from schools, the prevalence and intensity levels among SAC are representative of the community (Mwinzi *et al.*, 2015b) and therefore, can be used to make intervention decisions for other age groups at the larger community.

### 3.5 Inclusion and Exclusion Criteria

#### 3.5.1 Inclusion Criteria

School-age children (9-12 years) who had been residents in the study area for the last 6 months or more and whose parents/guardians gave a written informed consent, and the children were willing to provide a voluntary assent to participate in the study.

#### 3.5.2 Exclusion Criteria

A child who was observably ill or had an underlying medical condition, as judged by the study nurse/clinician. Also excluded was any child who did not provide assent, or whose parent did not consent to the study procedures. A child who at the time of the study had recent anthelmintic treatment (in the last 4 weeks) based on information from the school head and or participation in another study that may have provided PZQ treatment was also excluded.

### 3.6. Sample Size Determination

The Cochran (1977) formula for sample size determination was used to obtain a reliable sample size.

$$n = \frac{Z^2pq}{e^2}$$

Where.

n = desired sample size

Z = standard normal deviate at 95% CI=1.96

p = estimated local prevalence of *S. mansoni* among SAC = 69% (Mwinzi *et al.*, 2015a)

q = 1-p

e = acceptable margin of error = 0.05

$$n = \frac{1.96^2 * 0.69 * 0.31}{0.05^2}$$

= 328.69 = 329 participants for each year

### 3.7. Sampling Procedure

Eight primary schools were purposively selected and groped into high prevalence (4 schools) and low prevalence (4 schools) depending on their proximity to the lake and based on results from previous studies. Recruitment of children per school was based on a random sample of all 9-12-year-old children on the school enrollment registers.

Simple random sampling technique was used to select the study participants. In each school, the field assistants with the help of school health teachers obtained a list of all 9-12 aged pupils from the school register. This eligible age group was invited under a tree and provided with health education in order to understand the etiology, preventive and control measures against schistosomiasis. The field assistants explained that a few of them would be randomly selected to provide samples (both stool and urine samples) and that their results would give the overall prevalence of the school. It was made clear that should the school qualify for MDA, all pupils, whether or not they were tested would receive treatment against schistosomiasis. The simple random selection ensured all the eligible pupils had an equal chance of selection. Random numbers were generated and pupils that picked the "yes" numbers were provided with sample collection materials. Unique pupil identity numbers were provided in the order they brought the sample and samples were recorded in the sample tracking form that was linked to the masterplan form.

### 3.8 Validity and Reliability

#### 3.8.1 Validity

Four thick smear slides from stool sample were prepared. These were meant to increase the sensitivity of KK. Both KK slides and POC-CCA cassettes were each examined by two laboratory technologists and each result computed.

#### 3.8.2 Reliability

Stool and urine specimens' evaluation were performed by trained microscopists who were blinded prior to analyzing the results. Before actual sample collection, volunteer samples from other studies, collected to examine the same parasites were processed by the laboratory

staff, and findings compared to those obtained in the parallel study. The two sets of results had over 95% agreement, assuring the procedures and the technologists were reliable.

### 3.9. Sample Collection

All eligible pupils that were randomly selected were provided with sample collection materials (Polly pot with scoop and tissue paper for stool sample and urine tube for urine specimen). An explanation with demonstration of how the samples are collected was provided before the pupils were released in small groups to discourage sample sharing. Few pupils were asked to repeat the whole sample collection procedures in the presence of the other pupils to ascertain that they well understood the whole sample collection processes. All pupils were provided with unique identification numbers that were linked to the samples that they provided.

### 3.10. Laboratory Procedures

#### 3.10.1. Stool testing by Kato-Katz

At the laboratory, stool samples were tested using the Kato-Katz method (41.7 mg template) for the detection of *Schistoma mansoni*. four slides were prepared, and the slides were allowed to clear for 24 hours before examination of schistosome eggs. The intensity of infection was expressed as eggs per gram (EPG) of feces.

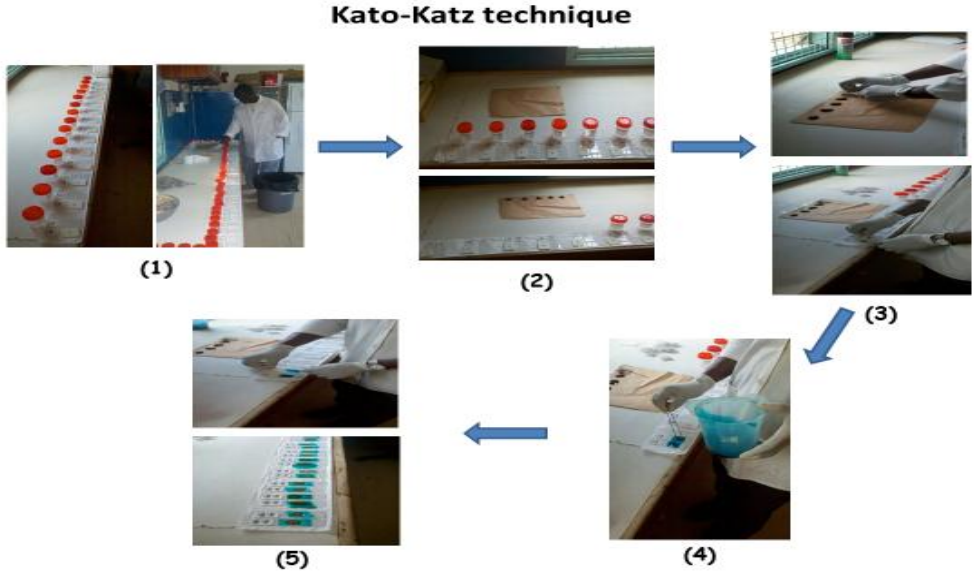


**Figure 3.10.1.1. Summary steps Kato Katz Assay**

### 3.10.2. Urine testing by POC-CCA


**Figure 3.10.2.1. POC-CCA Cassette**

(*Rapid Medical Diagnostics, Pretoria, South Africa*)

POC-CCA assay is a semi-quantitative rapid test that detects an antigen secreted by the adult Schistosoma worm and excreted in the urine of the host/man.

**Principle of the test:** After applying urine on the CCA test cassette, the urine CCA antigen if present will bind to the labelled monoclonal antibody on the CCA cassette forming an antibody-antigen complex. The solution then spreads over the strip where the antibody-antigen complex attaches to another monoclonal antibody immobilized at the test line. It then reacts with it and a pink-colored line appears at the Test line (T). The second is a procedural control line (C), which should always appear to ensure that the test is working correctly. The intensity of the line is qualitatively related to the intensity of infection.

Urine samples (one sample per child) collected one week before MDA were tested for positivity and band intensity using a commercially available POC-CCA assay (Rapid Medical Diagnostics, Pretoria, South Africa), according to the manufacturer's instructions. In summary, two drops of urine were added to the well of the testing cassette and allowed to absorb, then allowed to develop for a further 20 minutes, and results read. The intensity of the test band was compared to that of the control band to score the intensity of the POC-CCA assay results. Positive results were scored as "Trace" if the band was barely visible, "1+" if the test band was readily visible but less intense than the control band, "2+" if the test band was of equal intensity as the control band, and "3+" if the test band was more

intense than the control band. Tests were considered "invalid" if an internal control band did not appear, or, if the tests were left to develop for more than 25 minutes before being read. All samples were also tested for hematuria using dipsticks, since blood in urine may cause false positives.

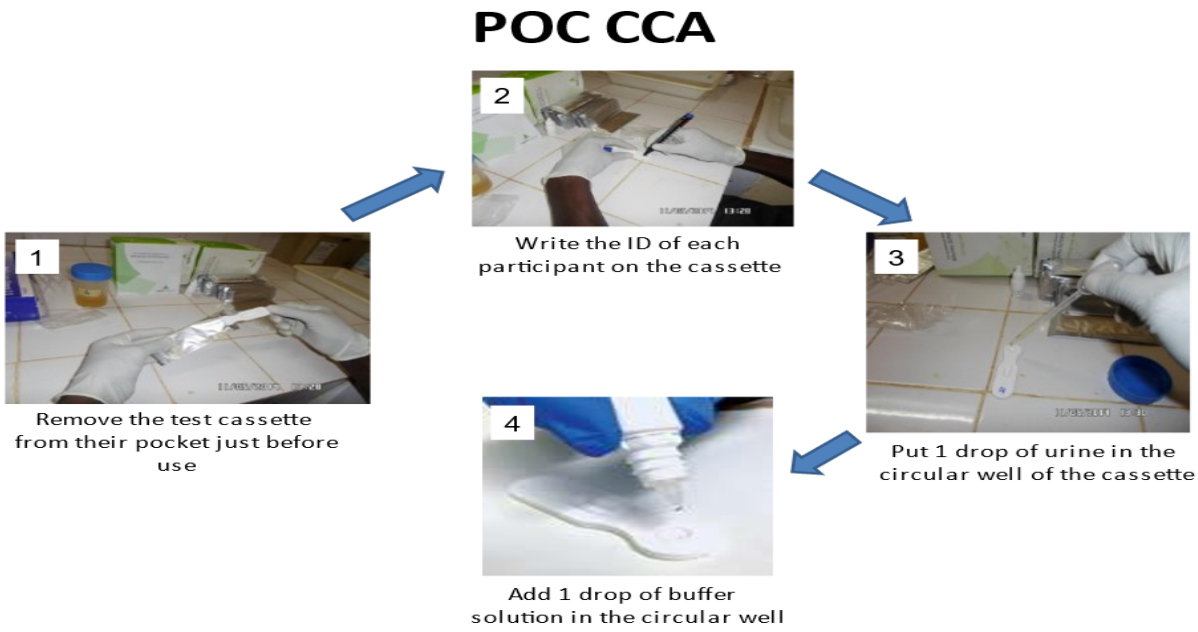


**Figure 3.10.2.2. Summary steps POC-CCA Assay**

### 3.10. Data Analysis

Egg counts were entered into printed data forms that had bar-codes unique to each participant. All results were then entered using CommCare® application installed in smartphones. The number of eggs per gram (EPG) of feces were calculated and used to estimate the infection intensity of the parasites using WHO (2002) guidelines for *S. mansoni* infections. Statistical analysis of the data was performed using STATA (v. 14), where a $p < 0.05$ was considered significant. The confidence interval was set at the level of 95%. Prevalence and intensity of the infection were obtained for each of the diagnostic tests. Data was tested for normality (using histogram and Shapiro-Wilk test) prior to analysis in order to determine whether to use parametric tests or their non-parametric alternatives. True positives (TP) were defined as the number of positive samples by both Kato-Katz and POC-CCA. True negatives (TN) were defined as the number of negative samples by both POC-

CCA and Kato Katz. False positives (FP) were defined as the number of positive samples by POC-CCA and negative samples by Kato Katz. Therefore, specificity = TN/(TN+FP) *100, sensitivity = TP(TP+FN) *100, positive predictive value PPV = TP/(TP+FP) *100, and negative predictive value NPV = TN/(TN+FN) *100. In this study, the performance of POC-CCA was evaluated against Kato-Katz as the reference test (gold standard).

The 2x2 contingency tables were also used to determine and compare the sensitivity and specificity between Kato Katz and POC-CCA. The strength/degree of agreement between POC-CCA test and Kato-Katz was assessed by Cohen's Kappa statistics (ƙ) according to previous studies (Coulibaly *et al.*, 2011a; Coulibaly *et al.*, 2013): $k < 0$ (no agreement), $k = 0.0–0.20$ (poor agreement), $k = 0.21–0.40$ (fair agreement), $k = 0.41–0.60$ (moderate agreement), $k = 0.61–0.80$ (substantial agreement), and $k = 0.81–1.0$ (almost perfect agreement). Receiver operating characteristic (ROC) curves were also used to compare the relationship between the two diagnostic tools per risk strata for each year.

### 3.11. Ethical Considerations

This study was approved by the School of Health Sciences, and the Board of Postgraduate Studies of Jaramogi Oginga Odinga University of Science and Technology. This study was nested in a bigger KEMRI study, which had earlier obtained research ethics approval from Maseno University Ethics Review Committee (MSU/DRP/MUERC/00538/18). Adequate information was given prospective study participants and their parents or guardians in the language they understood best (English, Kiswahili, or Dholuo). Informed consent for study participation was obtained from each parent or guardian of the children (9 - 12 years old), and assent obtained from each child. Recruitment was voluntary and enrollees were encouraged to ask questions concerning the research procedures, and their rights as participants. All information regarding the study participants was kept confidential: a coded, unique identification number was assigned to each participant and used only for sample tracking. All the data collected from the participants was kept in password-protected computers and physical files secured under lock-and-key, with strict access control.

### 3.12. Preventive chemotherapy with Praziquantel

MDA was implemented in every school calendar year by the National School Based Deworming Programme (NSBDP) and KEMRI. A proper coordination mechanism by KEMRI/SWAP and NSBDP ensured that the distribution of praziquantel happened each year after sample collection in the study schools. This was critical in monitoring the impact of the annual MDA by Kato Katz and POC-CCA assays. Drugs were distributed by trained school health teachers under the supervision of nurses who ensured drug compliance and dealt with cases Severe Drug Events (SAEs). The dates for drug distribution would be communicated to pupils and parents and encouraged on treatment day to ensure proper feeding to prevent side effects brough about by effect of PZQ to worm burden and empty stomach.

The NSBDP strove to attain effective treatment coverages (75% for SCH and STH) per school as recommended by WHO. Where effective treatment coverages were not achieved, treatment mop ups were conducted to improve the coverage.

## CHAPTER FOUR: RESULTS

This section provides summaries and presents in tables and graphs the findings of the study as per the research questions. The results are presented in text, tables, and graphs to provide clarity.

### 4.1: Demographic Characteristics of Participants

An equal number of participants were enrolled from the 8 schools (4 schools in low-risk stratum and 4 schools in high-risk stratum), n=329 each year. An almost equal number of participants were enrolled per risk strata (n=165 for low-risk stratum and n=164 for high-risk stratum). A fairly even proportion by gender was represented in the enrollment across the 3 years, with a mean age of 10.5 years to 10.6 years and a median age of 10 years (Table 4.1). Notably, more males than females were enrolled across the three years.

**Table 4.1. Demographic Characteristics of Participants**

| Characteristic | Year 1 (2019) | Year 2 (2020) | Year 3 (2021) |
|---|---|---|---|
| Number of Schools enrolled (n) | 8 | 8 | 8 |
| Number of participants enrolled (n) | 329 | 329 | 329 |
| **Gender** | | | |
| Male (n, %) | 188(57.1) | 192 (58.4) | 211(64.1) |
| Female (n, %) | 141(42.9) | 137(41.6) | 118(35.9) |
| **Risk Strata** | | | |
| Low-4 schools | 165(50.2) | 165(50.2) | 165(50.2) |
| High-4 schools | 164(49.8) | 164(49.8) | 164(49.8) |
| **Age** | | | |
| Mean age (±SD) | 10.5 (1.1) | 10.6 (1.0) | 10.5 (1.0) |
| Median age (±SD) | 10.0(9-12) | 10.0 (9-12) | 10.0 (9-12) |

### 4.2 Prevalence of S. mansoni by Kato-Katz and POC-CCA assays

#### 4.2.1. General prevalence of S. mansoni by Kato Katz and POC-CCA

Table 4.2 below presents the prevalence (P, %) of *Schistosoma mansoni* and soil-transmitted helminthiasis (STHs) and relative reduction in prevalence (RRP, %) and absolute reduction in prevalence (ARP, %) from year 1 (baseline) to year 3 (endline). Results indicate that the general prevalence of *S. mansoni* reduced across the 3 years, from 29.5% in 2019 to 28% in 2021 by KK and 70.3% (year 2019) to 47% (year 2021) by POC-CCA. However, the

prevalence of STH increased from 6.4% in 2019 to 6.7% in 2021. The overall relative reduction in prevalence of *S. mansoni* infection was 5.1% and 33.1% by KK and POC-CCA, respectively. The absolute reduction in prevalence was 1.5% and 23.3% by KK and POC-CCA, respectively.

**Table 4.2: Overall prevalence of Schistosoma mansoni and STH**

| Variable | Year 1 (2019) | | Year 2 (2020) | | Year 3 (2021) | | RRP (%) for *S. m* (Year 1-3) | ARP (%) for *S. m* (Year 1-3) |
|---|---|---|---|---|---|---|---|---|
| | *S. m* Prev. (%) | STH Prev. (%) | *S. m* Prev. (%) | STH Prev. (%) | *S. m* Prev. (%) | STH Prev. (%) | | |
| Kato-Katz | 29.5 | 6.4 | 19.5 | 4.9 | 28.0 | 6.7 | 5.1 | 1.5 |
| POC-CCA | 70.3 | N/A | 64.7 | N/A | 47.0 | N/A | 33.1 | 23.3 |

### 4.3. Prevalence of Schistosoma mansoni and STH in low and high-risk strata

The low-risk stratum showed an increase in prevalence of *S. mansoni* by KK from 3.0% in 2019 to 4.9% in 2021. However, the POC-CCA assay revealed a decrease with 54.8% relative reduction and 34.5% absolute reduction. In high-risk areas, both KK and POC CCA diagnostic tools revealed a reduction in prevalence of *S. mansoni* from 2019 to 2021; KK showed 13% RRP and 7.3% ARP while POCCCA had 15.7% and 12.2% RRP and ARR respectively. As indicated in the overall prevalence, the STH in low-risk stratum had increased prevalence across the years from 4.9% in 2020 to 7.3% in 2021.

**Table 4.3: Prevalence of Schistosoma mansoni and STH in low and high-risk strata**

| ***S. mansoni* prevalence** | | **Year 1 (2019)** | | **Year 2(2020)** | | **Year 3(2021)** | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | *S. m* Prev. (%) | STH Prev. (%) | *S. m* Prev. (%) | STH Prev. (%) | *S. m* Prev. (%) | STH Prev. (%) | **RRP (%) for *S. m* (Year 1-3)** | **ARP (%) for *S. m* (Year 1-3)** |
| **low risk (<10%)** | KK | 3.0 | 4.9 | 3.6 | 3.6 | 4.9 | 7.3 | ↑ | ↑ |
| | POC | 63.0 | N/A | 42.4 | N/A | 28.5 | N/A | 54.8 | 34.5 |
| **high risk (>20%)** | KK | 56.1 | 7.9 | 35.4 | 6.1 | 48.8 | 6.1 | 13.0 | 7.3 |
| | POC | 77.8 | N/A | 87.2 | N/A | 65.6 | N/A | 15.7 | 12.2 |

**↑ denotes increase in prevalence; KK= Kato-Katz; POC=POC-CCA**

### 4.4: Prevalence of intensity levels of *S. mansoni* infection by POC-CCA

The infection intensity was categorized according to WHO where egg counts of 1 to 99 constituted low infection intensity, egg counts of 100 to 399 were categorized of medium/moderate infection intensity while egg counts of 400 and above constituted heavy/high infection intensity.

Results by POC-CCA showed a general decrease of *S. mansoni* infection intensity from 2019 to 2021 across intensity levels. However, for the low level, the infection intensity increased in 2020 before dropping in 2021 (Figure 4.4.1). That is, for the low infection category, 42% of SAC had egg counts of 0-99 which is equivalent to trace and +1 of the intensity of the test band on the POC- CCA cassette., which increased to 44% of SAC in 2020 before steadily reducing to 30% in 2021. Notably, there were steady decreases in prevalence of infection intensity across the years for medium and high/heavy infection categories as determined by the intensity of the POC CCA test band equated as +2 for moderate intensity and ++3 for heavy infection.

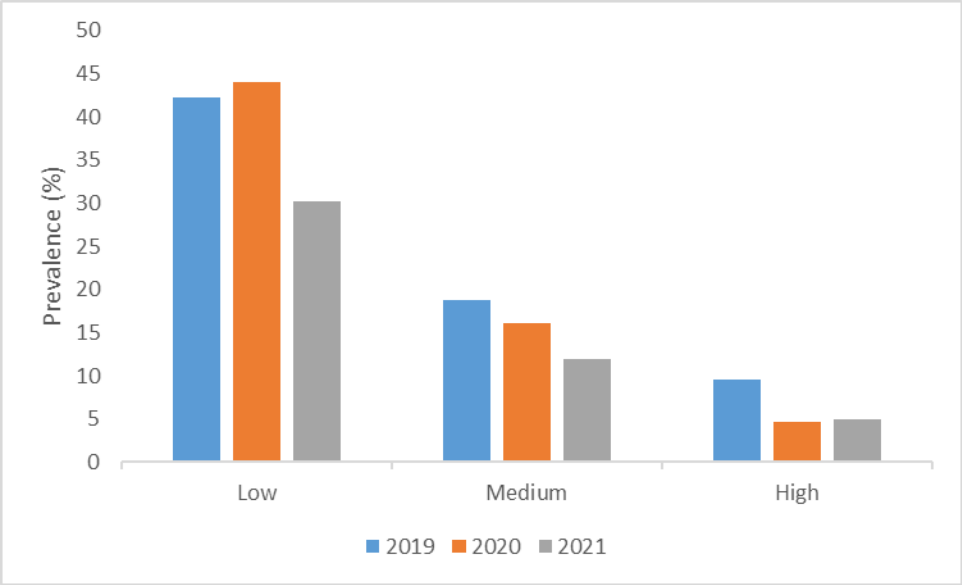


**Figure 4.4.1: Prevalence of intensity levels of *S. mansoni* infection by POC-CCA**

Kato Katz assay indicated fluctuations on prevalence of infection intensity in medium (egg counts of 100 to 399) and high/heavy (egg counts of >400) infection categories. Figure 4.4.2 displays the Kato-Katz assay results, which shows a decrease in prevalence for low intensity (prevalence of SAC with *Schistosoma mansoni* egg counts between 0-99) level from 2019 to 2021 (2019= 15%, 2020= 12% and 2021= 11%) but for medium (100 to 299 *S. mansoni* egg counts) and high (over 400 *S. mansoni* egg counts) intensity levels the prevalence decreases from 2019 to 2020 and later increased in 2021.

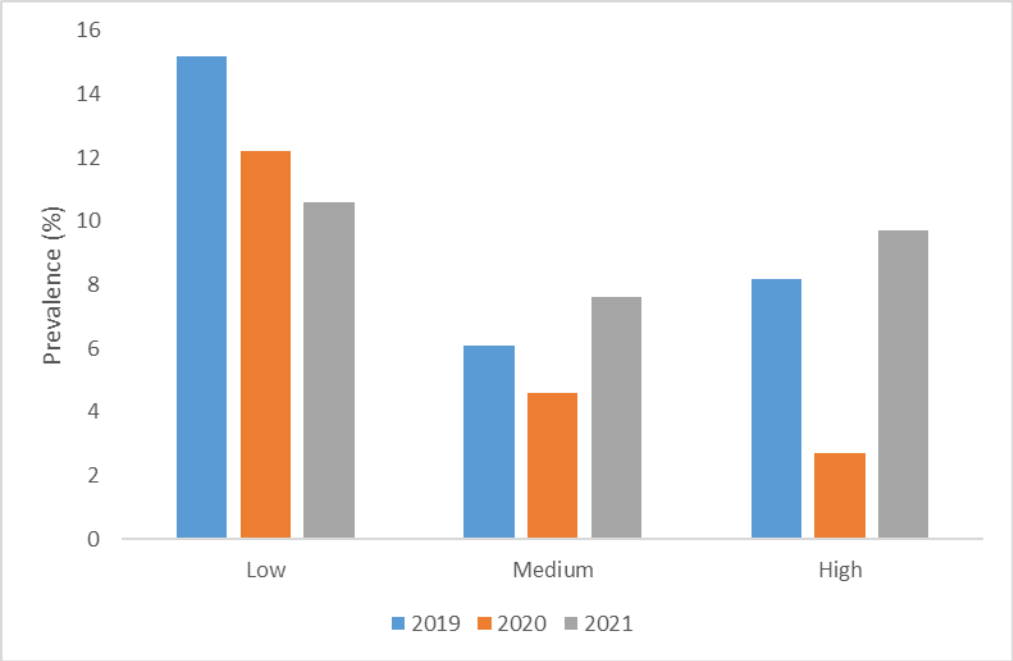


**Figure 4.4. 2: *Schistosoma mansoni* intensity levels by Kato-Katz**

The *S. mansoni* egg count data was tested for normality. Both the histogram plots and Shapiro-Wilk tests: 2019 ($w=0.45$, $p<0.001$), 2020 ($w=0.38.$, $p<0.001$), 2021($w=0.37$, $p<0.01$), which indicated that the data deviated significantly from a normal distribution.

### 4.5: Sensitivity, specificity, and degree of agreement of Kato-Katz and POC-CCA

The results indicate a poor agreement between the 2 diagnostic test in 2019 ($K=0.2005$, $p<0.001$), a fair agreement in 2020 ($K=0.2325$, $p<0.001$). But for 2021, the agreement was moderate ($K=0.5174$, $p<0.001$). Generally, across all the 3 years, POC-CCA reported higher sensitivity and negative predictive value and lesser specificity and positive predictive value than Kato Katz. In low prevalence areas, the sensitivity ranged between 87.5-100% while specificity ranged between 38.1-74.5%. In high-risk areas, the sensitivity ranged between 92.8-100% and specificity between 19.8-62.5% (Table 4.5.1).

**Table 4.5.1: Kappa test for degree of agreement between POC-CCA and Kato Katz tests**

| **2019(n=329)** | | **Kato-Katz** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Diagnostic Test | Results | Positive | Negative | Sensitivity | Specificity | Accuracy | PPV | NPV | Agreement (%) | k | P value | Interpretation |
| POC-CCA | Positive | 86 | 88 | 90.5 | 62.0 | 70.3 | 49.4 | 94.1 | 53.2 | 0.2005 | <0.001 | Poor agreement |
| | Negative | 9 | 144 | | | | | | | | | |
| **2020(n=329)** | | **Kato-Katz** | | | | | | | | | | |
| Diagnostic Test | Results | Positive | Negative | Sensitivity | Specificity | Accuracy | PPV | NPV | Agreement (%) | k | P value | Interpretation |
| POC-CCA | Positive | 64 | 149 | 100.0 | 43.8 | 54.7 | 70.0 | 100.0 | 54.71 | 0.2325 | <0.001 | Fair agreement |
| | Negative | 0 | 116 | | | | | | | | | |
| **2021(n=329)** | | **Kato-Katz** | | | | | | | | | | |
| Diagnostic Test | Results | Positive | Negative | Sensitivity | Specificity | Accuracy | PPV | NPV | Agreement (%) | k | P value | Interpretation |
| POC-CCA | Positive | 84 | 70 | 92.3 | 70.5 | 76.5 | 54.5 | 96.0 | 76.52 | 0.5174 | <0.0001 | Moderate agreement |
| | Negative | 7 | 167 | | | | | | | | | |

The low-risk stratum had significantly poor agreement between the 2 diagnostic tools across all the 3 years. With K=0.0360 in 2019, K=0.0449 in 2020 and K=0.1872 in 2021.

**Table 4.5.2: Kappa test for degree of agreement between POCCCA and Kato Katz tests (Low risk stratum)**

| **2019(n=165)** | | **Kato-Katz** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Diagnostic Test | Results | Positive | Negative | Sensitivity | Specificity | Accuracy | PPV | NPV | Agreement (%) | k | P value | Interpretation |
| POC-CCA | Positive | 5 | 99 | 100.0 | 38.1 | 40.0 | 4.8 | 100.0 | 37.76 | 0.0360 | 0.0410 | Poor agreement |
| | Negative | 0 | 61 | | | | | | | | | |
| **2020(n=165)** | | **Kato-Katz** | | | | | | | | | | |
| Diagnostic Test | Results | Positive | Negative | Sensitivity | Specificity | Accuracy | PPV | NPV | Agreement (%) | k | P value | Interpretation |
| POC-CCA | Positive | 6 | 64 | 100.0 | 59.7 | 61.2 | 8.6 | 100.0 | 61.21 | 0.0449 | 0.0018 | Poor agreement |
| | Negative | 0 | 95 | | | | | | | | | |
| **2021(n=165)** | | **Kato-Katz** | | | | | | | | | | |
| Diagnostic Test | Results | Positive | Negative | Sensitivity | Specificity | Accuracy | PPV | NPV | Agreement (%) | k | P value | Interpretation |
| POC-CCA | Positive | 7 | 40 | 87.5 | 74.5 | 75.2 | 14.9 | 99.2 | 75.15 | 0.1872 | 0.0001 | Poor agreement |
| | Negative | 1 | 117 | | | | | | | | | |

Results in Table 4.6 shows kappa analysis findings for the high-risk stratum, there was a poor level of agreement between KK and POC CCA assays in 2019(K=0.0692) and 2020 (K=0.1488) and a moderate agreement in 2021 (K=0.5557).

**Table 4.5.3: Kappa test for degree of agreement between POCCCA and Kato Katz tests (High risk stratum)**

| **2019(n=164)** | | **Kato-Katz** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Diagnostic Test | Results | Positive | Negative | Sensitivity | Specificity | Accuracy | PPV | NPV | Agreement (%) | k | P value | Interpretation |
| POC-CCA | Positive | 81 | 45 | 90.0 | 37.5 | 66.7 | 64.3 | 75.0 | 53.09 | 0.0692 | <0.001 | Poor agreement |
| | Negative | 9 | 27 | | | | | | | | | |
| **2020(n=164)** | | **Kato-Katz** | | | | | | | | | | |
| Diagnostic Test | Results | Positive | Negative | Sensitivity | Specificity | Accuracy | PPV | NPV | Agreement (%) | k | P value | Interpretation |
| POC-CCA | Positive | 58 | 85 | 100.0 | 19.8 | 48.2 | 40.6 | 100.0 | 48.17 | 0.1488 | 0.0001 | Poor agreement |
| | Negative | 0 | 21 | | | | | | | | | |
| **2021(n=164)** | | **Kato-Katz** | | | | | | | | | | |
| Diagnostic Test | Results | Positive | Negative | Sensitivity | Specificity | Accuracy | PPV | NPV | Agreement (%) | k | P value | Interpretation |
| POC-CCA | Positive | 77 | 30 | 92.8 | 62.5 | 77.9 | 72.0 | 89.3 | 77.91 | 0.5557 | <0.0001 | Moderate agreement |
| | Negative | 6 | 50 | | | | | | | | | |

### 4.6 Receiver Operating Characteristic (ROC) curves for POCCCA against Kato-Katz

The ROC curves below show the values of sensitivity vs. specificity as the value of the cut-off point moves from 0 to 1 for each year. The area under the curve (AOC) gives an idea of how well the model is able to distinguish between positive and negative values. The POC-CCA was plotted with KK as the gold standard. The ROC curves below (Figure 4.3a-f) shows that the POC-CCA was more sensitive than KK, and the sensitivity was much higher in high-risk areas. The area under the curve range between 0.60 to 0.81 for POC-CCA. This shows the ability of the POC-CCA tool to distinguish between positive and negative values.

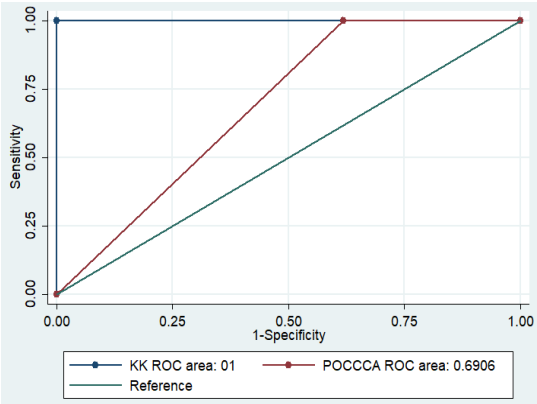


**Figure 4.6a: Area under the curve for low-risk areas (2019)**

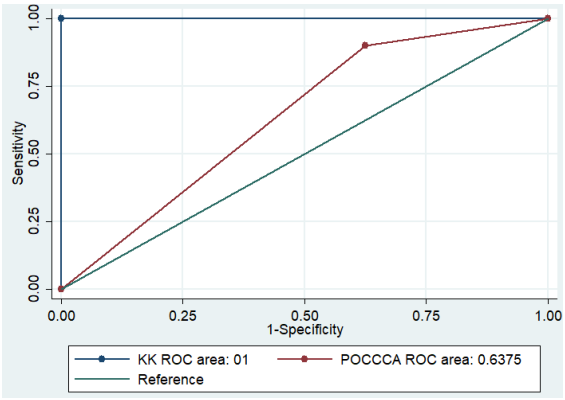


**Figure 4.6b: Area under the curve for high-risk areas (2019)**

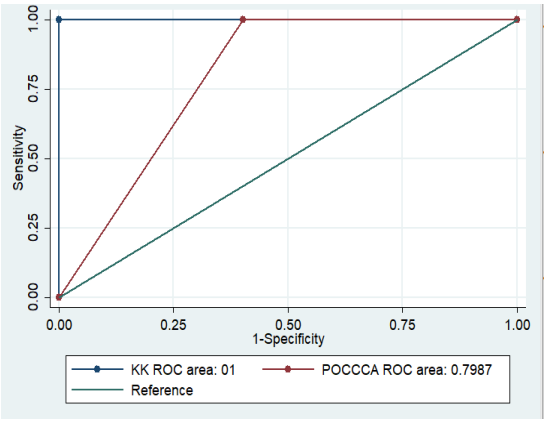


**Figure 4.6c: Area under the curve for low-risk areas (2020)**

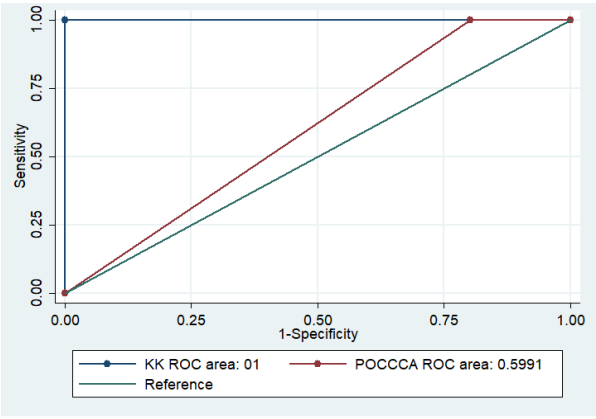


**Figure 4.6d: Area under the curve for high-risk areas (2020)**

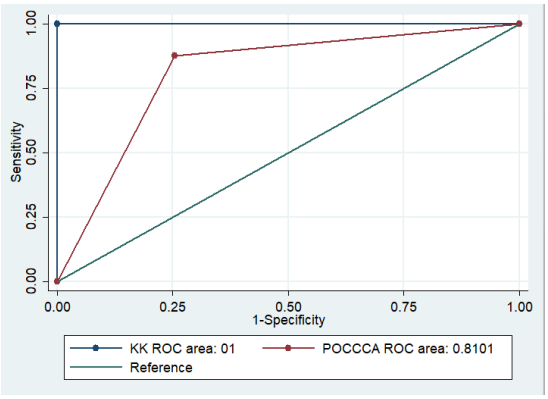


**Figure 4.6e: Area under the curve for low risk areas (2021)**

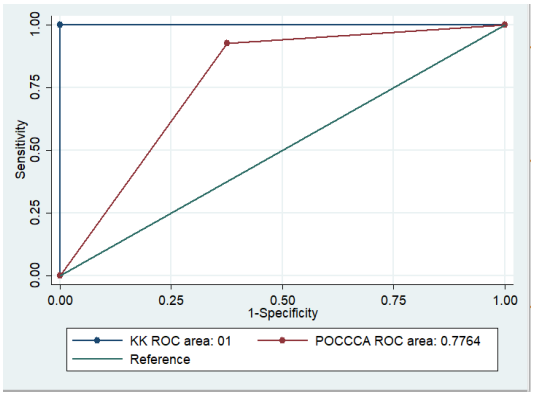


**Figure 4.6f: Area under the curve for high-risk areas (2021)**

# CHAPTER FIVE: DISCUSSION

For accurate identification of at-risk population groups for infection with schistosomiasis that would warrant preventive chemotherapy and for proper monitoring of interventions including MDA, an accurate and effective diagnosis technique should be emphasized (Becker *et al.*, 2011; Saelens & Gabriël, 2020). Kato Katz is currently the primary used method used for monitoring the impact of mass drug administration with praziquantel (PZQ) but has a number of limitations; low sensitivity especially when more rounds of treatment are expanded that suppress transmission of the disease and therefore in low prevalence areas Kato Katz may under-estimate the true prevalence (Legesse & Erko, 2008; Turner *et al.*, 2017).

## 5.1. Prevalence of *S. mansoni* by Kato-Katz and POC-CCA assays in low and high prevalence areas.

As per the first objective that sought to establish or determine the research sites to be endemic for intestinal schistsomiasis, the results agree with previous studies that supports the endemicity of *S. mansoni* along Lake Victoria. This study reported a significantly high overall schistosomiasis prevalence by the two diagnostic tests (Sang *et al.*, 2014; Siza *et al.*, 2015; Trienekens *et al.*, 2022). As expected, the prevalence in high prevalence areas was higher. Notably, in the low-risk stratum (<10%), the prevalences by POC-CCA were much higher across the three years. The observed difference in prevalence between the low and high-risk areas could be due to the focal distribution of *S. mansoni* in this case proximity to the lake for high-risk groups. Other studies have also shown that the proximity to the lake is inversely proportional to *S. mansoni* prevalence *(Odiere et al., 2012; Ruganuza et al., 2015).*

## 5.2. Sensitivity, Specificity, and degree of Agreement of Kato-Katz and POC-CCA assays in low and high prevalence areas.

Regarding objective two that sought to compare the sensitivity, specificity, and degree of agreement of Kato-Katz and POC-CCA assays in low and high prevalence areas, the findings across the years reveal high sensitivity of POC-CCA and lower specificity as compared to Kato Katz. This finding corroborates the findings by (Colley *et al.*, 2017; Colley *et al.*, 2020a; de Freitas Bezerra *et al.*, 2021; Mewamba *et al.*, 2021). However, there were more false negatives in low-risk areas by POC-CCA. The frequency of false negatives

was of great concern in this study. Other studies for instance (Okoyo *et al.*, 2018) reported a false negative rate of 1.3% almost similar to (Lindholz *et al.*, 2018) who reported at 1.7%. The POC-CCA test manufacturer states that low worm burden can lead to false-negatives (Rapid Medical Diagnostics 2018). On the other hand, there were a higher number of false positives in the high risk stratum possibly attributable to the high sensitivity level of POC-CCA assay (de Freitas Bezerra *et al.*, 2021).

Apart from high sensitivity, POC-CCA also recorded a higher accuracy in both low and high risk areas agreeing with a previous study by (Lindholz *et al.*, 2018; Okoyo *et al.*, 2018) which demonstrated that the POC-CCA has higher sensitivity and accuracy in low prevalence settings and (Kittur *et al.*, 2016) who stated that in areas having <50% prevalence, the POC-CCA is more sensitive than Kato Katz. Even on using 4 slides of Kato Katz thick smears, the POC-CCA assay proved more sensitive than Kato Katz in this setting. Considering that the sensitivity of the Kato Katz test using a single stool sample is likely to be low (Lamberton *et al.*, 2014), the effect is miss out infections and therefore continued transmission. The lack of concordance between these two tools makes translation of results as per the guidelines difficult.

There has been a lot of questions surrounding the manufacturing and batch numbers for POC-CCA kits and how this affects the results. This study used different batch numbers for POC-CCA kits, but this did not affect our findings. This finding contradicts previous studies including a study by (Viana *et al.*, 2019b) which informs that different POC-CCA batches tested on same urine sample provide contrary results and (Graeff-Teixeira *et al.*, 2021a) who also found out that different POC-CCA batches provide different specificities and that manufacturers should optimize the production to ensure reproducibility and quality of the assay.

Comparing the prevalence as reported by the two diagnostic techniques, the POC-CCA and Kato Katz tests reported a higher difference in prevalence in low-risk settings. In high-risk settings the difference was minimal. Moreover, the degree of agreement as revealed by Cohen's kappa test stated a low agreement between POC-CCA and Kato-Katz assays in

low-risk stratum and a poor/moderate agreement in high-risk areas. This aligns with previous studies that inform the two tests tending to agree when the prevalence is higher and disagreeing when the prevalence is low (Mewamba et al., 2021).

### 5.3. Effectiveness of Kato-Katz and POC-CCA assays in monitoring of preventive chemotherapy.

On objective three that sought to determine the effectiveness of Kato-Katz and POC-CCA assays in monitoring of preventive chemotherapy, overall results reported decline in the prevalence and intensity of *S. mansoni* across the years from 2019 to 2021 following annual rounds of MDA, reported by both POCCCA and Kato Katz. This was in line with previous study that recorded a reduction in prevalence after MDA (Muok *et al.*, 2013). A similar pattern was seen in the low and high prevalence areas where the prevalence of *S. mansoni* decreased over time following annual rounds of MDA as reported by both POCCCA and Kato Katz assays. However, this was not the case in low prevalence areas as only the POCCCA was able to report the decrease in prevalence over the years, while the Kato Katz reported an increase in prevalence over time. Possibly, the observed difference could be attributable to high sensitivity and accuracy nature of the POCCCA assay in low prevalence areas as shown by other studies (Okoyo *et al.*, 2018; Siqueira *et al.*, 2016). In contrast, Kato Katz being the primary diagnostic tool for monitoring the impact of national school-based deworming program for *S. mansoni* was not sensitive enough to monitor the reduction in *S. mansoni* prevalence in low prevalence areas. Therefore, these results show that POCCCA is more effective due to high sensitivity as a screening tool for monitoring the impact of MDA in low prevalence areas. This equally corroborates with a study by (Okoyo *et al.*, 2018) which recommends use of POC-CCA over Kato-Katz in low transmission settings.

The prevalence detected by POC-CCA was always higher than that of Kato Katz. Previous studies have demonstrated similar results when the two diagnostic tools are compared (Colley *et al.*, 2013; Straily *et al.*, 2022). Moreover, unlike Kato-Katz, the POC-CCA assay reported relatively higher prevalence in the low prevalence regions, this was contrary to our expectations since these were areas known to be of low prevalence and further away from the lake shores.

# CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

## 6.1: Conclusion

This study demonstrates that the POC-CCA assay is an effective, sensitive and accurate screening tool for *Schistosoma mansoni* infection in both low and high prevalence areas as compared to Kato Katz. There was poor agreement between POC-CCA and Kato-Katz in low prevalence areas, and the difference in POC-CCA and Kato-Katz assays results in high prevalence areas is little compared to low prevalence areas, the two tending to agree more in high *S. mansoni* transmission settings. Because the prevalence of *S. mansoni* (as shown by the two tests) would decrease over time following annual rounds of MDA, only POC-CCA assay was able to monitor the decrease of prevalence in both low and high-risk areas. Therefore, the POC-CCA could be used in 1). Mapping or determining the prevalence of *Schistosoma mansoni* in both low and high transmission settings due to its high sensitivity and 2). Monitoring and evaluation of control and elimination programs for *S. mansoni* in both high and low prevalence areas. Critical to note is the possibility that a good number of the positives by POC CCA could be false may lead to overtreatment and administration of MDA to communities that might not need it, increasing the costs incurred in treatment and monitoring of interventions.

The study findings are relevant to the Kenya National and County governments and NTD partners as policy makers and implementers respectively in their efforts to control and eliminate schistosomiasis in the country. These results are also applicable in regional and global settings where the fight against schistosomiasis is underway.

## 6.2. Recommendations

This study recommends 1). The adoption of POC-CCA assay for the screening/mapping of schistosomiasis to ensure accurate measurements of its prevalence in both low and high transmission areas, while Kato-Katz should still be used to examine worm burden, particularly in high-transmission areas and 2). Monitoring and evaluation of the performance of mass drug administration for control and elimination of *S. mansoni*.

### 6.3 Suggestions for Future Research

This study recommends that more research should be conducted on POC-CCA, particularly focusing on place-specific factors that may affect its sensitivity, specificity in order to enhance its efficacy in monitoring and evaluation of *S. mansoni* control programs. Such a study should also consider the potential confounding from common co-morbidities in the region, mainly parasitic and viral. This study should apart from spreading over a wider geographic area also include both young and adult populations.

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## APPENDICES

### Appendix 1: Child Enrollment Questionnaire

**School Name**: _____**School Id**: _____ **Year: _____**

| **Child's Name** | **Parent\ Guardian name** | **Child Age** (Years) | **Child Sex** **M**=Male **F**=Female | **Child ID (Put Barcode Label)** | **Class** | **Consent** **Y**=yes **N**=no | **Assent** **Y**=yes **N**=no | **Stool collected** **Y**=yes **N**=no **(DATE)** | **Urine collected** **Y**=yes **N**=no **(DATE)** | **Remarks** |
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## Appendix 2: Stool Lab Results Form

School Name: _____School Id: _____

| **Date** | **Participant ID** | **Slide A *S. mansoni* results**<br><br>**#eggs** | **Slide B *S. mansoni* results**<br><br>**#eggs** | **Slide C *S. mansoni* results**<br><br>**#eggs** | **Slide D *S. mansoni* results**<br><br>**#eggs** | **Remarks** |
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**3. Urine Lab Result Form**

**SCHOOL NAME_____SCHOOL ID: _____ YEAR: _____**

| **Date** | **Person ID (Put barcode label)** | **Hematuria Dipstick result** 1=Pos 0=Neg 2=Not tested | **POC CCA Result** 1=Pos 0=Neg 2=Not tested | **CCA band intensity (+ve samples only)** 1 = Trace 2 = + 3 = ++ 4= +++ | **Remarks** |
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## APPENDIX 3: ETHICAL APPROVALS

**MASENO UNIVERSITY ETHICS REVIEW COMMITTEE**

Tel: +254 057 351 622 Ext: 3050
Fax: +254 057 351 221
Private Bag – 40105, Maseno, Kenya
Email: muerc-secretariate@maseno.ac.ke

**FROM**: Secretary - MUERC

**DATE**: 25th June, 2018

**TO**: Dr. Maurice Odiere
Safe Water and Aids Project (SWAP)
P.O. Box 3323-40100, Kisumu Kenya

**REF**: MSU/DRPI/MUERC/00538/18

**RE: Evaluation of the Point of Care Circulating Cathodic Antigen (POCCCA) Assay for Mapping and Monitoring Mass Drug Administration (MDA) for *Schistosoma mansoni* Control Program in Western Kenya. Proposal Reference Number MSU/DRPI/MUERC/00538/18**

This is to inform you that the Maseno University Ethics Review Committee (MUERC) determined that the ethics issues raised at the initial review were adequately addressed in the revised proposal. Consequently, the study is granted approval for implementation effective this 25th day of June, 2018 for a period of one (1) year.

Please note that authorization to conduct this study will automatically expire on 24th June, 2019. If you plan to continue with the study beyond this date, please submit an application for continuation approval to the MUERC Secretariat by 15th May, 2019.

Approval for continuation of the study will be subject to successful submission of an annual progress report that is to reach the MUERC Secretariat by 15th May, 2019.

Please note that any unanticipated problems resulting from the conduct of this study must be reported to MUERC. You are required to submit any proposed changes to this study to MUERC for review and approval prior to initiation. Please advice MUERC when the study is completed or discontinued.

Thank you.

MASENO UNIVERSITY SECRETARY 25 JUN 2018 ETHICS REVIEW COMMITTEE

Dr. Bonuke Anyona,
Secretary,
Maseno University Ethics Review Committee.

Cc: Chairman,
Maseno University Ethics Review Committee.

REPUBLIC OF KENYA

**MINISTRY OF EDUCATION**

**State Department of Basic Education**

COUNTY DIRECTOR OF EDUCATION
SIAYA COUNTY
P.O. BOX 564
SIAYA

E-mail:cdesiaya2016@gmail.com

When replying please quote
SCA.10 /VOL.I

Tuesday, April 04, 2017

Emmy Kavere, MPH
Study Co-ordinator
Safe Water & Aids Project

**RE: AUTHORITY TO CONDUCT A STUDY ON DEFINING CUT-OFFs FOR POINT-OF- CARE CIRCULATING CATHODIC ANTIGEN (POC-CCA) ASSAY IN PRIMARY SCHOOLS**

Reference is made to your letter dated 28th March, 2017 on the above referenced subject.

Your request to conduct the study in primary schools is approved by this office. It is noted that ethical approval was granted by KEMRI (SSC No.3279). Please ensure that at no time should the implementation of school curriculum be interfered with by your study. Arrange and plan well.

By a copy of this letter the Field Education Officers, Head teachers and teachers are requested to accord you the necessary assistance.

**MASIBO J. KITUYI**
**COUNTY DIRECTOR OF EDUCATION**
**SIAYA COUNTY**

**c.c.**

Dr. Maurice R. Odiere, Ph. D
Principal Investigator, POC CCD Study

**JARAMOGI OGINGA ODINGA UNIVERSITY OF SCIENCE AND TECHNOLOGY**

**SCHOOL OF HEALTH SCIENCES**

**INTERNAL MEMO**

**TO:** Director, Board of Postgraduate Studies **DATE:** 1 /03/2022

**FROM:** Postgraduate Coordinator - SHS **REF:** JOOUST/SHS/217

**SUBJECT: ETHICAL APPROVAL (GEOFFREY MUCHIRI NJUHI- H153/4201/2016)**

The above matter refers.

This is to verify that the above mentioned is a postgraduate student in JARAMOGI OGINGA ODINGA UNIVERSITY OF SCIENCE AND TECHNOLOGY in the School of Health Sciences undergoing a course leading to MASTER in Epidemiology and Biostatistics.

He has completed his course work. On 16th July, 2021, at departmental level, he defended his proposal. After working on the comments given and with the approval of his supervisors as evidenced in the signed proposal, the title is "*Diagnostic Performance of Kato Katz and Circulating Antigen assays for Detection of Schistosoma mansoni in Low and high prevalence areas in western Kenya*''.

The purpose of this letter therefore is to request you to write him an introductory letter so that he can submit his proposal for ethical approval at JOOUST Ethics Committee.

Attached is the abstract and copy of a proposal for your action.

Thank you.

**Esther Osir, PhD**
Postgraduate Coordinator
School of Health Sciences

**Copied, Dean, SHS**

# JARAMOGI OGINGA ODINGA UNIVERSITY OF SCIENCE & TECHNOLOGY

BOARD OF POSTGRADUATE STUDIES

*Office of the Director*

Tel. 057-2501804
Email: bps@jooust.ac.ke

P.O. BOX 210 - 40601
**BONDO**

**Our Ref**: H153/4201/2016

**Date:** 15th March 2022

## TO WHOM IT MAY CONCERN

## RE: GEOFFREY MUCHIRI NJUHI - H153/4201/2016

The above person is a bonafide postgraduate student of Jaramogi Oginga Odinga University of Science and Technology in the School of Health Sciences pursuing Master of Science in Epidemiology and Biostatistics. He has been authorized by the University to undertake research on the topic: **"Diagnostic Performance of Kato Katz and Circulating Cathodic Antigen Assays for Detection of *Schistosoma mansoni* in low and High Prevalence Areas and their Utility in Monitoring Preventive Chemotherapy in Western Kenya".**

Any assistance accorded him shall be appreciated.

Thank you.

JARAMOGI OGINGA ODINGA
DIRECTOR BOARD OF
POST GRADUATE STUDIES
DATE

Prof. Dennis Ochuodho
**DIRECTOR, BOARD OF POSTGRADUATE STUDIES**

10TH February 2019

To:

The School of Health Sciences,

Jaramogi Oginga Odinga University of Science and Technology

P.O Box 210-40601

Bondo.

Dear Sir/Madam

**RE: LETTER OF AUTHORIZATION LETTER TO COLLECT DATA ON STUDY**

This is to authorize Geoffrey Muchiri Njuhi REG No. H132/4201/2016 to collect data and use data from our larger study titled "**Evaluation of the Point-of-Care Circulating Cathodic Antigen (POC-CCA) assay for Mapping and Monitoring Mass Drug Administration (MDA) for *Schistosoma mansoni* control program in western Kenya"** for his Masters of Science in Epidemiology and Biostatistics project. This larger study is being conducted at Safe Water and Aids Project (SWAP) in collaboration with KEMRI.

If any clarification is required, please feel free to contact me.

Sincerely,

Maurice Odiere, PhD

Principal Investigator-POC-CCA Study

KEMRI & Safe Water and AIDS project(SWAP) Kenya

Email: mauriceodiere@gmail.com