IDENTIFYING ENTRY POINTS FOR INTEGRATED DISEASE CONTROL PROGRAMS AND EFFECTIVE PREVENTION AND CONTROL STRATEGIES FOR MALARIA AND SCHISTOSOMIASIS IN TANZANIA AND BENIN

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Abstract

Malaria and schistosomiasis are two diseases that are preventable, treatable, and affect people living in vulnerable circumstances - in particular, young children in rural areas of sub-Saharan Africa. Yet, in sub-Saharan Africa in 2021, there were an estimated 237 million malaria cases and 226 million people requiring preventative treatment for schistosomiasis. Important prevention and control strategies for malaria include long-lasting insecticidal nets, access to early diagnostics and treatment with artemisinin-based combination therapy, among others; while prevention and control strategies for schistosomiasis primarily focus on mass drug administration campaigns that deliver praziquantel tablets without prior diagnosis to at-risk populations [23–26]. There is a critical need to revise and optimize current disease prevention and control strategies for malaria and schistosomiasis to meet the goals set out by the Sustainable Development Goals – especially given that current strategies are vulnerable to disruptions such as those experienced during the COVID-19 pandemic. This doctoral thesis aimed to understand population vulnerabilities, infection exposures and risk factors for malaria and schistosomiasis to inform targeted, and possibly integrated, interventions using two mixed-methods studies in two different settings (Tanzania and Benin) and a scoping review. We found that malaria and schistosomiasis overlap geographically and co-infect the same people living in vulnerable circumstances in the Mwanza Region of Tanzania, and that there remains widespread exposure to both diseases despite ongoing prevention and control efforts. The results from the study in Benin demonstrate that malaria prevention and control strategies are vulnerable to disruptions and there is a need to emphasize the importance of sustaining malaria control interventions during health emergencies. The results from the scoping review concludes that there is an opportunity to link control programs to increase access and coverage of interventions to improve

outcomes for malaria, schistosomiasis, and their co-infection. We suggest that current prevention and control measures for malaria and schistosomiasis are not sufficient in reducing disease exposures and propose to combine interventions within and between disease prevention and control programs to increase program resiliency.

CHAPTER 1

Introduction

1.1.Introduction

Malaria and schistosomiasis are two diseases that are preventable, treatable, and affect people living in vulnerable circumstances , in particular, children under 14 years old and pregnant women in sub-Saharan Africa [14,27–30]. Yet, in sub-Saharan Africa in 2021, there were an estimated 237 million malaria cases (96% of the global burden) and 226 million people requiring preventative treatment for schistosomiasis (90% of the global burden) [14,31,32]. To put these numbers in perspective, 230 million people equals more than 6 times the population of Canada or half of the global burden of diabetes [33,34]. While malaria is widely recognized, schistosomiasis remains relatively unknown. Schistosomiasis is one of the twenty-one Neglected Tropical Diseases (NTD), and as the name suggests, it is a disease that primarily affects people living in vulnerable and marginalized circumstances in tropical areas of the world, and has historically been neglected by funding agencies [35]. While schistosomiasis does not cause the same level of mortality as malaria (estimated 12,000 deaths per year [36] compared to more than 600,000 for malaria [37]), it causes significant morbidity, estimated at 1.6 million disability adjusted life years annually in 2019[38].

Human malaria is caused by five different *Plasmodium* parasites and transmitted by the bite of infected *Anopheles (An.)* vector mosquitoes [39]. Several important tools to control and prevent malaria have been introduced in the past two decades, including long lasting insecticidal nets (LLIN), early diagnosis with rapid diagnostic tests, a vaccine, and treatment with artemisinin-based combination therapy [40], with LLINs being the main vector control tool for preventing malaria. In sub-Saharan Africa, there are two forms of schistosomiasis caused by two different *Schistosoma* species each with their respective snail intermediate hosts [23,41]. Prevention strategies for schistosomiasis have primarily focused on mass drug administration (MDA)

campaigns that deliver Praziquantel tablets without prior diagnosis to at-risk populations in endemic areas, at a frequency that depends on the endemicity of the community to reduce worm burden [23–26]. In contrast with malaria, schistosomiasis has limited strategic interventions and there remains significant gaps in the scientific understanding, diagnostics, and other effective interventions[42].

The connection between malaria and schistosomiasis may not be readily apparent given the historical lack of integration of funding and initiatives targeting these diseases. However, throughout this thesis, it will be argued that the prevention and control of these two diseases could be viewed as a singular and integrated challenge, rather than separate and siloed problems. As a primary consideration, malaria and schistosomiasis are known to overlap geographically, co-infect people living in vulnerable circumstances (i.e., school-aged children), share common risk factors, and have the potential for integrated control strategies.

The control and elimination of malaria was addressed in the Millennium Development Goals (MDGs) (specifically MDG 6: combat HIV/AIDS, malaria and other diseases) and was further targeted by the Sustainable Development Goals (SDGs) (specifically SDG 3.3: by 2030, [we should] end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases") [43,44]. One important change from MDG 6 to SDG 3.3 was the explicit inclusion of NTDs which were only previously included as 'other diseases' [44,45]. The SDGs are a group of 17 interrelated goals set by the United Nations for 2030 that provide a global framework to address global challenges such as poverty, hunger, diseases, and discrimination against women and girls [46]. The goals are interrelated because progress in one goal will affect the outcomes of others. This is particularly true for malaria and schistosomiasis elimination, which can be achieved by targeting

multiple SDGs, including but not limited to SDG 3: good health and well-being, and SDG 6: access to safe and affordable water and sanitation [46–49]. Therefore, just like the interrelated nature of the SDGs, this thesis will identify opportunities and entry points for integrated malaria and schistosomiasis prevention and control.

Current prevention and control strategies for malaria and schistosomiasis are valuable and effective, but it is important to recognize their limitations. Malaria and schistosomiasis prevention and control strategies depend on human uptake and adherence which are limited by the extent of their accessibility and acceptability by the population. Strategies that rely on individuals to take action are vulnerable to disruptions, including those experienced during the COVID-19 pandemic and from impacts due to climate change. For example, malaria cases and deaths in the African Region both increased from 2019 to 2020 from 213 million to 228 million and 534 000 to 602 000, respectively - likely due to a decrease in outpatient attendance, a decrease in malaria testing during the initial phase of the pandemic, and disruptions in LLIN distribution, resulting in a reduction in treatment access and disease prevention [50]. As for schistosomiasis, the impact of MDA delays during the pandemic depended on the baseline prevalence, burden of infection in adults, duration of delay, and the stage of the MDA program [51], where disruptions were modelled to have a greater impact in areas with high transmission due to the greatest risk of resurgence [52].

As highlighted in the title of this thesis, “Identifying Entry Points for Integrated Disease Control Programs and Effective Prevention and Control Strategies for Malaria and Schistosomiasis in Tanzania and Benin”, the challenge does not lie in identifying solutions and treatments for these two diseases, but rather innovating more efficient strategies for their delivery and implementation. The goal of this research is thus to understand population vulnerabilities and to

identify infection exposures and risk factors for malaria and schistosomiasis across two different settings to help identify entry points for integrated disease control (or determine whether integration is a viable solution) for malaria and schistosomiasis.

1.2. Thesis Organization

This thesis is organized in an article format following the University of Ottawa doctoral thesis guidelines. This thesis research began amidst the challenging circumstances of the COVID-19 pandemic, which presented unique challenges and restrictions (i.e., reduced interaction and collaboration opportunities with in-country partners, travel restrictions, and increased uncertainties). Despite these obstacles, this research leveraged ongoing malaria intervention studies in Tanzania and Benin to form a cohesive body of work that examines risk factors for malaria and schistosomiasis in different geographic settings using mixed-methods approaches. As a mixed-methods epidemiologist, the epistemological stance of this thesis is grounded in pragmatism, recognizing that both quantitative and qualitative approaches are essential for a comprehensive understanding of the thesis question and goals. A brief overview of each chapter is provided below:

1.2.1 Chapter 1: Introduction

This section introduces malaria and schistosomiasis as two major preventable and treatable parasitic vector-borne diseases that are a particular threat to young children in sub-Saharan Africa. It emphasizes how current disease prevention and control strategies for malaria focus on LLINs and early diagnosis and treatment with artemisinin-based combination therapy, while prevention and control strategies for schistosomiasis rely heavily on MDA of praziquantel tablets. This introduction is followed by an overview of the thesis objectives and the conceptual

framework used throughout the thesis to fulfill these objectives. The first chapter concludes with a brief description of the problem addressed throughout the thesis – namely that there is a need for sustained effort and revised control strategies for malaria and schistosomiasis in order to attain the targets set out by the SDGs. We conclude this chapter by proposing one approach to achieve these goals which is to identify potential entry points for integrated disease prevention and control.

1.2.2 Chapter 2: Background

The second chapter delves into a literature review of factors associated with malaria and schistosomiasis infection to support the conceptual framework used throughout the thesis. This chapter then provides a rationale for identifying opportunities for local integrated control strategies using the socio-ecological framework.

1.2.3 Chapter 3: Methods

The third chapter provides a rationale and explanation of the methods used throughout the thesis, beyond what was described in each manuscript. I first present a comprehensive overview of all three study designs then further provide a detailed explanation of all statistical approaches used in the subsequent thesis manuscripts (i.e., variable definition and derivation, choice of appropriate statistic tool to use, model building rationale).

1.2.4 Chapter 4-6: Articles

Chapters four through six contain my thesis articles. For each article, I include a preface with my contribution to each project and ethics approval obtained to carry out the project. The first article of the thesis is titled “Assessing risk factors for malaria and schistosomiasis among children in

Misungwi, Tanzania, an area of co-endemicity: a mixed methods study" where I focused on understanding population vulnerability and risk factors for malaria and schistosomiasis. The findings from this article highlight the widespread exposure to malaria and schistosomiasis among children in Misungwi, Tanzania, and that integrated or supplementary control strategies are necessary to reduce disease transmission. This article was accepted to PLOS Global Public Health on October 18, 2023 [53]. The second article of the thesis is titled "Community-level impacts of the coronavirus pandemic on malaria prevention and health-seeking behaviours in rural Benin: a mixed methods study" where I focused on assessing the impact of the COVID-19 pandemic on community-level malaria prevention and health seeking practices. The findings from this article highlight that there were minimal community-level impacts of the coronavirus pandemic on malaria prevention and health seeking behaviours in rural Benin, emphasizing the importance of efforts to sustain malaria prevention and control interventions in the context of the COVID-19 pandemic. This article was published in PLOS Global Public Health on May 19, 2023 [54]. The third article of the thesis is titled "Have there been efforts to integrate malaria and schistosomiasis prevention and control programs? A scoping review of the literature" which identifies whether there have been previous efforts to integrate malaria and schistosomiasis programs. The findings from this article suggest that there is an opportunity to link control programs to increase access and coverage of interventions to improve outcomes for malaria, schistosomiasis, and their co-infection. This article was accepted to PLOS Neglected Tropical Diseases on January 24, 2024[55].

1.2.5 Chapter 7: Discussion

Chapter seven summarizes the overall thesis findings and provides recommendations. Briefly, it states that malaria and schistosomiasis overlap geographically and co-infect the same people

living in vulnerable circumstances and that there remain widespread exposures to both diseases despite ongoing prevention and control efforts. We then provide future recommendations for research, which include the evaluation of integrated malaria and schistosomiasis interventions to increase program resiliencies, especially during disruptions such as those experienced during the COVID-19 pandemic. We also emphasize the need for environmental control strategies such as access to safe water and sanitation facilities to inform public health guidelines and further sustain malaria and schistosomiasis prevention and control.

1.3. Conceptual Framework

This thesis uses a conceptual framework that was inspired by the socio-ecological model and framework for prevention defined by the Centers for Disease Control and Prevention in the United States of America [2] to describe factors associated with malaria and schistosomiasis disease transmission that span across four levels (individual, relationships, community, and physical environment) (Fig. 1.1) [56,57]. This conceptual framework is crucial to understanding the complex and interrelated factors that enable and prevent malaria and schistosomiasis transmission and human disease. The processes and pathways in the conceptual framework will be described in detail in the literature review (chapter 2).

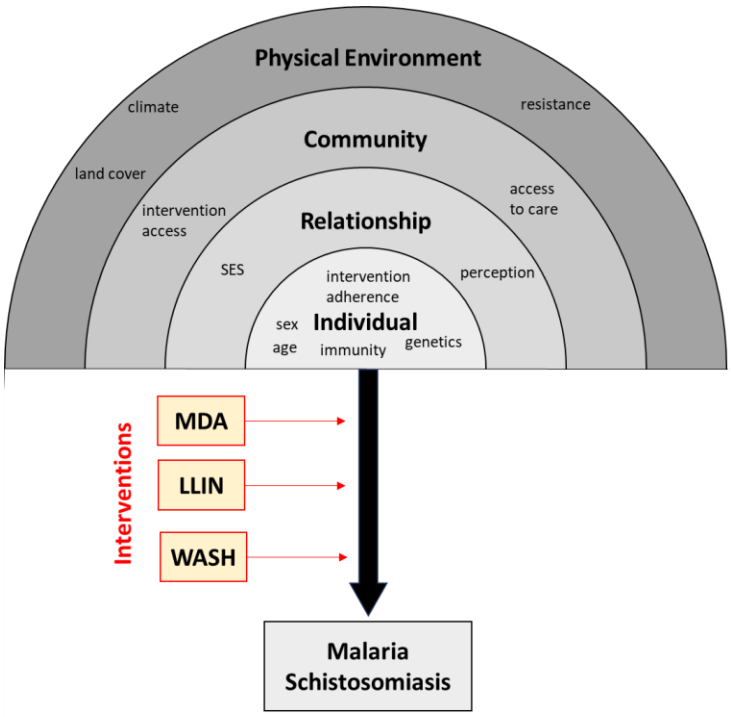

Fig. 1.1 A conceptual framework to describe the complex interaction of factors associated with malaria and schistosomiasis disease transmission and their influence on prevention and control strategies adapted from the social-ecological model defined by the Centers for Disease Control and Prevention in the United States [2]. The framework shows key factors for each level that are described further in thesis chapter 2. Abbreviations: MDA: mass drug administration; WASH: water, sanitation, hygiene, LLIN: long lasting insecticidal nets; SES: socioeconomic status.

The individual level lies at the core of the framework, but the order of the levels holds little significance due to the interrelated nature of the framework. The individual level focuses its attention on a singular person at risk for disease (i.e., a child) and factors that increase their own likelihood of exposure and susceptibility to disease. This includes their biological features and non-biological factors that are either intrinsic to an individual (i.e., age, sex) or extrinsic to an individual (i.e., adherence to intervention), respectively. Disease is not solely dictated by an individual; the next level in the framework includes a person's social circle and relationships that can increase their risk of exposure to diseases and adherence with prevention and control

strategies. This encompasses factors such as a family's socioeconomic status that could impact their housing structure which could increase the risk of a family's exposure to malaria by allowing mosquitoes to enter their home [12,63], or can determine their access to safe water and sanitation facilities, or an individual's knowledge and behaviours that could be influenced by a friend or a family member's experience during a public health campaign (e.g., side effects during an MDA). Now broadening the focus, the following level of the framework includes a person's community, which impacts a person's vulnerability to disease and their ability to receive timely and adequate care. For example, access to a health centre or the local availability of diagnostic and treatment capabilities all play a crucial role in disease transmission and control. The broadest and final level of this framework includes the physical environment in which a person lives. Environmental determinants include factors that create favourable conditions for malaria and schistosomiasis vectors and parasites such as: climate, land cover, and distance and exposure to breeding sites, as well as characteristics of the vector populations (e.g. insecticide resistance). All these factors together lead to an individual being exposed to malaria and schistosomiasis infections. To mitigate these exposures and infections, prevention and control strategies for each disease are routinely implemented in endemic settings. Prevention strategies for schistosomiasis have primarily focused on school-based or community-based MDA campaigns that deliver praziquantel tablets without prior diagnosis to school-aged children, or all community members above the age of two, at a frequency that depends on the endemicity of the community to reduce worm burden [23–26]. Several important tools to control and prevent malaria have also been introduced in the past two decades. The global malaria control strategy places emphasis on LLIN distributions, early diagnosis, and treatment with ACT, however other strategies exist [40].

Although there are other factors at play that go beyond the scope of this thesis, including policy-level factors that encompass donors, funders, and government priorities, as well as novel interventions such as the RTS,S vaccine for malaria [14], this framework will focus on the factors and the levels outlined above that are explored further in the thesis manuscripts. Gaining insights into each level of this framework can help understand the complex and multi-faceted nature of disease transmission and challenges posed by current malaria and schistosomiasis prevention and control programs. Recognizing that public health interventions have historically over-emphasized the role of the individual, this thesis will outline the importance of social (relationship, community) and environmental determinants in disease prevention and control [58].

In the following chapter, I elaborate on each of the factors that are highlighted in the above conceptual framework.

1.4. Global Targets and Challenges

1.4.1 NTD Roadmap

The WHO 2030 NTD roadmap (Ending the neglect to attain the Sustainable Development Goals: a roadmap for neglected tropical diseases 2021-2030) outlines a set of global targets and milestones to prevent, control and eliminate NTDs (including schistosomiasis) by the year 2030 [42]. One of the specific goals is to reduce the number of people requiring intervention against NTDs by 90% compared to the 2010 baseline [12,42]. However, for schistosomiasis, since its establishment, there has been a 4% increase in the number of people requiring preventative chemotherapy, not accounting for population growth, from 2010 to 2021 (237 to 251 million people) as seen in Fig. 1.2 [3,13]. One of the challenges can be attributed to an insufficient

number of praziquantel tablets to fulfill the demands of the WHO recommendations. Between 2011 and 2020, Merck KGaA donated 1.26 billion praziquantel tablets for the prevention and control of schistosomiasis for school-aged children [59] and will continue to donate 250 million tablets a year to school-aged children until schistosomiasis ceases to be a public health problem [60]. This is a great commitment by a pharmaceutical company, but it is not sufficient to reach the total number of people requiring preventative chemotherapy as estimated by the WHO. For instance, a person who is 100 lbs (45 kg) would require three tablets for a single treatment (dosage: 40mg/kg, tablet: 600mg) – which means that if 251 million people required preventive chemotherapy for schistosomiasis in 2021 (most recent year of information), we would need 753 million tablets each year if every person was given an annual dose of praziquantel [32]. Therefore, it is not surprising that the number of people requiring preventative chemotherapy has essentially not changed in the last decade.

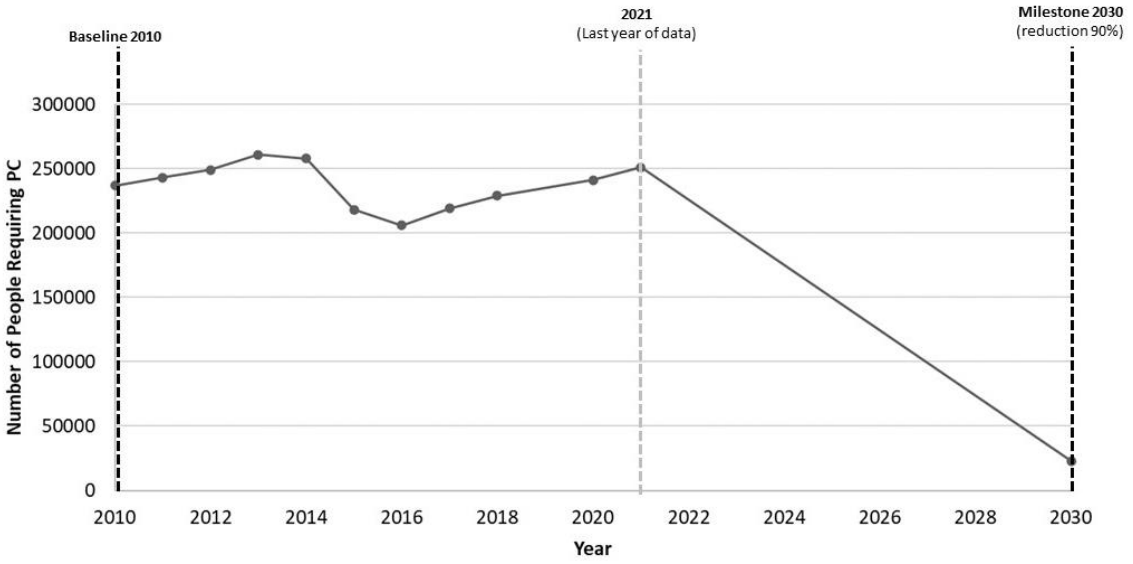

Fig. 1.2 Trends in absolute number of people requiring preventative chemotherapy for schistosomiasis and projected NTD roadmap targets for 2030. Data retrieved from WHO Weekly Epidemiological Records between the years of 2010-2021 [3–13].

1.4.2 Malaria Targets

The WHO Global Technical Strategy for malaria was developed in 2015 to help guide malaria-endemic countries to reduce human suffering from malaria [15]. Specific targets and milestones have been set for 2025 and 2030, with the aim of at least a 75% reduction in malaria cases and deaths (158,000 fewer cases and 406,000 fewer deaths) by 2025, and at least a 90% reduction in malaria cases and deaths (190,000 fewer cases and 488,000 fewer deaths) by 2030 [14,15], compared to the 2015 baseline. However, since its establishment, there has been an 11% and 9% increase in malaria cases and deaths, respectively, from 2015 to 2021 (the most recent year of data collection), not accounting for population growth, as seen in Fig. 1.3 [14]. This increase is likely due to biological threats (e.g., pyrethroid resistance in mosquito vectors that is reducing the efficacy of LLINs), reduced coverage of LLINs in endemic regions, a plateau in funding despite growing annual investment requirements for malaria control, and further challenges because of the COVID-19 pandemic (disruptions in malaria testing and LLIN distributions) – all of which points to the need for sustained efforts and new control strategies[15,61–64]. Given recent trends, the global health community will need to address malaria and schistosomiasis prevention and control differently, and the current WHO recommended strategies (i.e., LLIN distribution, antimalarials and preventive treatment for malaria and MDA for schistosomiasis) are likely inadequate to reach the 2030 targets. While new vaccines for malaria may help to accelerate progress, sustained efforts and new investments will be required.

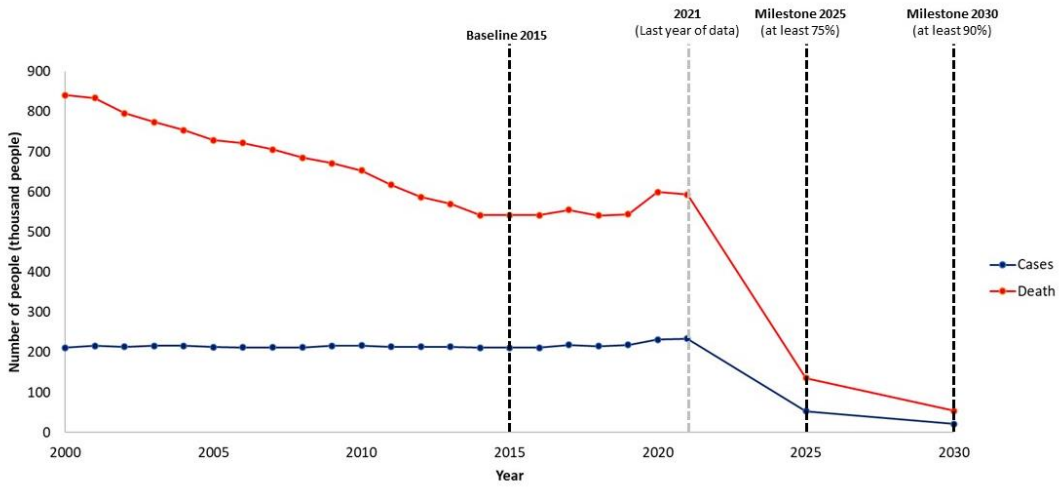

Fig. 1.3 Trends in absolute number of malaria cases and deaths from 2000-2021 and projected Global Technical Strategy targets for 2025 and 2030. Data retrieved from the World Malaria Report 2022 [14] and the Global Technical Strategy for Malaria 2016-2030 [15].

1.4.3 The Challenge

A key challenge is that current disease prevention and control strategies emphasize the person and the disease, but fail to account for the health inequalities and inequities that lead them to experience the disease. This highlights the critical need to broaden our way of thinking about diseases by using the socio-ecological framework that accounts for the interconnected breadth of factors contributing to disease and illness [65]. The conceptual framework shown in Fig. 1.1, which provides the foundation for this thesis, emphasizes that malaria and schistosomiasis share individual-, relationship-, community-, and environmental-level determinants and drivers, and that these factors are complex and interrelated. Throughout the next chapter, each factor will be described in detail to demonstrate how disease prevention and control is complex and is a multi-layer challenge that requires a multi-layer strategy.

1.5. Chapter Summary

This chapter introduces the thesis goal which is to fill knowledge gaps on potential entry points for integrated disease control programs and effective prevention and control strategies for malaria and schistosomiasis. It further emphasizes that current control strategies for both disease programs may not be sufficient to achieve the targets set out by the SDGs, the WHO Global Technical Strategy and 2030 NTD roadmap, and that novel approaches and opportunities are warranted. Using the social-ecological framework, this thesis will particularly aim to understand population vulnerabilities and identify infection exposures and risk factors for malaria and schistosomiasis across two different settings in sub-Saharan Africa.

CHAPTER 2

Literature Review

2.1. Malaria and Schistosomiasis Transmission and Prevention

2.1.1 Schistosomiasis Transmission

In sub-Saharan Africa, there are two forms of schistosomiasis caused by two different *Schistosoma* species each with their respective snail intermediate host– *Schistosoma mansoni* that infects *Biomphalaria* snails and causes intestinal schistosomiasis, and *Schistosoma haematobium* that infects *Bulinus* snails and causes urogenital schistosomiasis. The transmission cycle for schistosomiasis is influenced by human behaviour and the availability of safe water and toilet facilities. That is, the transmission cycle of schistosomiasis begins with the practice of open urination and defecation, where an infected person passes parasitic eggs through their urine or feces (depending on the parasite species) into a freshwater source (i.e., lakes, ponds, streams) or near a freshwater source where rainwater can then carry the excrement into the water source. The eggs hatch and release miracidia that penetrate freshwater snails (*Bulinus* snails in seasonal bodies of water, and *Biomphalaria* snails in permanent sources such as Lake Victoria) where they develop and are released back into the water as an infective form of the parasite (cercariae) [23,66,67]. *Biomphalaria* and *Bulinus* snails are crucial intermediate hosts and some species can estivate and survive during the dry season, thereby increasing the risk of schistosomiasis during the rainy season [68]. The cercariae can also remain in the water searching for a secondary host (a human) for up to 72 hours, and come into contact with a person's skin that is exposed to the parasite during activities such as fetching water, fishing, playing, and doing laundry [69]. Once the cercariae burrows through the skin of the secondary host (a human), it migrates to the circulatory system where it develops and matures into its adult form; male and female adult worms mate and reside in the mesenteric veins of the bladder or intestine, where female *Schistosoma* can then again release their eggs through the urine and feces of the host to continue

the transmission cycle [66,69]. The lifespan of adult *Schistosoma* is approximately 3-6 years within their human host [67].

2.1.2 Malaria Transmission

Malaria is transmitted to humans through the bites of infected female *Anopheles* mosquitoes, with most transmission attributable to species that are anthropophilic (take their blood meals from humans), endophagic (feed indoors), and bite from dusk till dawn [70,71]. The primary vector species in sub-Saharan Africa include members of the *An. gambiae* sensu lato (s.l.) complex, such as *An. gambiae* sensu stricto (s.s.), *An. arabiensi*s, and *An. coluzzii*, and members of the *An. funestus* s.l. complex, such as *An. funestus* s.s. One crucial factor influencing the malaria transmission is the abundance of infected *Anopheles* mosquitoes in the environment, and therefore the life cycle of the mosquito is important – female mosquitoes lay their eggs on a stagnant freshwater source (i.e., rain puddles and ponds) where they develop into their larval then pupal stage, to finally emerge as an adult mosquito [72]. The lifespan, biting rate, development rate, reproduction rate and survival of *Anopheles* mosquitoes are associated with temperature [73,74], while the availability of larvae breeding sites for some *Anopheles* species depends on shallow bodies of water – all of which are vulnerable to changes due to climate change [70,74–76]. Malaria transmission occurs when a female mosquito feeds on an infected person (host) thereby ingesting the *Plasmodium* parasite. The parasite then multiplies in the mosquito and is transmitted to another person (healthy or infected) during their next blood meal. People face an increased risk of getting infected from dusk till dawn, with the greatest transmission risk occurring indoors, depending on *Anopheles* species.

2.1.3 Schistosomiasis Prevention and Control

Prevention strategies for schistosomiasis have primarily focused on school-based or community-based MDA campaigns that deliver praziquantel tablets without prior diagnosis to school-aged children, or all community members above the age of two (including pregnant women after their first trimester and lactating women), at a frequency that depends on the endemicity of the community to reduce worm burden [23–26]. Praziquantel does not prevent reinfection, but it prevents disease progression in an infected person and reduces the risk of transmission to others by reducing the number of mature *Schistosome* worms in the host [77,78]. Praziquantel is effective on both *Schistosoma* species however it is important to note that even after treatment with praziquantel, there may still be *Schistosome* eggs present in the host's body [79,80]. While praziquantel is a valuable tool for treatment at the individual-level and prevention at the population-level, it does not address the underlying factors contributing to the persistence of the disease in the community (i.e., reinfection). Annual MDAs are recommended for communities with an estimated schistosomiasis endemicity of ≥10% and have the goal of reaching at least 75% of the population at-risk [80]. Factors that can influence a person's participation in MDAs include acceptability of the intervention, which could be defined as: opinions surrounding the efficacy of the treatment, trust in those administering the intervention, the information provided prior to the intervention, and perceived severity of the disease and their own susceptibility [81]. Although often more resource-intensive, snail control with molluscicides and providing safe water and sanitation are critical components at the environmental- and community-level to break the schistosomiasis transmission cycle and reduce the need for treatment at the individual-level [41,69,82,83]. However, these interventions often fall outside of the scope of health programs, requiring intersectoral collaboration.

The gold standard diagnostic tests for intestinal and urogenital schistosomiasis are both processed in a laboratory that requires trained personnel. These include a duplicate Kato-Katz from one stool sample to quantify the number of *Schistosoma mansoni* eggs, and urine filtration methods to identify the presence of *Schistosoma haematobium* eggs[80]. However, these two current methods do not meet the ASSURED (affordable, sensitive, specific, user-friendly, rapid, equipment-free, and delivered to those who need it) criteria for diagnostic tests since they are not easily administered at the community-level, where access to schistosomiasis diagnosis and treatment is needed [84]. Most symptoms for schistosomiasis are non-specific and therefore challenging to diagnose, which emphasizes the need for adequate and accessible point-of-care testing. The significance of testing in remote health care centers also lies in the increased ability to provide an informed treatment plan, since the WHO recommends that praziquantel be available in health facilities for the treatment of schistosomiasis [25,85].

2.1.4 Malaria Prevention and Control

Several important tools to control and prevent malaria have been introduced in the past two decades. The global malaria control strategy places emphasis on LLIN distributions, early diagnosis, and treatment with ACT, however other strategies exist [40]. LLINs and indoor residual spraying (IRS) are the two key malaria vector control tools that target the adult stage of *Anopheles* mosquitoes and are most effective against mosquito species that are endophagic and endophilic [61,86–88]. Although LLIN distributions are the main vector control strategies in sub-Saharan Africa, 1.8% of the population at risk for malaria are protected by IRS [37]. LLINs not only provide a protective barrier for those sleeping under them, but they benefit the community surrounding them since they are treated with an insecticide (i.e., pyrethroids) that repels and kills mosquitoes [89]. IRS involves applying insecticides to internal walls and ceilings of homes

(where mosquitoes rest) and therefore its effect takes place after a mosquito has taken a blood meal and prevents that mosquito from transmitting the malaria parasite any further [88]. Due to increasing pyrethroid resistance in sub-Saharan Africa, a combination of insecticides or other dual ingredients (e.g., pyrethroid and piperonyl butoxide) are now being used on LLINs to ensure continued protection against malaria transmission [14].

Another strategy that targets the immature stage of the *Anopheles* mosquitoes includes larval source management (i.e., habitat modifications, habitat manipulations, biological control, and larviciding) [87]. Although larval source management is only recommended where larval breeding sites are few, findable and fixed, reducing the mosquito population early in its life cycle can reduce the transmission of malaria [87].

Early diagnosis and treatment with artemisinin-based combination therapy are also critical components for the prevention and control of malaria by treating infection in the individual and subsequently reducing transmission in their community. However, universal access to antimalarial medicines is crucial for effective and timely treatment[15].

The WHO also recommends the delivery of preventative chemotherapy to at-risk populations depending on the endemicity and seasonality of malaria in a community [89]. For pregnant women and age groups at high risk of severe malaria in moderate-to high transmission settings with perennial or seasonal transmission, the WHO recommends intermittent or seasonal malaria chemoprevention, irrespective of infection status, to treat existing infections and prevent new infections of malaria [89].

As the most recent advancement in malaria prevention efforts, the malaria vaccine RTS,S/AS01 (RTS,S) is being rolled out in select countries as of early 2024[90]. An initial distribution of 18

million doses is planned across 12 countries, targeting areas of greatest need[90]. This vaccine will present a crucial addition to existing interventions outlined above.

2.1.5 Schistosomiasis and Malaria Prevention

There are twelve major diseases associated with inadequate access to water, sanitation and hygiene (WASH), including malaria and schistosomiasis, that account for 3.3% of the total deaths (approximately 2 million people) globally each year [91]. Although WASH interventions may be targeted towards either malaria or schistosomiasis, these interventions could have a significant impact on both diseases.

Annually, access to safe water could prevent 500,000 malaria-related deaths [92]. This impact stems from better management of water sources that eliminate the accumulation of standing and stagnant water which can serve as mosquito larval breeding sites [91]. Having access to safe water does not directly translate to using safe water, and the real change comes when individuals alter their behaviour and consistently use these sources (i.e., piped water, protected well) [93,94]. If stagnant water persists within the community, the mosquitoes will not recognize boundaries and transmission will persist affecting those with and without access to safe water– therefore universal access to safe water is necessary [93].

While the most significant and lasting impact for WASH and malaria prevention is achieved through community-level efforts, for schistosomiasis the effects of access to safe WASH benefit both the individual and the community. The transmission of schistosomiasis requires direct contact with water contaminated with cercariae. These water sources, typically unimproved (i.e., unprotected springs, surface water [94]), are contaminated when an infected individual either practices open defecation/urination near/in a water source or an infected individual uses an unimproved sanitation facility (i.e., pit latrines without slab [94]) that does not properly keep the

sewage out of the environment. Therefore, access to safe water and sanitation facilities plays a pivotal role in both the transmission and prevention of schistosomiasis. Contact with contaminated water can be influenced by individual-level factors such as age (i.e., young boys swimming and playing in water [91]), specific gender-roles (i.e., women and girls tasked with collecting water [94]) and socio-economic status (SES) (i.e., water infrastructure, cost of water [95,96]). An individual can avoid infection by avoiding contact with contaminated water, but the dynamics with proper sanitation facilities are more complex as it requires community-wide access and commitment. The use of proper sanitation facilities not only relies on having the physical infrastructure available (influenced by socioeconomic status [95]), but the individual and their community must also consistently use them [97]. This means that toilet facilities must also be present in the community, including at schools and health centers [97], as well as the adoption of new consistent behaviours.

2.2. Integrating Prevention and Control Interventions for Malaria and Schistosomiasis

The concept of integration can include the joint delivery of interventions to a single at-risk population or the utilization of pre-existing infrastructures to address the needs of novel or additional diseases. For example, the WHO recommends the joint delivery of praziquantel and albendazole for the simultaneous control of schistosomiasis and soil transmitted helminths (STH) (two NTDs), respectively. This approach is particularly beneficial since the MDA can leverage a single platform (school), and safely administer two treatments to a single target population (school-aged children) [4]. Another noteworthy example comes from Madagascar where there was an integrated maternal and child health campaign to address the control of three diseases (measles, STH, and malaria). This intervention had fixed and temporary sites that consisted of:

1) measles vaccination, 2) mebendazole distribution, 3) insecticide treated net distributions, and 4) vitamin A distribution [98]. A final example of integration that utilized pre-existing infrastructure to address a disease outbreak occurred in Nigeria where the health system leveraged an existing platform (skilled personnel, contact tracing, risk communication, disease surveillance) used to fight polio in 2012 to successfully and quickly address the Ebola outbreak in 2014 [99].

Malaria and schistosomiasis do not infect and exist in isolation. Co-infection is likely to occur where malaria and schistosomiasis are co-endemic because of the overlapping factors contributing to the spread of both diseases. There is an opportunity for local integrated control strategies for malaria and schistosomiasis, such as combining activities (i.e., preventative chemotherapy for malaria and schistosomiasis) [100] that could optimize the use of existing resources as well as increase access and/or coverage for an improved outcome. In addition to local integrated control strategies, there is an opportunity to emphasize the importance of environmental control to reduce the risk of exposure to malaria and schistosomiasis and to promote sustainable prevention and control strategies. Current strategies (i.e., LLINs and MDA) rely heavily on human uptake and adherence as well as on donor support and national level funding to sustain the prevention and control programs, which pose an additional challenge during health emergencies such as the COVID-19 pandemic or threats posed by climate change. For instance, early public health messaging during the pandemic was to stay home if someone was experiencing a fever to reduce COVID-19 transmission and to postpone planned MDAs until further notice [86,101]. However, these messages were quickly reversed to continue with planned malaria prevention and control programs and to resume MDA based on a risk-benefit assessment [86,101–103].

2.3. Factors associated with Malaria and Schistosomiasis Exposure and Infection

As presented in the chapter 1 conceptual framework, many factors, operating at multiple levels, may influence an individual's exposure to and infection with malaria and schistosomiasis. These factors are each described in further detail below, recognizing that some factors span multiple levels in the socio-ecological framework.

2.3.1 Age

Age is an important individual-level factor for malaria and schistosomiasis. For malaria, younger children (below 5 years old) are more vulnerable to severe illness and death, although the risk of malaria infection remains prevalent for all children [28,104–106]. For schistosomiasis, the prevalence of infection rises until adolescence (14 years old) then decreases and plateaus into adulthood [29,30,107–109]. Although most epidemiologic studies look at biological age, these trends appear to be more closely associated with non-biological factors such as immunity through repeated exposures throughout a lifetime [110,111], and behaviours and knowledge linked to specific age groups that differ over time like fetching or playing in water [30,112], than intrinsic biological factors. It is worth noting that many of the factors outlined in the conceptual framework described in the previous thesis chapter are intricately interconnected.

2.3.2 Sex and Gender

Sex and gender are important individual-level factors in epidemiologic research and capture different aspects of disease exposure and susceptibility [113]. However, the distinction between sex and gender is not often made in the literature investigating risk factors for malaria and schistosomiasis. Boys are noted as having increased odds and risk of infection for both malaria [105] and schistosomiasis [30,114,115], but the subtleties between sex and gender are not well

explored. Sex refers to biological and physical characteristics (i.e., an individual's sexual anatomy), while gender refers to a broader range of socially and culturally constructed roles, expectations, and behaviors (i.e., women in a caregiver role and men in a provider role) [116]. While the biological association between sex and disease remains unclear, and may relate in part to sex differences in immune function [117], gender differences are evident for malaria and schistosomiasis. Women are reported to be treated differently by health care providers leading to delayed health-seeking behaviors and unequal access to treatment [118], while men (and boys) may engage in higher-risk water activities than women (and girls) through their occupational (fishing in contaminated water) and recreational activities (swimming in contaminated water) which increases their exposure to schistosomiasis [115,119].

2.3.3 Immunity

Immunity is intricately connected to both age and sex, but nonetheless is an important individual-level factor associated with malaria and schistosomiasis infection. That is, men and women differ in their immune responses to pathogens (i.e., *Schistosoma* and *Plasmodium* parasites) [117], individuals gain protective immunity against malaria after repeated exposure [120], and pregnant women are more at risk for malaria given their lower immunity [104]**.** However, non-immune individuals such as travellers and displaced populations are also noted to have an increased risk of malaria which is not related to age and sex, but can be a result of climate change due to shifting disease transmission patterns that expose immunologically naïve populations [104,121].

2.3.4 Genetics

Genetics, but more specifically sickle cell disease, is an important protective individual-level factor for severe malaria [104]. Sickle cell disease is a genetic disorder that results in a change in the structure of an individual's red blood cells which is protective against severe malaria [122].

2.3.5 Intervention adherence

The primary protective benefits of LLINs are contingent on whether an individual sleeps under the LLIN. Studies have documented that individuals may report that LLINs are not comfortable (i.e., too hot, itchy) or failed to recognize the utility of the LLIN [123], which influenced their LLIN usage.

MDAs serve as both a treatment and prevention measure for schistosomiasis. On an individual-level, MDAs with praziquantel tablets treat schistosomiasis by reducing the number of adult worms in the host [79,80]. Reducing the worm burden also reduces the potential for shedding eggs in the environment, thereby reducing the risk of infection to others in the community [79,80]. However, this is reliant on the participation by an individual (i.e., swallowing the tablets delivered during an MDA) which can be influenced by numerous factors. One factor often noted as barrier to adherence is linked to the side effects following praziquantel administration, including nausea, headache, vomiting - likely due to dying schistosomes [124]. Although it is beyond the scope of this doctoral research, it is important to understand the enablers and barriers that drive an individual to participate in an MDA since this is crucial to see the treatment and preventative effects of the program (i.e., acceptability of the treatment) [125].

2.3.6 Socioeconomic status

Globally, from 1990 to 2017, there was a 41% decrease in communicable diseases and a 40% increase in non-communicable diseases [126]. However, those living in low-income countries continue to bear most of the communicable disease burden - this is due in part because people living in high-income countries are avoiding and surviving communicable diseases due to reduced exposure and/or increased healthcare access, and surviving to older ages where non-communicable diseases are a threat [127]. To further highlight this inequity, the healthy life expectancy is significantly higher in those living in high-income countries compared to low-income countries (69.8 vs 56.7), and those living in high-income countries live on average an additional 16 years compared to those in low-income countries (80.9 vs 65.1) [127]. Although the differences between countries are astonishing, there are also dramatic differences in health within countries due to social disadvantages [128]. These within and between countries differences have been described by the WHO as a social gradient, where lower socio-economic status is associated with worse health [129], and malaria and schistosomiasis are tightly linked with poverty [28,104,106,107,130].

This association is a vicious cycle where poverty promotes disease (i.e., insufficient funds to seek medical attention when sick, unimproved sanitation facilities, housing structures), and disease impedes economic growth (i.e., lost wages due to illness) [104,110,131]. There are also other factors that play a crucial role in the association between poverty and disease, where disease leads to lower education (days lost at school), and lower education (proxy of knowledge) leads to disease [132].

2.3.7 Perception of Disease

Although most epidemiologic studies investigate the association between education and disease, in this thesis, education will fall under a broader category of "perceptions of diseases". Malaria and schistosomiasis are closely linked with education [104,133], but this association may better reflect the association between education and knowledge [112], occupation [108], and socioeconomic status [110] – which are all tightly related to other factors in the conceptual model. For example, a parent may decide to invest less in the education of their girls because they will spend more years in child-bearing activities than in the workforce [110]

Higher education is often associated with better knowledge about diseases; however, knowledge does not directly translate to behaviour change. Behaviour, and as an extension behaviour change, is complex and is shaped by a multitude of factors. In 1931, Lewin described behaviour as a function of a person (i.e., beliefs, knowledge) and their environment (i.e., access to improved sanitation facilities, ability to pay for treatment) [134]. To take this one step further, in 2018, James Clear wrote that "we don't choose our earliest habits, we imitate them" [135]. Finally, in the famous 1956 study conducted by Solomon Asch, he investigated social pressures and their impact on individual conformity [136] and ultimately concluded that people tend to go along with the group even if the group is wrong. Taken all together, we can start to see that many factors lead to a specific behaviour that can expose someone to malaria and schistosomiasis and how behaviour change can be difficult. To put this in perspective, we can look at the example of water contact behaviour and exposure to schistosomiasis. People are exposed to schistosomiasis when they come into contact with cercariae-contaminated water – this could be by fetching drinking water, doing laundry or playing. For this example, we will follow an example using a young boy playing in an unimproved water source. He could be playing in this location because

it is where his friends play (the norm) and because there is no safe chlorinated swimming pool to play in (access to improved water sources). If people in his family have always played in this water source, he may not view this as risky behaviour. Therefore, if in school, he is taught that swimming in water sources is a source of exposure for schistosomiasis, he may not change his behaviour because it has become an imbedded habit for him, and his friends.

2.3.8 Access to Care

Access to care encompasses many aspects of healthcare delivery including the physical number of healthcare facilities, getting to the facility, and the facilities being adequately equipped with staff, supplies and resources. One of the targets in SDG 3 is to achieve universal health coverage which includes access to quality essential health-care services (SDG 3.8) [46]. A modelling study showed that in sub-Saharan Africa, there is a need to build 6,200 new facilities by 2030 to meet this target and that at least one-sixth of the population in sub-Saharan Africa lives more than two hours from a public hospital [137]. Evidently, there is a shortage of healthcare facilities coupled with substantial travel times to reach the available ones. This also highlights the second challenge in access to care – travelling to the facilities, which could include walking long distances, transportation costs, and missing work to travel to the health center, which can all influence an individual's choice in seeking medical attention [104,112].

Prompt diagnosis and treatment (and subsequently the facilities being adequately equipped with supplies and personnel administer the test) is also essential for effective and appropriate management of communicable diseases. Symptoms for malaria and schistosomiasis are non-specific and are both typically characterized by a fever - emphasizing the need for adequate and accessible testing. Up until 2010, all persons presenting to a health facility with a fever in sub-

Saharan Africa were presumed to have malaria and received treatment. However, in 2010, the recommendations by the WHO were revised to include that all persons experiencing a fever should also receive a parasitological confirmation of malaria diagnosis prior to receiving antimalarial treatment since only 50% of all fever cases were found to be caused by malaria [138,139]. While this approach works well for malaria, given the availability of rapid diagnostic tests (RDT) and ACTs, the same cannot be said for schistosomiasis.

2.3.9 Climate

Malaria and schistosomiasis prevalence are intricately associated with temperature and precipitation [28,140,141]. Temperature influences the lifespan, biting rate, development rate, reproduction rate and survival of *Anopheles* mosquitoes [73,74], the development rate of *Plasmodium falciparum* within *Anopheles* mosquitoes [140], and the survival and distribution of *Bulinus* and *Biomphalaria* snails (indirectly through water temperatures) [142–144]. Precipitation, alongside landcover (e.g. forests, urban lands or other vegetation types), influences the availability of mosquito larval breeding sites (i.e., shallow temporary bodies of water) created after rainfall, which is directly related to *Anopheles* density, a key predictor for malaria transmission and prevalence [28,140].

Temperature and precipitation shifts as a result of climate change threaten to change the geographic distribution and dynamics of malaria and schistosomiasis [140,145]. The effects of climate change on temperature and precipitation work together where rising temperatures can result in either more frequent and intense storms or droughts creating more suitable (or less suitable) areas for malaria and schistosomiasis vectors [146,147]. When the temperature range falls outside the suitable conditions for *Anopheles* mosquitoes and *Bulinus* and *Biomphalaria*

snails or there are no water sources for the larval breeding sites and snail habitats, these vectors may need to migrate to find a more suitable habitat or adapt to their new environment. This could be detrimental in areas where these vectors are not currently present because they will shift into areas where the immunity in the population is low and are currently outside the range of control programs [121,144]. However, it could be advantageous in areas with established malaria and schistosomiasis vectors since without the vectors, the transmission cycles for malaria and schistosomiasis are broken.

2.3.10 Behavioural and Insecticide Resistance

Three types of resistance are a particular threat to the prevention and control of malaria including 1) behavioural adaptations, 2) vector resistance to insecticides (pyrethroids), and 3) antimalarial drug resistance.

Behavioral and insecticidal resistance in *Anopheles* mosquitoes pose a threat to the effectiveness of LLINs at the individual- and community-level [148,149]. LLINS are most effective against mosquito species that feed indoors from dusk until dawn – which is when individuals are most likely sleeping. Studies have found that mosquitoes may feed earlier [150] or shift from biting indoors to outdoors [151,152] when individuals are not sleeping under a LLIN. This means that at the individual-level, in areas where the mosquitoes have demonstrated behavioural resistance, LLINs might not provide a protective barrier even if an individual has access to and uses them [153].

Pyrethroid resistance, impacting the primary insecticide used in LLINs, has been reported in Tanzania and Benin, among many other countries [148,154]. The spread of this resistance is a threat to effectively control and reduce mosquito populations. This means that even despite high

LLIN coverage with nets treated with pyrethroid, there may be continued and sustained malaria transmission [153]. However, there are currently studies looking at different types of treated LLINs (with two insecticides instead of one) to see if this can mitigate the challenges faced with insecticide resistance [155,156].

ACTs are still efficacious at treating malaria, but the heavy reliance on this treatment raises concern for the potential emergence of drug resistance[14]. There have not been reports of the emergence of praziquantel resistance, however like with ACTs, repeated annual (or semi-annual) MDAs over an extended period of time due to persistent transmission (i.e., inadequate adherence, rapid reinfection) poses a risk for drug resistance [80]. As the main control tool for schistosomiasis, drug resistance can reverse progress made to date on reducing the number of schistosomiasis cases.

2.4. Chapter Summary

In this chapter, we present malaria and schistosomiasis control as a singular integrated challenge, rather than separate and siloed public health issues. We also recognize that effective solutions and treatments for these diseases exist, but there is an opportunity to improve methods for delivery and implementation. Drawing on the conceptual framework outlined in the previous chapter, this chapter describes the range of complex and interrelated factors that malaria and schistosomiasis share at the individual-, relationship-, community-, and environmental levels.

CHAPTER 3

Methods

3.1. Chapter Overview

This chapter provides a general overview of the study designs for the study in Tanzania (chapter 4) and Benin (chapter 5) as well as a rationale and explanation of the methods used throughout the thesis, beyond what was described in each manuscript. Specifically, this chapter will provide a detailed explanation of all statistical approaches used in the subsequent thesis manuscripts including variable definitions and derivations, choice of appropriate statistic tools, and model building rationale.

3.2. Study Design Overview

Two of the three studies that form this doctoral research were nested in large-scale cluster randomized control trials that assessed the effectiveness and efficacy of dual-active ingredient LLINs for reducing malaria in Tanzania (2018-2022) [149,155,157] and Benin (2019-2023) [156,158]. With the rise in pyrethroid resistance in malaria vectors across sub-Saharan Africa, these two studies investigated the impact of dual-active ingredient LLINs compared to standard pyrethroid-only LLINs for reducing malaria: 1) Royal Guard nets that combine a pyrethroid and another insecticide which disrupt the reproduction of mosquitoes and egg fertility (pyriproxyfen); 2) Intercept G2 nets that combine two adulticides (a pyrethroid and chlorfenapyr) to kill adult mosquitoes; and 3) Olyset Plus nets that combine a pyrethroid and piperonyl butoxide to enhance the potency of the pyrethroid [155,156,159]. In order for the WHO to recommend new LLINs, two randomized control trials need to be conducted in different settings and need to demonstrate that they are more effective than the standard best practice pyrethroid-only nets [160]**.** The findings from these two studies provided evidence for the efficacy of new classes of LLINs, resulting in recommendations by the WHO. These trials were

led by the London School of Hygiene & Tropical Medicine (LSHTM) in conjunction with partner institutions in Tanzania (Kilimanjaro Christian Medical University College and the National Institute for Medical Research, Mwanza Station) and Benin (Centre de Recherche Entomologique de Cotonou, CREC). Dr. N. Protopopoff (thesis advisory committee member) was the PI for the trials in Tanzania and Benin, while Dr. M. Kulkarni (thesis supervisor) was a co-investigator for the trial in Tanzania and PI for a linked study on COVID-19 pandemic impacts in Benin with CREC and LSHTM, facilitating the incorporation of specific doctoral research elements.

For this thesis, we leveraged cross-sectional surveys that were being conducted as part of the ongoing trials in Tanzania and Benin (i.e., infrastructure, staff, participant recruitment, survey questionnaire, testing component) as well as data from a single cohort visit in Benin (further detailed in Appendix 3.1: Benin Survey Descriptions) to address the thesis research objectives. We did so by adding different qualitative and quantitative data collection components in each country, including supplemental survey questions in both countries, focus group discussions in Benin, community mapping combined with direct field observations in Tanzania, and a schistosomiasis testing component in Tanzania to understand population vulnerabilities, identify infection exposures and risk factors for malaria and schistosomiasis. By leveraging these studies, I was able to engage in field research with populations in areas with intense malaria transmission in both countries (and schistosomiasis transmission in Tanzania) and incorporate an objective to examine the impacts of the COVID-19 pandemic on malaria prevention and control in Benin.

3.3. Mixed-Methods Approach

The studies in Tanzania (chapter 4) and Benin (chapter 5) both used mixed-methods to address study objectives – namely an explanatory sequential design for the study in Tanzania (chapter 4) and a convergent parallel design for the study in Benin (chapter 5). These two different approaches were chosen based on pre-determined study objectives to use a mixed-methods approach for the study in Benin (chapter 5) and based on the evolution of study objectives for the study in Tanzania (chapter 4) to incorporate additional qualitative data based on results from the quantitative study.

3.3.1 Explanatory Sequential

In the study in Tanzania (chapter 4), we took a two-stage study design approach which followed an explanatory sequential mixed-methods design (Fig. 3.1). We first started with a quantitative study using cross-sectional data, which was used to address the main study's purpose of identifying factors associated with malaria, schistosomiasis, and co-infection. To explain the results from the quantitative study, we conducted a follow-up qualitative study to explain the higher-than-hypothesized schistosomiasis seroprevalence that was observed. To do this, we conducted community participative mapping along with direct field observations to understand water use behaviours in selected villages. We initially developed the instructions for the community maps, which included the identification of the location of water sources and their uses by community members, because we hypothesized that the higher schistosomiasis seroprevalence was due to exposure to contaminated water – and therefore we wanted to understand water contact and use behaviour in the study area. In the direct field observations, we identified water sources in all three villages using the community maps as a guide by using

different assets (roads, health centres) as reference points. We also identified other water sources that were not identified in the community map to understand water access for drinking and other domestic uses. These two components were used to support and explain the higher than hypothesized schistosomiasis seroprevalence in the study area – beyond what was captured by the questions in the cross-sectional survey.

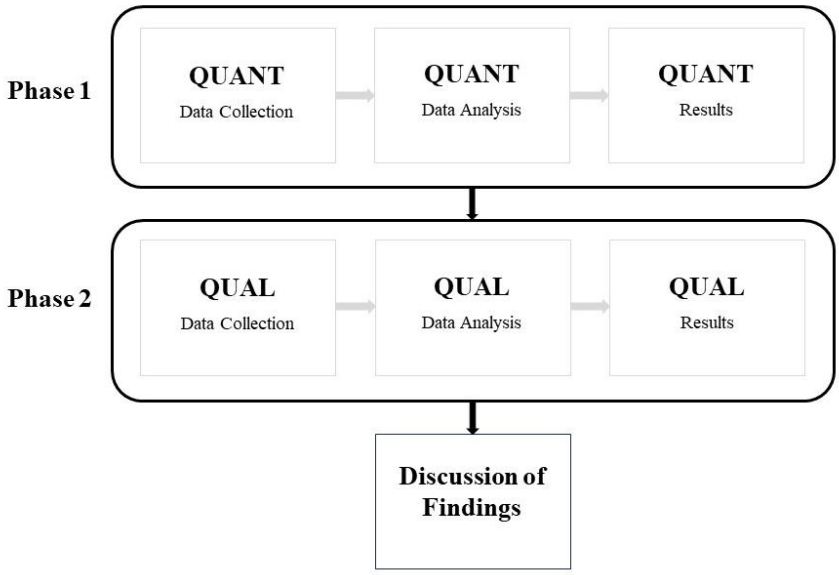

Fig. 3.1 Overview of explanatory sequential mixed-methods design. Illustration inspired by [16]. Abbreviations: QUANT: Quantitative study; QUAL: Qualitative Study.

3.3.2 Convergent Parallel

In the study in Benin (chapter 5), we also took a mixed-methods approach, but in this study, we used a convergent parallel mixed-methods design that collects quantitative and qualitative data separately but at similar time points, as seen in Fig. 3.2. Our strategy with this mixed-methods approach was to uncover valuable narratives that emerged from the qualitative focus group discussions (FGDs) and to see if we were being told similar stories and conclusions from the quantitative statistical models (and vice versa). We accomplished this by first creating a

codebook for the FGDs deductively based on the guidebook, then further refining it inductively by identifying themes and subthemes that arose from reading the transcripts. We then applied the final codebook to the FGD transcripts and compared these themes and subthemes to the results from the statistical models from the quantitative portion of the study[16]. For instance, in the second aim of the study in Benin (chapter 5), we sought to understand the impact of the COVID-19 pandemic on LLIN access. The descriptive statistics and statistical models revealed that LLIN access increased during the pandemic (from 62% in 2019 to 73% in 2021 with a p-value <0.05 in the model). Taking these metrics at face value, we could have deduced that LLIN access did not decrease during the pandemic (a victory for malaria control and prevention) and these conclusions would have been valid (statistically). However, the stories and narratives in the FGDs surrounding LLIN access provided a different perspective in that people were no longer sharing LLINs because they were informed to social distance. So, although access did not decrease during the pandemic, people changed their behaviours surrounding LLINs which could have resulted in a shortage of LLINs. Therefore, this method of investigating the FGD transcripts to see what stories were being told by the participants and to see in what ways they converge and diverge with the quantitative results was also employed for the other aims of the study. By employing this mixed methods approach, we gained a better understanding of the factors influencing COVID-19 knowledge, the impact of COVID-19 on LLIN access, and the avoidance of healthcare centres because of the pandemic.

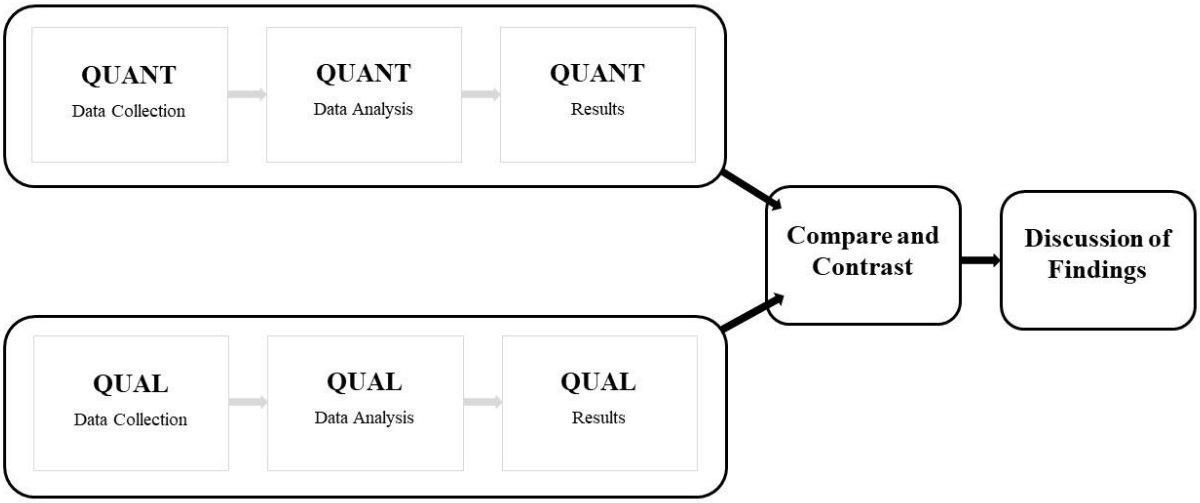

Fig. 3.2 Overview of convergent parallel mixed-methods design. Illustration inspired by [16]. Abbreviations: QUANT: Quantitative study; QUAL: Qualitative Study.

3.4. Mixed-Effects Logistic Regression

The study in Tanzania (chapter 4) and Benin (chapter 5) both used mixed-effects logistic regressions to address study objectives. This type of model was best suited for both studies because the outcomes for both study objectives were dichotomous (i.e., malaria infection presence or absence, avoided or did not avoid health centres because of the pandemic) and both studies had a clustered sampling design – further explanation and model decision rationale are detailed below.

3.4.1 Assumptions

One of the objectives for the study in Tanzania (chapter 4) was to assess factors associated with malaria, schistosomiasis, and co-infection, while two objectives for the study in Benin (chapter 5) were to evaluate factors influencing COVID-19 knowledge and factors associated with

avoiding health centres because of the pandemic. To address these objectives, we used a multivariable model to assess the relationship of several pre-defined factors on each outcome. Since all these models had a dichotomous outcome, the first step was to investigate the logistic regression model.

There are three key assumptions for logistic regression models [161]:

1. The outcome follows a binomial distribution.
2. Observations are independent.
3. Predictors are related linearly to the logit of the outcome.

The data used for the studies in Tanzania (chapter 4) and Benin (chapter 5) failed the second assumption (observations are independent) for logistic regression models because we were dealing with hierarchical data (Fig. 3.3) and the degree of clustering of each outcome was not negligible. The degree of clustering for both studies was measured using the intracluster correlation (ICC) which measures the similarity in the outcome among observations (children for Tanzania or households for Benin) within a cluster to observations from different clusters [162]. When the ICC is close to 0 (negligible degree of clustering), it indicates that the observations (children or households) within the cluster are completely independent from each other compared to those from other clusters[162]. In contrast, when the ICC increases closer to 1, it indicates that the observations (children or households) within the clusters are more similar to each other, than observations from other clusters[162].

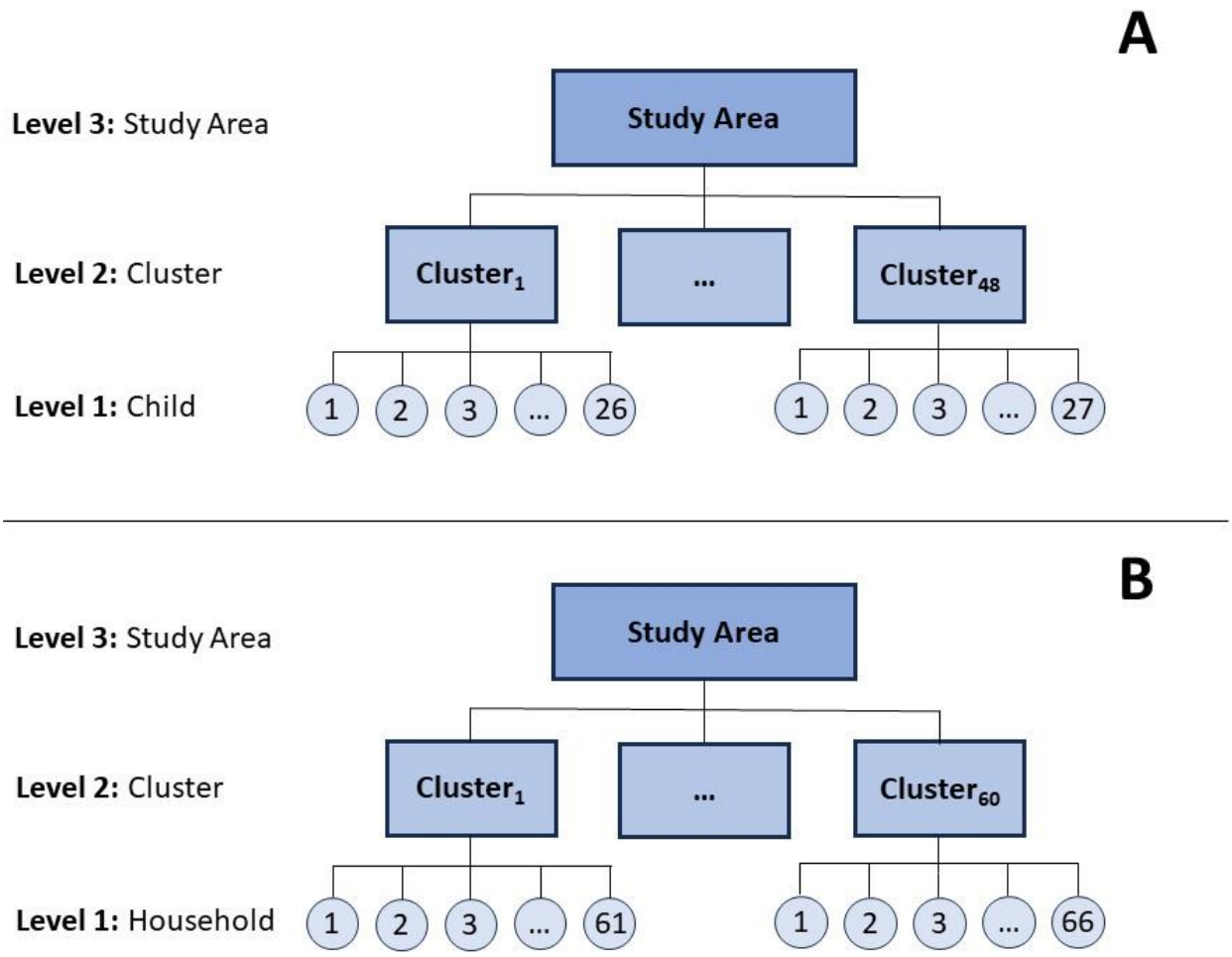

Fig. 3.3 Hierarchical structure of study designs for the studies in Tanzania (A) and Benin (B)

The ICC, outlined in Table 3.1, shows the degree of clustering and how observations (selected child for the study in Tanzania and households for the study in Benin) within the same cluster are more alike than observations in different clusters indicating that the assumptions for the logistic regression have failed (ICC greater than 0).

Table 3.1: Intracluster correlation of each outcome for the study in Tanzania and Benin

Study	Outcome	ICC
Tanzania	Malaria prevalence	0.215
Tanzania	Schistosomiasis seroprevalence	0.461
Tanzania	Co-infection	0.117
Tanzania	Strong schistosomiasis seroprevalence	0.103
Tanzania	Strong co-infection	0.058
Benin	Knowledge of COVID-19	0.255
Benin	Avoiding health centres because of the pandemic	0.455

To accommodate this, we used mixed-effects logistic regression models which are an extension of the logistic regression model that accounts for observations that are not independent from one another [163].

3.4.2 Model Building

Step 1: Full Model

The first step in the model building process was to identify variables that could effectively address the objectives and sub-objectives for the studies in Tanzania (chapter 4) and Benin (chapter 5) (Fig. 3.4). Based on our conceptual framework and what data were feasible to collect during the cross-sectional surveys of the main trial, we constructed a list of variables hypothesized to be associated with each outcome for the studies in Tanzania (chapter 4) and Benin (chapter 5). A list of the variables their description, derivation, and rationale for selection are outlined in Appendix 3.2: Variables Included in Models.

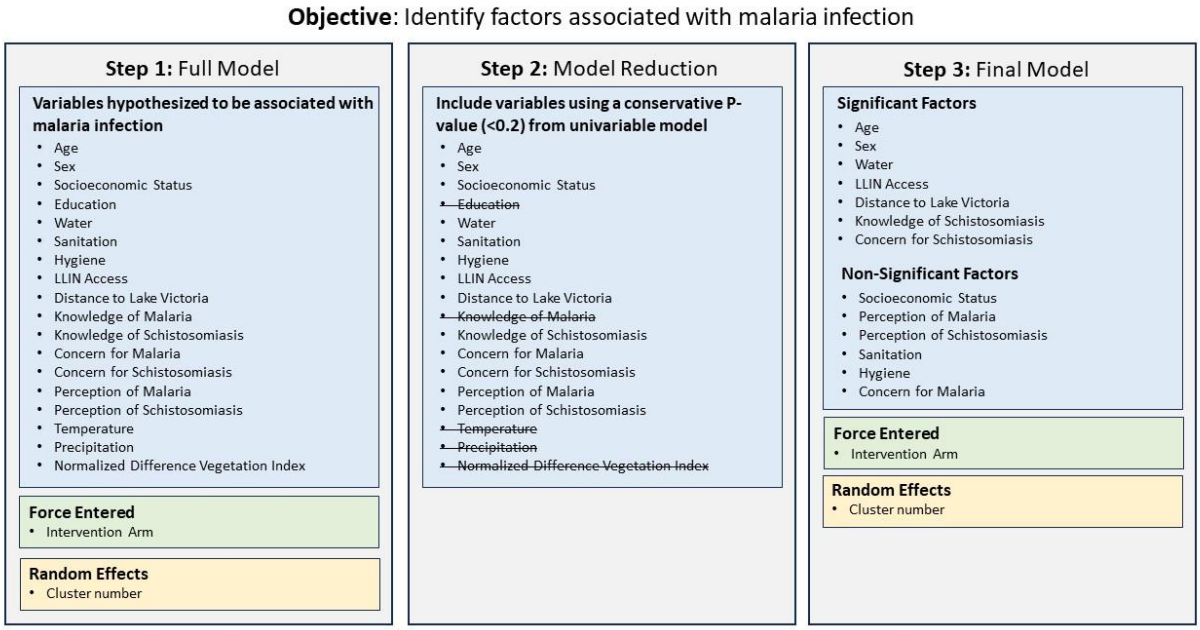

Fig. 3.4 Model building example for one of the sub-objectives for the study in Tanzania (chapter 4)

For the studies in Tanzania (chapter 4) and Benin (chapter 5), we force entered the intervention arm assigned as part of the main trial (i.e., for the study in Tanzania): 1) Royal Guard, 2) Intercept G2, 3) Olyset Plus, and 4) pyrethroid-only) [155]. This was done because we aimed to investigate the association between socio-ecological variables and each outcome (i.e., malaria infection) and we did not want the results to be influenced by the intervention that a household received as part of the main trial.

Since we established that there was clustering in the outcomes within the observations (ICC $\neq 0$) in the study clusters, we used random effects, specifically a random intercept (typically used for hierarchical data [164]), to model the association between the outcomes and the pre-determined variables.

Step 2: Model Reduction

The second step in the model building process was to select variables to be included in the final model. We used the rule of thumb for logistic regression models to include one variable for every ten events which would allow us to have precise estimates in each model [161]. Given the allowance for the number of variables based on the number of events in each outcome (Table 3.2) and that we wanted to use the same approach for an entire chapter for consistency, we used a different model selection approach for the studies in Tanzania (chapter 4) and Benin (chapter 5).

Table 3.2: Summary of number of events, total variables, and variables allowed for all models in the studies in Tanzania and Benin

Study	Outcome	Number of Events	Total Number of Variables*	Total Number of Variables Allowed#
Tanzania	Malaria prevalence	454	38	~45
Tanzania	Schistosomiasis seroprevalence	1058	38	~105
Tanzania	Co-infection	428	38	~42
Tanzania	Strong schistosomiasis seroprevalence	328	38	~32
Tanzania	Strong co-infection	156	38	~15
Benin	Good COVID-19 knowledge	378	26	~37
Benin	LLIN access	3254	19	~325
Benin	Avoidance of Health Centres because of the pandemic	714	27	~71

* The total number of variables denotes the number of pre-defined variables hypothesized to be associated with the outcome.

The red highlight indicates that the model cannot accommodate all variables in the final model. The green highlight indicates that the model can accommodate all variables in the final model.

The final models in the study in Tanzania (chapter 4) could not accommodate all pre-defined variables. Therefore, we looked at the univariable association between all pre-defined explanatory variables with each outcome and used a conservative p-value (0.2) as an inclusion criterion for the final, multivariable model.

The final models in the study in Benin (chapter 5) could accommodate for all pre-defined variables but given the objective to evaluate factors associated with 1) COVID-19 knowledge, 2) the impact of COVID-19 on LLIN usage and 3) avoidance of healthcare centres because of the pandemic, we wanted to statistically assess the best combination of explanatory variables for each model. To accomplish this, we used the Dredge function in RStudio for all three models to fit the final reduced multivariable model. The Dredge function is a model selection tool that ranks every candidate model (2^n models, where n is the number of predictors in the full model) based on the Akaike Information Criterion. A limit of ten events per variable was placed for the model selection, and the final model based on minimizing the Akaike Information Criterion was fit. The Dredge function would also allow us to not overfit the three final models and to only include variables that best modelled the association between the pre-defined explanatory variables and each outcome.

Step 3: Final Model

After the models were reduced and fit, we proceeded to assess for multicollinearity between explanatory variables in each model (further detailed in each manuscript) and for the model fit

by assessing the area under the receiver operating characteristic curve (further detailed in each manuscript) and for spatial autocorrelation (further detailed in the section 3.5 below).

3.4.3 Software

Fitting univariable and multivariable mixed-effect logistic regression are computationally intensive and mathematically complex. For instance, the models used for the studies in Tanzania (chapter 4) and Benin (chapter 5) (mixed-effect logistic regression models with random intercepts) are expressed as the following [164]:

$$log\left(\frac{\pi_{ij}}{1-\pi_{ij}}\right) = \beta_o + \beta 1X1_{ij} + \beta 2X2_{ij} + \cdots + \gamma_{oj}$$

Where:

Variable	Description
i	Finest scale observation (i.e., selected child or household)
j	Cluster number
π_{ij}	The probability of an event (i.e., malaria infection) occurring for child (or household) i in cluster j
β_o	Fixed intercept
$\beta 1$	Fixed regression coefficient for predictor X1(i.e., age)
γ_{oj}	Random intercept for cluster j

Therefore, we used two different statistical software packages (SAS and RStudio) to fit the mixed-effects logistic regression models and carry out the statistical analysis for the studies in Tanzania (chapter 4) and Benin (chapter 5), respectively. Although SAS and RStudio can both fit mixed-effects logistic regression models, RStudio provided the flexibility in the study in Benin (chapter 5) to employ the Dredge function which is not available in SAS. A detailed explanation

of the procedures and specifications used to model each outcome in SAS and RStudio are outlined in Appendix 3.3: Explanation and example of PROC GLIMMIX in SAS and GLMER in RStudio.

Briefly, the PROC GLIMMIX procedure in SAS version 9.4 (SAS Institute, Cary, NC, USA) and the GLMER function in the lme4 package in RStudio version 4.1.3 (R Core Team, 2018) are used to fit the generalized linear mixed model (GLMM). For both studies, we specified that the outcomes were binary and followed a logit link to model logistic mixed-effects models. We also used a random effects term for the cluster to allow for a random intercept for each cluster. The random effects were assumed to follow a normal distribution.

3.5. Spatial Cluster Analysis

The studies in Tanzania (chapter 4) and Benin (chapter 5) both incorporated spatial cluster analyses to address their study objectives. There are different types of cluster analyses depending on the type of question that is being asked and the format of the data - including global and local clustering methods that test for clustering and for specific clusters, respectively[165]. For the analyses used in both studies, we utilized global spatial tests to investigate if there was spatial autocorrelation in the residuals of each model outlined in section 3.4. To assess if the models violated logistic regression model assumptions (observations are independent), we used the global Moran's I to assess if there existed any clustering in the model residuals. We also utilized local spatial tests and spatial scan statistics to test for specific clusters – specifically, to identify areas of high and low infection status for the study in Tanzania (chapter 4), and for good COVID-19 knowledge, LLIN access, and health centre avoidance during the pandemic COVID-19 knowledge for the study in Benin (chapter 5). With these two methods

(local spatial test and spatial scan statistics), we aimed to visually identify clusters of each outcome using Getis-Ord-Gi* while concurrently quantifying the magnitude and boundary of each cluster using the Kulldorff spatial scan statistics.

3.5.1 Global Spatial Test – Global Moran's I

In section 3.4.1 we determined that the data used for both studies violated the independence assumptions for logistic regression models. To address this violation, random effect terms for the intercepts were incorporated into the mixed-effect logistic regression models. To ensure that we adequately addressed the clustering in the data, we confirmed that there was no spatial autocorrelation in the residuals in each model using the global Moran's I statistic.

The goal of the global Moran's I test is to assess whether there is clustering in the data rather than identifying specific clusters[165]. For our analyses, we were interested in investigating if there was any spatial association in the values of the residuals, meaning if large residuals tended to be located close to other large residuals. In the Geographic Information System (GIS) ArcMap version 10.7.1 (ESRI, Redlands, CA, USA), the global Moran's I tool returns five values, three of which were of interest in our analyses: the Moran's I indices and the z-scores and p-values [166].

The Moran's I index

The Moran's I index is expressed by the following equation and indicates how similar neighbours are to each other compared to the overall variability of the variable (i.e., the model residuals) [165]:

$$I = \frac{n \sum_i \sum_j w_{ij}(X_i - \bar{X})(X_j - \bar{X})}{\left(\sum_i \sum_j w_{ij}\right) \sum_i (X_i - \bar{X})^2}$$

Where:

Variable	Description
n	Number of observations
w_{ij}	Weight matrix
X_i	Value of the variable at spatial unit i
X_j	Value of the variable at spatial unit j

The Moran's I index is not bounded by any range, but it typically ranges from -1 to 1 where if the index is less than zero, it indicates that the values of the selected variable are dispersed (scattered), if the index is greater than zero, the values of the selected variable are clustered (grouped closely together), and if the index is equal to zero, the values of the selected variable are spatially random [165]. The Global Moran's I test requires that you select a weight matrix that defines which neighbour will be considered. For our analyses, we used the default weight matrix in GIS ArcMap which was the inverse distance where features close together in space have a greater influence on one another than features that are farther away [167].

Z-score and P-values

The z-scores and p-values are interrelated, and they indicate the significance of the clustering where very high or very low z-scores (<1.96 or >1.96) are associated with very small p-values (<0.05) [168]. The null hypothesis for this test is that the data are spatially random [168] –

therefore, if we reject the null hypothesis, it means that we have violated the assumption of independence in our models.

3.5.2 Local Spatial Test - Getis-Ord-Gi*

The goal of local spatial tests is to evaluate the specific location of clusters in spatial data given the location and magnitude of a specified variable [165]. This type of test was particularly useful for one of the sub-objectives in both studies that aimed to investigate spatial patterns and identify hotspots of malaria, schistosomiasis, and co-infection exposure in school-aged children in Misungwi, Tanzania (chapter 4); and to investigate spatial patterns and identify hot and cold spots and gaps of COVID-19 knowledge, and malaria prevention and care-seeking practices during the pandemic in Benin (chapter 5). For our analyses, we used the Getis-Ord-Gi* tool in GIS ArcMap which is a local hot spot analysis tool that not only allows you to visually identify clusters, but it produces an output that highlights the significance and intensity of each cluster[169]. The Getis-Ord Gi* tool investigates the value of a selected variable (i.e., malaria infection) in relation to its neighbour (i.e., malaria infection presence or absence) compared to the average of all observations, expressed below [169]:

$$G_i^* = \frac{\sum_{j=1}^{n} w_{i,j}x_j - \bar{X}\sum_{j=1}^{n} w_{i,j}}{S\sqrt{\frac{\left[n\sum_{j=1}^{n} w^2{}_{i,j} - \left(\sum_{j=1}^{n} w_{i,j}\right)^2\right]}{n-1}}}$$

Where:

Variable	Description
n	Number of observations

x_i	Value at i
x_j	Value at j
w_{ij}	Weight matrix
$\bar{X}$	$\bar{X} = \frac{\sum_{j=1}^{n} x_j}{n}$ = mean of the variable across spatial units
S	$S = \sqrt{\frac{\sum_{j=1}^{n} x^2{}_j}{n} - (\bar{X})^2}$= standard deviation of the variable across spatial units

Like with the Global Moran's I, this tool requires the selection of a weight matrix that defines which neighbour will be considered. For our analyses, we used the default weight matrix in GIS ArcMap version 10.7.1 (ESRI, Redlands, CA, USA) which was the inverse distance where features close together in space have a greater influence on one another than features that are farther away [167]. Also like the Global Moran's I tool in ArcMap, the Getis-Ord Gi* tool outputs a z-score and p-value for each observation in the spatial dataset[169]. The null hypothesis for this test is that the values in the selected variable are randomly distributed. These clusters are determined at the 99%, 95% and 90% confidence interval, which correspond to the following p-value and z-scores [168]:

Confidence level	**p-value**	**z-score**
99%	<0.01	<-2.58 or >2.58
95%	<0.05	<-1.96 or >1.96
90%	<0.1	<-1.65 or >1.65

3.5.3 Spatial Scan Statistics – SaTScan

In addition to the local spatial test that identified the specific location of clusters, we concurrently quantified the elevated risk of an event within each cluster compared to that outside the cluster and delineated the boundaries of each potential cluster using spatial scan statistics. We specifically used SaTScan (v 9.4.1 Kulldorff and Information Management Services, Inc.), a free software developed by Martin Kulldorff, to automate this process and to overlay the output in GIS ArcMap version 10.7.1 (ESRI, Redlands, CA, USA) [170]. This automated process can be divided into three distinct steps:

Step 1: Investigate all possible scanning windows

The first step in the Kulldorff spatial scan statistic is to investigate all possible scanning windows in the study area[170]. This is an automated process where there is an infinite number of circular scanning windows of varying sizes (radii) that are classified as potential clusters [170]. The software is capable of defining different shapes of scanning windows (i.e., cylindrical), but we kept the default which were circles [170]. For each circle, the observed number of events within the scanning window is compared to the expected number of events under the null hypothesis of spatial randomness [170]**.**

Step 2: Calculate and rank all possible likelihood functions

SaTScan then computes a likelihood ratio statistic to determine the statistical significance of each potential cluster by determining how well the observed data fits an expected distribution[170]. The software allows you to define different distributions (i.e., Poisson, Bernoulli) - we defined the Bernoulli distribution since we were working with binary data [170].

Therefore, for each scanning window (all locations and sizes), SaTScan calculates the likelihood function, expressed below [170,171]:

$$\left(\frac{c}{n}\right)^{c}\left(\frac{n-c}{n}\right)^{n-c}\left(\frac{C-c}{N-n}\right)^{C-c}\left(\frac{(N-n)-(C-c)}{N-n}\right)^{(N-n)-(C-c)} I()$$

Where:

Variable	Description
C	Total number of events over the whole study area
c	Observed number of events in the scanning window
N	Total number of events and non-events over the whole study area
n	Total number of events and non-events in the scanning window
I()	Indicator function to indicate that an area is a hotspots or a coldspot.

Step 3: Calculate the significance of the most likely cluster

The final step is to calculate the significance of the most likely cluster, which is the scanning window with the greatest difference between the expected and observed number of events, under the null hypothesis of spatial randomness [170]. The cluster p-value is derived from ranking the observed distribution compared to many simulated distributions, based on Monte Carlo simulation [170]. The Monte Carlo simulation generates a large number of random spatial distributions, for which likelihood values are also calculated. Then, all likelihood values

including the one from the observed dataset, are ranked [170]. The higher the likelihood, the higher the rank and the less likely the spatial distribution was given to chance (high significance, low p-value) [170]. A p-value less than 0.05 for the observed dataset would indicate that it was among the top 50 likelihood values if for example there were 999 simulations, and it would be considered statistically significant, indicating that the observed data is unlikely to have occurred by chance alone, as expressed below [170]:

$$p - value = \frac{R}{(1 + m)}$$

Where:

Variable	Description
R	Rank of the likelihood function
m	Number of simulations. Typically, there are 999 simulations, or other numbers ending in 9, to have clean and simple math (1+999 = 1000).

A relative risk for each identified cluster is then generated to compare the probability of an event inside the scanning window from outside the scanning window, expressed below:

$$RR = \frac{(A/A + B)}{(C/C + D)}$$

Where:

	Event (i.e., malaria infection)	**Not an Event** (i.e., no malaria infection)
Inside scanning window	A	B
Outside scanning window	C	D

3.6. Chapter Summary

This chapter further details the methods used to address the objectives of the studies in Tanzania (chapter 4) and Benin (chapter 5), beyond what was described in each manuscript. Overall, the three studies that form this doctoral thesis include two mixed-methods studies and one scoping review. In the study in Tanzania (chapter 4), we used an explanatory sequential mixed-methods design where we started with a cross-sectional survey in January 2022 followed by a community mapping activity and direct field observations in August of that same year to provide context to the cross-sectional results (higher than hypothesized schistosomiasis seroprevalence). This study was nested in a four-arm, cluster randomized control trial, where we specifically used data from the 36-month post net distribution cross-sectional survey. We used mixed-effects logistic regression models accounting for a clustered sampling design to identify factors associated with all five outcomes (malaria prevalence, schistosomiasis seroprevalence, co-infection, and strong-positive schistosomiasis and strong-positive co-infection). For the qualitative component, we conducted a thematic analysis identifying themes and sub-themes arising from the community maps and field observations to support and explain the higher than hypothesized schistosomiasis seroprevalence in the study area.

For the study in Benin (chapter 5), we used a convergent parallel mixed methods design where we collected data from a cross-sectional survey and qualitative data through FGD at the same time point. This study was nested in a three-arm, cluster randomized control trial, where we used data from the 18-month post net distribution cross-sectional and cohort survey. We used mixed-effects logistic regression models accounting for a clustered sampling design to evaluate factors influencing COVID-19 knowledge, understand the impact of COVID-19 on LLIN usage and

access, and assess changes in access to health centres during the pandemic. For the qualitative component, we used thematic analysis identifying themes and sub-themes arising from the FGDs to provide context to the cross-sectional results.

CHAPTER 4

Malaria and Schistosomiasis in Tanzania

4.1. Article Preface

4.1.1 Article Preface

This article was accepted to PLOS Global Public Health on October 18, 2023. The objective of this article was to understand population vulnerabilities, and identify socio-ecological factors associated with malaria and schistosomiasis mono- and co-infection among school-aged children in Misungwi, Lake Victoria Zone, Tanzania, using an explanatory sequential mixed-methods approach. This is the first of three manuscripts that form this doctoral research. The goal of this first manuscript was to establish and understand population vulnerabilities and socio-ecological factors associated factors for malaria, schistosomiasis, and co-infection in an area with known co-endemicity – which has not previously been done. Malaria and schistosomiasis are two of the major parasitic vector-borne diseases that remain a significant public health challenge, especially in sub-Saharan Africa. Although significant progress has been made in reducing the number of cases, deaths, and people at-risk for these two diseases, disease elimination continues to face significant challenges. By understanding common risk factors for malaria and schistosomiasis, we could have a better understanding of populations at risk and to inform targeted, and possibly integrated, interventions.

4.1.2 Contribution

I conceived the research question with guidance from my thesis supervisor, Dr. Manisha Kulkarni, and important input from members of my thesis advisory committee including Drs. Alison Krentel, Natacha Protopopoff, and Cindy Feng. I developed additional survey questions, participated in the cross-sectional survey alongside field team members, performed laboratory validation studies alongside Ms. Doris Mangalu, and carried out the field observations alongside Ms. Tatu Aziz and Mr. Charles Thickstun. I developed the methodological approach with

guidance from my thesis supervisor, Dr. Manisha Kulkarni, and thesis advisory committee members including Drs. Alison Krentel and Cindy Feng. I performed all the analyses and completed the first draft of the manuscript. All authors contributed to the editing and revision of this article. I reported the findings of this chapter in the form of a manuscript, a dissemination meeting in Tanzania, an oral presentation at the American Society of Tropical Medicine and Hygiene annual meeting, and an oral presentation at Research Day at the University of Ottawa.

4.1.3 Ethics approval

The protocol (including amended protocols) for this study was reviewed and approved by the institutional review boards of the University of Ottawa (Canada) and Medical Research Coordinating Committee of the National Institute for Medical Research (Tanzania).

4.1.4 Citation

Duguay C, Mosha JF, Lukole E, Mangalu D, Thickstun C, Mallya E, et al. Assessing risk factors for malaria and schistosomiasis among children in Misungwi, Tanzania, an area of co-endemicity: A mixed methods study. Falcão De Oliveira E, editor. PLOS Glob Public Health. 2023;3: e0002468. doi:10.1371/journal.pgph.0002468

4.2. Article Content

4.2.1 Title

Assessing risk factors for malaria and schistosomiasis among children in Misungwi, Tanzania, an area of co-endemicity: a mixed methods study

4.2.2 Authors

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4.2.4 Abstract

Malaria and schistosomiasis are two major parasitic vector-borne diseases that are a particular threat to young children in Sub-Saharan Africa. In the present study, we investigated factors that are associated with malaria, schistosomiasis, and co-infection among school-aged children, using an explanatory sequential mixed-methods approach. A cross-sectional study was conducted in January 2022 in Misungwi, Tanzania, that sampled 1,122 children aged 5 to 14 years old for malaria and schistosomiasis infection. Mixed-effect logistic regression models were used to assess the association between infection prevalence or seroprevalence, and environmental determinants that create favorable conditions for vectors and parasites and social determinants that relate to disease exposure. Community mapping combined with direct field observations

were conducted in August 2022 in three selected villages from the cross-sectional study to understand specific water use behaviors and to identify potential malaria mosquito larval breeding sites and freshwater snail habitat. The prevalence of malaria, seroprevalence of schistosomiasis, and co-infection in this study were 40.4%, 94.3%, and 38.1%, respectively. Individual-level factors emerged as the primary determinants driving the association with infection, with age (every one-year increase in age) and sex (boys vs girls) being statistically and positively associated with malaria, schistosomiasis, and co-infection ($P<0.05$ for all). Community maps identified many unimproved water sources in all three villages that were used by humans, cattle, or both. We found that children primarily fetched water, and that unprotected wells were dedicated for drinking water whereas ponds were dedicated for other domestic uses and cattle. Although not identified in the community maps, we found hand pumps in all three villages were not in use because of unpleasant taste and high cost. This study improves our understanding of individual, social and environmental factors that are associated with malaria, schistosomiasis, and co-infection, which can inform potential entry points for integrated disease prevention and control.

4.2.5 Introduction

Eighty percent of the world's population are at risk of one or more vector-borne diseases [47]. Malaria and schistosomiasis are two of the major parasitic vector-borne diseases that are a particular threat to young children in rural areas of sub-Saharan Africa (SSA) [47,89]. This is due to a complex interplay between their exposures to malaria and schistosomiasis vectors and intermediate hosts (*Anopheles* mosquitoes, *Biomphalaria* and *Bulinus* snails), parasites (*Plasmodium, Schistosoma)*, biological susceptibility, and adaptive capabilities (e.g., access to preventive measures and treatment) [40,86,172].

Human malaria is caused by five different *Plasmodium* parasites, with *P. falciparum* being the predominant species in SSA [39]. The dominant *Anopheles (An.)* vector mosquitoes in Africa include *An. arabiensi*s, *An. gambiae* sensu stricto (s.s.), and *An. funestus*, all with their own unique ecological niches [75,173]. *An. funestus* and *An. gambiae* s.s. share similar feeding and biting habits as they are both anthropophilic, endophagic, and bite from dusk till dawn [70,71].

Several important tools to control and prevent malaria have been introduced in the past two decades, including long lasting insecticidal nets (LLIN), early diagnosis with rapid diagnostic tests, and treatment with artemisinin-based combination therapy [40], with LLINs being the main vector control tool for preventing malaria. Two billion insecticide treated nets, including LLINs, have been distributed between 2004-2020 with 65% of households in SSA now owning at least one LLIN [50]. Despite efforts to combat the disease, malaria remains a significant public health challenge in Tanzania, accounting for 4.1% total global malaria deaths, ranking third behind Nigeria and the Democratic Republic of Congo [61].

In SSA, there are two forms of schistosomiasis caused by two different *Schistosoma* species each with their respective snail intermediate host– *S. mansoni* that infects *Biomphalaria* snails and causes intestinal schistosomiasis, and *S. haematobium* that infects *Bulinus* snails and causes urogenital schistosomiasis [23,41]. Like malaria, environmental and sociodemographic factors are important for the survival of the *Schistosoma* species, snail intermediate hosts, and the transmission of schistosomiasis [67].

The transmission cycle for schistosomiasis is influenced by human behavior, specifically the practice of open defecation, where an infected person passes parasitic eggs through their urine or feces into a freshwater source (i.e. lakes, ponds, streams) [23]. The eggs hatch and release

miracidia that penetrate freshwater snails (*Bulinus* in seasonal bodies of water, and *Biomphalaria* in permanent bodies of water) where they develop and are released back into the water as an infective form of the parasite (cercariae) [23,66,67]. The cercariae can remain in the water searching for a secondary host for up to 72 hours [69]. Once the cercariae burrows through the skin of the secondary host, it migrates to the circulatory system where it develops and matures into its adult form; male and female adult worms mate and reside in the mesenteric veins of the bladder or intestine, where female *Schistosoma* can then again release their eggs through the urine and feces of the host to continue the transmission cycle [66,69]. The lifespan of adult *Schistosoma* can survive approximately 3-6 years within their human host [67].

Prevention strategies for schistosomiasis have primarily focused on mass drug administration (MDA) campaigns that deliver praziquantel tablets without prior diagnosis to at-risk populations in endemic areas, at a frequency that depends on the endemicity of the community to reduce worm burden [23–26]. Praziquantel is effective on both *Schistosoma* species and not only treats schistosomiasis, but reduces transmission by decreasing the number of worms in the host [79,80]. Although more resource intensive and logistically complex, snail control with molluscicides and provision of safe water, sanitation, and hygiene (WASH) have also been critical for schistosomiasis prevention and control [41,69,82,83].

Schistosomiasis does not typically result in death but can lead to long-term health challenges and chronic morbidity. Tanzania has been reported to have moderate to high prevalence of schistosomiasis (irrespective of species) with considerable geographic variation, with studies reporting a prevalence of schistosomiasis between 6% and 53% in a single region of Tanzania [174–176].

Co-infection is likely to occur where malaria and schistosomiasis are co-endemic. This is

especially likely in the Lake Victoria Zone in Tanzania where malaria and schistosomiasis are both endemic. Four studies between the years of 2010 and 2017 determined the prevalence of malaria and intestinal schistosomiasis co-infection as between 22.6% and 27.2% in the Lake Victoria Zone region [18,109,177,178]. Co-endemicity is likely due to the interaction between environmental and social factors contributing to the spread of both diseases, however, there is a limited body of evidence on the risk factors associated with malaria and schistosomiasis co-infection [18,20,109,177,179–182]. Identifying factors associated with mono- and co-infection are crucial for effective prevention strategies. By moving away from a purely disease-centered approach and towards broader and integrated disease prevention strategies, we can optimize the use of limited resources to eliminate these diseases. The goal of this research is to understand population vulnerabilities, and identify socio-ecological factors associated with malaria, schistosomiasis, and co-infection among school-aged children in Misungwi, Lake Victoria Zone, Tanzania, using an explanatory sequential mixed-methods approach.

4.2.6 Methods

4.2.6.1 Study setting

This study was conducted in the district of Misungwi, which is located on the southern border of Lake Victoria in Tanzania (Fig. 4.1A). Misungwi has two rainy seasons from March to May (Masika – long rains), and from October to January (Vuli – short rains). In the study region, *An. funestus s.l.* is the predominant malaria vector species, followed by *An. gambiae s.l.* [148]. Misungwi, and subsequently the Lake Victoria Zone, provides ample habitat for *Biomphalaria* snail species (intermediate host for intestinal schistosomiasis) that are present all year round in and around Lake Victoria, and for *Bulinus* snail species (intermediate host for urogenital schistosomiasis) found in seasonal water bodies and rice fields situated inland [174,183,184].

Misungwi covers an area of over 2100 km^2 and includes 27 wards, 78 villages and a population of approximately 351,000 people; this area was divided into 86 clusters according to the main study protocol of a cluster randomized trial of malaria vector control interventions, 48 of which were used for this study (Fig. 4.1B) [155].

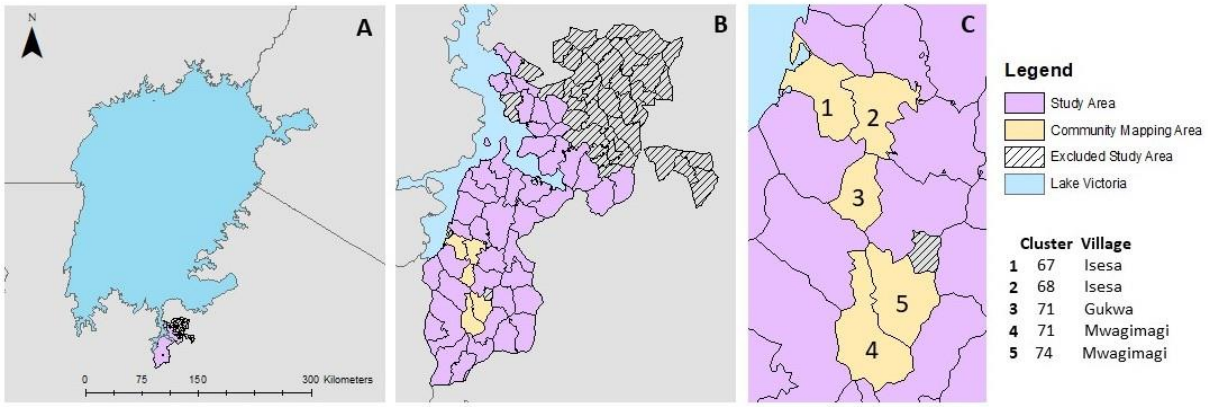

Fig. 4.1 Map highlighting the study area in reference to Lake Victoria (A), a detailed view of the 48 study clusters (B), and the three villages selected for the community mapping component (C). Map content was produced with Esri ArcGIS software using study data and data provided by GADM and Natural Earth available online: https://gadm.org/download_country.html and https://www.naturalearthdata.com/.

4.2.6.2 Sample size

The availability of limited funds necessitated schistosomiasis testing to be conducted on a smaller sample of children - 1,296 children compared to 4,200. Although we collected survey information for all 4,200 children, the analysis was restricted to the subset of children that were tested for schistosomiasis (1,296 children). The sample size of 1,296 children (27 children per cluster in 48 clusters instead of 50 children per cluster in 84 clusters) was determined based on hypothesized schistosomiasis seroprevalence. Using the sample size equation for two proportions in a cross-sectional survey with clustered sampling design, this sample size was sufficient to estimate the seroprevalence of schistosomiasis (as measured by IgG and IgM antibody detection)

with 80% power and 5% precision, assuming a seroprevalence of 50% and an intracluster correlation of 0.23 [175]. Under these assumptions it allowed us to detect an absolute 20% difference in anti-*Schistosoma* IgM and IgG antibody prevalence between two groups for any hypothesized risk factors (e.g., low and high risk) [185,186]. A detailed explanation of the calculation can be found in the supplementary file (Appendix 4.1: Sample Size Derivation).

4.2.6.3 Study design

Cross-sectional survey

The quantitative data for this study were obtained from a cross-sectional community-based survey that was nested in a four-arm, single blinded, parallel, cluster randomized control trial assessing the efficacy of three dual active-ingredients LLIN for the control of malaria [155]. Additional survey questions and a schistosomiasis testing component were added to data collection activities for the main malaria intervention trial to assess exposures that are independently and jointly associated with malaria and schistosomiasis. Data collection methods are described in detail elsewhere [155]; briefly, 45 households were randomly selected from each cluster using a census list generated at the trial baseline, and data were electronically captured using tablets/smartphones installed with ODK. Questionnaire data were collected in January 2022, three years after the trial's distribution of LLINs, from approximately 1,300 head of households (HoHs), and one child per household between the ages of five and fourteen were randomly selected for malaria and schistosomiasis testing the following day. All selected children were tested for malaria parasitemia using malaria rapid diagnostic tests (mRDTs) (CareStart RDTs; HRP2, (pf), DiaSys, Wokingham, UK), and schistosomiasis exposure (does not distinguish between *S. mansoni* and *S. haematobium)* using immunochromatographic (ICT) IgG-IgM rapid tests (sRDTs) (LDBio Diagnostics Inc, Lyon, France). When mRDTs and sRDTs

were positive, free artemether-lumefantrine and Praziquantel tablets were provided, respectively. The mRDTs were kept at ambient temperature in sealed bags with desiccant packs for up to six weeks before being transferred to 4°C where they were kept until September 2022. Pictures of all complete sRDTs were taken using tablets/smartphones and classified based on the intensity of the test band with more intense bands hypothesized to reflect higher IgM antibody titers (i.e., recent infection) relative to IgG antibody titers (i.e., past infection). A strong-positive test was characterized by a sRDT with a clear and distinct test band (recent infection) (Fig. 4.2A), whereas a weak-positive test was characterized by a faint test band (past infection) (Fig. 4.2B).

Fig. 4.2 Example of *Schistosoma* immunochromatographic IgG-IgM rapid test classification: strong-positive test (A), weak-positive test (B), negative test (C)

Environmental data

The environmental data for this study (temperature, precipitation, NDVI, population density and distance to Lake Victoria) were obtained from publicly accessible satellite imagery and are

defined in the supplementary file (Appendix 4.2: Variable Definitions). Briefly, daytime land surface temperature (LST) and NDVI were obtained from the Moderate Resolution Imaging Spectroradiometer (MODIS)[187,188], precipitation was obtained from WorldClim [189], population density was obtained from WorldPop [190], and distance to Lake Victoria was calculated using data from Natural Earth[191]. The finest spatial resolution available from each source were chosen including: 1km for LST, 250 m for NDVI, 1 km for population density and precipitation. These data were then linked to each household from the cross-sectional survey.

Performance of schistosomiasis rapid diagnostic test

The performance of the sRDTs were assessed by measuring the sensitivity and specificity of the test compared to a gold standard enzyme-linked immunosorbent assay (ELISA) kit. We retrieved and eluted blood spots from 188 (15%) mRDTs from the cross-sectional to detect anti-Schistosoma *mansoni* and *haematobium* IgG and IgM antibodies using Human Schistosoma *mansoni* Antibody IgM ELISA kits, Schistosoma *mansoni* Antibody IgG ELISA kits, and Schistosoma *haematobium* Antibody ELISA kits (MyBiosource Inc, San Diego, USA). The elution procedure followed the methods outlined by Williams et al., 2009 [192]. Briefly, the mRDTs were dismantled and the blood exposed areas were cut into small pieces and placed in a 1.5 mL microtubes immersed in: 1) 0.5mL Phosphate-buffered saline (Invitrogen), 2) 0.05% (v/v) Tween-20 (Sigma), and 3) 0.1% (w/v) Sodium Azide (Aldrich). The microtubes were agitated overnight, and the eluted solution was used as directed by the manuals outlined in the ELISA kits.

Community mapping

The qualitative data collection for this study was conducted in August 2022 through a community mapping activity combined with direct field observations. Two villages from the

cross-sectional study (Isesa and Mwagimagi) were selected based on malaria, schistosomiasis, and co-infection prevalence (one with high prevalence for all and one with low prevalence for all), and proximity to Lake Victoria (one inland and one by the lake). At some point between the formation of the study area and the community mapping, Gukwa seceded from Mwagimagi to become a separate village – therefore, additional maps were created for Gukwa. Ten community members above the age of 18 from each village (at least 5 men and 5 women per village) were selected by village leaders to create a map of their village (one map for men, and one map for women) to identify the location of temporary and permanent bodies of water (which can serve as mosquito larval breeding sites and snail habitats) as well as their specific uses (i.e., bathing, laundry, fetching water). We then identified the features in the community maps, along with other bodies of water that were not identified in the map, to understand water access and use behaviors.

4.2.6.4 Statistical approach

Data analysis focused on three primary outcomes: 1.1) malaria prevalence, 1.2) schistosomiasis seroprevalence, and 1.3) malaria and schistosomiasis co-infection; and two secondary outcomes: 2.1) strong-positive schistosomiasis seroprevalence (based on picture classification) and 2.2) malaria and strong-positive schistosomiasis co-infection.

Candidate individual-level determinants, household-level social determinants and environmental determinants hypothesized to be associated with malaria, schistosomiasis, and co-infection are detailed below and further defined in a supplementary file (Appendix 4.2: Variable Definitions). To identify overlapping determinants across the two diseases and for comparability across the models, the same set of variables were included in all three models. Individual determinants, such as age and sex, are biological features that are often associated with disease. Social

determinants include social and economic factors that may expose someone to malaria or schistosomiasis which include household socioeconomic status (SES), HoH education, HoH occupation, HoH knowledge of diseases, and HoH perception of the diseases. Environmental determinants include factors that create favorable conditions for malaria and schistosomiasis vectors and parasites and include climate, urbanization, and distance and exposure to breeding sites. A wealth score, as a proxy for household SES, was calculated based on household durable assets and dwelling characteristics using a Principal Component Analysis. The wealth score was ranked and categorized into quintiles where the first quintile represented the poorest group and the fifth quintile the least poor group [193,194]. LLIN access is defined by the WHO as the percentage of population that could be protected by a LLIN, if each LLIN in a household could be used by two people [14]. The water, sanitation, and hygiene (WASH) indicators were dichotomized as either improved or unimproved sources as defined by the Joint Monitoring Programme for Water Supply, Sanitation and Hygiene [94]. A knowledge score was calculated based on spontaneously identifying at least one correct symptom and at least one mechanism of transmission for each disease [195,196]. Perception of each disease was measured for the head of household by the question "in your opinion, how many people in your village have malaria/schistosomiasis?" with the following options: none, few, some, many, everyone, don't know (was not read out as an option). The following categories were collapsed: few/some and many/everyone due to low response rates in some categories. Concern of each disease was measured for the head of household by the question "are you concerned about malaria/schistosomiasis personally?" with the following options: not at all concerned, slightly concerned, somewhat concerned, moderately concerned, extremely concerned, don't know (was not read out as an option). The following categories were collapsed: somewhat to slightly

concerned and moderately to extremely concerned due to low response rates in some categories. A households distance to Lake Victoria was categorized as near (<1km) and far (>5km) based on previously published definitions [174,197].

Descriptive statistics

Descriptive statistics were used to summarize the characteristics of the study population. Frequencies and proportions for categorical variables and median, minimum, and maximum values for continuous variables were generated in SAS version 9.4 (SAS Institute, Cary, NC, USA). The differences in study population in the two selected villages for the community mapping (Mwagimagi and Gukwa are combined for this analysis) were compared using chi-square, Fisher's exact, or a Kruskal-Wallis tests. p-values less than 0.05 were considered statistically significant.

Mixed-effect logistic regression models

Mixed-effects logistic regression models accounting for a clustered sampling design were used to identify individual- and household-level social determinants, and environmental determinants that were associated with all five outcomes. The PROC GLIMMIX procedure in SAS version 9.4 (SAS Institute, Cary, NC, USA) was used to fit the generalized linear mixed model (GLMM) using the Laplace parameter approximation, a logit link, and random effects at the cluster level. A random effect term for the cluster in which the individual belonged was included to account for the heterogeneity in the 48 clusters – the random effect was assumed to follow a normal distribution. The models were also adjusted for the study intervention arm to account for potential biases or effects introduced by the type of LLIN assigned as part of the main trial protocol. Using SAS version 9.4 (SAS Institute, Cary, NC, USA), the univariable association between all candidate explanatory variables and each outcome was assessed, and variables with a

p-value of less than 0.2 were entered into a multivariable model. For models that could not accommodate all candidate explanatory variables due to low numbers of events (co-infection secondary analysis), the "Dredge" function in the MuMIn package in RStudio version 4.1.3 (R Core Team, 2018) was used to determine the best combination of explanatory variables from those selected using a p-value of less than 0.2 [199]. The Dredge function is a model selection tool that ranks every candidate model (2n models, where n is the number of predictors in the full model) based on the Akaike Information Criterion (AIC). A limit of ten events per variable was placed for the model selection and the final model based on minimizing the AIC for the models using the "Dredge" function was fit.

Multicollinearity between explanatory variables in the mixed-effects logistic regression models for all five outcomes was assessed – a variance inflation factor of greater than 2.5 was considered substantial collinearity [200]. Model fit was assessed in SAS version 9.4 (SAS Institute, Cary, NC, USA) by the area under a receiver operating characteristic curve (AUC) which is a measure of discrimination that evaluates the models' ability to correctly classify cases and non-cases. AUC values range from 0.5 to 1, with higher values indicating better discrimination. AUC values between 0.5 and 0.7 indicated poor discrimination, values between 0.7 and 0.8 indicated acceptable discrimination, values between 0.8 and 0.9 indicated excellent discrimination and 0.9 or higher indicated outstanding discrimination [201]. Spatial autocorrelation was then assessed by computing the Global Moran's I statistic, which measures the degree of spatial autocorrelation of the regression residuals, which was implemented in ArcMap version 10.8.1 (ESRI, Redlands, CA, USA) [202]. A p-value less than 0.05 was considered statistically significant, indicating the presence of significant spatial autocorrelation in the residuals.

4.2.6.5 Cluster analysis

Spatial clusters of high and low infection at the household-level for all five outcomes were assessed using Getis-Ord-Gi* in ArcMap version 10.8.1 (ESRI, Redlands, CA, USA) and further analyzed using SatScan software (v 9.4.1 Kulldorf and Information Management Services, Inc.) [169]. Getis-Ord-Gi* is a statistical technique used to identify hotspots (high value surrounded by high value) and coldspots (low value surrounded by low value) that are determined at the 99%, 95% and 90% confidence levels. For example, at a 5% level of significance, a Getis-Ord-Gi* z-score greater than 1.96 indicates statistically significant hotspots and values less than -1.96 indicate statistically significant coldspots. In this analysis, the data were analyzed at the household-level using the default settings (fixed distance band and a Euclidean distance between features) to identify hotspots and coldspots in the study area. SatScan is a software that detects clusters of high or low values in spatial data by using a scanning window of varying radii that moves across the study area. A relative risk for each cluster is then generated, where a risk ratio (RR) of greater than 1 represents a cluster where the probability of being an event within the scanning window is greater than the probability of being an event outside the scanning window (RR>1). A p-value less than 0.05 was considered statistically significant, indicating that the observed cluster is unlikely to have occurred by chance alone. Results from the Getis-Ord-Gi* and SatScan were overlaid in ArcMap and visually inspected to identify hotspots and coldspots of infection.

4.2.6.6 Qualitative approach

The community mapping activity combined with direct field observations were conducted to strengthen our understanding of the risk factors and exposures to malaria and schistosomiasis. We observed and engaged with individuals fetching water to understand their water use

behaviors. Along with structured visual observations (initial plan determined by community maps), we took detailed notes on topics such as: 1) water use (i.e., drinking water, bathing water), 2) number of times a day the water source was frequented, and 3) the rationale for visiting a particular water source. Themes and subthemes from the community maps and field observations were used to support and explain the higher than hypothesized schistosomiasis seroprevalence in the study area – beyond what was captured by the questions in the cross-sectional survey.

4.2.6.7 Ethics statement

The protocol for this study was reviewed and approved by the institutional review boards, of the University of Ottawa (Canada) and Medical Research Coordinating Committee of the National Institute for Medical Research (Tanzania). Written informed consent forms were obtained from the HoH, adult guardian in the household, or participant prior to data collection activities. Study data did not include information that could be used to identify individual study participants. All participants were anonymized using study numbers as unique participant identifiers. . Additional information regarding the ethical, cultural, and scientific considerations specific to inclusivity in global research is included in the Supporting Information (Appendix 4.3: Inclusivity in Global Research).

4.2.7 Results

4.2.7.1 Characteristics of the study population

1122 children were included in this study. The median age of selected children was 9 years old, and there were an equal number of girls (n=563, 50.2%) and boys (n=559, 49.8%) (Table 4.1). Nearly two thirds of HoHs had a primary school education (n=754, 67.2%) and most were farmers (n=1055, 94.0%). LLIN ownership (households with at least 1 LLIN) was high (n=1077,

96.0%), but adequate household-level LLIN access (1 LLIN for every 2 people in the household) was low (n=314, 28.0%). The majority (81.1%) of households had unimproved sanitation facilities, with 17.6% (n=198) of households without any toilet facility (bush toilets). The prevalence of malaria, seroprevalence of schistosomiasis, and co-infection, were 40.5%, 94.3%, and 38.1% respectively (Table 4.1). For the secondary analysis, the seroprevalence of strong-positive schistosomiasis and strong-positive co-infection in this study were 29.7% and 14.2%, respectively. Children in Mwagimagi had a higher malaria prevalence than Isesa (83.3% vs 30.6%, $P<0.0001$) and households in this village were further away from Lake Victoria compared to Isesa (100% of households in Mwagimagi >5km from Lake Victoria vs 44.9% households in Isesa >5 km from Lake Victoria, $P<0.0001$).

Table 4.1: Characteristics of the study participants and child infection/seropositivity status in the 48 clusters and the two selected villages for the qualitative activities in Misungwi district, Lake Zone, Tanzania, in January 2022

		Total* (n = 1122)	Mwagimagi (n = 42)	Isesa (n = 49)	P-value[%]
Child Infection					
	Malaria	454 (40.5%)	35 (83.3%)	15 (30.6%)	<0.0001
	Schistosomiasis	1058 (94.3%)	38 (90.5%)	49 (100%)	0.0898
	Co-infection	428 (38.1%)	31 (73.8%)	15 (30.6%)	<0.0001
	Schistosomiasis#	328 (29.7%)	13 (31.7%)	14 (29.2%)	0.9772
	Co-infection#	156 (14.2%)	10 (24.4%)	7 (14.6%)	0.3667
Individual Determinant (child)					
Age of selected child (median)					
		9 (5, 14)	10 (5, 14)	10 (5, 14)	0.7122
Sex of selected child					
	Girl	563 (50.2%)	19 (45.2%)	30 (61.2%)	
	Boy	559 (49.8%)	23 (54.8%)	19 (38.8%)	0.1888
Social Determinants (household)					
Head of household education					
	None	318 (28.3%)	16 (38.1%)	11 (22.4%)	
	Primary	754 (67.2%)	26 (61.9%)	37 (75.5%)	
	Secondary or higher	50 (4.5%)	0	1 (2.1%)	0.1894

Head of household occupation					
	Farming	1055 (94.0%)	41 (97.6%)	48 (98.0%)	
	Other	67 (6.0%)	1 (2.4%)	1 (2.0%)	1
Socioeconomic status					
	Lowest	233 (20.8%)	12 (28.6%)	8 (16.3%)	
	Low	235 (20.9%)	10 (23.8%)	12 (24.5%)	
	Average	240 (21.4%)	7 (16.7%)	12 (24.5%)	
	High	202 (18.0%)	8 (19.0%)	9 (18.4%)	
	Highest	212 (18.9%)	5 (11.9%)	8 (16.3%)	0.6401
Malaria-only					
Knowledge of disease					
	Yes	882 (78.6%)	36 (85.7%)	41 (83.7%)	
	No	240 (21.4%)	6 (14.3%)	8 (16.3%)	0.7879
Perception of disease					
	None	18 (1.6%)	0	0	
	Few/some	346 (30.8%)	11 (26.2%)	14 (28.6%)	
	Many/everyone	462 (41.2%)	17 (40.5%)	17 (34.7%)	
	Don't know	296 (26.4%)	14 (33.3)	18 (36.7%)	0.8507
Concern of disease personally					
	Not at all concerned	255 (22.7%)	3 (7.1%)	15 (30.6%)	
	Somewhat to slightly concerned	196 (17.5%)	6 (14.3%)	6 (12.2%)	
	Moderately to extremely concerned	642 (57.2%)	32 (76.2%)	28 (57.1%)	
	Don't know	29 (2.6%)	1 (2.4%)	0	0.03236
LLIN Access					
	Yes	314 (28.0%)	8 (19.0%)	9 (18.4%)	
	No	808 (72.0%)	34 (81.0%)	40 (81.6%)	1
Schistosomiasis-only					
Knowledge of disease					
	Yes	419 (37.3%)	17 (40.5%)	17 (34.7%)	
	No	703 (52.7%)	25 (59.5%)	32 (65.3%)	0.5698
Perception of disease					
	None	99 (8.8%)	3 (7.1%)	3 (6.1%)	
	Few/some	450 (40.1%)	21 (50.0%)	19 (38.8%)	
	Many/everyone	141 (12.6%)	2 (4.8%)	6 (12.2%)	0.5221

	Don’t know	432 (38.5%)	16 (28.1%)	21 (42.9%)	
Concern of disease personally					
	Not at all concerned	375 (33.4%)	9 (21.4%)	4 (8.2%)	
	Somewhat to slightly concerned	197 (17.6%)	11 (26.2%)	4 (8.2%)	
	Moderately to extremely concerned	488 (43.5%)	17 (40.5%)	22 (44.9%)	
	Don’t know	62 (5.5%)	5 (11.9%)	0	0.002213
Drinking Source					
	Improved	245 (21.8%)	0	0	
	Unimproved	877 (78.2%)	42 (100%)	49 (100%)	NA
Sanitation facility					
	Improved	169 (15.1%)	0	6 (12.2%)	
	Pit latrine	755 (67.3%)	30 (71.4%)	38 (77.6%)	
	Bush toilet	198 (17.6%)	12 (28.6%)	5 (10.2%)	0.0094
Hygiene					
	Improved	751 (66.9%)	28 (66.7%)	32 (65.3%)	
	Unimproved	371 (33.1%)	14 (33.3%)	17 (34.7%)	1
Environmental Determinants					
Temperature (°C)					
		30.0 (22.7, 34.7)	30.0 (27.9, 31.5)	29.1 (23.8, 30.8)	<0.0001
Precipitation (mm)					
		98 (94, 103)	98 (96, 101)	99 (97, 101)	0.3073
NDVI					
	Sparse vegetation	972 (86.6%)	35 (83.3%)	39 (79.6%)	
	Dense vegetation	150 (13.4%)	7 (16.7%)	10 (20.4%)	0.8519
Population Density (per km^2)					
	<100 per km^2	128 (11.4%)	14 (33.3%)	2 (4.1%)	
	100-200 per km^2	642 (57.2%)	28 (66.7%)	15 (30.6%)	
	>200 per km^2	352 (31.4%)	0	32 (65.3%)	<0.0001
Distance to Lake Victoria (km)					
	Near (<1km)	87 (7.8%)	0	5 (10.2%)	
	Middle	412 (36.7%)	0	22 (44.9%)	<0.0001

	Far (>5km)	623 (55.5%)	41 (100%)	22 (44.9%)	

Data are displayed as n (%), median (min, max)
* Includes Mwagimagi and Isesa
%P-values (significant differences between two selected villages for community mapping, by using the chi squared test or fisher exact test for comparison of proportions, and Kruskal-Wallis test for medians.
Secondary analysis based on picture classification where a strong-positive test was characterized by a sRDT with a clear and distinct test band (recent infection), and a weak-positive test was characterized by a faint test band (past infection).
Abbreviations: LLIN: Long Lasting Insecticidal Nets; LST: Land Surface Temperature; NDVI: Normalized Difference Vegetation Index

4.2.7.2 Determinants of malaria, schistosomiasis, and co-infection

The univariable association between all factors are included in the appendix (Appendix 4.4: Univariable Associations). Individual determinants, including age and sex of the selected child, emerged as the primary determinants driving the association with infection status. Older age was associated with higher infection prevalence for malaria (aOR = 1.19; P<0.0001), schistosomiasis (aOR = 1.26; P<0.0001), and co-infection (aOR = 1.20; P<0.0001); while boys had higher odds of infection compared to girls for malaria (aOR = 1.44; P=0.0083), and co-infection (aOR = 1.54; P=0.0016) (Table 4.2). A limited number of household-level social determinants were found to be associated with infection status. Not having adequate LLIN access was positively associated with malaria (aOR = 1.67; P=0.0013), schistosomiasis (aOR = 1.94; P=0.0389), and co-infection (aOR = 1.67; P=0.0015) and having unimproved water sources was positively associated with malaria (aOR = 2.02; P=0.0003) and co-infection (aOR = 1.96; P=0.0005). Two environmental determinants, namely population density and distance to Lake Victoria, were key factors associated with malaria and co-infection, but not with schistosomiasis. Households in less densely populated areas (<100 compared to >200 people per km^2) had higher odds of malaria infection (aOR = 2.59; P=0.0008) and co-infection (aOR = 2.40; P=0.0012), and households further from the lake (≥ 5km compared to <1km from the lake) had higher odds of

malaria infection (aOR = 1.84; *P*=0.0444). The final multivariable models for malaria and co-infection had acceptable discrimination (malaria: AUC = 0.76, co-infection: AUC = 0.75), while the model for schistosomiasis had outstanding discrimination (AUC = 0.91). There was no evidence of spatial autocorrelation for any primary model (malaria: *P* = 0.4120, schistosomiasis: *P* =0.9796, co-infection: *P* = 0.3947) based on Global Moran's I test.

Table 4.2: Results of primary mixed-effects logistic regression analysis of factors associated with malaria, schistosomiasis, and co-infection (n = 1122)

		Malaria			Schistosomiasis			Co-infection		
		aOR*	(95% CI)	P-value	aOR*	(95% CI)	P-value	aOR*	(95% CI)	P-value
Significant Determinants										
Age of Selected Child										
		1.19	(1.13-1.25)	<0.0001	1.26	(1.12-1.41)	<0.0001	1.20	(1.14-1.26)	<0.0001
Sex of Selected Child										
	Girl	REF	-	-	REF	-	-	REF	-	-
	Boy	1.44	(1.10-1.88)	0.0083	1.64	(0.90-3.01)	0.1080	1.54	(1.18-2.02)	0.0016
LLIN Access										
	Yes	REF	-	-	REF	-	-	REF	-	-
	No	1.67	(1.22-2.30)	0.0013	1.94	(1.03-3.62)	0.0389	1.67	(1.21-2.29)	0.0015
Knowledge of disease (schistosomiasis)										
	Yes	0.69	(0.51-0.94)	0.0167	-	-	-	0.71	(0.53-0.97)	0.0308
	No	REF	-	-	-	-	-	REF	-	-
Concern of disease personally (schistosomiasis)										
	Not at all concerned	0.67	(0.48-0.92)	0.0150	-	-	-	0.96	(0.50-1.86)	0.0324
	Somewhat to slightly concerned	0.68	(0.46-1.00)	0.0508	-	-	-	1.75	(1.09-2.82)	0.0057
	Moderately to extremely concerned	REF	-	-	-	-	-	REF	-	-
	Don’t know	0.58	(0.31-1.12)	0.1035	-	-	-	1.80	(1.08-2.99)	0.1099
Drinking water										
	Improved	REF	-	-	-	-	-	REF	-	-
	Unimproved	2.02	(1.38-2.97)	0.0003	-	-	-	1.96	(1.35-2.86)	0.0005
Population density										
	<100 per km^2	2.59	(1.49-4.51)	0.0008	-	-	-	2.40	(1.41-4.08)	0.0012
	100-200 per km^2	2.04	(1.41-2.95)	0.0002	-	-	-	2.10	(1.47-3.00)	<0.0001
	>200 per km^2	REF	-	-	-	-	-	REF	-	-
Distance to Lake Victoria (km)										
	Near (<1km)	REF	-	-	-	-	-	REF	-	-

	Middle	1.10	(0.61-1.98)	0.7346	-	-	-	1.04	(0.56-1.82)	0.9622
	Far (>5km)	1.84	(1.01-3.32)	0.0444	-	-	-	1.68	(0.95-2.96)	0.0718
Non-Significant Determinants										
Socioeconomic status										
	Lowest	1.30	(0.81-2.07)	0.2794	-	-	-	1.21	(0.75-1.94)	0.4316
	Low	1.52	(0.96-2.41)	0.0738	-	-	-	1.51	(0.95-2.38)	0.0818
	Average	1.00	(0.64-1.48)	0.9857	-	-	-	0.96	(0.61-1.52)	0.8738
	High	0.95	(0.59-1.54)	0.8570	-	-	-	0.92	(0.57-1.49)	0.7342
	Highest	REF	-	-	-	-	-	REF	-	-
Perception of disease (malaria)										
	None	0.99	(0.34-2.88)	0.9946	0.32	(0.04-2.45)	0.2749	1.11	(0.38-3.21)	0.8411
	Few/some	1.01	(0.91-1.95)	0.9533	1.17	(0.56-2.40)	0.6782	1.05	(0.74-1.47)	0.7859
	Many/everyone	REF	-	-	REF	-	-	REF	-	-
	Don’t know	1.33	(0.91-1.95)	0.1404	2.13	(0.85-5.35)	0.1061	1.32	(0.91-1.94)	0.1399
Concern of disease personally (malaria)										
	Not at all concerned	-	-	-	1.68	(0.72-3.90)	0.2260	-	-	-
	Somewhat to slightly concerned	-	-	-	1.67	(0.64-4.40)	0.2955	-	-	-
	Moderately to extremely concerned	-	-	-	REF	-	-	-	-	-
	Don’t know	-	-	-	0.16	(0.04-0.68)	0.0136	-	-	-
Perception of disease (schistosomiasis)										
	None	0.81	(0.43-1.55)	0.5234	1.22	(0.38-3.86)	0.7352	0.70	(0.51-0.97)	0.9259
	Few/some	1.46	(0.92-2.32)	0.1101	1.59	(0.68-3.73)	0.2805	0.57	(0.38-0.85)	0.0213
	Many/everyone	REF	-	-	REF	-	-	REF	-	-
	Don’t know	1.40	(0.85-2.30)	0.1833	1.83	(0.73-4.57)	0.1923	0.59	(0.31-1.12)	0.0230
Sanitation facility										
	Improved	REF	-	-	-	-	-	REF	-	-
	Pit latrine	1.14	(0.73-1.80)	0.5777	-	-	-	1.15	(0.72-1.83)	0.5535
	Bush Toilet	1.18	(0.68-2.04)	0.5557	-	-	-	1.34	(0.65-1.98)	0.6549
Hygiene										
	Improved	REF	-	-	-	-	-	REF	-	-

	Unimproved	1.06	(0.79-1.42)	0.6980	-	-	-	1.10	(0.82-1.48)	0.5211

* Random effects for cluster and adjusted for intervention arm

Abbreviations: aOR: Adjusted Odds Ratio; LLIN: Long Lasting Insecticidal Nets; LST: Land Surface Temperature; NDVI: Normalized Difference Vegetation Index

Results from the primary analysis were comparable to results obtained from the secondary analysis that investigated factors associated with strong-positive schistosomiasis seropositivity and strong-positive co-infection, in terms of identified determinants and associated strength of association. Individual-level social determinants continued to be the primary determinants driving the association with strong-positive schistosomiasis seropositivity and strong-positive co-infection. Aligned with the primary analysis, older age was associated with higher prevalence for strong-positive schistosomiasis seropositivity (aOR = 1.20; $P<0.0001$), and strong-positive co-infection (aOR = 1.28; $P<0.0001$); while boys had higher odds compared to girls for strong-positive schistosomiasis seropositivity (aOR = 2.56; $P<0.0001$), and strong-positive co-infection (aOR = 2.46; $P<0.0001$) (Table 4.3). Differences in the two analyses were present for the association between LLIN access; unlike the primary analysis that indicated an association with co-infection prevalence and not schistosomiasis seroprevalence, the secondary analysis demonstrated a positive association between inadequate LLIN access and strong-positive schistosomiasis seropositivity (aOR 1.43; $P= 0.0342$) as well as strong-positive co-infection (aOR = 1.93; $P = 0.0043$). The final multivariable models for the secondary analyses had acceptable discrimination (strong-positive schistosomiasis: AUC = 0.77, strong-positive co-infection: AUC = 0.78). There was no evidence of spatial autocorrelation for any secondary model (strong-positive schistosomiasis: $P = 0.9626$, strong-positive co-infection: $P = 0.9662$) based on Global Moran's I test.

Table 4.3: Results of secondary mixed-effects logistic regression analysis of factors associated with malaria infection, strong-positive schistosomiasis seropositivity, and malaria and strong-positive schistosomiasis co-infection (n = 1122)

		Malaria			**Schistosomiasis**			**Co-infection**		
		aOR*	(95% CI)	P-value	aOR*	(95% CI)	P-value	aOR*	(95% CI)	P-value
Significant Determinants										
Age of Selected Child										
		1.19	(1.13-1.25)	<0.0001	1.20	(1.13-1.27)	<0.0001	1.28	(1.19-1.38)	<0.0001
Sex of Selected Child										
	Girl	REF	-	-	REF	-	-	REF	-	-
	Boy	1.44	(1.10-1.88)	0.0083	2.56	(1.91-3.43)	<0.0001	2.46	(1.68-3.61)	<0.0001
Knowledge of disease (malaria)										
	Yes	-	-	-	0.61	(0.43-0.87)	0.0073	-	-	-
	No	-	-	-	REF	-	-	-	-	-
LLIN Access										
	Yes	REF	-	-	REF	-	-	REF	-	-
	No	1.67	(1.22-2.30)	0.0013	1.43	(1.03-2.01)	0.0342	1.93	(1.23-3.02)	0.0043
Knowledge of disease (schistosomiasis)										
	Yes	0.69	(0.51-0.94)	0.0167	-	-	-	-	-	-
	No	REF	-	-	-	-	-	-	-	-
Drinking water										
	Improved	REF	-	-	-	-	-	-	-	-
	Unimproved	2.02	(1.38-2.97)	0.0003	-	-	-	-	-	-
Population density										
	<100 per km^2	2.59	(1.49-4.51)	0.0008	0.94	(0.49-1.82)	0.8598	1.98	(0.97-4.05)	0.0600
	100-200 per km^2	2.04	(1.41-2.95)	0.0002	1.53	(1.01-2.31)	0.0427	2.83	(1.74-4.59)	<0.0001
	>200 per km^2	REF	-	-	REF	-	-	REF	-	-
Distance to Lake Victoria (km)										
	Near (<1km)	REF	-	-	REF	-	-	-	-	-
	Middle	1.10	(0.61-1.98)	0.7346	0.65	(0.32-1.33)	0.2400	-	-	-
	Far (>5km)	1.84	(1.01-3.32)	0.0444	0.46	(0.20-1.06)	0.0707	-	-	-

Non-Significant Determinants										
Socioeconomic status										
	Lowest	1.30	(0.81-2.07)	0.2794	-	-	-	-	-	-
	Low	1.52	(0.96-2.41)	0.0738	-	-	-	-	-	-
	Average	1.00	(0.64-1.48)	0.9857	-	-	-	-	-	-
	High	0.95	(0.59-1.54)	0.8570	-	-	-	-	-	-
	Highest	REF	-	-	-	-	-	-	-	-
Perception of disease (malaria)										
	None	0.99	(0.34-2.88)	0.9946	0.98	(0.32-2.99)	0.9747	-	-	-
	Few/some	1.01	(0.91-1.95)	0.9533	1.66	(1.18-2.35)	0.0036	-	-	-
	Many/everyone	REF	-	-	REF	-	-	-	-	-
	Don’t know	1.33	(0.91-1.95)	0.1404	1.37	(0.94-2.00)	0.0976	-	-	-
Concern of disease personally (malaria)										
	Not at all concerned	-	-	-	-	-	-	-	-	-
	Somewhat to slightly concerned	-	-	-	-	-	-	-	-	-
	Moderately to extremely concerned	-	-	-	-	-	-	-	-	-
	Don’t know	-	-	-	-	-	-	-	-	-
Perception of disease (schistosomiasis)										
	None	0.81	(0.43-1.55)	0.5234	-	-	-	1.31	(0.48-3.59)	0.5951
	Few/some	1.46	(0.92-2.32)	0.1101	-	-	-	2.78	(1.31-5.90)	0.0079
	Many/everyone	REF	-	-	-	-	-	REF	-	-
	Don’t know	1.40	(0.85-2.30)	0.1833	-	-	-	2.25	(1.05-4.81)	0.0351
Concern of disease personally (schistosomiasis)										
	Not at all concerned	0.67	(0.48-0.92)	0.0150	-	-	-	-	-	-

	Somewhat to slightly concerned	0.68	(0.46-1.00)	0.0508	-	-	-	-	-	-
	Moderately to extremely concerned	REF	-	-	-	-	-	-	-	-
	Don’t know	0.58	(0.31-1.12)	0.1035	-	-	-	-	-	-
Sanitation facility										
	Improved	REF	-	-	-	-	-	-	-	-
	Pit latrine	1.14	(0.73-1.80)	0.5777	-	-	-	-	-	-
	Bush Toilet	1.18	(0.68-2.04)	0.5557	-	-	-	-	-	-
Hygiene										
	Improved	REF	-	-	-	-	-	-	-	-
	Unimproved	1.06	(0.79-1.42)	0.6980	-	-	-	-	-	-
Environmental determinants										
Temperature (°C)										
		-	-	-	0.94	(0.84-1.07)	0.3940	-	-	-

* Random effects for cluster and adjusted for intervention arm

Abbreviations: aOR: Adjusted Odds Ratio; LLIN: Long Lasting Insecticidal Nets; LST: Land Surface Temperature; NDVI: Normalized Difference Vegetation Index

4.2.7.3 Spatial patterns and hotspots of malaria, schistosomiasis, and co-infection

There were geographic variations in infection prevalence and seroprevalence in the study area. Significant hotspots (defined visually and numerically based on overlayed results from Getis-Ord-Gi* and SatScan) of children with malaria were identified in the southern region of the study area (Cluster 1: RR = 1.68; P<0.001), while two significant coldspots were identified in the northern region of the study area (Cluster 2: RR = 0.07; P<0.001 - Cluster 3: RR = 0.44; P=0.022) (Fig. 4.3A). Although there were statistically significant clusters of schistosomiasis infection in the study area, the spatial variation in seroprevalence was not clear with evidence of coldspots of infection along the inlet of Lake Victoria (Cluster 1: RR = 0.84; P<0.001 - Cluster 2: RR = 0.83; P<0.001) (Fig. 4.3B). The spatial patterning of co-infection followed that of malaria with significant hotspots and coldspots in the southern and northern region of the study area, respectively (Fig. 4.3C).

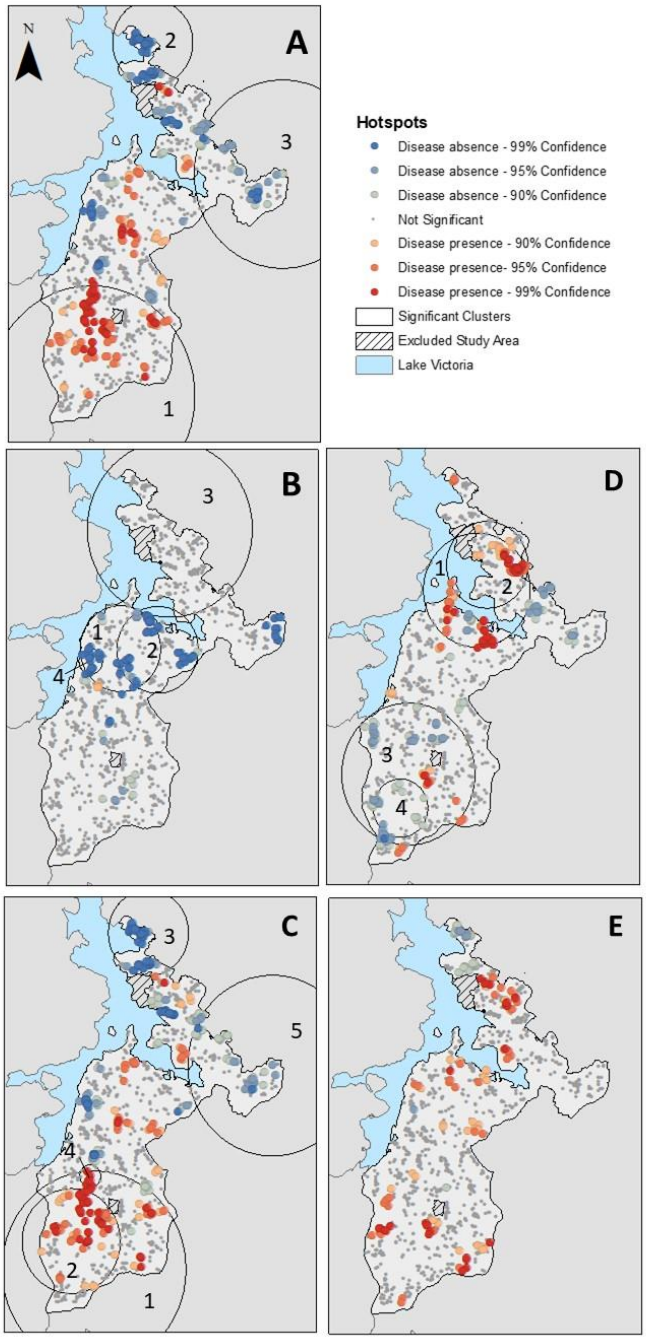

Fig. 4.3 Spatial clusters of malaria prevalence (A), schistosomiasis seroprevalence (B), malaria and schistosomiasis co-infection (C), strong-positive schistosomiasis seroprevalence (D) and malaria and strong-positive schistosomiasis co-infection (E). Map content was produced with Esri ArcGIS software using study data and data provided by GADM available online: https://gadm.org/download_country.html.

The primary (malaria, schistosomiasis, and co-infection) and secondary (strong-positive schistosomiasis, and strong-positive co-infection) analysis both identified comparable factors

associated with child infection status, however the spatial patterns in disease prevalence and seroprevalence exhibited notable differences between the primary and secondary analyses. There were two significant hotspots of strong-positive schistosomiasis seropositivity (Cluster 1: RR = 1.47; P=0.001 - Cluster 2: RR = 1.53; P=0.012) (Fig. 4.3D) in the inlet of Lake Victoria, where coldspots were previously identified in the primary analysis. There were also no significant clusters of strong-positive co-infection in the secondary analysis, compared to five that were identified in the primary analysis (Fig. 4.3E).

4.2.7.4 Performance of schistosomiasis rapid diagnostic test

The results from the Human S. mansoni Antibody IgM ELISA test, IgG ELISA test, and S. haematobium Antibody ELISA test using eluate from mRDTs collected during the cross-sectional survey, were all negative – likely reflecting the methods used to elute Schistosoma antibodies from the mRDTs.

4.2.7.5 Community mapping and field observations

Six maps were created in the three selected villages (Isesa, Mwagimagi and Gukwa) (Appendix 4.5: Six Community Maps). Community maps identified many unimproved water sources in both villages that were used by humans, cattle, or both. Overall, there were four themes that may provide an explanation for the higher than hypothesized schistosomiasis seroprevalence observed during the cross-sectional survey (Table 4.4).

Table 4.4: Emerging themes from community maps to understand and explain high schistosomiasis seroprevalence observed in children in Misungwi, Tanzania, during January 2022 cross-sectional survey.

Theme	Supporting Evidence
1. Ponds and wells	• Ponds and wells were sourced from the same body of water, separated by an arbitrary border. • Community members fetch drinking water from wells and use ponds (shared by cattle) for other domestic uses including bathing and washing.
2. Hand pumps	• Working hand pumps sourced from wells or boreholes were available in all three villages but were not in use because of unpleasant taste and cost.
3. Seasonality	• Landscapes and sources of water can look different during rainy and dry season in all three villages.
4. Health-centres	• Malaria diagnosis and treatment using RDTs and antimalarials were available in all three villages. There were no control strategies for schistosomiasis outside of annual school-based MDA.

Ponds and wells

Community maps identified many water sources, often noting ponds next to wells (Fig. 4.4A) Some maps made the distinction between cattle-only and human-only water sources, while others did not. In observing and interacting with the community map features, we found that ponds and wells were sourced from the same body of water separated by size and an arbitrary border, with the ponds being the larger body of water of the two (Fig. 4.4B-D). Wells were exclusively used for drinking water, while ponds were typically used by cattle and for all domestic uses (i.e., bathing, washing, playing). Children and women were often noted fetching water from an open water source (primarily unprotected wells) with jerry cans, up to four-times a day, while boys were found playing in the ponds.

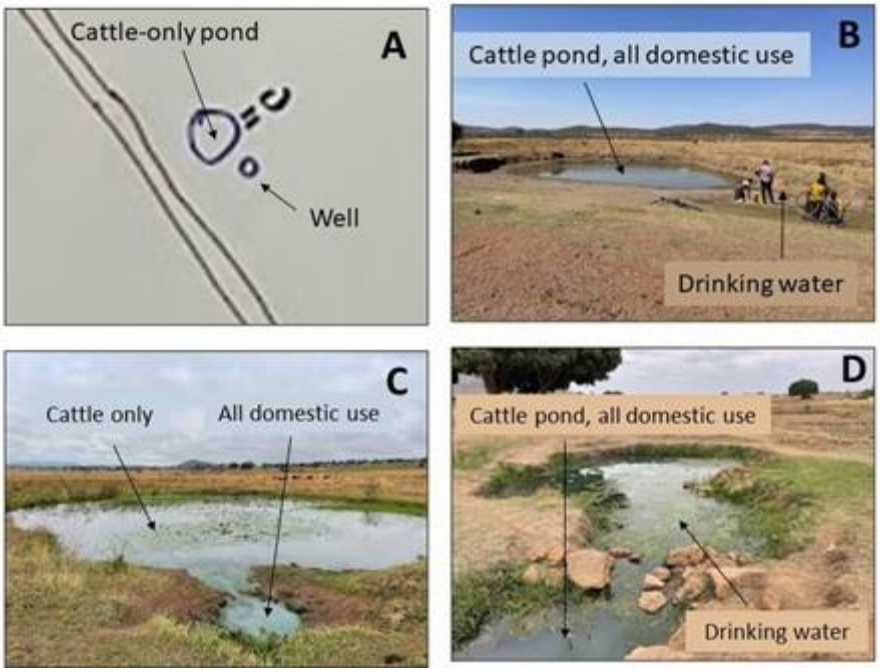

Fig. 4.4 Cattle pond and well identified in community map (A), pond and well in Mwagimagi identified in the village (B), pond and well in Gukwa identified in the village (C), pond and well in Isesa identified in the village (D)

Hand pumps

Only women in Isesa identified a hand pump as a water source in their community map. We found multiple working hand pumps sourced from either wells or boreholes in all three villages, however they were not in use because of unpleasant taste and cost. The hand pumps in both villages cost roughly 50 TSH (converted to $0.02 USD) for 20 litres of water. The quality and safety of the water sourced from the hand pumps were not assessed by the research team.

Seasonality

All six community maps identified temporary and permanent water sources in their community maps (Fig. 4.5A). The community mapping and field observations were conducted during the dry season before the Vuli (short rains from October to January). Community members from Isesa noted that the border of Lake Victoria extends up to 50-meters inland during the rainy season (Fig. 4.5B). We also found that some riverbeds and ponds were dry and were further informed

that water levels can go up-to one meter deep during the rainy season (Fig. 4.5C). Some residents also noted that rainfall provides additional sources of water for their household during the rainy seasons.

Fig. 4.5 Temporary and permanent water sources identified in male community map in Mwagimagi (A), area along Lake Victoria during dry season in Isesa (B), dry pond during dry season in Mwagimagi (C)

Health-centres

Community maps for both women and men in Isesa, Mwagimagi, and the women's map in Gukwa identified a health centre in their village. There were two health centres in Isesa, one in Mwagimagi, and none in Gukwa. Malaria RDTs and antimalarials were present at the health centres, but there were no schistosomiasis testing capacities nor praziquantel available in the three villages, including pharmacies. Pharmacies were often noted to also have inconsistent working hours.

4.2.8 Discussion

This mixed-method study assessed risk factors for malaria and schistosomiasis among children in Misungwi, Lake Victoria zone, Tanzania, an area of co-endemicity. The prevalence of malaria infection, seroprevalence of schistosomiasis, and co-infection in this study were 40.4%, 94.3%, and 38.1%, respectively. Individual-level factors emerged as the primary determinants driving the association with infection status, with age and sex (boys vs girls) being statistically and positively associated with malaria, schistosomiasis, and co-infection outcomes. Despite efforts to

examine household-level social determinants and environmental determinants, a limited number of factors were found to be associated with infection prevalence and seroprevalence which could be attributed to the high levels of exposures to mosquito larval breeding sites and snail habitats in the study area. The widespread exposure to malaria and schistosomiasis diminishes the association and distinction between social and environmental factors such as socioeconomic status or temperature with infection prevalence and seroprevalence since everyone is already exposed and vulnerable to infection. Community maps identified unimproved water sources in all three villages that were used by humans, cattle, or both. We found that children primarily fetched water, and that unprotected wells were dedicated for drinking water whereas ponds were dedicated for other domestic uses and cattle.

The results from this study suggest that malaria and schistosomiasis share a common population at risk, and that older boys are particularly vulnerable to both diseases which is consistent with other studies[174,177]. The relationship between age and schistosomiasis infection likely reflects prolonged exposures to contaminated water (i.e., fetching watching with jerry cans, bathing, laundry) in older compared to younger age groups, while the sex disparity likely reflects gender norms and water contact activities[203,204]. We found that boys were exposed to schistosomiasis by playing in potentially contaminated water and exposed to malaria by herding cattle and ensuring they grazed and had access to water.

Neither knowledge nor perception questions regarding malaria and schistosomiasis were found to have a significant association with infection prevalence and seroprevalence, likely reflecting exposures to both diseases. For instance, although housing structure was included in the wealth score as a proxy for household SES, we found that majority of households had unimproved housing (eaves: 31.6%; grass/leaf roofs: 24.6%) that could increase the risk of a child's exposure

to malaria by allowing mosquitoes to enter their home [61,205]. It is also important to note that most of the households were exposed to potentially contaminated water that can serve as mosquito larval breeding sites and snail habitats. This was evidenced by the community walkthrough and the high percentage of households with unimproved sources of water (78.2%) and sanitation facilities (84.9%). Considering these results, 2 of the 17 Sustainable Development Goals specifically state that everyone (100%) should have access to safe and affordable water and sanitation coverage by 2030 (SDG 6), and that we should end the epidemics of malaria and schistosomiasis (among others diseases) (SDG 3) [46]. It is evident that we are facing significant challenges in meeting both the Sustainable Development Goal on clean water and sanitation and on good health and well-being, which not only have serious implications for malaria and schistosomiasis, but to other water-borne diseases and neglected tropical diseases as well.

Another key factor to consider regarding risk factors for malaria and schistosomiasis and the Sustainable Development Goals, are that cattle are also present in and around human water sources in this study area. Cattle are not considered to be a significant source of transmission of schistosomiasis in SSA (intestinal and urogenital), but there is evidence of a hybrid species of *S. haematoboum* and *S. bovis* (the livestock *Schistosome*) in west Africa [206]. It is crucial to consider a One Health approach such as implementing environmental control and/or access to clean water and sanitation strategies, in high transmission areas such as Misungwi, to prevent even further public health problems.

The results of our analysis support the consideration of environmental control measures in high transmission areas like Misungwi, such as access to safe water and sanitation (for malaria and schistosomiasis), larval source management (for malaria), and snail control (for schistosomiasis), given the potential added benefits. Larval source management including mosquito larval habitat

modifications, habitat manipulations, biological control, and larviciding, targets the immature stage of the *Anopheles* mosquitoes, whereas LLINs target the adult stage – thereby making these effective and complementary approaches [87]. Although larval source management is only recommended where larval breeding sites are few, findable and fixed, it may be beneficial to investigate this integrated approach with LLIN distribution in high transmission areas like Misungwi to reduce malaria transmission [87]. Similarly for snail control for schistosomiasis, snail populations can be greatly reduced with molluscicide application, but they are rarely eliminated [69]. MDA are crucial in controlling schistosomiasis, but it is evident that there is a need to more holistically integrate environmental control strategies to reduce exposures to and transmission of schistosomiasis.

The WHO recommends that praziquantel be available in health facilities for the treatment of schistosomiasis [25,85], and a study conducted in North-western Tanzania in 2021 found that 91.3% of the public health facilities had praziquantel tablets available to patients[207]. However, we found that praziquantel was not available outside of the school-based MDA (in dispensaries or health centres) in the three selected villages. In Tanzania, school-aged children are targeted for MDA with the goal of reaching at least 75% of the population at risk for schistosomiasis [80]. Despite a current endemicity of ≥50%, there have been more than five effective rounds of MDA (>75% population covered) in Tanzania, with a national coverage of 94%, 47%, and 65%, in 2021, 2020, and 2019, respectively [80,208]. Having completed five effective rounds of MDA (based on population coverage), a recent modelling study by Li et al., revealed that while there is a reduction in prevalence during the first two rounds of MDA, the prevalence can level off during subsequent cycles [209]. In this study, we found that almost all children had been exposed to schistosomiasis at least once in their life (seroprevalence of 94.3%). Praziquantel does not

prevent reinfection, but it prevents disease progression and reduces the risk of transmission to others by reducing the number of mature *Schistosome* worms in the host [77,78]. Studies have found that there are stark decreases in the number of worms four-weeks after the administration of praziquantel, and that the number of worms return to initial levels after six-months, in high transmission areas [210,211]. Although repeated MDA poses a greater threat to praziquantel resistance, biannual MDA combined with environmental control may be more effective than annual MDA at reducing the prevalence of schistosomiasis in persistent and high-transmission areas such as Misungwi [22,75].

This study was nested in an ongoing four-arm, single blinded, parallel, cluster randomized control trial assessing the efficacy of three dual active-ingredients LLIN for the control of malaria. Although the LLIN metrics may not be generalizable to the entire population of Tanzania, it highlights important limitations in the availability and behaviors surrounding the main malaria vector control tool. Usual malaria vector control prevention strategies are based on a three year LLIN campaign targeting one LLIN for every two people [89]. In Tanzania, the national average for household-level LLIN ownership and access are 78% and 63%, respectively [213]. In our study, we found that while LLIN ownership within the household was high (96.0%), access to LLIN was limited (28.0%), for unspecified reasons. These results suggest that LLIN, as per the WHO's definition (one LLIN for two people [14]), may not align with actual practices, where individuals might find themselves sharing LLIN with three or more people. While the models did not identify any spatial autocorrelation, there were hotspots of malaria prevalence in the study area, namely in the southern area of the study area, which may indicate the need for local strategies and targeted interventions. These hotspots could be attributed to unmeasured determinants or the use of publicly available environmental data which are not

available at a fine spatial resolution (the spatial resolution of the data utilized in this study ranged between 250 meters and 1 kilometer).

Insecticide resistance in *Anopheles* mosquitoes, coupled with their behavioral resistance, also poses a threat to current efforts aimed at controlling malaria. Current control measures for malaria (LLIN) are most effective against mosquito species that are both anthropophilic (prefer to take their blood meals from human compared to other animals) and endophagic (feed indoors). Studies have however found that after LLIN distribution or community wide LLIN use, the mosquito vectors have the ability to alter their behavior by either feeding earlier [150] or shifting from endophilic to exophagic tendencies [151,152] to feed on human hosts while they are not using LLINs. There is also evidence of shifts in malaria vector species to those that are exophagic, thereby evading the protective barrier offered by LLINs and sustaining malaria transmission despite high LLIN coverage [153]. In a recent study (2018) in the Lake Region of Tanzania, An. *funestus* s.l. were the dominant malaria vector followed by An. *arabiensis* and An. *gambiae* s.s. where they all showed similar feeding patterns of feeding indoors and outdoors [148]. Current control measures for malaria (LLINs) and schistosomiasis (MDA) are not sufficient in reducing exposures to these diseases, further emphasizing the need for environmental control.

4.2.8.1 Limitations

This study was subject to some limitations. We were unable to distinguish between current and past infection of schistosomiasis, which likely explains the findings of very high (94.3%) schistosomiasis seroprevalence in the study area. Children between five and fourteen were included in this study since praziquantel tablets were not recommended for children under four years old (or under 94 cm in height) at the time of recruitment [24]. As of February 2022,

children over the age of two could be treated with praziquantel – if children between the ages of two and five were recruited in our study, we could have investigated a more discernible age-infection profile for schistosomiasis [25]. Previous research in communities along Lake Victoria found that children between the ages of one and five could demonstrate high schistosomiasis infection prevalence (i.e., 39.3% prevalence of intestinal schistosomiasis in an Ugandan community along Lake Victoria) and that IgG antibodies can persist for years after initial exposure [214–216]. To mitigate this challenge, we conducted a secondary analysis to assess the performance of the sRDT by measuring the sensitivity and specificity of the sRDT using ELISA kits as the diagnostic standard and the potential distinction between current and past infection, using the sRDT. The results from the ELISA kits were all negative – likely reflecting the methods used to elute Schistosoma antibodies from the mRDTs. The clear and distinct test bands distinguished by photos of the sRDT also likely reflect higher antibody titers (i.e., recent infection) and faint test band likely reflect lower antibody titers (i.e., past infection). In this analysis, we conducted a secondary analysis to investigate whether accounting for sRDTs with clear and distinct band (i.e., high antibody titers, recent infection), would influence the factors associated with schistosomiasis, but the results from the preliminary and secondary analysis were consistent, with no additional findings arising from the secondary analysis. We were also unable to distinguish between intestinal and urogenital schistosomiasis infections since the sRDT detects both *Schistosoma* species. This restricted our ability to evaluate the gradient of infection exposures to *S. mansoni* (intestinal schistosomiasis) near the lake and *S. haematobium* (urogenital schistosomiasis) inland [184,214]. The gold standard diagnostic test for intestinal and urogenital schistosomiasis are both processed in a laboratory that require trained personnel and include a duplicate Kato-Katz from one stool sample, and urine filtration methods,

respectively [80]. These two current methods do not meet the ASSURED (affordable, sensitive, specific, user-friendly, rapid, equipment-free, and delivered to those who need it) criteria for diagnostic tests since they are not easily administered at the village-level, where access to schistosomiasis diagnosis and treatment are needed [84]. Symptoms for malaria and schistosomiasis are non-specific which emphasize the need for adequate and accessible testing. Rapid diagnostic tests, such as the Schistosoma ICT IgG-IgM, have the potential to strengthen the health system by adequately diagnosing and providing the correct treatment for schistosomiasis [80,89].

Another limitation to note is that the cross-sectional survey and community mapping were both administered and conducted during the dry season in January and August, respectively. Malaria transmission in Misungwi is year-round, which is indicative of the breeding site preference (i.e., permanent, or semi-permanent, medium-sized ponds with water most of the year) of *An. funestus,* the dominant *Anopheles* species in the study area. However, seasonality could play an important role for schistosomiasis transmission since there are many species of *Biomphalaria* and *Bulinus* snails, each with their own unique aquatic niche and breeding site preference (i.e., permanent lakes, temporary ponds) [217,218]. Some *Biomphalaria* and *Bulinus* snails species can also aestivate and survive during the dry season, which increases the risk of schistosomiasis during the rainy season [68]. The dry season may also alter water-contact behaviors and increase the risk for schistosomiasis, which was noted in other longitudinal studies investigating risk factors for schistosomiasis but could not be assessed in this cross-sectional study [203]. This once again emphasizes the importance of effective environmental control and supplementary prevention strategies for malaria and schistosomiasis.

Conclusion

The utilization of both qualitative and quantitative data allowed us to gain a comprehensive understanding of population vulnerabilities and socio-ecological factors associated with malaria, schistosomiasis, and co-infection among school-aged children in Misungwi, Lake Victoria Zone, Tanzania. To our knowledge, this is the first study to investigate individual- and household-level social determinants, and household-level environmental determinants associated with malaria, schistosomiasis, and co-infection using a mixed-method approach in an African setting. The geographic overlap and co-infection of malaria and schistosomiasis in Misungwi, Tanzania, suggest that integrated or supplementary control strategies are necessary to reduce disease transmission. Future studies can examine the coordination between stakeholders or funding sources for malaria and schistosomiasis control programs to assess the feasibility of integrating environmental control with current strategies. This study improves our understanding of social and environmental factors that are associated with malaria, schistosomiasis, and co-infection which can inform potential entry points for integrated disease prevention and control.

4.2.9 Acknowledgements

The authors would like to thank colleagues and staff at the Kilimanjaro Christian Medical University College and those at the National Institute of Medical Research Mwanza who were involved in the project; the Regional Medical Office in Mwanza for the continuous support provided; the Misungwi District Medical Officer (Clement Mworabu), the Misungwi District Malaria Health Folk Person (Dismas Dotto) and the community health workers for facilitating and supervising the different project activities.

CHAPTER 5

COVID-19 Pandemic Impacts on Malaria Prevention in Benin

5.1. Article Preface

5.1.1 Article Preface

This article was published in PLOS Global Public Health on May 19, 2023. The objective of this article was to assess the impact of COVID-19 on community-level malaria prevention and health-seeking practices by evaluating factors influencing COVID-19 knowledge, the impact of COVID-19 on LLIN usage and access, and avoidance of healthcare centres because of the pandemic. This is the second of three manuscripts that form this doctoral research. The main goal of this thesis is to understand population vulnerabilities and to identify infection exposures and risk factors for malaria and schistosomiasis. However, unlike the other two manuscripts (study in Tanzania and the scoping review), this manuscript (Benin study) focuses on malaria only (and not schistosomiasis) in a different setting. Public health emergencies, like the Ebola epidemic, have historically posed a threat to ongoing prevention and control programs, and we anticipated a similar impact with the COVID-19 pandemic on malaria prevention and control [219]. Therefore, this study served as a case study to understand population vulnerabilities in terms of malaria prevention and control during the COVID-19 pandemic, which would us to identify entry points for sustainable and resilient programs to maintain the efforts for the control and elimination of malaria.

5.1.2 Contribution

I conceived the research question with guidance from my thesis supervisor, Dr. Manisha Kulkarni, and important input from members of my thesis advisory committee including Drs. Alison Krentel, Natacha Protopopoff, and Cindy Feng. Data used for this chapter was collected by team members at CREC including Drs. Ludovic N'Tcha and Bruno Akinro, and Mr. Edouard

Dangbenon and Mr. Landry Assogba. I developed the methodological approach with guidance from my thesis supervisor, Dr. Manisha Kulkarni, and thesis advisory committee members including Drs. Alison Krentel and Cindy Feng. I performed the majority of the analyses with the assistance of Ms. Samantha Yee, and completed the first draft of the manuscript. All authors contributed to the editing and revision of this article. I reported my findings in the form of a manuscript, a dissemination meeting in Benin, and two oral presentations at conferences in Canada (Canadian Conference on Global Health) and Benin (5iemes Journées Scientifiques de l'Institut Régional de Sante Publique).

5.1.3 Ethics Approval

The protocol for this study was reviewed and approved by the institutional review board of the University of Ottawa (Certificate H-07-20-5944) (Canada); the institutional review board of the London School of Hygiene and Tropical Medicine (LSHTM Ethics Ref: 22637) (United Kingdom); and the ethical review committee of the Benin National Ethics Committee for Health Research (N° 047/MS/DRFMT/CNERS/SA) (Benin)

5.1.4 Citation

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5.2. Article Content

5.2.1. Title

Community-level impacts of the coronavirus pandemic on malaria prevention and health-seeking behaviours in rural Benin: a mixed methods study

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5.2.4 Abstract

Globally, negative impacts of the COVID-19 pandemic on malaria prevention and control efforts have been caused by delayed distributions of long-lasting insecticidal nets (LLIN), decreased outpatient attendance, and disruptions to malaria testing and treatment. Using a mixed-methods approach, we aimed to evaluate the impact of COVID-19 on community-level malaria prevention and health-seeking practices in Benin more than one year after the start of the COVID-19 pandemic. We collected data through community-based cross-sectional surveys with 4200 households and ten focus group discussions (FGDs). Mixed-effect logistic regression models accounting for a clustered sampling design were used to identify variables associated with main outcomes (good COVID-19 knowledge, LLIN usage and access, and avoidance of health centres). Consistent with the experiences of FGD participants, receiving information from radios or televisions was significantly associated with good COVID-19 knowledge and avoiding health centres because of the pandemic ($p<0.001$ for both). Qualitative findings also revealed varying and polarizing changes in health-seeking behaviours with participants noting that they either did not change their health-seeking behaviours or went to health centres less or more often because of the pandemic. LLIN usage and access did not decrease in the study area because of the pandemic (LLIN usage: 88% in 2019 to 99.9% in 2021; LLIN access: 62% in 2019 to 73% in 2021). An unexpected change and unintended challenge for sustained malaria prevention included families socially distancing in their homes, resulting in a shortage of LLINs. Our findings showed that there were minimal community-level impacts of the coronavirus pandemic on malaria prevention and health seeking behaviours in rural Benin, which highlights the importance of efforts to sustain malaria prevention and control interventions in the context of the COVID-19 pandemic.

5.2.5 Introduction

In 2020, there was an increase in the number of malaria cases and deaths in sub-Saharan African (SSA) countries compared to 2019 – with malaria control having already been stalled since 2015 [86]. In 2020, more than 240 million malaria cases were estimated, with over 600,000 deaths [50]. Benin, along with 29 other countries predominantly in SSA, accounts for 95.7 % of malaria deaths globally [50]. Three important tools to control and prevent malaria have been introduced in the past two decades, including long-lasting insecticidal nets (LLIN), early diagnosis with rapid diagnostic tests, and treatment with artemisinin-based combination therapy (ACT) [40]. In Benin, LLINs are a key vector control strategy, with a bed net campaign every three years (most recently in 2020) that is supplemented with targeted LLIN delivery services for children under five and pregnant women [178,179].

As of April 2020, the coronavirus disease (COVID-19) had spread to all malaria-endemic countries [86]. Benin reported its first COVID-19 case on March 9th, 2020, three weeks before its planned LLIN distribution [222]. As of April 26, 2022, Benin had a total of 26,952 recorded cases and 163 recorded deaths due to COVID-19 with three surges of new cases followed by declines: a wave in February 2021, a second wave in August/September 2021, and a third wave in January 2022 [223,224]. Benin received its first shipment of COVID-19 vaccines in March 2021, and as of May 1, 2022, 23 % of the population in Benin were fully vaccinated [220,221,225].

Early public health messaging in many malaria-endemic countries during the COVID-19 pandemic, including Benin, was to stay home rather than seek care if someone was experiencing a fever to prevent COVID-19 transmission [86]. However, this message was quickly reversed to

continue with suggested malaria control [103]. It is critical to respond to the COVID-19 pandemic, while also continuing to prevent and control malaria [226], yet malaria cases and deaths in the WHO African region both increased between 2019 to 2020 from 213 million to 228 million and 534 000 to 602 000, respectively [50]. This could be attributed to a decrease in outpatient attendance, malaria testing during the initial phase of the pandemic, or disruptions in LLIN distribution [50].

Using a mixed-methods approach, we aim to assess the impact of COVID-19 on community-level malaria prevention and health-seeking practices by evaluating factors influencing COVID-19 knowledge, the impact of COVID-19 on LLIN usage and access, and avoidance of healthcare centres because of the pandemic.

5.2.6 Methods

5.2.6.1 Study setting

This study was conducted in three of the nine districts in the Zou department in central Benin: Covè, Zagnanado, and Ouinhi. The Zou department is made up of 850,000 inhabitants with only one major ethnic group (Fon) representing 92.3% of the department [227]. The most cultivated items in the three study districts are cassava (Ouinhi and Zagnanado) and peanuts (Covè) [227]. Malaria transmission is year-round and the incidence per 100 population in the Zou department in 2019 was higher than the national incidence among children one- to four-years old (80.8% compared to 54.2%), and five- to fourteen-years old (24.1% compared to 21.2%), as reported by the 2019 Annuaire des statistiques [228].

The study area in the three districts was divided into 60 clusters according to the main study protocol with each cluster comprising one village or group of villages for an average of 200 households (approximately 1,200 residents) (Fig. 5.1) [229].

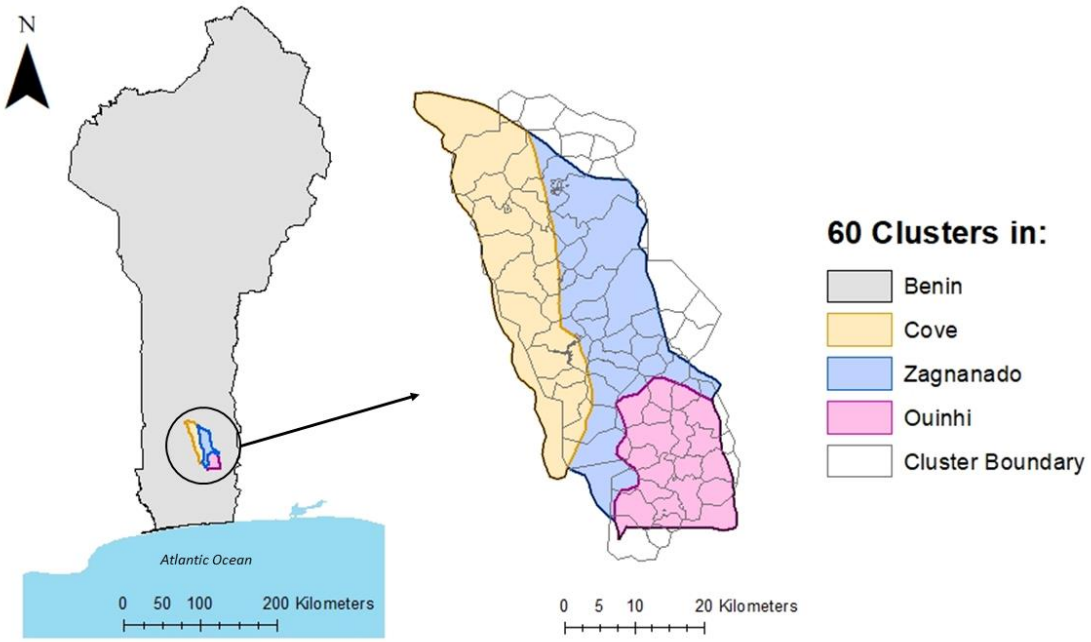

Fig. 5.1 Study area map highlighting Benin and the 60 study clusters within three districts of interest: Zagnanado, Cove, and Ouinhi. Map content was produced with Esri ArcGIS software using study data and data provided by GADM and Natural Earth available online: https://gadm.org/download_country.html and https://www.naturalearthdata.com/.

5.2.6.2 Study design

This study was a convergent parallel mixed-methods design that collected quantitative data through a cross-sectional community-based study nested in an ongoing three-arm, single-blinded, parallel, cluster randomized control trial assessing the efficacy of two dual active-ingredients LLINs for the control of malaria and qualitative data through Focus Group Discussions (FGDs) [229]. Data on household demographics, assets, and location, as well as malaria prevention and care-seeking practices were collected through the main trial. For the current study, ten FGDs and

supplemental COVID-19 Knowledge, Attitude, Practice (KAP) survey questions were added to the 2021 cohort and 2021 cross-sectional survey instruments.

The surveys were administered by trained field team workers to 2,400 head of households (HoHs) from the cross-sectional surveys and 1,800 HoHs from the cohort follow-up activity. Residents were eligible if they lived in the village during the previous 3 months, provided written consent, and if their children did not have severe illness. The surveys were captured in electronic forms on smartphones installed with Open Data Kit (ODK) collected and stored on a secure server located at the London School of Hygiene and Tropical Medicine (LSHTM).

Ten FGDs of ten people (five groups of ten women and five groups of ten men) were conducted in the three districts in rural Benin (four in Covè, four in Zagnanado, and two in Ouinhi). The FGDs were facilitated by two investigators: the first one moderating the discussion and the second one taking notes. The moderator used a topic guide (in French), and the participants responded and discussed either in French or in their local language. As required, a translator translated the questions from French to the respective local language, then repeated the answers for the moderator from the local language to French. The FGDs were recorded, transcribed verbatim, translated to French, captioned, and validated for the analysis. Select quotes were translated from French to English for their inclusion in this article.

5.2.6.3 Qualitative approach

A preliminary codebook for the FGDs was created deductively based on the FGD guidebook and further refined inductively to identify themes and subthemes that arose from reading the transcripts. Two researchers independently coded a selection of two transcripts to ensure interrater reliability. The final codebook was applied to the remaining FGD transcripts using NVivo Qualitative Data Analysis Software (QSR International, Version 12).

5.2.6.4 Statistical approach

Data analysis focused on four outcomes: 1) good knowledge of COVID-19, 2) LLIN usage, 3) LLIN access, and 4) avoidance of health centre because of the pandemic. The supplemental COVID-19 KAP survey included twenty-five questions across three domains (symptoms, modes of transmission, and modes of prevention) that had three possible responses: yes, no, and I do not know. We created a score based on the number of correct responses, where a correct response was awarded one point and an incorrect or 'I don't know' response was not awarded any points [230–233]. The total points awarded for each response ranged from 0-25. Using Bloom's cutoff, good COVID-19 knowledge was defined as a score between 20 and 25, and poor knowledge as a score of 19 or lower [230,234]. LLIN usage and access reflect important LLIN metrics, given the importance of this intervention as a key malaria prevention and control tool, and are existing indicators defined by the Household Survey Indicators for Malaria Control; LLIN usage is defined as the proportion of individuals who report sleeping under LLINs the previous night, and population LLIN access is defined as the proportion of individuals with access to a LLIN within the households, assuming one LLIN is used by two people [235]. Avoidance of health centres, defined as the proportion of the population who either avoided routine or urgent visits because of the pandemic, was derived from two KAP survey questions (not included in generating good knowledge of COVID-19 score – one addressing avoidance of routine visits (i.e., vaccinations and check-up visits) and another one addressing avoidance of urgent visits (i.e., febrile child)). This metric reflects changes in health-seeking behaviours during the pandemic which points to disruptions in malaria control (i.e., early diagnosis and treatment with ACT).

Candidate explanatory variables hypothesized to be associated with a good knowledge of COVID-19, LLIN usage, LLIN access, and avoidance of health centres include: 1) household

demographics (district, ethnicity, marital status, occupation, education), 2) socioeconomic status (SES), 3) population density, 4) distance to nearest health centre facility, 5) source of information of COVID-19 (for good COVID-19 knowledge and avoidance of health centres outcomes only) and 6) good COVID-19 knowledge (avoidance of health centres outcome only). We constructed a wealth score as a proxy for SES using a Principal Components Analysis (PCA) of household assets and dwelling characteristics [193,194]. The PCA scores were ranked and categorized into quintiles where the first quintile represents the poorest SES group and the fifth quintile the least poor SES group. Data on population density, defined as the number of 100 people per kilometer^2 in 2020, was retrieved from WorldPop in a grided raster format with a resolution of 1km^2 [236]. For each household, the population density (as a proxy for urbanicity) was extracted and the Euclidian distance to the nearest health centre (GPS location collected during baseline cross-sectional survey in 2019) was calculated using GIS ArcMap version 10.7.1 (ESRI, Redlands, CA, USA).

Descriptive statistics, including frequencies and proportions for categorical variables and median and interquartile ranges for continuous variables, were generated in SAS version 9.4 (SAS Institute, Cary, NC, USA) (Table 5.1). Differences between districts and demographic characteristics were compared using a chi-square or a Kruskal Wallis test. P-values less than 0.05 were considered to be statistically significant. Mixed-effects logistic regression models accounting for a clustered sampling design were used to identify variables that were associated with each outcome. The "GLMER" function in the lme4 package in RStudio version 4.1.3 (R Core Team, 2018) was used to fit the generalized linear mixed model (GLMM) using the default Laplace approximation, a logit link, and random effects at the cluster level [198]. The univariable association between all candidate explanatory variables and each outcome was

assessed and entered into a multivariable model. The "Dredge" function in the MuMIn package in Rstudio version 4.1.3 (R Core Team, 2018) was used to determine the best combination of explanatory variables for each model [199]. The Dredge function is a model selection tool that ranks every candidate model (2^n models, where n is the number of predictors in the full model) based on the Akaike Information Criterion (AIC). The model with the lowest AIC was selected and a reduced model was refit using the GLMER function.

Model fit was assessed by the area under a receiver operating characteristic curve (AUC) using the GLIMMIX procedure (GLMM using the Laplace approximation) in SAS version 9.4 (SAS Institute, Cary, NC, USA). Spatial autocorrelation was assessed by mapping the regression residuals to identify significant clusters using Global Moran's I in ArcMap version 10.7.1 (ESRI, Redlands, CA, USA) [202].

5.2.6.5 Cluster analysis

Spatial clusters of 1) good COVID-19 knowledge, and 2) avoidance of health centres because of the pandemic were assessed using the Getis-Ord-Gi* in ArcMap version 10.7.1 (ESRI, Redlands, CA, USA) [169]. Getis-Ord-Gi* is a tool that detects statistically significant spatial clusters, which are features of high values surrounded by high values (hotspots) and low values surrounded by low values (coldspots). The output includes z-scores and p-values which indicate either high or low clusters spatially – a p-value less than 0.05 was considered statistically significant.

Data were further analyzed using SaTScan software (v 9.4.1 Kulldorf and Information Management Services, Inc.). A Bernoulli-based probability model using a purely spatial scan was used to identify clusters of high and low rates (i.e., households of good COVID-19 knowledge surrounded by households of good COVID-19 knowledge and households of poor

COVID-19 knowledge surrounded by households of poor COVID-19 knowledge). Circular windows of varying radii compared events within the circular window to those expected, with the null hypothesis that there is no difference in the number of events inside and outside the circular window. A relative risk was then generated for each cluster, where a risk ratio (RR) of greater than 1 represents a cluster where the probability of being an event within the circular window is greater than the probability of being an event outside the circular window (RR>1). Results from the Getis-Ord-Gi* and SatScan were then visually inspected to see in what ways they converge or diverge from each other.

5.2.6.6 Mixed-methods approach

The themes and subthemes that were identified from the FGDs were then compared with the results from the four statistical models to have a complete understanding of the factors influencing the outcome in each model: 1) good knowledge of COVID-19, 2) LLIN usage, 3) LLIN access, and 4) avoidance of health centre because of the pandemic. We then assessed in what way do the qualitative and quantitative results 1) converge or diverge from each other, 2) relate to one another, and 3) combine to create a better understanding of the results [237].

5.2.6.7 Ethics statement

The protocol for this study was reviewed and approved by the institutional review board of the University of Ottawa (Certificate H-07-20-5944) (Canada); the institutional review board of the London School of Hygiene and Tropical Medicine (LSHTM Ethics Ref: 22637) (United Kingdom); and the ethical review committee of the Benin National Ethics Committee for Health Research (N° 047/MS/DRFMT/CNERS/SA) (Benin). All participants in this study were adults aged 18 years or older. Each participant was read an informed consent form by data collectors,

which was read and signed by each participant prior to commencing data collection and focus group discussion.

5.2.7 Results

5.2.7.1 Characteristics of the study population

The majority of HoHs were from the Fon ethnic group (n=2329, 60%), were in a monogamous marriage (n=2301, 60%), were farmers (n=2755, 71%), and had no education (n=2697, 70%) (Table 5.1). Households were located at a median Euclidean distance of 2.7 km from a health centre with a median population density of 238 people per km^2. There was a statistically significant difference between the demographic profiles and all three districts. Notably, the Holli ethnic group was the most represented in Ouinhi (n=269, 22%), compared to Covè (n=4, 1%) and Zagnanado (n=117, 6%). Variability was also present in education across the district with 72% (n=1525) of HoHs in Zagnanado having no education compared to 68% (n=846) in Ouinhi and 65% (n=326) in Covè.

Table 5.1: Demographic profile of the study participants by districts (n = 3858)

	Total (n = 3858)	Cove (n = 505)	Ouinhi (n = 1242)	Zagnanado (n = 2111)	P-value*
Ethnicity					
Fon	2329 (60.4)	355 (70.3)	593 (47.8)	1381 (65.4)	
Holli	390 (10.1)	4 (0.8)	269 (21.7)	117 (5.5)	
Mahi	1083 (28.1)	134(26.5)	369 (29.7)	580 (27.5)	
Other	56 (1.5)	12(2.4)	11(0.9)	33 (1.6)	<0.001
Marital status					
Married monogamous	2301 (59.6)	322 (63.8)	668 (53.8)	1311 (62.1)	
Married polygamous	1120 (29.0)	116 (23.0)	427 (34.4)	577 (27.3)	
Other	437 (11.3)	67 (13.3)	147 (11.8)	223 (10.6)	<0.001
Occupation					
Farming	2755 (71.4)	327 (64.8)	860 (69.2)	1568 (74.3)	
Other	1103 (28.6)	178 (35.3)	382 (30.8)	543 (25.7)	<0.001
Education					
No education	2697 (69.9)	326 (64.6)	846 (68.1)	1525 (72.2)	
Some education	1161 (30.1)	179 (35.5)	396 (31.9)	586 (27.8)	<0.001

SES					
Lowest	786 (20.5)	101 (20.2)	212 (17.1)	473 (22.6)	
Low	769 (20.1)	69 (13.8)	261 (21.1)	439 (20.9)	
Average	744 (19.4)	73 (14.6)	280 (22.6)	391 (18.6)	
High	765 (19.9)	94 (18.8)	375 (22.2)	396 (18.9)	
Highest	770 (20.1)	162 (32.5)	209 (16.9)	399 (19.0)	<0.001
Distance to nearest health facility (km)					
	2.69 (0,14)	1.90 (0,9)	2.50 (0,6)	3.23 (0,14)	<0.001
Population density (per km^2)					
	238 (29,1181)	417 (42,936)	279 (129,1182)	105 (29,779)	<0.001

Data are displayed as n (%) or median (min, max)
*P-values (significant differences between the three districts, by using the chi squared test for comparison of proportions and Kruskal-Wallis test for medians
Abbreviations: SES: socioeconomic status

5.2.7.2 Factors influencing COVID-19 knowledge.

Overall, 9.8% (n=378) participants had a good knowledge of COVID-19 based on questions surrounding knowledge of symptoms, modes of transmission, and preventative measures of the disease (Table 5.2). While the minority of HoHs had a good knowledge of COVID-19, the majority were able to identify fevers (n=2818, 73%) and coughs (n=2973, 77%) as symptoms of COVID-19, and identified handwashing (n=3549, 92%) and facemasks (n=3192, 83%) as methods of prevention of COVID-19 (Appendix 5.1: Supplemental Table). Key themes from the FGDs surrounding COVID-19 knowledge were the symptoms, modes of transmission, and preventative measures of COVID-19 which provided more context to the quantitative results. Participants frequently mentioned more than one symptom of COVID-19 - most often noting fever and coughs, followed by fatigue and headaches. Other notable symptoms of COVID-19 were anemia, sneezing, loss of taste, and vomiting. Participants also noted that COVID-19 was dangerous, destructive, and deadly, however only men noted themes surrounding the financial burden of the disease.

Table 5.2: Emerging themes surrounding COVID-19 knowledge.

	n (%)	Supporting Quote
Good COVID-19 Knowledge	378 (9.8%)	"When someone is infected, and rubs up against me, or even shakes my hand, they can transmit the disease." Male, Ouinhi "The rules like staying 1-meter apart while we travel, mask-wearing, not shaking hands, and not coughing in the air. If we respect these rules, we will stay away from the disease." Male, Zagnanado
Poor COVID-19 Knowledge	3480 (90.2%)	"What I know from this disease is that when you cough and spit on the ground, and someone sweeps the dust with the spit, this person can inhale the dust and can contract the disease." Female, Covè "We can transmit this disease by our sweat, which is why we need to respect a distance of 1 meter." Female, Covè

Although participants had a varying understanding of the modes of transmission for COVID-19, they often noted effective preventative measures. The modes of transmission given by participants ranged from direct contact (i.e., handshake, sweat, bumping into an infected person), indirect contact (i.e., dust, an infected persons breath, sneezing or coughing in the air, being near an infected person), and contaminated foods (i.e., bushmeat).

"If I sneeze or cough in the air, the wind can transport this virus to contaminate others" ***Male, Covè***

Despite a poor understanding of the modes of transmission for COVID-19, all participants mentioned "gestes barrières", which include handwashing, mask-wearing, and social distancing, as measures to reduce the spread of COVID-19. Many participants also commented that they installed a handwashing station in their homes to prevent COVID-19, changed the way that they greeted others (i.e., with their elbows or feet), and sneezed and coughed in their masks.

Unanticipated preventative measures perceived to be associated with COVID-19 by respondents emerged from the FGDs and included themes surrounding cleanliness (i.e., sweeping around the house, and doing dishes, laundry, and bathing).

"We organized a group of women to clean up the roads in our village every day" ***Male, Covè***

Participants cited radios (specifically spoken in Fon) and public criers (crieur publique) as the most reliable sources of information for disseminating information surrounding COVID-19.

"According to myself, if the public criers pass the information, a lot of people will be informed and will have the information on time, because not everyone has the money for a radio" ***Male, Zagnanado***

To quantitatively understand factors associated with good COVID-19 knowledge, HoH ethnicity, HoH education, distance to the nearest health facility, population density, and select sources of information about COVID-19 (radio, television, health centres, and religious leaders) were included in a multivariable model. HoH education [some vs none] (adjusted odds ratio [aOR] 1.44, 95% CI 1.11-1.86, p<0.001); distance to nearest health facility [per km] (aOR 1.11, 95% CI 1.01-1.23, p=0.033); radios (aOR 2.23, 95% CI 1.48-3.38, p<0.001), televisions (aOR 2.92, 95% CI 2.18-3.91, p<0.001) and religious leaders (aOR 1.74, 95% CI 1.34-2.27, p<0.001) as sources of information for COVID-19 were significantly associated with a good COVID-19 knowledge (Table 5.3). Although included in the final multivariable model, ethnicity, and health centres as a source of information were not significantly associated with good COVID-19 knowledge. The final multivariable model had excellent discrimination (AUC = 0.875) and there was no evidence of spatial autocorrelation (p=0.085).

Table 5.3: Results of mixed-effects logistic regression analysis of factors associated with knowledge of the novel coronavirus disease 2019 (n = 3858)

		Univariable Model			Adjusted Model		
	%	**OR**	**(95% CI)**	**P-value**	**AOR***	**(95% CI)**	**P-value**
District							
Cove	12	REF	-	-	-	-	-
Ouinhi	10	0.45	(0.17-1.19)	0.110	-	-	-
Zagnanado	9	0.64	(0.27-1.54)	0.320	-	-	-
Ethnicity							
Fon	12	REF	-	-	REF	-	-
Mahi	6	0.37	(0.26-0.52)	<0.001	0.79	(0.54-1.16)	0.235
Holli	6	0.44	(0.23-0.78)	<0.001	0.60	(0.33-1.11)	0.105
Other	7	0.65	(0.19-1.71)	0.419	0.78	(0.26-2.38)	0.665
Marital status							
Married monogamous	10	REF	-	-	-	-	-
Married polygamous	10	1.02	(0.80-1.31)	0.862	-	-	-
Other	6	0.57	(0.37-0.86)	<0.001	-	-	-
Occupation							
Farming	9	REF	-	-	-	-	-
Other	11	1.21	(0.93-1.57)	0.150	-	-	-
Education							
No education	8	REF	-	-	REF	-	-
Some education	14	1.93	(1.52-2.45)	<0.001	1.44	(1.11-1.86)	<0.001
SES							
Lowest SES	6	REF	-	-	-	-	-
Low SES	10	1.49	(1.00-2.22)	0.043	-	-	-
Average	11	1.74	(1.17-2.61)	<0.001	-	-	-
High SES	9	1.60	(1.06-2.41)	0.025	-	-	-
Highest SES	13	2.80	(1.87-4.26)	<0.001	-	-	-
Distance to nearest health facility (km)							
	2.78	1.09	(0.99-1.20)	0.067	1.11	(1.01-1.23)	0.033
Population density (100 people/km^2)							
	2.66	1.07	(0.97-1.19)	0.160	1.12	(1.00-1.26)	0.053
Source of information							
Radio							
No	4	REF	-	-	REF	-	-
Yes	11	2.96	(2.00-4.51)	<0.001	2.23	(1.48-3.38)	<0.001
Tv							
No	8	REF	-	-	REF	-	-
Yes	25	4.24	(3.19-5.62)	<0.001	2.92	(2.18-3.91)	<0.001
Health centre							
No	8	REF	-	-	REF	-	-
Yes	16	2.50	(1.94-3.22)	<0.001	1.22	(0.92-1.61)	0.161
Village leaders							
No	9	REF	-	-	-	-	-

Yes	12	1.46	(1.12-1.89)	0.004	-	-	-
Religious leaders							
No	7	REF	-	-	REF	-	-
Yes	12	2.06	(1.61-2.65)	<0.001	1.74	(1.34-2.27)	<0.001
Word of Mouth							
No	9	REF	-	-	-	-	-
Yes	10	1.07	(0.79-1.45)	0.670	-	-	-
Other							
No	9	REF	-	-	-	-	-
Yes	25	4.33	(3.11-6.01)	<0.001	-	-	-

*Full models adjusted for intervention arm, survey number, and cluster number
Abbreviations: SES: Socioeconomic status, AOR: Adjusted Odds Ratio, OR: Odds Ratio

The results of the Getis-Ord-Gi* test showed hotspots of households with good and poor COVID-19 knowledge which were overlapped by the locations of statistically significant clusters detected using Kulldorf spatial scan statistic in SaTScan (Fig. 5.2A). The two tests detected similar patterns with significant clusters of good COVID-19 knowledge in Zagnanado North (Cluster 2: RR = 2.38) and Ouinhi North (Cluster 4: RR = 4.67), and significant clusters of poor knowledge in Covè North (Cluster 1: RR = 0.29), and Ouinhi South (Cluster 5: RR = 0 and Cluster 6: RR = 0.03).

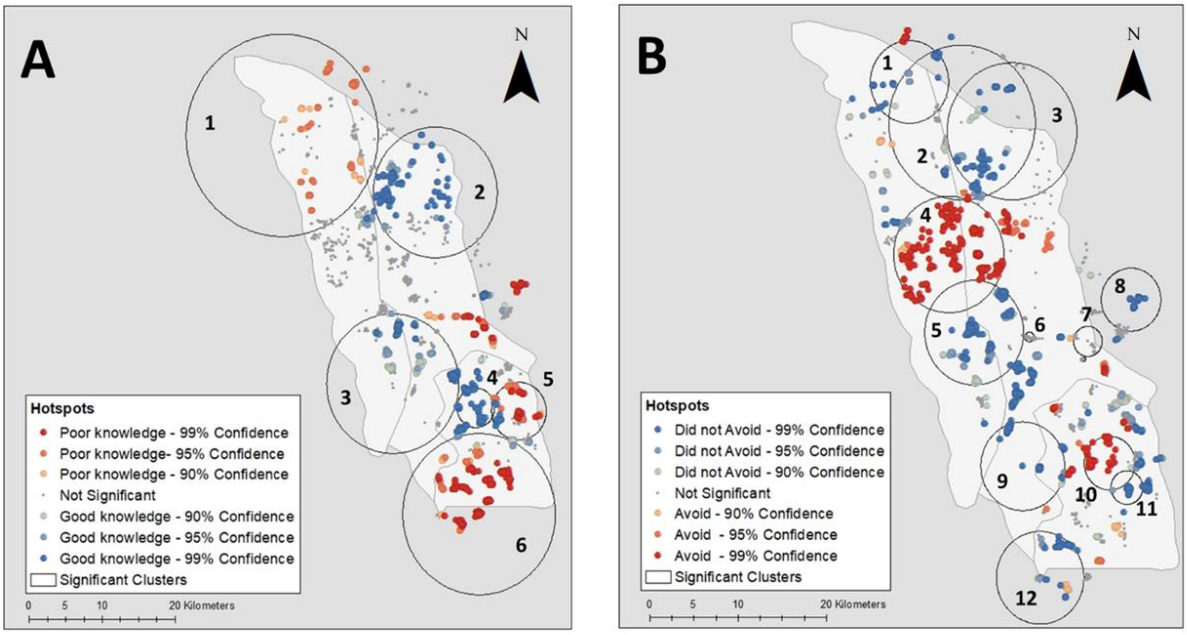

Fig. 5.2 Spatial clusters of good COVID-19 knowledge (A) and avoidance of health centres during the COVID-19 pandemic (B). Map content was produced with Esri ArcGIS software using study data and data provided by GADM available online: https://gadm.org/download_country.html.

5.2.7.3 Impact of COVID-19 on LLIN usage and access

LLIN usage and access did not decrease as a result of the pandemic (LLIN usage: 88% in 2019 to 99.9% in 2021; LLIN access: 62% in 2019 to 73% in 2021); indeed, a slight increase in both indices was noted, which likely reflects the LLIN distribution that took place as part of the malaria intervention trial (Table 5.4). Although not statistically significant, there were differences in LLIN usage and access between the three districts with Covè having greater LLIN usage and access compared to Zagnanado and Ouinhi (Fig. 5.3A and 5.3B).

Table 5.4: Emerging themes surrounding LLIN Usage and Access

	n (%)	**Supporting Quote**
LLIN Usage	2414 (87.5%) in 2019 2126 (99.9%) in 2021	"If the child does not sleep under the bed-net, they can have a fever, so have malaria and miss blood." Female, Covè

		"If you're not in the habit of sleeping under an insecticide treated bed-net, the mosquito will bite you." Male, Covè
No LLIN Usage	346 (12.5%) in 2019 3 (0.01%) in 2021	"At nightfall, the kids go play or watch television. In that brief time, they get mosquito bites which brings malaria." Male, Zagnanado "Staying under a bed-net is too warm. We have to stand outside of mosquito nets to get some air." Male, Covè
LLIN Access	1704 (61.7%) in 2019 1550 (72.8%) in 2021	No supporting quotes available.
No LLIN Access	1056 (38.3%) in 2019 579 (27.2%) in 2021	"When the coronavirus came, we separated the kids and adults' beds, we don't sleep with the kids anymore and they feel better about that." Female, Covè "They said that we should not gather, so we don't have enough of bed-nets." Female, Zagnanado "My children often have malaria because we don't have any bed-nets at home." Female, Zagnanado

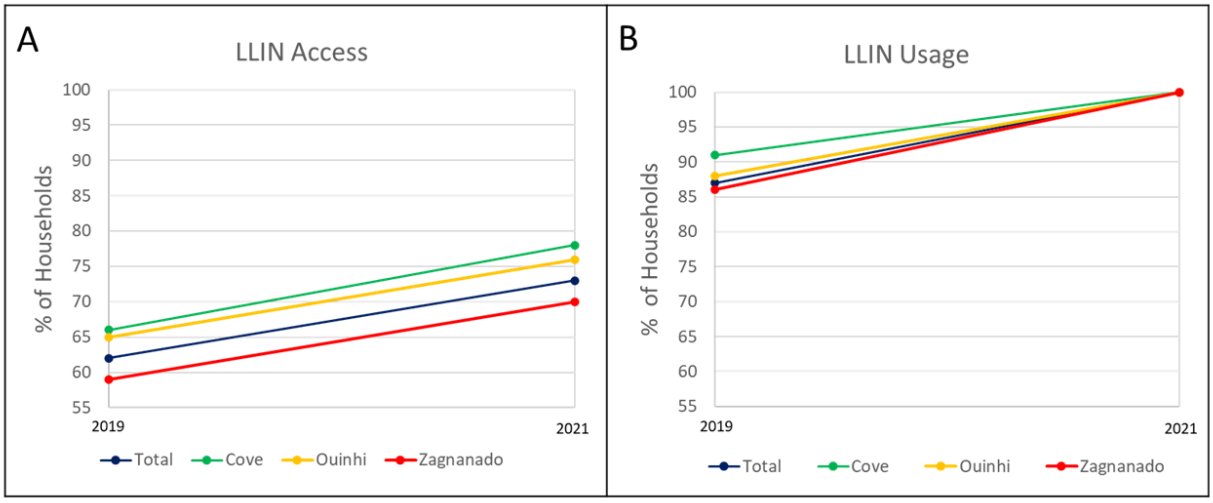

Fig. 5.3 Temporal trends of LLIN access (A) and LLIN usage (B) before and during the COVID-19 pandemic

At least one participant in every FGD stated that mosquitoes transmit malaria and noted bed nets and other measures to prevent mosquito bites (i.e., weeding, eliminating standing water) as measures to prevent malaria. Malaria was most often noted as the most important disease (i.e., top priority, most prevalent, most deadly), and therefore participants commented on the importance of preventing malaria.

"To put it simply, malaria is the chief disease in Benin" ***Male, Ouinhi***

The barrier that was most often noted in preventing malaria (before the pandemic) related to difficulties in entering a bed net prior to when mosquitoes were active at night. An unexpected change and barrier in malaria prevention during the COVID-19 pandemic was that families were socially distancing in their homes – specifically no longer sharing beds and bed nets, resulting in a shortage of bed nets.

"We don't have enough bed-nets because someone that has 10 children and we give them 5 bed-nets and we sleep one child per bed-net, this person is missing 5 bed-nets, as before we only needed 6 to 7 bed-nets. This means that we need to gather the children under one bed-net. So, the risk of getting a mosquito bite is increased." ***Male, Zagnanado***

Since 99.9% of the households in 2021 used a LLIN the night before (LLIN usage), a multivariable model was not run to assess the effect of the pandemic on LLIN usage. However, based on the univariable model, ethnicity [Holli vs Fon] (OR 2.85, 95% CI 1.90-4.31, p<0.001), highest vs lowest SES (OR 2.03, 95% CI 1.40-2.94, p<0.001), high vs lowest SES (OR 2.20, 95% CI 1.53-3.18, p<0.001) , average vs lowest SES (OR 1.89, 95% CI 1.32-2.66, p<0.001), and

low vs lowest SES (OR 1.58, 95% CI 1.14-2.17, <0.001) were significantly associated with LLIN usage (Table 5.5).

Table 5.5: Results of mixed-effect logistic regression analysis of demographic factors associated with long lasting insecticidal net usage (n = 4889)

		Univariable Model		
	%	**OR**	**(95% CI)**	**P-value**
Time points				
Pre COVID-19	88	REF	-	-
Post COVID-19	99.9	109.3	(41-443)	<0.001
District				
Cove	95	REF	-	-
Ouinhi	93	0.69	(0.30-1.50)	0.340
Zagnanado	92	0.65	(0.30-1.40)	0.250
Ethnicity				
Fon	92	REF	-	-
Holli	97	2.85	(1.90-4.31)	<0.001
Mahi	92	0.97	(0.60-1.60)	0.890
Other	79	0.32	(0.20-0.52)	<0.001
Marital status				
Married monogamous	94	REF	-	-
Married polygamous	92	0.82	(0.63-1.08)	0.144
Other	91	0.66	(0.49-0.91)	<0.001
Occupation				
Farming	93	REF	-	-
Other	92	0.89	(0.68-1.20)	0.360
Education				
No education	92	REF	-	-
Some education	94	1.30	(0.98-1.70)	0.068
SES				
Lowest SES	89	REF	-	-
Low SES	92	1.58	(1.14-2.17)	<0.001
Average	94	1.89	(1.34-2.66)	<0.001
High SES	95	2.20	(1.53-3.18)	<0.001
Highest SES	95	2.03	(1.40-2.94)	<0.001
Population density (100 people/km^2)				
	2.37	0.97	(0.88-1.10)	0.57

Abbreviations: SES: Socioeconomic status, OR: Odds Ratio

To quantitatively investigate the effect of the pandemic on LLIN access, the time point (2021 or 2019), HoH ethnicity, HoH marital status, HoH education, and population density were included

in the multivariable model. The time point [2021 (post COVID-19) vs 2019 (pre COVID-19)] (aOR 1.48, 95% CI 1.28-1.70, p<0.001), ethnicity [Holli vs Fon] (aOR 1.44, 95% CI 1.19-1.74, p<0.001), marital status [polygamous vs monogamous] (aOR 0.80, 95% CI 0.69-0.92, p<0.001), marital status [other vs monogamous] (aOR 2.19, 95% CI 1.76-2.73, p<0.001), and population density [per100 people/km^2](aOR 1.07, 95% CI 1.01-1.12, p=0.014) were statistically associated with LLIN access (Table 5.6). Although included in the final multivariable, ethnicity (Mahi vs Fon, and other vs Fon), and HOH education were not significantly associated with LLIN access. The final multivariable model had poor discrimination (AUC = 0.679) and there was no evidence of spatial autocorrelation (p=0.306).

Table 5.6: Results of mixed-effect logistic regression analysis of demographic factors associated with long lasting insecticidal net access (n = 4889)

		Univariable Model			**Adjusted Model**		
	%	**OR**	**(95% CI)**	**P-value**	**AOR***	**(95% CI)**	**P-value**
Time points							
Pre COVID-19	62	REF	-	-	-	-	-
Post COVID-19	73	1.70	(1.50-1.90)	<0.001	1.48	(1.28-1.70)	<0.001
District							
Cove	71	REF	-	-	-	-	-
Ouinhi	70	0.96	(0.62-1.50)	0.860	-	-	-
Zagnanado	64	0.74	(0.49-1.10)	0.150	-	-	-
Ethnicity							
Fon	62	REF	-	-	REF	-	-
Holli	75	1.80	(1.52-2.10)	<0.001	1.44	(1.19-1.74)	<0.001
Mahi	71	1.20	(0.87-1.60)	0.300	1.09	(0.80-1.48)	0.603
Other	70	1.10	(0.74-1.60)	0.710	1.24	(0.85-1.80)	0.272
Marital status							

Married monogamous	66	REF	-	-	REF	-	-
Married polygamous	59	0.78	(0.68-0.90)	<0.001	0.80	(0.69-0.92)	<0.001
Other	82	2.22	(1.79-2.80)	<0.001	2.19	(1.76-2.73)	<0.001
Occupation							
Farming	66	REF	-	-	-	-	-
Other	68	0.91	(0.79-1.10)	0.220	-	-	-
Education							
No education	67	REF	-	-	REF	-	-
Some education	65	0.81	(0.70-0.94)	<0.001	0.89	(0.76-1.03)	0.109
SES							
Lowest SES	70	REF	-	-	-	-	-
Low SES	62	0.75	(0.61-0.91)	<0.001	-	-	-
Average	66	0.83	(0.68-1.02)	0.071	-	-	-
High SES	66	0.77	(0.62-0.94)	0.011	-	-	-
Highest SES	70	0.86	(0.69-1.07)	0.172	-	-	-
Population density (100 people/km^2)							
	2.46	1.10	(1.00-1.10)	<0.001	1.07	(1.01-1.12)	0.014

*Full models adjusted for intervention arm and cluster number

Abbreviations: SES: Socioeconomic status, AOR: Adjusted Odds Ratio, OR: Odds Ratio

5.2.7.4 Health care avoidance during pandemic

There were varying, and polarizing, changes in health-seeking behaviours because of the pandemic. A fifth of the participants (n=714, 18.5%) avoided health centres because of the coronavirus 2019 pandemic, and FGD participants noted that they either did not change their health-seeking behaviours or went to health centres less or more often because of the pandemic (Table 5.7). Reasons for avoiding health centres because of the pandemic for FDG participants included fear of disease exposure and fear that they would be forced into a quarantine facility.

For similar reasons, participants commented that their fear of COVID-19 (i.e., overlapping symptoms, deadly) led them to go to health centres more often because of the pandemic.

Table 5.7: Emerging themes surrounding avoidance of health-centres because of the coronavirus 2019 pandemic.

	n (%)	Supporting Quote
Avoided health-centre	714 (18.5%)	"When your child is sick, they said that we have to go to the hospital, but the child refuses because they said that the health centres is where people can catch the disease [coronavirus]." Female, Zagnanado "We don't have money and when we go to the hospital and you don't have money, the doctors won't take care of you." Female, Zagnanado
Did not avoid health-centre	3144 (81.5%)	"If you have malaria and you don't go quickly to the hospital, or if it's a child and you don't take care of them by taking them to the hospital, you can lose the child." Female, Covè "We used to keep our kids at home…but since the coronavirus came…we go quickly to the hospital to get the child tested for malaria or coronavirus." Male, Covè

Even before the pandemic, there were polarizing health-seeking behaviours amongst the FGD participants - noting that they either avoid health centres (e.g., too expensive) or go quickly to the health centre when someone is sick (e.g., fear of death, when someone is febrile, to receive treatment).

"We go to the hospital to treat the children despite the situation with coronavirus" ***Female, Ouinhi***

"What concerns us about malaria is that when you get it, you spend all your money at the hospital, when this happens you have nothing but loss of life, this is what concerns me the most about malaria" ***Female, Covè***

To quantitatively understand factors associated with avoidance of health centres, HoH ethnicity, HoH education, SES, good COVID-19 knowledge, and select sources of information about COVID-19 (radio, television, health centres, village leaders, religious leaders, and word of mouth) were included in the multivariable model. Good COVID-19 knowledge (aOR 2.16, 95% CI 1.54-3.04, p<0.001); and radios (aOR 3.04, 95% CI 2.20-4.21, p<0.001) and television (aOR 1.68, 95% CI 1.20-2.33, p<0.001) as sources of information for COVID-19 were significantly associated with avoiding health centres because of the pandemic (Table 5.8). In contrast, HoH ethnicity [Holli vs Fon] (aOR 0.42, 95% CI 0.31-0.59, p<0.001), HoH education [some vs none] (aOR 0.75, 95%CI 0.58-0.96, p=0.021), high vs lowest SES (aOR 0.57, 95%CI 0.40-0.81, p<0.001), highest vs lowest SES (aOR 0.67, 95%CI 0.46-0.97, p=0.037), religious leaders as a source of information for COVID-19 (aOR 0.78, 95% CI 0.61-0.99, p = 0.040) were significantly associated with not avoiding health centres because of the pandemic (Table 5.8). Although included in the final multivariable, ethnicity (Mahi vs Fon, and other vs Fon, average vs lowest SES, low vs lowest SES, and select sources of information for COVID-19 (health centres, village leaders, and word of mouth) were not significantly associated with avoiding health centres because of the pandemic. The final multivariable model had excellent discrimination (AUC = 0.875) and there was no evidence of spatial autocorrelation (p=0.957).

Table 5.8: Results of mixed-effect logistic regression analysis of factors associated with avoidance of health-centres because of the coronavirus 2019 pandemic (n = 3858)

		Univariable Model			Adjusted Model		
	%	**OR**	**(95% CI)**	**P-value**	**AOR***	**(95% CI)**	**P-value**
District							
Cove	17	REF	-	-	-	-	-
Ouinhi	19	1.20	(0.30-5.31)	0.768	-	-	-
Zagnanado	19	1.10	(0.32-4.41)	0.831	-	-	-
Ethnicity							
Fon	19	REF	-	-	REF	-	-
Mahi	17	1.23	(0.94-1.59)	0.070	0.58	(0.33-1.01)	0.056
Holli	20	0.62	(0.36-1.03)	0.120	0.42	(0.31-0.59)	<0.001
Other	18	1.71	(0.74-3.69)	0.180	1.32	(0.56-3.15)	0.524
Marital status							
Married monogamous	19	REF	-	-	-	-	-
Married polygamous	18	0.89	(0.72-1.11)	0.400	-	-	-
Other	19	1.14	(0.84-1.54)	0.300	-	-	-
Occupation							
Farming	20	REF	-	-	-	-	-
Other	16	0.95	(0.75-1.20)	0.680	-	-	-
Education							
No education	20	REF	-	-	REF	-	-
Some education	15	0.75	(0.60-0.94)	0.010	0.75	(0.58-0.96)	0.021
SES							
Lowest SES	26	REF	-	-	REF	-	-
Low SES	22	0.99	(0.75-1.31)	0.947	0.98	(0.72-1.32)	0.922
Average	18	093	(0.69-1.26)	0.663	0.88	(0.64-1.21)	0.444
High SES	12	0.61	(0.44-0.85)	<0.001	0.57	(0.40-0.81)	<0.001
Highest SES	16	1.02	(0.73-1.42)	0.906	0.67	(0.46-0.97)	0.037
COVID-19 Knowledge							
Poor	18	REF	-	-	REF	-	-
Good	25	1.47	(1.09-1.99)	0.011	2.16	(1.54-3.04)	<0.001
Distance to nearest health facility (km)							
	3.06	0.96	(0.87-1.06)	0.410	-	-	-
Population density (100 people/km^2)							
	1.90	1.11	(0.99-1.24)	0.069	-	-	-
Source of information							
Radio							
No	10	REF	-	-	REF	-	-
Yes	21	2.46	(1.83-3.34)	<0.001	3.04	(2.20-4.21)	<0.001
Tv							
No	18	REF	-	-	REF	-	-
Yes	21	1.31	(0.98-1.74)	0.065	1.68	(1.20-2.33)	<0.001
Health centre							
No	19	REF	-	-	REF	-	-

Yes	16	0.79	(0.62-1.00)	0.050	1.27	(0.96-1.69)	0.094
Village leaders							
No	20	REF	-	-	REF	-	-
Yes	14	0.77	(0.60-0.97)	0.027	0.77	(0.59-1.02)	0.067
Religious leaders							
No	22	REF	-	-	REF	-	-
Yes	15	0.66	(0.54-0.81)	<0.001	0.78	(0.61-0.99)	0.040
Word of Mouth							
No	22	REF	-	-	REF	-	-
Yes	18	0.83	(0.65-1.06)	0.130	0.78	(0.59-1.03)	0.040
Other							
No	19	REF	-	-	-	-	-
Yes	14	1.05	(0.71-1.52)	0.800	-	-	-

*Full models adjusted for intervention arm, survey number, and cluster number
Abbreviations: SES: Socioeconomic status, AOR: Adjusted Odds Ratio, OR: Odds Ratio

The results of the Getis-Ord-Gi* test showed hotspots of households that did not avoid health centres and those that did avoid health centres because of the pandemic which were overlapped by the locations of statistically significant clusters detected using Kulldorf spatial scan statistic in SaTScan (Fig. 5.2B). The two tests detected similar patterns with significant clusters of households that avoided health centres as a result of the pandemic in Covè centre (Cluster 4: RR = 3.17) and Ouinhi North (Cluster 10: RR = 3.91), and clusters of households that did not avoid health centres in Covè North (Cluster 1: RR = 0.12), Zagnanado/Covè (Cluster 5: RR =0.27) and Ouinhi South (Cluster 11: RR = 0 and Cluster 12: RR = 0.16).

5.2.8 Discussion

In this mixed-methods study, the quantitative and qualitative results together create a better understanding of the community-level impacts of the coronavirus pandemic on malaria prevention and health seeking behaviours in rural Benin. Although there were minimal observed impacts, our findings highlight the need for and the importance of efforts to sustain malaria prevention and control interventions during health emergencies. To understand the level of understanding of COVID-19 among the study participants, which is reflective of community-

level knowledge, a knowledge score was calculated based on questions surrounding symptoms, modes of transmission, and preventative measures of the disease. The quantitative results show that a tenth of the participants had a good knowledge of COVID-19, while the FGDs provided further insight on this metric. Particularly, FGD participants had a varying understanding of the symptoms and modes of transmission of COVID-19, but they could identify and practice effective preventative measures such as social distancing, mask-wearing, and handwashing, coined as the "gestes barrière". For example, participants wore masks to prevent inhaling SARS-CoV-2 infected dust, or participants socially distanced from one another to prevent touching an infected person's sweat. Two metrics were used to assess the impact of the pandemic on malaria prevention, including LLIN usage and access. The quantitative results indicate that LLIN usage and access did not decrease as a result of the pandemic, but the qualitative results provide evidence that there were challenges in sharing LLINs during the pandemic due to social distancing measures which resulted in a shortage of LLINs. Lastly, changes in health seeking behaviours during the pandemic were assessed with a metric that asked participants whether they avoided health centres for urgent or routine visits during the pandemic. The quantitative results indicate that a fifth of the participants avoided health centres during the pandemic, but the qualitative results demonstrate that some participants went to health centres more often, less often or did not change their behaviours during the pandemic – all of which were not captured in the quantitative results.

Our results also indicate that accessible and audible sources of information, specifically radios, televisions, and public criers, are effective measures to disseminate novel and salient information during a health emergency. The qualitative findings highlight those radios broadcasted in a dominant language and public criers reached all the population in rural areas; including those

who are illiterate, from any socioeconomic status, and without any time constraints. The quantitative and qualitative findings also point to the importance of providing information on preventative measures rather than focusing on educational campaigns on the novel disease (i.e., knowledge of symptoms and modes of transmission).

There are, however, negative effects of disseminating information during health emergencies that should be addressed. COVID-19 knowledge was a strong indicator of health centre avoidance because of the pandemic. This is likely due to early messaging during the pandemic which advised sick people to stay home to reduce the transmission of COVID-19. Those who were well informed were hesitant to visit health centres, even after stay-at-home orders were lifted. This association was also evident spatially, where there were clusters of people that avoided health care centres, but that also had good COVID-19 knowledge. This could have strong negative implications when it comes to disease management and transmission, when certain populations do not seek medical care when sick (i.e., testing and prompt treatment). Another misinterpretation of health information is evidenced by people social distancing while sleeping and no longer sharing LLINs. Although public health messaging urges people to social distance, it should not be at the expense of other significant infectious diseases causing mortality, like malaria.

Understanding the different population sub-groups is also crucial in tailoring messages or strategies during health emergencies. For instance, Ouinhi had the greatest population of people from the Holli ethnic background compared to Covè and Zagnanado; and had significant clusters of people with lower levels of COVID-19 knowledge. Those from the Holli ethnic background were described as being more isolated from people outside their ethnic group, which poses a challenge during health emergencies – including the current COVID-19 vaccination campaign in

the district (Dr. P. Davodoun, personal communications). Therefore, typical approaches and sources of information may not be as effective for people in Ouinhi compared to other districts.

This study also has some limitations that should be considered. In this study, LLIN usage and access did not decrease because of the pandemic. However, this study leveraged an ongoing LLIN trial which began in 2019, and the country had a national LLIN campaign in 2020. In fact, Benin was one of 31 malaria endemic countries scheduled to have a national LLIN distribution in 2020 [50]. In response to the pandemic, the LLIN distribution in Benin was modified and delayed by a couple of weeks. Up until 2020, households in Benin received vouchers that they had to bring to a centralized distribution site to receive their LLIN. For the 2020 distribution, community health workers went door-to-door to distribute the LLIN [238,239]. This has major implications for the impact of LLIN usage and access during the pandemic since LLINs were not only distributed with the trial, but houses received LLINs through the national campaign. However, this highlights the importance of maintaining malaria control during health emergencies since only three-quarters of planned LLIN distributions in malaria endemic countries in 2020 had been completed by the end of their planned distribution year [50]. Indeed, if Benin did not have a LLIN campaign and their LLIN distribution reduced by 25% (described as scenario 1 in the modeling scenarios outlined by the WHO Global Malaria Programme), the country could have seen a 22% increase in malaria cases and death [240].

Another limitation was the method in which the additional KAP questions were administered during the cross-sectional study. All the possible answers for each domain (i.e., all the possible symptoms of COVID-19) were listed and asked to the participant. This approach led to the generation of a KAP score that reflects a participant that answered at least 80% of the questions correctly, which reflects the low knowledge score found in this study. With spontaneous

responses (i.e., the respondent volunteers a response), a different knowledge score could have been calculated with a binary variable for good COVID-19 knowledge reflecting a participant naming at least one correct answer per domain (i.e., naming at least one COVID-19 symptom rather than identifying at least 80% of the symptoms correctly)– which might better reflect the responses from the FGDs [241,242]. Although a minority of respondents had a good knowledge of COVID-19, the metric that was calculated in this study pointed to important statistical associations with health seeking behaviours and spatial clustering of households with good and poor COVID-19 knowledge in the study area.

We also did not account for transportation challenges and service disruptions in evaluating factors associated with health centre avoidance because of the pandemic. Transportation challenges for health care workers and patients as a result of the pandemic (i.e., financial limitations, social distancing measures, price of fuel) have all been noted as barriers in accessing health care centres, while malaria service disruptions have been noted in Rwanda, Uganda, Nigeria and Ghana [243–248]. Despite this limitation, the mixed-methods study design allowed us to reveal differences in health-seeking behaviour within our study participants. Prior to the pandemic, there was a dichotomy of people avoiding and going to health centres when they were sick. Consistent with other studies, the pandemic exacerbated the dichotomy of people going to and avoiding health centres [245,247,249]. Namely, fear of exposure to COVID-19 at the hospitals and financial barriers associated with health centres (i.e., cost of care, reduced income) led some people to avoid health centres because of the pandemic, while fear of COVID-19 and its overlapping symptoms with malaria lead some people to go to the health centre more often than before the pandemic.

5.2.8.1 Conclusion

This study assessed community-level impacts of the COVID-19 pandemic on malaria prevention and health-seeking behaviours in rural Benin. This study shows the importance of sustaining malaria prevention and control and highlights recommendations for disseminating important information during health emergencies. These results can be used to provide insight and tailor malaria prevention and control for future health emergencies.

5.2.9 Acknowledgements

The authors gratefully acknowledge all community members who participated in the study and community leaders of the Zou region for supporting the trial and agreeing to collaborate with the study investigators. A special thanks to Dr. Amber Gigi Hoi for her guidance and assistance with the MuMIn package in Rstudio.

CHAPTER 6

Scoping Review of Integrated Malaria and Schistosomiasis Programs

6.1. Article Preface

6.1.1 Article Preface

This article was accepted to PLOS Neglected Tropical Diseases on January 24, 2024. The objective of this article was to identify whether there have been previous efforts to integrate malaria and schistosomiasis programs and to summarize the strategies and approaches used in these programs. This is the third and final manuscript that forms this doctoral research. The goal of this manuscript was to see what type of research (if any) has been published on the integration of malaria and schistosomiasis prevention and control programs which would directly complement the first manuscript that forms this doctoral research (Tanzania study). The first manuscript (Tanzania study) aims to understand population vulnerabilities, and identify socio-ecological factors associated with malaria, schistosomiasis, and co-infection which would point to the possible evidence for integrating malaria and schistosomiasis prevention and control strategies. Then, with this manuscript (scoping review), we could look at successful (or failed) strategies that have been used in different settings. These two manuscripts would allow us to identify entry points for integrated disease control.

6.1.2 Contribution

I worked collaboratively with my thesis supervisor, Dr. Manisha Kulkarni, and my thesis advisory committee members, Drs. Alison Krentel, Natacha Protopopoff, and Cindy Feng to refine the scope and objective of this chapter. I worked closely with librarians at the University of Ottawa to systematically search three academic databases, each with their unique search strategies. I worked with two undergraduate students, Ms. Sydney Raduy and Ms. Engluy Khov to help with screening relevant articles based on abstract and full text review. I conducted a grey

literature search, followed by data extraction from each included source. I prepared and analyzed the data and reported the findings in the form of a manuscript. All authors contributed to the editing and revision of this article.

6.1.3 Ethics Approval

The scoping review did not involve data on human subjects and ethical approval was not required.

6.1.4 Citation

Duguay C, Raduy S, Khov E, Protopopoff N, Feng C, Krentel A, et al. (2024) Have there been efforts to integrate malaria and schistosomiasis prevention and control programs? A scoping review of the literature. PLoS Negl Trop Dis 18(1): e0011886. https://doi.org/10.1371/journal.pntd.0011886

6.2. Article Content

6.2.1 Title

Have there been efforts to integrate malaria and schistosomiasis prevention and control programs? A scoping review of the literature

6.2.2 Authors

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6.2.4 Abstract

Malaria and schistosomiasis are two important parasitic diseases that are a particular threat to young children and pregnant women in sub-Saharan Africa. Malaria and schistosomiasis prevention and control strategies primarily focus on the distribution of long-lasting insecticidal nets and the delivery of praziquantel tablets to at-risk populations in high burden settings through mass drug administration, respectively. The objective of this scoping review was to identify previous efforts to integrate malaria and schistosomiasis prevention and control programs in the literature and to summarize the strategies and approaches used in these programs following the PRISMA-ScR guidelines. We reviewed published and grey literature using a combination of keywords and search terms following themes surrounding "malaria", "*Plasmodium falciparum"*, "*Anopheles*", "schistosomiasis", "*Schistosoma haematobium"*, "*Schistosoma mansoni", and* "snails". Neither a date limit nor relevant terms for prevention and control were used. Out of 6374, eight articles were included in the scoping review - three articles investigated the integration of mass drug administration for schistosomiasis with the administration of antimalarials, four articles investigated the effect of administering antimalarials on malaria, schistosomiasis, and their co-infection, and one article assessed the impact of an educational intervention on malaria and schistosomiasis knowledge and preventative behaviors. Our findings suggest that there is an opportunity to link disease control programs to increase access and coverage of interventions to improve outcomes for malaria, schistosomiasis, and their co-

infection. Further research is needed on the potential benefits, feasibility, and cost-effectiveness of integrating malaria and schistosomiasis prevention and control programs.

6.2.5 Author Summary

Malaria and schistosomiasis are two diseases that are preventable, treatable, and affect people living in vulnerable circumstances - in particular, young children in rural areas of sub-Saharan Africa. These two diseases overlap geographically, co-infect people living in vulnerable circumstances, share common risk factors, and have the potential for integrated control strategies. The objective of this scoping review was to identify previous efforts to integrate malaria and schistosomiasis prevention and control programs in the literature and to summarize the strategies and approaches used in these programs. Eight articles were included in the scoping review – three articles investigated the integration of mass drug administration for schistosomiasis with the administration of antimalarials, four articles investigated the effect of administering antimalarials on malaria, schistosomiasis, and their co-infection, and one article assessed the impact of an educational intervention on malaria and schistosomiasis knowledge and preventative behaviors. Our findings suggest that there is an opportunity to link disease control programs to increase access and coverage of interventions to improve outcomes for malaria, schistosomiasis, and their co-infection.

6.2.6 Introduction

Malaria and schistosomiasis are two preventable and treatable parasitic diseases that are a particular threat to young children under 14 years old and pregnant women in sub-Saharan Africa [14,27–30]. Malaria is transmitted by *Anopheles* mosquitoes and is caused by five different *Plasmodium* parasite species, with *P. falciparum* being the predominant species in sub-Saharan

Africa [14]. There are two forms of schistosomiasis in sub-Saharan Africa caused by two different *Schistosoma* species – *S. mansoni* causes intestinal schistosomiasis and *S. haematobium* causes urogenital schistosomiasis.

There are three important tools to control and prevent malaria which are responsible for most of the decline in the number of malaria cases and deaths between 2000 and 2015 - including long lasting insecticidal nets (LLIN), indoor residual spraying, and treatment with artemisinin-based combination therapies[14,62]. Globally, there were an estimated 247 million malaria cases in 2021 across 84 countries, which was a 7% increase since the establishment of the World Health Organizations (WHO's) Global Technical Strategy for malaria in 2015 [14,250]. The Global Technical Strategy was developed to set targets to reduce malaria incidence and mortality rates by at least 90% compared to the 2015 baseline, yet there have been challenges in reducing the number of malaria cases and deaths since its establishment. This is likely due to biological threats (pyrethroid resistance in LLINs, antimalarial drug resistance), a reduced coverage of LLINs, and further challenges as a result of the COVID-19 pandemic (disruptions in malaria testing and LLIN distributions) – all of which points to the need for sustained efforts and new control strategies [14,62,63,250].

Other malaria measures such as preventative chemotherapy have been recommended by WHO since 2022 to reach people living in vulnerable circumstances of various age groups [89]. In moderate-to high transmission settings with perennial or seasonal transmission, the WHO recommends the use of intermittent preventative treatment in pregnancy and in school-aged children (IPTp and IPTsc), irrespective of infection status, to treat existing infections and prevent new infections of malaria [89]. For children belonging to age groups at high risk of severe malaria in areas of perennial and seasonal transmission of malaria, the WHO recommends

perennial or seasonal malaria chemoprevention, respectively (PMC and SMC) [89] . PMC, formerly intermittent preventative treatment in infants, has extended its target age group to all children at risk for severe malaria[89]. SMC differs from PMC in that it is administered in periods of greatest risk of malaria in areas with seasonal transmission [89].

The WHO recommends the delivery of preventative chemotherapy to at-risk populations, at a frequency that depends on the endemicity of the community, as a prevention and control tool for five neglected tropical diseases, including schistosomiasis [27,32,251]. For example, the delivery of praziquantel tablets is targeted to all age groups, including children over the ages of two, pregnant women after the first trimester, and lactating women, once a year in areas with schistosomiasis prevalence of ≥10%. In many countries, mass drug administration (MDA) for schistosomiasis relies on the donation of praziquantel tablets to be distributed in endemic communities through school and community health structures. Between 2011 and 2020, Merck KGaA donated 1.26 billion praziquantel tablets for the prevention and control of schistosomiasis [59]. Despite these efforts, 236 million people across 51 countries still require preventive chemotherapy for schistosomiasis in 2021 [32].

While praziquantel is a valuable tool for treating and preventing schistosomiasis, it does not address the underlying social and ecological determinants. Although more resource intensive and logistically complex, snail control with molluscicides and providing safe water and sanitation are critical components to break the schistosomiasis transmission cycle and reduce the need for treatment in at-risk populations [41,69,82,83].

Where malaria and schistosomiasis are co-endemic, co-infection is likely to occur. Afolabil et al. (2022), published a systematic review of 16 articles investigating malaria and schistosomiasis

co-infections in children living in endemic countries, and a meta-analysis of raw extracted data from the included articles [100]. This systematic review found that malaria and schistosomiasis co-infection ranged from 0.2% in one study in Tanzania to 62.9% in Mali, with a pooled co-infection prevalence of 19.2% [100,252–254]. Although the co-infection in the Pwani region of Tanzania was low (n=2/992, 0.2%), there were only two children in the study who were infected with schistosomiasis, both of whom were also co-infected with malaria [253]. Given the potential for co-infection in endemic areas, there is an opportunity for local integrated control strategies for malaria and schistosomiasis, such as combining activities (i.e., IPTsc for malaria and MDA for schistosomiasis) to optimize the use of existing resources as well as increase intervention access and/or coverage for an improved outcome. There is currently a proof-of-principle modeling tool published by Standley et al. 2018, designed for local public health officials or policy makers to provide guidance on how and when to integrate malaria and schistosomiasis control methods – however, only for LLIN distribution, indoor residual spraying, and schistosomiasis MDA [255]. There is also evidence of other types of integration. For instance, MDAs for soil transmitted helminth (STH) and schistosomiasis are frequently combined since children are often co-infected and the simultaneous administration of praziquantel and albendazole is safe [4]. There is also evidence of successful integration of a prevention strategy, which included LLIN distribution with an MDA for lymphatic filariasis, another neglected tropical disease, for the control of malaria and lymphatic filariasis [256]. The objective of this scoping review is to identify previous efforts to integrate malaria and schistosomiasis prevention and control programs and to summarize the strategies and approaches used in these programs. To our knowledge, a review identifying the available evidence for

integrating malaria and schistosomiasis prevention and control programs has not yet been conducted.

6.2.7 Methods

To conduct and report this scoping review, we followed the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews) (Appendix 6.1: PRISMA-ScR Checklist) [257,258]. The detailed published protocol is available on Protocol.io [259].

A systematic search of three academic databases (Medline (Ovid), EMBASE, and Web of Science) was conducted on August 17, 2022. A detailed search strategy for each database was designed and piloted in consultation with a librarian at the University of Ottawa to identify the optimal combination of keywords used. We examined the available electronic databases using combination searches of the following terms: "malaria" OR "*Plasmodium falciparum"* OR "*Anopheles*" AND "schistosomiasis" OR "*Schistosoma haematobium"* OR "*Schistosoma mansoni"* OR "snails". Detailed search strategies and terms used for each database are reported elsewhere [259]. To ensure a comprehensive search of all relevant articles, key terms for prevention and control were excluded from the electronic database searches, and two stages of article screening were conducted with incremental inclusion criterions with each stage. All identified articles were imported into COVIDENCE, a systematic review management software, to screen and manage the results of the search [260].

The first stage of the review involved two of the three reviewers (CD, SR, ELK) independently identifying potentially relevant articles based on information provided in the title and abstract. Articles were included if 1) they addressed malaria and schistosomiasis, and 2) evaluated or described an intervention or control method for malaria and schistosomiasis (Table 6.1). Articles

were also included if the information provided in the title and abstract was not sufficient to determine if it met the inclusion criteria.

The second stage of the review involved at least two of the three reviewers independently identifying relevant publications based on information provided in the full article. Studies were included if they 1) addressed malaria, schistosomiasis, and their co-infection, 2) evaluated or described a joint delivery of malaria and schistosomiasis prevention or control activity (i.e., educational program) or evaluated or described a common platform to deliver an integrated malaria and schistosomiasis intervention (i.e., mass drug administration for schistosomiasis and IPTsc in schools), 3) reported on primary research or protocol for primary research, and 4) were published in French or in English. Articles were excluded if they were a laboratory-based study. Any discordance in the process was discussed among all three reviewers.

Table 6.1: Inclusion and exclusion criteria

Key Theme	**Screening Phase 1** (Title and abstract review)	**Screening Phase 2** (Full text review)
Malaria and schistosomiasis	1. Address malaria and schistosomiasis	1. Address malaria, schistosomiasis, and their co-infection
Integrated prevention and control	1. Evaluate or describe an intervention or control method for malaria and schistosomiasis	1. Evaluate or describe joint delivery of malaria and schistosomiasis prevention or control activity (i.e., educational program) 2. Evaluate or describe a common platform to deliver integrated malaria and schistosomiasis intervention (i.e., mass drug administration for schistosomiasis and LLIN distribution for malaria)
Study Type		1. Primary research or protocol for primary research 2. Not a laboratory-based study

Language		1. Published in English or in French

The grey literature search was conducted after the completion of the peer-review literature search. A systematic search of four grey literature databases (Google search engine, WHO Institutional Repository for Information Sharing search engine, clinical trial registry (https://clinicaltrials.gov), and targeted website search) and forward and backward citation search of the included articles were conducted between December 16, 2022, and January 4, 2023. Detailed search strategies and terms used for each database can be found as a supplementary file (Appendix 6.2: Search Strategy). The first 25 hits for each search in Google and WHO search engine (as sorted by relevance) were screened. Where abstracts were not available, tables of contents were reviewed, followed by full-text screening. Microsoft Excel was used to manage the grey literature search.

From the included articles (academic and grey literature search), one reviewer (CD) extracted data from the articles following a pre-specified extraction sheet (Appendix 6.3: Extraction Sheet). Extracted data included descriptive elements of the study (first author, year of publication, study period, study type, year of program implementation, country of program implementation), and program/intervention characteristics (target population, program/intervention objectives, program/intervention type, key findings, and items from the Template for Intervention Description and Replication (TIDieR) checklist). TIDieR is a 12-item checklist that includes the brief name, why, what (materials), what (procedure), who provided, how, where, when and how much, tailoring, modifications, how well (planned), how well (actual) of a program [261].

6.2.8 Results

6374 citations were generated from the electronic database searches on Medline (Ovid) (n = 1864), EMBASE (n = 2874), Web of Sciences (n = 1197), Google Search (n=50), WHO Search engine (n=25), clinical trial registry (n=14), forward and backward citation search (n=349), and targeted website (n=1) for which only eight articles were included in the scoping review (Fig. 6.1). A complete list of all screened studies can be found as a supplementary file (Appendix 6.4: Complete Data File). Characteristics of the included articles are summarized in Table 6.2. The eight articles were published in English from 1988-2022. The target populations were predominantly pre-school-aged children and school-aged children, with two studies also targeting adults. The interventions outlined in the articles were carried out in sub-Saharan Africa and based in schools (n=3), health centres (n=2), schools and health centres (n=1), or were not specified (n=2). The eight interventions fit into one of the following categories: 1) integration of MDA and the administration of antimalarials, 2) antimalarials to treat malaria and schistosomiasis co-infection, or 3) an educational program.

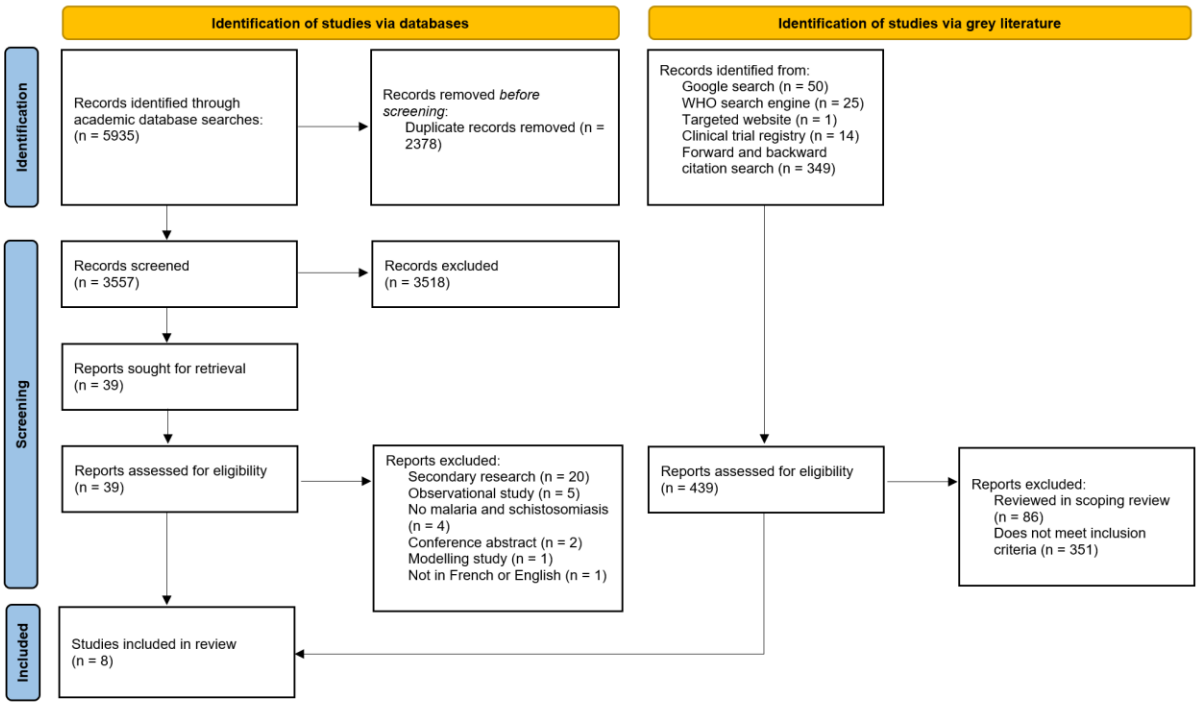

Fig. 6.1 Preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews (PRISMA-ScR) checklist

Table 6.2: Summary of included studies

Authors	**Country**	**Age of Study population**	**Type of intervention**	**Disease targeted**
Midzi et al. (2011)	Zimbabwe	5-17 years old	• MDA (praziquantel, albendazole) and antimalarials (chloroquine, sulphadoxine and pyrimethamine) • Educational program	Malaria, schistosomiasis, and STH
Cohee et al. (2018)	Malawi	5-15 years old	• MDA (praziquantel, albendazole) and antimalarials (artemether-lumefantrine) • Educational program	Malaria, schistosomiasis, and STH
Afolabi et al. (2022)	Senegal	1-14 years old	MDA (praziquantel) and antimalarials (amodiaquine and sulphadoxine-pyrimethamine)	Malaria and schistosomiasis

Ekeh & Adeniyi (1988)	Nigeria	Second year of high school	Educational program	Malaria. Schistosomiasis, dracunculiasis, and onchocerciasis
Boulanger et al. (2007)	Senegal	15-74 months	Antimalarials (artesunate-pyrimethamine) to treat co-infection	Malaria and schistosomiasis
Abay et al. (2012)	Ethiopia	5 years and older	Antimalarials (artemether-lumefantrine) to treat co-infection	Malaria and schistosomiasis
Zoleko-Manego et al. (2022)	Gabon	All ages	Antimalarials (artesunate-pyronaridine) to treat co-infection	Malaria and schistosomiasis
Adedoja et al. (2015)	Nigeria	1-15 years old	Antimalarials (artemether-lumefantrine) to treat co-infection	Malaria and schistosomiasis
Abbreviations: MDA: mass-drug administration; STH: soil-transmitted helminthiasis				

6.2.8.1 Integration of MDA and the administration of antimalarials

Three articles examined the integration of school-based MDAs and the administration of antimalarials [262–264]. Midzi et al. (2011), aimed to reduce malaria and schistosomiasis co-infection by combining the schistosomiasis and STH MDA with an educational campaign for malaria, schistosomiasis, and STH – specifically to recognize the signs of malaria for prompt health seeking behavior [262]. A cohort of school-aged children were followed for nearly three years and were tested for urinary schistosomiasis using urine filtration methods, intestinal schistosomiasis using the Kato Katz method, and malaria using thick smears of slides from venous blood [262]. Schistosomiasis was only tested during the follow-up visit, but children were encouraged to seek prompt malaria treatment between visits if they experienced any malarial-like symptoms [262]. A child was only treated with praziquantel (schistosomiasis) or chloroquine, sulphadoxine and pyrimethamine (malaria) when they tested positive for either respective disease [262]. This study found that, after 33-months, administering praziquantel at school and sustained prompt malaria treatment significantly reduced the prevalence of malaria,

schistosomiasis, and their co-infection by 50.6% (8.1% to 4.0%), 12.9% (31.7% to 27.6%), and 80.2% (13.1% to 2.6%), respectively [262].

Cohee et al. (2018), assessed the participation, safety, and tolerability of adding antimalarial treatment and an educational program to an existing schistosomiasis and STH combined MDA [263]. The education campaign was student-led and was used to increase knowledge about the symptoms, modes of transmission, and prevention for malaria, schistosomiasis, and STH; and to promote participation in the MDA [263]. Unlike Midzi et al. (2011), they distributed artemether-lumefantrine, praziquantel, and albendazole irrespective of infection status to all students in the school [263]. Overall, the enhanced MDA with antimalarials and the educational program was well accepted and did not result in more adverse events compared to the scheduled MDA program [263].

Unlike the two other studies, the article by Afolabi et al. 2022, is a protocol for a randomized control trial evaluating the safety and effectiveness of delivering schistosomiasis MDA through the SMC platform for children in Senegal [264]. Children will be allocated to either the SMC-only group (amodiaquine and sulphadoxine-pyrimethamine) or SMC and MDA group (amodiaquine, sulphadoxine-pyrimethamine, and praziquantel), and the authors will assess adverse reaction for each intervention arm as well as the prevalence and intensity of co-infection [264]. There will also be a qualitative component which includes structured interviews to assess the acceptability, feasibility, enablers, and barriers of combining these two interventions [264].

6.2.8.2 Antimalarials to treat malaria and schistosomiasis co-infection

Boulanger et al. (2007), Abay et al. (2012), Zoleko-Manego et al. (2022), and Adedoja et al. (2015), investigated the effect of administering antimalarials on malaria, schistosomiasis, and their co-infection [265–268]. These studies investigated the efficacy of two different antimalarial combinations (artesunate-pyrimethamine and artemether-lumefantrine) and found them both to be effective for treating malaria and schistosomiasis [265–268]. In the studies by Boulanger et al. (2007) and Zoleko-Manego et al. (2022), only confirmed cases of malaria were tested for urinary schistosomiasis and treated with artesunate-pyrimethamine [265,267]. This combination of antimalarial was found to be effective with cure rates of 56% [267] and 92.6% [265] after four weeks. In the studies by Abay et al. (2012), and Adedoja et al. (2015), only confirmed cases of malaria were tested for intestinal schistosomiasis and urogenital schistosomiasis and treated with artemether-lumefantrine [266,268]. This combination of antimalarial was also found to be effective with cure rates of 100% for intestinal and urogenital schistosomiasis after four weeks [266,268].

6.2.8.3 Educational program

Ekeh & Adeniyi (1988), investigated the impact of an educational intervention on the prevention of malaria and schistosomiasis, and other neglected tropical diseases (onchocerciasis and dracunculiasis) [269]. This four-day education campaign focused on educating school-aged children on the causes, prevention, and treatment of these diseases while emphasizing changes in behavior to mitigate disease exposure [269]. In this study, the authors found that when knowledge was supported by enabling (i.e., environmental) and reinforcing factors (i.e., someone's ability to sustain or maintain a change in behavior), changes in behaviors can occur [269].

6.2.9 Discussion

This scoping review identified different types of integrated prevention and control programs for malaria and schistosomiasis that were effective in reducing co-infection prevalence and yielded additional benefits. The integrated strategies included: 1) school-based MDA for schistosomiasis along with the administration of antimalarials for malaria; 2) the use of antimalarials to treat malaria and schistosomiasis; and 3) an educational campaign. The studies included in this scoping review emphasize the importance of multi-sectoral approaches for each disease - including an educational campaign to mitigate disease exposure along with a pharmaceutical intervention to prevent and control infection in target populations [262,263,269]. This review highlights that the integration of prevention and control programs goes beyond these two diseases, and can include other diseases that are co-endemic with similar intervention strategies (i.e., STH, onchocerciasis, dracunculiasis) [262,263,269].

Progress towards malaria and schistosomiasis elimination will have a positive effect on multiple Sustainable Development Goals (SDGs), including but not limited to SDG 3.3 that states "by 2030, [we should] end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases" [43,46]. The SDGs recognize the importance and need for integrated approaches and solutions such as working together across sectors, government, organizations, and disciplines (among others) to achieve a common goal and to build a more sustainable and resilient future [270,271]. Researchers and agencies have also highlighted the opportunity of integrating disease control activities for neglected tropical diseases, including schistosomiasis, with one of the more funded "big three" (malaria, HIV/AIDS, and tuberculosis) programs, however little research has been done to provide evidence for such integration [272–274]. For instance, a WHO publication

reviewed in the grey literature search (but excluded from the scoping review) noted the possibility to integrate malaria and schistosomiasis control programs by integrating snail control with malaria vector control, but did not provide concrete recommendations or supporting evidence [27].

Where malaria and schistosomiasis are co-endemic, co-infection is likely to occur. Given the shared population at risk, there is an opportunity to leverage and capitalize on existing infrastructures and resources to optimize current prevention and control programs for malaria and schistosomiasis. For example, three studies investigated the integration of MDA and the administration of antimalarials in schools, recognizing the potential to coordinate efforts in a single venue (schools) to an at-risk population (school-aged children) [262–264]. The other five studies investigated the administration of one intervention to address both diseases (pharmaceutical and educational) [265–269]. An important feature to note is that 88% (7/8) of the interventions outlined in this scoping review include a pharmaceutical intervention. Although artemisinin-based combination treatments and praziquantel tablets are still efficacious in treating malaria and schistosomiasis, respectively, the heavy reliance on these treatments raises concerns for the potential emergence of drug resistance [14,27].

There is evidently a missed opportunity for other types of integrated efforts, including non-pharmaceutical interventions such as the provision of safe water, sanitation, and hygiene (WASH) that could result in a significant reduction in exposures to malaria and schistosomiasis. There are twelve major diseases associated with inadequate WASH, including malaria and schistosomiasis, that account for 3.3% of the total deaths (approximately 2 million people) globally[91]. Access to safe water and sanitation facilities plays a pivotal role in both the transmission and prevention of malaria and schistosomiasis. For malaria, better management of

water sources eliminate the accumulation of standing and stagnant water which can serve as mosquito larval breeding sites [91]. For schistosomiasis, the transmission cycle requires direct contact with water contaminated with cercaria. These water sources, typically unimproved (i.e., unprotected springs, surface water [94]), are contaminated when an infected individual either practices open defecation/urination near/in a water source or an infected individual uses an unimproved sanitation facility (i.e., pit latrines without slab [94]) that does not properly keep the sewage out of the environment. Therefore, interventions that address safe WASH could have a positive effect on both malaria and schistosomiasis – yet we did not find any studies that investigated this type of intervention.

The majority of the studies in this scoping review (n=5) also state that the integration of schistosomiasis and malaria prevention and control programs have the potential to be cost-effective, but fail to provide any definition or breakdown of such costs [262–266]. The tablets for school-based schistosomiasis MDAs are largely donated by pharmaceutical companies, and the cost for delivering such programs is approximately $0.50 USD per child (reflecting the cost of delivering the tablets rather than the tablets themselves) [27]. As for malaria, the total funding for its prevention and control fell short of the 2021 targets to remain on track for the Global Technical Strategy, for the third consecutive year [14]. With more than 247 million malaria cases and 236 million people requiring preventative chemotherapy for schistosomiasis, now, more than ever, there is a need and opportunity to link control programs to increase access and coverage for improved outcome, while reducing intervention costs and combat donor fatigue [14,32].

This review has several potential limitations. First, some relevant documents may have been excluded unintentionally from this scoping review, but this risk was mitigated by reviewing both

academic and grey literature databases. Although the grey literature search did not contribute many sources in this scoping review (n=2), it did highlight a knowledge gap and ongoing work in the field (i.e., an active randomized controlled trial investigating the safety and effectiveness of delivering MDA and IPTsc as well as a non-randomized study published three months after the initial electronic database search investigating the effectiveness of artemisinin-based combination therapy on malaria, schistosomiasis, and their co-infection [264,267]). The majority (88%, n=44) of the custom Google searches were also research articles that either did not meet the inclusion criteria (n=11) or were already included in the scoping review search results (n=33), which highlights the ongoing research and focus on advancing the evidence for integrating malaria and schistosomiasis prevention and control strategies. These ongoing efforts could lead to concrete guidelines and recommendations. A second limitation is that scoping reviews are exploratory in nature and are meant to address broad questions such as identifying the type of efforts made to integrate malaria and schistosomiasis prevention and control programs [275,276]. Although the scope was wide, it is evident and clear from this scoping review that while there is a need to move away from siloed approaches for disease prevention, more evidence is needed to inform such policies.

6.2.9.1 Conclusion

It is imperative to build resilient, and sustainable programs to maintain efforts for the control and elimination of malaria and schistosomiasis. To date, this is the first scoping review that identifies previous efforts to integrate malaria and schistosomiasis programs. Future research priorities should include additional randomized control trials that combine malaria and schistosomiasis activities, such as the one being conducted by Afolabil et al. (2022), to inform the integration of programs targeting these two diseases [264]. Non-pharmaceutical interventions (i.e., access to safe WASH and the impact of nutritional supplementation) should also be investigated further to

assess their effectiveness on reducing malaria and schistosomiasis infection. Despite associations between safe WASH and nutritional supplementation and mono-infections with malaria and schistosomiasis, no studies were identified in this scoping review likely because these outcomes were not investigated in the same article. The different types of interventions outlined in this review highlight the need to identify key stakeholders for each disease prevention and control program, and to understand local contexts to establish the feasibility of integrating malaria and schistosomiasis prevention and control programs. Such research can support malaria and schistosomiasis program stakeholders to work together in the critical window of opportunity to reach the 2030 targets outlined by the SDGs, Global Technical Strategy, and WHO 2030 neglected tropical disease roadmap.

6.2.10 **Acknowledgements**

The authors would like to thank Peter Farrell, Sarah Visintini, Karine Fournier and Lindsey Sikora, librarians at the University of Ottawa, for their advice regarding the search strategy, guidance throughout the grey literature search process, and help with the interlibrary loan requests to access all articles needed for this scoping review.

CHAPTER 7

Discussion

7.1. Chapter Overview

The overarching goal of this thesis was to understand population vulnerabilities, infection exposures and risk factors for malaria and schistosomiasis to inform targeted, and possibly integrated, interventions. There is a critical need to revise and optimize current disease prevention and control strategies for malaria and schistosomiasis to meet the goals set out by the SDGs – especially given that current strategies are vulnerable to disruptions such as those experienced during the COVID-19 pandemic. We addressed this goal through a set of interrelated objectives using two mixed-methods studies (explanatory sequential and convergent parallel) and a scoping review. The results of these studies are synthesized in the following sections to highlight key public health implications.

7.2. Bridging Epidemiology and Action

The fundamental premise of this thesis is that a geographical overlap exists between populations at risk for malaria and schistosomiasis, leading to concurrent infection in children. The Lake Victoria zone of Tanzania has historically been an endemic area for malaria and schistosomiasis with five studies in recent years establishing that the prevalence of malaria and schistosomiasis co-infection (either urogenital or intestinal) among school-aged children ranging between 10.9% and 27.2% (Fig. 7.1) [17–21]. In the Tanzania study (chapter 4), we found that the prevalence of malaria and schistosomiasis co-infection among school-aged children was 38.1% based on rapid diagnostic testing. The higher estimate may reflect the test methods, which included the detection of recent or current malaria infection, as well as recent or past infection for schistosomiasis. Nonetheless, this marked the initial step in assessing whether we should

approach malaria and schistosomiasis as a singular integrated challenge rather than two siloed problems.

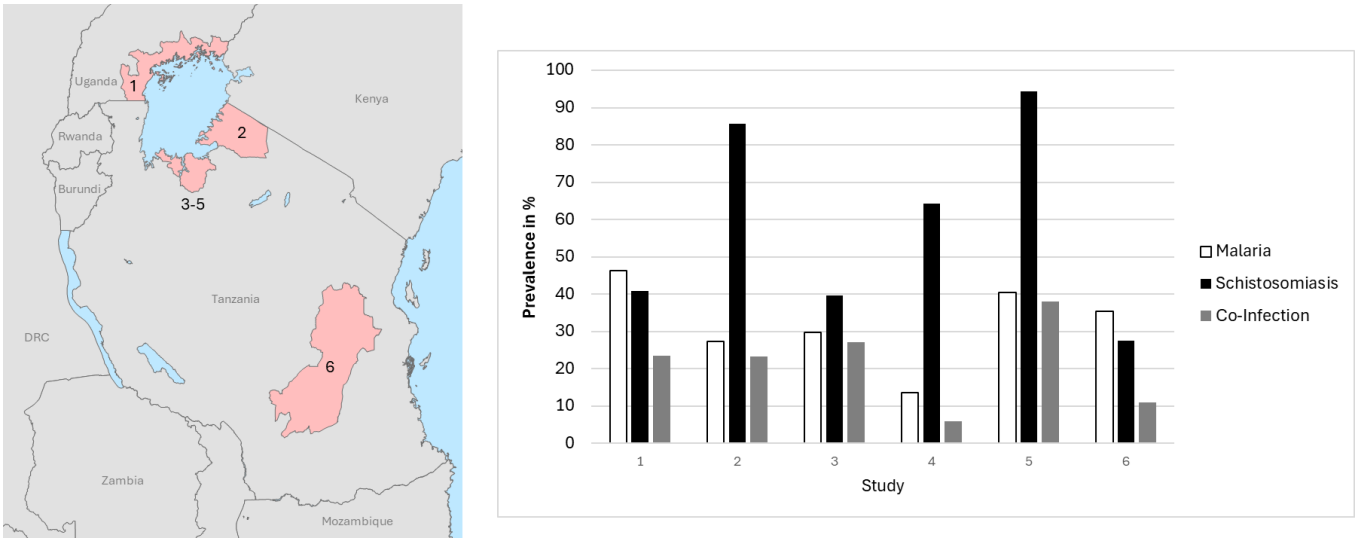

Fig. 7.1 Malaria and schistosomiasis mono- and co-infection in Tanzania and bordering Lake Victoria. Data retrieved from published literature [17–21].

It is evident from the results of this thesis that the epidemiology of malaria and schistosomiasis (i.e., geographic overlap and co-infection) suggests that these two diseases may be viewed as singular and integrated challenge, rather than separate and siloed problems. However, the strategic plans for malaria and schistosomiasis control and elimination programs are structured in siloes, focusing on a single disease without establishing connections or integrated efforts with each other, as outlined in Table 7.1.

Table 7.1: Comparison of strategic plans for malaria and schistosomiasis control and elimination programs; adapted from the World Health Organization document outlining the use of integrated vector management for malaria and lymphatic filariases [1].

	Malaria	**Schistosomiasis**
Document	Global Technical Strategy for Malaria 2016-2030 [250]	A Road Map for Neglected Tropical Diseases 2021-2030 [277]
Goal	By 2030, reduce malaria mortality rate and incidence case globally by at least 90% compared with 2015.	By 2030, number of countries validated for elimination as a public health problem 78/78 (100%).
Timeline	2030	2030
Core Strategy	Vector control: LLIN and IRS	Regular treatment through MDA with praziquantel
Funding	Current annual spending: USD$ 2.7 billion. By 2030, annual spending needs to increase to USD$ 8.7 billion	In 2016, US$ 300 million was donated annually for NTDs. By 2020, WHO estimates that NTDs could cost up to USD$ 750 million a year.
Principle	Country ownership and leadership are essential to accelerating progress.	Country ownership is essential for meeting the 2030 NTD targets with the support of regional and global stakeholders.
Abbreviations: LLIN: long lasting insecticidal nets; IRS: Indoor Residual Spraying; MDA: mass drug administration; NTD: Neglected Tropical Diseases		

It is worth noting that there are also striking resemblances in the strategic plans for malaria and schistosomiasis including their goals, timelines, and principles[250,277]. Despite the epidemiology and shared goal of disease reduction for the same target population, malaria and schistosomiasis control strategies are implemented vertically with disease-specific interventions [278]. This thesis strongly emphasizes that there is a missed opportunity for combining malaria

and schistosomiasis activities or taking a more holistic approach (i.e., the social-ecological framework) to disease prevention such as improving safe water access and improving housing structures.

7.3. Current State of Malaria and Schistosomiasis Prevention and Control Strategies

One of the key objectives of this thesis was to help identify entry points for integrated disease control, or to determine whether integration was a viable solution to address malaria and schistosomiasis. Briefly, based on the results from the study in Tanzania (chapter 4), we might be faced with significant challenges in reducing malaria and schistosomiasis burden if we rely heavily on siloed approaches with LLIN distributions for malaria control and MDA for schistosomiasis control. For instance, in the study in Tanzania, we were nested in an ongoing LLIN trial where each household was distributed LLINs according to WHO recommendations (1 net for every 2 people) with the most recent distribution being 3 years prior to data collection; and there were also more than five effective (≥75% coverage) MDA rounds in Tanzania (most recently in 2021, 2020, 2019) one, two and three years prior to data collection. Yet, we found that children were still vulnerable to both diseases with a malaria prevalence of 40.5% and schistosomiasis seroprevalence of 94.3%. This urges us to question why we are met with challenges in meeting the targets set out by the WHO Global Technical Strategy for malaria and the WHO 2030 NTD roadmap for schistosomiasis, despite adherence to current WHO guidelines. The following sections will delve into the current challenges in malaria and schistosomiasis control programs, focusing on each disease in isolation.

7.3.1 Malaria control programs

Despite a 64% and 7% reduction in malaria prevalence since 2000 in Tanzania and Benin, respectively, progress in these countries (as with global trends) has recently stalled (Fig. 7.2) [14]. Indeed, the WHO Global Technical Strategy for malaria set specific targets to reduce the number of malaria cases by 90% by 2030 compared to the 2015 baseline – in contrast, we have observed a global 11% increase over this period [14]. The challenges in malaria control strategies are well documented and namely include vector resistance, incomplete coverage of LLINs, and impacts due to climate change (i.e., population displacement, changes in vector distribution) [37]. While not extensively addressed in the literature, a significant challenge that emerged as a major concern included the potential misalignment between WHO recommendations for LLIN access and actual practices.

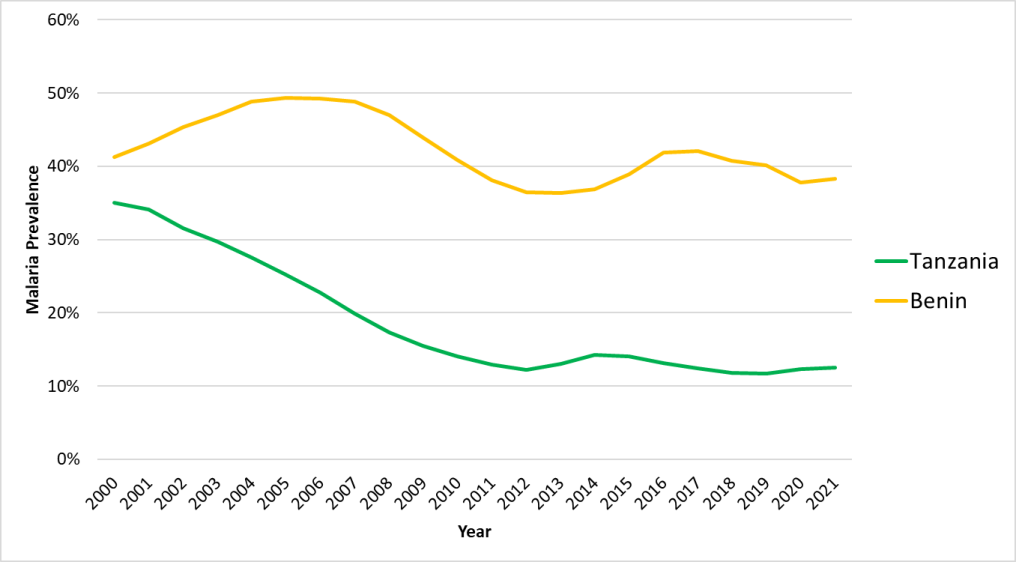

Fig. 7.2 Malaria prevalence trends for malaria in Tanzania and Benin from 2000-2021. Data retrieved from World Malaria Report 2022[14]

7.3.1.1 Challenge 1: Behavioural and insecticidal resistance in Anopheles mosquitoes

A key factor contributing to the resurgence in malaria prevalence is the development of behavioral and insecticidal resistance in *Anopheles* mosquitoes, which have been widely reported in sub-Saharan Africa and pose a threat on the effectiveness of LLINs [37,148,149]. *Anopheles* mosquitoes in many regions are exhibiting changes in their behaviours and may feed earlier [150] or shift from biting indoors to outdoors [151,152] to feed on individuals when they are not likely to be sleeping under a LLIN. Pyrethroid resistance in *Anopheles* mosquitoes, which is reducing the efficacy of the primary insecticide used in LLINs, has been reported in Tanzania and Benin, among other countries [148,154]. To mitigate this challenge, studies are investigating the efficacy of dual-active ingredient LLIN against the standard pyrethroid-only LLIN [149,155,157,158,229], however new vector control tools may be warranted.

7.3.1.2 Challenge 2: Deviation in WHO recommendations for LLIN access and actual practices

The challenge in malaria control that was identified in this thesis was the deviation between WHO recommendations for LLIN access (one LLIN for every two people) and actual practices. For example, in the study in Benin (chapter 5), we found that LLIN access did not decrease during the first year following the start of the pandemic (62% in 2019 compared to 73% in 2021), but the focus group discussions provided a different perspective on these cross-sectional survey results. One of the key themes from the focus group discussions was that actual practices of sharing a net may not align with WHO recommended distribution of one LLIN for every 2 people in a household. For example, people in our study were practicing social distancing in their home by separating their beds or sleeping apart, resulting in a shortage of LLINs. Similarly in our study in Tanzania (chapter 4), we had a contrary challenge where the results demonstrated a

low household LLIN access (28.0%), but it was anecdotally noted that individuals were sharing LLINs with more than 2 people. Therefore, while LLINs are a valuable tool, they rely on human uptake and adherence. LLIN access reflects the metrics used to supply nets to households, but if LLINs are not used as anticipated, as observed in the studies in Tanzania and Benin, this could partly explain and provide insight into the socio-behavioural factors contributing to malaria resurgence.

7.3.2 Schistosomiasis control programs

The global challenges surrounding schistosomiasis control align with the challenges seen in Tanzania (chapter 4), where despite continued praziquantel distribution, the number of people requiring treatment, or the number of people exposed to schistosomiasis, remains high.

7.3.2.1 Challenge 1: Widespread exposure to schistosomiasis

One of the challenges with current schistosomiasis interventions identified in this thesis was rapid reinfection due to widespread exposure to schistosomiasis. In the study in Tanzania (chapter 4), schistosomiasis seroprevalence among school-aged children was high (94.3%) which suggests high levels of exposure and reinfection after treatment. The preventative effect of praziquantel is only temporary and the number of worms returns to initial levels after six-months in highly endemic areas if an individual is not retreated [210,211]. In endemic areas that do not observe a reduction in schistosomiasis prevalence despite adequate treatment coverage, the WHO suggests biannual rather than annual MDAs [80]. This however leads to the subsequent challenge that there is an insufficient production of praziquantel tablets to reach the entire population at risk [279] Therefore, while praziquantel is a valuable tool for treating and preventing schistosomiasis temporarily, it does not address the underlying factors contributing to

the persistence of the disease in the community (i.e., contact with contaminated water, lack of adequate sanitation facilities (latrines)).

7.3.2.2 Challenge 2: Insufficient production of praziquantel tablets

Another challenge that was not investigated in this thesis but was one major point of concern during the Global Schistosomiasis Alliance annual meeting in 2023, was the insufficient production of praziquantel tablets to reach the entire population at risk for schistosomiasis, which is outlined as a critical action to achieve the targets outlined in the roadmap [42,279]. Between 2011 and 2020, Merck KGaA donated 1.26 billion praziquantel tablets for the prevention and control of schistosomiasis [59] and will continue to donate 250 million tablets a year to school-aged children until schistosomiasis is eliminated. This is a great commitment by a pharmaceutical company, but it does not provide sufficient tablets to reach the total number of people requiring preventative chemotherapy for schistosomiasis. For instance, with 251 million people requiring preventative chemotherapy, we would need at least 753 million tablets if every person was given a single annual dose of praziquantel if we are considering a 3 tablet dose per person (dose is calculated based on a person's weight; weight: 100 pounds, dosage: 40mg/kg, tablet: 600 mg) [32].

7.4. The Essential Role of Environmental Interventions in Malaria and Schistosomiasis Prevention and Control Strategies

The results of the study in Tanzania (chapter 4) and Benin (chapter 5) suggest that incorporating environmental interventions into current malaria and schistosomiasis control strategies may have a significant impact on the efficacy and sustainability of each control program. Environmental interventions, including WASH, do not solely rely on human uptake and can offer a

comprehensive and multi-faceted approach to malaria and schistosomiasis control. The advantage of the inclusion of WASH is that it will not only benefit malaria and schistosomiasis control, but other WASH-attributable diseases as well. To visually represent this idea, we can think of these different interventions (LLIN, MDA) as pillars that form the foundation for disease prevention and control (Fig. 7.3A). If we combine interventions within a disease program (i.e., LLIN and WASH for malaria prevention) and between disease programs (i.e., WASH for malaria and schistosomiasis prevention), we are not just relying on one pillar for structural integrity, but rather we are distributing our weight across multiple pillars for structural integrity (i.e., program resiliency) (Fig. 7.3B). The following sections will delve into the current evidence supporting the inclusion of environmental interventions to current malaria and schistosomiasis prevention and control strategies.

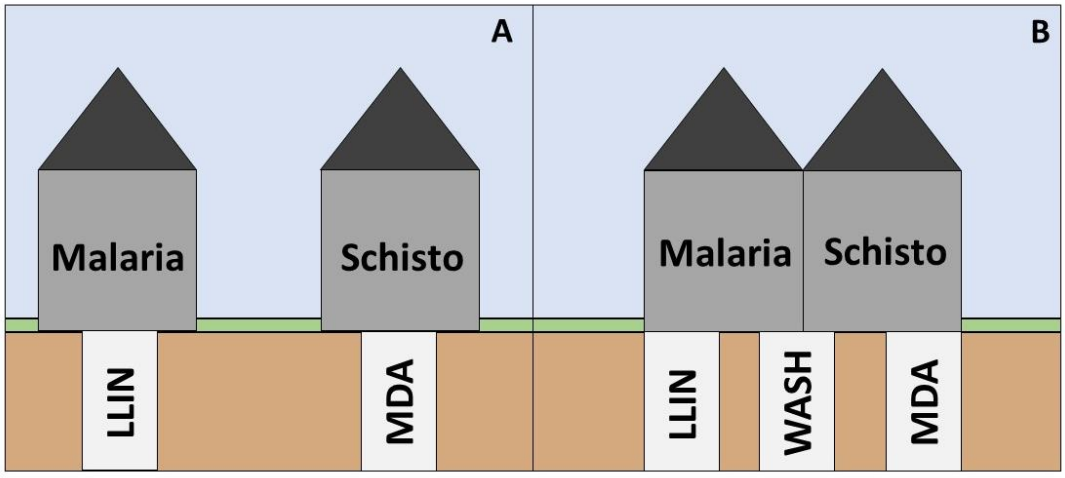

Fig. 7.3 Proposed integrated and combined intervention (B) for malaria compared to the current siloed approach (A). Abbreviations: Schisto: schistosomiasis; LLIN: long lasting insecticidal nets; MDA: mass drug administration; WASH: water, sanitation and hygiene.

7.4.1 WASH strategies and their impact on malaria prevention

The existing literature on the association between WASH interventions and malaria risk is limited, but the conceptual plausibility is evident. Yang et. al (2020) used the Demographic Health Survey and the Malaria Indicator Survey data to model the association between WASH and malaria risk and found that poor drinking water (unprotected vs protected) and sanitation (no facility vs facility) significantly increased malaria risk among children under five years across sub-Saharan Africa, after adjusting for age, gender, IRS, LLIN use and mother's education [280]. One of the caveats with this study is that the Demographic Health Survey data only includes data on types of drinking water even though WASH-attributable disease can be spread from a range of transmission routes including ingestion, contact with contaminated water (i.e., schistosomiasis) and through vectors that need water to complete their lifecycle (i.e., malaria) [281,282].

Despite the limited existing research, the association between unsafe water practices and malaria risk is evident (Fig. 7.4). There are three dominant *Anopheles* vector mosquitoes in sub-Saharan Africa, including *An. arabiensi*s, *An. gambiae* sensu stricto (s.s.), and *An. funestus*, all with their own preferred larval site characteristics [75,173]. *An. arabiensi*s and *An. gambiae* sensu stricto (s.s.) often prefer stagnant water collections (i.e., puddles, wells, dips in the ground) that could be created as a result of unsafe water practices [283]. This availability of larval breeding sites is associated with an increase in malaria vector density, thereby increasing malaria risk. While *An. funestus* is also a dominant malaria vector, it prefers larger bodies of water (i.e., lakes, streams, springs) as its larval breeding sites which are not often associated with unsafe water practices [283].

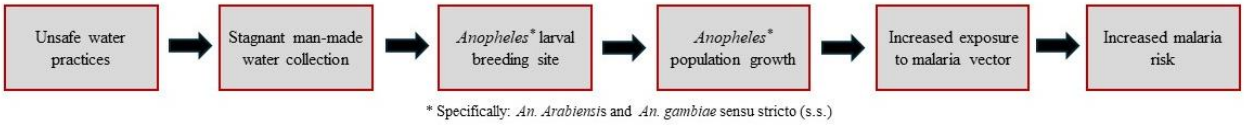

Fig. 7.4 Illustrating the association between unsafe water practices and increased malaria risk.

7.4.2 WASH strategies and their impact on schistosomiasis prevention and control

In contrast to malaria, the association between unsafe water and sanitation practices and schistosomiasis risk is extensively documented [7–11] and recognized by the WHO in their global strategy on WASH and NTDs [12]. In 2014, Grimes et al. conducted a systematic review and a meta-analysis investigating the association between WASH and schistosomiasis risk and found that safe water supplies and adequate sanitation were significantly associated with lower odds of schistosomiasis [7]. The global strategy on WASH and NTDs outlined by the WHO also states and aims to "substantially improve health through the safe management of water, sanitation and hygiene" [284]. Despite the strong rational and guidelines highlighting the importance of WASH the prevention and control for schistosomiasis, MDAs with praziquantel remain a core strategic intervention for schistosomiasis [42].

7.4.3 The urgent need for the inclusion of WASH strategies to current malaria and schistosomiasis prevention and control strategies.

The concept of integrating WASH to disease control is not a novel idea. In fact, the provision of safe drinking water, among other interventions, played a significant role in efforts towards the eradication of guinea worm disease (one of the twenty-one NTDs as defined by WHO) which is transmitted by drinking contaminated water [285]. Thanks to integrated disease control, including WASH, guinea worm disease is now on the verge of eradication with 13 human cases

reported in 2022 [285,286]. Below, I will present a rationale for integrating WASH interventions into both malaria and schistosomiasis control programs to sustain the benefits of other interventions (LLINs, MDA).

The results from the study in Tanzania (chapter 4), clearly indicate that access to safe water and sanitation should be an important consideration for the prevention of malaria and schistosomiasis. For instance, children were potentially infected with schistosomiasis through contact with contaminated water while fetching drinking water (Fig. 7.5A) or doing laundry (Fig. 7.5B) or infected with malaria due to the accumulation of standing water. These widespread exposures made it challenging to discern any meaningful and actionable associations between socio-ecological determinants and infection status from the mixed-effect logistic regression models. For example, it was not conceptually meaningful if an individual had a good knowledge of the symptoms of schistosomiasis when it was clear that those living in the study area were potentially being exposed to contaminated water three times a day while fetching drinking water.

Fig. 7.5 Example of potential sources of exposure to schistosomiasis in Misungwi, Tanzania: unimproved water source for drinking water (A), unimproved water source for domestic uses (laundry) (B).

7.4.4 WASH strategies to increase malaria and schistosomiasis program resiliency.

It is also important to consider that the COVID-19 pandemic was not the first and will not be the last public health emergency that can pose a threat to ongoing malaria or schistosomiasis prevention and control programs. For example, less than a decade ago, the Ebola epidemic posed a threat to malaria programs in West Africa which resulted in an increase in malaria cases, which in turn was attributed to a decrease in outpatient attendance and disruptions in LLIN distributions [219]. The effects of climate change can also serve as another current example, where for the first time since its inception, the 2023 publication of the World Malaria Report included climate change to the global malaria response [37].

As for the COVID-19 pandemic, potential threats to ongoing malaria and schistosomiasis prevention and control programs were a result of early public health messaging that recommended that LLIN distributions and MDAs be delayed until further notice [86,101]. There were 31 malaria endemic countries scheduled to have a national LLIN distribution in 2020, including Tanzania and Benin, but only slightly more than half (18/31) of the countries had successfully completed the distribution by the end of the year [50]. Benin was one of the countries that had successfully completed their distribution by the end of the year, but they had modified and delayed their distribution by a couple of weeks. Up until 2020, households in Benin received vouchers that they had to bring to a centralized distribution site to receive their LLIN, but for the 2020 distribution, community health workers went door-to-door to distribute the LLIN [238,239]. This was in fact one of the instrumental reasons why in the study in Benin

(chapter 5), we saw that LLIN access did not decrease during the pandemic (62% in 2019 compared to 73% in 2021). The study results could have been different if the National Malaria Control Program in Benin did not follow-through with the LLIN distribution in 2020 as planned. For schistosomiasis programs, the impacts of MDA delays and interruptions were dependent on the baseline prevalence, burden of infection in adults, duration of delay, and the stage of the MDA program[51]. Disruptions in MDA were modelled to have a greater impact in areas with high transmission due to the greatest risk of resurgence [52]. In the study in Tanzania (chapter 4), the 2020 schistosomiasis MDA proceeded as scheduled [*personal communication with Misungwi District NTD Coordinator*].

Presently, malaria and schistosomiasis prevention programs both prioritize a singular intervention, but it is evident that they are vulnerable to disruptions such as the ones posed by the COVID-19 pandemic. Given the intricate and multifaceted nature of malaria and schistosomiasis infection, as evidenced by the conceptual framework highlighted in Fig. 1.1, the prevention and control should equally be multifaced and comprehensive. Although WASH interventions are also vulnerable to public health emergencies, the inclusion of a complementary intervention that addresses other aspects of the socio-ecological framework could prove to be beneficial – especially during public health emergencies when LLIN distribution or MDA may not proceed as planned [65,287].

7.5. Limitations and Research Recommendations

7.5.1 Thesis Limitations and Challenges

This thesis has several potential limitations. First, this thesis began in May 2020 during the COVID-19 pandemic, which not only posed some logistical challenges due to travel restrictions

and project funding, but limited some aspects of the thesis research. Namely, the project in Benin (chapter 5) was initially proposed to be completed in Tanzania as another component of the cross-sectional survey. However, due to challenges in obtaining approvals for COVID-19 related studies in Tanzania during the early stages of the pandemic (i.e., 2020 and 2021), the proposed project had to relocate to Benin. Despite the relocation of this component of the project, it allowed us to assess the vulnerability of siloed disease programs in another setting. However, it did not allow us to investigate the impact of the pandemic on schistosomiasis risk factors or programs, since this disease was only being investigated in Tanzania.

7.5.2 Strength of evidence for integrated disease control.

The objective of this thesis was to identify entry points for integrated disease control or to determine whether integration was a viable solution for malaria and schistosomiasis. In the study in Tanzania (chapter 4), we provided evidence that children were concurrently infected and exposed to malaria and schistosomiasis. In the Benin study (chapter 5), we revealed that current malaria programs are vulnerable to disruptions such as the COVID-19 pandemic, pointing to the need for revised program priorities. Finally, in the scoping review (chapter 6), we demonstrated that there were previous efforts to integrate malaria and schistosomiasis prevention and control programs in the literature.

All the evidence presented in this thesis was derived from cross-sectional studies or a scoping review. Although these types of studies are valuable, they do not provide the same level of rigor and weight of evidence as cohort studies or randomized controlled trials [289]. We chose these types of studies (cross sectional study design and scoping review) for two key reasons: 1) practical limitations and 2) the current state of research in the field. First, we leveraged ongoing

bed net trials and strategically incorporated additional questions into their cross-sectional surveys to address alternative objectives for this thesis. Although it would have been valuable to follow a cohort of participants to investigate the temporal association between risk factors (i.e., changes in seasons, changes in LLIN access) and infection status or to investigate changes in impacts of the impact of the COVID-19 pandemic (i.e., as public health messaging evolved) on malaria prevention practices, it was not feasible given resource constraints. Second, considering the novelty of the topic (malaria and schistosomiasis integration), the cross-sectional surveys allowed us to establish foundational knowledge about the topic that could inform future research, including cohort studies and randomized control trials. The objective of this thesis was exploratory in nature and was not intended to investigate the effect of a singular risk factor or an intervention on infection status, therefore the cross-sectional study design was a fitting approach.

However, to mitigate the potential limitations and biases of the cross-sectional approaches, we used multiple methods (triangulation) to increase the overall validity and reliability of the study results. We used statistical, qualitative, and spatial approaches to gain a comprehensive understanding of the determinants associated with malaria and schistosomiasis infections as well as the impacts of the COVID-19 pandemic on malaria prevention. The statistical approaches allowed us to study the strength and direction of the association (not causal effect) of multiple variables on each outcome [290,291]. The qualitative approaches allowed us to gain a deeper understanding of participants' experiences with each objective, beyond what was captured by the quantitative surveys [292]. Finally, as Tobler's First Law of Geography states: "everything is related to everything else but near things are more related than distant things", and therefore the spatial analysis allowed us uncover important spatial patterns of each outcome [165].

7.5.3 A call for research on the feasibility of integrated malaria and schistosomiasis programs.

The objective of this thesis was to identify entry points for integrated disease control and not to evaluate the efficacy of integrated disease control programs. The findings from this thesis demonstrated that there was a conceptual rationale for combining malaria and schistosomiasis programs given their co-infection among children in Tanzania (results from chapter 4) and the vulnerabilities of siloed approaches during public health emergencies (results from chapter 5). Although the evidence from this thesis suggests that integration can be a valuable tool to achieve the SDGs, future research on the feasibility and effectiveness of integrating malaria and schistosomiasis is needed.

In this thesis, we did not evaluate the feasibility and practical considerations of combining interventions within a disease program (i.e., LLIN and WASH for malaria prevention) and between disease programs (i.e., WASH for malaria and schistosomiasis prevention). Challenges in integrating these types of interventions may arise given their varied levels of governments and funding sources. Briefly, LLIN distributions and MDAs are coordinated at the national level through the Ministry of Health and/or Ministry of Education while WASH interventions are coordinated at the district/local level either through the Ministry of Public Works, Ministry of Water Resources, Ministry of Education or Ministry of Finance [293]. The funding structure (i.e., type of donor and time scale) for LLIN distributions, MDAs, and WASH interventions also vary from sustained and ongoing commitments with an indefinite time scale for WASH

interventions (i.e., infrastructure, operations, maintenance, management) to temporary, intensive commitment for a finite duration for MDAs [293].

There also remains a critical knowledge gap in quantifying the effect of integrating malaria and schistosomiasis prevention and control programs. One proposed study design includes a cluster randomized stepped wedge trial to evaluate the advantages and disadvantages of combining MDA and LLIN distribution activities as compared to siloed intervention, on malaria and schistosomiasis outcomes (Fig. 7.6). This study design is an alternative to parallel cluster trial designs, but because it would be unethical to deny clusters (i.e., villages, districts) of either schistosomiasis or malaria interventions, this design allows for comparison through a gradual introduction of an integrated approach across the different clusters [294]. This design includes an initial period (orange squares) in which no clusters are exposed to the intervention (standard operating procedure of siloed approaches), and they serve as their own control. Over time (i.e., with every annual LLIN distribution for example), a group of clusters gradually transition to receiving the intervention which is the integrated activities (blue squares). At each step, information such as intervention coverage, disease prevalence, intervention acceptability from the individual perspective or from the community health worker perspective can be collected. This study design would establish a causal effect between the types of intervention and infection status to determine if there are any additional (or multiplicative) benefits of combining interventions within a program [291,295].

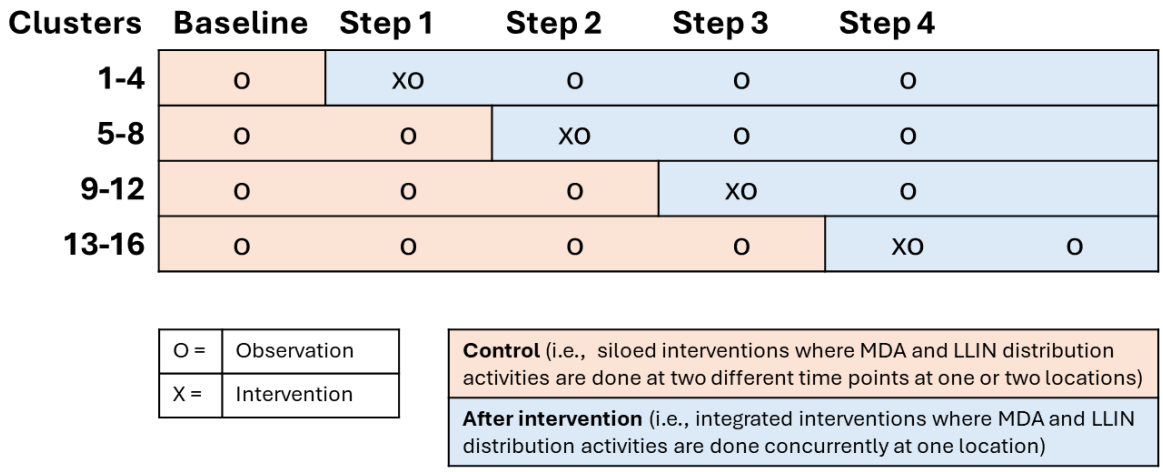

Fig. 7.6 Proposed study design to evaluate the advantages and disadvantages of combining MDA and LLIN distribution activities as compared to siloed intervention, on malaria and schistosomiasis outcomes. This figure is adapted from Figure 2 in Reygada et al. 2015 [22].

There is also an urgent call to increase the body of evidence of the health benefits of safe water and sanitation on malaria and schistosomiasis prevention and control. An important finding from the scoping review (chapter 6) was not only that there was a limited body of literature investigating the integration of malaria and schistosomiasis, but that not a single study investigated the integration of an environmental intervention. Additional evidence would inform key stakeholders that set program priorities to recognize WASH as a valuable tool in disease control.

7.6. Conclusion

In this thesis, we aimed to understand population vulnerabilities and infection exposures and risk factors for malaria and schistosomiasis to inform targeted, and possibly integrated, interventions. We found that malaria and schistosomiasis overlap geographically and co-infect the same people

living in vulnerable circumstances and that there remain widespread exposures to both diseases despite ongoing prevention and control efforts. We suggest that current control measures for malaria (LLIN distribution) and schistosomiasis (MDAs) are not sufficient in reducing exposures to malaria and schistosomiasis.

We propose that we need to combine interventions to increase program resiliencies, and that we need to emphasize environmental control such as access to safe water and sanitation facilities to further sustain malaria and schistosomiasis prevention and control. The results from this thesis point to the need for more research on the integration of environmental interventions as a complementary tool for malaria and schistosomiasis prevention and control.

Changes in malaria and schistosomiasis prevention and control strategies are crucial to meet the targets outlined by the SDGs (including but not limited to SDG 3: good health and well-being, and SDG 6: access to safe and affordable water and sanitation), Global Technical Strategy (90% reduction in malaria cases and death compared to 2015 baseline), and WHO 2030 NTD roadmap (90% decrease in the number of people requiring praziquantel compared to 2010 baseline). We cannot continue on our current path with our current prevention and control strategies for malaria and schistosomiasis and expect to see different results by 2030.

CHAPTER 8

References

8.1. References

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CHAPTER 9

Appendices

9.1. Appendices

Appendix 3.1. Benin Survey Descriptions

Cross-Sectional Survey	Sample Size	Variables Collected	Purpose
Baseline XS (Baseline cross-sectional survey)	2,400	**Main Trial Questions** • District • Ethnicity • Marital status • Education • SES • Location of health facility • Malaria control and prevention (LLIN access and usage)	• The baseline cross-sectional survey from the main trial was used to compare LLIN access and usage in 2019 (before the COVID-19 pandemic) compared to 2021 (during the pandemic) using the KAP 2 survey. Using a mixed-effects logistic regression model, we aimed to determine the statistical significance of the time point variable (2019 vs 2021), while controlling for other socio-ecological variables (i.e., ethnicity, district, education) to understand the impact of the COVID-19 pandemic on malaria prevention and control. Since 99% of the respondent used a LLIN the night prior (LLIN usage), we were not able to run a mixed-effect logistic regression model – rather we descriptively illustrated the changes in usage from 2019 to 2021. • This survey also collected information on the location of the health facilities in the study area. We calculated the Euclidean distance from each household in the study to the nearest health facility (using the GPS location) using the "Extract Multi Values to Point" tool in ArcMap version 10.8.1 (ESRI, Redlands, CA, USA). This metric was used in the analysis for aim one and three.
KAP 1 ("cohort" cross-sectional survey	1,800	**Main Trial Questions** • District • Ethnicity	• KAP 1 denotes the first cross-sectional survey (May-July 2021) from the main trial that included additional questions about COVID-19 (knowledge, source of information). We denoted this survey

with the COVID-19 questions)		• Marital status • Education • SES **Additional COVID-19 Questions** • COVID-19 knowledge (symptoms, transmission, prevention) • COVID-19 source of information	as KAP 1 to make the distinction with another cross-sectional survey used for this chapter (KAP 2). The additional COVID-19 questions were embedded and collected during one of the routine follow-up visits for the cohort from the main trial. • KAP 1 and KAP 2 were combined to answer the first and third aims which were to evaluate factors influencing COVID-19 knowledge and to assess changes in access to health-care centres during the COVID-19 pandemic. • KAP 1 was not used for aim two because it did not include information on who slept under the bed the night prior, and therefore we could not calculate LLIN usage.
KAP 2 ("cross-sectional" cross-sectional survey with the COVID-19 questions)	2,400	**Main Trial Questions** • District • Ethnicity • Marital status • Education • SES **Additional COVID-19 Questions** • COVID-19 knowledge (symptoms, transmission, prevention) • COVID-19 source of information • Malaria control and prevention (LLIN access and usage)	• KAP 2 denotes the second cross-sectional survey (October 2021) from the main trial that included additional questions about COVID-19. KAP 2 stems from the traditional cross-sectional survey format from the main trial (18-months post-net distribution). The same additional COVID-19 questions that were included for KAP 1 were included in KAP 2. • KAP 1 and KAP 2 were combined into one dataset with an indicator distinguishing which survey was which.
SES: Socioeconomic status; **LLIN**: Long lasting insecticidal net			

Appendix 3.2. Variables Included in Models

Variables included in Tanzania Models

Socio-Ecological Level	Variable	Derivation
Force included variables		
N/A	Intervention arm	The intervention arm assigned to the cluster was included in these models to account for potential differences in the intervention arm on the outcome, specifically for malaria prevalence and co-infection (it's hypothesized that some LLINs are more effective which could influence malaria infection).
N/A	Cluster number	Each cluster in this trial is comprised of approximately 1 village (72 villages in 86 clusters)[155]. The degree of clustering of each outcome was not negligeable (greater than 0) and we had to account for this by using a random effect at the cluster level. The intracluster correlations (ICC) below show the degree of clustering and how households within the same clusters are more alike than households in different clusters: • ICC for malaria prevalence: 0.215 • ICC for schistosomiasis seroprevalence: 0.461 • ICC for co-infection: 0.117 • ICC for strong schistosomiasis seroprevalence: 0.103 • ICC for strong co-infection: 0.058
Variables that were included in the models		
Individual	Age of selected child	Numeric age between five and fourteen years old.
Individual	Sex of selected child	Sex of selected child as reported by their head of household. Information on gender was not collected as part of the main trial, but we assumed that biological sex and gender norms were aligned.
Relationship*	Head of household education	The highest level of school attended by the head of household (none, primary, secondary/technic, higher). We collapsed secondary/technic and higher because only 0.69% of the respondents had a higher education.
Individual	Socioeconomic status	The main trial did not collect information on income, but we used available data on household durable assets (electricity, radio, mobile phone, bicycle, car, boat,

		motorbike, sewing machine, television, livestock) and dwelling characteristics (roof, floor, walls, walls plastered, ceiling, eaves) to generate a single composite score that reflects a households relative socioeconomic status (SES) compared to other households in the study[296]. We derived a SES score using the Princomp procedure in SAS version 9.4 (SAS Institute, Cary, NC, USA) to perform a principal component with dichotomized household assets (yes/no) and dwelling characteristics (improved/unimproved based on the demographic and health survey classifications or yes/no), and verified that the scores were normally distributed [297–299]. We then ranked the scores into quintiles (approximately 225 households per group), with the first and fifth group representing the poorest and least poor household, respectively[298].
Relationship*	Knowledge of malaria	A binary variable for relevant knowledge of malaria and schistosomiasis were created by identifying at least one correct mode of transmission and at least one correct symptom for each disease (one score per disease) [195,196]. Knowledge related questions were spontaneously answered (without reading out options) by the head of household and categorized as follows: Malaria transmission • Correct = Mosquito bites • Incorrect = contaminated air, unsafe water, eating unsafe food, other insects/vectors, contact with animals, contact with someone who has malaria, wet weather, spirits Malaria symptom • Correct = fever, nausea, diarrhea, confusion, loss of energy, pain Schistosomiasis transmission • Correct = entering rivers, entering lakes, poor hygiene • Incorrect =drinking water, black magic Schistosomiasis symptoms • Correct = bloody diarrhea, blood in urine, swelling of belly, swelling of legs, stomach ache, vomiting of blood, infertility
Relationship*	Knowledge of schistosomiasis	

		We decided to investigate knowledge of symptoms and modes of transmission as one binary variable to preserve the degree of freedom in the model and because we hypothesized that there would be multicollinearity between these two variables.
Relationship[#]	Perception of malaria	Perception of the disease was measured for the head of household by the question "in your opinion, how many people in your village have malaria (schistosomiasis)?" with the following options: none, few, some, many, everyone, don't know (was not read out as an option). The following categories were collapsed: few/some and many/everyone due to low cell sizes.
Relationship[#]	Perception of schistosomiasis	
Relationship[#]	Concern of malaria personally	Concern of the disease was measured for the head of household by the question "are you concerned about malaria (schistosomiasis) personally?" with the following options: not at all concerned, slightly concerned, somewhat concerned, moderately concerned, extremely concerned, don't know (was not read out as an option). The following categories were collapsed: somewhat to slightly concerned and moderately to extremely concerned due to low cell sizes.
Relationship[#]	Concern of schistosomiasis personally	
Individual, Community[@]	LLIN access	LLIN access is defined by the WHO as the percentage of population that could be protected by a LLIN, if each LLIN in a household could be used by two people [14].
Individual, Community[@]	Drinking source	The water, sanitation, and hygiene (WASH) indicators were dichotomized as either improved or unimproved sources as defined by the Joint Monitoring Programme for Water Supply, Sanitation and Hygiene [94]: • The proportion of the population that uses a water source that delivers safe water (main source of drinking water) o Improved: piped water, protected wells, rainwater o Unimproved: unprotected wells, water from spring, surface water • The proportion of the population that uses improved sanitation facilities (toilet facility household usually uses) o Improved: flush toilet, ventilated improved pit latrines o Unimproved: traditional pit latrines, none/bush
Individual, Community[@]	Sanitation facility	
Individual, Community[@]	Hygiene	

		• The proportion of the population that uses a handwashing facility with soap and water
Environmental	Temperature (°C)	Daytime land surface temperature and the average Normalized Difference Vegetation Index (NDVI) for January 2022 (data collection month) were obtained from the Moderate Resolution Imaging Spectroradiometer at a resolution of 1km and 250 m, respectively [187,188]. Land surface temperature was scaled by a factor 0.02 and converted from Kelvin to Celsius (-273.15), and NDVI was scaled by a factor of 0.0001 [187,188]. NDVI was then categorized as either sparse vegetation (NDVI = 0.2-0.5) or dense vegetation (NDVI = 0.6-0.9).
Environmental	NDVI	
Environmental	Precipitation (mm)	The precipitation average for January (1970-200) was obtained from WorldClim at a resolution of 1km [189]. This was the finest geographic and time scale that was publicly available for the study site.
Environmental	Population density	Population density in 2020 was obtained from WorldPop at a resolution of 1km [190] and categorized into three equal groups <100, 100-200, >200 people per km^2. This variable was a proxy for urbanicity which is hypothesized to be associated with malaria and schistosomiasis infection.
Environmental	Distance to Lake Victoria	Distance to Lake Victoria was calculated using data from Natural Earth and the Euclidean distance from each household to the nearest point of the Lake was calculated using GIS ArcMap version 10.8.1 (ESRI, Redlands, CA, USA) [191]. A households distance to Lake Victoria was categorized as near (<1km) and far (>5km) based on previously published definitions [174,197].
Variables that were not included in the models		
	Head of household occupation	This is the main income for the household with the options: fishing/farming/selling cash crops, mining, business/shop, medical/teacher/government, other. The majority (94%) of the households had fishing/farming/selling cash crops as their main income and with the lack of variability, we omitted this variable from the analysis.
	How often does (NAME) go to the lake	It was apparent after data collection that the lake was not the only source of exposure of schistosomiasis. The community mapping along with the direct field observations provided a better indicator of exposure to mosquito larval breeding and snail habitats.
	LLIN ownership	LLIN ownership is defined by the WHO as the percentage of households that owned at least one LLIN [14]. The majority (96%) of the households owned at

		least one LLIN and with the lack of variability, we omitted this variable from the analysis.
	LLIN usage	LLIN usage is defined by the WHO as the proportion of individuals who report sleeping under a LLIN the previous night [14]. We could not link a specific resident to a LLIN and therefore found that ownership and access were better indicators of coverage.
	Access diagnosis malaria infection	The denominator for these variables was the number of children with a fever in the past two weeks (17.7%). To use all outcome data, we decided that we would omit these variables.
	Access antimalarial treatment	
	Appropriate malaria care-seeking	

* These determinants are typically classified as individual-level determinants, but in this study, they are collected in terms of the head of household.

These determinants are classified as a relationship-level determinant not only because they are collected in terms of the head of household, but because these perceptions and concern can be influenced by the people (family, friends) they surround themselves with.

@ These determinants are classified as both individual- and community level determinants because they not only benefit the selected child (sleeping under a LLIN or having an improved sanitation facility), but the community when more individuals adhere to the interventions/resources (repels and kills mosquitoes, clean water).

Variables included in the Benin Models

Socio-ecological Level	Variable	Derivation
Force included variables		
NA	Cluster number	Each cluster in this trial is comprised of 1 village or a group of villages for an average of 200 households (1200 residents) per cluster. The degree of clustering of each outcome was not negligeable (greater than 0) and we had to account for this by using a random effect at the cluster level. The ICCs below show the degree of clustering and how households within the same clusters

		are more alike than households in different clusters: • ICC for knowledge of COVID-19 = 0.255 • ICC for LLIN Usage = 0.157 • ICC for avoiding health centres because of the pandemic ICC = 0.455
NA	Survey number	The study number (KAP 1 or KAP 2) was included in the model to account for potential differences that could be attributed to the potential that children that were part of the cohort were different than the people selected in the cross-sectional survey. Although both surveys asked the same questions in the same manner, children that were part of the cohort had continued contact with study staff which could alter their responses, specifically for the outcomes (COVID-19 knowledge, LLIN usage, and avoiding health centres because of the pandemic). We therefore included this the study number to better understand the association between each outcome and the hypothesized explanatory variables, that are not due to the survey their data was collected in.
	Intervention arm	The intervention arm assigned to the cluster was for in these models to account for potential differences in the intervention arm on the outcome, specifically for LLIN usage (hypothesized that some participant may prefer to use some LLIN compared to others) and avoiding health centres because of the pandemic (hypothesized that some LLIN may be more effective and therefore people may not require to go to the health centres during the pandemic thus changing their behaviour and beliefs surrounding this outcome). This was done to better understand the association between each outcome and the hypothesized explanatory variables.
Variables that were included in the models		
Individual, Community[@]	COVID-19 knowledge	A binary variable for relevant knowledge of COVID-19 was created using 25 knowledge questions across three domains: correct symptoms, modes of transmission, and preventative measures of COVID-19. Each question and question were asked to the head of and a correct responses as awarded one point and an incorrect or "I don't know" response was not awarded any point [230–233]. Using Bloom's cutoff, good COVID-19 knowledge was defined as a score between 20 and 25,

		and poor knowledge as a score of 19 or lower [230,234]. Knowledge related questions were not spontaneously answered (read out each option) by the head of household and categorized as follows: COVID-19 symptoms • Correct: fever, cough, shortness of breath, runny nose, muscle aches, headache, fatigue, diarrhea, loss of taste COVID-19 transmission • Correct: cough, contact with infected surfaces, contact with infected person • Incorrect: contaminated food COVID-19 prevention • Correct: handwashing, avoid touching eyes/nose/mouth, using disinfectants, stay home when sick, cover mouth/nose when cough/sneeze, facemask, social distancing, avoid public gatherings, • Incorrect: using herbal supplements, traditional treatment, buying medicine that could treat COVID-19, buying personal protective equipment We decided to investigate knowledge of symptoms, modes of transmission, and prevention as one binary variable to preserve the degree of freedom in the model and because we hypothesized that there would be multicollinearity between these three variables.
Individual, Community@	LLIN Usage	LLIN usage is defined by the WHO as the proportion of individuals who report sleeping under a LLIN the previous night [14]. This metric was calculated during the 2019 baseline cross-sectional survey and again during the 2021 cross-sectional survey (KAP 2).
Individual, Community@	LLIN Access	LLIN access is defined by the WHO as the percentage of population that could be protected by a LLIN, if each LLIN in a household could be used by two people [14]. This metric was calculated during the 2019 baseline

		cross-sectional survey and again during the 2021 cross-sectional survey (KAP 2).
Individual, Community[@]	Avoiding health centres because of the COVID-19 pandemic	Avoidance of health centres is defined as the proportion of the population who either avoided routine (i.e., vaccinations and check-up visits) or urgent (i.e., febrile child) visits because of the pandemic. A binary variable was created where if a head of household stated that they either avoided routine or urgent visits, they were classified as avoiding health centres because of the COVID-19 pandemic.
Relationship	Head of household ethnicity	This is the ethnicity of the head of household. Based on the number of respondents in each ethnic group and based on in-country partner input, the following ethnic groups were analyzed: Fon, Holli, Mahi, Other (Yourba, Goun, Mina, Sahoue)
Individual	Head of household marital status	This is the marital status of the head of household. Based on the number of respondents in each group and based on in-country partner input, the following martial status groups were analyzed: monogamous, polygamous, other (widow, separated, single)
Individual	Main activity done by the head of household	The main activity done by the head of household was dichotomized based on the number of farmers in the study (71.4%): farming, other (tradesman, household worker, small business, transport driver, public admin worker, fishing, factory worker, none, watchman, large business, restaurant)
Individual	Highest level of education completed by the head of household	The highest level of education completed by the head of household was dichotomized based on the number of respondents with no education (69.9%): no education, some education (primary incomplete, secondary incomplete, primary complete, higher secondary incomplete, secondary complete, college, higher secondary complete, primary incomplete)
Individual	Socioeconomic status	Like in the Tanzania trial, this questionnaire did not collect information on income, but we used available data on household durable assets (livestock, phone, solar panel, bed ceiling fan, solar lamp, mattress, sofa, computer, cd player, stove, canoe, sheep, cattle, donkey, freezer, radio, tv, fan, generator, running water, electricity, cart, car, motorbike, bikes) and dwelling characteristics (observed materials for roof, floor, exterior walls) to generate a single composite score that

		reflects a households relative socioeconomic status (SES) compared to other households in the study[45]. The variables included in the principle component analysis score is different from those in the Tanzania analysis because these variables were selected and tailored to the Benin setting through the main trial. We derived a SES score using the princomp procedure in SAS version 9.4 (SAS Institute, Cary, NC, USA) to perform a principal component with dichotomized household assets (yes/no) and dwelling characteristics (improved/unimproved based on demographic and health survey classifications or yes/no), and verified that the scores were normally distributed [46–48]. We then ranked the scores into quintiles (approximately 225 households per group), with the first and fifth group representing the poorest and least poor household, respectively[47].
Environmental	Distance to nearest health facility	The Euclidian distance to the nearest health centre (GPS location collected during baseline cross-sectional survey in 2019) was calculated using GIS ArcMap version 10.7.1 (ESRI, Redlands, CA, USA).
Environmental	Population density	Data on population density, defined as the number of 100 people per kilometer^2 in 2020, was retrieved from WorldPop in a grided raster format with a resolution of 1km^2 [236]. For each household, the population density (as a proxy for urbanicity) was extracted.
Individual, Community@	Source of information	This is the source of information for COVID-19 where multiple responses were allowed: radio, tv, paper, social media, internet, health centre, village leaders, religious leaders, word of mouth
	Time point	This indicator was used for the models that investigated the impact of the COVID-19 on LLIN usage and access. An indicator for timepoint (either 2019 or 2021) was used to see if there were significant differences in LLIN usage and access during the pandemic.
Variables that were excluded in the models		
	Age	This analysis was done at the household-level because all the outcomes were measured by the head of household. The information on age and sex in this trial was used for the clinical component where two people from each household were selected for malaria testing – since these people do not coincide with the people who
	Sex	

		answered the survey, we omitted age and sex from the analyses.
	Access to diagnosis for malaria	The denominator for these variables is the number of children with a fever in the past two weeks, however, only information on fever in the past month or 48 hours are collected during the cross-sectional survey. This is problematic when combining the information for the cohort and the cross-sectional survey if we are not working with the same definitions for each variable.
	Access to antimalarial treatment	
	Appropriate malaria care-seeking behaviour	
@ These determinants are classified as both individual-and community level determinants because they not only benefit the selected child (sleeping under a LLIN or visiting a health centre when sick), but the community when more individuals adhere to the interventions/resources (repels and kills mosquitoes, avoidance of health centres).		

Appendix 3.3. Explanation and example of proc glimmix in SAS and glmer in RStudio

Explanation of proc glimmix procedure in SAS

```
proc glimmix data = dataset method=laplace;
    class variable1 (ref = "x");
    model outcome (event = "1") = variable1 variable2 / dist = binary link = logit solution ODDSRATIO;
    random intercept /subject = cluster;
run;
```

Component	Explanation
Proc glimmix	• The glimmix procedure in SAS allows you to model a GLMM. Rather than modeling a linear model, we can specify that our outcome is binary and has a logit link.
Data	• This step specifies the input dataset.
Method	• This specifies the estimation method, and the default is the residual pseudo-likelihood. In this chapter, we specified a Laplace estimation method, which is the default in RStudio.
Class	• This specifies which variable we want to treat as a categorical variable rather than a numeric variable.

Model	• This step specifies the fixed effects and the outcome.
Dist, link	• These two steps specify that the outcome is binary and follows a logit link to model the mixed-effect logistic regression.
Solution	• This requests a listing of the all the solutions for the parameter estimates.
Oddsratio	• This requests a listing of the all the solutions, specifically the calculated odds ratio, for the parameter estimates.
Random, subject	• This step specifies that we want a random intercept for each modeled cluster.

This code was used in chapter 4 (malaria and schistosomiasis in Tanzania) for the sub-objective to identify factors associated with malaria infection. The same procedure was used for the four other sub-objectives – the only changes are in the outcome and the explanatory variables included in the model which were dictated by the model selection procedure outlined earlier.

```
proc glimmix data = tz.tz_scluster_SCHISTO method=laplace;

     class clusterno arm (ref = "C")
             selectedchild_sex (ref ="female") PCAL (ref ="Least P") llinaccess (ref ="1")
             water (ref ="1") toilet3 (ref ="0") hygiene (ref ="1")
             concern_malaria2 (ref ="3") people_infected2 (ref ="3")
             schistok(ref ="0") concern_schisto2 (ref ="3") tot_schistoinfected2 (ref ="3")
             dlake (ref ="1");

     model rdtresults (event = "1") = arm age_yr2 selectedchild_sex PCAL llinaccess
                                      water toilet3 hygiene concern_malaria2 people_infected2
                                      schistok concern_schisto2  tot_schistoinfected2 dlake/

                                      dist = binary link = logit solution ODDSRATIO;

     random intercept /subject = clusterno;

run;
```

Fig. 1 Example of procedure used to model the multivariable mixed-effect logistic regression for one of the sub-objectives for chapter four (malaria and schistosomiasis in Tanzania) using SAS. Abbreviations: rdtresults: malaria infection status; age_yr2: age of selected child; selectedchild_sex: sex of selected child; PCAL: socioeconomic status; llinaccess: LLIN access, water: drinking water source; toilet3: sanitation facility; concern_malaria2: concern for malaria personally; people_infected2: perception of malaria; schistok: knowledge of schistosomiasis; concern_schisto2: concern for schistosomiasis personally tot_schistoinfected2: perception of schistosomiasis; dlake: distance to lake Victoria; clusterno: cluster number.

Explanation of glmer function in RStudio

```
output <-glmer (outcome ~ variable1 + variable2 + (1|Cluster),
                        data = dataset,
                        family = binomial (link="logit"),
                        control = glmerControl(optimizer = "bobyqa"))
```

Component	**Explanation**[300]
glmer	• The glmer function in RStudio allows you to model a GLMM. Rather than modeling a linear model, we can specify that our outcome is dichotomous using the family component (binomial, and outcome follows a logit link).
Outcome, varibale1	• The first thing that you specify in the function is the formula. This is two-sided formula describing the fixed-effect terms and the random effects part of the model. We could add as many variables as we want in this formula by separating the variables with a plus sign.
1|cluster	• The random effects term is specified by the "|". In our models, we are specifying that we want a random intercept for each cluster.
Data	• The data step specifies which data frame contains the variables in the formula.
Family	• Gaussian is the default. We specified the binomial family with an outcome following a logit link to model the mixed-effect logistic regression.
Control	• This specifies how we want control the fit the GLMM. Bobyqa is often used for optimizing nonlinear functions, like the ones used in this chapter.

This code was used in chapter 5 (COVID-19 pandemic impacts on malaria prevention in Benin) for the sub-objective to identify factors associated with good COVID-19 knowledge. The same procedure was used for the two other sub-objectives – the only changes are in the outcome and the explanatory variables included in the model which were dictated by the model selection procedure outlined earlier.

```
knowledge_full<-glmer (KapoverallF~ KapF+ district + ArmF + ethF + wedF + profF +
                       eduF+ PcaLF + near_distkm+ popproj2 + cov_cradioF + cov_ctvF+
                       cov_chcentF + cov_cleadeF+ cov_creligF + cov_cpersoF +
                       (1|Cluster),

                       data = aim1,

                       family = binomial (link="logit"),


                       control = glmerControl(optimizer = "bobyqa"))
```

Fig. 2 Example of procedure used to model the multivariable mixed-effect logistic regression for one of the sub-objectives for chapter five (COVID-19 pandemic impacts on malaria prevention in Benin) using RStudio. Abbreviations: KapoverallF: COVID-19 knowledge; KapF: survey number; ArmF: intervention arm; ethF: ethnicity; wedF: marital status; prof: occupation; eduF: education; PcalF: socioeconomic status; mear_distkm: distance to nearest health facility; popproj2: population density; cov_radioF: source of information from radios; cov_tvF: source of information from television; cov_chcentF: source of information from health centres; cov_creligF: source of information from religious leaders; cov_cpersoF: source of information from word of mouth.

Appendix 4.1. Sample Size Derivation

The sample size for collection of questionnaire data is based on the number of children that will be targeted during the January 2022 cross-sectional survey as part of the Misgungwi Net Trial (50 children per cluster in 84 clusters; n=4300) and available funding (1,300 children maximum). In order to estimate the prevalence of past and recent schistosomiasis infection (as measured by IgG and IgM antibody detection, respectively) with 80% power and 5% precision, and to detect a difference of 30% and 50% in schistosomiasis IgM and IgG antibody prevalence between two groups for hypothesized risk factors (e.g. low and high knowledge scores), we need to use the sample size calculation for comparing two proportions for cluster randomized trials (equation 1). Equation 1 is a standard sample size calculation for two proportions but inflated by a factor of: (1+(m-1) ρ) to account for the independence violation in the outcome[185,186].

$$n = \frac{\left(z_{\frac{\alpha}{2}} + z_{\beta}\right)^2 [P1(1-P1)+P2(1-P2)][1+(m-1)\rho]}{(P1-P2)^2} \quad (1)$$

Using the constraints and parameters of the study (that are displayed in equation 2), we can estimate the number of children required in each cluster: $z_{\alpha/2} = 1.96$ (α =0.05), $z_{\beta} = 0.84$ (80% power), P1 = 0.5 (hypothesized schistosomiasis prevalence in Tanzania), P2 = 0.3 (detect a 20% difference between high-risk (50%) and moderate-risk (10-50%) communities that have different recommended strategies for schistosomiasis prevention), n=650 (number of individuals in two groups with 1300 total tests), m = 15-50 (13 clusters of 50 children [m] or 42 clusters with 15 children[m])[24]:

$$650 = \frac{(1.96+0.84)^2 [0.5(0.5)+0.3(0.7)][1+(m-1)\rho]}{(0.5-0.3)^2} \quad (2)$$

The intra cluster correlation (ρ) for the schistosomiasis prevalence within the clusters in the study is not known. We do however know that the value of ρ is between 0 (independence of schistosomiasis prevalence among children in the cluster) and 1 (total dependence of schistosomiasis prevalence among children of the clusters) and that the number of children per cluster can range between 15-50 (based on the number of households being targeted). We can then solve for the number of children per cluster for this study using a range of ρ and m that make right side of equation 2 as close to 650 children per group without going over.

For m= 15, the intra cluster correlation is assumed to be 0.44 with 646 children per group; and when m = 50, the intracluster correlation is assumed to be 0.12 with 620 children per group. Accounting for increasing power with an increasing number of clusters and to conservatively select an intra cluster correlation above 0.2, we can then look at the baseline cross-sectional study from this trial to determine the number of children who would be eligible for Praziquantel tablets during MDA (children greater than or equal to 5) [185]. In figure 1, we can see that the

number of children eligible for MDA in the baseline cross-sectional study varied by cluster, for a total of 3023 children from 2122 houses – which is over the limit of 1300 rapid diagnostic tests.

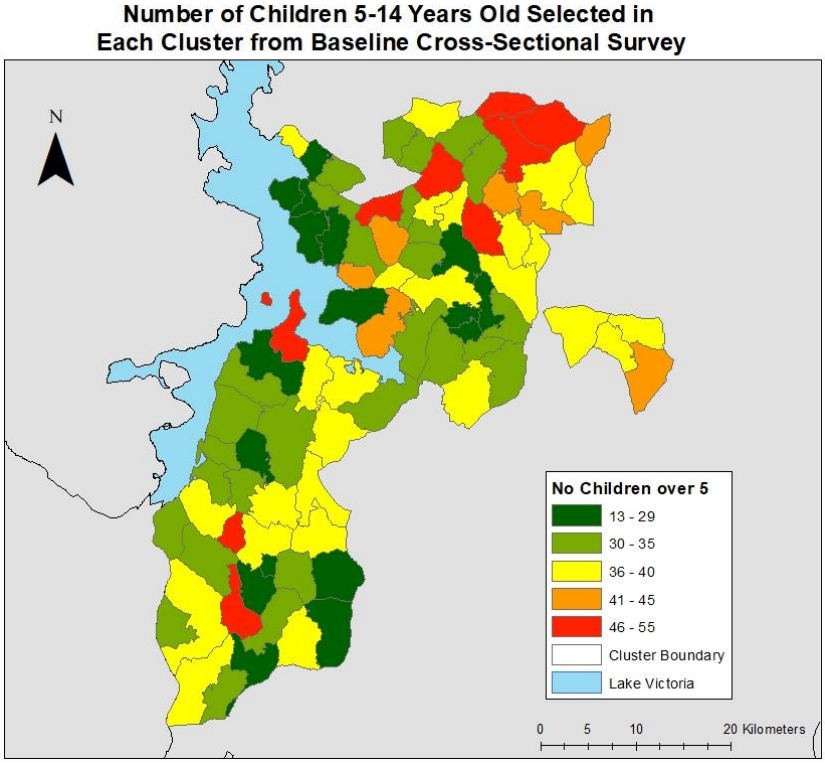


Figure 1: Number of children 5-14 years old selected in the baseline cross-sectional survey in 2018

The main goal of this chapter is to understand factors that are independently and jointly associated with malaria and schistosomiasis. One objective is to report the prevalence of malaria, schistosomiasis, and co-infection and another objective is to assess determinants that are associated with malaria and schistosomiasis. We should target clusters that have a higher percentage of malaria prevalence to ensure that we are examining clusters with children that are infected with both malaria and schistosomiasis. However, we should not restrict our sample to only clusters with a high prevalence to ensure variability in the results of the 36-months cross-sectional study in January 2022.

Figure 2A outlines the percent of children eligible for MDA (5 years old or greater) in each cluster, that were tested for malaria using a rapid diagnostic test (RDT), and who tested positive for malaria. The distribution of the prevalence of infection as measured by RDT is skewed (as seen in figure 3), with a median cluster prevalence of 53% and a minimum and maximum cluster prevalence of 0% and 89%, respectively. By restricting the sample to clusters with a prevalence of malaria infection greater than 40% (as seen in figure 2B), the sample is reduced to 2180 children from 1519 households. For ease of sampling, we can select one child per household to be tested for schistosomiasis, but that would still be an excess of 219 children. Returning to figure 2A and 2B, we can visually identify two areas of higher malaria prevalence in yellow, orange, and red (prevalence of malaria between 41% and 89%) - one in the southern region and one in the northern region along Lake Victoria. By geographically selecting clusters in these areas (as seen in figure 2C), we can reduce the sample to 48 clusters with 1612 children from 1140 households. We removed cluster 22 and 69 from the sample because: 1) cluster 22, which is in the northern region along lake Victoria, did not meet the eligibility requirement for the ongoing bed-net trial and has been excluded from the study and 2) cluster 69, a smaller cluster in the southern region, is comprised of a small number of households (i.e. 11 households sampled at baseline and 13 households sampled in a recent cross-sectional survey). Returning to equation 3 - with 48 clusters (cluster number 15-16,18-21,23,25-26,31-33,37,48,50-51,54-68, 70-86; illustrated in figure 4), there is a sufficient number of schistosomiasis RDTs to select 27 children (one per household) per cluster with an intra cluster correlation of 0.23 for a total of 648 children in each group.

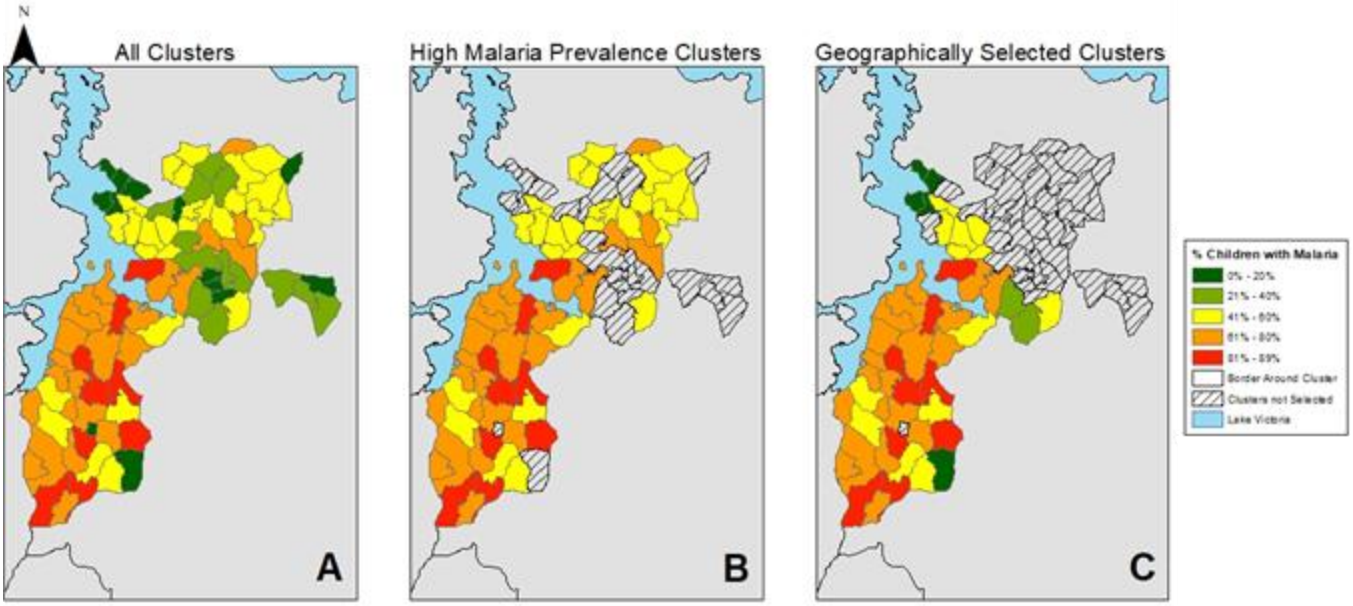


Figure 2: Percent of Children 5-14 years old with positive RDTs in selected clusters from the baseline cross-sectional survey in 2018

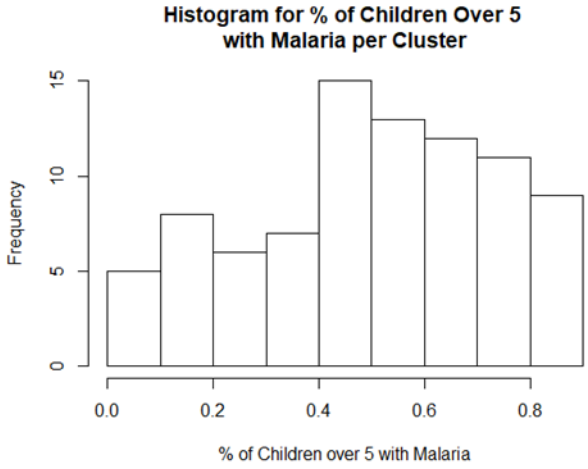


Figure 3: Distribution of prevalence of malaria infection as measured by RDT in the baseline cross-sectional survey in 2018

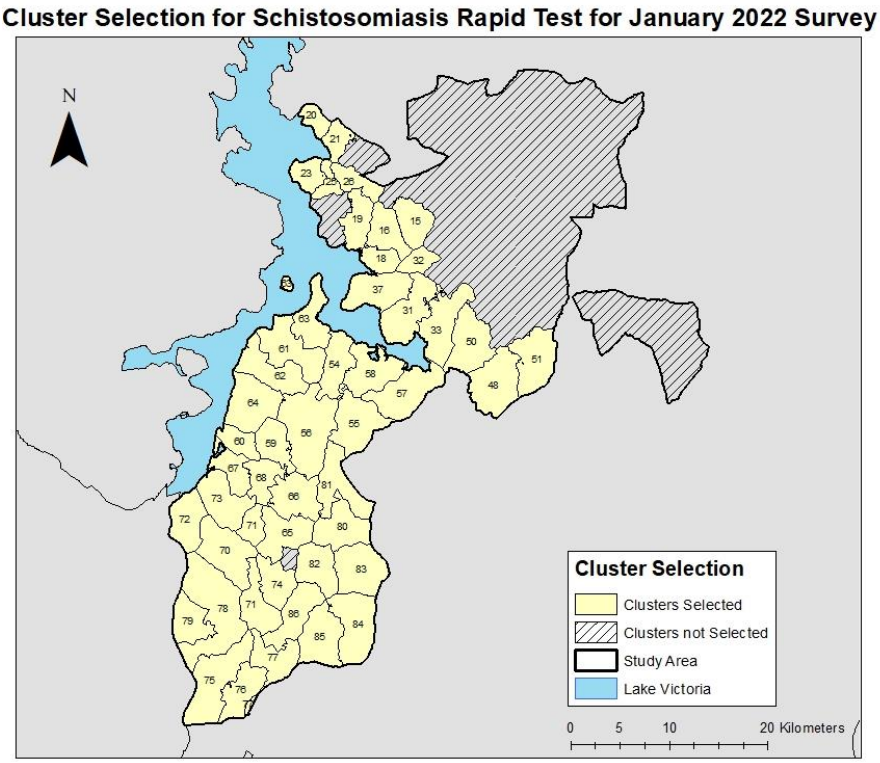


Figure 4: Clusters Selected for Schistosomiasis Rapid Diagnostic Test in 36-Month Cross-Sectional Survey (one child ≥5 years old per household)

Appendix 4.2. Variable Definition

Variable	Variable Definition
Social determinant (individual-level)	
Age	Age of selected child
Sex	Sex of selected child
Social determinant (household-level)	
Malaria and schistosomiasis	
Socioeconomic status	Wealth score as a proxy for household socioeconomic status using a Principal Component Analysis of household assets and dwelling characteristics. [193,194]
Education	Head of household education
Occupation	Head of household occupation

Malaria only	
Knowledge of disease	Head of household identifies at least once correct malaria symptoms (fever, nausea, diarrhea, loss of energy, pain) and identifies mosquito bites as mechanism of transmission of malaria. [195,196]
Perception of number of people with disease in village	Perception of the disease was measured for the head of household by the question "in your opinion, how many people in your village have malaria?" with the following options: none, few, some, many, everyone, don't know (was not read out as an option).
Concern of disease personally	Concern of the disease was measured for the head of household by the question "are you concerned about malaria personally?" with the following options: not at all concerned, slightly concerned, somewhat concerned, moderately concerned, extremely concerned, don't know (was not read out as an option).
LLIN ownership	Proportion of households with at least one LLIN [61,89]
LLIN access	Proportion of population that could sleep under a LLIN if each LLIN in the household were used by 2 people [89]
Schistosomiasis only	
Knowledge of disease	Head of household identifies at least once correct schistosomiasis symptoms (blood in diarrhea, blood in urine, swelling of belly, stomach-ache, vomiting, infertility, no symptoms) and identifies at least once correct schistosomiasis mode of transmission (entering river, entering lake, poor hygiene). [195,196]
Perception of number of people with disease in village	Perception of the disease was measured for the head of household by the question "in your opinion, how many people in your village have schistosomiasis?" with the following options: none, few, some, many, everyone, don't know (was not read out as an option).
Concern of disease personally	Concern of the disease was measured for the head of household by the question "are you concerned about schistosomiasis personally?" with the following options: not at all concerned, slightly concerned, somewhat concerned, moderately concerned, extremely concerned, don't know (was not read out as an option).
Improved drinking Water Source	The proportion of the population that uses a water source that delivers safe water (piped water and dug wells). [301]

Improved Sanitation Facility	The proportion of the population that uses improved sanitation facilities (flush toilet, ventilated improved pit latrines). [301]
Improved Hygiene	The proportion of the population that uses a handwashing facility (sink in dwelling, sink in yar, bucket/jug/kettle) with soap and water. [301]
Environmental determinant	
Temperature	Retrieved for each household. Daytime LST from January 1-February 1, 2022, at a 1km spatial resolution, scaled by a factor 0.02 and converted from Kelvin to Celsius (-273.15). Gridded raster data retrieved from Moderate Resolution Imaging Spectroradiometer (MODIS). [302]
Precipitation	Retrieved for each household. Precipitation average (1970-2000) for January and February at a 1km spatial resolution. Gridded raster data retrieved from WorldClim. [303]
NDVI	Retrieved for each household. Normalized Vegetation index for January 2022, at a 250 m spatial resolution, scaled by a factor of 0.0001. Gridded raster data retrieved from MODIS. [304]
Population density (people/km^2)	Retrieved for each household. Population density defined as the number of 100 people per kilometer^2 in 2020 at a 1km spatial resolution. Gridded raster data retrieved from WorldPop. [190]
Distance to Lake Victoria	Retrieved for each household. The Euclidean distance to Lake Victoria calculated using GIS ArcMap version 10.8.1 (ESRI, Redlands, CA, USA). [191]

Appendix 4.3. Inclusivity in Global Research

PLOS' policy on inclusivity in global research aims to improve transparency in the reporting of research performed outside of researchers' own country or community and ensures that PLOS publications reporting global research adhere to high standards for research ethics and authorship. Authors of relevant research articles may be asked to complete the questionnaire below, which outlines ethical, cultural, and scientific considerations specific to inclusivity in

global research. This questionnaire may be requested when researchers have travelled to a different country to conduct research, if research uses samples collected in another country, research with Indigenous populations or their lands, or if research is on cultural artefacts. Researchers travelling to another country solely to use laboratory equipment will not normally be required to complete the questionnaire. However, the questionnaire can be requested at the journal's discretion for any submission – if you have been requested to complete this questionnaire by the PLOS journal you submitted to, please do so.

Please complete the questionnaire below and include this as a Supporting Information file with your manuscript. Note that if your paper is accepted for publication, this checklist will be published with your article in the supporting information files. Please ensure that you reference the checklist in the main body of your manuscript. We suggest adding a subsection 'Inclusivity in global research' to your Methods section and adding the following sentence: "Additional information regarding the ethical, cultural, and scientific considerations specific to inclusivity in global research is included in the Supporting Information (SX Checklist)"

The questions have been designed to be applicable to a wide range of study types, and there are subsections for both human subjects research and non-human subjects research. If any of the questions are not relevant to your research please mark them as "N/A" as appropriate.

Ethical considerations, permits and authorship

This section is applicable to all research types.

Provide details as to who granted permissions and/or consent for the study to take place in the Methods section of your manuscript. This should include the names of **all** ethics boards,

governmental organizations, community leaders or other bodies that provided approval for the study. If individuals provided approval refer to these people by their role or title but do not list their name(s).

Reported on page number: 16-17

If there were any deviations from the study protocol after approval was obtained please provide details of these changes in the Methods section of your manuscript.

Reported on page number: Not applicable

Did this study involve local collaborators that are residents of the country where the research was conducted or members of the community studied? If you do not have any authors from said communities, please provide an explanation for this below.

We worked collaboratively with local partners in Tanzania at the Kilimanjaro Christian Medical University College (KCMUCo) and National Institute of Medical Research (NIMR).

Everyone listed as an author should meet PLOS' criteria for authorship and all individuals who meet these criteria should be included in the author byline, rather than the acknowledgements. For further information please see the journal's Authorship Policy.

Human subjects research (e.g. health research, medical research, cross-cultural psychology)

Did you obtain written informed consent from a representative of the local community or region before the research took place? How did you establish who speaks for the community? Details of

written informed consent obtained from study participants should be reported separately in the Methods section of your manuscript.

Written informed consent was obtained from an adult guardian in the household by study staff. Details on the consenting procedures are outlined on line 400.

How did members of the local community provide input on the aims of the research investigation, its methodology, and its anticipated outcome(s)?

Prior to any project activities, village and hamlet leaders were invited to sensitisation sessions conducted by district health officers. Written informed consent was sought before starting data collection from the local leader.

When engaging with the local community, how did you ensure that the informed consent documents and other materials could be understood by local stakeholders?

The consent form was written in Swahili and indicated the purpose of the study, the procedures, risks and benefits, that participation is completely voluntary, and that they may withdraw at any time. In case the participant did not understand Swahili, study staff were trained to practice oral translation of consent into local dialects.

Will the findings of the research be made available in an understandable format to stakeholders in the community where the study was conducted (e.g. via a presentation, summary report, copies of publications, etc.)? Please provide details of how this will be achieved.

The findings will be disseminated at local level (District and Regional stakeholders) via a presentation and also at national level to the NMCP and international level (WHO-VCAG, Conferences ASTMH etc.) via copies of publications and conference presentations.

Non-human subjects research using specimens/ animals collected as part of the study, or those housed in archival collections. Examples include archaeology, paleontology, botany and zoology.

Did the permission you obtained from a local authority to perform the study include an agreement on access to outputs and benefit sharing? This may include procedures to enable fair distribution of the benefits and resources arising from the research performed. Please include any details of Prior Informed Consent and Benefit Sharing Agreements obtained. These may be required by field-specific regulations, for example the Convention on Biological Diversity (CBD) and the associated Nagoya Protocol.

Not applicable

If the material used in your study was imported, please A) provide the year it was imported and B) indicate whether permits were obtained to import/export the materials used, C) provide details of any permits obtained. If this information is not available, please indicate this.

Not applicable

If you used archival specimens, please state how the material used in your study was acquired by the institute it is held in and provide details of any permits obtained for the original excavations/ sample collection. If this information is not available, please indicate this.

Not applicable

How was the potential cultural significance of the materials collected in your study to local communities considered in your research design? Were Indigenous peoples and/or local researchers and institutions involved with archaeological excavations / collection of specimens? If so, please provide a description of their involvement.

Not applicable

If your manuscript includes photographs of human remains please indicate whether authors obtained permission from descendants or affiliated cultural communities to do so.

Not applicable

Appendix 4.4. Univariable Association

Supplemental Table 1: Results of primary mixed-effects logistic regression analysis of factors associated with malaria, schistosomiasis, and co-infection (n = 1122)

	Malaria			**Schistosomiasis**			**Co-infection**		
	OR*	(95% CI)	P-value	OR*	(95% CI)	P-value	OR*	(95% CI)	P-value
Individual determinants (child)									
Age of Selected Child									
	1.16	(1.11-1.22)	<0.0001	1.23	(1.10-1.37)	0.0002	1.17	(1.11-1.23)	<0.0001
Sex of Selected Child									
Girl	REF	-	-	REF	-	-	REF	-	-
Boy	1.44	(1.12-1.86)	0.0050	1.65	(0.94-2.91)	0.0785	1.52	(1.18-1.97)	0.0012
Social determinants (household)									
Socioeconomic status									

	Lowest	1.83	(1.19-2.81)	0.0053	1.32	(0.51-3.35)	0.5615	1.78	(1.16-2.73)	0.6784
	Low	1.92	(1.12-2.92)	0.0025	0.85	(0.35-2.05)	0.7288	1.92	(1.26-2.93)	0.1413
	Average	1.39	(0.92-2.12)	0.1203	1.06	(0.42-2.65)	0.8917	1.37	(0.90-2.01)	0.0024
	High	1.13	(0.72-1.76)	0.5804	0.80	(0.32-1.97)	0.6349	1.09	(0.70-1.71)	0.0078
	Highest	REF	-	-	REF	-	-	REF	-	-
Head of household education										
	None	1.34	(0.67-2.66)	0.4041	0.73	(0.18-2.90)	0.6556	1.35	(0.68-2.70)	0.3862
	Primary	1.10	(0.56-2.12)	0.7798	0.85	(0.22-3.23)	0.8207	1.12	(0.57-2.18)	0.7316
	Secondary or higher	REF	-	-	REF	-	-	REF	-	-
Knowledge of disease (malaria)										
	Yes	0.82	(0.60-1.12)	0.2173	0.67	(0.32-1.39)	0.2902	0.82	(0.60-1.12)	0.2270
	No	REF	-	-	REF	-	-	REF	-	-
Perception of disease (malaria)										
	None	1.44	(0.52-3.96)	0.4797	0.47	(0.08-2.75)	0.4029	1.62	(0.59-4.46)	0.3470
	Few/some	1.11	(0.82-1.51)	0.4866	1.49	(0.76-2.93)	0.2435	1.17	(0.86-1.59)	0.3146
	Many/everyone	REF	-	-	REF	-	-	REF	-	-
	Don’t know	1.97	(0.93-4.18)	0.0737	1.97	(0.93-4.18)	0.0737	1.67	(1.21-2.30)	0.0018
Concern of disease personally (malaria)										
	Not at all concerned	0.92	(0.66-1.26)	0.6024	1.75	(0.80-3.83)	0.1609	0.97	(0.70-1.34)	0.8821
	Somewhat to slightly concerned	0.94	(0.66-1.34)	0.7472	1.89	(0.74-4.79)	0.1783	0.92	(0.64-1.31)	0.6565

	Moderately to extremely concerned	REF	-	-	REF	-	-	REF	-	-
	Don’t know	1.55	(0.67-3.40)	0.3183	0.34	(0.10-1.19)	0.0927	1.23	(0.54-2.78)	0.6157
LLIN Access										
	Yes	REF	-	-	REF	-	-	REF	-	-
	No	1.64	(1.22-2.21)	0.0011	1.76	(0.98-3.17)	0.0579	1.62	(1.20-2.18)	0.0014
Knowledge of disease (schistosomiasis)										
	Yes	0.71	(0.53-0.93)	0.0120	0.86	(0.48-1.53)	0.6137	0.71	(0.54-0.94)	0.0161
	No	REF	-	-	REF	-	-	REF	-	-
Perception of disease (schistosomiasis)										
	None	0.94	(0.52-1.71)	0.8634	1.52	(0.53-4.34)	0.4325	1.17	(0.64-2.13)	0.6082
	Few/some	1.32	(0.85-2.02)	0.2103	1.51	(0.68-3.31)	0.3068	1.54	(0.99-2.40)	0.0539
	Many/everyone	REF	-	-	REF	-	-	REF	-	-
	Don’t know	1.73	(1.13-2.66)	0.0116	2.49	(1.10-5.57)	0.0279	2.18	(1.41-3.39)	0.0005
Concern of disease personally (schistosomiasis)										
	Not at all concerned	0.73	(0.54-0.98)	0.0411	1.39	(0.72-2.67)	0.3239	0.80	(0.59-1.07)	0.1413
	Somewhat to slightly concerned	0.75	(0.52-1.09)	0.1336	0.99	(0.47-2.11)	0.9963	0.66	(0.46-0.96)	0.0320
	Moderately to extremely concerned	REF	-	-	REF	-	-	REF	-	-
	Don’t know	0.78	(0.43-1.41)	0.4181	1.59	(0.41-6.14)	0.4985	0.84	(0.47-1.50)	0.5627
Drinking water										
	Improved	REF	-	-	REF	-	-	REF	-	-

	Unimproved	2.08	(1.42-3.07)	0.0002	1.01	(0.41-2.43)	0.9871	2.02	(1.38-2.98)	0.0003
Sanitation facility										
	Improved	REF	-	-	REF	-	-	REF	-	-
	Pit latrine	1.81	(1.18-2.73)	0.0059	1.18	(0.52-2.67)	0.6806	1.83	(1.20-2.79)	0.0049
	Bush Toilet	2.00	(1.21-3.29)	0.0063	1.11	(0.39-3.16)	0.8359	1.92	(1.16-3.17)	0.0105
Hygiene										
	Improved	REF	-	-	REF	-	-	REF	-	-
	Unimproved	1.21	(0.92-1.60)	0.1621	1.09	(0.60-1.98)	0.7644	1.27	(0.97-1.63)	0.0796
Environmental determinants										
Temperature (°C)										
		1.07	(0.98-1.18)	0.1239	0.98	(0.79-1.21)	0.8717	1.06	(0.97-1.17)	0.1475
Precipitation (mm)										
		0.94	(0.85-1.04)	0.2443	1.04	(0.82-1.30)	0.7638	0.94	(0.86-1.04)	0.2809
NDVI										
	Sparse vegetation	1.13	(0.76-1.68)	0.5437	1.37	(0.69-3.15)	0.4560	1.13	(0.76-1.69)	0.5223
	Dense vegetation	REF	-	-	REF	-	-	REF	-	-
Population density										
	<100 per km^2	3.02	(1.76-5.17)	<0.0001	1.43	(0.44-4.66)	0.5478	2.79	(1.66-4.69)	0.0001
	100-200 per km^2	2.34	(1.64-3.33)	<0.0001	1.35	(0.57-3.15)	0.4877	2.38	(1.68-3.36)	<0.0001
	>200 per km^2	REF	-	-	REF	-	-	REF	-	-
Distance to Lake Victoria (km)										
	Near (<1km)	REF	-	-	REF	-	-	REF	-	-

	Middle	1.18	(0.66-2.09)	0.5656	1.11	(0.38-3.25)	0.8397	1.12	(0.63-1.98)	0.6962
	Far (>5km)	2.54	(1.36-4.75)	0.0034	1.39	(0.33-5.84)	0.6526	2.37	(1.29-4.35)	0.0051

* Random effects for cluster and adjusted for intervention arm

Abbreviations: OR: Odds Ratio; LLIN: Long Lasting Insecticidal Nets; NDVI: Normalized Difference Vegetation Index

Supplemental Table 2: Results of secondary mixed-effects logistic regression analysis of factors associated with malaria infection, strong-positive schistosomiasis seropositivity, and malaria and strong-positive schistosomiasis co-infection (n = 1122)

		Malaria			**Schistosomiasis**			**Co-infection**		
		OR*	(95% CI)	P-value	OR*	(95% CI)	P-value	OR*	(95% CI)	P-value
Individual determinants (child)										
Age of Selected Child										
		1.16	(1.11-1.22)	<0.0001	1.18	(1.12-1.24)	<0.0001	1.24	(1.15-1.33)	<0.0001
Sex of Selected Child										
	Girl	REF	-	-	REF	-	-	REF	-	-
	Boy	1.44	(1.12-1.86)	0.0050	2.40	(1.81-3.18)	<0.0001	2.45	(1.70-3.53)	<0.0001
Social determinants (household)										
Socioeconomic status										
	Lowest	1.83	(1.19-2.81)	0.0053	0.87	(0.56-1.36)	0.3488	1.43	(0.82-2.52)	0.7543
	Low	1.92	(1.12-2.92)	0.0025	1.17	(0.76-1.80)	0.4122	1.32	(0.75-2.32)	0.6988
	Average	1.39	(0.92-2.12)	0.1203	0.83	(0.54-1.28)	0.4548	1.12	(0.63-1.98)	0.3239
	High	1.13	(0.72-1.76)	0.5804	0.80	(0.51-1.26)	0.5520	0.90	(0.49-1.67)	0.2089

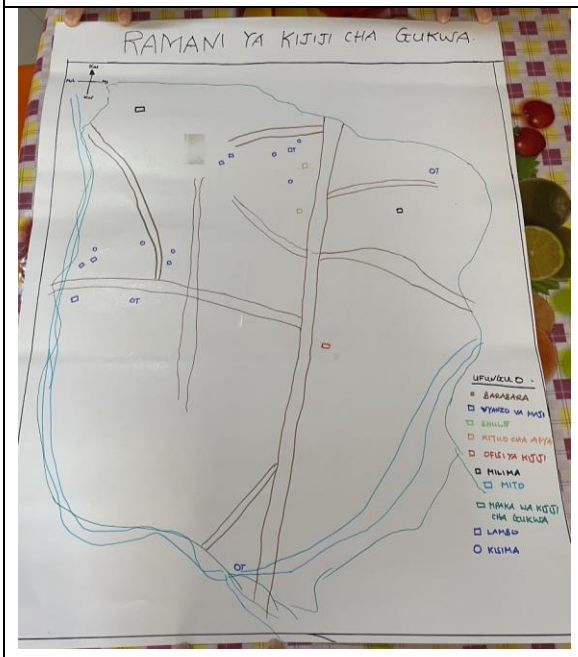
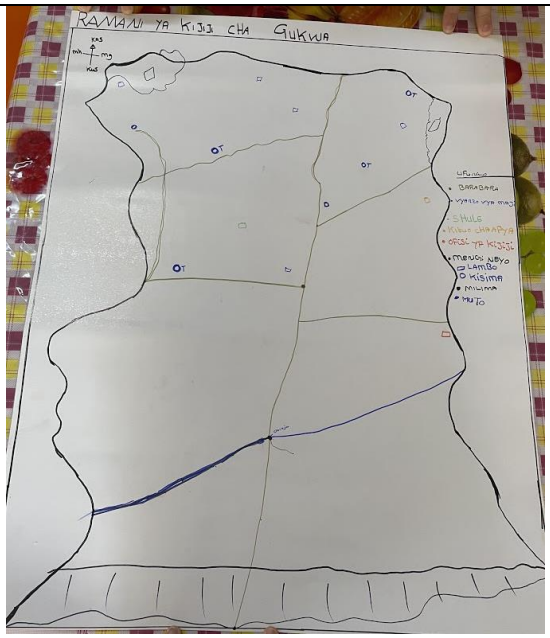
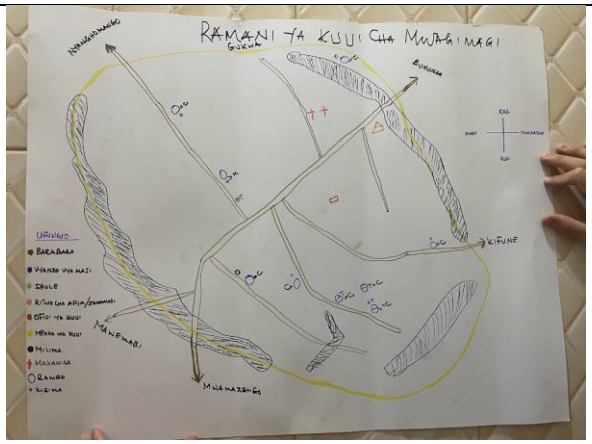
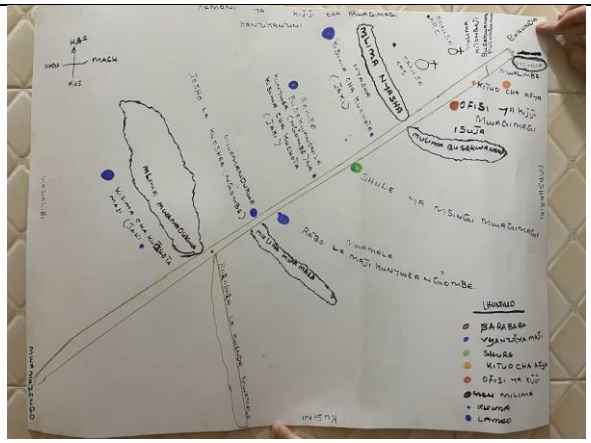
	Highest	REF	-	-	REF	-	-	REF	-	-
Head of household education										
	None	1.34	(0.67-2.66)	0.4041	1.13	(0.54-2.37)	0.7401	1.60	(0.53-4.83)	0.3957
	Primary	1.10	(0.56-2.12)	0.7798	1.15	(0.56-2.35)	0.6902	1.72	(0.60-5.03)	0.3088
	Secondary or higher	REF	-	-	REF	-	-	REF	-	-
Knowledge of disease (malaria)										
	Yes	0.82	(0.60-1.12)	0.2173	0.65	(0.47-0.90)	0.0097	0.69	(0.46-1.03)	0.0723
	No	REF	-	-	REF	-	-	REF	-	-
Perception of disease (malaria)										
	None	1.44	(0.52-3.96)	0.4797	1.40	(0.48-4.08)	0.5277	2.22	(0.67-7.32)	0.1870
	Few/some	1.11	(0.82-1.51)	0.4866	1.66	(1.19-2.30)	0.0023	1.45	(0.95-2.21)	0.0832
	Many/everyone	REF	-	-	REF	-	-	REF	-	-
	Don’t know	1.97	(0.93-4.18)	0.0737	1.53	(1.09-2.17)	0.0143	1.56	(1.01-2.41)	0.0440
Concern of disease personally (malaria)										
	Not at all concerned	0.92	(0.66-1.26)	0.6024	1.10	(0.78-1.55)	0.5771	1.01	(0.66-1.56)	0.9398
	Somewhat to slightly concerned	0.94	(0.66-1.34)	0.7472	1.06	(0.73-1.55)	0.7372	0.91	(0.56-1.49)	0.7216
	Moderately to extremely concerned	REF	-	-	REF	-	-	REF	-	-
	Don’t know	1.55	(0.67-3.40)	0.3183	2.06	(0.92-4.58)	0.0758	2.19	(0.87-5.46)	0.0929
LLIN Access										
	Yes	REF	-	-	REF	-	-	REF	-	-

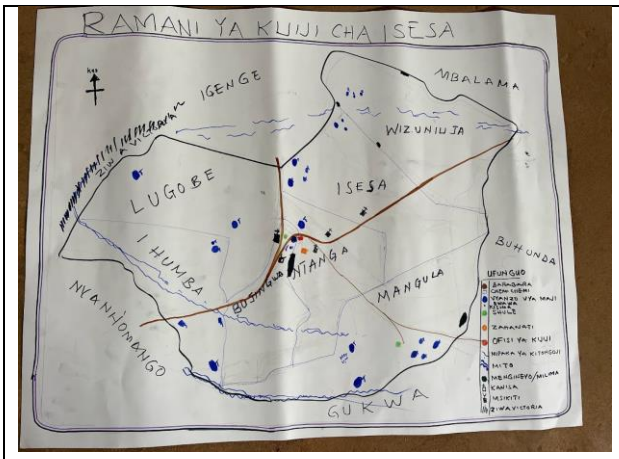
	No	1.64	(1.22-2.21)	0.0011	1.30	(0.95-1.78)	0.0963	1.79	(1.16-2.76)	0.0079
Knowledge of disease (schistosomiasis)										
	Yes	0.71	(0.53-0.93)	0.0120	1.18	(0.89-1.57)	0.2394	0.85	(0.59-1.23)	0.3975
	No	REF	-	-	REF	-	-	REF	-	-
Perception of disease (schistosomiasis)										
	None	0.94	(0.52-1.71)	0.8634	1.14	(0.60-2.13)	0.6790	1.43	(0.53-3.81)	0.4701
	Few/some	1.32	(0.85-2.02)	0.2103	1.48	(0.91-2.31)	0.1093	2.77	(1.33-5.78)	0.0064
	Many/everyone	REF	-	-	REF	-	-	REF	-	-
	Don't know	1.73	(1.13-2.66)	0.0116	1.38	(0.87-2.19)	0.1665	2.62	(1.25-5.54)	0.0102
Concern of disease personally (schistosomiasis)										
	Not at all concerned	0.73	(0.54-0.98)	0.0411	0.83	(0.61-1.14)	0.2675	0.71	(0.48-1.06)	0.0974
	Somewhat to slightly concerned	0.75	(0.52-1.09)	0.1336	0.94	(0.64-1.38)	0.7752	0.57	(0.33-0.97)	0.0385
	Moderately to extremely concerned	REF	-	-	REF	-	-	REF	-	-
	Don't know	0.78	(0.43-1.41)	0.4181	0.83	(0.44-1.57)	0.5705	0.70	(0.31-1.56)	0.3863
Drinking water										
	Improved	REF	-	-	REF	-	-	REF	-	-
	Unimproved	2.08	(1.42-3.07)	0.0002	1.17	(0.79-1.74)	0.4241	1.90	(1.12-3.23)	0.0175
Sanitation facility										
	Improved	REF	-	-	REF	-	-	REF	-	-
	Pit latrine	1.81	(1.18-2.73)	0.0059	1.30	(0.86-1.98)	0.2015	1.87	(1.01-3.48)	0.0465

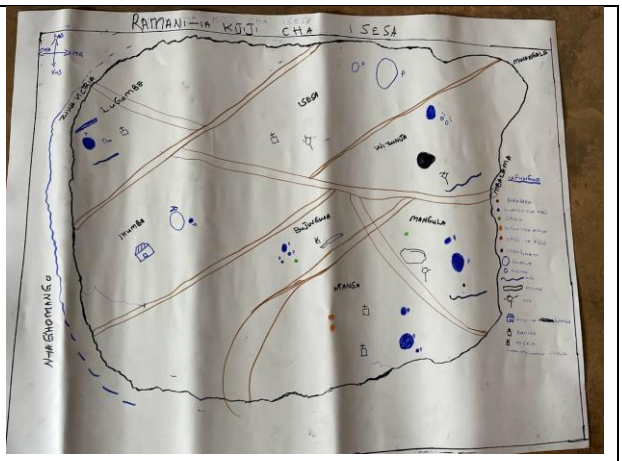
	Bush Toilet	2.00	(1.21-3.29)	0.0063	1.38	(0.83-2.28)	0.2063	2.42	(1.21-4.86)	0.0125
Hygiene										
	Improved	REF	-	-	REF	-	-	REF	-	-
	Unimproved	1.21	(0.92-1.60)	0.1621	0.99	(0.73-1.33)	0.9464	1.11	(0.77-1.62)	0.5582
Environmental determinants										
Temperature (°C)										
		1.07	(0.98-1.18)	0.1239	0.92	(0.84-1.01)	0.1137	1.05	(0.94-1.17)	0.3491
Precipitation (mm)										
		0.94	(0.85-1.04)	0.2443	0.96	(0.87-1.06)	0.4835	0.91	(0.81-1.02)	0.1106
NDVI										
	Sparse vegetation	1.13	(0.76-1.68)	0.5437	1.13	(0.74-1.74)	0.5570	1.78	(0.96-3.30)	0.0652
	Dense vegetation	REF	-	-	REF	-	-	REF	-	-
Population density										
	<100 per km^2	3.02	(1.76-5.17)	<0.0001	1.02	(0.55-1.88)	0.9379	1.87	(0.93-3.77)	0.0775
	100-200 per km^2	2.34	(1.64-3.33)	<0.0001	1.53	(1.05-2.24)	0.0272	2.69	(1.67-4.33)	<0.0001
	>200 per km^2	REF	-	-	REF	-	-	REF	-	-
Distance to Lake Victoria (km)										
	Near (<1km)	REF	-	-	REF	-	-	REF	-	-
	Middle	1.18	(0.66-2.09)	0.5656	0.62	(0.35-1.06)	0.0949	1.00	(0.48-2.11)	0.9837
	Far (>5km)	2.54	(1.36-4.75)	0.0034	0.46	(0.25-0.85)	0.0136	1.25	(0.59-2.63)	0.5519
* Random effects for cluster and adjusted for intervention arm										

Abbreviations: OR: Odds Ratio; LLIN: Long Lasting Insecticidal Nets; NDVI: Normalized Difference Vegetation Index

Appendix 4.5 Six Community Maps

Gukwa, male	**Gukwa, female**
	
Mwagimagi, male	**Mwagimagi, female**
	
Isesa, male	**Isesa, female**





Appendix 5.1 Supplemental Table

Table 1: Knowledge of COVID-19 and malaria of the study participants by districts (n = 3858)

		Total (n = 3858)	Cove (n = 505)	Ouinhi (n = 1242)	Zagnanado (n = 2111)
COVID-19 Transmission					
	Cough	2916 (75.58)	371 (73.47)	923 (74.32)	1622 (76.84)
	Infected Surface	1858 (48.16)	304 (60.20)	542 (43.64)	1012 (47.94)
	Contaminated meat/dairy	1468 (38.05)	208 (41.19)	441 (35.51)	819 (38.80)
	Infected individual	2216 (57.44)	318 (62.97)	718 (57.81)	1180 (55.90)
COVID-19 Symptoms					
	Fever	2818 (73.04)	362 (71.68)	867 (69.81)	1589 (75.27)
	Cough	2973 (77.06)	378 (74.85)	965 (77.70)	1630 (77.21)
	Shortness of breath	1248 (32.35)	166 (32.87)	438 (35.27)	644 (30.51)
	Sore throat	680 (31.94)	72 (26.67)	258 (37.34)	350 (29.97)
	Runny nose	1361 (35.28)	221 (43.76)	378 (30.43)	762 (36.10)
	Muscle aches	862 (22.34)	131 (25.94)	285 (22.95)	446 (21.13)
	Headache	1709 (44.30)	230 (45.54)	478 (38.49)	1001 (47.42)
	Fatigue	1647 (42.69)	212 (41.98)	508 (40.90)	927 (43.91)
	Diarrhea	954 (24.73)	133 (26.34)	258 (20.77)	563 (26.67)
	Loss of taste	707 (18.33)	151 (29.90)	168 (13.53)	388 (18.38)

COVID-19 Protection					
	Handwashing	3549 (91.99)	453 (89.70)	1165 (93.80)	1931 (91.47)
	Touching eyes/nose/mouth	1256 (32.56)	166 (32.87)	350 (28.18)	740 (35.05)
	Using disinfectants	994 (25.76)	136 (26.93)	257 (20.69)	601 (28.47)
	Stay home when sick	922 (23.90)	171 (33.86)	200 (16.10)	551(26.10)
	Using herbal supplements	2843 (73.69)	359 (71.09)	930 (74.88)	1554 (73.61)
	Cover mouth/nose when cough/sneeze	2379 (61.66)	324 (64.16)	698 (56.20)	1357 (64.28)
	Facemask	3192 (82.74)	384 (76.04)	948 (76.33)	1860 (88.11)
	Social distancing	2292 (59.41)	275 (54.46)	758 (61.03)	1259 (59.64)
	Traditional treatments	2674 (69.31)	336 (66.53)	870 (70.05)	1468 (69.54)
	Public gathering	2360 (61.17)	280 (55.45)	777 (62.56)	1303 (61.72)
	Going to health clinic for visit that could be postponed	624 (16.17)	74 (14.65)	210 (16.91)	340 (16.11)
	Going to health clinic when you have a fever	569 (14.75)	60 (11.88)	204 (16.43)	305 (14.45)
	Visiting family/friends	683 (17.70)	52 (10.30)	217 (17.47)	414 (19.61)
	Buying drugs that treat COVID-19	2636 (68.33)	365 (72.28)	841 (67.71)	1430 (67.74)
	Buying PEE	2605 (67.52)	319 (63.17)	982 (79.07)	1304 (61.77)
Malaria Transmission*					
	Mosquitoes	2072 (97.32)	263 (97.41)	678 (98.12)	1131 (96.83)
	Water	1827 (85.81)	241 (89.26)	602 (87.12)	984 (84.25)
	Food	1829 (85.91)	244 (90.37)	601 (86.98)	984 (84.25)
	Air	1883 (88.45)	244 (90.37)	613 (88.71)	1026 (87.84)
	Animal	1709 (80.27)	244 (90.37)	548 (79.31)	917 (78.51)
	Season	1295 (60.83)	166 (61.48)	402 (58.18)	727 (62.24)
	Sunshine	1231 (57.82)	172 (63.70)	362 (52.39)	697 (59.67)
	Witchcraft	1500 (70.46)	186 (68.89)	470 (68.02)	844 (72.26)

	Person-to-person	1568 (73.65)	198 (73.33)	492 (71.20)	878 (75.17)
Malaria Symptoms*					
	Fever	2105 (98.87)	267 (98.89)	688 (99.57)	1150 (98.46)
	Fatigue	1927 (90.51)	247 (91.48)	623 (90.16)	1057 (90.50)
	Headache	1917 (90.04)	235 (87.04)	636 (92.04)	1046 (89.55)
	Diarrhea	701 (32.93)	51 (18.89)	261 (37.77)	389 (33.30)
	Nausea	1273 (59.79)	117 (43.33)	445 (64.40)	711 (60.87)
	Stomach-ache	652 (30.62)	70 (25.93)	267 (38.64)	315 (26.97)
	Convulsion	665 (31.24)	63 (23.33)	283 (40.96)	319 (27.31)

Data are displayed as n (%)

*Denominator for knowledge of transmission was n=2129

Appendix 6.1 PRISMA-ScR Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	3-6

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	6
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	6
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	6-8
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	6 and 8
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Appendix 6.2
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	6-8
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	8

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	8
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	N/A
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	6 and 8
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	9
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	9-10
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	N/A
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	9-10
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	10-12
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	13

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Limitations	20	Discuss the limitations of the scoping review process.	15
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	15-16
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	Included in submission

Appendix 6.2 Search Strategy

Table 1. Search results – Custom Google search engines

#	Search	# Results	# Results screened	# Results retained
1	malaria AND schistosomiasis	~ 1,830,000	25	0
2	falciparum AND schistosoma	~ 309,000	25	0

Table 2. Search results – Custom advanced World Health Organization Institutional Repository for Information Sharing search engine

#	Search	# Results	# Results screened	# Results retained
1	malaria schistosomiasis	417	25	0
Sorted by relevance				

Table 3. Websites identified through targeted web searches

#	Search	# Results	# Results screened	# Results retained
1	malaria schistosomiasis	6	6	0

2	falciparum schistosoma	8	8	0

Table 4. Websites identified through targeted web searches

#	Website name/organization	Link
1	TDR	https://tdr.who.int/

Appendix 6.3 Extraction Sheet

1. Article characteristics

1.1. Title
1.2. First author
1.3. Year of publication
1.4. Publication language

2. Study Description

2.1. Study location (north America, south America, Europe, Africa, Australia)
  2.1.1. Please specify country
2.2. Study type (RCT, quasi RCT, cohort, repeated XS, longitudinal, other)
  2.2.1. If other – please specify
2.3. Intervention type (education, integrated drug, single drug)
  2.3.1. Specify intervention type
2.4. Start and end date of intervention
2.5. Target population
2.6. Inclusion criteria
2.7. Exclusion criteria
2.8. Method of recruitment
2.9. Total number of participants

3. TIDierR (for detailed description of program)

1	BRIEF NAME	Provide the name or a phrase that describes the intervention.
2	WHY	Describe any rationale, theory, or goal of the elements essential to the intervention.
3	WHAT	**Materials:** Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).
4		**Procedures:** Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities

5	WHO PROVIDED	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.
6	HOW	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.
7	WHERE	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.
8	WHEN and HOW MUCH	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.
9	TAILORING	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.
10	MODIFICATIONS	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).
11	HOW WELL	**Planned**: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.
12		**Actual**: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.

Appendix 6.4 Complete data file

Complete Data File.xlsx