



School of Public Health
College of Medicine and Health Science
Hawassa University

Schistosoma mansoni infection among preschool children in
southern Ethiopia: burden, treatment, community behavior, and
association with undernutrition and anaemia

A PhD Dissertation

Tafese Tadele

Hawassa University, Hawassa, Ethiopia, June 2024

Schistosoma mansoni infection among preschool children in southern Ethiopia: burden, treatment, community behavior, and association with undernutrition and anaemia

Tafese Tadele

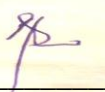
A dissertation submitted to the School of Public Health, College of Medicine and Health Science, Hawassa University, Hawassa, Ethiopia in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Public Health (PhD)

June 2024

Declaration

I hereby declare that this PhD dissertation is my original work and has not been presented for a degree in any other University, and all the resources and materials used for this dissertation have been duly acknowledged.

Name: **Tafese Tadele**

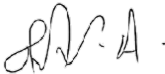

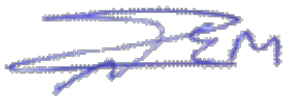
Signature:  _____

Date: June 23, 2024

Place: Hawassa, Ethiopia

SCHOOL OF GRADUATE STUDIES
HAWASSA UNIVERSITY
SUPERVISORS' APPROVAL SHEET-1
(Submission sheet-1)

This is to certify that the dissertation entitled "*Schistosoma mansoni* infection among preschool children in southern Ethiopia: burden, treatment, community behavior, and association with undernutrition and anaemia" submitted in partial fulfillment of the requirements for the PhD degree in Public Health, the Graduate program of the School of Public Health has been carried out by Tafese Tadele ID No PhDPUHeR/004/12 under my/our supervision. Therefore, I/we recommend that the student has fulfilled the requirements and hence hereby can submit the dissertation to the School.

<u>Associate Professor Ayalew Astatkie</u>		<u>26 June 2024</u>
Name of primary supervisor	Signature	Date
<u>Professor Eleni Aklillu</u>		<u>26 June 2024</u>
Name of co-supervisor	Signature	Date
<u>Professor Eyasu Makonnen</u>		<u>26 June 2024</u>
Name of co-supervisor	Signature	Date

SCHOOL OF GRADUATE STUDIES
HAWASSA UNIVERSITY
EXAMINERS' APPROVAL SHEET-2

(Submission sheet-2)

As members of the Board of Examiners of the final PhD open defense, we certify that we have read and evaluated the thesis prepared by Tafese Tadele under the title "*Schistosoma mansoni* infection among preschool children in southern Ethiopia: burden, treatment, community behavior, and association with undernutrition and anaemia" and recommended that it be accepted as fulfilling the requirement for the degree of **Doctor of Philosophy**.

Associate Professor Taye Gari

Name of the Chairperson

Signature

Date

Associate Professor Ayalew Astatkie

Signature

26 June 2024

Name of Primary Supervisor

Signature

Date

Professor Eleni Aklillu

26 June 2024

Name of Co-supervisor

Signature

Date

Professor Eyasu Makonnen

26 June 2024

Name of Co-supervisor

Signature

Date

Professor Kassahun Alemu

Name of Primary Examiner

Signature

Date

Professor Takele Tadesse

Name of Secondary Supervisor

Signature

Date

Final approval and acceptance of the dissertation is contingent upon the submission of the final copy of the thesis to the candidate's department. Thesis approved by

Signature _____ Date _____

Public Health Academic and Service Directorate

Certification of the final Dissertation

I hereby certify that all the corrections and recommendations suggested by the Board of Examiners are incorporated into the final Thesis entitled "*Schistosoma mansoni* infection among preschool children in southern Ethiopia: burden, treatment, community behavior, and association with undernutrition and anaemia" by Tafese Tadele.

Name of the Designate

Signature

Date

Stamp of SGS

Date

Remark

- Use this form to submit the thesis with major corrections suggested by the examining board
- 6 copies

Dedication

I dedicate this work to my dear wife Medihanet Gebrekidan; daughters (Lidiya and Firehiwot), and sons (Nahom and Dagim).

FUNDING SOURCE AND COLLABORATION

This PhD dissertation was conducted through the collaboration of the School of Public Health, College of Medicine and Health Sciences, Hawassa University, Hawassa, Ethiopia, and the Department of Global Public Health, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden. It was funded by the European & Developing Countries Clinical Trials Partnership (EDCTP) 2 program through the Pharmacovigilance Infrastructure and Post-marketing Surveillance System Capacity Building for Regional Medicine Regulatory Harmonization in East Africa (PROFORMA) project (Grant number CSA2016S-1618) and PrazOpt project (Grant number TMA2018CDF-2345).

The research was carried out in Ethiopia and the laboratory analysis work component of this PhD was conducted at Karolinska Institutet, Karolinska University Hospital, and Hawassa University. The primary supervisor was Associate Professor Ayalew Astatkie at the School of Public Health, Hawassa University Ethiopia, together with Professor Eleni Akililu at the Department of Global Public Health, Karolinska Institutet, and Professor Eyasu Makonnen at the College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia as co-supervisors.

Ethical clearance was obtained from the Institutional Review Board of Hawassa University (IRB) (Ref. No: IRB/200/13) and the National Research Ethics Review Committee (Ref no MoSHE//RD/401/0974/20).

The material transfer agreement was prepared and signed between the Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT Africa), College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia and the Department of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska Institutet, Stockholm, Sweden.

ACKNOWLEDGMENTS

Above all, praise and thanks be to the Almighty GOD for His daily guidance, strength, and wisdom that enabled me to complete my dissertation work successfully.

Many people have contributed to this PhD accomplishment, and I take this chance to thank you all. However, let me take this opportunity to express my sincere appreciation to the following:

My sincere thank goes to my main supervisor Associate Professor Ayalew Astatkie; I have learned so many things under your mentorship. I am impressed by your dedication, ability to mentor, and way of analyzing things. I am very grateful for your support, patience, encouragement, and understanding which provided me with the energy and motivation to complete this work. Your determined critical review, insightful feedback, and encouragement contributed to the success of my PhD journey. Thank you very much for all the irreplaceable support!

I convey my genuine gratefulness to my co-supervisor, Professor Eleni Aklillu (KI, Sweden). You created a safe space for me to learn and grow. It was a great pleasure meeting you during the familiarization workshop of the PROFORMA project. When I asked you to give me the opportunity of a PhD, at the moment you said “You are in my thoughts, and will try my best to involve you whenever the opportunity arises for higher education. Let God help us!”. Finally, with the help of God, you believed in me and changed my dream into reality. Also, your excellent guidance and analytical skills helped me in the journey of the research work, as well as repeated discussions even during the laboratory work at Karolinska University Hospital. I have greatly benefited from your dynamic support and input to each discussion and communication step; starting from the inception of the study and especially while we were working on rewriting papers

one and two. I appreciate your kind and meaningful input to encourage researchers from East African countries especially Ethiopians to become highly qualified. Thank you very much!

My deepest gratitude goes to my co-supervisor, professor Eyasu Makonnen (Addis Ababa, Ethiopia) who believed in me and supported me since day one. Your scientific guidance and advice made this PhD possible. Your good collaboration and advice facilitated my development to be an independent researcher. Indeed, no more words can explain how thankful I am to you. Be blessed!

To Associate Professor Solomon Mequanenete (Addis Ababa, Ethiopia), thank you so much for your continued devotion to support me starting from the proposal development phase. I am grateful for your outstanding devotion and guidance during my PhD journey and for that, I am forever grateful.

My sincere thanks go to Dr. Birkneh Tilahun; he was also approachable throughout my dissertation research journey and always encouraged me to keep going. Thank you, a lot!

I am grateful to data collectors, supervisors, and study participants for their vital contribution to the successful implementation of the dissertation study.

I am grateful to CDT Africa, Addis Ababa University staff namely Mr. Tesfaye (Head of Finance division), Getahun (Procurement expert), Yodit (Administration Assistant), Michele (Clinical Trial coordinator) for facilitation of budget, duplication, and data entry activities during implementation of the research.

Dr. Nigus Fikre, thank you for your humble guidance and for creating an excellent learning environment during my laboratory work at KI.

My mother (Dikashe) and father (Tadele) have encouraged me during my PhD journey. Thank you very much!! Your help to my wife and children during my absence cannot be forgotten.

My darling wife, Medihanet Gebrekidan, without your support, this could not have been feasible. You have been patient during my absence and worked hard for our children when I was away to collect data, attend courses, and do laboratory work. I am forever grateful for your partnership and for making this difficult journey easier. To my kids, sorry for compromising your age-specific interests in the last five years, I promise to do better. This achievement is for my beloved wife and children. Be blessed!

My sincere thanks continue to my beloved brothers (Dr. Tare and Tarekegn), for your love and encouragement. My special thanks go to Dr. Tare and his wife Medihanet for their unique support particularly when I was at Karolinska University Hospital, Sweden for laboratory work. You invested a lot in arranging visits to Finland, Denmark, and Norway while I was in Stockholm, and had a very joyful time. God bless you all!

I would like to thank my friends especially Asfaw for his humble support and outstanding positivity. Also, I would like to convey my appreciation to the Southern Regional Health Bureau staff for their tireless support.

Finally, I want to remark how grateful I am to the study participants who are at the center of this dissertation.

LIST OF SCIENTIFIC PAPERS ON WHICH THIS DISSERTATION IS BASED

1. **Tadele T**, Astatkie A, Abay SM, Tadesse BT, Makonnen E, Aklillu E. Prevalence and Determinants of *Schistosoma mansoni* Infection among Pre-School Age Children in Southern Ethiopia. *Pathogens*. 2023;12(7).10.3390/pathogens12070858. **(paper I)**
2. **Tadele T**, Astatkie A, Tadesse BT, Makonnen E, Aklillu E, Abay SM. Efficacy and safety of praziquantel treatment against *Schistosoma mansoni* infection among pre-school age children in southern Ethiopia. *Trop Med Health*. 2023 Dec 20;51(1):72. doi: 10.1186/s41182-023-00562-4. PMID: 38124206; PMCID: PMC10731898. **(paper II)**
3. **Tadele T**, Astatkie A, Abay SM, Tadesse BT, Makonnen E, Aklillu E. Knowledge, attitude, and practice of mothers/primary caregivers of pre-school age children towards schistosomiasis in southern Ethiopia. (Manuscript) **(paper III)**
4. **Tadele T**, Astatkie A, Abay SM, Tadesse BT, Makonnen E, Aklillu E. Health effects of *S. mansoni* infection on undernutrition and anaemia among pre-SAC in southern Ethiopia. (Manuscript submitted for publication) **(paper IV)**

List of Abbreviations and Acronyms

AEs	Adverse events
AOR	Adjusted odds ratio
BAZ	Body mass index (BMI) for Age Z score
BMI	Body mass index
CIs	Confidence intervals
COR	Crude odds ratio
CR	Cure rate
CRF	Clinical record form
DALYs	Disability-adjusted life years
DNA	Deoxyribonucleic Acid
EPG	Eggs per gram of stool
ERR	Egg reduction rate
HAZ	Height for Age Z score
HAZ	Height for Age Z score
IQR	Interquartile range
IRB	Institutional review board
KAP	Knowledge, attitude, and practice
MDA	Mass drug administration
MOSHE	Ministry of Science and Higher Education
NTDs	Neglected Tropical Disease
PC	Preventive chemotherapy

PCR	Polymerase chain reaction
Pre-SAC	Pre-school age children
PZQ	Praziquantel
SAC	School-age children
SD	Standard deviation
SDGs	Sustainable development goals
SSA	Sub Saharan Africa
STH	Soil-transmitted helminths
USAID	United States Agency for International Development
WASH	Access to safe water, sanitation, and hygiene
WAZ	Weight for Age Z score
WHO	World Health Organization

 TABLE OF CONTENTS

Contents	Page
FUNDING SOURCE AND COLLABORATION	viii
ACKNOWLEDGMENTS	ix
LIST OF SCIENTIFIC PAPERS ON WHICH THIS DISSERTATION IS BASED.....	xii
TABLE OF CONTENTS.....	xv
ABSTRACT.....	xix
1. Introduction.....	1
1.1 Global Burden of Neglected Tropical Diseases	1
1.2 The Global Burden of Schistosomiasis.....	2
1.3 Epidemiology of Schistosomiasis in Ethiopia	3
1.3.1 Risk factors of schistosomiasis among pre-SAC	4
1.3.2 Environmental factors	4
1.3.3 Sociodemographic factors	5
1.3.4 Socioeconomic factors.....	5
1.3.5 Life cycle and transmission of schistosomiasis	6
1.3.6 Clinical features of schistosomiasis.....	7
1.3.7 Diagnosis of schistosomiasis	8
1.4 Schistosomiasis Control and Elimination Strategies	9
1.4.1 Mass praziquantel Administration (MDA).....	10
1.4.2 Access to WASH services	12
1.4.3 Health Education.....	12
1.4.4 Snail control.....	13
1.5 Targets of Control and Elimination of Schistosomiasis.....	13
1.6 KAP of mothers/primary caregivers of pre-SAC about schistosomiasis	14
1.7 Effect of <i>S. mansoni</i> infection on undernutrition and anaemia	16
1.8 The rationale for this study	18
2. Research Aims.....	20
2.1 General objective	20
2.1.1 Specific objectives:	20

3.	Materials and Methods	21
3.1	Study area	21
3.2	Study Design	22
3.3	Sample size	23
3.4	Study participants and recruitment	24
3.5	Variables of the study	24
3.6	Data collection tools and procedures	28
3.6.1	Interview	28
3.6.2	Collection of stool samples, processing, and examination	28
3.6.3	Anthropometry	29
3.6.4	Collection of blood samples and determination of haemoglobin	29
3.7	Data quality assurance techniques	29
3.8	Statistical Analysis	31
3.9	Ethical Considerations	33
4.	Results	34
4.1	Study population characteristics	34
4.2	Characteristics of mothers/primary caregivers	34
4.3	<i>S. mansoni</i> infection prevalence and determinants in pre-SAC (paper I)	36
4.4	Efficacy and safety of praziquantel against <i>S. mansoni</i> infection and determinants of cure and adverse events among pre-SAC (Paper II)	36
4.5	Level and determinants of KAP towards schistosomiasis among mothers/primary caregivers of pre-SAC (Paper III)	37
4.6	Association between <i>S. mansoni</i> infection and undernutrition and anaemia among pre-SAC (Paper IV)	38
5.	Discussion	38
5.1	The main findings	38
5.2	Methodological discussion	43
5.2.1	Study design	43
5.2.2	Sampling	43
5.2.3	Validity	44
5.2.4	Selection bias	44
5.2.5	Information bias	45

5.2.7	Random error	46
5.2.8	External validity	47
6.	Implications for policy	47
7.	Conclusions and Recommendations	48
7.1	Conclusion	48
7.2	Recommendations	49
7.2.1	Operational recommendations	49
7.2.2	Policy Recommendation	49
7.2.3	Recommendations for Further Study	50
8.	References	50

List of Figures

Figure 1. Twenty Neglected Tropical Diseases NTDs prioritized by the WHO.	1
Figure 2. The life cycle of <i>Schistosoma</i>	7
Figure 3: Conceptual framework outlining the main risk factors and impacts of <i>S. mansoni</i> infection	18
Figure 4. Map of the study site	22
Figure 5: Study flow chart	35

ABSTRACT

Introduction: Intestinal schistosomiasis presents a significant health threat, predominantly in sub-Saharan Africa including Ethiopia. Preschool children (pre-SAC) are omitted from preventive chemotherapy (PC) intervention aimed at accelerating the control and elimination of this threat due to scarce evidence on the burden of the disease, its effect, and the efficacy and safety of praziquantel (PZQ) in this population group. Despite the growing spread of schistosomiasis among pre-SAC, evidence is insufficient on the knowledge, attitude, and practices (KAP) of caregivers in communities with limited access to safe drinking water and basic sanitation.

Objective: The overall objective of this PhD work was to determine the extent and risk factors of *S. mansoni* infection among pre-SAC, to investigate the efficacy and safety of PZQ in the treatment of the disease, to assess the KAP about schistosomiasis among caregivers of pre-SAC, and to investigate the association of the disease with undernutrition and anaemia among pre-SAC in Hawella Tulla district of Sidama region, Southern Ethiopia from August to December 2021.

Methods: A mix of study designs was used based on the different objectives of this dissertation. A community-based cross-sectional study was conducted for papers (I, III, and IV). A single-arm before-and-after quasi-experimental study was carried out among pre-SAC infected with *S. mansoni* for the second paper. A multistage sampling technique was applied and the study participants were selected by a simple random sampling technique (papers I, III, and IV). All *S. mansoni*-infected participants were recruited (paper II). A multilevel logistic regression model was used to investigate the determinants of *S. mansoni* infection (paper I). The determinants of cure rate were assessed using a standard logistic regression model, while a log-binomial regression model was used to investigate the predictors of adverse events (AEs) following praziquantel treatment (paper II). Further, multivariable logistic regression with a cluster-robust variance

estimation method was used to assess determinants of KAP (paper III); and the association between *S. mansoni* infection and undernutrition and anaemia (paper IV).

A total of 1683 randomly selected children aged 4 to 7 years were involved in a baseline survey to establish baseline data (paper I). A structured questionnaire was used to interview mothers/primary caregivers to obtain sociodemographic and behavioral information. Two duplicate thick slides were prepared from a single fresh stool sample and tested for *S. mansoni* on the same day using the Kato-Katz technique for each study participant. Efficacy and safety assessment of a single-dose 40 mg/kg PZQ was done among 240 *S. mansoni*-infected pre-SAC. Follow-up was carried out at day 28 post-treatment among 236 pre-SAC for efficacy, while safety monitoring was done among 234 pre-SAC at day 1, 2, and eight post-PZQ administration. KAP about schistosomiasis was assessed among 887 mothers/primary caregivers of pre-SAC. Anthropometric measurements and blood samples for haemoglobin were taken from 565 pre-SAC to investigate the association of *S. mansoni* infection with undernutrition and anaemia.

Results: The findings of this study indicated a moderate (14.3%) prevalence of the disease among pre-SAC in the study setting. Being 6-year-old and 7-year-old had increased odds of *S. mansoni* infection. Accompanying others to water sources sometimes or all the time, and living within less than one-kilometer radius of the infested water source also had a significant association with *S. mansoni* infection.

The present study detected that PZQ is effective and safe against the disease given at 40 mg/kg body weight in this population segment. In general, the egg reduction rate (ERR) was 93.3% while the cure rate (CR) was 85.2% at day 28 after treatment. A significant association was detected

between baseline infection intensity and CRs. A baseline *S. mansoni* egg count per gram of stool (EPG) increase in 100 had reduced the odds of cure by 26%.

The occurrence of AEs was 23.1% with stomachache being the most common. Pre-treatment moderate or heavy-intensity infection was a significant risk factor for AEs.

A low level of good knowledge (37.0%) about schistosomiasis was detected among caregivers of pre-SAC. Only 486 (54.8%) caregivers had favorable attitude about schistosomiasis, while over half (57.8%) of mothers/primary caregivers had good practice related to predisposing factors of schistosomiasis. Being from the poorest and poorer household wealth categories had reduced odds of reporting good knowledge relative to those from the richest wealth households. Besides, study participants' age, not having formal education, and household wealth were significant determinants of attitude. Marital status and lack of information about the disease were significant determinants of practice.

Overall, of the total 565 pre-SAC examined, 24.3% were stunted, 6.6% were wasted, 2.0% were underweight whereas 28.0% had anaemia. Pre-SAC having *S. mansoni* with soil-transmitted helminths (STH) co-infection had significantly higher odds of stunting relative to those infected only with *S. mansoni*. Besides, *S. mansoni* infection had an independent significant association with anaemia, but not stunting, wasting, or underweight.

Conclusion: The study detected a moderate prevalence of the disease among pre-SAC. In *S. mansoni*-infected pre-SAC, a single-dose 40 mg/kg PZQ is safe and effective, and most treatment-associated AEs detected were mild-to-moderate and transient. The current study detected a low level of knowledge, an unfavorable attitude, and poor practice about schistosomiasis. Further, *S. mansoni* with STH co-infection had higher odds of stunting, whereas *S. mansoni* infection had an

independent association with anaemia among the infected pre-SAC. Thus, these findings call for policymakers and other stakeholders to consider the inclusion of pre-SAC in schistosomiasis control and elimination programs to enhance the elimination efforts of the disease in endemic communities.

Keywords: Schistosoma mansoni, neglected tropical diseases, public health problem, mass drug administration, preschool age children, prevalence, southern Ethiopia, efficacy, safety, praziquantel, knowledge, attitude, practice, primary caregivers, stunting, wasting, underweight, anaemia

1. Introduction

1.1 Global Burden of Neglected Tropical Diseases

A total of 20 Neglected Tropical Diseases (NTDs) have been prioritized by the World Health Organization (WHO) based on their public health significance [1]. NTDs are linked with disabilities, poor growth and cognitive development, poor academic performance, increased absenteeism of children from school, and a dramatic impact on productivity in their future lives [2,3]. Besides, infected adults have not been productive for their families and communities and the situation continues to overstress limited resources in many poor nations [4,5]. Annually, NTDs cause about 534,000 deaths and Disability-Adjusted Life Years (DALYs) for more than 57 million people globally [6]. Moreover, the health and socio-economic consequences of NTDs accelerate the burden of poverty on individuals, families, communities, and countries in endemic regions.

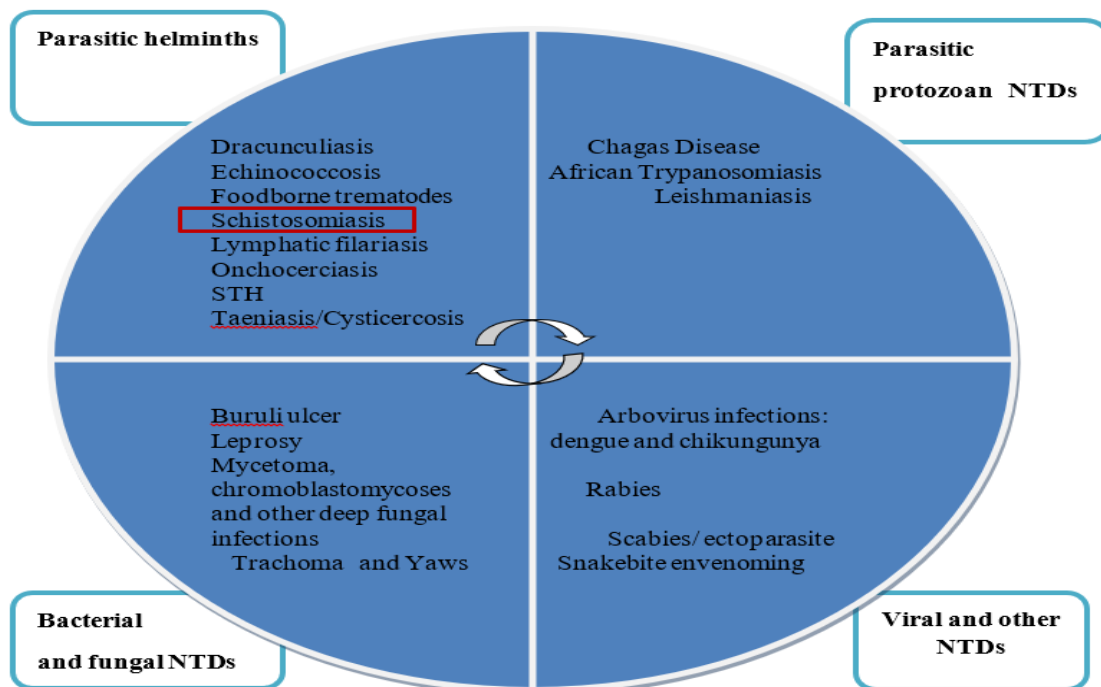


Figure 1. Twenty Neglected Tropical Diseases NTDs prioritized by the WHO. (Source https://www.researchgate.net/figure/The-20-neglected-tropical-diseases-recognised-by-the-WHO_tbl1_330977022 (accessed 18 July 2023)).

1.2 The Global Burden of Schistosomiasis

Schistosomiasis is a poverty-related NTD caused by a parasitic blood fluke (trematode) of the genus *Schistosoma* [7]. Next to malaria, it is the most prevalent with enormous health, education, and socio-economic impacts [8]. Humans are the definitive host for adult schistosome parasites, while specific freshwater snails act as intermediate hosts [9,10]. Globally, six species of schistosomes affect human beings [7]. Intestinal schistosomiasis (*S. mansoni*), urogenital schistosomiasis (*S. haematobium*), and *S. japonicum* are the three common schistosome species that cause disease in humans but, *S. mansoni* and *S. haematobium* are widespread [7]. Among the two endemic species occurring in sub-Saharan Africa (SSA), *S. mansoni* is the most predominant species [7]. Schistosomiasis is endemic in 78 countries worldwide [7,11]. Globally, more than 252 million people are infested, and a higher risk of getting the disease was estimated for about 800 million people [11,12]. The majority (90%) of the infected people live in SSA [11,13]. Schistosomiasis is responsible for about 280,000 deaths per year only in African countries [14,15]. Also, 3.3 million DALYs are attributed to schistosomiasis annually [14]. Globally around 123 million children were infected by schistosomiasis altogether. The share of pre-SAC is around 50 million [16].

It is an avoidable and curable disease but, if not treated, may cause upper gastrointestinal bleeding resulting from portal hypertension, and cancer due to chronic inflammation resulting from migrating parasite eggs in body tissues [8]. These health consequences further increase the burden and cost of the healthcare system in the affected countries. Additionally, it also causes undernutrition (stunting and wasting) [5,17], but the presence of undernutrition (e.g. stunting) is associated with a high egg count among those infected [18]. All these negative outcomes of

schistosomiasis can be significantly reduced if the disease is controlled or eliminated among all at-risk populations.

1.3 Epidemiology of Schistosomiasis in Ethiopia

In Ethiopia, both intestinal schistosomiasis and urogenital schistosomiasis are endemic, with the prevalence varying from region to region [19]. The endemicity of the disease is primarily influenced by the existence and distribution of an intermediate host of the parasite (i.e., snails) [20]. *S. mansoni* is widely distributed in Ethiopia whereas *S. haematobium* is mainly restricted to the Rift Valley areas (i.e. the Somali region) [21].

To date, despite the ongoing praziquantel mass drug administration, WASH, and health education interventions, schistosomiasis is highly predominant around Lake Hawassa, where a 24.6% prevalence of the disease has been reported among SAC after five successive yearly rounds of MDA [22]. Additionally, a more than 37% infection rate of *S. mansoni* was reported in a systematic review conducted in Ethiopia among children [23], while another study done in Ethiopia [19] revealed a 25% prevalence in pre-SAC. In Ethiopia, evidence revealed that the overall treatment coverage of PZQ against schistosomiasis was 75.5% [24], while the reduced PZQ effectiveness in moderate-to-heavy infection was reported in the same study area among SAC [25]. However, still, this at-risk population segment was excluded from praziquantel (PZQ) mass treatment campaigns in the country and, therefore, served as a reservoir of infection for many years.

This overall unrecognized infection in overlooked at-risk population groups hinders the achievement of elimination efforts per the predetermined national timeline. Thus, it is critical to

establish the level of infection and potential determinants of the disease in the country across all population segments. Assessment of disease prevalence is the mainstay to inform relevant stakeholders and policymakers about the fair inclusion of all at-risk population segments in the intervention strategies [26].

1.3.1 Risk factors of schistosomiasis among pre-SAC

Several potential risk factors that are already identified in other age groups can facilitate the spread of the infection among pre-SAC, and these risk factors are summarized in three broad categories, namely environmental, sociodemographic, and economic factors [27].

1.3.2 Environmental factors

The spread of the disease in resource-limited settings can be facilitated by various factors, such as living close to freshwater bodies (e.g., rivers, small dams, irrigation schemes, and lakes) [27]. It has been revealed that an increased risk of contamination may occur during the dry seasons' when snail vectors and larval schistosomes become concentrated at permanent and slow-moving water sources [28]. Factors related to climate change like higher temperatures and longer hotter seasons increase the frequency of water contact to regulate body temperature [27]. Besides, passive contact with infective water can facilitate the transmission of the infection among pre-SAC, while accompanying their caregivers [29]. Infection rates are often elevated close to lakes and irrigation schemes [30]. Studies revealed that the practice of taking the child to the river, child washing/swimming habit in the river, child washing tradition with freshly fetched water at home, high-frequency swimming habit of the child in the infested water source per week, and proximity of household to the water body have contributed the increased exposure to schistosomiasis in Ethiopia [31,32]. The evidence from sub-Saharan countries also shows that in the presence of suitable

snails, the continuous risk of local transmission was linked to the increased levels of cumulative water contact among pre-SAC [33].

In high infection transmission areas, young infants and pre-SAC children can be infected passively if they bathed with water that has been fetched from infested water sources at home [34].

1.3.3 Sociodemographic factors

The infection extent is significantly higher among male participants relative to females in endemic communities related to increased risky-infested water bodies contact [28]. Increasing age also might have an age-related variation in exposure to predisposing factors of the disease through playing with shallow waters [35]. Although most pre-SAC might not be able to play on their own in out-of-doors activities, most of them accompany their mothers /primary caregivers, and elder siblings while carrying out domestic activities in/around water bodies [36]. In high endemic settings, pre-SAC may be exposed to infection in year one and exposed to advanced morbidities linked with the disease [36]. As children six years and above used to learn how to swim and play in the water, they are much more at risk [15].

1.3.4 Socioeconomic factors

Mother /primary caregiver's occupation (farming, fishing, activities around irrigation canals, dams, etc.), poverty, illiteracy, and malnutrition are contributing socioeconomic exposure factors for schistosomiasis in pre-SAC [27]. Schistosomiasis transmission may be related to the active contact of infested water resources for agricultural and other economic needs [35]. Poor people without running water at home are also more likely to contact infested freshwater bodies [37]. Children from poor communities with limited access to potable water and adequate basic sanitation exhibited higher infection rates [38].

1.3.5 Life cycle and transmission of schistosomiasis

Schistosomes have two different hosts and two developmental stages in their life cycle (mature and immature stages) [39]. The human being is the definitive host and acquires the infection through contaminated freshwater bodies (lakes, dams, ponds, and rivers) with an infective larvae stage of the parasite called cercariae [39]. The cercariae penetrate human skin and develop into immature or juvenile worms called schistosomula [39]. This stage of the parasite is less affected by PZQ, the drug currently used to treat schistosomiasis [40].

The immature schistosomula are then carried in the blood to the vein surrounding the liver to develop into mature adult worms and this process takes about 4 to 6 weeks [8,39]. After that, a pair of matured female and male adults migrate against venous blood from the liver (portal vein) to the perivesical venous plexus of the bladder (*S. haematobium*) and venous plexus of mesenteries of the bowel and portal veins (*S. mansoni*) [39]. Within these venules, female parasites start to lay up to several hundred eggs for several years per day. Adult schistosome parasites can survive for 3 to 10 years, while eggs can survive for 1 to 2 weeks [39]. The eggs pierce the tissue causing intensive inflammation and organ damage, while other eggs reach the lumen of the bladder (*S. haematobium*) or colon (*S. mansoni*) excreted in either urine or stool, respectively.

The excreted eggs hatch in freshwater to release miracidia which penetrate the freshwater snails (intermediate host), multiplying by asexual reproduction to form cercariae, the infective stage of the parasite. This process takes about 4 to 6 weeks [39]. Then the infective cercariae are released into the water to search for a definitive human host to complete the cycle (Figure 2). Intermediate snail hosts of the *Bulinus* 5 species transmit *S. haematobium* while intestinal schistosomiasis is spread by *Biomphalaria* species [41].

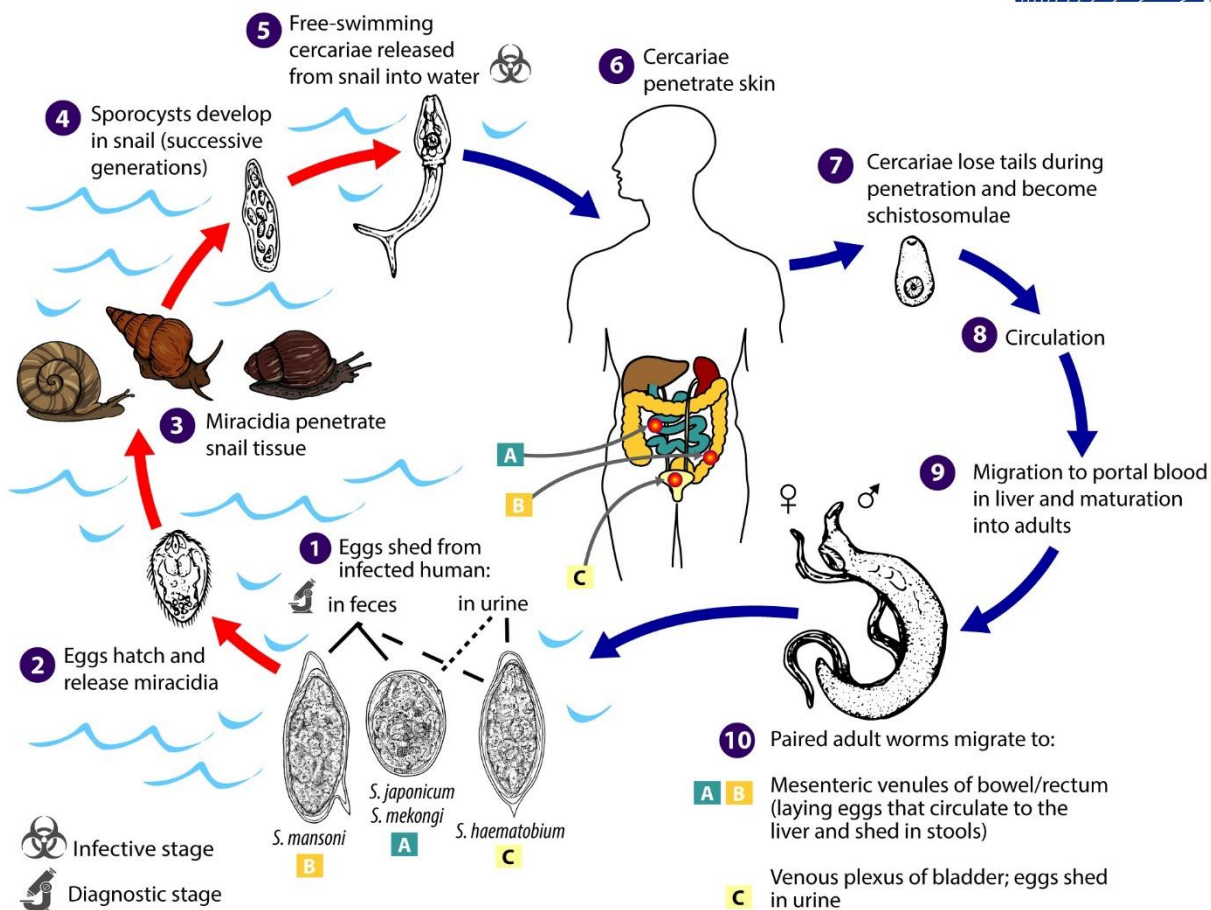


Figure 2. The life cycle of *Schistosoma*. (Source: <http://www.cdc.gov/dpdx/schistosomiasis/>) (accessed on 4 April 2023).

1.3.6 Clinical features of schistosomiasis

Most infected people in endemic countries are asymptomatic. Overall, schistosomiasis causes disabilities more than it kills. Most morbidities associated with schistosomiasis result from the body's immune reaction to the migrating parasite eggs [42]. Schistosomiasis has three main clinical phases; the first phase is characterized by dermatitis and is generated by penetrating cercariae [43]. The second phase is marked by fever (Katayama fever) and other constitutional

complaints, e.g., headache, fatigue, and cough due to migrating schistosomula and eggs [44]. The last phase results in chronic inflammation and tissue damage which is caused by parasite eggs trapped in host tissue [45]. Classic symptoms of *S. mansoni* comprise abdominal pain, diarrhoea, or bloody diarrhoea [45]. The advanced stage of the disease may lead to enlargement of the liver (hepatomegaly) [42]. Hepatomegaly is frequently accompanied by fluid in the peritoneal cavity and raised blood pressure in the portal veins (portal hypertension), which may further cause upper gastrointestinal bleeding as a complication [42]. Hepatomegaly is also accompanied by enlargement of the spleen (splenomegaly) in advanced cases [42].

1.3.7 Diagnosis of schistosomiasis

PC using PZQ is among the current robust strategies aimed at controlling and eliminating schistosomiasis. The assumption is that in such settings, all or majority of the residents are infected with the disease. However, in a situation where the diagnosis is important, e.g. individual case management in clinics, in epidemiological studies, or in investigations of drug efficacy, examination of the infection can be done by microscopic examination of schistosome eggs in stool or urine samples using the Kato-Katz method (intestinal schistosomiasis) or urine filtration method (urinary schistosomiasis). Deoxyribonucleic Acid (DNA) detection, antigen tests such as the point of care circulating cathodic or anodic antigen (POC CCA/CAA), and molecular diagnostics such as the loop-mediated isothermal amplification (LAMP) or polymerase chain reaction (PCR) can also be used [45].

The non-microscopy-based tests are more sensitive in diagnosing schistosomiasis [46,47], but the WHO still recommends microscopic examination as a gold standard method for the diagnosis of schistosomiasis, especially in resource-limited settings [48,49]. Multiple stool samples collected on two or three consecutive days could increase the sensitivity of the Kato-Katz method, especially

in clinical trials; however, in routine disease surveillance, this approach may be costly [45]. In endemic nations with limited resources, the diagnostic test's choice greatly depends on its simplicity, accuracy, less laborious, most importantly, cost [49,50]. At the disease elimination stage or in very low infection intensity, it is very important to have more sensitive diagnostic tools for disease surveillance [46,51]. Although the more sensitive tests are expensive at the elimination stage, the cost should be outweighed by the long-term benefits [48,52].

1.4 Schistosomiasis Control and Elimination Strategies

The global goal is estimated to eliminate schistosomiasis to a level where it is no longer a public concern by 2030 and Ethiopia aimed to eliminate schistosomiasis to a level where it is no longer a public concern by 2025 [53,54]. The objectives prioritized to be implemented in all target woredas are achieving 100% geographical coverage with MDA, attaining and sustaining $\geq 75\%$ therapeutic coverage, and decreasing the infection intensity by below 1% from baseline [53]. To achieve those goals, the major pillars of strategies expected to be conducted are annual school-based deworming using PZQ among SAC, expansion of treatment to pre-SAC and adults where feasible, health education and promotion, collaboration with access to safe water, basic sanitation, and the promotion of hygiene practices (WASH) sector to improve access and utilization of safe water and sanitation services, and operational research on feasibility and effectiveness of vector control [55].

However, only MDA with PZQ has been executed against schistosomiasis in most of sub-Saharan Africa overlooking other intervention pillars [53]. For that reason, let alone the elimination of the disease, the spread of the disease continues after treatment due to the possibility of re-infection that could challenge the control [55]. Bearing in mind this, in 2012, WHO member states including Ethiopia endorsed the resolution that provides equal focus to the MDA with PZQ and other integrated interventions including WASH, health education, and snail control to ensure the control

and elimination of schistosomiasis [56]. A combination of these intervention measures can interrupt the lifecycle of the parasite [57]. Otherwise moving from control to elimination could be difficult [57].

The WHO recommended five core intervention strategies such as praziquantel preventive chemotherapy, access to improved drinking water, better sanitation, hygiene education, environmental management, and snail control against schistosomiasis [49,58] in all at-risk population groups. However, in most prevalent nations, including Ethiopia, preventive chemotherapy targeting SAC is the main strategy for treating, preventing, and controlling schistosomiasis. Without integrating all interventions and inclusion of all at-risk populations achieving control and elimination targets could not be feasible [59].

1.4.1 **Mass praziquantel Administration (MDA)**

Concerning the WHO recommendation, currently, periodic MDA using PZQ, the only available drug effective against schistosomiasis, is the main intervention strategy against schistosomiasis in SSA including Ethiopia [59,60]. PZQ acts by affecting the permeability of the cell membrane resulting in the contraction of schistosomes by disrupting the calcium channels. The drug further causes vacuolization and disintegration of the parasites' outer tegument. The effect of the drug is more prominent on adult worms relative to immature/juvenile worms [61].

In Ethiopia, mass praziquantel treatment targeting SAC started in the year 2014 G.C [21] aiming to eliminate schistosomiasis to a level where it is no longer a public health threat by 2025 [54]. In the presence of schistosomiasis and STH co-infection in endemic areas, MDA in SAC, aimed to control and eliminate schistosomiasis and STH are done together [54].

Even though praziquantel has served as a cornerstone to reduce the increasing burden of schistosomiasis for many years, pre-SAC have not benefited from the public health preventive interventions being implemented against schistosomiasis [62]. The contributing factors for the omission of pre-SAC from preventive chemotherapy measures were the assumption of pre-SAC to be safe from schistosomiasis, the absence of adequate evidence on PZQ efficacy and safety, and the nonexistence of relevant formulation [28].

Results of small-scale studies showed that praziquantel is effective and safe in treating schistosomiasis in pre-SAC [19]. Based on the cure rate and efficacy profile of praziquantel in SAC and adults, praziquantel at an ordinary dose of 40 mg/kg has been started in pre-SAC [63]. This unverified prescription of praziquantel dosage cannot give similar outcomes due to physiological variations compared with SAC and adults [64]. A single dose of 40 mg/kg PZQ achieved a 96.4% cure rate in a small-scale study conducted in Ethiopia [19]. Nausea and tiredness were common minor unwanted events seen within 4 hours of ingestion of the drug but moderate and serious side effects including skin rashes were not detected [65]. However, the safety and efficacy of PZQ need to be urgently established in pre-SAC to inform the national NTD program and policymakers. A study conducted in Sudan [66] reported that praziquantel achieved a cure rate of 90.5% against *S. mansoni* infections one month after treatment.

According to the WHO, in areas with high schistosomiasis prevalence (50%), all SAC and adult people at risk of infection (from special groups to entire communities living in endemic areas) should be treated annually [49]. In areas with moderate endemicity (prevalence 10% but < 50%), all SAC and adults considered to be at risk (special groups only) should be treated once every two years, and only SAC twice during their primary schooling, and PZQ should be available in

dispensaries and clinics for the treatment of suspected cases in low-risk communities where the baseline prevalence was < 10% [49].

1.4.2 Access to WASH services

Access to safe water and adequate sanitation are critical to impact the incidence and morbidity or death resulting from vector-borne and water-related diseases. In Ethiopia, according to the United States Agency for International Development (USAID), access to safe drinking water has reached 57%, while access to improved sanitation was only 28% [67]. Despite the ongoing efforts, WASH coverage remains insufficient. Thus, inadequate access to safe water and sanitation services and poor hygiene practices negatively impact health and nutrition; the situation is also favoring the continued transmission of NTDs in Ethiopia [67]. Besides, hygiene promotion is a vital, low-cost, and simple component of a WASH intervention. It is needed to educate people on hygiene practices to maximize the health benefits of safe water sources and sanitation facilities [67].

The Ministry of Health of Ethiopia (MOHE) has established a national WASH–NTD framework that strongly emphasizes coordination between the NTD and WASH sectors to create an enabling environment for sustainable disease reduction [68]. Previously, interventions against NTD were the agenda of the health sector alone [68]. Several rounds of repeated deworming were conducted neglecting other robust integrated interventions that facilitated continuous reinfection. The coordination has added value for WASH and NTD sectors in improving the efficacy of their interventions and reducing the spread of NTDs in endemic communities [68].

1.4.3 Health Education

Health education is key to improving the health and well-being of individuals and communities through increasing their knowledge or influencing their attitudes [69]. In resource-limited

countries, health education is a vital intervention with low cost and an enormous impact on breaking the transmission of disease in endemic areas. Since NTD spread is facilitated by human activities and behavior, regular health education about the disease can prevent reinfection within the community. Increasing their knowledge about the predisposing factors and self-care every day can interrupt the chain of disease progression [70]. It is realized that the reduction of NTDs-related disabilities might be influenced by the local culture, beliefs, and practices of people [69].

1.4.4 Snail control

The most successful strategy for long-term schistosomiasis control and successive elimination is snail control because snails are the intermediate host and play an essential role in the schistosome life cycle [71]. The larvae (cercaria) that infect humans are released by intermediate snail hosts existing in infested water sources [59,60]. Snail control targets destroy the snails to interrupt the transmission chain. This can be attained with different measures such as environmental control, biological control, and chemical control [72].

1.5 Targets of Control and Elimination of Schistosomiasis

Global: The WHO 2030 target is to eliminate schistosomiasis as a public health problem (defined as <1% prevalence of heavy-intensity infections) [49,53,73].

National: A target for control (prevalence of infection < 2%) and elimination (heavy intensity infection < 1%) as a public health problem by the year 2025 [54]. However, due to the nonexistence of a clear inclusion strategy in Ethiopia, pre-SAC are not part of MDA campaigns and, therefore, served as a source of reinfection for many years.

1.6 KAP of mothers/primary caregivers of pre-SAC about schistosomiasis

The success of community-based control interventions depends on community acceptance of the program [74]. Programs should first intend to realize the community's knowledge, attitude, and practices (KAP) towards schistosomiasis before the execution of the program activities [75]. Among community members, mothers/primary caregivers are regarded as an essential group due to their practical role as immediate caregivers [55]. Mothers/ primary caregivers are extremely dominant within their families and society; nevertheless, without sufficient knowledge, they are inclined to misinform others or be involved in risky practices that subject their young children to *S. mansoni* infections [76,77].

Low educational level among women is an additional contributor to infection [5]. Recent findings point out that the omission of under-fives from MDA programs and subsequent exclusion of caregivers from health education programs contributed to the increased prevalence of schistosomiasis in endemic areas [78]. Mostly school-going children are the target of schistosomiasis-related educational programs, as they are easy to reach and wrongly SAC considered the only vulnerable population segment [79]. This however excludes caregivers of pre-SAC related to presumed safety to schistosomiasis infection [79]. For all health-promoting interventions, health education is the cornerstone to produce sustainable positive behavioral changes [80]. The desired effect of comprehensive knowledge, favorable attitude, and practices could accelerate the reduction of parasitic infections [57]. The level of such effect may vary due to the difference in the level of understanding among community members [36].

Preventive chemotherapy is the mainstay to tackle schistosomiasis globally [5]. However, to improve the acceptance of the planned interventions comprehensive understanding of the sociocultural issues of the community is critical [36]. For infants and pre-SAC, it becomes difficult

to realize how these children acquire infection, when they are supposed to stay at home or under strict observation by their mothers and caregivers [65]. The prevailing facts have pointed out that mothers /caregivers have approved taking their infants and pre-SAC to bathe in the stream, while older pre-SAC children visit the water bodies for washing, fetching water, bathing, and swimming [28]. According to the available evidence infants and pre-SAC become a significant source of transmission in the absence of any intervention in communities where schistosomiasis is prevalent [10].

Lack of knowledge and unfavorable perceptions may result in the utilization of unprotected water sources or contamination of water bodies [57,81]. Evidence showed that in endemic areas women conduct most of the water contact activities putting themselves and their pre-SAC at high risk of infection [57,82]. A study revealed that 16.2% of the mothers/caregivers engaged in open defecation in surrounding bushes, 1.8% directly to the river, and 13.2% still depended solely on water from the river for domestic usage [4]. Some studies have also shown that the KAP of individuals regarding schistosomiasis is influenced by sociodemographic characteristics such as age, sex, occupation, level of education, and religion [80]. Such data are imperative for recognizing, designing, and executing effective community-based interventions against schistosomiasis.

In rural areas of prevalent nations including Ethiopia, where schistosomiasis [15,36] is predominant, community-based KAP studies about schistosomiasis among caregivers of pre-SAC have been unrecognized. This adversely hinders the attainment and sustainability of the control interventions targeted toward eliminating schistosomiasis as a public health threat [54]. Mothers/caregivers are critical to combat schistosomiasis among pre-SAC [83]. A report from Nigeria revealed that the spread of schistosomiasis among children was linked to risky water-

related practices of caregivers [84]. There are insufficient explanations for the underlying causes of such actions by mothers/primary caregivers. A report of a review in SSA on KAP about schistosomiasis also emphasized the importance of caregivers' involvement in the planning and execution of control programs aimed at improved efficiency among pre-SAC [55].

1.7 Effect of *S. mansoni* infection on undernutrition and anaemia

Intestinal schistosomiasis causes devastating health problems including nutritional disorders, anaemia, and related pathological effects among infected individuals [85]. This infection has also been strongly linked with undernutrition which is known to contribute to more than one-third of all deaths of under-five children [4]. Undernutrition and anemia continue to be public concerns in resource-limited areas where they are recognized to mostly affect children [4]. The two are known to affect physical and mental maturity and impaired immunity thereby rendering the already vulnerable group more susceptible to infections with other commonly occurring bacterial and viral pathogens [62].

Infected individuals' nutritional status can be altered through a decline in food intake, an increase in nutrient wastage through loss of blood, vomiting, and diarrhoea, and can be aggravated by helminth infection [4]. Some health effect of pre-SAC includes anemia, poor nutrition, and growth [4]. Pre-SAC are also most at risk of long-lasting infection which can harm growth, development, cognition, iron status, and immaturity of the immune system which further increases defenselessness to infection and future production [10]. In co-endemic communities, schistosomiasis and intestinal helminths critically deprive hosts of essential nutrients [65]. Moreover, pre-SAC are a nutritionally susceptible group, and defects during this early developmental stage may continue for a long [4,28].

Evidence shows that among the SAC who acquired *S. mansoni* infection, 42.3% were anemic, 21% stunted, 6.8% were wasted, and 1.3% were underweight [10]. *S. mansoni* is responsible for causing blood loss through fecal occult blood and further affects iron balance and leads to undernutrition [10]. SAC particularly suffer growth retardation, low school performance, cognitive impairments, and remarkable pathological illness from egg granuloma [86]. In pre-SAC chronic morbidity can occur quickly due to the pro-inflammatory response generated even with low parasite burdens [57]. Also, future cognitive deficits and educational loss are related to schistosome infection [55].

A chronic form of intestinal schistosomiasis is mainly characterized by bloody diarrhea, bowel ulceration, hepatomegaly, and periportal fibrosis that can cause portal hypertension, esophageal varices, and hematemesis [4]. If left untreated, the disease can progress to hepatosplenomegaly [87]. In tropical regions, pre-SAC are at risk of coinfections and consequently, comorbidities similar to SAC [27]. Evidence in children aged 5–18 years shows that the incidence of multiple infections in endemic areas favored the occurrence of significant morbidities, such as anemia and malnutrition that are critical in the developmental years of pre-SAC [4].

Parasitic infections like schistosomiasis continue causing anaemia and negative effects on the nutritional status of preschool children [85]. Yet, only limited small-scale studies addressed the association between *S. mansoni* infection and undernutrition or anaemia among pre-SAC.

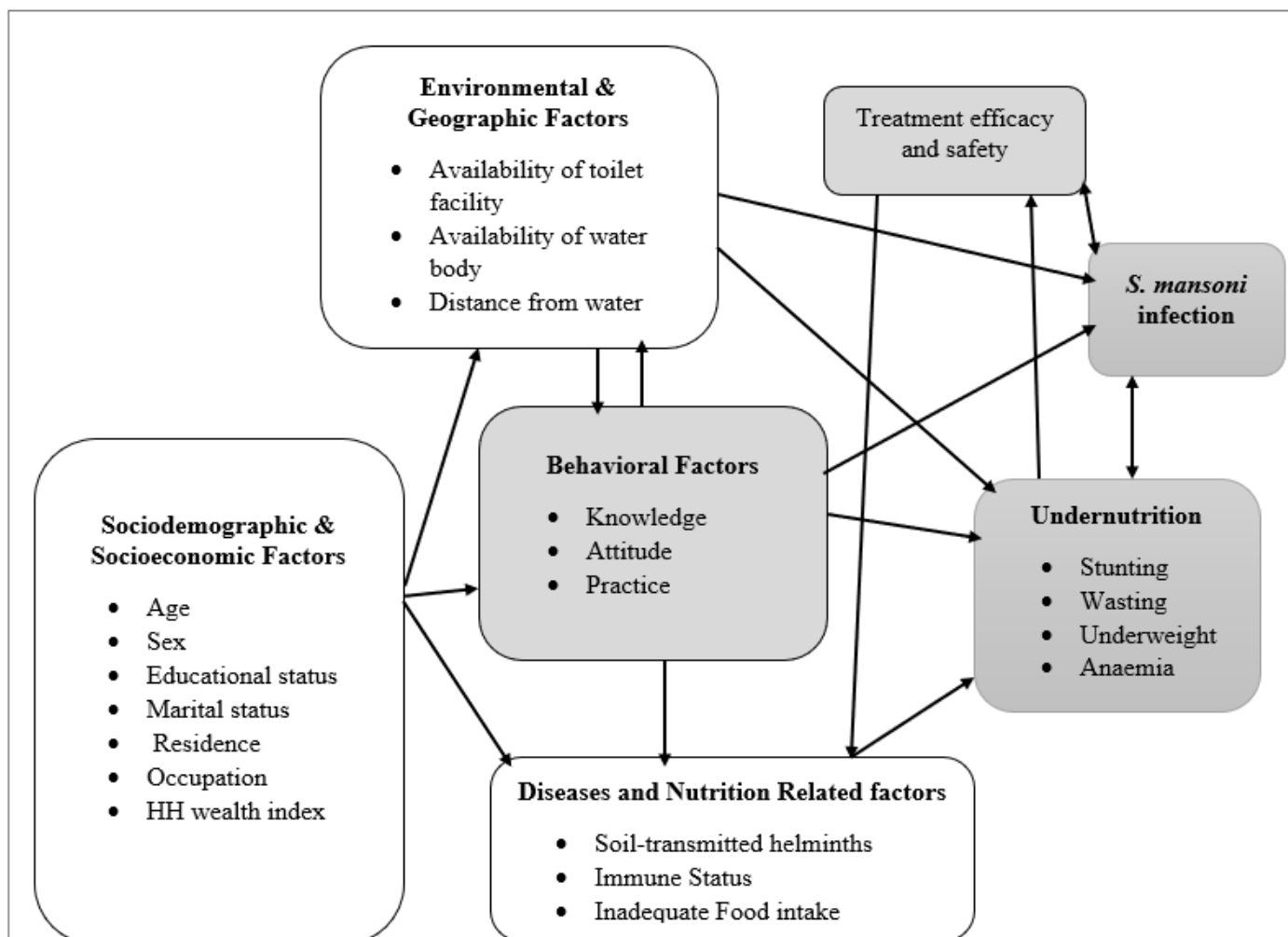


Figure 3: Conceptual framework outlining the main risk factors and impacts of *S. mansoni* infection. Source: adapted from the previous study: https://www.researchgate.net/figure/Conceptual-framework-outlining-the-main-elements-of-schistosomiasis-control-The-inner_fig1_26289078 (Accessed January 2020)

1.8 The rationale for this study

Though there is increasing evidence of schistosomiasis among pre-SAC, there are still many dimensions that need to be studied about the disease. In high schistosomiasis endemic areas, children are prone to chronic infection due to the possibility of getting the infection at the age of

2 years [88], however, this at-risk population is overlooked from intervention due to limited evidence.

Most of the available limited pieces of evidence regarding the burden and its determinants, and efficacy and safety of PZQ were conducted in other countries [66,89,90]. Concerning the variations in the intensity of focal transmission of schistosome parasite attributed to the difference in the density of the snail host, frequency of contact to the infested water source, etc., consequently, the effect may differ from setting to setting and from nation to nation [80]. So, in paper I the magnitude of the disease and its determinants was assessed as it is needed from countries like Ethiopia where pre-SAC could be a potential source of reinfection and contribute to the delay in the attainment of the elimination target of the disease (paper I).

To date, the shortage of sufficient evidence coupled with contradictory findings made several issues related to the inclusion of pre-SAC in control and elimination strategies of schistosomiasis unresolved. Thus, pre-SAC are treated with the extrapolated prescription of PZQ which has been estimated from SAC and adult dosage due to scarce data, but they are not little adults. In paper II, the efficacy and safety of a single-dose praziquantel was investigated.

The success of any community-based intervention depends on the knowledgeable involvement of community members [74]. Mothers/primary caregivers may predispose themselves and their young pre-SAC to *S. mansoni* infection due to insufficient knowledge, unfavorable attitude, and poor practices. However, evidence is scarce on the KAP of caregivers of pre-SAC about schistosomiasis related to the presumed safety of their young children and has an enormous contribution to the delay of elimination target of the disease. Thus, the level of knowledge, attitude, and practice of caregivers about schistosomiasis was assessed (paper III). Furthermore, parasitic

infections like schistosomiasis continue causing anaemia and negative effects on the nutritional status of pre-SAC. Yet, only limited small-scale studies addressed the association between *S. mansoni* infection and undernutrition or anaemia among pre-SAC. Paper IV of the present thesis exhibited the link between *S. mansoni* infection and undernutrition or anaemia among this young population group.

2. Research Aims

2.1 General objective

This dissertation aimed to determine the prevalence and determinants of *S. mansoni* infection, investigate the efficacy and safety of praziquantel for the treatment of *S. mansoni* infection, assess the KAP of mothers/ primary caregivers of pre-SAC towards schistosomiasis, and evaluate the association of *S. mansoni* infection with undernutrition and anaemia among pre-SAC children in southern Ethiopia

2.1.1 Specific objectives:

1. To determine the prevalence and risk factors of *S. mansoni* infection among pre-SAC in southern Ethiopia (**paper I**)
2. To investigate the efficacy and safety of praziquantel in the treatment of *S. mansoni* infection among pre-SAC southern Ethiopia (**paper II**)
3. To assess the KAP of mothers/primary caregivers of pre-SAC towards schistosomiasis in southern Ethiopia (**paper III**)
4. To investigate the association of *S. mansoni* infection with undernutrition [stunting, wasting, and underweight] and anemia among pre-SAC southern Ethiopia (**paper IV**)

3. Materials and Methods

3.1 Study area

The study was conducted in the Hawella Tulla district of Sidama region, in Ethiopia. The study district is situated 289 km from Addis Ababa, the capital of Ethiopia southward (Figure 1). The district was identified as endemic for *S. mansoni* according to the report of NTDs burden assessment conducted in Ethiopia [21]. It is located at an altitude of 1800m above sea level and has an annual rainfall of 1123mm and a temperature of 13–27°C. The residents of the district depend on Lake Hawassa for domestic, agricultural, fishing, and other uses. According to the Central Statistics Agency (CSA), the district has a total population of 142,191 (69,674 males and 72,518 females). The district has one primary hospital, six health centers, and one non-governmental health center and none of them provide health services for schistosomiasis. The details of the study district are presented in Figure 4.

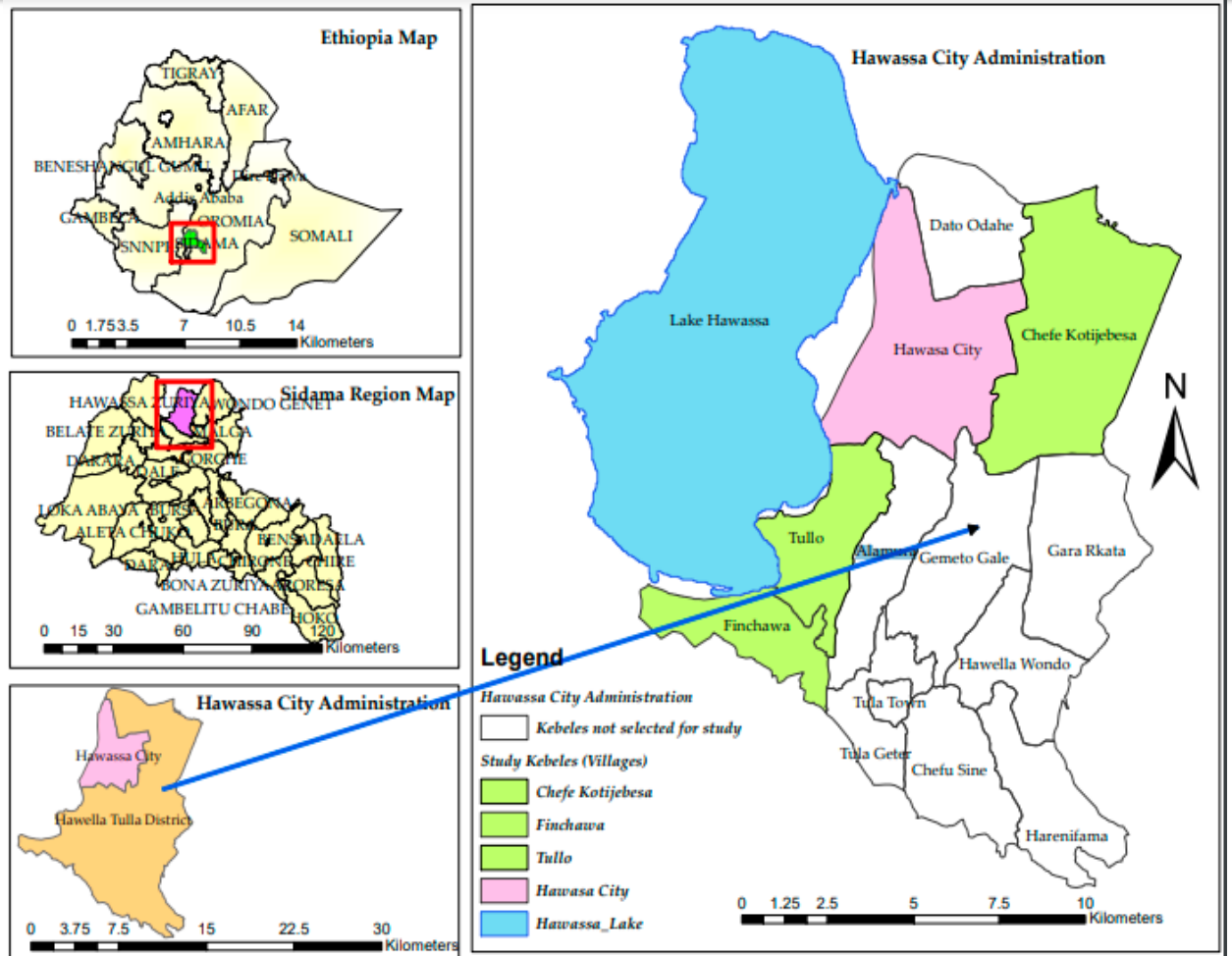


Figure 4. Map of the study site. The (**top left**) is the map of Ethiopia. The (**middle left**) figure shows the map of the Sidama region, and the (**bottom left**) figure indicates the map of Hawassa City administration where the study districts are located. The figure on the right shows the map of Lake Hawassa and the *Kebeles* where the study was conducted.

3.2 Study Design

This dissertation encompassed a community-based cross-sectional study (paper I, III, and IV) and a before-and-after quasi-experimental study (paper II) where the participants for the before-and-after study were drawn from paper I.

3.3 Sample size

Hawella Tulla district was purposively selected, mainly for the confirmed moderate to high *S. mansoni* infection among SAC and the feasibility of conducting efficacy and safety investigation of PZQ at ease. For the first paper, a prevalence (p) of 25% from a prior study in pre-SAC in Ethiopia [19], 3% absolute precision, and a design effect of 2 were the assumptions used to calculate the sample size. Accordingly, after adjusting for a 10% non-response rate the final sample size was 1778. The sample size was also calculated considering the various possible determinants of *S. mansoni* infection, and that the sample size based on the prevalence was the largest. In paper II, the assumptions used from a previous study SAC [91] were: arithmetic mean (AM) egg count at pre-treatment of $365.06 \pm$ standard deviation (SD) of 437.8, AM egg count at post-treatment of $78.6 \pm$ SD of 65.6, power of 0.9, alpha (α) of 0.05, effect size of 0.2, and within-subject correlation of 0.5. A larger sample size ($n= 265$) calculated considering the smaller effect size of 0.2 was used.

The sample size of paper III was computed using the assumptions: considering schistosomiasis as a serious disease among parents age < 40 Vs ≥ 40 years from a previous study [92], the percent of unexposed with outcome 70.3, the percent of exposed with the outcome of 82.4, fixing the level of confidence at 95%, power at 90%, the ratio of unexposed-to-exposed at 1, and anticipated non-response rate of 10%, and design effect of 1.5. The sample sizes were also estimated considering the levels of knowledge, attitude, and practice; and the determinants of KAP. Accordingly, the estimated largest final sample size was 910. In paper IV, the sample size was calculated for all outcome variables and determinants using the findings of the previous studies [93,94].

The final largest sample size ($n= 620$) was calculated using the assumptions, the prevalence of underweight among unexposed with the outcome (24.5%) and exposed with the outcome (39.5%)

fixing the level of confidence at 95%, power at 85%, the ratio of unexposed-to-exposed at 1, and expected non-response rate at 10%.

3.4 Study participants and recruitment

The sampling was a multistage involving sampling at different levels (*Kebele*, household, and child). Of the twelve *kebeles* of the study district, six were designated for the current study due to the endemicity report of *S. mansoni* infection generated in Ethiopia [21] among SAC. Of which three *kebeles* (Tullo, Finchawa, and Chafe Kotijebessa) were selected by using the lottery method. Then, a sampling frame of pre-SAC (children aged 4 to 7 years) was prepared through census in three randomly selected *kebeles*. At baseline, 1778 children were selected using a simple random sampling technique, in which the mother/primary caregiver was the targeted respondent.

The children included in the cross-sectional studies were four-to-seven-year-olds who lived in the area (papers I and IV). All *S. mansoni*-infected children at baseline screening were involved in the before-and-after study (paper II). Pre-SAC who received PZQ treatment within a month time of the study commencement period were excluded for the possible parasites' clearance with the prior treatment. Mothers/primary caregivers of 887 pre-SAC were included in the KAP assessment using simple random sampling from the sampling frame of pre-SAC (paper III). Six hundred twenty children were selected using a simple random sampling technique from the list of participants (paper IV). Sick or severely ill participants were also not included (paper I-IV).

3.5 Variables of the study

The outcome variable for the first paper was *S. mansoni* infection: It was detected using Kato-Katz (a gold standard method) for diagnosing *S. mansoni* by microscopic examination [95]. *S. mansoni* infection was recorded as infected (1 = if *S. mansoni* infection detected) or uninfected (0 = if no *S.*

mansoni infection detected). Egg counts were quantified and classified for *S. mansoni* infection according to the WHO guidelines as light (1-99 EPG), moderate (100-399 EPG), or heavy (> 400 EPG) [26] (paper I, II, & IV).

The exposure variables comprised age, sex, educational level of caregivers, occupation of the caregivers of pre-SAC, marital status of caregivers, contact with infested water, frequency of accompany to the water source, household wealth index, and distance from the infested water body (paper I). A smartphone with a map application was used to estimate the distance of the house from the water body in kilometers during data collection [96]. The wealth index of the household was computed based on the possession of assets, availability of safe drinking water, toilet facility, and housing conditions using the principal component analysis (PCA). The indicator weights for the household wealth index were assigned using the principal component analysis (PCA). Wealth quintiles were categorized into five linked to the scores [97].

The outcome variables of paper II were efficacy (ERR and CR) based on the thick smear Kato-Katz method at four weeks post-treatment. The ERR was calculated as $100 \times [1 - (\text{Arithmetic mean egg counts at follow-up} / \text{Arithmetic mean egg counts at baseline})]$ per the recommendation of the WHO [26]. The proportion of infected (egg-positive) children before treatment who became egg-free (egg-negative) at day 28 post-treatment was used to determine the CR. As an outcome variable, the treatment-associated AEs experienced or reported within 8 days of praziquantel administration were recorded [98].

Praziquantel treatment administered in a single dose of 40mg/kg was the major exposure variable. Other covariates comprise age, sex, and co-infection with the three common STHs, namely *Ascaris lumbricoides*, *Trichuris trichuria*, and hookworm (paper II).

The outcome variables of paper III were:

Knowledge: The knowledge of respondents about schistosomiasis was measured by asking a series of 5 close-ended questions containing multiple options regarding signs and symptoms, prevention strategies, control and treatment methods, and modes of transmission. Participants who responded “NO” to the screening question were given a score of “0” and included in the knowledge level assessment. Questions related to knowledge were scored and pulled together and the mean knowledge score was then calculated by distributing a scaled score by the number of respondents responding on a scale. Knowledge was recorded as high if more than or equal to the mean score, while low for a score less than the mean [36].

Attitude: The perception of participants concerning the severity of the disease, risk factors, signs and symptoms, mode of transmission, prevention strategies, treatment, and control of schistosomiasis was assessed using close-ended questions. It was measured using a questionnaire containing 7 questions. The participant’s response and each question were assigned and ranked by a Likert scale using a numerical score encompassing from 1 to 5. (Strongly disagree = 1, Disagree = 2, neutral = 3, Agree = 4, Strongly agree = 5). The overall attitude score of a participant was determined based on the mean scores computed by dividing on-scale scores by the number of participants responding on the scale. The attitude was delineated as a favorable attitude if the mean attitude score was more than or equal to the mean and an unfavorable attitude for caregivers who had responded less than the mean attitude score [36].

Practice: The respondents’ practice with schistosomiasis was evaluated by asking a single question that had nine major response options about where the study participants wash clothing often. The response options listed were grouped into predisposing and protective practices. Respondents who reported at least one predisposing practice were categorized as having poor

practice, while those who reported “NO” for any predisposing practices were labeled as having good practice [99].

The exposure variables encompass age, educational level, marital status, occupation, wealth quintile, and source of information about schistosomiasis.

The exposure variables encompass age, educational level, marital status, occupation, wealth quintile, and source of information about schistosomiasis (paper III).

The outcome variables of paper IV were:

Stunting: A height-for-age Z-score less than minus two standard deviations (SD) of the WHO Anthro /Anthroplus median Child Growth Standards [100,101].

Wasting: A height-for-weight/ body mass index-for-age Z-score less than minus 2SD of the WHO Anthro /Anthroplus median Child Growth Standards [100,101].

Underweight: A weight-for-age Z-score less than minus 2SD of the WHO Anthro /Anthroplus median Child Growth Standards [100,101].

Anaemia: Haemoglobin concentrations were then classified as mild (11.0 – 11.4 g/dL), moderate (8.0 – 10.9 g/dL), and severe anaemia (< 8 g/dL) for 5 to 11 years old children according to the WHO guideline [102], while mild (10.0 – 10.9 g/dL), moderate (7.0 – 9.9 g/dL) and severe anaemia (< 7 g/dL) for children aged 6 to 59 months adjusted for age and altitude according to the WHO Guideline [102].

Exposure variables were *S. mansoni* infection and other covariates such as age, sex, education level of caregivers, household wealth index, and *S. mansoni* with STHs co-infection (paper IV).

3.6 Data collection tools and procedures

The research team visited the homes of the study participants to collect the required data, including a structured questionnaire with stool and blood sample collections, and anthropometry. Interviews, stool and blood sample collection, and anthropometric measurements were conducted with the households.

3.6.1 Interview

The research team visited the homes of the study participants to collect the data. The pre-tested, structured questionnaire was used to collect data. The tools were translated into local languages (Amharic and Sidamu Afoo). It was used to collect data on socio-demographic and economic characteristics, and morbidity patterns using eight-degree holder-trained data collectors. The data collection process was regularly supervised by two experienced experts and the principal investigator to ensure the completeness and accuracy of the data.

3.6.2 Collection of stool samples, processing, and examination

A single fresh stool sample was collected from each enrolled participant before treatment (papers I, II, and IV) and after treatment (paper II) and tested at Bushullo Health Center. Two duplicate thick slides were prepared using the Kato-Katz method from each stool sample [103]. The intensity of infection for each study participant was calculated by multiplying the average egg count from the two slides with a constant factor of 24. Baseline infection intensity was classified based on the WHO guidelines as light-intensity (1 – 99 EPG), moderate-intensity (100 – 399 EPG), and heavy-intensity (≥ 400 EPG) infections [26].

3.6.3 Anthropometry

Anthropometric measurements, namely weight and height, were taken to assess the child's nutritional status. A height board with a sliding headpiece was used to measure height when the child was standing straight. It was ensured that the head, buttocks, and heels were touching the board. Measurements were taken to the nearest 0.1 cm [104]. A calibrated flat scale was used to take the weight with the child barefoot and wearing light clothing. The scale was calibrated to zero before weighing a child and recalibrated after every measurement with a known heaviness. Measurements were taken with 0.1 kg accuracy [104]. Height-for-age Z-score (HAZ), Body Mass Index (BMI)-for-age Z-score (BAZ), and weight-for-age Z-score (WAZ) for each participant were then calculated using the WHO Anthro Plus software version 1.0.4 [100] for children aged 5 – 11 years, while weight-for-height Z-score (WHZ) was determined using WHO Anthro software version 3.2.2 among children aged 6 – 59 months [101]. Children with scores less than minus two standard deviations for HAZ were stunted, BAZ/WHZ wasted, and WAZ considered underweight (paper IV).

3.6.4 Collection of blood samples and determination of haemoglobin

A finger prick blood sample was collected from enrolled children by four expert laboratory technologists using a microcuvette. Haemoglobin concentration was measured using the HemoCue Hb 301+ method in g/dL (HemoCue AB Angelholm, Sweden). The method is effective and suitable in resource-limited settings [105].

3.7 Data quality assurance techniques

To ensure the quality of data, various data quality assurance techniques were applied. First, a structured questionnaire with several contents adapted from Sacolo-Gwebu et al., 2019 [36]. So,

we used the tools that have been used in different situations and populations and assumed to have known reliability and validity.

Secondly, the questionnaire was translated into locally understandable languages (i.e. Amharic and Sidamu Afoo) so that the respondents may realize the item and give their responses. To check the consistency of the intended meaning of the item. The tool was back-translated to English by an independent English language expert.

Thirdly, the questionnaire was pretested in another schistosomiasis endemic district (namely Wondo Gennet) about 22 km far from eastward from Hawella Tulla district. The assumption for doing the pretest of the questionnaire in another district was to avoid possible information contamination. Then we revised the tools based on the problems that we faced during the pretesting of data collection tools.

Fourthly, the research team consisted of eighteen members, and two supervisors having master's degrees were recruited and trained on the purpose, objectives, data collection, and methods of drug administration and adverse event monitoring. Ten medical laboratory technologists were trained in how to collect fresh stool and blood samples and haemoglobin analysis using the Hemacue machine. Four trained data collectors were used to collect sociodemographic, economic, and behavioral data using a pretested questionnaire. One pediatric physician and a nurse were trained on appropriate drug dosage, preparation, administration, and pre-treatment assessment of concomitant morbidities, post-treatment active monitoring of the AEs, and referral system at the Health Center. The principal researcher guided the whole process of the research. Orientation on ethical issues was given to all research teams. The data collection was checked daily for accuracy,

consistency, and completeness by the supervisors. Anthropometry and haemoglobin instruments were checked at every measurement [104,105].

Finally, the data was entered into the RedCap database by two data entry clerks. The data were cleaned in the Excel spreadsheet. Further data cleaning was carried out through investigative analysis of the data.

3.8 Statistical Analysis

All analyses for papers I, II, III, and IV were undertaken using Stata version 14 software [StataCorp LLC, College Station, TX, USA]. Initially, an intercept-only model was fitted to check the appropriateness of the data for standard logistic regression versus multilevel logistic regression.

Then, the suitability of multilevel analysis was confirmed based on an intra-class correlation coefficient (ICC) value of 8.4% and a significant likelihood ratio test (LR) with a corresponding p-value less than 0.001 (paper I).

Besides, to conduct a multilevel binary logistic regression analysis, three models were fitted. The null model (a model without the explanatory variables) was the first model that showed the extent of variability in *S. mansoni* infection due to cluster- (*kebele*-) level effect without accounting for covariate effects. Model I which comprised individual-level determinants with random intercept was the second model. Model II, which encompassed a random coefficient for the distance of the household from an infested water source, random intercept, and individual-level predictors was the third, and final model.

Model fitness was assessed using: I) the presence or absence of significant improvement on the LR in the fitted models; II) the changes in Akaike's information criterion (AIC) and Bayesian information criterion (BIC) values; best-fitted models have smaller values of AIC and BIC; IV) a

26% change in the odds ratio for distance less than 1 km from model I to model II; and V) logical plausibility was also considered (paper I). The analysis began with univariable multilevel logistic regression. Relevant interaction effects of age and sex variables were checked but no significant effect was detected. The interaction term was removed from the model and the analysis was rerun without the interaction term. Then variables were selected to be included in the multivariable multilevel model using a purposeful variable selection technique based on the literature [106]. Variables with a p-value less than 0.25 on the bivariable model and those variables considered important in other literature were entered into the multivariable model. Thus, the determinants of *S. mansoni* infection were assessed using a multilevel logistic regression model (paper I).

For paper II, the dependent variable consisted of a continuous outcome (egg reduction rate) and two binary outcomes: cure rate and adverse events. Predictors of the cure were assessed using bivariable followed by multivariable logistic regression (paper II). As described in Paper I, all predictor variables in the bivariable analysis were entered into the multivariable model using a purposeful variable selection procedure based on the literature [106] (paper II). Besides, in paper II, a log-binomial regression model was used to investigate the predictors of AEs. The overall significance of the log-binomial model was investigated using the Wald test for all parameters in the model [107].

For paper III, a multivariable logistic regression with the cluster-robust variance estimation method was used. The variable included in the multivariable model followed purposeful selection variables with a p-value less than 0.25 on the bivariable model and those variables are considered important in other literature (papers III and II). For paper IV, initially, anthropometric data (weight, height, age) were converted to z-scores and percentiles; and the haemoglobin level was determined.

Then, the association between *S. mansoni* infection and undernutrition and anaemia (paper IV) was investigated using multivariable logistic regression with the cluster-robust variance estimation method proceeded as in paper III. Variable selection and the model building and assessment of the overall significance of the model in the same way as (paper III).

For all papers (papers I-IV), the variance inflation factor (VIF) was used to diagnose multicollinearity among the independent variables. There was no VIF greater than 5 and the mean VIF was not more than 1 showing multicollinearity was not a problem [108]. In all of the four papers statistical significance was set at $p < 0.05$, and 95% confidence interval (CI).

3.9 Ethical Considerations

The Institutional Review Board (IRB) of the College of Medicine and Health Sciences of Hawassa University (Ref. No: IRB/200/13) and the National Research Ethics Review Committee (Ref no MoSHE//RD/401/0974/20) approved the study. It has been conducted as per the Declaration of Helsinki. Written permission was obtained from the Sidama Regional Health Bureau Public Health Institute. Written consent was obtained from the mothers/caregivers of pre-SAC. The respondents were the caregivers of pre-SAC as the children at this age were too young to respond. The research purpose and protocols were explained in detail to the local administration and community leaders, and permissions were granted before the data collection.

The caregivers were informed of the benefits of the study, which were expected to improve the health condition of the pre-SAC, and the anticipated risks of participating in this study in Amharic and the local language (Sidamu Afoo). The anticipated risks were mild pain during blood collection at pre and post-intervention screening. There was merely voluntary participation and the

respondents were assured of confidentiality, which was maintained during and after the study, and also assured that any information from the study was only used for the study.

4. Results

4.1 Study population characteristics

One thousand six hundred eighty-three pre-SAC participated in this study with a response rate of 95%. Out of 1683 children, 241 (14.3%) were positive for intestinal schistosomiasis (paper I). Of those who were positive for *S. mansoni*, 99.6% (240/241) were eligible for the efficacy and safety study and received PZQ. Of 240 (14.3%) cases, 12.6% were males and 12.0% were females (paper II).

In a before-and-after study, 236/240 (98.3%) completed follow-up for efficacy evaluation, while 234/240 (97.5%) completed follow-up for safety assessment. Two children withdrew, while 4 were recorded as lost-to-follow-up for reasons that could not be traced (paper II-Figure 1)

From a total of 620 sampled pre-SAC, 565 (91.1%) were involved in the study on the effect of *S. mansoni* on undernutrition and anaemia (paper IV). Two hundred eighty-seven (50.8%) were males, while (51.2%) belonged to the age category of 6 to 7 years (paper IV).

4.2 Characteristics of mothers/primary caregivers

Eight hundred eighty-seven mothers/caregivers were assessed and their median age was 30 years (IQR 27–35). Of the mothers/caregivers, 643 (72.5%) were housewives (working at home) and 395 (44.5%) had no formal education (paper III). Fig 5 shows the whole study flow.

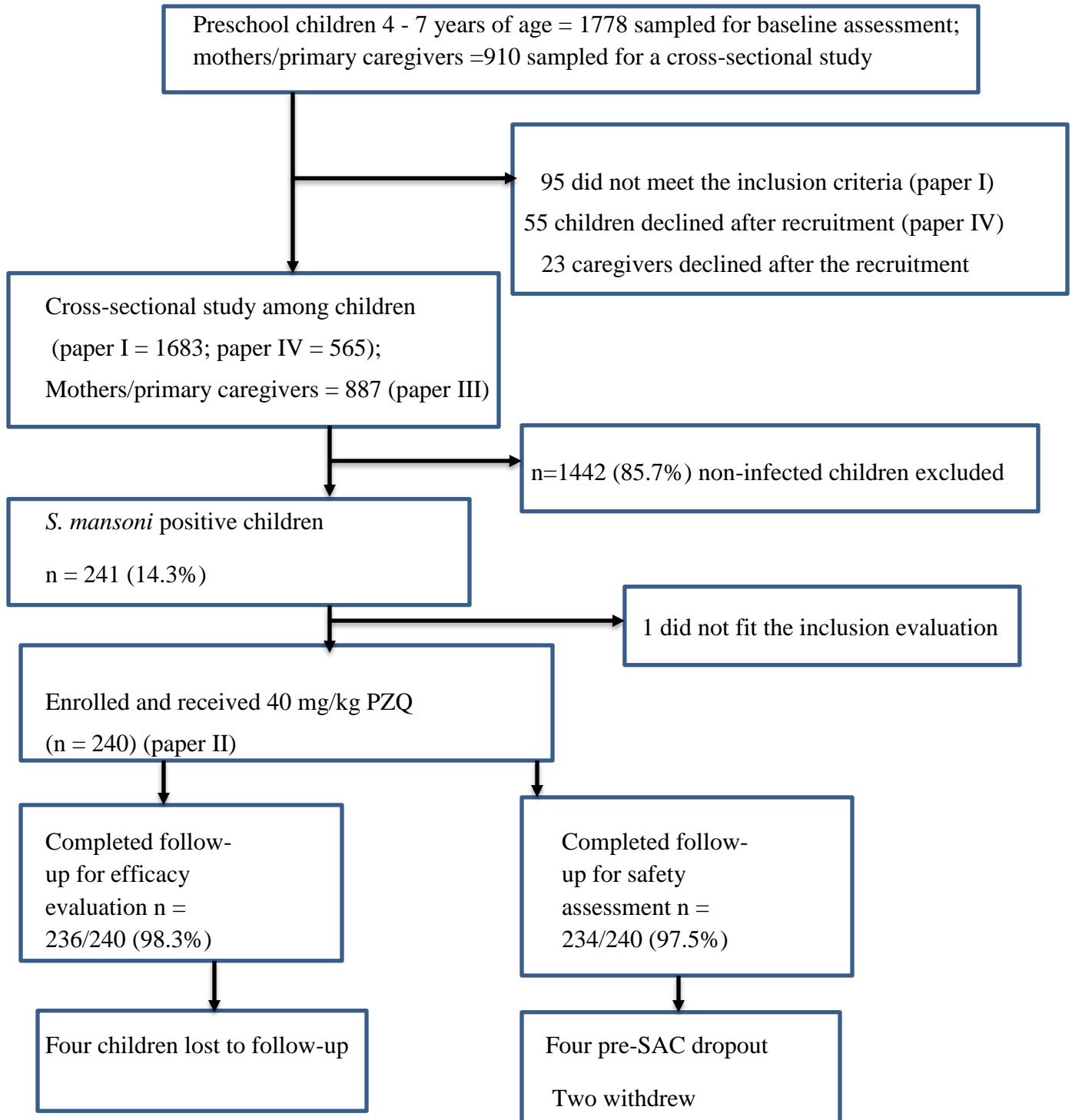


Figure 5: Study flow indicating participants in the cross-sectional studies, a before-and-after quasi-experimental study, and the number of exclusions at the various stages

4.3 *S. mansoni* infection prevalence and determinants in pre-SAC (paper I)

Out of 1683 pre-SAC screened, *S. mansoni* infection was detected among 14.3% (95% CI: 12.6%, 16.0%) children with a 16.4% (144/880) prevalence in males and the share of females being 12.1% (97/803). A high prevalence (24.7%) of the disease was observed among the older age group (7 years), while a moderate prevalence of 6.9% was exhibited in the youngest age group (4 years).

Varied prevalence of infection was also seen among the three study villages (the highest (21.4%) in Tullo *kebele* and the least in Chefe Kotijebesa *kebele* (6.6%)).

The egg count of *S. mansoni* ranged from 12 to 2560 EPG among 241 who were positive at baseline screening. The heaviest infection intensity (1.7%) was detected in Tullo *kebele* followed by Chefe Kotijebesa *kebele* (0.3%).

A higher odds of *S. mansoni* infection was detected among children at the age of 6 years (AOR= 2.58, 95% CI: 1.55, 4.27) and 7 years (AOR= 4.63, 95% CI: 2.82, 7.62). Children who went along with others to water sources sometimes ($p = 0.03$) and all the time ($p < 0.001$), and living within less than one-kilometer distance from the infested water source ($p = 0.003$) were also significant determinants of *S. mansoni* infection. After adjusting for other covariates, 31.8% of the variability on the risk of *S. mansoni* infection was accounted for residing in the *kebele*.

4.4 Efficacy and safety of praziquantel against *S. mansoni* infection and determinants of cure and adverse events among pre-SAC (Paper II)

Overall, 93.3% ERR was achieved with PZQ at 28 days among 236 pre-SAC who received the treatment. No significant variation in median ERR by age group ($p = 0.86$) and sex ($p = 0.95$) at pre and post-treatment (Table 2 of paper II). Overall, 85.2% (201/236) cure rate was detected among pre-SAC (paper II).

Treatment-related AEs were assessed within four hours of PZQ administration because the majority of adverse events were observed following PZQ intake. Overall, a total of 23.1% (95% CI: 17.6%, 28.5%) of the children experienced at least one form of AE (paper II). An increase of 100 in baseline *S. mansoni* egg count decreases the odds of cure by 26% (paper II). A significant association was observed between AEs ($p < 0.001$) and pre-treatment moderate ($p < 0.001$) or heavy infection intensity ($p < 0.001$).

4.5 Level and determinants of KAP towards schistosomiasis among mothers/primary caregivers of pre-SAC (Paper III)

Overall, a low 37.0% (95% CI: 33.8%, 40.2%) level of knowledge about the disease was observed. About 54.8% (95% CI: 51.5%, 58.1%) caregivers had favorable attitudes toward the disease, while 57.8% of mothers/primary caregivers had good practice about predisposing factors of the disease (paper III).

Reduced odds of reporting good knowledge was detected being from the poorest (AOR = 0.75, 95% CI: 0.57, 0.99), poorer (AOR = 0.55, 95% CI: 0.47, 0.65) wealth index households compared to the richest.

The odds of reporting a favorable attitude toward *S. mansoni* infection was significantly higher in the age category of 23 – 29 years (AOR = 1.18, 95% CI: 1.01, 1.37 compared to being ≥ 40 years. Not having formal education (AOR= 0.80, 95% CI: 0.65, 0.98) also increased the odds of reporting a favorable attitude toward *S. mansoni* infection relative to those with a higher education level. Further, reduced odds of reporting a favorable attitude about the disease was observed from the poorest (AOR = 0.42, 95% CI: 0.28, 0.62) wealth households relative to those from the richest counterparts.

Being unmarried had a significant association with reporting good practice about predisposing factors of the disease (AOR = 0.57, 95% CI: 0.36, 0.89) compared to married caregivers. Lack of information about the disease from any source had 60% (AOR = 0.40, 95% CI: 0.26, 0.62) lesser odds of reporting good practices about the disease among mothers/primary caregivers relative to those who used health extension workers as the information source.

4.6 Association between *S. mansoni* infection and undernutrition and anaemia among pre-SAC (Paper IV)

Out of 565 recruited children, 24.3% (95% CI: 20.7%, 27.8%) had stunting, 6.6% (95% CI: 4.5%, 8.6%) had wasting, and 2.0% (95% CI: 0.8%, 3.1%) had underweight, whereas 28.0% (95% CI: 24.3%, 31.7%) had anaemia (paper IV).

S. mansoni with soil-transmitted helminths co-infection resulted in significantly increased odds of stunting (AOR = 4.1, 95% CI: 1.47, 11.11) compared to those infected only with *S. mansoni*.

S. mansoni infection (AOR = 1.9, 95% CI: 1.03, 3.44) had an independent significant association with anaemia among infected pre-SAC compared to non-infected ones. However, *S. mansoni* infection had no independent significant association with stunting, wasting, or underweight.

5. Discussion

5.1 The main findings

The main focus of this dissertation was to assess the burden of *S. mansoni*, how 40 mg/kg PZQ is effective and tolerable in treating schistosomiasis, KAP of mothers/primary caregivers, and the effect of *S. mansoni* on undernutrition and anemia in pre-SAC. Out of the 1683 children examined, the disease was detected among 241 (14.3%). Overall, the burden of *S. mansoni* among pre-SAC

was moderate, with a median infection intensity of 72 eggs per gram (EPG) (IQR 24 – 228) as per the WHO guideline [49].

The overall prevalence of *S. mansoni* infection in the current study is lower than the report of a previous SAC study in the same area in 2020 G.C. [22]. The observed relative reduction in the magnitude of the disease among pre-SAC be attributed to the impact of praziquantel MDA initiated among SAC in 2014 G.C. through reducing the ongoing transmission of the infection in the community among all population groups according to the WHO 2022 Guideline [73].

Children 6-years-old (16.3%, 69/424) and 7-years-old (24.7%, 99/401) were more infected than those 4-years-old (6.9%, 27/393). We observed that going along with others which is considered normal for older pre-SAC could have contributed to the higher risk of infection compared to younger children. We didn't see significant variation in the magnitude of the disease between males and females ($p = 0.16$). Based on the univariable and multilevel model, going along with others to water sources sometimes or all the time, and living within less than one-kilometer radius of water bodies also were significant determinants of the disease. The possible justification for these associations could be linked to the increased chance of frequent contact with the infested water body due to the proximity of the households to the infested water sources [22].

Adjusting for other covariates, 31.8% of the variability in the risk of the infection was accounted for by village membership. The justification for this finding might be variation in the proximity of the water sources, differential intensity of infection, and difference in the density of intermediate host (snail) among the study *kebeles* [22].

The observed CR (85.2%) and ERR (93.3%) in our study were within the acceptable range. ERR of $\geq 90\%$ is considered satisfactory according to the WHO guideline [49]. Based on ERR, these

results indicate that PZQ is effective against *S. mansoni* in pre-SAC. Treatment-related AEs were assessed within four hours of PZQ administration, as reported previously in other studies [109,110]. We detected decreased odds of cure with a higher baseline egg count. This finding agrees with the reports of several studies that shared similar findings [25,91,111]. This is related to the poor immature/juvenile stage killing ability of PZQ that contributed to the variation in cure among various infection intensity groups [91,112].

A significant association was detected between pre-treatment infection intensity and AEs. A study done in SAC in the same area [113] reported a similar finding. This association could be attributed to the release of chemicals from dying parasites in the presence of a high infection load [22].

A low level of knowledge (37.0%) was observed about schistosomiasis among caregivers. Previous studies from South Africa [36], Kenya [114], and elsewhere [10] also reported similar findings. This indicates the weaknesses in the health education structures and a lack of community members' experiences on the health and social effects of schistosomiasis among respondents. In our study, the level of favorable attitude (54.8%) was not in favor of the predetermined elimination target of the disease. The level of good practices (57.8%) was low which could favor the spread of the disease. The present finding is lower than the one reported from Uganda [83] which was 65.5% of parents/guardians had appropriate practices towards urogenital schistosomiasis among under-five children. Exclusion of caregivers of pre-SAC from schistosomiasis-related robust interventions such as MDA, WASH, health education, and vector control considering their young child safe from the infection might have accounted for the observed poor practice [82].

The present study revealed being in the poorest (25%), and poorer (45%) wealth categories reduced the odds of reporting good knowledge compared to the richest wealth category. The possible

reason for this association might be linked to the lower likelihood of having access to diverse information sources among members of the households in the lower wealth quantiles than those in higher wealth quantiles. Often higher wealth quantiles are taken as a proxy for improved health services and health message access [115].

The current study also revealed that younger age (23–29 years) had 1.18 times higher odds of reporting a favorable attitude relative to the older age group (≥ 40 years). The factor that has accounted for the observed higher odds of reporting a favorable attitude might be that younger people are more likely to recognize the importance of avoiding contact with lake water by considering the long-lasting health impacts of persistent infested water contact relative to older counterparts [92].

In the study region, not having formal education decreased the odds of reporting a favorable attitude by 20% relative to those in the higher education level. In Ethiopia, caregivers who lack formal education have a lesser chance of employment. Also, not having education may reduce the chance of involvement in formal health information dissemination channels and infrequent contact with health extension workers which might have accounted for the reported unfavorable attitude relative to those who have diverse information sources due to their higher education level [92].

The study has also revealed that being in the poorest wealth category had 58% lower odds of reporting a favorable attitude relative to the richest households. The justification for this association may be that the respondents with lower wealth quintiles had more attachment to lake water to obtain their living from compared to those with higher wealth quintiles [92].

Being unmarried had 43% lesser odds of reporting good practice compared to married caregivers in the study setting. The possible explanation for this finding is that reduced access to resources

among unmarried individuals may affect access to health information more than those who are married and may be involved in riskier health-related behaviors [116].

A 60% lesser odds of reporting good practice was observed among caregivers who did not receive any information about schistosomiasis from any source relative to health extension workers as a source of information in the current study. The gap in understanding a disease process and recommended prevention and control interventions related to low health literacy accounted for this finding as mentioned elsewhere [117].

S. mansoni with soil-transmitted helminths co-infected children had 4.1 times higher odds of developing stunting relative to those infected only with *S. mansoni*. This finding agrees with a finding of a Tanzanian study [118] that reported co-infected children had higher rates of stunting than children who were not co-infected. For this association, the effect of *S. mansoni* with STH co-infection could be responsible for the observed increased risk of nutritional deficit evident among pre-SAC who had co-infection compared to those infected only with *S. mansoni*. This finding could be linked to repeated exposure to chronic parasitic infections, and impaired immunologic response resulting from heavy-intensity infections [119].

While the mechanism underlying the linkage between *S. mansoni* with STH infection and stunting might not be straightforward, considering the complex nature of stunting the mechanism seems to work vice versa. Repeated chronic *S. mansoni* with STH co-infection may lead to stunting; stunting, in turn, may lead to immunosuppression, thereby decreasing resistance to disease and increasing susceptibility to parasitic infections and together accelerating childhood nutritional deficit.

S. mansoni infection also had an independent significant effect on anaemia in pre-SAC; those who had the disease were at 2.7 times the odds of having anaemia. This might be attributed to occult bleeding caused by *S. mansoni* infection-induced perforation of the intestine, impaired iron absorption resulting from inflammatory mechanisms, insufficient iron intake due to poor appetite, and micronutrient deficiencies [120] contributed to the increased odds of anaemia among pre-SAC infected with *S. mansoni* relative to not-infected counterparts.

5.2 Methodological discussion

5.2.1 Study design

This dissertation used two types of study design: a cross-sectional study (paper I, III, and IV) and a before-and-after study (paper II). A single arm before -and- after the study is less effective compared to a randomized controlled trial due to the lack of random assignment of study participants [121]. However, its limitation was minimized by implementing the study protocol appropriately to detect a causal association between the test drug and outcome.

5.2.2 Sampling

Sampling is the process of selecting several subjects from all the subjects in a particular group [122]. This is a practical option when one cannot select everybody from that group [123]. This dissertation used purposive sampling to select the study area and six *Kebeles* due to *S. mansoni* infection endemicity and closeness to Lake Hawassa. Then, three *kebeles* and study participants were selected using a simple random sampling technique for papers I, III, and IV within a strictly defined sampling frame generated through house-to-house enumeration to minimize the introduction of bias.

5.2.3 Validity

Validity of research refers to how the information collected accurately answers the research question [124]. In this dissertation, the emphasis is on internal validity, measurement validity, and external validity [123]. A study is not valid if it cannot provide accurate information, or cannot allow logical interpretations to be drawn from the population studied. Internal validity can be affected by selection bias, information bias, uncontrolled confounding, and a small study sample [124].

5.2.4 Selection bias

Selection bias is a systematic error in a study that results from deviations from the procedures used to select study participants and from factors that influence them [122]. It occurs when the association between exposure and health outcomes is different for those who participate and those who do not participate in the study [124]. Paper II which was the subset of paper I included all *S. mansoni*-positive participants, but the study Kebeles and study participants were recruited using a simple random sampling method to minimize the selection bias (paper I, III, and IV).

The simple random sampling method gives an equal non-zero chance for each of the participants within the list of participants to be selected, hence sampling bias for the cross-sectional study was less likely. In the before-and-after study, the study decreased the dropout rate by conducting active follow-ups through health extension workers and caregivers. Health extension workers actively monitored children who were involved in the intervention every day. After the study, a non-response of 1.7% from efficacy assessment and 2.5% from safety evaluation was observed. This might have introduced minimal loss to follow-up. However, selection bias might be minimized in this work mainly due to a clear definition of the study participants, setting clear inclusion and exclusion criteria, and random selection of the study participants.

5.2.5 Information bias

Information bias is a distortion in the outcome caused by incorrect information or measurements of important study variables. It can arise due to the wrong information collected about or from study participants. It could be observer bias, subject bias, or instrument bias [124]. All four papers in this dissertation are susceptible to information bias in one way or another.

It is difficult to avoid information bias, but could be minimized by developing and following well-designed protocols. To minimize information bias, all data collectors in the research studies received training in the tools, including informed consent forms, measurements, and questionnaires. Following training, a community pretest was conducted, and the tools were revised before the initiation of the actual study. Recall bias may happen in the findings of studies of all four papers. In all the papers, age was one of the variables with a high chance of recall bias. To reduce the magnitude of recall bias related to age the mothers (immediate caregivers) were asked about the last birth date of the child to minimize the bias as it was difficult to access the immunization cards, vital event records, and birth certificates to validate the information.

This dissertation is also prone to instrumentation bias resulting from changes to the ways that an instrument functions across conditions (e.g., from pre-test to post-test). To minimize this bias, adequate training was given to measuring anthropometry for the data collectors, and the instruments were checked every morning before starting data collection using a standard weight and height. The average of two measurements was taken to reduce intra-observer bias, and close follow-up was done during the anthropometry measurements. In papers, I, II, and IV, stool examination was done by two laboratory technicians, each of whom had experience with *S. mansoni* detection using the Kato-Katz technique. The same laboratory technicians did baseline and endline investigations.

5.2.6. Confounding

Confounding is the distortion of the association between an exposure and health outcome by an extraneous, third variable called a confounder [123]. Confounding should be identified to avoid systematic errors in the interpretation of results. It can be controlled in two phases: the design phase and the analysis. In the design phase, it can be controlled by randomization, restriction, and matching [124]. This study didn't use restriction, matching, and randomization. The study controlled the bias in the analysis phase using multivariable multilevel logistic regression (paper I) and multivariable logistic regression with the cluster-robust variance estimation method (papers III and IV). Uncontrolled confounding affects the association between an exposure and an outcome. So, it may underestimate or overestimate or nullify the association. However, it does not affect the outcome variable of interest (paper IV).

5.2.7 Random error

A random error is the error that remains after a systematic error is eliminated. It can arise from the sampling variability of a study when an inference about the entire population is based on a sample of the population. Chance cannot be avoided without including the whole population, but increasing the sample size can minimize it [125]. It can also be estimated by performing appropriate statistical tests using p-values and confidence intervals [124]. A p-value indicates incompatibility between a particular set of data and a proposed statistical model for the data [126]. If the p-value is low (e.g. <0.05), it is unlikely that the observed results are caused by chance alone. If it is high, it is more likely that the results are due to chance. Further, the confidence interval provides a range of values in which the true estimated effect is likely to lie, with a certain degree of assurance. The confidence interval is more informative than the p-value because it provides a range of magnitude of the effect and variability in the estimate due to sample size [124]. In this

dissertation, we evaluated the role of chance using appropriate statistical models by applying both p-values (<0.05) and 95% confidence intervals.

5.2.8 External validity

External validity depends on adequate internal validity. It refers to whether or not a research finding can be generalized to a population not in the study or outside the study area [124]. purposive sampling technique was used to select the study area related to its unique feature (endemicity of *S. mansoni* infection).

However, the study used a representative sample using a simple random sampling technique at a community level. Hence, the result of all papers I -IV could be generalized to rural areas of Ethiopia with a similar context as the present study area, and in a similar setting in other low-income countries.

6. Implications for policy

NTDs affect the human development index's (HDI) key components, such as living standards, quality education and years of schooling, and years of life lived with good health in resource-limited countries including Ethiopia [3]. The current study may provide useful insight into the magnitude, determinants, and effect of *S. mansoni* infection together with the efficacy and safety of single-dose 40 mg/kg PZQ with variation in cure rate and egg reduction rates against light, moderate, and heavy intensity infection among pre-SAC. WHO recommends the inclusion of pre-SAC in control and elimination programs of schistosomiasis at 2 years of age using the available dosage of the drug based on the efficacy and safety profile of the SAC population [73].

However, in endemic communities in Ethiopia, this population group is excluded from control and elimination intervention strategies against schistosomiasis. Thus, the present research makes

substantial contributions to knowledge, policy, practice, and future research by broadening the scope of only SAC-focused PC intervention towards extensive commitments to the inclusion of the overlooked at-risk populations to tackle schistosomiasis.

The present evidence may also contribute to alleviating inequity propagated by the socioeconomic and other determinants for the formulation of equitable and inclusive policies for underestimated population segments exposed to *S. mansoni* infection in endemic communities.

7. Conclusions and Recommendations

7.1 Conclusion

A moderate (14.3%) prevalence of *S. mansoni* was detected in pre-SAC in the study setting. Increasing age increased the risk of the disease; the highest risk was observed in 6-year-old and 7-year-old children. PZQ at 40 mg/kg is effective in curing light-to-moderate infection intensities and reducing morbidity in heavy infections among *S. mansoni*-infected pre-SAC. Only 29.4% of cases with baseline heavy intensity infection category showed complete parasitological cure at day 28 post praziquantel treatment. AEs associated with PZQ treatment are tolerable and mostly mild-to-moderate and transient resolving within a week after praziquantel treatment. The low level of knowledge, unfavorable attitude, and poor practices observed among caregivers indicate the presence of critical gaps in integrated strategies to interrupt the transmission of the disease. Stunting was a major public concern among pre-SAC followed by anaemia with a prevalence of 28.0%. *S. mansoni* with STH co-infection increased the odds of stunting whereas *S. mansoni* had an independent significant association with anaemia among infected pre-SAC relative to those not infected.

7.2 Recommendations

7.2.1 Operational recommendations

- ✚ Preventive chemotherapy using praziquantel should involve pre-SAC in schistosomiasis-endemic communities
- ✚ Pre-SAC (and other caregivers) presenting with acute febrile illness or chronic morbidities need to be properly assessed for schistosomiasis
- ✚ Pre-SAC (and other caregivers) presenting with advanced morbidities should be referred to higher health facilities with appropriate diagnostic and treatment services
- ✚ Mothers/caregivers of pre-SAC presenting to the health facilities in endemic areas should be provided health education about the disease
- ✚ Pre-SAC in schistosomiasis prevalent communities should benefit from nutritional and anaemia screening to reduce the long-term effects linked to these health problems
- ✚ The national and regional Neglected Tropical Diseases (NTDs) control program should strengthen the interventions aimed at breaking the transmission of the disease and contribute to the achievement of sustainable development goals
- ✚ The Ministry of Health should enforce and oversee the inclusion of pre-SAC in control and elimination strategies and conduct an impact assessment per the recommendation of WHO to evaluate the success of the intervention

7.2.2 Policy Recommendation

- ✚ Equitable policies and strategies need to be established to ensure the inclusion of pre-SAC in control and elimination interventions at national and regional levels.

7.2.3 Recommendations for Further Study

- ✚ Studies that assess community-level determinants that account for the village-level variability of the disease in pre-SAC are worth undertaking.
- ✚ Studies that investigate praziquantel dose study among pre-SAC need to be considered.
- ✚ In future studies, other alternative treatment strategies, such as drug combinations targeting the different developmental stages of the parasite need to be considered in pre-SAC.
- ✚ Longitudinal studies need to be conducted to determine the temporal relationship between *S. mansoni* infection and undernutrition or anaemia among pre-SAC in endemic communities.

8. References

1. World Health Organization. 2023. Neglected tropical diseases (NTDs). See <https://www.who.int/health-topics/neglected-tropical-diseases> (accessed 18 July 2023).
2. Jukes MC, Nokes CA, Alcock KJ, Lambo JK, Kihamia C, Ngorosho N, *et al.* Heavy schistosomiasis associated with poor short-term memory and slower reaction times in Tanzanian schoolchildren. *Tropical medicine & international health: TM & IH.* 2002;7(2):104-17.
3. Hotez PJ, Herricks JR. Helminth elimination in the pursuit of sustainable development goals: a “worm index” for human development. *PLoS neglected tropical diseases.* 2015;9(4):e0003618.
4. Adeniran AA, Mogaji HO, Aladesida AA, Olayiwola IO, Oluwole AS, Abe EM, *et al.* Schistosomiasis, intestinal helminthiasis and nutritional status among preschool-aged

-
- children in sub-urban communities of Abeokuta, Southwest, Nigeria. *BMC Res Notes*. 2017;10: 637. doi:10.1186/s13104-017-2973-2.
5. Redekop WK, Lenk EJ, Luyendijk M, Fitzpatrick C, Niessen L, Stolk WA, *et al*. The Socioeconomic Benefit to Individuals of Achieving the 2020 Targets for Five Preventive Chemotherapy Neglected Tropical Diseases. *PLoS Negl Trop Dis*. 2017;11: e0005289. doi:10.1371/journal.pntd.0005289.
 6. Deribew A, Kebede B, Tessema G, Adama Y, Misganaw A, Gebre T, *et al*. Mortality and Disability-Adjusted Life-Years (Dalys) for Common Neglected Tropical Diseases in Ethiopia, 1990-2015: Evidence from the Global Burden of Disease Study 2015. 2017; 15.
 7. World Health Organization. Schistosomiasis Fact Sheet [online]. Available: <http://www.who.int/mediacentre/factsheets/fs115/en/index.html>. Accessed 13/2/2020.
 8. Adenowo AF, Oyinloye BE, Ogunyinka BI, Kappo AP. Impact of human schistosomiasis in sub-Saharan Africa. *The Brazilian Journal of Infectious Diseases*. 2015;19: 196–205. doi:10.1016/j.bjid.2014.11.004.
 9. McManus DP, Dunne DW, Sacko M, Utzinger J, Vennervald BJ, Zhou X-N. Schistosomiasis. *Nat Rev Dis Primers*. 2018;4: 13. doi:10.1038/s41572-018-0013-8.
 10. Faust CL, Osakunor DNM, Downs JA, Kayuni S, Stothard JR, Lamberton PHL, *et al*. Schistosomiasis Control: Leave No Age Group Behind. *Trends in Parasitology*. 2020;36: 582–591. doi:10.1016/j.pt.2020.04.012.

11. Mazigo HD. Participatory integrated control strategies and elimination of schistosomiasis in sub-Saharan Africa. *The Lancet Global Health*. 2019;7: e998–e999. doi:10.1016/S2214-109X(19)30271-2.
12. Maier T, Wheeler NJ, Namigai EKO, Tycko J, Grewelle RE, Woldeamanuel Y, *et al*. Gene drives for schistosomiasis transmission control. *PLoS neglected tropical diseases*. 2019;13(12):e0007833.
13. Hotez PJ, Kamath A. Neglected tropical diseases in sub-saharan Africa: review of their prevalence, distribution, and disease burden. *PLoS neglected tropical diseases*. 2009;3(8):e412.
14. Hotez PJ, Alvarado M, Basanez MG, Bolliger I, Bourne R, Boussinesq M, *et al*. The global burden of disease study 2010: interpretation and implications for the neglected tropical diseases. *PLoS neglected tropical diseases*. 2014;8(7):e2865.
15. Amal Mitra, Anthony Mawson. Neglected Tropical Diseases: Epidemiology and Global Burden. *TropicalMed*. 2017;2: 36. doi:10.3390/tropicalmed2030036.
16. Trienekens SCM, Faust CL, Meginnis K, Pickering L, Ericsson O, Nankasi A, *et al*. Impacts of host gender on *Schistosoma mansoni* risk in rural Uganda—A mixed-methods approach. *PLoS Negl Trop Dis*. 2020;14: e0008266. doi:10.1371/journal.pntd.0008266.
17. Frigerio S, Macario M, Iacovone G, Dussey-Comlavi KJ, Narcisi P, Ndiaye AT, *et al*. *Schistosoma haematobium* infection, health and nutritional status in school-age children in a rural setting in Northern Senegal. *Minerva pediatrica*. 2016;68(4):282-7.

18. Mnkugwe RH, Minzi OS, Kinung'hi SM, Kamuhabwa AA, Aklillu E. Prevalence and correlates of intestinal schistosomiasis infection among school-aged children in North-Western Tanzania. *PLoS ONE*. 2020;15: e0228770. doi:10.1371/journal.pone.0228770.
19. Kemal M, Tadesse G, Esmael A, Abay SM, Kebede T. Schistosoma mansoni infection among preschool age children attending Erer Health Center, Ethiopia and the response rate to praziquantel. *BMC Res Notes*. 2019;12: 211. doi:10.1186/s13104-019-4246-8.
20. Mazigo HD, Nuwaha F, Kinung'hi SM, Morona D, Pinot de Moira A, Wilson S, *et al*. Epidemiology and control of human schistosomiasis in Tanzania. *Parasites & vectors*. 2012;5:274.
21. Federal Democratic Republic of Ethiopia Ministry of Health. National Master Plan for Neglected Tropical Diseases (NTDs) 2013-2015. Available online: http://ec2-18-210-136-214.compute-1.amazonaws.com/sites/default/files/docs/national_ntd_master_plan_ethiopia_2013-2015 (accessed on 4 April 2023).
22. Gebreyesus TD, Tadele T, Mekete K, Barry A, Gashaw H, Degefe W, *et al*. Prevalence, Intensity, and Correlates of Schistosomiasis and Soil-Transmitted Helminth Infections after Five Rounds of Preventive Chemotherapy among School Children in Southern Ethiopia. *Pathogens*. 2020;9: 920. doi:10.3390/pathogens9110920.
23. Bisetegn H, Eshetu T, Erkihun Y. Prevalence of Schistosoma mansoni infection among children in Ethiopia: a systematic review and meta-analysis. *Trop Dis Travel Med Vaccines*. 2021;7: 30. doi:10.1186/s40794-021-00156-0.

-
24. Chisha Y, Zerdo Z, Asnakew M, Churko C, Yihune M, Teshome A, *et al.* Praziquantel treatment coverage among school age children against Schistosomiasis and associated factors in Ethiopia: a cross-sectional survey, 2019. *BMC Infect Dis.* 2020;20: 872. doi:10.1186/s12879-020-05519-0.
 25. Gebreyesus TD, Makonnen E, Tadele T, Mekete K, Gashaw H, Gerba H, *et al.* Efficacy and safety of praziquantel preventive chemotherapy in *Schistosoma mansoni* infected school children in Southern Ethiopia: A prospective cohort study. *Front Pharmacol.* 2023;14: 968106. doi:10.3389/fphar.2023.968106.
 26. World Health Organization. Assessing the Efficacy of Anthelmintic Drugs against Schistosomiasis and Soil- Transmitted Helminthiases; World Health Organization: Geneva, Switzerland, 2013. Available online: <https://apps.who.int/iris/handle/10665/79019> (accessed on 6 November 2019).
 27. Osakunor DNM, Woolhouse MEJ, Mutapi F. Paediatric schistosomiasis: What we know and what we need to know. *PLoS Negl Trop Dis.* 2018;12: e0006144. doi:10.1371/journal.pntd.0006144.
 28. Ekpo UF, Oluwole AS, Abe EM, Etta HE, Olamiju F, Mafiana CF. Schistosomiasis in infants and pre-school-aged children in sub-Saharan Africa: implication for control. *Parasitology.* 2012;139: 835–841. doi:10.1017/S0031182012000029.
 29. Sousa-Figueiredo JC, Pleasant J, Day M, Betson M, Rollinson D, Montresor A, *et al.* Treatment of intestinal schistosomiasis in Ugandan preschool children: best diagnosis,

-
- treatment efficacy and side-effects, and an extended praziquantel dosing pole. *International Health*. 2010;2: 103–113. doi:10.1016/j.inhe.2010.02.003.
30. Araujo Navas AL, Hamm NAS, Soares Magalhães RJ, Stein A. Mapping Soil Transmitted Helminths and Schistosomiasis under Uncertainty: A Systematic Review and Critical Appraisal of Evidence. Akogun OB, editor. *PLoS Negl Trop Dis*. 2016;10: e0005208. doi:10.1371/journal.pntd.0005208.
31. Alemu A, Tegegne Y, Damte D, Melku M. *Schistosoma mansoni* and soil-transmitted helminths among preschool-aged children in Chuahit, Dembia district, Northwest Ethiopia: prevalence, intensity of infection and associated risk factors. *BMC Public Health*. 2016;16: 422. doi:10.1186/s12889-016-2864-9.
32. Nyantekyi L, Legesse M, Belay M, Tadesse K, Manaye K, Macias C, *et al*. Intestinal parasitic infections among under-five children and maternal awareness about the infections in Shesha Kekele, Wondo Genet, Southern Ethiopia. *Ethiopian Journal of Health Development*. 2011;24. doi:10.4314/ejhd.v24i3.68383.
33. Poole H, Terlouw DJ, Naunje A, Mzembe K, Stanton M, Betson M, *et al*. Schistosomiasis in pre-school-age children and their mothers in Chikhwawa district, Malawi with notes on characterization of schistosomes and snails. *Parasit Vectors*. 2014;7: 153. doi:10.1186/1756-3305-7-153.
34. Stothard JR, Sousa-Figueiredo JC, Betson M, Bustinduy A, Reinhard-Rupp J. Schistosomiasis in African infants and preschool children: let them now be treated! *Trends in Parasitology*. 2013;29: 197–205. doi:10.1016/j.pt.2013.02.001.

35. Ruganuza DM, Mazigo HD, Waihenya R, Morona D, Mkoji GM. *Schistosoma mansoni* among pre-school children in Musozi village, Ukerewe Island, North-Western-Tanzania: prevalence and associated risk factors. *Parasites Vectors*. 2015;8: 377. doi:10.1186/s13071-015-0997-9.
36. Sacolo-Gwebu H, Kabuyaya M, Chimbari M. Knowledge, attitudes and practices on schistosomiasis and soil-transmitted helminths among caregivers in Ingwavuma area in uMkhanyakude district, South Africa. *BMC Infect Dis*. 2019;19: 734. doi:10.1186/s12879-019-4253-3.
37. Angora EK, Boissier J, Menan H, Rey O, Tuo K, Touré AO, *et al*. Prevalence and Risk Factors for Schistosomiasis among Schoolchildren in two Settings of Côte d’Ivoire. *TropicalMed*. 2019;4: 110. doi:10.3390/tropicalmed4030110.
38. Wubet K, Damtie D. Prevalence of *Schistosoma mansoni* Infection and Associated Risk Factors among School Children in Jiga Town, Northwest-Ethiopia: A Cross-Sectional Study. *Journal of Parasitology Research*. 2020;2020: 1–7. doi:10.1155/2020/6903912.
39. Nelwan ML. Schistosomiasis: Life Cycle, Diagnosis, and Control. Current therapeutic research, clinical and experimental. 2019;91:5-9.
40. Inobaya MT, Olveda RM, Chau TN, Olveda DU, Ross AG. Prevention and control of schistosomiasis: a current perspective. *Research and reports in tropical medicine*. 2014;2014(5):65-75.
41. Abe EM, Guan W, Guo YH, Kassegne K, Qin ZQ, Xu J, Chen JH, Ekpo UF, Li SZ, Zhou XN. Differentiating snail intermediate hosts of *Schistosoma* spp. using molecular

-
- approaches: fundamental to successful integrated control mechanism in Africa. *Infect Dis Poverty*. 2018 Mar 26;7(1):29. doi: 10.1186/s40249-018-0401-z.
42. Colley DG, Secor WE. Immunology of human schistosomiasis. *Parasite immunology*. 2014;36(8):347-57.
 43. Kolarova L, Horak P, Skirnisson K, Mareckova H, Doenhoff M. Cercarial dermatitis, a neglected allergic disease. *Clinical reviews in allergy & immunology*. 2013;45(1):63-74.
 44. Ross AG, Vickers D, Olds GR, Shah SM, McManus DP. Katayama syndrome. *Lancet Infect Dis*. 2007;7(3):218-24.
 45. Weerakoon KG, Gobert GN, Cai P, McManus DP. Advances in the Diagnosis of Human Schistosomiasis. *Clinical microbiology reviews*. 2015;28(4):939-67.
 46. Bergquist R, Gray DJ. Schistosomiasis Elimination: Beginning of the End or a Continued March on a Trodden Path. *Tropical medicine and infectious disease*. 2019;4(2).
 47. Fuss A, Mazigo HD, Tappe D, Kasang C, Mueller A. Comparison of sensitivity and specificity of three diagnostic tests to detect *Schistosoma mansoni* infections in school children in Mwanza region, Tanzania. *PloS one*. 2018;13(8):e0202499.
 48. Turner HC, Bettis AA, Dunn JC, Whitton JM, Hollingsworth TD, Fleming FM, *et al*. Economic Considerations for Moving beyond the Kato-Katz Technique for Diagnosing Intestinal Parasites As We Move Towards Elimination. *Trends in parasitology*. 2017;33(6):435-43.

-
49. World Health Organization, Geneva (2013). Schistosomiasis: progress report 2001 - 2011, strategic plan 2012 - 2020. Available at <https://www.who.int/schistosomiasis/resources/9789241503174/en/>. Accessed 6/11/2019.
 50. Ajibola O, Gulumbe BH, Eze AA, Obishakin E. Tools for Detection of Schistosomiasis in Resource Limited Settings. *Medical sciences (Basel, Switzerland)*. 2018;6(2).
 51. Weerakoon KG, McManus DP. Cell-Free DNA as a Diagnostic Tool for Human Parasitic Infections. *Trends in parasitology*. 2016;32(5):378-91.
 52. Tchuem Tchuente LA, Rollinson D, Stothard JR, Molyneux D. Moving from control to elimination of schistosomiasis in sub-Saharan Africa: time to change and adapt strategies. *Infectious diseases of poverty*. 2017;6(1):42.
 53. WHO. Ending the neglect to attain the Sustainable Development Goals: a road map for neglected tropical diseases 2021–2030. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO. 2020.
 54. FMOH. Federal Democratic Republic of Ethiopia Ministry of Health. The Third National Neglected Tropical Diseases Strategic Plan 2021-2025. Addis Ababa, Ethiopia: 2021. Available online: <https://www.acteast.org/news/ethiopia-launches-third-national-ntd-strategic-plan-and-sustainability-plan-for-neglected> (accessed on 16 June 2019).
 55. Sacolo H, Chimbari M, Kalinda C. Knowledge, attitudes and practices on Schistosomiasis in sub-Saharan Africa: a systematic review. *BMC Infect Dis*. 2018;18: 46. doi:10.1186/s12879-017-2923-6.

-
56. Midzi N, Zinyowera SM. Impact of School Based Health Education on Knowledge, Attitude and Practice of Grade Three Primary School Children in Zimbabwe. *J Community Med Health Educ.* 2014;04. doi:10.4172/2161-0711.1000295.
 57. Ross A, Inobaya M, Olveda R, Chau T, Olveda D. Prevention and control of schistosomiasis: a current perspective. *RRTM.* 2014; 65. doi:10.2147/RRTM.S44274.
 58. World Health Organization, Geneva (2015). Investing to overcome the global impact of Neglected Tropical Diseases, Third WHO report on Neglected Tropical Diseases. Available at https://apps.who.int/iris/bitstream/handle/10665/152781/9789241564861_eng.pdf?sequence=1. Accessed on 6/11/2019.
 59. Fenwick A, Webster JP, Bosque-Oliva E, Blair L, Fleming FM, Zhang Y, *et al.* The Schistosomiasis Control Initiative (SCI): rationale, development and implementation from 2002-2008. *Parasitology.* 2009;136(13):1719-30.
 60. Sokolow SH, Wood CL, Jones IJ, Swartz SJ, Lopez M, Hsieh MH, *et al.* Global Assessment of Schistosomiasis Control Over the Past Century Shows Targeting the Snail Intermediate Host Works Best. *PLoS Negl Trop Dis.* 2016;10(7):e0004794.
 61. Tesfie A, Getnet G, Abere A, Yihenew G, Belete Y, Kassa M, *et al.* Praziquantel is an effective drug for the treatment of *Schistosoma Mansoni* infection among school-aged children in Northwest Ethiopia. *Tropical medicine and health.* 2020;48(1):28.
 62. Coulibaly JT, Panic G, Yapi RB, Kovač J, Barda B, N'Gbesso YK, *et al.* Efficacy and safety of ascending doses of praziquantel against *Schistosoma haematobium* infection in

-
- preschool-aged and school-aged children: a single-blind randomised controlled trial. *BMC Med.* 2018;16: 81. doi:10.1186/s12916-018-1066-y.
63. Montresor A, Garba A. Treatment of preschool children for schistosomiasis. *Lancet Glob Health.* 2017;5(7):e640-e1. doi:10.1016/S2214-109X(17)30202-4.
64. Olliaro PL, Coulibaly JT, Garba A, Halleux C, Keiser J, King CH, *et al.* Efficacy and safety of single-dose 40 mg/kg oral praziquantel in the treatment of schistosomiasis in preschool-age versus school-age children: An individual participant data meta-analysis. *PLoS Negl Trop Dis.* 2020;14: e0008277. doi:10.1371/journal.pntd.0008277.
65. Mwinzi PMN, Odhiambo K, Montgomery SP, Karanja DMS, Secor WE, Muok EM, *et al.* Mechanism of Anemia in *Schistosoma mansoni*-Infected School Children in Western Kenya. *The American Journal of Tropical Medicine and Hygiene.* 2012;87: 862–867. doi:10.4269/ajtmh.2012.12-0248.
66. Amin MA, Swar M, Kardaman M, Elhussein D, Nouman G, Mahmoud A, *et al.* Treatment of pre-school children under 6 years of age for schistosomiasis: safety, efficacy and acceptability of praziquantel. 2012;7: 11.
67. USAID report of Access to safe water and basic sanitation. <https://www.acteast.org/news/ethiopia-launches-third-national-ntd-strategic-plan-and-sustainability-plan-for-neglected> (accessed on 16 June 2019).
68. Federal Ministry of Health Ethiopia WASH-NTDs coordination Framework for control and elimination of NTDs. Available online:

-
- <http://repository.iifphc.org/bitstream/handle/123456789/531/WASH-NTD>(accessed on 6 November 2021).
69. Feng J, Wang X, Zhang X, Hu H, Xue J, Cao C, *et al.* Effect of Health Education on Schistosomiasis Control Knowledge, Attitude, and Practice after Schistosomiasis Blocking: Results of a Longitudinal Observational Study in the Field. *TropicalMed.* 2023;8: 267. doi:10.3390/tropicalmed8050267.
 70. Spencer SA, Andriamasy EH, Linder C, Penney JMStJ, Henstridge-Blows J, Russell HJ, *et al.* Impact of a Novel, Low-Cost and Sustainable Health Education Program on the Knowledge, Attitudes, and Practices Related to Intestinal Schistosomiasis in School Children in a Hard-to-Reach District of Madagascar. *The American Journal of Tropical Medicine and Hygiene.* 2022;106: 685–694. doi:10.4269/ajtmh.21-0220.
 71. McManus DP, Dunne DW, Sacko M, Utzinger J, Vennervald BJ, Zhou X-N. Schistosomiasis. *Nature Reviews Disease Primers.* 2018;4(1):13.
 72. Meleko A, Li S, Turgeman DB, Bruck M, Kesete NZ, Zaadnoordijk W, *et al.* Schistosomiasis Control in Ethiopia: The Role of Snail Mapping in Endemic Communities. *TropicalMed.* 2022;7: 272. doi:10.3390/tropicalmed7100272.
 73. WHO. WHO guideline on control and elimination of human schistosomiasis. Geneva: World Health Organization; 2022. Available: <https://www.who.int/publications-detail-redirect/9789240041608>.
 74. Martin S, Rassi C, Antonio V, Graham K, Leitão J, King R, *et al.* Evaluating the feasibility and acceptability of a community dialogue intervention in the prevention and control of

-
- schistosomiasis in Nampula province, Mozambique. *PLoS ONE*. 2021;16: e0255647. doi:10.1371/journal.pone.0255647.
75. Anyolitho MK, Poels K, Huyse T, Tumusiime J, Mugabi F, Tolo CU, *et al*. Knowledge, attitudes, and practices regarding schistosomiasis infection and prevention: A mixed-methods study among endemic communities of western Uganda. *PLoS Negl Trop Dis*. 2022;16: e0010190. doi:10.1371/journal.pntd.0010190.
76. Bosompem KM, Bentum IA, Otchere J, Anyan WK, Brown CA, Osada Y, *et al*. Infant schistosomiasis in Ghana: a survey in an irrigation community. *Trop Med Int Health*. 2004;9: 917–922. doi:10.1111/j.1365-3156.2004.01282.x.
77. Tadele T, Astatkie A, Abay SM, Tadesse BT, Makonnen E, Aklillu E. Prevalence and Determinants of *Schistosoma mansoni* Infection among Pre-School Age Children in Southern Ethiopia. 2023.
78. Mduluzza T, Mutapi F. Putting the treatment of paediatric schistosomiasis into context. *Infect Dis Poverty*. 2017;6: 85. doi:10.1186/s40249-017-0300-8.
79. Macharia JW, Ng'ang'a ZW, Njenga SM. Factors influencing community participation in control and related operational research for urogenital schistosomiasis and soil-transmitted helminths in rural villages of Kwale County, coastal Kenya. *Pan Afr Med J*. 2016;24. doi:10.11604/pamj.2016.24.136.7878.
80. Colley DG, Fleming FM, Matendechero SH, Knopp S, Rollinson D, Utzinger J, *et al*. Contributions of the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) to Schistosomiasis Control and Elimination: Key Findings and Messages for

-
- Future Goals, Thresholds, and Operational Research. *The American Journal of Tropical Medicine and Hygiene*. 2020;103: 125–134. doi:10.4269/ajtmh.19-0787.
81. Mbereko A, Chimbari MJ, Manyangadze T, Mukaratirwa S. Knowledge and perceptions of schistosomiasis, a water-borne disease, in two semi-arid rural areas of South Africa (Ndumo) and Zimbabwe (Ntalale). *Food and Waterborne Parasitology*. 2020;21: e00091. doi:10.1016/j.fawpar.2020.e00091.
82. Mutsaka-Makuvaza MJ, Matsena-Zingoni Z, Tshuma C, Katsidzira A, Webster B, Zhou X-N, *et al*. Knowledge, perceptions and practices regarding schistosomiasis among women living in a highly endemic rural district in Zimbabwe: implications on infections among preschool-aged children. *Parasites Vectors*. 2019;12: 458. doi:10.1186/s13071-019-3668-4.
83. Kibira SPS, Ssempebwa JC, Ssenyonga R, Radloff S, Makumbi FE. Schistosomiasis infection in pre-school aged children in Uganda: a qualitative descriptive study to identify routes of exposure. *BMC Infect Dis*. 2019;19: 165. doi:10.1186/s12879-019-3803-z.
84. Ekpo UF, *et al*. Urinary schistosomiasis among preschool children in a rural community near Abeokuta, Nigeria. *Parasit Vectors*. 2010;3:58. doi: 10.1186/1756-3305-3-58.
85. Dawaki S, Al-Mekhlafi HM, Ithoi I, Ibrahim J, Abdulsalam AM, Ahmed A, *et al*. PREVALENCE AND RISK FACTORS OF SCHISTOSOMIASIS AMONG HAUSA COMMUNITIES IN KANO STATE, NIGERIA. *Rev Inst Med trop S Paulo*. 2016;58. doi:10.1590/S1678-9946201658054.

-
86. Mwai J, Njenga S, Barasa M. Knowledge, attitude and practices in relation to prevention and control of schistosomiasis infection in Mwea Kirinyaga county, Kenya. *BMC Public Health*. 2016;16: 819. doi:10.1186/s12889-016-3494-y.
 87. Wilson S, Vennervald BJ, Dunne DW. Chronic Hepatosplenomegaly in African School Children: A Common but Neglected Morbidity Associated with Schistosomiasis and Malaria. *PLoS Negl Trop Dis*. 2011;5: e1149. doi:10.1371/journal.pntd.0001149.
 88. Verani, J.R.; Butler, S.E.; Montgomery, S.P.; Karanja, D.M.S.; Mwinzi, P.N.M.; Shane, H.L.; Abudho, B.; Secor, W.E. Schistosomiasis among Young Children in Usoma, Kenya. *Am. J. Trop. Med. Hyg.* 2011, 84, 787–791.
 89. Coulibaly JT, N’Gbesso YK, Knopp S, Keiser J, N’Goran EK, Utzinger J. Efficacy and Safety of Praziquantel in Preschool-Aged Children in an Area Co-Endemic for *Schistosoma mansoni* and *S. haematobium*. *PLoS Negl Trop Dis*. 2012;6: e1917. doi:10.1371/journal.pntd.0001917.
 90. Rujeni N, Morona D, Ruberanziza E, Mazigo HD. Schistosomiasis and soil-transmitted helminthiasis in Rwanda: an update on their epidemiology and control. *Infect Dis Poverty*. 2017;6: 8. doi:10.1186/s40249-016-0212-z.
 91. Mnkugwe RH, Minzi O, Kinung’hi S, Kamuhabwa A, Aklillu E. Efficacy and safety of praziquantel and dihydroartemisinin piperaquine combination for treatment and control of intestinal schistosomiasis: A randomized, non-inferiority clinical trial. *PLoS Negl Trop Dis*. 2020;14(9):e0008619. doi:10.1371/journal.pntd.0008619.

-
92. Sady H, Al-Mekhlafi HM, Atroosh WM, Al-Delaimy AK, Nasr NA, Dawaki S, *et al.* Knowledge, attitude, and practices towards schistosomiasis among rural population in Yemen. *Parasites Vectors*. 2015;8: 436. doi:10.1186/s13071-015-1050-8.
 93. Munisi DZ, Buza J, Mpolya EA, Kinung'hi SM. *Schistosoma mansoni* Infections, Undernutrition and Anaemia among Primary Schoolchildren in Two Onshore Villages in Rorya District, North-Western Tanzania. *PLoS ONE*. 2016;11: e0167122. doi:10.1371/journal.pone.0167122.
 94. Al-Haidari SA, Mahdy MAK, Al-Mekhlafi AM, Al Murisi WMS, Thabit AAQ, Al-Amad MA, *et al.* Intestinal schistosomiasis among schoolchildren in Sana'a Governorate, Yemen: Prevalence, associated factors and its effect on nutritional status and anemia. *PLoS Negl Trop Dis*. 2021;15: e0009757. doi:10.1371/journal.pntd.0009757.
 95. WHO. Prevention and control of schistosomiasis and soil-transmitted helminthiasis: report of a WHO expert committee. Technical Report Series. Geneva: World Health Organization; 2002. Report No.: 912.
 96. Measure distance between points-Android-Google Maps help. Available online: <https://support.google.com/maps/answer/1628031?hl=en&co=GENIE.Platform%3DAndroid> (Accessed June 2019).
 97. Howe LD, Hargreaves JR, Huttly SR. Issues in the construction of wealth indices for the measurement of socio-economic position in low-income countries. *Emerg Themes Epidemiol*. 2008;5: 3. doi:10.1186/1742-7622-5-.3

-
98. Common Terminology Criteria for Adverse Events (CTCAE). 2017; 155. Available online. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7 (Accessed July 2019).
 99. Ul Haq N, Hassali MA, Shafie AA, Saleem F, Farooqui M, Aljadhey H. A cross sectional assessment of knowledge, attitude and practice towards Hepatitis B among healthy population of Quetta, Pakistan. *BMC Public Health*. 2012;12: 692. doi:10.1186/1471-2458-12-692.
 100. World Health Organization, Geneva (2009). WHO Anthroplus Software; Software for assessing Growth and Development of the World's Children and Adolescents. Available at https://www.who.int/growthref/tools/who_anthroplus_manual.pdf. Accessed on 6/11/2019.
 101. World Health Organization, . WHO Anthro Software; Software for assessing Growth and Development of the World's Children aged below five years
 102. World Health Organization, Geneva (2011). Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Available at <https://www.who.int/vmnis/indicators/haemoglobin/en/>. Accessed on 6/11/2019.
 103. Katz N, Chaves A, Pellegrino J. A simple device for quantitative stool thick-smear technique in Schistosomiasis mansoni. *Revista do Instituto de Medicina Tropical de Sao Paulo*. 1972;14(6):397-400. Epub 1972/11/01. PubMed PMID: 4675644.
 104. The Royal children's. Growth_measuring_over2 2013. Available Online:https://www.rch.org.au/uploadedFiles/Main/Content/childgrowth/Growth_measuring_over2. (accessed on 6 December 2022).

-
105. Nkrumah B, Nguah SB, Sarpong N, Dekker D, Idriss A, May J, *et al.* Hemoglobin estimation by the HemoCue® portable hemoglobin photometer in a resource poor setting. *BMC Clin Pathol.* 2011;11: 5. doi:10.1186/1472-6890-11-5.
 106. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. *Source Code Biol Med.* 2008;3: 17. doi:10.1186/1751-0473-3-17.
 107. Heeringa SG. *Applied survey data analysis* . Boca Raton Fl. Chapman & Hall 2010.
 108. Rabe-Hesketh a hand book of statistical analysis using Stata. Boca Roten. London, New York , Washington 2004.
 109. Ajanga A, Lwambo NJ, Blair L, Nyandindi U, Fenwick A, Brooker S. *Schistosoma mansoni* in pregnancy and associations with anaemia in northwest Tanzania. *Transactions of the Royal Society of Tropical Medicine and Hygiene.* 2006;100(1):59-63.
 110. Erko B, Degarege A, Tadesse K, Mathiwos A, Legesse M. Efficacy and side effects of praziquantel in the treatment of *Schistosomiasis mansoni* in schoolchildren in Shesha Kekele Elementary School, Wondo Genet, Southern Ethiopia. *Asian Pacific Journal of Tropical Biomedicine.* 2012;2: 235–239. doi:10.1016/S2221-1691(12)60049-5.
 111. Mnkugwe RH, Minzi OS, Kinung’hi SM, Kamuhabwa AA, Aklillu E. Efficacy and Safety of Praziquantel for Treatment of *Schistosoma mansoni* Infection among School Children in Tanzania. *Pathogens.* 2019;9: 28. doi:10.3390/pathogens9010028.
 112. Molehin AJ. *Schistosomiasis vaccine development: update on human clinical trials.* *J Biomed Sci.* 2020;27: 28. doi:10.1186/s12929-020-0621-y.

-
113. Gebreyesus TD, Makonnen E, Tadele T, Gashaw H, Degefe W, Gerba H, *et al.* Safety Surveillance of Mass Praziquantel and Albendazole Co-Administration in School Children from Southern Ethiopia: An Active Cohort Event Monitoring. *JCM.* 2022;11: 6300. doi:10.3390/jcm11216300.
 114. Masaku J, *et al.* High prevalence of helminths infection and associated risk factors among adults living in a rural setting, Central Kenya: a crosssectional study. *Trop Med Health.* 2017;45(1):15.
 115. Bhusal UP, Sapkota VP. Predictors of health insurance enrolment and wealth-related inequality in Nepal: evidence from Multiple Indicator Cluster Survey (MICS) 2019. *BMJ Open.* 2021;11: e050922. doi:10.1136/bmjopen-2021-050922.
 116. Pandey KR, Yang F, Cagney KA, Smieliauskas F, Meltzer DO, Ruhnke GW. The impact of marital status on health care utilization among Medicare beneficiaries. *Medicine.* 2019;98: e14871. doi:10.1097/MD.00000000000014871.
 117. Mwai J, Njenga S, Barasa M. Knowledge, attitude and practices in relation to prevention and control of schistosomiasis infection in Mwea Kirinyaga county, Kenya. *BMC Public Health.* 2016;16:819.
 118. Kinung'hi SM, Mazigo HD, Dunne DW, Kepha S, Kaatano G, Kishamawe C, *et al.* Coinfection of intestinal schistosomiasis and malaria and association with haemoglobin levels and nutritional status in school children in Mara region, Northwestern Tanzania: a cross-sectional exploratory study. *BMC Res Notes.* 2017;10: 583. doi:10.1186/s13104-017-2904-2.






-
119. Fauziah N, Aviani JK, Agrianfanny YN, Fatimah SN. Intestinal Parasitic Infection and Nutritional Status in Children under Five Years Old: A Systematic Review. *TropicalMed.* 2022;7: 371. doi:10.3390/tropicalmed7110371.
 120. Oliveira D, Ferreira FS, Atouguia J, Fortes F, Guerra A, Centeno-Lima S. Infection by Intestinal Parasites, Stunting and Anemia in School-Aged Children from Southern Angola. Weber CR, editor. *PLoS ONE.* 2015;10: e0137327. doi:10.1371/journal.pone.0137327.
 121. Alsaggaf R, O'Hara LM, Stafford KA, Leekha S, Harris AD, for the CDC Prevention Epicenters Program. Quasi-experimental Studies in the Fields of Infection Control and Antibiotic Resistance, Ten Years Later: A Systematic Review. *Infect Control Hosp Epidemiol.* 2018;39: 170–176. doi:10.1017/ice.2017.296.
 122. Taherdoost H. Sampling Methods in Research Methodology; How to Choose a Sampling Technique for Research. *SSRN Journal.* 2016. doi:10.2139/ssrn.3205035.
 123. Porta M. A dictionary of epidemiology, 5th edition. A call for submissions through an innovative wiki. *J Epidemiol Community Health.* 2006 Aug;60(8):653.
 124. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology.* 3rd ed. Lippincott, Williams, Wilkins, editors2008.
 125. Zaccai JH. How to assess epidemiological studies. *Postgrad Med J.* 2004 Mar;80(941):140-7. doi: 10.1136/pgmj.2003.012633. PMID: 15016934; PMCID: PMC1742948.

-
126. Wasserstein RL, Lazar NA. The ASA Statement on p-Values: Context, Process, and Purpose. *The American Statistician*. 2016;70(2):129-33. <https://doi.org/10.1080/00031305.2016.1154108>.

Paper I

Article

Prevalence and Determinants of *Schistosoma mansoni* Infection among Pre-School Age Children in Southern Ethiopia

Tafese Tadele ¹, Ayalew Astatkie ¹, Solomon Mequanente Abay ², Birkneh Tilahun Tadesse ³, Eyasu Makonnen ^{2,4} and Eleni Aklillu ^{5,*}

- ¹ School of Public Health, College of Medicine and Health Sciences, Hawassa University, Hawassa P.O. Box 1560, Ethiopia
- ² Department of Pharmacology and Clinical Pharmacy, College of Health Sciences, Addis Ababa University, Addis Ababa P.O. Box 9086, Ethiopia
- ³ Department of Pediatrics, College of Medicine and Health Sciences, Hawassa University, Hawassa P.O. Box 1560, Ethiopia
- ⁴ Center for Innovative Drug Development and Therapeutic Trials for Africa, College of Health Sciences, Addis Ababa University, Addis Ababa P.O. Box 9086, Ethiopia
- ⁵ Department of Global Public Health, Karolinska Institutet, Karolinska University Hospital, 171 77 Stockholm, Sweden
- * Correspondence: eleni.akillu@ki.se

Abstract: School-based deworming program is implemented to control and eliminate *Schistosoma mansoni* infection in many endemic countries, including Ethiopia. However, pre-school-age children (pre-SAC) are not targeted to receive preventive chemotherapy against *S. mansoni* infection, partly due to a lack of information on the disease burden. We assessed the prevalence and correlates of *S. mansoni* infection among pre-SAC in Southern Ethiopia. A total of 1683 pre-SAC aged 4 to 7 years were screened for *S. mansoni* infection. A multilevel binary logistic regression was fitted to detect the significant determinants of *S. mansoni* infection. Adjusted odds ratios (AORs) with a 95% confidence interval (CI) were used to identify determinants of *S. mansoni* infection. The overall prevalence of *S. mansoni* infection was 14.3% (95% CI: 12.6, 16.0%). *S. mansoni* infection was significantly higher among 6-year-old (AOR = 2.58, 95% CI: 1.55, 4.27) and 7-year-old children (AOR = 4.63, 95% CI: 2.82, 7.62). Accompanying others to water sources sometimes (AOR = 2.60, 95% CI: 1.12, 6.01) and all the time (AOR = 5.91, 95% CI: 2.51, 13.90), and residing in less than one kilometer from the infested water source (AOR = 3.17, 95% CI: 1.47, 6.83) increased the odds of *S. mansoni* infection. In conclusion, the prevalence of *S. mansoni* infection among pre-SAC in the study area was moderate. The study highlights the urgent need to include pre-SAC aged 4 to 7 years in annual preventive chemotherapy campaigns to reduce the risk of possible sources of infection and enhance the achievement of the elimination target.

Keywords: *Schistosoma mansoni*; neglected tropical diseases; public health problem; mass drug administration; pre-school age children; prevalence; Southern Ethiopia



Citation: Tadele, T.; Astatkie, A.; Abay, S.M.; Tadesse, B.T.; Makonnen, E.; Aklillu, E. Prevalence and Determinants of *Schistosoma mansoni* Infection among Pre-School Age Children in Southern Ethiopia. *Pathogens* **2023**, *12*, 858. <https://doi.org/10.3390/pathogens12070858>

Academic Editors: Silvana Belo, Ana Afonso, Pedro Ferreira and Fernanda de Freitas Anibal

Received: 11 May 2023
Revised: 12 June 2023
Accepted: 18 June 2023
Published: 21 June 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Schistosomiasis is one of the prominent neglected tropical diseases causing major public health threats in different parts of the world [1]. It affects mostly people living in the tropics and subtropics, predominantly the deprived and utmost poor societies [2,3]. In schistosomiasis endemic areas, the most dominant form is chronic schistosomiasis, resulting from repeated exposure to the infectious larval stage [4,5].

Children are often infected at the age of 2 years, and many of them remain chronically infected throughout their school-age years [6]. During pre-school age (pre-SAC), the exposure to infection is progressive, and practically all children in hyper-endemic areas can be exposed to infective cercariae at one year of age [7,8]. Once individuals are infected

with *S. mansoni* parasites, they are at risk of acquiring related morbidity [9–13]. *S. mansoni* morbidity is initiated principally by injurious immunologic responses to *S. mansoni* eggs deposited in the liver and intestine by adult female worms living in the vasculature surrounding these organs [14,15]

The burden of *S. mansoni* infection shows wide geographical variations across endemic countries in Sub-Saharan Africa (SSA). Some studies reported a higher prevalence of *S. mansoni* infection in pre-SAC ranging from 11.8% to 70.5% [16–21], while some reported a lower rate ranging from 0.9% to 5.9% [15,22,23]. Small-scale studies reported that daily exposure to infested water bodies and high levels of cumulative water contact in habitats where snail hosts are found is linked with the risk of transmission among pre-SAC [8,24–26]. Moreover, children's habit of swimming as well as the frequency of swimming in rivers and children's habit of crossing rivers barefoot are associated with intestinal schistosomiasis in Ethiopia [27,28].

The revised World Health Organization (WHO) roadmap targets the elimination of schistosomiasis as a public health problem by 2030 and the interruption of schistosome transmission in selected countries by 2030 [29]. One of the WHO-recommended public health interventions to interrupt transmission is the large-scale periodic administration of praziquantel to all at-risk populations as preventive chemotherapy (PC) [30]. Ethiopia is among the high schistosomiasis burden countries in SSA with recent surveys reporting prevalence levels between 24 to 76.3% among school-age children (SAC) [31]. The disease prevalence varies across the country, the southern region being the most affected (40%) [32]. The Ethiopian neglected tropical diseases (NTDs) program initiated school-based PC in 2014 primarily targeting SAC to control schistosomiasis [33]. Despite substantial progress in reducing the overall burden, a recent study conducted after several rounds of PC implementation among SAC reported an overall *S. mansoni* infection prevalence of 25.8% (range between schools 11.6% to 54.1%) in Southern Ethiopia [3].

Expansion of preventive chemotherapy to all in need, including pre-SAC, and a single prevalence threshold to conduct preventive chemotherapy and its frequency is among the recent six evidence-based recommendations by WHO for the elimination of morbidity and interruption of disease transmission [34]. The Ethiopian National NTD control program aims to eliminate schistosomiasis from being public health problem by 2025 defined as a prevalence of schistosomiasis of <2%, or maintain <1% prevalence of heavy infection in at-risk populations [35]. Currently, the national NTD program implements school-based targeted PC with praziquantel, and the frequency of PC is based on prevalence data. Pre-SAC is not yet included in the PC program. Epidemiological studies are imperative to provide evidence-based recommendations for policymakers on whether to include pre-SAC in PC campaigns and determine its frequency. Therefore, we conducted this study to generate evidence on the magnitude and potential determinants of *S. mansoni* infection to guide the inclusion of pre-SAC in the mass drug administration (MDA) program in Southern Ethiopia.

2. Materials and Methods

2.1. Study Area, Population, and Design

A cross-sectional study was conducted from August to December 2021 among pre-SAC (children aged 4 to 7 years) in the Hawella Tulla district of Sidama region, Southern Ethiopia. The study district was found to have a higher prevalence of schistosomiasis as per the general mapping exercise of NTDs conducted in Ethiopia between 2013 and 2014 [36]. Hawella Tulla district is located along the shore of Lake Hawassa and Tikur Wuha River at 289 km south of Addis Ababa, the capital city of Ethiopia. It is situated at an altitude of 1800 m above sea level and has an annual rainfall of 1123 mm and a temperature of 13–27 °C. Lake Hawassa is the water source for the residents of Hawella Tulla for their domestic, agricultural, fishing, and other uses. A map of the study district is presented in Figure 1.

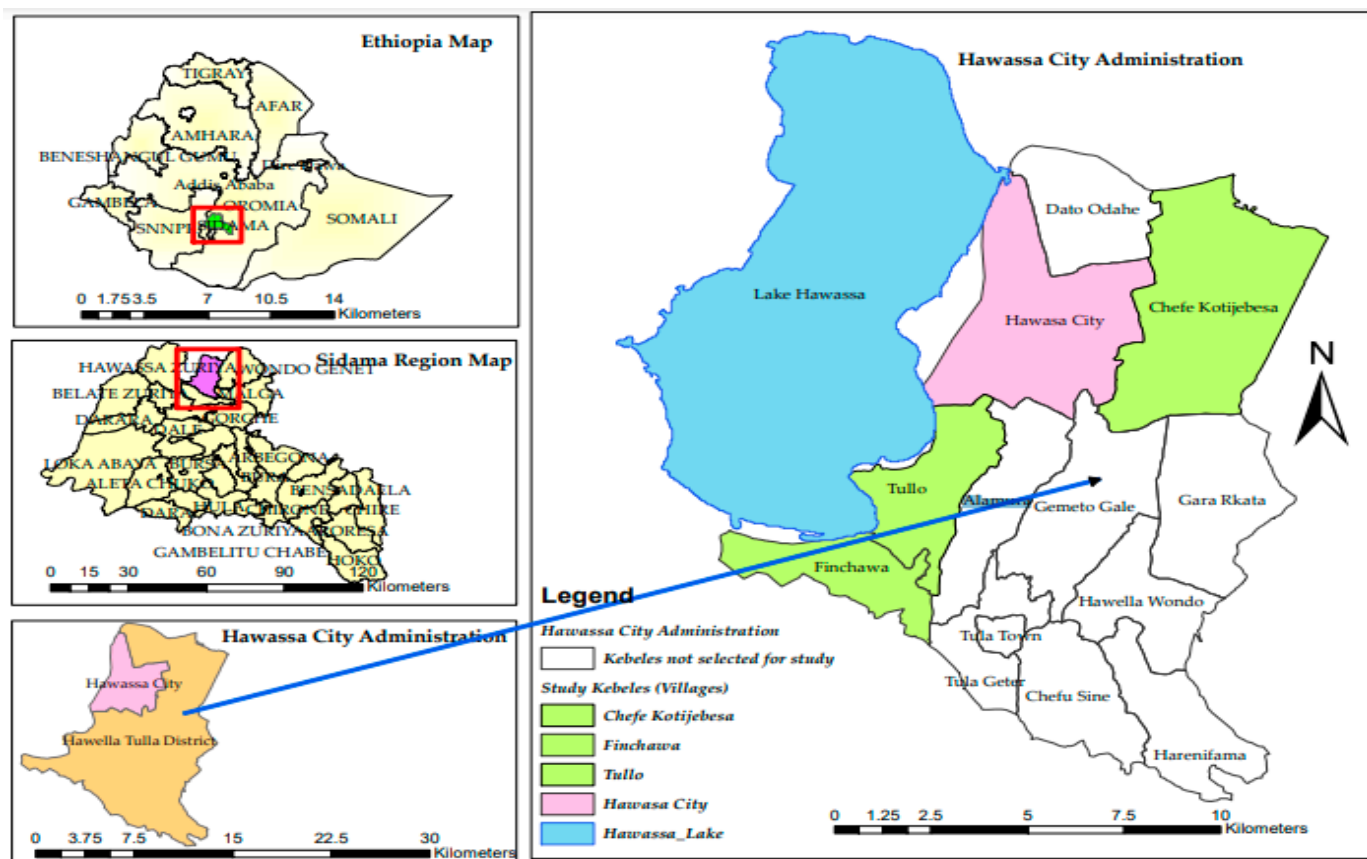


Figure 1. Map of the study site. The (top left) is the map of Ethiopia. The (middle left) figure shows the map of the Sidama region, and the (bottom left) figure indicates the map of Hawassa City administration where the study districts are located. The figure on the right shows the map of Lake Hawassa and the villages where the study was conducted.

2.2. Eligibility Criteria

Children aged 4 to 7 years who resided at least six months in the selected villages of Hawella Tulla district before the study were included. Pre-SAC who were treated with praziquantel within a month of the study recruitment period based on the verbal information obtained from the mothers/primary caregivers were excluded for the parasites could be cleared because of prior treatment. Children who were sick or with severe medical conditions and unable to produce stool samples were also excluded.

2.3. Sample Size Determination

OpenEpi (a free web-based open-source epidemiological statistics) was used to estimate the sample size for the assessment of the outcome and infection rate of *S. mansoni* in pre-SAC. The sample size was computed using the prevalence and risk factors to address its representativeness to the large population. The assumptions used were a prevalence (p) of 25% from a previous study in the same age group in Ethiopia [19], 3% absolute precision, and a design effect of 2. Accordingly, the minimum sample size (n) was found to be 1600, and the total sample size was 1778 after adjustment for a 10% nonresponse rate. The sample size needed to identify the risk factors associated with *S. mansoni* infection was calculated considering variables significantly associated with *S. mansoni* infection in previous studies and fixing the level of confidence at 95%, power at 90%, the ratio of unexposed-to-exposed at 1% and anticipated nonresponse rate at 10%. The sample sizes calculated for risk factors using the findings of the previous report were then 138, 134, and 214. Hence, the sample size calculated from the prevalence ($n = 1778$) was used as the final sample size for the present study as it would meet all objectives of the study.

2.4. Sampling Procedure

A multistage sampling technique was used to recruit the study participants. Hawella Tulla district has twelve kebeles (lowest administrative units in Ethiopia, hereafter referred to as village(s)), of which, six were selected for this study based on the *S. mansoni* infection rate in school-age children as per the mapping study of the Ethiopian Public Health Institute in collaboration with the Ministry of Health of Ethiopia [36]. In the first stage, three villages (Tullo, Finchawa, and Chefe Kotijebeba) were selected by simple random sampling technique from six villages. In the selected villages, the sampling frame of the eligible study participants was prepared through house-to-house enumeration by health extension workers before the commencement of actual data collection. Whenever more than one eligible child was found in the same selected household, only one was included in the sampling frame using the lottery method. In the second sampling stage, the number of study participants included in each village was determined by proportional allocation based on the total number of participants found in each village. Then, the study participants were selected by a simple random sampling method. At times when the sampled child was absent from home, two repeated visits (one out of marketing days and one during the weekend) were made. Those pre-SAC who were not traced after three visits were considered non-respondents.

2.5. Study Variables

The outcome variable for this study was *S. mansoni* infection which was detected using Kato–Katz (a gold standard method) for diagnosing *S. mansoni* by microscopic examination [30,37]. This takes a binary outcome, such that *S. mansoni* infection was regarded as infected (1 = if *S. mansoni* infection detected) or uninfected (0 = if no *S. mansoni* infection detected). Egg counts were quantified and classified for *S. mansoni* infection according to the WHO guideline as light (1–99 EPG), moderate (100–399 EPG), or heavy (>400 EPG) [30,37].

The exposure variables included age, sex, educational level, and occupation of the mothers/primary caregivers of pre-SAC, sanitary practices, water contact behavior, distance from the infested water body, latrine use, and the wealth index of the household. The age of the study participant was determined by asking about their last birthday. The wealth index of the household was constructed from the household asset and its interquartile range was fixed. The distance from the infested water body was categorized according to the predetermined classification of the distance (less than 1 km, 1 to 2 km, and greater than 2 km) using the GPS before the actual data collection period.

2.6. Data Collection Tools and Procedures

Data were collected using a pre-tested structured Amharic or *Sidaamu Afoo* (the local language) version questionnaire using an interview technique. Eight research assistants with public health expertise who were trained on how to apply the questionnaire interviewed the mothers/primary caregivers of the participants. The interview was conducted at the respondent's home. The questionnaire was prepared in English, translated into Amharic and *Sidamu Afoo* languages, and translated back to English to check the consistency. The Amharic or *Sidamu Afoo* questionnaire was used for interviews based on the language proficiency of the respondents and their preferences. Two senior experts and the principal investigator supervised the data collection process.

A stool specimen was collected from each study participant using a wide-mouth 100 mL screw-capped dry and clean container pre-labeled with the participant's unique identification number. The collected stool samples were transported within an hour of collection in suitable cool boxes at temperatures between 4 and 60c for subsequent examination at Bushulo health center. Samples were examined using the Kato–Katz technique for the detection of parasite eggs, with two slides per stool. A portion of the sample was processed by the Kato–Katz method using a template holding 41.7 mg of stool [32]. Two experienced laboratory technologists examined the slides, and the difference in the test

results was managed using the third experienced laboratory technologist. The number of eggs was counted and multiplied by 24 to obtain the number of EPG of stool.

The presence of *S. mansoni*, *Ascaris lumbricoides*, *Trichuris trichuria*, and hookworm eggs was recorded. Examination for hookworm infection was performed within an hour of smear preparation, while examination for *S. mansoni*, *A. lumbricoides*, and *T. trichuria* was performed within 24 h after smear preparation.

2.7. Data Analysis

Data were recorded on standard record forms, entered into the RedCap database, and exported to an Excel file for cleaning. The data analysis was conducted using Stata software version 14 [StataCorp LLC, College Station, TX, USA]. Descriptive analyses were conducted by calculating frequencies and percentages for categorical variables and mean with standard deviations and medians with interquartile ranges. The determinants of *S. mansoni* infection were investigated using multilevel logistic regression.

The suitability of the data for standard logistic regression versus multilevel logistic regression was checked by fitting an intercept-only model and comparing it with the null model from a standard logistic regression. An intra-class correlation coefficient (ICC) of 0.084 from the intercept-only model and a significant likelihood ratio test (LR) with a corresponding *p*-value less than 0.005, and lower Akaike's information criterion (AIC) and Bayesian information criterion (BIC) for the intercept-only model vis-à-vis the null model from standard logistic regression showed the need for multilevel analysis. Hence, multilevel logistic regression was applied to identify the determinants of *S. mansoni* infection as it provides a more accurate description of relationships in clustered data by correcting underestimated standard errors, estimating components of variance at several levels, and estimating cluster-specific intercepts and slopes than standard logistic regression.

To conduct a multilevel binary logistic regression analysis, three models were fitted. The first model was the null model (a model without the explanatory variables), which shows the extent of variability in *S. mansoni* infection due to cluster- (village-) level effect without accounting for covariate effects. The second model, model I, comprised individual-level determinants with random intercept. The third model, model II, which included individual-level predictors with random intercept and random-coefficient for the distance of the household from an infested water source, was the final model. An interaction effect was checked between the age and sex of the participants. However, no significant interaction effect was detected. To identify the best-fitting model, comparison was conducted between model I and model II. The result revealed that there was no significant improvement in the fit of model II relative to model I based on the likelihood ratio test. The changes in AIC and BIC values were also minimal. However, the ICC increased by 177% (from 11.5% to 31.8%) after accounting for the random coefficient for the distance of the households from an infested water source in model II. In addition, the odds ratio for distance less than 1 km changed by about 26% from model I to model II. Furthermore, the variance of the coefficient of the distance of households from infested water sources in model II across village was significant. It is also logically plausible to assume that the effect of distance from infested water sources on the risk of *S. mansoni* infection varies across villages. Therefore, we took the third model, model II, as our final model. See supplementary file S1 (Table S1) for the details of the model comparison. The selection of variables for inclusion into the multivariable multilevel analysis was conducted based on a *p*-value < 0.25 from the crude analysis.

Based on the final model, adjusted odds ratios (AORs) with a 95% confidence interval (CIs) were reported based on the fixed-effects component of the model. See supplementary file S2 (Table S2) for results from all models. Random effects for the intercept and coefficients were reported based on variances across clusters with 95% CIs. Ninety-five percent of CIs of AORs that do not embrace 1 indicated statistically significant fixed effects, whereas 95% of CIs of variances that do not embrace 0 implied statistically significant village-level random effects.

3. Results

3.1. Study Participants' Characteristics

A total of 1683 (95%) pre-SAC aged 4 to 7 years participated in the study. Out of the total participants, 52.3% were males ($n = 880$). The mean (\pm standard deviation (SD)) age of the children was 5.49 (± 1.09) years (Table 1).

Table 1. The individual characteristics of pre-school age children and their mothers/primary caregivers in Southern Ethiopia, August to December 2021.

Variable	Category	Frequency N (%)
Age (in years)	Four	393 (23.4)
	Five	465 (27.6)
	Six	424 (25.2)
	Seven	401 (23.8)
Sex	Female	803 (47.7)
	Male	880 (52.3)
Educational level of mothers/primary caregivers of pre-SAC	No formal education	701 (41.6)
	Primary education	486 (28.9)
	Secondary education	232 (13.8)
	College and above	264 (15.7)
Current major occupation of mothers/primary caregivers of pre-SAC	Farmer	397 (23.6)
	Full-time housewife	1139 (67.7)
	Merchant/employed	147 (8.7)
Wealth Index	Poorest	413 (24.5)
	Poorer	357 (21.2)
	Middle	271 (16.1)
	Richer	313 (18.6)
	Richest	329 (19.6)
District	Tullo	763 (45.3)
	Finchawa	447 (26.6)
	Chefe Kotijebeba	473 (28.1)
Distance from the water sources	Less than 1 km	304 (18.1)
	1 km to 2 km	977 (58.0)
	More than 2 km	402 (23.9)

N = total number of participants; Pre-SAC: pre-school age children; km: kilometer.

3.2. Prevalence of *S. mansoni* Infection

A total of 241/1683 pre-SAC, 14.3%, (95% CI: 12.6%, 16.0%) were found to be infected with *S. mansoni*, with a prevalence of 16.4% (144/880) in males and 12.1% (97/803) in females. The prevalence of infection increased with increasing age; the youngest age group (4 years) exhibited a moderate prevalence of 6.9% and the much older age group (7 years) had a high prevalence of 24.7% (Table 2). The prevalence of infection varied by study villages. Among the three villages that participated in this study, Tullo village had the highest prevalence of *S. mansoni* infection (21.4%), followed by Finchawa village (10.5%), and Chefe Kotijebeba village (6.6%). Microscopic examinations of stool samples showed that about 73 (30.3%) *S. mansoni*-infected pre-SAC had multiple parasite infections.

Table 2. Prevalence and intensity of *S. mansoni* infection by age groups among pre-school age children in Southern Ethiopia, August to December 2021.

Age	<i>S. mansoni</i> Infection Prevalence	<i>S. mansoni</i> Infection Intensity in Pre-SAC		
		Light	Moderate	Heavy
Overall	14.3%	8.1%	4.1%	2.1%
4 years	6.9%	4.1%	2.3%	0.5%
5 years	9.9%	5.5%	3.0%	1.3%
6 years	16.3%	9.9%	3.6%	2.8%
7 years	24.7%	13.2%	7.7%	3.8%

S. mansoni; *Schistosoma mansoni*; Pre-SAC: pre-school age children.

3.3. Intensity of *S. mansoni* Infection in Pre-SAC

S. mansoni egg count in test stool of the 241 pre-SAC who were microscopy positive ranged from 12 to 2560 EPG. Most of the infected pre-SAC had a low egg count of 12 to 96 EPG (n = 137; 8.1% light infection). The remaining (n = 69; 4.1% moderate infection) pre-SAC had 108 to 396 EPG, while (n = 35) (2.1%; heavy infection) had 400 to 2560 EPG (Table 2). The heaviest infection intensity was detected from Tullo kebele (1.7%) followed by Chefe Kotijebesa kebele (0.3%), and Finchawa kebele (0.2%).

3.4. Determinants of *S. mansoni* Infection in Pre-SAC

3.4.1. Effect of Determinants on *S. mansoni* Infection

In the multivariable multilevel logistic regression analysis, *S. mansoni* infection was significantly associated with higher age, i.e., a child aged 6 years (AOR = 2.58, 95% CI: 1.55, 4.27) and a child aged 7 years (AOR = 4.63, 95% CI: 2.82, 7.62). Accompanying others to water sources sometimes (AOR = 2.60, 95% CI: 1.12, 6.01) and all the time (AOR = 5.91, 95% CI: 2.51, 13.90), and living in less than 1 km radius from the nearby water body, Lake Hawassa, (AOR = 3.17, 95% CI: 1.47, 6.83) were also found to be the variables significantly associated with *S. mansoni* infection. The occupation and wealth index of the mothers/primary caregivers of pre-SAC had no association with *S. mansoni* infection (Table 3).

Table 3. Rates and determinants of *S. mansoni* infection among pre-school age children in Southern Ethiopia using multilevel logistic regression.

Variable	Category	<i>S. mansoni</i> Infection		Univariable Multilevel LR		Multivariable Multilevel LR	
		Non-Infected	Infected	COR (95%CI)	p Value	AOR (95%CI)	p Value
Age (in years)	Four	366 (93.1%)	27 (6.9%)	1 ^a		1 ^a	
	Five	419 (90.1%)	46 (9.9%)	1.62 (0.98, 2.68)	0.06	1.57 (0.93, 2.66)	0.09
	Six	355 (83.7%)	69 (16.3%)	3.00 (1.86, 4.83)	<0.001	2.58 (1.55, 4.27)	<0.001
	Seven	302 (75.3%)	99 (24.7%)	5.72 (3.59, 9.12)	<0.001	4.63 (2.82, 7.62)	<0.001
Marital status of parents	Married	1412 (86.1)	228 (13.9)	1 ^a		1 ^a	
	Not married	30 (69.8)	13 (30.2)	2.28 (1.16, 4.51)	0.02	1.40 (0.65, 3.01)	0.39
Sex	Female	706 (87.9)	97 (12.1)	1 ^a		1 ^a	
	Male	736 (83.6)	144 (16.4)	1.49 (1.12, 1.97)	0.006	1.25 (0.92, 1.70)	0.16
The educational level of mothers/primary caregivers of pre-SAC	College and above	235 (89.1)	29 (10.9)	1 ^a		1 ^a	
	No formal education	594 (84.7)	107 (15.3)	1.68 (1.08, 2.62)	0.02	1.18 (0.68, 2.02)	0.56
	Primary education	410 (84.4)	76 (15.6)	1.81 (1.13, 2.88)	0.01	1.46 (0.86, 2.49)	0.17
	Secondary education	203 (87.5)	29 (12.5)	1.24 (0.71, 2.17)	0.44	1.03 (0.56, 1.89)	0.92
Contact to infested water	No	676 (90.5)	71 (9.5)	1 ^a		1 ^a	
	Yes	766 (81.8)	170 (18.2)	2.16 (1.60, 2.92)	<0.001	0.71 (0.31, 1.60)	0.40
Frequency of accompany to the water source	Never	675 (91.5)	63 (8.5)	1 ^a		1 ^a	
	Sometime	631 (84.5)	116 (15.5)	1.96 (1.41, 2.72)	<0.001	2.60 (1.12, 6.01)	0.03
	All the time	136 (68.7)	62 (31.3)	5.05 (3.35, 7.63)	<0.001	5.91 (2.51, 13.90)	<0.001

Table 3. Cont.

Variable	Category	<i>S. mansoni</i> Infection		Univariable Multilevel LR		Multivariable Multilevel LR	
		Non-Infected	Infected	COR (95%CI)	<i>p</i> Value	AOR (95%CI)	<i>p</i> Value
Wealth index	Richest	283 (86.0)	46 (14.0)	1.0		1 ^a	
	Poorest	361 (87.4)	52 (12.6)	1.08 (0.70, 1.68)	0.72	1.06 (0.62, 1.80)	0.84
	Poorer	304 (85.2)	53 (14.9)	1.35 (0.87, 2.09)	0.18	1.10 (0.65, 1.85)	0.72
	Middle	227 (83.8)	44 (16.2)	1.64 (1.03, 2.60)	0.04	1.54 (0.90, 2.63)	0.11
	Richer	267 (85.3)	46 (14.7)	1.23 (0.78, 1.93)	0.37	1.05 (0.63, 1.76)	0.85
Distance to the water sources	More than 2 km	356 (88.6)	46 (11.4)	1 ^a		1 ^a	
	Less than 1 km	215 (70.7)	89 (29.3)	3.50 (2.34, 5.24)	<0.001	3.17 (1.47, 6.83)	0.003
	1 km to 2 km	871 (89.2)	106 (10.9)	1.04 (0.72, 1.52)	0.81	1.04 (0.63, 1.72)	0.89

^a: Reference category; LR: logistic regression; COR: crude odds ratio; AOR: adjusted odds ratio; CI: 95% confidence interval.

3.4.2. Between-Village Variability on the Risk of *S. mansoni* Infection

There was significant village-level variability in the intercept of the model (variance = 0.30; 95% CI: 0.05, 1.65). Similarly, the effect of the distance of households from infested water sources on the risk of *S. mansoni* infection was variable across villages (variance = 0.077; 95% CI: 0.07653, 0.07654). Controlling for other covariates, 31.8% of the variability on the risk of *S. mansoni* infection was explained by village membership. Supplementary file S1 shows the details of the models.

4. Discussion

This study aimed to explore the burden of *S. mansoni* infection among pre-SAC in Southern Ethiopia and determine the factors associated with the infection. The present study found that the prevalence of *S. mansoni* infection among pre-SAC was 14.3%, with significant variation across villages. The prevalence was higher among children aged 6 and 7 years, those residing within one-kilometer radius of the nearby water body, and those who accompanied others to water sources all the time or sometimes. The effect of distance of households from infested water sources on the risk of infection varied across villages. Furthermore, village membership accounted for 31.8% of the variability in the risk of infection.

The burden of *S. mansoni* infection among pre-SAC significantly varies across geographical localities in endemic settings. Thus, the present study compared the results with a previous study among SAC in the same area [3], which reported an overall *S. mansoni* infection prevalence of 24.6%, as there was no previous study among pre-SAC in the study area. The overall *S. mansoni* infection prevalence of 14.3% reported in the present study was lower than the prevalence previously reported among SAC in the same area [3]. The difference in prevalence between the current study and the previous study among SAC may be attributed to the reduction of infection in the study area which resulted from the initiation of praziquantel MDA to SAC in 2014. There is evidence that treating SAC infected with schistosomiasis tends to lower the prevalence among the entire population by reducing the ongoing transmission of the infection [38]. However, the MDA among SAC was interrupted in 2015 and low treatment coverage was reported in 2016 which may have contributed to the spread of infection among pre-SAC in the study area.

The prevalence and heavy-intensity infection of *S. mansoni* detected in the present study is above the national NTD program target to eliminate schistosomiasis [35]. Concerning the national NTD target, the current study highlights the urgent need to include pre-SAC in control and elimination interventions against schistosomiasis, as WHO recommends starting from the age of 2 years [38]. Moreover, the observed heavy-intensity infection rate in the most affected village among pre-SAC indicates that *S. mansoni* infection may continue to be a major public health threat in the study area. Hence, the WHO target to reach <1% prevalence of heavy infection intensity in children aged 5–14 years by 2030 [39], could be difficult to achieve. The authors suggest that the burden of this disease found in the present study and in the previous report of the SAC study indicate the need for the

inclusion of pre-SAC in MDA, rather than only relying on and sustaining the involvement of SAC in schistosomiasis control and elimination programs in Ethiopia. Thus, the recently initiated Ethiopian Ministry of Health community-based deworming strategy that takes place integrated with a regular health extension program [40], would be the best way to reach pre-SAC once the praziquantel pediatric formulation becomes available.

The current study found that the odds of *S. mansoni* infection were higher among children aged 6 and 7 years compared to younger age groups. Older pre-SAC were observed to have more opportunities to go with their elder siblings and parents to the infested water source compared to younger pre-SAC. During the interview, the reported increased contact of contaminated stagnant water for playing purposes among older pre-SAC may contribute to the higher risk of infection. Additionally, the hot weather condition of the study area and the increased density of infected intermediate snail hosts in the water bodies, especially during the hot hours of the day, may favor the spread of *S. mansoni* infection among pre-SAC in the study area.

The present study revealed accompanying others to water sources sometimes and all the time was a significant determinant of *S. mansoni* infection among pre-SAC. The reason for this association is that in rural parts of Ethiopia, it is common for pre-SAC to accompany their mothers/elder siblings to infested water bodies, which could expose them to acquiring the infection at a young age. Another explanation could be the fact that mothers or primary caregivers of the rural community may not give due attention to actively and closely monitoring pre-SAC compared to their urban counterparts, thus pre-SAC living around lake shore villages are potentially exposed to high risk of *S. mansoni* infection.

In the present study, children who are living within less than 1 km radius distance of an infested water body had three times more odds to be infected compared to those who are residing in greater than 2 km distance. A similar finding was previously reported among SAC in the same area [3], in schools found in villages located less than 1 km from infested water bodies. This might be associated with the frequency of infested water contact, low knowledge in prevention and control of *S. mansoni* infection among mothers/primary caregivers, and more engagement in predisposing practices among pre-SAC in the study area.

The current study findings indicate that the effect of the distance of households from infested water sources on the risk of *S. mansoni* infection varied significantly across villages. Additionally, from our village-specific analysis of the prevalence of *S. mansoni* infection, children from villages closest to Lake Hawassa were at a higher risk of infection than children away from the lake. Moreover, the intensity of other risk factors such as frequency of contact with infested water may vary based on distance from the infested water source, which may in turn lead to differences in the effect of distance across villages.

In the present study, 31.8% of the variability in *S. mansoni* infection was attributed to the village membership whereas between-individual variation explained the remaining 68.2% of the total variability. This indicates the existence of significant heterogeneity in the risk of *S. mansoni* infection across different villages due to differences in the chance of acquiring the infection among pre-SAC. The difference could be attributed to the differential proximity of the infested water source, increased water contact, socioeconomic status, and variation in the magnitude of snail hosts among the study villages.

The study has some limitations. First, the Kato–Katz technique that we employed may underestimate the egg counts in an area with low prevalence. Second, the diarrheic consistency of the stool samples from study participants rendered the preparation of Kato–Katz slides difficult, which may result in an underestimation of the prevalence of *S. mansoni* infection. Third, the study did not assess the community-level determinants to investigate village-level predictors, which account for the village-level variability of *S. mansoni* infection among pre-SAC.

5. Conclusions

The prevalence of *S. mansoni* infection among pre-SAC in the schistosomiasis endemic Hawella Tulla district of Southern Ethiopia was moderate. The prevalence varies widely by age of the children, with those at the age of 6 and 7 years having the highest risk. The risk of infection also varies across villages. Further, the frequency of accompanying others to infested water sources and living at less than 1 km from infested water sources increased the risk of *S. mansoni* infection. The effect of distance on the risk of *S. mansoni* infection varies significantly across villages. Therefore, we recommend the inclusion of pre-SAC in annual PC integrated with potable water supplies, sanitation, and hygiene (WASH) interventions, and vector control to reduce the morbidity of chronic schistosomiasis and reduce transmission, which helps achieve the elimination target of schistosomiasis. Moreover, the provision of health education for behavior change to avoid contaminated water contact is recommended for all village communities.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/pathogens12070858/s1>, Table S1: Model comparison using multivariable multilevel logistic regression analysis among pre-school age children (Pre-SAC) infected with *S. mansoni* in Southern Ethiopia, August to December 2021; Table S2: Multilevel logistic regression analysis of determinants of *S. mansoni* infection among pre-school age children (Pre-SAC) in Southern Ethiopia, August to December 2021.

Author Contributions: Conceptualization, T.T., A.A., B.T.T., S.M.A., E.M. and E.A.; data curation, T.T., A.A., S.M.A., E.M. and E.A.; formal analysis, T.T., A.A., S.M.A. and E.A.; funding acquisition, E.A., E.M. and S.M.A.; methodology, T.T., A.A., S.M.A., B.T.T., E.M. and E.A.; project administration, S.M.A. and E.A.; resources, T.T., A.A., S.M.A., E.M. and E.A.; supervision, T.T., A.A., B.T.T.; S.M.A., E.M. and E.A.; visualization, A.A., E.M. and E.A.; writing an original draft, T.T.; writing—review and editing, T.T., A.A., B.T.T., S.M.A., E.M. and E.A. All authors have read and agreed to the published version of the manuscript.

Funding: This study was conducted as part of the Pharmacovigilance infrastructure and post-marketing surveillance system capacity building for regional medicine regulatory harmonization in East Africa (PROFORMA) project funded by the European and Developing Countries Clinical Trials Partnership (EDCTP) 2 program supported by the European Union (Grant number CSA2016S-1618) and the Swedish International Development Cooperation Agency (SIDA), and PrazOpt project funded by the EDCTP 2 program supported by the European Union (grant number TMA2018CDF-2345).

Institutional Review Board Statement: The study was conducted per the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of the College of Medicine and Health Sciences of Hawassa University before commencing the study (Ref. No: IRB/200/13). Before initiating the study, a support letter was also received from Sidama Regional State Health Bureau.

Informed Consent Statement: Written informed consent was obtained from parents/primary caregivers of each study participant after clarifying the purpose, method, possible risks/benefits, rights, confidentiality, nature of the study, and the scope of their involvement in the study.

Data Availability Statement: All data presented in this study are contained within the manuscript.

Acknowledgments: We convey our genuine thanks to Sidama Regional State Health Bureau Disease Prevention and Health Promotion Directorate, and the Public Health Institute for their kind assistance. We thank the Hawassa City Health Department, Hawella Tulla Health Office, Hawassa University Comprehensive Specialized Hospital, and the staff of Bushullo Health Center for the favorable working environment and their support in fieldwork planning, sample collection, processing, and storage. We thank the administrators of Tullo, Finchawa, and Chefe Kotijebesa *kebeles* for permitting us to undertake this study. We also thank the parents/primary caregivers and pre-SAC that participated in the study.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. WHO Schistosomiasis. 2023. Available online: <https://www.who.int/news-room/fact-sheets/detail/schistosomiasis> (accessed on 4 April 2023).
2. Osakunor, D.N.M.; Woolhouse, M.E.J.; Mutapi, F. Paediatric schistosomiasis: What we know and what we need to know. *PLoS Negl. Trop. Dis.* **2018**, *12*, e0006144. [[CrossRef](#)] [[PubMed](#)]
3. Gebreyesus, T.D.; Tadele, T.; Mekete, K.; Barry, A.; Gashaw, H.; Degefe, W.; Tadesse, B.T.; Gerba, H.; Gurumurthy, P.; Makonnen, E.; et al. Prevalence, Intensity, and Correlates of Schistosomiasis and Soil-Transmitted Helminth Infections after Five Rounds of Preventive Chemotherapy among School Children in Southern Ethiopia. *Pathogens* **2020**, *9*, 920. [[CrossRef](#)] [[PubMed](#)]
4. Colley, D.G.; Bustinduy, A.L.; Secor, W.E.; King, C.H. Human schistosomiasis. *Lancet* **2014**, *383*, 2253–2264. [[CrossRef](#)]
5. Abudho, B.O.; Ndombi, E.M.; Guya, B.; Carter, J.M.; Riner, D.K.; Kittur, N.; Karanja, D.M.S.; Secor, W.E.; Colley, D.G. Impact of Four Years of Annual Mass Drug Administration on Prevalence and Intensity of Schistosomiasis among Primary and High School Children in Western Kenya: A Repeated Cross-Sectional Study. *Am. J. Trop. Med. Hyg.* **2018**, *98*, 1397–1402. [[CrossRef](#)]
6. Verani, J.R.; Butler, S.E.; Montgomery, S.P.; Karanja, D.M.S.; Mwinzi, P.N.M.; Shane, H.L.; Abudho, B.; Secor, W.E. Schistosomiasis among Young Children in Usoma, Kenya. *Am. J. Trop. Med. Hyg.* **2011**, *84*, 787–791. [[CrossRef](#)] [[PubMed](#)]
7. Faust, C.L.; Osakunor, D.N.; Downs, J.A.; Kayuni, S.; Stothard, J.R.; Lamberton, P.H.; Reinhard-Rupp, J.; Rollinson, D. Schistosomiasis Control: Leave No Age Group Behind. *Trends Parasitol.* **2020**, *36*, 582–591. [[CrossRef](#)]
8. Ekpo, U.F.; Oluwole, A.S.; Abe, E.M.; Etta, H.E.; Olamiju, F.; Mafiana, C.F. Schistosomiasis in infants and pre-school-aged children in sub-Saharan Africa: Implication for control. *Parasitology* **2012**, *139*, 835–841. [[CrossRef](#)] [[PubMed](#)]
9. Munisi, D.Z.; Buza, J.; Mpolya, E.A.; Kinung'hi, S.M. Schistosoma mansoni Infections, Undernutrition and Anaemia among Primary Schoolchildren in Two Onshore Villages in Rorya District, North-Western Tanzania. *PLoS ONE* **2016**, *11*, e0167122. [[CrossRef](#)] [[PubMed](#)]
10. Kinung'hi, S.M.; Mazigo, H.D.; Dunne, D.W.; Kepha, S.; Kaatano, G.; Kishamawe, C.; Ndokeji, S.; Angelo, T.; Nuwaha, F. Coinfection of intestinal schistosomiasis and malaria and association with haemoglobin levels and nutritional status in school children in Mara region, Northwestern Tanzania: A cross-sectional exploratory study. *BMC Res. Notes* **2017**, *10*, 583. [[CrossRef](#)]
11. Njiru, J.; Muhoho, N.; Simbauni, J.; Kabiru, E. Effects of Soil-Transmitted Helminths and Schistosoma Species on Nutritional Status of Children in Mwea Irrigation Scheme, Kenya. *J. Appl. Life Sci. Int.* **2016**, *5*, 1–8. [[CrossRef](#)]
12. Abera, B.; Alem, G.; Yimer, M.; Herrador, Z. Epidemiology of soil-transmitted helminths, Schistosoma mansoni, and haematocrit values among schoolchildren in Ethiopia. *J. Infect. Dev. Ctries.* **2013**, *7*, 253–260. [[CrossRef](#)]
13. Mnkugwe, R.H.; Minzi, O.S.; Kinung'hi, S.M.; Kamuhabwa, A.A.; Aklillu, E. Prevalence and correlates of intestinal schistosomiasis infection among school-aged children in North-Western Tanzania. *PLoS ONE* **2020**, *15*, e0228770. [[CrossRef](#)]
14. Nigo, M.M.; Odermatt, P.; Nigo, D.W.; Salieb-Beugelaar, G.B.; Battagay, M.; Hunziker, P.R. Morbidity associated with Schistosoma mansoni infection in north-eastern Democratic Republic of the Congo. *PLoS Negl. Trop. Dis.* **2021**, *15*, e0009375. [[CrossRef](#)]
15. Sakari, S.S.W.; Mbugua, A.K.; Mkoji, G.M. Prevalence of Soil-Transmitted Helminthiases and Schistosomiasis in Preschool Age Children in Mwea Division, Kirinyaga South District, Kirinyaga County, and Their Potential Effect on Physical Growth. *J. Trop. Med.* **2017**, *2017*, 1–12. [[CrossRef](#)]
16. Alemu, A.; Tegegne, Y.; Damte, D.; Melku, M. Schistosoma mansoni and soil-transmitted helminths among preschool-aged children in Chuahit, Dembia district, Northwest Ethiopia: Prevalence, intensity of infection and associated risk factors. *BMC Public Health* **2016**, *16*, 422. [[CrossRef](#)]
17. Mazigo, H.D.; Uisso, C.; Kazyoba, P.; Nshala, A.; Mwingira, U.J. Prevalence, infection intensity and geographical distribution of schistosomiasis among pre-school and school aged children in villages surrounding Lake Nyasa, Tanzania. *Sci. Rep.* **2021**, *11*, 295. [[CrossRef](#)] [[PubMed](#)]
18. Mugono, M.; Konje, E.; Kuhn, S.; Mpogoro, F.J.; Morona, D.; Mazigo, H.D. Intestinal schistosomiasis and geohelminths of Ukara Island, North-Western Tanzania: Prevalence, intensity of infection and associated risk factors among school children. *Parasites Vectors* **2014**, *7*, 612. [[CrossRef](#)] [[PubMed](#)]
19. Kemal, M.; Tadesse, G.; Esmael, A.; Abay, S.M.; Kebede, T. Schistosoma mansoni infection among preschool age children attending Erer Health Center, Ethiopia and the response rate to praziquantel. *BMC Res. Notes* **2019**, *12*, 211. [[CrossRef](#)] [[PubMed](#)]
20. Cisse, M.; Sangare, I.; Djibougou, A.D.; Tahita, M.C.; Gnissi, S.; Bassinga, J.K.W.; Konda, S.; Diallo, A.H. Prevalence and risk factors of Schistosoma mansoni infection among preschool-aged children from Panamasso village, Burkina Faso. *Parasites Vectors* **2021**, *14*, 185. [[CrossRef](#)]
21. Sheehy, C.; Lawson, H.; Andriamasy, E.H.; Russell, H.J.; Reid, A.; Raderalazaso, G.U.; Dodge, G.; Kornitschky, R.; Penney, J.M.S.; Ranaivoson, T.N.; et al. Prevalence of intestinal schistosomiasis in pre-school aged children: A pilot survey in Marolambo District, Madagascar. *Infect. Dis. Poverty* **2021**, *10*, 87. [[CrossRef](#)]
22. Sacolo-Gwebu, H.; Chimbari, M.; Kalinda, C. Prevalence and risk factors of schistosomiasis and soil-transmitted helminthiases among preschool aged children (1–5 years) in rural KwaZulu-Natal, South Africa: A cross-sectional study. *Infect. Dis. Poverty* **2019**, *8*, 47. [[CrossRef](#)] [[PubMed](#)]
23. Ayele, A.; Tegegne, Y.; Derso, A.; Eshetu, T.; Zeleke, A.J. Prevalence and Associated Factors of Intestinal Helminths Among Kindergarten Children in Gondar Town, Northwest Ethiopia. *Pediatr. Health Med. Ther.* **2021**, *12*, 35–41. [[CrossRef](#)]

24. Sousa-Figueiredo, J.C.; Pleasant, J.; Day, M.; Betson, M.; Rollinson, D.; Montresor, A.; Kazibwe, F.; Kabatereine, N.B.; Stothard, J.R. Treatment of intestinal schistosomiasis in Ugandan preschool children: Best diagnosis, treatment efficacy and side-effects, and an extended praziquantel dosing pole. *Int. Health* **2010**, *2*, 103–113. [CrossRef] [PubMed]
25. Poole, H.; Terlouw, D.J.; Naunje, A.; Mzembe, K.; Stanton, M.; Betson, M.; Lalloo, D.G.; Stothard, J.R. Schistosomiasis in pre-school-age children and their mothers in Chikhwawa district, Malawi with notes on characterization of schistosomes and snails. *Parasit Vectors* **2014**, *7*, 153. [CrossRef]
26. Rujeni, N.; Bayingana, J.B.; Nyandwi, E.; Ntakarutimana, A.; Kagabo, J.; Rutayisire, R.; Shema, E.; Kanimba, P.; Mbonigaba, J.B.; Ruberanziza, E. Prevalence Mapping of *Schistosoma mansoni* Among Pre-school Age Children in Rwanda. *Front. Pediatr.* **2022**, *10*, 906177. [CrossRef]
27. Bekana, T.; Berhe, N.; Egual, T.; Aemero, M.; Medhin, G.; Tulu, B.; G/Hiwot, Y.; Liang, S.; Hu, W.; Erko, B. Prevalence and factors associated with intestinal schistosomiasis and human fascioliasis among school children in Amhara Regional State, Ethiopia. *Trop. Med. Health* **2021**, *49*, 35. [CrossRef]
28. Ansha, M.G.; Kuti, K.A.; Girma, E. Prevalence of Intestinal Schistosomiasis and Associated Factors among School Children in Wondo District, Ethiopia. *J. Trop. Med.* **2020**, *2020*, 1–8. [CrossRef]
29. World Health Organization. *Ending the Neglect to attain the Sustainable Development Goals: A Road Map for Neglected Tropical Diseases 2021–2030*; World Health Organization: Geneva, Switzerland, 2020; Licence: CC BY-NC-SA 3.0 IGO.
30. World Health Organization. *Preventive Chemotherapy in Human Helminthiasis*; WHO: Geneva, Switzerland, 2006.
31. Aula, O.P.; McManus, D.P.; Jones, M.K.; Gordon, C.A. Schistosomiasis with a Focus on Africa. *Trop. Med. Infect. Dis.* **2021**, *6*, 109. [CrossRef] [PubMed]
32. Woldeyohannes, D.; Sahiledengle, B.; Tekalegn, Y.; Hailemariam, Z. Prevalence of Schistosomiasis (*S. mansoni* and *S. haematobium*) and its association with gender of school age children in Ethiopia: A systematic review and meta-analysis. *Parasite Epidemiol. Control* **2021**, *13*, e00210. [CrossRef]
33. Ethiopia | ESPEN. Available online: <https://espen.afro.who.int/countries/ethiopia> (accessed on 4 April 2023).
34. World Health Organization. WHO Recommendation Expansion of Preventive Chemotherapy to All in Need. Available online: <https://www.who.int/activities/expanding-preventive-chemotherapy-to-all-in-need> (accessed on 12 April 2023).
35. Ministry of Health of Ethiopia. Neglected Tropical Diseases (NTDs) Program. Available online: https://www.moh.gov.et/site/initiatives-4-col/Neglected_Tropical_Diseases_Program (accessed on 3 April 2023).
36. Federal Democratic Republic of Ethiopia Ministry of Health. National Master Plan for Neglected Tropical Diseases (NTDs). Addis Ababa; 2013–2015. Available online: http://ec2-18-210-136-214.compute-1.amazonaws.com/sites/default/files/docs/national_ntd_master_plan_ethiopia_2013-2015 (accessed on 4 April 2023).
37. World Health Organization. Bench Aids for the Diagnosis of Intestinal Parasites. WHO, 1994. Available online: <http://apps.who.int/iris/bitstream/10665/37323/1/9789241544764> (accessed on 4 April 2023).
38. World Health Organization. *WHO Guideline on Control and Elimination of Human Schistosomiasis*; World Health Organization: Geneva, Switzerland, 2022; Available online: <https://www.who.int/publications-detail-redirect/9789240041608> (accessed on 4 April 2023).
39. WHO. *Schistosomiasis: Progress Report 2001–2011, Strategic Plan 2012–2020*; World Health Organization: Geneva, Switzerland, 2013; ISBN 978-92-4-150317-4.
40. Federal Ministry of Health, Ethiopia. *Guideline for the Transition of the Enhanced Outreach Strategy (EOS) to the Community Health Days/Health Extension Programme (CHD/HEP)*; Federal Ministry of Health: Addis Ababa, Ethiopia, 2012.

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.

Paper II

RESEARCH

Open Access



Efficacy and safety of praziquantel treatment against *Schistosoma mansoni* infection among pre-school age children in southern Ethiopia

Tafese Tadele¹, Ayalew Astatkie¹, Birkneh Tilahun Tadesse², Eyasu Makonnen^{3,4}, Eleni Aklillu^{5*}  and Solomon Mequanente Abay⁴

Abstract

Background Preventive chemotherapy with a single dose of praziquantel given to an all-at-risk population through mass drug administration is the cornerstone intervention to control and eliminate schistosomiasis as a public health problem. This intervention mainly targets school age children, and pre-school age children (pre-SAC) are excluded from receiving preventive chemotherapy, partly due to scarcity of data on praziquantel treatment outcomes.

Methods We conducted active efficacy and safety surveillance of praziquantel treatment among 240 *Schistosoma mansoni*-infected pre-SAC who received a single dose of praziquantel (40 mg/kg) in southern Ethiopia. The study outcomes were egg reduction rates (ERR) and cure rates (CRs) four weeks after treatment using the Kato–Katz technique and treatment-associated adverse events (AEs) that occurred within 8 days post-treatment.

Results The overall ERR was 93.3% (WHO reference threshold $\geq 90\%$), while the CR was 85.2% (95% CI = 80.0–89.5%). Baseline *S. mansoni* infection intensity was significantly associated with CRs, 100% among light infected than moderate (83.4%) or heavy (29.4%) infected children. An increase of 100 in baseline *S. mansoni* egg count per gram of stool resulted in a 26% (95% CI: 17%, 34%) reduction in the odds of cure. The incidence of experiencing at least one type of AE was 23.1% (95% CI: 18.0%, 29.0%). Stomachache, diarrhea, and nausea were the most common AEs. AEs were mild-to-moderate grade and transient. Pre-treatment moderate (ARR = 3.2, 95% CI: 1.69, 6.14) or heavy infection intensity (ARR = 6.5, 95% CI: 3.62, 11.52) was a significant predictor of AEs ($p < 0.001$). Sex, age, or soil-transmitted helminth coinfections were not significant predictors of CR or AEs.

Conclusions Single-dose praziquantel is tolerable and effective against *S. mansoni* infection among pre-SAC, and associated AEs are mostly mild-to-moderate and transient. However, the reduced CR in heavily infected and AEs in one-fourth of *S. mansoni*-infected pre-SAC underscores the need for safety and efficacy monitoring, especially in moderate-to-high infection settings. Integrating pre-SACs in the national deworming programs is recommended to accelerate the elimination of *schistosomiasis* as a public health problem.

*Correspondence:

Eleni Aklillu
eleniakillu@ki.se

Full list of author information is available at the end of the article



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

Keywords Efficacy, Safety, Praziquantel, Pre-school age children, Schistosomiasis, *Schistosoma mansoni*, Cure rate, Egg reduction rate, Pharmacovigilance, Ethiopia

Background

Schistosomiasis is a common Neglected Tropical Disease (NTD) and a public health problem in the tropical and subtropical regions of Africa, Asia, the Caribbean, and South America, mainly affecting poor and rural communities [1]. Sub-Saharan Africa (SSA) is the most significantly affected continent, bearing more than 90% of the global burden of schistosomiasis, with an estimated annual death rate of 280,000 and 800 million people at risk of infection [2–4]. In SSA, intestinal schistosomiasis is mainly caused by *Schistosoma mansoni* infection, and children living in poor communities without access to safe drinking water and adequate sanitation are the most affected population. The disease can cause growth retardation, fatigue, weakness, memory impairment, anemia, poor cognition, and academic performance in infected children [4, 5]. In Ethiopia, schistosomiasis is a major public health problem causing marginalization and stigmatization, as well as a social and economic burden [6]. Schistosomiasis is highly prevalent in Ethiopia, affecting mostly preschool-aged children (pre-SAC) and school-aged children (SAC) children [7–9]. The revised NTD master plan aims to halt transmission of *S. mansoni* infection and eliminate the disease as a public health problem by 2025 [6].

For over 40 years, praziquantel (PZQ) has been the only approved drug by the World Health Organization (WHO) to treat schistosomiasis [10]. Except for the ongoing clinical trials, no approved vaccine for preventing schistosomiasis is on the market to date [11]. The WHO guideline recommends large-scale periodic administration of single-dose PZQ and albendazole combination to all at-risk populations in endemic areas through mass drug administration (MDA) as a preventive chemotherapy to control and halt transmission of *S. mansoni* and soli-transmitted helminths (STH) infections, respectively [10, 12]. In 2021, 75.3 million people received treatment for schistosomiasis in endemic areas worldwide, of which 94% of all therapy delivered globally was in the African region [13].

The MDA programs mainly target SAC and pre-SAC are excluded from deworming programs due to limited PZQ safety and efficacy information in this age group and the lack of suitable pediatric formulation [14]. Recognizing the unmet medical needs of schistosome-infected pre-SAC, a public–private partnership called Pediatric Praziquantel Consortium was formed to develop an oral dispersible tablet formulation of PZQ to treat pre-SAC

infected with schistosomiasis. This Consortium supports the WHO strategic plan for schistosomiasis control and elimination in children [15]. Over a decade of annual school-based deworming with single-dose PZQ, MDA with scaled-up coverage resulted in a significant decrease in the number of disability-adjusted life years lost due to schistosomiasis [16]. However, the reduction has been less in pre-SAC mainly because they are not targeted for MDA [16]. Hence, the inclusion of pre-SAC in mass PZQ administration remains a priority to reduce the possible source of re-infection to at-risk populations covered with MDA and the occurrence of chronic schistosomiasis among pre-SAC. The safety and effectiveness of single-dose PZQ and associated factors are well-documented in SAC, but data are scarce from pre-SAC [17–20]. Few studies that assessed single-dose PZQ in pre-SAC reported its safety and tolerability but with varying egg reduction rate (ERR) and cure rate (CR) [21–25]. The most frequently reported adverse events (AEs) include abdominal pain, vomiting, nausea, dizziness, and diarrhea. The type and frequency of treatment-related AEs vary among populations due to genetic differences, nutritional status, age, intensity of infection, and other factors [17–20].

Preventive chemotherapy with single-dose PZQ is crucial to control and eliminate schistosomiasis as a public health problem and to fulfill the WHO strategy—Ending the Neglect to Attain the Sustainable Development Goals: A Road Map for Neglected Tropical Diseases 2021–2030 [26]. Achieving this goal relies, among others, on drug effectiveness and scaling up the program to involve all at-risk groups since untreated infected individuals can serve as parasite reservoirs for continued transmission in the community. The recent WHO guideline recommends the inclusion of pre-SAC in mass PZQ administration starting from the age of 2 years based on the efficacy and safety evidence reported from SAC and adult studies [1]. In the absence of other treatment alternatives, a single dose of PZQ of 40 mg/kg, which is recommended by the WHO for *S. mansoni* infections in SAC, is suggested for pre-SAC with proper efficacy and safety monitoring [22, 27]. Establishing the safety and efficacy of PZQ in pre-SAC children is urgently needed to inform the national NTD program and policymakers before nationwide scaling up of the intervention in this vulnerable age group. Therefore, the present study investigated the efficacy and safety of PZQ among *S. mansoni*-infected pre-SAC in southern Ethiopia.

Methods

Study area, setting, and design

A facility-based efficacy and safety surveillance study was conducted among pre-SAC (children aged 4–7 years) who were identified positive for *S. mansoni* infection during the baseline screening using Kato–Katz for *S. mansoni* infection in Hawella Tulla district, Sidama Region, southern Ethiopia. The study was conducted during August to December 2021 at Bushulo Health Center with comprehensive pediatric healthcare services, including laboratory facility enrolling cases linked from three catchment villages/*kebeles* (lowest administrative units in Ethiopia). The villages were Tullo, Finchawa, and Chefe Kotijebesa. According to the results of NTD mapping done in Ethiopia [28], these villages were categorized as high schistosomiasis prevalent areas.

The sample size based on anticipated ERR was estimated using G* power sample size calculation software. The assumptions used from a previous study [29] conducted among SAC were arithmetic mean (AM) \pm standard deviation (SD) of egg count before and after treatment being 365.06 ± 437.8 and 78.6 ± 65.6 respectively, power of 0.9, alpha (α) of 0.05, effect size of 0.2, and within-subject correlation of 0.5. The smaller effect size of 0.2 was considered to get a larger sample size, and the total sample size was 265. However, during the baseline screening for *S. mansoni* infection, 241 children tested positive for *S. mansoni* and constituted the final sample.

Study population

The study population were pre-SAC diagnosed with *S. mansoni* infection. The eligibility criteria for enrollment were being *S. mansoni*-infected aged 4–7 years, living in the study area permanently, and whose parents or primary caregivers gave written consent. Pre-SAC with known chronic medical conditions confirmed by the study physician on the day of the treatment were excluded from the study. Children who received PZQ treatment within the past 4 weeks and those who participated in any other drug trial during the data collection period were excluded to avoid the impact of other medications on the study. Except for one child who received PZQ before enrollment, all *S. mansoni*-infected pre-SAC from the three villages were enrolled for PZQ efficacy and safety evaluation.

Diagnosis, treatment, and follow-up

The study employed a community-based recruitment strategy that involved screening of pre-SAC at households in the catchment area of the health center. A total of 1683 pre-SAC (4 to 7 years old) residing at three study villages in the Hawella Tulla district of southern Ethiopia were screened for *S. mansoni* infection using

the Kato–Katz technique. *S. mansoni*-infected pre-SAC were linked to the health facility to get treatment. Children diagnosed with *S. mansoni* infection ($n=241$) were recruited and enrolled in this safety and efficacy surveillance study. After recording baseline sociodemographic data including age, sex, and medical history including pre-existing clinical symptoms, and comorbidities, concomitant medications, participants received a single dose of PZQ (40 mg/kg) as recommended by WHO [30]. Praziquantel 600 mg tablets (Batch M00761, Merck KGaA, Darmstadt, Germany) were obtained from the Ethiopian NTD control program. After meal intake, the treating physician gave each child the appropriate dosage calculated based on the child's body weight. The tablet was crushed with a mortar and pestle, and the powder was mixed and suspended in 10 ml of syrup-flavored water to mask the bitter taste. Crushing of the tablets avoids the risk of choking, which is a potential adverse event in pre-SAC and helpful to make suspension with syrup-flavored water [31]. The appropriate 40 mg/kg PZQ treatment was given to each participant through direct observed therapy by a trained nurse who prepared the medication. Study participants were followed for 8 days to monitor any treatment-associated adverse events, and efficacy was monitored at 4 weeks post-treatment as described previously [17, 20, 30, 32].

Stool exam using Kato–Katz technique

A single fresh stool sample was collected both at the baseline (pre-treatment) for diagnosis 4 weeks after drug administration (28 days) for monitoring drug efficacy in terms of ERR and CR following the WHO guideline for assessing the efficacy of anthelmintic drugs against schistosomiasis [30]. The stool samples were assessed through duplicate Kato–Katz thick smears (standard template of 41.7 mg) and *S. mansoni* eggs per gram of stool (EPG) was calculated by multiplying the mean egg count by a constant factor of 24 [33]. *S. mansoni* infection intensities were classified according to light infection (EPG < 100), moderate infection (EPG 100–399), and heavy infection intensities (EPG \geq 400) following the WHO guideline, as per the recommendation of the WHO [30].

Assessment of treatment-associated adverse events

Study participants were closely monitored for any treatment-associated AEs, including gastrointestinal, neurological, and dermatological symptoms within 4, 24, and 192 h of drug administration. The intensities of the reported AEs were graded as mild, moderate, and severe. Severity grading of treatment-associated AEs was done using the following Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 [34]:

Grade 1 (mild): asymptomatic or mild symptoms that require clinical or diagnostic observations only, with no indication of intervention.

Grade 2 (moderate): moderate AEs limiting age-appropriate Instrumental Activities of Daily Living (ADL); minimal, local, or non-invasive interventions indicated.

Grade 3 (severe): severe or medically significant AEs not immediately life-threatening but that are disabling and/or limiting self-care ADL. Hospitalization or prolongation of hospitalization indicated.

Grade 4 (serious)—comprises life-threatening consequences with an indication of urgent intervention.

Grade 5—death related to AE.

Before the commencement of the study, referral arrangements to a health facility with specialized pediatric care were in place for study participants with definite or suspected serious AEs (any event > grade 2) for further evaluation.

Study outcomes

The primary study outcome was efficacy (ERR and CR) based on the thick smear Kato–Katz method at 4 weeks post-treatment. The ERR was calculated as 100 times [1 – (Arithmetic mean egg counts at follow-up/Arithmetic mean egg counts at baseline)] per the recommendation of the WHO [30]. The CR was determined as the proportion of infected (egg-positive) children before treatment who became egg-free (egg-negative) at 4 weeks post-treatment. The secondary outcome was treatment-associated AEs experienced or reported within 8 days of drug administration. The major exposure variable was PZQ treatment administered in a single dose of 40 mg/kg. Other covariates for efficacy and safety included age, sex, and co-infection with the three common STHs: hookworm, *Ascaris lumbricoides*, and *Trichuris trichuria*.

Statistical analysis

All data were recorded on standard record forms, entered the RedCap database, and exported to an Excel file for cleaning. The data analysis was done using Stata version 14 (StataCorp LLC, College Station, Texas, US). Descriptive analyses were done by calculating frequencies and percentages for categorical variables, mean with standard deviations and medians with interquartile ranges for continuous variables. Associations between cure rates and predictor variables were analyzed using binary logistic regression. Predictors of the cure rate for *S. mansoni* infection were analyzed using univariate followed by multivariate logistic regression.

All predictor variables in the univariate analyses were entered into the multivariate model. Adjusted odds

ratios (AORs) with a 95% confidence interval (CIs) were reported based on the multivariable logistic regression model. Safety data were analyzed using descriptive statistics and presented in tables and graphs. The log-binomial regression was used to analyze the associations between having any AEs or not with predictor variables. Variables with a p value ≤ 0.25 on the crude analysis were included in the multivariable log-binomial regression model. Adjusted risk ratios (ARRs) with 95% confidence intervals (CIs) were reported based on the multivariable log-binomial model. A p value ≤ 0.05 was considered statistically significant.

Results

Sociodemographic and baseline characteristics

A total of 1683 pre-SAC were screened for *S. mansoni* infection, and 241 (14.3%) had detectable *S. mansoni* infection. Infected children ($n=240$) were enrolled in this safety and efficacy surveillance study and one child who had received PZQ treatment before enrollment was excluded from the study. Study participants received a single dose of 40 mg/kg PZQ. They were actively followed for 1 week to document any treatment-associated adverse event (safety) and for 28 days to assess the CR and ERR (efficacy). Complete data for efficacy and safety were available from 236 and 234 respectively. Two children withdrew from the study based on the informed decision of their parents. Two pre-SACs from efficacy evaluation and four pre-SACs from safety assessments were lost to follow-up. Figure 1 shows the study flow chart. Table 1 presents the sociodemographic characteristics of the study participants.

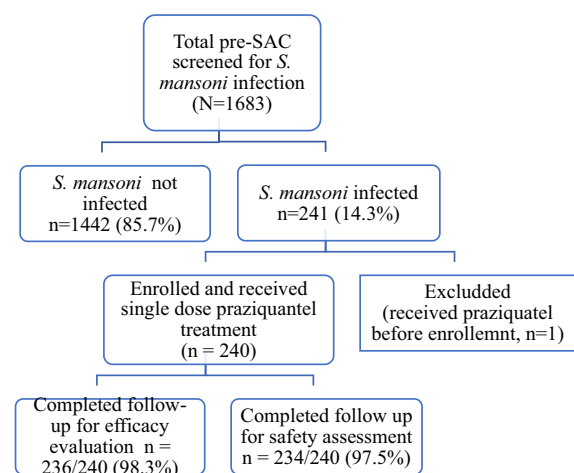


Fig. 1 Study flow chart of study participant pre-screening, recruitment, and follow-up among pre-school children

Table 1 Sociodemographic characteristics of the study participants

Characteristics		N (%)
Age (years)	Mean ± SD	5.99 ± 1.03
Age groups	4 to < 6 years	165 (69.9%)
	≥ 6 years	71 (30.1%)
Sex	Male	140 (59.3%)
	Female	96 (40.7%)
District	Tullo	160 (67.8%)
	Finchawa	45 (19.1%)
	Chefe Kotijebesa	31 (13.1%)

N: Total number of participants within each category; SD: standard deviation

Egg reduction rate and cure rate

The pre-treatment egg count among the pre-SAC ranged from 12 to 2560 EPG (median = 72 EPG; IQR = 24–228 EPG). The overall ERR (93.3%) was above the WHO reference threshold for efficacy regardless of sex, age category, status of STH co-infection or pre-treatment *S. mansoni* infection intensity (Table 2).

Of the 236 pre-SAC, 201 children became egg-free at 4 weeks post-treatment. The overall cure rate was 85.2% (95% CI = 80.0%, 89.5%). There was no significant difference in cure rate between females and males, age categories, or STH co-infection status. However, the cure rate was significantly different based on pre-treatment infection intensity, 100% among children with light infection intensity compared to those with moderate (83.3%) or heavy infections (29.4%).

Pre- and post-treatment *S. mansoni* infection intensity

All participants with light infection intensity showed 100% parasitological cure, while pre-treatment moderate infection intensity progressed to heavy infection intensity after treatment in one participant (1.5%). No persistent heavy infection intensity following PZQ treatment among pre-SAC was observed (Table 3).

Predictors of parasitological cure rate

Predictors of cure rate were analyzed using univariate followed by multivariate logistic regression. Sociodemographic characteristics, including age, sex, STH

Table 3 Cure rate stratified by the pre-treatment and post-treatment infection intensity among *S. mansoni*-infected pre-school children

Pre-treatment infection intensity	N (%)	Post-treatment	N (%)
Light infection	136 (57.6%)	Light	0
		Moderate	0
		Heavy	0
		Cured	136 (100%)
Moderate infection	66 (28.0%)	Light	7 (10.6%)
		Moderate	3 (4.6%)
		Heavy	1 (1.5%)
		Cured	55 (83.3%)
Heavy infection	34 (14.4%)	Light	12 (35.3%)
		Moderate	7 (20.6%)
		Heavy	0
		Cured	15 (44.1%)

N: Total number of participants within each category; CR: Cure rate

Table 2 Praziquantel cure rate and egg reduction rate stratified by sex, age category, infection intensity, and co-infection status among *S. mansoni*-infected pre-school children

Variables		Pre-treatment egg count per gram of stool Median (IQR)	Cure status			Egg reduction rate (ERR)	WHO reference threshold for ERR [30]
			Cured, n (%)	Not Cured, n (%)	P		
Overall		72 (24–228)	201 (85.2%)	35 (14.8%)		93.3%	≥ 90
Sex	Female	84 (24–216)	82 (85.4%)	14 (14.6%)	0.92	92.0%	
	Male	72 (24–231)	119 (85.0%)	21 (15.0%)		94.5%	
Age category	< 6 years	72 (24–168)	61 (85.9%)	10 (14.1%)	0.83	92.5%	
	≥ 6 years	72 (24–240)	140 (84.9%)	25 (15.2%)		93.7%	
Infection intensity at baseline	Light	24 (12–60)	136 (100%)	–	< 0.001	100.0%	
	Moderate	186 (132–288)	55 (83.3%)	11 (16.7%)		93.2%	
	Heavy	816 (627–1242)	10 (29.4%)	24 (70.6%)		92.0%	
STH co-infection	No	60 (24–192)	143 (86.1%)	23 (13.9%)	0.42	92.2%	
	Yes	96 (48–288)	58 (82.9%)	12 (17.1%)		95.8%	

IQR = Interquartile range; SD = Standard deviations; STH = soil-transmitted helminths

co-infection, and baseline egg count in hundred, were analyzed in the univariate and multivariable regression model. An increase of 100 in baseline egg count resulted in a 26% (95% CI: 17%, 34%) reduction in the odds of cure. None of the other variables had a significant association with the odds of cure (Table 4).

Incidence and type of treatment-associated adverse events

Two hundred thirty-four participants completed the 8-day post-treatment safety follow-up period, and 54 reported experiencing 169 treatment-associated AEs. The overall incidence of experiencing at least one type of treatment-associated AEs was 23.1% (95% CI: 18.0–29.0%). Among the participants who experienced AEs,

33 (61.1%) experienced three or more types of AEs, 15 (27.8%) experienced two types of AEs, and the remaining 6 (11.1%) experienced one type of AE. Of the 169 AEs that occurred after treatment, 110 (65.1%) of the AEs occurred within 4 h of receiving treatment, and 59 (34.9%) occurred during day 2 to 8 follow-up period (Table 5).

Stomachache (16.0%), diarrhea (11.2%), nausea (10.7%), drowsiness and fever (10.1%), vomiting (9.5%), headache (7.7%), dizziness (8.9%), and loss of appetite (8.3%) were the most common AEs following PZQ treatment among *S. mansoni*-infected pre-SAC. The least reported AEs were confusion (3.0%), cough and itching (1.8%), and other symptoms (1.2%) (Fig. 2).

Table 4 Predictors of parasitological cure at week four post praziquantel treatment among pre-school children infected with *S. mansoni*

Variable	Category	<i>S. mansoni</i> infection status after treatment		COR (95%CI)	p value	AOR (95% CI)	p value
		Cured	Not cured				
Age groups (years)	4 to < 6 years	61 (85.9%)	10 (14.1%)	1.0		1.0	
	≥ 6 years	140 (84.9%)	25 (15.2%)	1.08 (0.49, 2.41)	0.8	0.65 (0.27, 1.58)	0.3
Sex	Female	82 (85.4%)	14 (14.6%)	1.0		1.0	
	Male	119 (85.0%)	21 (15.0%)	0.97 (0.47, 2.01)	0.9	0.93 (0.39, 2.18)	0.9
Infection status	<i>S. mansoni</i> only infected	143 (86.1%)	23 (13.9)	1.0		1.0	
	<i>S. mansoni</i> and STH infected	58 (82.9%)	12 (17.1%)	0.78 (0.36, 1.67)	0.5	0.88 (0.36, 2.13)	0.8
Baseline egg count in hundreds		201 (85.2%)	35 (14.8%)	0.75 (0.67, 0.84)	< 0.001	0.74 (0.66, 0.83)	< 0.001

COR: Crude odds ratio; AOR: Adjusted odds ratio; CI: confidence interval; STH: Soil-transmitted helminths

Table 5 Proportion of treatment-associated adverse events stratified by type and time

Type of AEs	N	Day1 at 4 h [N (%)]	Day2 at 24 h [N (%)]	Day 8 at 192 h [N (%)]
Stomachache	27	19 (70.4)	8 (29.6)	
Diarrhea	19	10 (52.6)	7 (36.8)	2 (10.5)
Nausea	18	12 (66.7)	4 (22.2)	2 (11.1)
Drowsiness	17	9 (52.9)	8 (47.1)	
Vomiting	16	10 (62.5)	4 (25.0)	2 (12.5)
Dizziness	15	11 (73.3)	4 (26.7)	
Fever	17	12 (70.6)	5 (29.4)	
Loss of appetite	14	9 (64.3)	5 (35.7)	
Headache	13	8 (61.5)	5 (38.5)	
Cough	3	2 (66.7)	1 (33.3)	
Confusion	5	5 (100.0)		
Itching	3	2 (66.7)		1 (33.3)
Other symptoms	2	1 (50.0)	1 (50.0)	
Total	169	110 (65.1)	52 (30.8)	7 (4.1)

AEs: adverse events; N: total number of AEs; h: hours

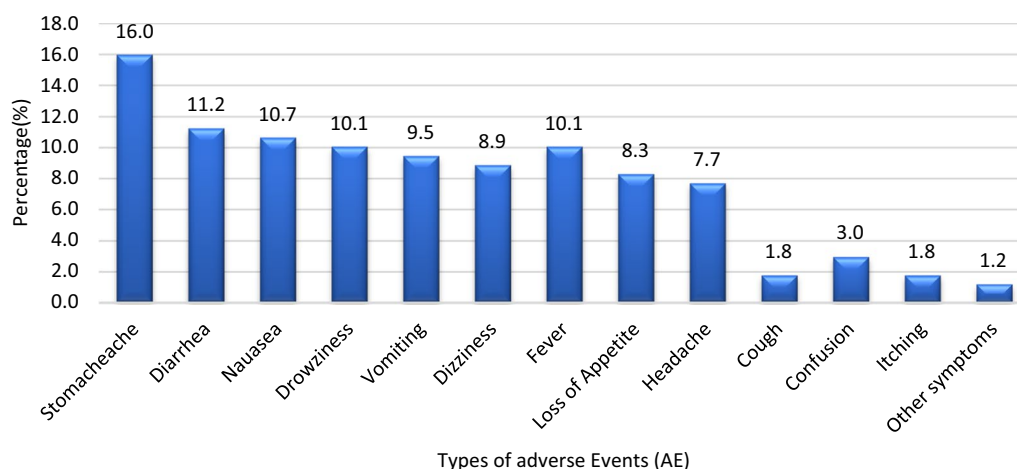


Fig. 2 Proportion of praziquantel treatment adverse events over the 8-day follow-up period

Severity grading of adverse events

Out of the total 169 treatment-associated AEs, 88.8% ($n=150$) were mild, 10.7% ($n=18$) were moderate, and only 0.6% ($n=1$) were severe. Most of the AEs were transient and resolved within 2 days of post-treatment. No life-threatening AE that required hospitalization (Grade 4) was reported (Table 6).

Predictors of treatment-associated adverse events

In multivariable log-binomial regression, residing in Tullo village (ARR=8.8, 95% CI: 1.28, 60.93) and pre-treatment moderate infection intensity (ARR=3.2, 95% CI: 1.69, 6.14) and heavy infection intensity (ARR=6.5, 95% CI: 3.6, 11.52) were significant predictors of PZQ treatment AEs (Table 7). The distribution of pre-treatment heavy

S. mansoni infection intensity varied greatly between villages, being higher in Tullo village (18%) followed by Chefe Kotijebesa (10%), and Finchawa village (7%).

Discussion

In this study, we assessed the safety, tolerability, and effectiveness of single-dose PZQ for the treatment of *S. mansoni* infection among pre-SAC in southern Ethiopia. The type, incidence, and severity grading of treatment-associated AEs that occurred within a week after receiving treatment were assessed. Reported post-treatment AEs were cross-checked and verified with any existing symptoms or clinical conditions before receiving treatment, and efficacy was measured in terms of CRs and ERR following the WHO guideline for assessing the

Table 6 Severity grading of reported adverse events following praziquantel treatment among *S. mansoni*-infected pre-school children

Type of AEs	Total number of AEs	Grade1 (Mild)	Grade2 (Moderate)	Grade3 (Severe)
Stomachache	27	20 (74.1%)	6 (22.2%)	1 (3.7%)
Diarrhea	19	17 (89.5%)	2 (10.5%)	
Nausea	18	16 (88.9%)	2 (11.1%)	
Drowsiness	17	15 (88.2%)	2 (11.8%)	
Fever	17	16 (94.1%)	1 (5.9%)	
Vomiting	16	13 (81.2%)	3 (18.8%)	
Dizziness	15	13 (86.7%)	2 (13.3%)	
Loss of appetite	14	14 (100%)		
Headache	13	13 (100%)		
Confusion	5	5 (100%)		
Cough	3	3 (100%)		
Itching	3	3 (100%)		
Other symptoms	2	2 (100%)		
Total	169	150 (88.8%)	18 (10.6%)	1 (0.6%)

N: Total number of AEs within each type; AEs: Adverse events

Table 7 Predictors of adverse events following praziquantel treatment among pre-school children infected with *S. mansoni*

Variable		AEs after treatment		CRR (95%CI)	p value	ARR (95% CI)	p value
		AEs	No AEs				
Age groups (years)	4 to <6 years	21 (22.3)	73 (77.7)	1.0		–	
	≥ 6 years	33 (23.6)	107 (76.4)	1.1 (0.65, 1.71)	0.8	–	
Sex	Female	18 (18.8)	78 (81.3)	1.0		1.0	
	Male	36 (26.1)	102 (73.9)	1.4 (0.84, 2.30)	0.2	1.2 (0.81, 1.73)	0.4
District	Chefe Kotijebesa	1 (3.2)	30 (96.8)	1.0		1.0	
	Tullo	49 (30.6)	111 (69.4)	9.5 (1.36, 66.18)	0.02	8.8 (1.28, 60.93)	0.03
	Finchawa	4 (9.3)	39 (90.7)	2.9 (0.34, 24.55)	0.3	4.4 (0.54, 35.31)	0.2
Infection status	<i>S. mansoni</i> only infected	35 (21.3)	129 (78.7)	1.0		1.0	
	<i>S. mansoni</i> +STH infected	19 (27.1)	51 (72.9)	1.3 (0.78, 2.06)	0.3	–	
Baseline infection intensity	Light	12 (9.0)	122 (91.0)	1.0			
	Moderate	19 (28.8)	47 (71.2)	3.2 (1.66, 6.22)	0.001	3.2 (1.69, 6.14)	<0.001
	Heavy	23 (67.7)	11 (32.4)	7.6 (4.20, 13.60)	<0.001	6.5 (3.62, 11.52)	<0.001
Praziquantel dose	≤ 1.5 tabs	24 (22.6)	82 (77.4)	1.0			
	> 1.5 tabs	30 (23.4)	98 (76.6)	1.0 (0.65, 1.66)	0.9	–	

CRR: Crude risk ratio, ARR: Adjusted risk ratio, CI: confidence interval

efficacy of anthelmintic drugs against schistosomiasis [30].

Our study had several notable findings. First, the overall PZQ treatment showed satisfactory ERR (93.3%) and CR (85.2%) against *S. mansoni* infection among pre-SAC; Second, pre-treatment infection intensity was a significant predictor of CR. While all children with light and 83.3% with moderate infection intensity were cured, only one-third of those with heavy infection intensity were cured. A higher baseline egg count was associated with reduced odds of cure. Third, overall, PZQ treatment was tolerated, and about one-fifth of pre-SAC (23.1%) experienced at least one type of treatment-associated mild-to-moderate grade AEs during the first 2 days of receiving treatment. Stomachache, diarrhea, and nausea were the most common AEs. The reported AEs were transient, resolving within a week. Fourth, pre-treatment moderate-to-heavy infection intensity was significantly associated with an increased risk of experiencing treatment-associated AEs. No significant effect of sex, age, or STH co-infection status on the safety and efficacy of PZQ was observed.

Monitoring efficacy after multiple rounds of MDA is recommended since repeated drug exposure may result in parasite tolerability and resistance [35]. Our finding indicates that single-dose PZQ significantly reduced *S. mansoni* infection among pre-SAC, and the overall ERR of 93.3% was above the 90% threshold for optimal PZQ efficacy set by the WHO [30]. Previous studies of single-dose PZQ (40 mg/kg) given to pre-SAC reported varying CR and ERR [23]. A randomized controlled trial conducted in southern Côte d'Ivoire to compare a

single dose of 20 mg/kg, 40 mg/kg, and 60 mg/kg PZQ reported the best cure (72%) with 40 mg/kg among pre-SAC [36]. A higher CR and ERR in pre-SAC from Sudan (geometric mean egg reduction rates ranging from 96.4% to 99.4%) [37] and from Eastern Ethiopia (96.4% CR, 99.4% ERR) were reported [25]. On the other hand, a considerably low CR (50.6%) and a geometric mean ERR of 66.7% at 6 weeks post-treatment from Niger were reported [38]. Nevertheless, the observed CR and ERR in pre-SAC in our study are in line with a recent report conducted among *S. mansoni*-infected SAC from the same study area (89.1% CR, 93.7% ERR) [20] and a systematic review of other studies from Ethiopia (pooled CR=89.2% (95% CI: 85.4–93.1), mean ERR=90.2%) [39].

The difference in the PZQ treatment outcome between populations could be due to variability in infection intensity prevalence in different geo-locations, and the follow-up time in the study setting might contribute to the difference in ERR among pre-SAC infected with *S. mansoni*. Furthermore, recent studies highlight the importance of genetic variation for PZQ disposition [19, 40], but the impact of genetic variations on PZQ treatment outcomes needs further investigation. Despite the relatively lower CR of pre-SAC with moderate-to-heavy intensity infection groups than the light-intensity infection, the moderate-to-heavy intensity showed satisfactory ERR. This finding indicates that PZQ could reduce morbidities associated with moderate-to-heavy intensity infections among pre-SAC in hyper-endemic communities. This might be related to the paralyzing effect of PZQ on the parasite

fecundity, which, in turn, results in low egg count post-treatment, as reported in a previous study [41].

In the present study, even though PZQ showed a high CR against *S. mansoni* infection, about 14.8% of the study participants were not cured of the infection 4 weeks after treatment. The CR among moderately to heavily infected pre-SAC was significantly lower (29.3%) than those who had light (100%) or moderate (83.3%) infection intensity. An increase of 100 in baseline egg count decreased the odds of cure by 26%. Several studies reported significantly reduced CR among moderate-to-heavy infected children than light infections [18, 20, 32]. This could be attributed to the poor efficacy of PZQ against the immature/juvenile stage of the parasites [11, 18]. Repeated infections leading to suppression of the immune response resulting in the survival of the adult worms to favor the spread of infection might also be responsible for the ineffectiveness of PZQ in curing all study participants. This highlights the need to integrate other intervention measures besides MDA, as WHO recommended, to enhance the achievement of the elimination target [1]. Although the observed ERR and CR in the present study indicate that PZQ is effective against *S. mansoni* infection to reduce morbidity among pre-SAC in endemic communities, the search for new anti-schistosome drugs or other alternative treatment strategies, such as drug combinations targeting the different developmental stages of the parasites, is imperative to eliminate the diseases [18, 42].

The present study showed that a single dose of PZQ (40 mg/kg) is tolerable among *S. mansoni*-infected pre-SAC. The overall cumulative incidence of experiencing at least one type of AE among pre-SAC was 23.1% within 8 days of PZQ administration. A recent study among *S. mansoni*-infected SAC (17.0%) from the same study area in Ethiopia and another study in Rwanda (20.6%) revealed a slightly lower incidence of AE compared to our study in pre-SAC [17, 20]. Our study finding aligns with previous reports of a higher incidence rate of AEs in pre-SAC than SAC [43]. The most common AEs observed after receiving PZQ were gastrointestinal disorders. Our finding aligns with previous reports in pre-SAC from elsewhere [38]. The difference in reported AE incidence may be due to variations in intensity of infections and parasite transmission. Genetic differences in the study population, physiological, nutritional, follow-up period, and other environmental factors may also cause variability in treatment outcomes [21, 43]. The difference in AE incidence in various population segments indicates the need for safety monitoring since results from SAC and adult studies may not apply to pre-SAC.

Fifty-four pre-SAC reported a total number of 169 AEs during the follow-up period. Of the total treatment-associated AEs, 65.1% occurred within 4 h of drug intake, and

the rest occurred between days 2 to 8 post-drug administration. The most common AEs reported in this study were stomachache, nausea, diarrhea, drowsiness, fever, and vomiting. This observation is similar to previous studies conducted among children aged 2 to 15 in Angola [43] and SAC in Ethiopia [29]. Cough and rash were the least reported AEs in the present study. Almost all the observed AEs were mild and self-limiting, which agrees with reports from studies among SAC in Rwanda [17], Ethiopia [20], and another previous study [44].

The present study showed residing in Tullo village with a higher moderate-to-heavy *S. mansoni* infection intensity was a significant predictor of AEs. The highest incidence of AEs (30.6%) was observed at Tullo village, followed by 9.3% at Finchawa village and 3.2% at Chefe Kotjebesa village. Residing in Tullo village increased the risk of experiencing at least one AE by 20% compared to living in Chefe Kotjebesa village. The increased risk of AEs in Tullo village children could be due to the high number of cases with heavy-intensity infection in this village. The village is closer to the infested water body bordering Lake Hawassa than the other study villages. Pre-SAC with heavy baseline infection intensity had a 6.5 times increased risk of experiencing an AE, and those with moderate infection intensity experienced a 3.2 times increased risk compared to those with light infection intensity. A similar finding was reported by a study conducted in the same area among SAC [45]. Thus, safety monitoring of PZQ administration to pre-SAC living in hyper-endemic villages and high pre-treatment infection intensity remains crucial.

Following the WHO guideline to assess anthelmintic drug efficacy [30], we used the Kato–Katz technique to determine CR and ERR and compare them with the threshold set in the guideline to conclude PZQ effectiveness. The Kato–Katz technique can accurately detect schistosome eggs in stool in high-intensity infection settings to diagnose the disease and conduct infection-intensity assessment, and program evaluation. However, in low-intensity infection settings, the Kato–Katz technique is less sensitive and may result in an overestimation of the efficacy. Hence, using this technique in our study can be considered a limitation. Nevertheless, our surveillance study was conducted in a moderate-to-high-intensity infection area [8], and the CR and ERR observed in our study may accurately estimate PZQ efficacy. On the other hand, point-of-care urine circulating cathodic antigen (POC-CCA), the other alternative diagnostic method, is not yet approved by WHO to assess anthelmintic drug efficacy, and it requires further evaluation, including post-treatment CCA clearance time in different age groups and epidemiological settings [46, 47]. Findings from this study provide valuable evidence on the

safety and efficacy of single-dose PZQ treatment among *S. mansoni*-infected pre-SAC for the national NTD program in Ethiopia and the SSA region that follows the WHO guidelines and NTD control strategies.

Conclusions

Single-dose PZQ (40 mg/kg) administered to *S. mansoni*-infected pre-SAC is effective in curing light-to-moderate infection intensities and reducing morbidity in heavy infections. The treatment is tolerable, and associated AEs are mostly mild-to-moderate and transient resolving within a week. Pre-treatment moderate-to-heavy intensity infection significantly predicts failure to cure and experience treatment-associated adverse events. The lack of cure in 35 (14.8%) and adverse events in one-fifth (23.1%) of *S. mansoni*-infected pre-SAC highlights the need for consistent and close monitoring of the efficacy and safety of the drug, especially in high-transmission and high infection-intensity endemic area. We advocate the inclusion of pre-SAC in the national deworming program and other disease control intervention measures to accelerate the achievement of eliminating schistosomiasis as a public health problem by 2030. Schistosomiasis control program could be extended to pre-SAC using crushed PZQ tablets before the availability of a pediatric formulation.

Abbreviations

CR	Cure rate
ERR	Egg reduction rate
MDA	Mass drug administration
PZQ	Praziquantel
Pre-SAC	Pre-school age children
STH	Soil-transmitted helminths
SSA	Sub-Saharan Africa

Acknowledgements

We thank the Neglected Tropical Diseases Control Program team of the Ministry of Health Ethiopia and the Ethiopian Public Health Institute Neglected Tropical Diseases Control Program team, officials from the Hawella Tulla District Health Office and kebele administrators for their support during the conduct of the study. We extend our gratitude to Bushulo Health Center and Hawassa University Comprehensive Specialized Hospital staff for the favorable working environment and their participation in the planning, awareness creation, and supervision during the data collection. We are grateful to the health extension workers from the three study villages for their facilitation during the data collection. We thank the study participants and their parents/primary caregivers from the three villages for their participation.

Author contributions

TT, EM, EA, and SMA conceived and designed the study. TT, AA, BTT, EM, EA, and SMA conducted the study and analyzed the data. AA, EM, EA, and SMA supervised the study. EA, EM, and SMA acquired funding. TT wrote the first draft, and all authors reviewed the manuscript. All authors read and approved the final manuscript.

Funding

Open access funding provided by Karolinska Institute. This study was conducted as part of the Pharmacovigilance infrastructure and post-marketing surveillance system capacity building for regional medicine regulatory harmonization in East Africa (PROFORMA) project funded by the European &

Developing Countries Clinical Trials Partnership (EDCTP) 2 program supported by the European Union (Grant number CSA2016S-1618) and the Swedish International Development Cooperation Agency (SIDA), and PrazOpt project funded by the EDCTP 2 program supported by the European Union (Grant number TMA2018CDF-2345).

Availability of data and materials

All data presented in this study are contained within the manuscript.

Declarations

Ethics approval and consent to participate

The study was conducted as per the Declaration of Helsinki and approved by the Institutional Review Board of the College of Medicine and Health Sciences of Hawassa University (Ref. No: IRB/200/13) and the national research ethics review committee (Ref no MoSHE/RD/401/0974/20). Written informed consent was obtained from parents/primary caregivers of each study participant after clarifying the purpose, method, possible risks/benefits, rights, confidentiality, nature of the study, and the scope of their involvement in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

Author details

¹School of Public Health, College of Medicine and Health Sciences, Hawassa University, P.O. Box 1560, Hawassa, Ethiopia. ²Department of Pediatrics, College of Medicine and Health Sciences, Hawassa University, P.O. Box 1560, Hawassa, Ethiopia. ³Center for Innovative Drug Development and Therapeutic Trials for Africa, College of Health Sciences, Addis Ababa University, P.O. Box 9086, Addis Ababa, Ethiopia. ⁴Department of Pharmacology and Clinical Pharmacy, College of Health Sciences, Addis Ababa University, P.O. Box 9086, Addis Ababa, Ethiopia. ⁵Department of Global Public Health, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden.

Received: 24 September 2023 Accepted: 9 December 2023

Published online: 20 December 2023

References

- World Health Organization. Guideline on control and elimination of human schistosomiasis. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO. 2022.
- van der Werf MJ, de Vlas SJ, Brooker S, Looman CW, Nagelkerke NJ, Habbema JD, Engels D. Quantification of clinical morbidity associated with schistosome infection in sub-Saharan Africa. *Acta Trop*. 2003;86(2–3):125–39. [https://doi.org/10.1016/s0001-706x\(03\)00029-9](https://doi.org/10.1016/s0001-706x(03)00029-9).
- Aula OP, McManus DP, Jones MK, Gordon CA. Schistosomiasis with a focus on Africa. *Trop Med Infect Dis*. 2021. <https://doi.org/10.3390/tropicalmed6030109>.
- Adenowo AF, Oyinyoye BE, Ogunyinka BI, Kappo AP. Impact of human schistosomiasis in sub-Saharan Africa. *Braz J Infect Dis*. 2015;19(2):196–205. <https://doi.org/10.1016/j.bjid.2014.11.004>.
- Stecher CW, Sacko M, Madsen H, Wilson S, Wejse C, Keita AD, Landouze A, Traore MS, Kallestrup P, Petersen E, Vennervald B. Anemia and growth retardation associated with *Schistosoma haematobium* infection in Mali: a possible subtle impact of a neglected tropical disease. *Trans R Soc Trop Med Hyg*. 2017;111(4):144–53. <https://doi.org/10.1093/trstmh/trx037>.
- Federal Democratic Republic of Ethiopia Ministry of Health. The Third National Neglected Tropical Diseases Strategic Plan 2021–2025. Addis Ababa, Ethiopia: 2021. Available online: <https://espen.afro.who.int/system/files/content/resources/Third%20NTD%20national%20Strategic%20Plan%202021-2025.pdf>. Accessed 15 Nov 2023.
- Bisetegn H, Eshetu T, Erkihun Y. Prevalence of *Schistosoma mansoni* infection among children in Ethiopia: a systematic review and meta-analysis.

- Trop Dis Travel Med Vaccines. 2021;7(1):30. <https://doi.org/10.1186/s40794-021-00156-0>.
8. Tadele T, Astatkie A, Abay SM, Tadesse BT, Makonnen E, Akillu E. Prevalence and determinants of *Schistosoma mansoni* infection among pre-school age children in Southern Ethiopia. *Pathogens*. 2023;12(7):858. <https://doi.org/10.3390/pathogens12070858>.
 9. Gebreyesus TD, Tadele T, Mekete K, Barry A, Gashaw H, Degefe W, Tadesse BT, Gerba H, Gurumurthy P, Makonnen E, Akillu E. Prevalence, intensity, and correlates of schistosomiasis and soil-transmitted helminth infections after five rounds of preventive chemotherapy among school children in southern Ethiopia. *Pathogens*. 2020;9(11):920. <https://doi.org/10.3390/pathogens9110920>.
 10. Preventive chemotherapy in human helminthiasis. Coordinated use of anthelmintic drugs in control interventions: a manual for health professionals and programme managers. Available online: <https://www.who.int/publications/i/item/9241547103>. Accessed 15 Nov 2023.
 11. Molehin AJ. Schistosomiasis vaccine development: update on human clinical trials. *J Biomed Sci*. 2020;27(1):28. <https://doi.org/10.1186/s12929-020-0621-y>.
 12. WHO. World Health Organization World Health Assembly. Schistosomiasis and Soil-Transmitted Helminth Infections. World Health Assembly 54.19 Available online: <https://apps.who.int/iris/bitstream/handle/10665/78794/ea54r19.pdf>. Accessed 10 Nov 2023.
 13. World Health Organization. Schistosomiasis and soil-transmitted helminthiasis: progress report, 2021. *Weekly Epidemiological Record*, 2022, 48, 97, 621–632. Latest information on epidemiology, distribution and progress made against schistosomiasis. Available online: <https://www.who.int/publications/i/item/who-wer9748-621-632>. Accessed 10 Nov 2023.
 14. Report of a meeting to review the results of studies on the treatment of Schistosomiasis in preschool-age children, WHO report. Geneva: World Health Organization, 2010. Available online: <https://www.who.int/publications/i/item/9789241501880>. Accessed 10 Nov 2023.
 15. Reinhard-Rupp J, Klohe K. Developing a comprehensive response for treatment of children under 6 years of age with schistosomiasis: research and development of a pediatric formulation of praziquantel. *Infect Dis Poverty*. 2017;6(1):122. <https://doi.org/10.1186/s40249-017-0336-9>.
 16. Montresor A, Mwinzi P, Mupfasoni D, Garba A. Reduction in DALYs lost due to soil-transmitted helminthiasis and schistosomiasis from 2000 to 2019 is parallel to the increase in coverage of the global control programmes. *PLoS Negl Trop Dis*. 2022;16(7): e0010575. <https://doi.org/10.1371/journal.pntd.0010575>.
 17. Kabatende J, Barry A, Mugisha M, Ntiringanya L, Bergman U, Bienvenu E, Akillu E. Safety of praziquantel and albendazole coadministration for the control and elimination of schistosomiasis and soil-transmitted helminths among children in Rwanda: an active surveillance study. *Drug Saf*. 2022;45(8):909–22. <https://doi.org/10.1007/s40264-022-01201-3>.
 18. Mnkugwe RH, Minzi O, Kinung'hi S, Kamuhabwa A, Akillu E. Efficacy and safety of praziquantel and dihydroartemisinin piperazine combination for treatment and control of intestinal schistosomiasis: a randomized, non-inferiority clinical trial. *PLoS Negl Trop Dis*. 2020;14(9): e0008619. <https://doi.org/10.1371/journal.pntd.0008619>.
 19. Mnkugwe RH, Minzi O, Kinung'hi S, Kamuhabwa A, Akillu E. Effect of pharmacogenetics variations on praziquantel plasma concentrations and schistosomiasis treatment outcomes among infected school-aged children in Tanzania. *Front Pharmacol*. 2021;12: 712084. <https://doi.org/10.3389/fphar.2021.712084>.
 20. Gebreyesus TD, Makonnen E, Tadele T, Mekete K, Gashaw H, Gerba H, Akillu E. Efficacy and safety of praziquantel preventive chemotherapy in *Schistosoma mansoni* infected school children in Southern Ethiopia: a prospective cohort study. *Front Pharmacol*. 2023;14: 968106. <https://doi.org/10.3389/fphar.2023.968106>.
 21. Sousa-Figueiredo JC, Betson M, Atuhaire A, Arinaitwe M, Navaratnam AM, Kabatereine NB, Bickle Q, Stothard JR. Performance and safety of praziquantel for treatment of intestinal schistosomiasis in infants and preschool children. *PLoS Negl Trop Dis*. 2012;6(10): e1864. <https://doi.org/10.1371/journal.pntd.0001864>.
 22. Olliaro PL, Coulibaly JT, Garba A, Halleux C, Keiser J, King CH, Mutapi F, N'Goran EK, Raso G, Scherrer AU, Sousa-Figueiredo JC, Stete K, Utzinger J, Vaillant MT. Efficacy and safety of single-dose 40 mg/kg oral praziquantel in the treatment of schistosomiasis in preschool-age versus school-age children: an individual participant data meta-analysis. *PLoS Negl Trop Dis*. 2020;14(6): e0008277. <https://doi.org/10.1371/journal.pntd.0008277>.
 23. Kabuyaya M, Chimbari MJ, Mukaratirwa S. Efficacy of praziquantel treatment regimens in pre-school and school aged children infected with schistosomiasis in sub-Saharan Africa: a systematic review. *Infect Dis Poverty*. 2018;7(1):73. <https://doi.org/10.1186/s40249-018-0448-x>.
 24. Kimani BW, Mbugua AK, Kihara JH, Ng'ang'a M, Njomo DW. Safety, efficacy and acceptability of praziquantel in the treatment of *Schistosoma haematobium* in pre-school children of Kwale County, Kenya. *PLoS Negl Trop Dis*. 2018;12(10): e0006852. <https://doi.org/10.1371/journal.pntd.0006852>.
 25. Kemal M, Tadesse G, Esmael A, Abay SM, Kebede T. *Schistosoma mansoni* infection among preschool age children attending Erer Health Center, Ethiopia and the response rate to praziquantel. *BMC Res Notes*. 2019;12(1):211. <https://doi.org/10.1186/s13104-019-4246-8>.
 26. WHO. Ending the neglect to attain the Sustainable Development Goals: a road map for neglected tropical diseases 2021–2030. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO. 2020.
 27. Montresor A, Garba A. Treatment of preschool children for schistosomiasis. *Lancet Glob Health*. 2017;5(7):e640–1. [https://doi.org/10.1016/S2214-109X\(17\)30202-4](https://doi.org/10.1016/S2214-109X(17)30202-4).
 28. Federal Democratic Republic of Ethiopia Ministry of Health. Second Edition of National Neglected Tropical Diseases Master Plan, Addis Ababa. Available online: [<https://www.afro.who.int/publications/second-edition-national-neglected-tropical-diseases-master-plan-ethiopia-2016>]. Accessed 10 Nov 2023.
 29. Erko B, Degarege A, Tadesse K, Mathiwas A, Legesse M. Efficacy and side effects of praziquantel in the treatment of *Schistosoma mansoni* in schoolchildren in Shesha Kekele Elementary School, Wondo Genet, Southern Ethiopia. *Asian Pac J Trop Biomed*. 2012;2(3):235–9. [https://doi.org/10.1016/S2221-1691\(12\)60049-5](https://doi.org/10.1016/S2221-1691(12)60049-5).
 30. World Health Organization, Geneva (2013). Assessing the efficacy of anthelmintic drugs against schistosomiasis and soil-transmitted helminthiasis. Available online: <https://apps.who.int/iris/handle/10665/79019>. Accessed 15 Nov 2023.
 31. Kernell JW, DePaola RV, Maglione AM, Ahern LN, Penney NG, Adhiss DG. Risk of adverse swallowing events and choking during deworming for preschool-aged children. *PLoS Negl Trop Dis*. 2018;12(6): e0006578. <https://doi.org/10.1371/journal.pntd.0006578>.
 32. Mnkugwe RH, Minzi OS, Kinung'hi SM, Kamuhabwa AA, Akillu E. Efficacy and safety of praziquantel for treatment of *Schistosoma mansoni* infection among school children in Tanzania. *Pathogens*. 2019. <https://doi.org/10.3390/pathogens9010028>.
 33. World Health Organization. (1991). Basic laboratory methods in medical parasitology. World Health Organization. Available online: <https://apps.who.int/iris/handle/10665/40793>. Accessed 10 Nov 2023.
 34. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Available online: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5x11.pdf. Accessed 10 Nov 2023.
 35. Crellen T, Walker M, Lambertson PH, Kabatereine NB, Tukahebwa EM, Cotton JA, Webster JP. Reduced efficacy of praziquantel against *Schistosoma mansoni* is associated with multiple rounds of mass drug administration. *Clin Infect Dis*. 2016;63(9):1151–9. <https://doi.org/10.1093/cid/ciw506>.
 36. Coulibaly JT, Panic G, Silue KD, Kovac J, Hattendorf J, Keiser J. Efficacy and safety of praziquantel in preschool-aged and school-aged children infected with *Schistosoma mansoni*: a randomised controlled, parallel-group, dose-ranging, phase 2 trial. *Lancet Glob Health*. 2017;5(7):e688–98. [https://doi.org/10.1016/S2214-109X\(17\)30187-0](https://doi.org/10.1016/S2214-109X(17)30187-0).
 37. Amin MA, Swar M, Kardaman M, Elhussein D, Nouman G, Mahmoud A, Appiah A, Babiker A, Homeida M. Treatment of pre-school children under 6 years of age for schistosomiasis: safety, efficacy and acceptability of praziquantel. *Sudan J Med Sci*. 2012;7(2):67–76.
 38. Garba A, Lamine MS, Djibo A, Tahirou A, Aouami MA, Alfari A, Phillips AE, Fenwick A, Utzinger J. Safety and efficacy of praziquantel syrup (Epiquantel(R)) against *Schistosoma haematobium* and *Schistosoma mansoni* in preschool-aged children in Niger. *Acta Trop*. 2013;128(2):318–25. <https://doi.org/10.1016/j.actatropica.2012.12.003>.
 39. Hailegebriel T, Nibret E, Munshea A. Efficacy of praziquantel for the treatment of human schistosomiasis in Ethiopia: a systematic review and

- meta-analysis. *J Trop Med*. 2021;2021:2625255. <https://doi.org/10.1155/2021/2625255>.
40. Barry A, Kabatende J, Telele NF, Mnkugwe RH, Mugisha M, Ntirenganya L, Bienvenu E, Aklillu E. Effect of pharmacogenetic variations on praziquantel plasma concentration and safety outcomes among school children in Rwanda. *Sci Rep*. 2023;13(1):1446. <https://doi.org/10.1038/s41598-023-28641-w>.
 41. Lambertson PHL, Faust CL, Webster JP. Praziquantel decreases fecundity in *Schistosoma mansoni* adult worms that survive treatment: evidence from a laboratory life-history trade-offs selection study. *Infect Dis Poverty*. 2017;6(1):110. <https://doi.org/10.1186/s40249-017-0324-0>.
 42. Cioli D, Pica-Mattoccia L, Basso A, Guidi A. Schistosomiasis control: praziquantel forever? *Mol Biochem Parasitol*. 2014;195(1):23–9. <https://doi.org/10.1016/j.molbiopara.2014.06.002>.
 43. Lemos M, Pedro JM, Fancony C, Moura S, Brito M, Nery SV, Sousa CP, Barros H. Schistosomiasis and soil-transmitted helminthiasis preventive chemotherapy: adverse events in children from 2 to 15 years in Bengo province, Angola. *PLoS ONE*. 2020;15(3): e0229247. <https://doi.org/10.1371/journal.pone.0229247>.
 44. Zwang J, Olliaro P. Efficacy and safety of praziquantel 40 mg/kg in preschool-aged and school-aged children: a meta-analysis. *Parasit Vectors*. 2017;10(1):47. <https://doi.org/10.1186/s13071-016-1958-7>.
 45. Gebreyesus TD, Makonnen E, Tadele T, Gashaw H, Degefe W, Gerba H, Tadesse BT, Gurumurthy P, Aklillu E. Safety surveillance of mass praziquantel and albendazole co-administration in school children from southern Ethiopia: an active cohort event monitoring. *J Clin Med*. 2022. <https://doi.org/10.3390/jcm11216300>.
 46. Mazigo HD, Fuss A, Mueller A. High egg reduction rate but poor clearance of circulating cathodic antigen three weeks after Praziquantel treatment among school children on Ijinga Island, north-western Tanzania. *Acta Trop*. 2021;218: 105871. <https://doi.org/10.1016/j.actatropica.2021.105871>.
 47. Straily A, Kavere EA, Wanja D, Wiegand RE, Montgomery SP, Mwaki A, Eleveld A, Secor WE, Odieri MR. Evaluation of the point-of-care circulating cathodic antigen assay for monitoring mass drug administration in a *Schistosoma mansoni* control program in Western Kenya. *Am J Trop Med Hyg*. 2021;106(1):303–11. <https://doi.org/10.4269/ajtmh.21-0599>.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions



Paper III

Knowledge, attitude, and practice of mothers/primary caregivers of preschool children towards schistosomiasis in southern Ethiopia

Tafese Tadele^{1*}, Ayalew Astatkie¹, Birkneh TilahunTadesse², Eyasu Makonnen^{3,4}, Solomon Mequanente Abay⁴, and Eleni Aklillu⁵

1. School of Public Health, College of Medicine and Health Sciences, Hawassa University, Hawassa P.O. Box 1560, Ethiopia
2. Department of Pediatrics, College of Medicine and Health Sciences, Hawassa University, Hawassa P.O. Box 1560, Ethiopia
3. Center for Innovative Drug Development and Therapeutic Trials for Africa, College of Health Sciences, Addis Ababa University, Addis Ababa P.O. Box 9086, Ethiopia
4. Department of Pharmacology and Clinical Pharmacy, College of Health Sciences, Addis Ababa University, Addis Ababa, P.O. Box 9086, Ethiopia
- ⁵. Department of Global Public Health, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden

***Corresponding author:** Tel: +251912144724;

E-mail: tafeseatudura@gmail.com

Abstract

Background and aims: Despite the growing spread of schistosomiasis among preschool children (pre-SAC), there is scarceness of evidence on knowledge, attitude, and practices (KAP) of caregivers in disadvantaged communities. The current study investigated the level and determinants of KAP of caregivers of pre-SAC towards schistosomiasis in southern Ethiopia.

Design and Methods: A cross-sectional study was conducted among 887 caregivers. A multistage sampling technique was applied and the study participants were selected by simple random sampling technique. A multivariable logistic regression with a cluster-robust variance estimation method was used to identify the determinants and a p-value <0.05 was considered statistically significant.

Results: The level of knowledge about schistosomiasis was low (37.0%). Only 54.8% of caregivers had a favorable attitude about schistosomiasis, while 57.8% of caregivers had good practices related to the disease. Being from the poorest (AOR = 0.75, 95% CI: 0.57, 0.99) and poorer (AOR = 0.55, 95% CI: 0.47, 0.65) wealth index households reduced the odds of good knowledge relative to their richest counterparts. The regression analyses revealed that being in the age group of 23 - 29 years, not having formal education, and being from the poorest wealth index households were significant determinants of attitude. Being unmarried and not receiving information about the disease from any source had a significant association with good practice.

Conclusion: The present study revealed the low level of knowledge, unfavorable attitude, and poor practice that indicated critical gaps in the elimination of schistosomiasis. Hence, schistosomiasis elimination efforts should ensure the involvement of caregivers.

Keywords: Knowledge, Attitude, Practice, Ethiopia, Preschool children, Primary caregivers, Schistosomiasis

Significance for public health:

This study has an imperative public health effect with the current targeted elimination effort of schistosomiasis. It exhibits the importance of tailored health education strategies to specific target groups. Besides, it reveals the nonexistence of KAP towards schistosomiasis among mothers/primary caregivers of pre-SAC in the Hawella Tulla district which needs to be addressed. It also offered recommendations for the schistosomiasis control and elimination program to encourage the knowledge, attitude, and practice of the caregivers through implementing the prevention and control measures while conducting various activities around infested water sources. Further, it highlights the need to consider the knowledgeable involvement of caregivers in schistosomiasis and probably other neglected tropical disease control and elimination strategies to accelerate the achievement of the elimination goals of these devastating public health problems.

Introduction

Schistosomiasis is associated with undesirable acute and chronic physical and cognitive outcomes [1–4]. The long-term effect of these infections may induce permanent disability or even death in some patients [5]. Schistosomiasis can be prevented using key approaches which include mass praziquantel administration; access to safe water, basic sanitation, and the promotion of hygiene practices (WASH), vector control, and health education [6,7]. These interventions need to be integrated to play a critical role in the successful control or elimination of schistosomiasis [8,9].

The success of community-based control interventions depends on community acceptance of the program [10]. Programs should first intend to realize the community's knowledge, attitude, and practices (KAP) towards schistosomiasis before the implementation of the program activities [11].

According to recent findings, mothers/caregivers are critical in the control of schistosomiasis

among preschool-aged children (pre-SAC) [10]. A review conducted in sub-Saharan Africa (SSA) indicated the importance of caregivers' involvement in the planning and implementation of control programs [13]. Nevertheless, lacking appropriate information and a favorable attitude, they may be involved in risky practices that predispose their young children to *S. mansoni* infections [14,15]. A Nigerian study [16] revealed that caregivers contributed to the spread of schistosomiasis among children through risky water-related practices.

Lack of knowledge and misperceptions may result in infesting water bodies [17,18]. Evidence shows that in endemic areas women perform most of the water contact activities putting themselves and their pre-SAC at high risk of infection [18,19]. A report from Nigeria [20] revealed that 16.2% of the mothers/caregivers engaged in open defecation in surrounding bushes, 1.8% directly to the river, and 13.2% depended solely on water from the river for domestic usage. In Ethiopia [21], 27.8% of households practiced open defecation. Studies have also shown that the KAP of individuals regarding schistosomiasis is influenced by socio-demographic characteristics, as well as economic and behavioral factors [22].

In endemic countries including Ethiopia, where schistosomiasis [23,24] is predominant, community-based KAP studies on schistosomiasis are scarce. These hinder the attainment and sustainability of the evidence-based control interventions targeted towards the elimination of schistosomiasis as a public health threat to at-risk population groups [25]. This study, therefore, assessed the level and determinants of KAP of pre-SAC towards schistosomiasis in southern Ethiopia.

Materials and Methods

Study design and setting

A cross-sectional community-based study was conducted from August to December 2021 among mothers/primary caregivers of pre-SAC (aged 4 to 7 years) in Hawella Tulla district, southern Ethiopia. The Neglected Tropical Diseases (NTDs) burden assessment conducted in Ethiopia between 2013 and 2014 revealed a higher prevalence of schistosomiasis in the study district [26]. The district is located 289 km south of Addis Ababa, the capital city of Ethiopia. It is situated at an altitude of 1,800m above sea level and has an annual rainfall of 1,123mm and a temperature of 13-27⁰C. Lake Hawassa is the water source of the residents of the district for domestic, agricultural, fishing, and other uses.

Mothers/primary caregivers who had pre-SAC aged 4 to 7 years and resided at least six months in the selected kebeles/villages of Hawella Tulla district before the study were included. Mothers/primary caregivers who had health problems that hindered their involvement were excluded from the study due to the inability to conduct interviews.

Sample size determination

OpenEpi sample size calculation software was used to compute the sample size. The level of knowledge, attitude, and practice, and the significant determinants of KAP were considered during the sample determination. The assumptions: the level of knowledge of at least one sign and/or symptom of schistosomiasis (54.4%), attitude of willingness to participate in praziquantel preventive chemotherapy campaigns (79.2%), and practice of washing in open water (61.2%) based on a previous study [27]; absolute precision of 5%; and a design effect of 1.5. Accordingly, the total sample sizes calculated after adjusting for the anticipated non-response rate (10%) were 636, 423, and 609. The sample size desired was also calculated using variables significantly linked with KAP in a previous study [28] setting the ratio of unexposed-to-exposed at 1%, the level of confidence at 95%, power at 90%, and the estimated non-response rate of 10%. The estimated

sample sizes accordingly were 317, 910, and 127. Then, the largest sample size computed from the risk factors (n=910) was used.

Sampling technique

A multistage sampling technique was applied to select the study *kebeles* (lowest executive units in Ethiopia). Out of the entire twelve *kebeles* of the district, six were designated based on the *S. mansoni* infection rate among SAC [26]. From the six *kebeles*, three (Tullo, Finchawa, and Chafe Kotijebessa) were chosen with the lottery technique. In the selected *kebeles*, the health extension workers prepared the list of community members eligible for the study through house-to-house enumeration before the study initiation. The sample size allocation was done proportionate to the population size of each *kebele*. Then, the study participants were selected using a simple random sampling method via a computer-generated random number. In cases where the chosen participant was not accessible at home during the initial visit, two repeated visits were made, after which the person was considered a non-respondent.

Variables of the study

Knowledge: The knowledge of respondents about schistosomiasis was measured by asking a series of 5 close-ended questions containing multiple options regarding signs and symptoms, prevention strategies, control and treatment methods, and modes of transmission. Participants who responded “NO” to the screening question were given a score of “0” and included in the knowledge level assessment. Questions related to knowledge were scored and pulled together and the mean knowledge score was then calculated by dividing a scaled score by the number of respondents responding on scale. Knowledge was recorded as high if more than the mean score, while low for a score less than the mean.

Attitude: The perception of participants regarding the severity of the disease, risk factors, signs and symptoms, mode of transmission, prevention strategies, treatment, and control of schistosomiasis was assessed using close-ended questions. It was measured using a questionnaire containing 7 questions. The participant's response and each question were assigned ranked by a Likert scale using a numerical score encompassing from 1 to 5. (Strongly disagree = 1, Disagree = 2, neutral = 3, Agree = 4, Strongly agree = 5). The overall attitude score of a participant was determined based on the mean scores computed by dividing on-scale scores by the number of participants responding on the scale. The attitude was delineated as a favorable attitude if the mean attitude score was more than the mean and an unfavorable attitude for caregivers who had responded less than the mean attitude score.

Practice: The respondents' practice with schistosomiasis was evaluated by asking a single question that had nine major response options about where the study participants wash clothing often. The response options listed were grouped into predisposing and protective practices. Respondents who reported at least one predisposing practice were categorized as having poor practice, while those who reported "NO" for any predisposing practices were labeled as having good practice.

The exposure variables encompass age, educational level, marital status, occupation, wealth quintile, and source of information about schistosomiasis.

Data collection procedures

A structured, face-to-face interviewer-administered questionnaire was used to collect data. The questionnaires prepared in the English language were translated into local languages (Amharic and Sidamu Afoo). The consistency of the tool was preserved by translating it back into English. Amharic or Sidamu Afoo questionnaire was applied based on the language preference of the

participants during the interview. The questionnaire covered such issues as socio-demographic features of the respondents; sources of information about schistosomiasis, signs and symptoms, modes of transmission, prevention, treatment and control, severity, predisposing, and preventive measures. Eight public health experts for data collection and two senior experts for supervision were recruited from public health institutions. Then, the data collectors and supervisors were trained in data collection tools, interview techniques, and their roles and responsibilities for two days by the research team. Before the study initiation, the questionnaire was pre-tested on 5% of the entire sample size of caregivers in the Wondo Genet district. Based on the pre-test findings the data collection tool has been revised. Regular supervision of data collectors was made to confirm the appropriate implementation of the study daily.

Statistical analysis

Stata software version 14 [StataCorp LLC, College Station, Texas, USA] was used to analyze data. Descriptive analyses were done by computing frequencies and proportions for categorical variables and mean with standard deviations. Data on a household's possession of particular assets such as radio, refrigerator, television, bicycle, motorbike, car, phone/cell phone; the household's amenities such as water supply, toilet, flooring, walls/house, roof, electricity, and cooking fuel were considered during the household wealth index calculation. The household wealth index was computed using the principal component analysis (PCA). The sampled households were categorized into five quantiles using the scores and each member of a household received that household's quintile category.

Multivariable logistic regression with cluster-robust variance estimation method was conducted to assess the effect of various background characteristics on knowledge, attitude, and practices about schistosomiasis. The variables were included in the multivariable model using the purposeful

variable selection technique as recommended in the literature [29]. Hence, variables with a p-value less than 0.25 on the bivariable model and those variables considered important in other literature were included in the multivariable.

Results were reported as adjusted odds ratios (AOR) with their 95% confidence intervals (CI). A statistically significance level was set at a p-value of < 0.05 .

Results

Sociodemographic characteristics

Of the total 910 mothers/primary caregivers (all females) of pre-SAC recruited, 887 (97.5%) have participated. The majority (48.7%) of the caregivers were in the age group of greater than 29 – 39 years, while 29 (3.2%) of them were unmarried (Table 1). The mean (\pm standard deviation (SD)) age of the caregivers was 31.4 (± 0.2) years.

Table 1 Sociodemographic characteristics of mothers/primary caregivers of preschool children
(N=887)

Characteristics	Category	N (%)
Age groups (years)	23-29 years	352 (39.7)
	>29-39 years	438 (49.4)
	≥ 40 years	97 (10.9)
Educational level	No formal education	395 (44.5)
	Primary education	202 (22.8)
	Secondary education	111 (12.5)
	College and above	179 (20.2)
Marital status	Married	862 (97.2)
	Not married	25 (2.8)
Household wealth index	Poorest	231 (26.0)
	Poorer	132 (14.9)
	Middle	188 (21.2)
	Richer	190 (21.4)
	Richest	146 (16.5)
District	Tullo	417 (47.0)
	Finchawa	230 (25.9)
	Chefe Kotijebesa	240 (27.1)

N: Entire number of participants within each category

Schistosomiasis knowledge among mothers/primary caregivers

Most of the study participants (73.8%) reported having previously heard of schistosomiasis. Only less than half knew the signs and symptoms (46.1%) and prevention measures (40.1%) of schistosomiasis. Moreover, 37.3% knew about the mode of transmission, while only 9.8% knew about the treatment and control of the disease (Figure 1). The overall knowledge level of the respondents about schistosomiasis was 37.0% (95% CI: 33.8%, 40.2%).

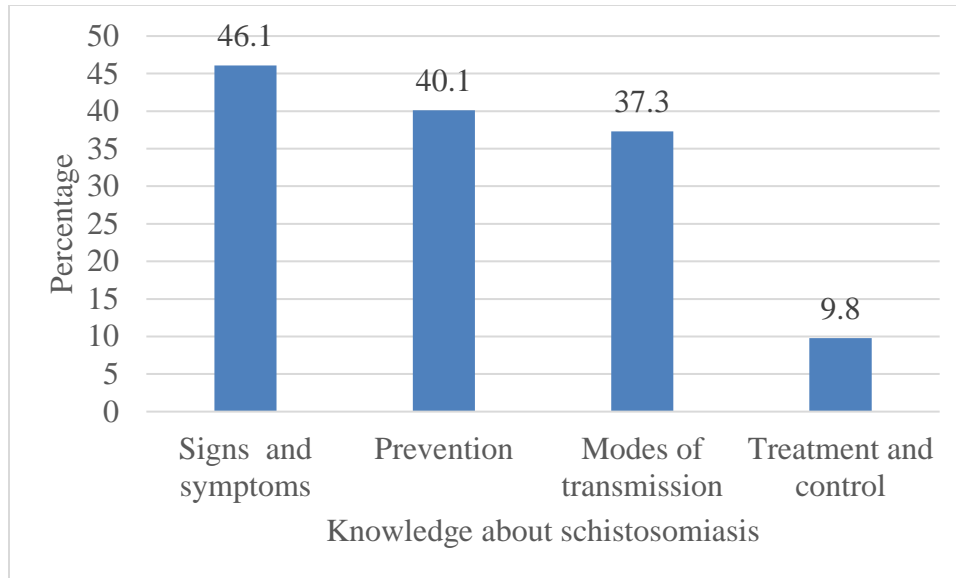


Figure 1 Knowledge of signs and symptoms, mode of transmission, prevention, and treatment among mothers/primary caregivers of preschool children

Health extension workers 181 (20.4%) and research institutions 104 (11.7%) were the most common sources of information, while community meetings 41 (4.6%) were distinguished as the least information source (Figure 2). The knowledge score among caregivers ranged from 0 to 14 (the maximum possible score was 22). The mean knowledge score of the caregivers was 4.08.

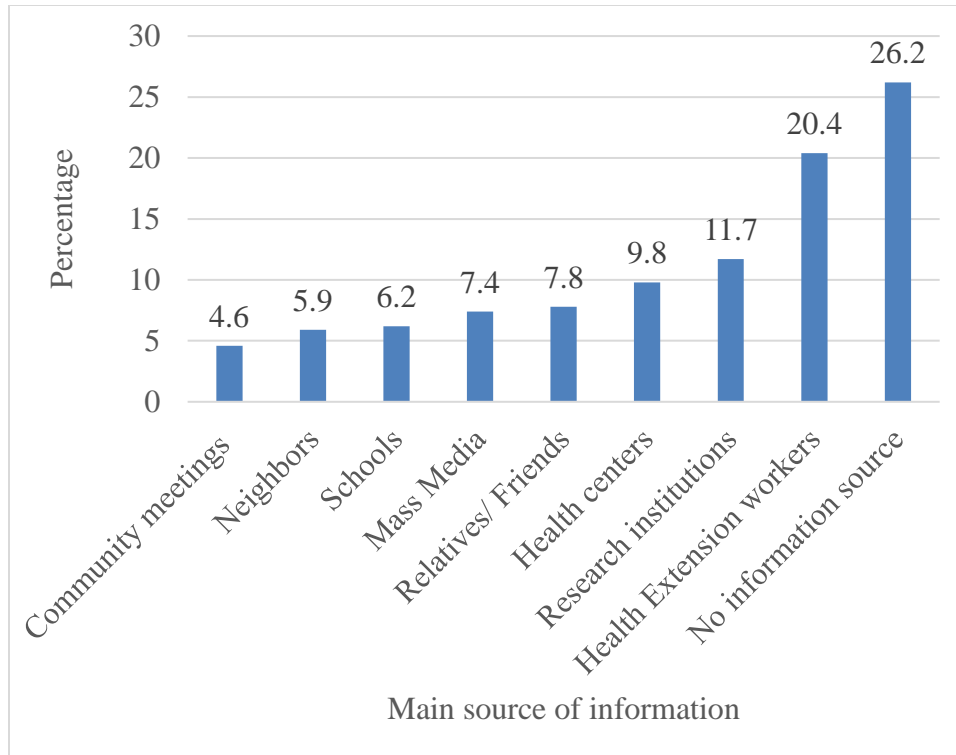


Figure 2 Main source of information about schistosomiasis among mothers/primary caregivers of preschool children

Determinants of knowledge level about schistosomiasis

Being in the poorest (AOR = 0.75, 95% CI: 0.57, 0.99) and poorer (AOR = 0.55, 95% CI: 0.47, 0.65) wealth index households exhibited reduced odds of reporting good knowledge of *S. mansoni* infection relative to those from the richest wealth households. No significant association was observed with other variables (Table 2).

Table 2 Determinants of knowledge level towards schistosomiasis among mothers/primary caregivers of preschool children (N=887)

Variable	Category	Level of knowledge about schistosomiasis		COR (95%CI)	AOR (95% CI)
		High N (%)	Low N (%)		
Age groups (years)	≥ 40 years	32 (33.0)	65 (67.0)	1.0	1.0
	23 – 29 years	124 (35.2)	228 (64.8)	1.10 (0.69, 1.78)	0.99 (0.63, 1.54)
	>29-39 years	172 (39.3)	266 (60.7)	1.31 (0.83, 2.09)	1.44 (0.87, 2.38)
Education level	College and above	68 (38.0)	111 (62.0)	1.0	1.0
	No formal education	145 (36.7)	250 (63.3)	0.95 (0.66, 1.36)	1.03 (0.77, 1.37)
	Primary education	71 (35.2)	131 (64.8)	0.88 (0.58, 1.34)	1.01 (0.72, 1.42)
	Secondary education	44 (39.6)	67 (60.4)	1.07 (0.66, 1.74)	0.85 (0.63, 1.14)
Occupation	Employed	34 (39.5)	52 (60.5)	1.0	1.0
	Not employed	294 (36.7)	507 (63.3)	0.89 (0.56, 1.40)	1.22 (0.75, 1.97)
Marital status	Married	320 (37.1)	542 (62.9)	1.0	1.0
	Not married	8 (32.0)	17 (68.0)	0.80 (0.34, 1.87)	0.63 (0.37, 1.07)
Wealth index	Richest	72 (49.3)	74 (50.7)	1.0	1.0
	Poorest	87 (37.7)	144 (62.3)	0.62 (0.41, 0.94)*	0.75 (0.57, 0.99)
	Poorer	38 (28.8)	94 (71.2)	0.42 (0.25, 0.68)*	0.55 (0.47, 0.65)*
	Middle	58 (30.9)	130 (69.1)	0.46 (0.29, 0.72)*	0.66 (0.42, 1.04)
	Richer	73 (38.4)	117 (61.6)	0.64 (0.41, 0.99)*	0.72 (0.38, 1.38)
Source of information	Health extension worker	78 (43.1)	103 (56.9)	1.0	1.0
	Mass media	24 (36.4)	42 (63.6)	0.75 (0.42, 1.35)	0.77 (0.27, 2.21)
	Health institution	45 (51.7)	42 (48.3)	1.41 (0.85, 2.36)	1.41 (0.43, 4.62)
	Neighbors	24 (46.2)	28 (53.8)	1.13 (0.61, 2.10)	1.11 (0.52, 2.36)
	Schools	35 (63.6)	20 (36.4)	2.31 (1.24, 4.31)*	2.28 (0.30, 17.34)
	Community meetings	24 (58.5)	17 (41.5)	1.86 (0.94, 3.71)	1.78 (0.18, 17.99)
	Relatives/ Friends	35 (50.7)	34 (49.3)	1.36 (0.78, 2.37)	1.35 (0.97, 1.88)
	Research institutions	63 (60.6)	41 (39.4)	2.03 (1.24, 3.32)	2.05 (0.47, 8.99)
	No information source	0 (0.0)	232 (100)	a	

COR: crude odds ratio; AOR: adjusted odds ratio; CI: confidence interval; N: Entire number of participants within each category; ^aOR: odds ratio could not be estimated because it predicts failure perfectly: * p-value <0.05, and bold font means statistically significant

Attitude of caregivers toward schistosomiasis

Four hundred eighty-six (54.8%) caregivers had a favorable attitude about the mode of transmission of schistosomiasis, prevention, treatment, and control methods (Table 3). The attitude score among caregivers ranged from 16 to 34 (maximum possible score, 35). The mean attitude score of the caregivers was 3.54.

Table 3 Item-by-item attitude distribution of mothers/ primary caregivers of preschool children towards schistosomiasis (N=887)

Questions	Strongly Disagree N (%)	Disagree N (%)	Neutral N (%)	Agree N (%)	Strongly agree N (%)
<i>S. mansoni</i> infection is a serious disease	5 (0.6)	23 (2.6)	95 (10.7)	716 (80.7)	48 (5.4)
<i>S. mansoni</i> is a minor infection that may clear over time without treatment	14 (1.6)	251 (28.3)	102 (11.5)	468 (52.8)	52 (5.9)
<i>S. mansoni</i> is not preventable	15 (1.7)	342 (38.6)	100 (11.3)	416 (46.9)	14 (1.6)
Feces/urine can be a source of infection for <i>S. mansoni</i> infection	2 (0.2)	32 (3.6)	81 (9.1)	739 (83.3)	33 (3.7)
<i>S. mansoni</i> infection can be treated	8 (0.9)	53 (6.0)	89 (10.0)	715 (80.6)	22 (2.5)
<i>S. mansoni</i> infection treatment results in severe, long-term side effects.	13 (1.5)	250 (28.2)	365 (41.2)	246 (27.7)	13 (1.5)
<i>S. mansoni</i> can affect pre-SAC aged 4-7 years	4 (0.5)	30 (3.4)	88 (9.9)	753 (84.9)	12 (1.4)

Pre-SAC: preschool children; N: Total number of participants

Determinants of attitude towards schistosomiasis

Being in the age group of 23–29 years (AOR = 1.18, 95% CI: 1.01, 1.37) increased the odds of reporting a favorable attitude toward *S. mansoni* infection relative to those in the age group of \geq 40 years. A significant association was detected between not having formal education (AOR= 0.80, 95% CI: 0.65, 0.98) and reporting favorable attitudes among mothers/primary caregivers compared to those having higher education levels. Being from the poorest wealth households (AOR = 0.42,

95% CI: 0.28, 0.62) was also a significant determinant of reporting favorable attitude among caregivers compared to those from the richest counterparts (Table 4).

Table 4 Determinants of attitude status towards schistosomiasis among mothers/ primary caregivers of preschool children (N=887)

Variable	Category	Attitude towards schistosomiasis		COR (95%CI)	AOR (95% CI)
		Favorable N (%)	Unfavorable N (%)		
Age groups (years)	≥ 40 years	48 (49.5)	49 (50.5)	1.0	1.0
	23 – 29 years	206 (58.5)	146 (41.5)	1.44 (0.92, 2.26)	1.18 (1.01, 1.37)*
	>29-39 years	232 (53.0)	206 (47.0)	1.15 (0.74, 1.79)	1.07 (0.86, 1.33)
Education level	College and above	111 (62.0)	68 (38.0)	1.0	1.0
	No formal education	187 (47.3)	208 (52.7)	0.55 (0.38, 0.79)*	0.80 (0.65, 0.98)*
	Primary education	120 (59.4)	82 (40.6)	0.90 (0.59, 1.35)	1.09 (0.84, 1.41)
	Secondary education	68 (61.3)	43 (38.7)	0.97 (0.60, 1.58)	0.94 (0.58, 1.52)
Occupation	Employed	53 (61.6)	33 (38.4)	1.0	1.0
	Not employed	433 (54.1)	368 (45.9)	0.73 (0.46, 1.16)	1.02 (0.57, 1.83)
Marital status	Married	474 (55.0)	388 (45.0)	1.0	1.0
	Not married	12 (48.0)	13 (52.0)	0.76 (0.34, 1.67)	0.95 (0.56, 1.61)
Wealth index	Richest	96 (65.8)	50 (34.2)	1.0	1.0
	Poorest	94 (40.7)	137 (59.3)	0.36 (0.23, 0.55)*	0.42 (0.28, 0.62)*
	Poorer	68 (51.5)	64 (48.5)	0.55 (0.34, 0.90)*	0.63 (0.36, 1.11)
	Middle	97 (51.6)	91 (48.4)	0.56 (0.36, 0.87)*	0.62 (0.33, 1.16)
	Richer	131 (69.0)	59 (31.0)	1.16 (0.73, 1.83)	0.19 (0.57, 2.47)
Source of information	Health extension worker	95 (52.5)	86 (47.5)	1.0	1.0
	Mass media	38 (57.6)	28 (42.4)	1.23 (0.70, 2.17)	1.26 (0.50, 3.18)
	Health institution	52 (59.8)	35 (40.2)	1.34 (0.80, 2.26)	1.32 (0.39, 4.47)
	Neighbors	32 (61.5)	20 (38.5)	1.45 (0.77, 2.72)	1.21 (0.57, 2.56)
	Schools	29 (52.7)	26 (47.3)	1.01 (0.55, 1.85)	1.09 (0.49, 2.42)
	Community meetings	23 (56.1)	18 (43.9)	1.16 (0.58, 2.29)	1.15 (0.57, 2.35)
	Relatives/ Friends	44 (63.8)	25 (36.2)	1.59 (0.90, 2.82)	1.53 (0.67, 3.46)
	Research institutions	62 (59.6)	42 (40.4)	1.34 (0.82, 2.18)	1.25 (0.47, 3.29)
	No information source	111(47.8)	121 (52.2)	0.83 (0.56, 1.23)	0.85 (0.63, 1.14)
	Knowledge level	High	187 (57.0)	141 (43.0)	
Low		299 (53.5)	260 (46.5)	0.87 (0.66, 1.14)	1.04 (0.66, 1.65)

COR: crude odds ratio; AOR: adjusted odds ratio; CI: confidence interval; N: overall number of participants within each category; * p-value <0.05, and bold font means statistically significant

Practice of mothers/ primary caregivers towards schistosomiasis

Five hundred thirteen (57.8%) of mothers/primary caregivers had good practice related to predisposing factors of schistosomiasis. Out of the remaining 42.2% of caregivers who engaged in predisposing practices, the majority used pond (17.9%) or lake (15.5%) water for washing clothes commonly.

Determinants of practice status towards schistosomiasis

A significant association was detected between being unmarried (AOR = 0.57, 95% CI: 0.36, 0.89) and reporting good practice about predisposing factors among caregivers compared to married. Mothers/primary caregivers who did not receive any information had 60% (AOR = 0.40, 95% CI: 0.26, 0.62) lesser odds of reporting good practices about the disease relative to those who acknowledged the health extension workers as the information source (Table 5).

Table 5 Determinants of practice towards schistosomiasis among mothers/primary caregivers of preschool children (N=887)

Variable	Category	Practice towards schistosomiasis		COR (95%CI)	AOR (95% CI)
		Good N (%)	Poor N (%)		
Age groups (years)	≥ 40 years	43 (44.3)	54 (55.7)	1.0	1.0
	23 – 29 years	204 (57.9)	148 (42.1)	0.58 (0.37, 0.91)*	0.66 (0.21, 2.05)
	>29-39 years	266 (60.7)	172 (39.3)	0.51 (0.33, 0.80)*	0.54 (0.19, 1.51)
Education level	College and above	111 (62.0)	68 (38.0)	1.0	1.0
	No formal education	198 (50.1)	197 (49.9)	1.62 (1.13, 2.33)*	1.30 (0.69, 2.46)
	Primary education	129 (63.9)	73 (36.1)	0.92 (0.61, 1.40)	0.87 (0.39, 1.95)
Occupation	Secondary education	75 (67.6)	36 (32.4)	0.78 (0.48, 1.29)	0.73 (0.42, 1.27)
	Employed	50 (58.1)	36 (41.9)	1.0	1.0
	Not employed	463 (57.8)	338 (42.2)	1.01 (0.65, 1.59)	0.89 (0.56, 1.37)
Marital status	Married	498 (57.8)	364 (42.2)	1.0	1.0
	Not married	15 (60.0)	10 (40.0)	0.91 (0.41, 2.05)	0.57 (0.36, 0.89)*
Wealth index	Richest	91 (62.3)	55 (37.7)	1.0	1.0
	Poorest	106 (45.9)	125 (54.1)	1.95 (1.28, 2.98)*	1.84 (0.55, 6.15)
	Poorer	64 (48.5)	68 (51.5)	1.76 (1.09, 2.84)*	1.79 (0.48, 6.78)
	Middle	126 (67.0)	62 (33.0)	0.81 (0.52, 1.28)	0.88 (0.49, 1.57)
	Richer	126 (66.3)	64 (33.7)	0.84 (0.54, 1.32)	0.88 (0.46, 1.71)
Source of information	Health extension worker	86 (47.5)	95 (52.5)	1.0	1.0
	Mass media	45 (68.2)	21 (31.8)	0.42 (0.23, 0.77)*	0.40 (0.12, 1.34)
	Health institution	41 (47.1)	46 (52.9)	1.02 (0.61, 1.70)	1.05 (0.31, 3.56)
	Neighbors	36 (69.2)	16 (30.8)	0.40 (0.21, 0.78)*	0.43 (0.02, 7.58)
	Schools	34 (61.8)	21 (38.2)	0.56 (0.30, 1.04)	0.52 (0.08, 3.26)
	Community meetings	21 (51.2)	20 (48.8)	0.86 (0.44, 1.70)	0.97 (0.38, 2.47)
	Relatives/ Friends	39 (56.5)	30 (43.5)	0.70 (0.40, 1.22)	0.74 (0.27, 2.04)
	Research institutions	61 (58.6)	43 (41.4)	0.64 (0.39, 1.04)	0.71 (0.28, 1.82)
	No information source	150 (64.7)	82 (35.3)	0.49 (0.33, 0.74)*	0.40 (0.26, 0.62)*
	Knowledge level	High	195 (59.4)	133 (40.6)	1.0
Low		318 (56.9)	241 (43.1)	1.11 (0.84, 1.47)	1.41 (0.94, 2.11)
Attitude status	Fovorable	289 (59.5)	197 (40.5)	1.0	1.0
	Unfovorable	224 (55.9)	177 (44.1)	1.16 (0.89, 1.51)	1.02 (0.59, 1.76)

COR: crude odds ratio; AOR: adjusted odds ratio; CI: confidence interval; N: total number of participants within each category; * p-value <0.05, and bold font means statistically significant

Discussion

Our finding indicated a low level of knowledge, unfavorable attitude, and poor practices about schistosomiasis among caregivers of pre-SAC. The overall level of good knowledge about schistosomiasis was 37.0%, with substantial disparity across signs and symptoms, prevention measures, means of transmission, and treatment and control. However, the favorable attitude was moderate (54.8%), while the prevailing (57.8%) good practices were inadequate to accelerate the intended elimination efforts of the schistosomiasis. A significant association was found between good knowledge and being in the poorer and poorest wealth index categories. Besides, a significant association was observed between a favorable attitude and being in the 23-29 years age group, not having formal education, and being in the poorest wealth index categories. Further, being unmarried and not receiving information from any source were significant determinants of good practices.

Overall low level of knowledge (37.0%) was observed about schistosomiasis among caregivers with significant differences across signs and symptoms, prevention measures, modes of transmission, treatment, and control. Studies conducted in South Africa [24], Kenya [30], and a systematic review in SSA [13] also reported similar findings. The knowledge level remained low partly due to weaknesses in the health education structures and a deficiency of community members' experiences on the health and social effects of schistosomiasis among respondents. However, knowledge was relatively high on signs and symptoms (46.1%), prevention measures (40.1%), and modes of transmission (37.3%), while least on control and treatment (9.8%). The observed difference in the knowledge level of some key aspects of schistosomiasis treatment and control demonstrates the neglect of the health education component in the morbidity control strategy in Ethiopia. Thus, contextual circumstances should be acknowledged when framing health

education intervention as a key component of the program to attain and sustain the interruption of disease transmission, particularly in rural settings. Besides, the current study revealed a moderate favorable attitude (54.8%). However, 86.1% of the respondents considered schistosomiasis as a dangerous disease. A comparable finding was reported in other studies elsewhere [31,32]. Most of the caregivers recognized that the disease could be treated, as was also reported in Tanzania [33]. However, in this study, nearly half of the respondents acknowledged the disease is preventable. The overall perception of the caregivers is not in favor of breaking the chain of disease transmission.

In our study, nearly 57.8% of the caregivers had good practices about the disease. The present finding is lower than the report from Uganda [34] that indicated 65.5% of parents/guardians had appropriate practices towards urogenital schistosomiasis among under-five children. The justification for the inadequate good practices could be that, in Ethiopia, schistosomiasis-related robust interventions such as mass praziquantel administration, health education, WASH, and vector control that channel the information dissemination for the required behavioral change were overlooked among caregivers of pre-SAC considering their young children to be safe from the infection due to the presumed reduced interaction with contaminated water sources. However, in our study, risky water-related practices were observed, especially among participants who rely on Lake Hawassa, and other exposed water sources due to scarce knowledge about the disease.

Our study showed that being in the poorest (25%) and poorer (45%) wealth index categories reduced the odds of reporting good knowledge compared to the richest wealth category. The possible reason for this might be linked to the lower likelihood of having access to diverse information sources among household members in the lower wealth quantiles than those in higher

wealth quantiles. Often higher wealth quantiles are taken as a proxy for improved health services and health message access [28].

This study revealed that the younger age group (23 – 29 years) had increased odds of reporting a favorable attitude relative to the older age group (≥ 40 years). The factor that has accounted for the observed higher odds of reporting a favorable attitude might be that younger people are more likely to recognize the importance of avoiding contact with lake water by considering the long-lasting health impacts of persistent infested water contact relative to older counterparts.

In the study region, not having formal education decreased the odds of reporting a favorable attitude by 20% relative to those in the higher education level. In Ethiopia, caregivers having lower education have a lesser chance of employment. Also, having lower education decreased the chance of active involvement in formal health information dissemination channels and infrequent contact with health extension workers which might have contributed to the reported unfavorable attitude relative to those who have diverse information sources due to their higher education level [28].

Our study has also revealed that being in the poorest (58%) wealth category had lower odds of reporting a favorable attitude relative to the richest households. The justification for this association may be that the respondents with lower wealth quintiles had more attachment to lake water to obtain their living relative to those with higher wealth quintiles [28].

The present study has found being unmarried leads to 43% lesser odds of good practice compared to married caregivers. The possible explanation for this finding might be attributed to the reduced access to resources that may affect health information access among unmarried caregivers compared to married and may be involved in riskier health-related behaviors [35]. Furthermore, the current study revealed that 60% lesser odds of reporting good practice were observed among caregivers who did not receive any information about schistosomiasis from any source relative to

health extension workers as a source of information. The gap in understanding a disease process and recommended prevention measures related to low health literacy accounted for this finding.

The current evidence on the level of KAP towards schistosomiasis among mothers/ caregivers of pre-SAC shapes the health and well-being of marginalized populations infected or affected by schistosomiasis. Thus, our research makes substantial contributions to knowledge, policy, practice, and future research by broadening the scope of SAC-focused interventions towards extensive commitments to the inclusion of the overlooked at-risk populations to tackle schistosomiasis in Ethiopia and other similar endemic settings.

As a portion of the limitations, the current study didn't determine the schistosome infection among caregivers that may benefit the infected participants and accelerate the information dissemination which enhances the improvement of KAP among women in a high-risk population in high endemic communities. The other limitation is that we did not exhaust all the prevailing potential behavioral practices with effects on the desired behavior change among caregivers that may overestimate the level of practice as an outcome. However, our results provide insight into the general situation of KAP towards schistosomiasis among caregivers of pre-SAC in Ethiopia.

Conclusions

Our study revealed the low level of knowledge, unfavorable attitude, and poor practices that indicated critical gaps in integrated intervention strategies for schistosomiasis. Hence, schistosomiasis elimination efforts should ensure the involvement of mothers/primary caregivers during the planning, execution, monitoring, and evaluation activities of the interventions in endemic settings. Moreover, we recommend that health education be implemented together with other strategies in the study setting.

Acknowledgments:

We are grateful to the health extension workers of the three study *kebeles* for their assistance. We also acknowledge the caregivers who participated in the study.

Authors Contributions:

T.T., A.A., B.T.T., S.M.A., E.M., and E.A.: conceptualization, data curation, and methodology.

T.T., A.A., B.T.T., S.M.A., E.M., and E.A.: formal analysis and investigation. S.M.A., E.M., and

E.A.: funding acquisition, E.A., and project administration. T.T.: drafted an original manuscript.

T.T., A.A., B.T.T., S.M.A., E.M., and E.A.: writing; review & editing. All authors approved of the final version of the article.

Data availability statement:

All the required supplementary material can be supplied by the corresponding upon reasonable request.

Ethical approval and consent to participate:

The Institutional Review Board (IRB) of the College of Medicine and Health Sciences of Hawassa University (Ref. No: IRB/200/13) approved the study. It has been conducted as per the Declaration of Helsinki with the relevant guidelines and regulations. A written consent was obtained from the participants to participate in the study. Participants were informed about their rights to withdraw from the study at any point without punishment, and that their withdrawal would not affect them.

Conflict of interest

The authors declare no conflict of interest.

Funding

The data collection work of this study was funded by the European & Developing Countries Clinical Trials Partnership (EDCTP) 2 program through pharmacovigilance infrastructure and

post-marketing surveillance system capacity building for regional medicine regulatory harmonization in East Africa (PROFORMA) (Grant number CSA2016S-1618) and PrazOpt (Grant number TMA2018CDF-2345) projects.

ORCID IDs

Tafese Tadele: <https://orcid.org/0009-0008-2894-6021>; Ayalew Astatkie: <https://orcid.org/0000-0002-4840-9601>; Birkneh Tilahun Tadesse: <https://orcid.org/0000-0003-4005-8605>; Eyasu Makonnen: <https://orcid.org/0000-0002-9259-5288>; Solomon Mequanente Abay: <https://orcid.org/0000-0002-7844-3771>; Eleni Aklillu: <https://orcid.org/0000-0002-9788-0790>

List of abbreviations:

SSA: Sub Saharan Africa

WASH: Access to safe water, sanitation, and hygiene

KAP: Knowledge, attitude, and practice

NTDs: Neglected Tropical Diseases

S. mansoni: *Schistosoma mansoni*

References

1. Adenowo AF, Oyinloye BE, Ogunyinka BI, Kappo AP. Impact of human schistosomiasis in sub-Saharan Africa. *The Brazilian Journal of Infectious Diseases*. 2015;19: 196–205. doi:10.1016/j.bjid.2014.11.004.
2. Gebreyesus TD, Tadele T, Mekete K, Barry A, Gashaw H, Degefe W, *et al*. Prevalence, Intensity, and Correlates of Schistosomiasis and Soil-Transmitted Helminth Infections after

Five Rounds of Preventive Chemotherapy among School Children in Southern Ethiopia. *Pathogens*. 2020;9: 920. doi:10.3390/pathogens9110920.

3. Mnkugwe RH, Minzi OS, Kinung'hi SM, Kamuhabwa AA, Aklillu E. Prevalence and correlates of intestinal schistosomiasis infection among school-aged children in North-Western Tanzania. Diemert DJ, editor. *PLoS ONE*. 2020;15: e0228770. doi:10.1371/journal.pone.0228770.
4. Kabongo MM, Linsuke S, Baloji S, Mukunda F, da Luz Raquel I, Stauber C, *et al*. *Schistosoma mansoni* infection and its association with nutrition and health outcomes: a household survey in school-aged children living in Kasansa, Democratic Republic of the Congo. *Pan Afr Med J*. 2018;31. doi:10.11604/pamj.2018.31.197.16364.
5. World Health Organization. Schistosomiasis- World Health Organization(WHO) long term impacts of schistosomiasis. Available online: <https://www.who.int/news-room/fact-sheets/detail/schistosomiasishttps>(accessed on 27 June 2023).
6. Adenowo AF, Oyinloye BE, Ogunyinka BI, Kappo AP. Impact of human schistosomiasis in sub-Saharan Africa. *Braz J Infect Dis*. 2015;19(2):196-205. Epub 2015/02/01. doi: 10.1016/j.bjid.2014.11.004. PubMed PMID: 25636189.
7. Nalugwa A, Olsen A, Tukahebwa ME, Nuwaha F. Intestinal schistosomiasis among preschool children along the shores of Lake Victoria in Uganda. *Acta Tropica*. 2015;142: 115–121. doi:10.1016/j.actatropica.2014.11.014.

8. WHO. WHO guideline on control and elimination of human schistosomiasis. Geneva: World Health Organization; 2022. Available: <https://www.who.int/publications-detail-redirect/9789240041608>.
9. WHO. Ending the neglect to attain the Sustainable Development Goals: a road map for neglected tropical diseases 2021–2030. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO. 2020.
10. Martin S, Rassi C, Antonio V, Graham K, Leitão J, King R, *et al*. Evaluating the feasibility and acceptability of a community dialogue intervention in the prevention and control of schistosomiasis in Nampula province, Mozambique. Diemert DJ, editor. PLoS ONE. 2021;16: e0255647. doi:10.1371/journal.pone.0255647.
11. Anyolitho MK, Poels K, Huyse T, Tumusiime J, Mugabi F, Tolo CU, *et al*. Knowledge, attitudes, and practices regarding schistosomiasis infection and prevention: A mixed-methods study among endemic communities of western Uganda. Dikomitis L, editor. PLoS Negl Trop Dis. 2022;16: e0010190. doi:10.1371/journal.pntd.0010190.
12. Kibira SPS, Ssempebwa JC, Ssenyonga R, Radloff S, Makumbi FE. Schistosomiasis infection in pre-school aged children in Uganda: a qualitative descriptive study to identify routes of exposure. BMC Infect Dis. 2019;19: 165. doi:10.1186/s12879-019-3803-z.
13. Sacolo H, Chimbari M, Kalinda C. Knowledge, attitudes and practices on Schistosomiasis in sub-Saharan Africa: a systematic review. BMC Infect Dis. 2018;18: 46. doi:10.1186/s12879-017-2923-6.

14. Bosompem KM, Bentum IA, Otchere J, Anyan WK, Brown CA, Osada Y, *et al.* Infant schistosomiasis in Ghana: a survey in an irrigation community. *Trop Med Int Health.* 2004;9: 917–922. doi:10.1111/j.1365-3156.2004.01282.x.
15. Tadele T, Astatkie A, Abay SM, Tadesse BT, Makonnen E, Aklillu E. Prevalence and Determinants of *Schistosoma mansoni* Infection among Pre-School Age Children in Southern Ethiopia. 2023. *Pathogens* 2023, 12, 858. <https://doi.org/10.3390/pathogens12070858>.
16. Ekpo UF, *et al.* Urinary schistosomiasis among preschool children in a rural community near Abeokuta, Nigeria. *Parasit Vectors.* 2010;3:58. doi: 10.1186/1756-3305-3-58.
17. Mbereko A, Chimbari MJ, Manyangadze T, Mukaratirwa S. Knowledge and perceptions of schistosomiasis, a water-borne disease, in two semi-arid rural areas of South Africa (Ndumo) and Zimbabwe (Ntalale). *Food and Waterborne Parasitology.* 2020;21: e00091. doi:10.1016/j.fawpar.2020.e00091.
18. Ross A, Inobaya M, Olveda R, Chau T, Olveda D. Prevention and control of schistosomiasis: a current perspective. *RRTM.* 2014; 65. doi:10.2147/RRTM.S44274.
19. Mutsaka-Makuvaza MJ, Matsena-Zingoni Z, Tshuma C, Katsidzira A, Webster B, Zhou X-N, *et al.* Knowledge, perceptions and practices regarding schistosomiasis among women living in a highly endemic rural district in Zimbabwe: implications on infections among preschool-aged children. *Parasites Vectors.* 2019;12: 458. doi:10.1186/s13071-019-3668-4.
20. Adeniran AA, Mogaji HO, Aladesida AA, Olayiwola IO, Oluwole AS, Abe EM, *et al.* Schistosomiasis, intestinal helminthiasis and nutritional status among preschool-aged

- children in sub-urban communities of Abeokuta, Southwest, Nigeria. *BMC Res Notes*. 2017;10: 637. doi:10.1186/s13104-017-2973-2.
21. Temesgen A, Molla Adane M, Birara A, Shibabaw T. Having a latrine facility is not a guarantee for eliminating open defecation owing to socio-demographic and environmental factors: The case of Machakel district in Ethiopia. Rezakazemi M, editor. *PLoS ONE*. 2021;16: e0257813. doi:10.1371/journal.pone.0257813.
 22. Colley DG, Fleming FM, Matendechero SH, Knopp S, Rollinson D, Utzinger J, *et al*. Contributions of the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) to Schistosomiasis Control and Elimination: Key Findings and Messages for Future Goals, Thresholds, and Operational Research. *The American Journal of Tropical Medicine and Hygiene*. 2020;103: 125–134. doi:10.4269/ajtmh.19-0787.
 23. Amal Mitra, Anthony Mawson. Neglected Tropical Diseases: Epidemiology and Global Burden. *TropicalMed*. 2017;2: 36. doi:10.3390/tropicalmed2030036.
 24. Sacolo-Gwebu H, Kabuyaya M, Chimbari M. Knowledge, attitudes and practices on schistosomiasis and soil-transmitted helminths among caregivers in Ingwavuma area in uMkhanyakude district, South Africa. *BMC Infect Dis*. 2019;19: 734. doi:10.1186/s12879-019-4253-3.
 25. FMOH. Federal Democratic Republic of Ethiopia Ministry of Health. The Third National Neglected Tropical Diseases Strategic Plan 2021-2025 (2013/14 – 2017/18 E.C.) November 2021. Available online: <https://espen.afro.who.int/system/files/content/resources>(accessed on 2 July 2023).

26. Federal Democratic Republic of Ethiopia Ministry of Health. National Master Plan for Neglected Tropical Diseases (NTDs) 2013-2015. Available online: http://ec2-18-210-136-214.compute-1.amazonaws.com/sites/default/files/docs/national_ntd_master_plan_ethiopia_2013-2015 (accessed on 4 April 2023).
27. Sánchez-Marqués R, Salvador F, Bocanegra C, Nindia A, Pintar Z, Martínez J, *et al.* Schistosoma haematobium infection and morbidity risk factors for pre-school age children in western Angola: A knowledge, attitudes and practices survey. Bowen RA, editor. PLoS Negl Trop Dis. 2023;17: e0011650. doi:10.1371/journal.pntd.0011650.
28. Sady H, Al-Mekhlafi HM, Atroosh WM, Al-Delaimy AK, Nasr NA, Dawaki S, *et al.* Knowledge, attitude, and practices towards schistosomiasis among rural population in Yemen. Parasites Vectors. 2015;8: 436. doi:10.1186/s13071-015-1050-8.
29. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. Source Code Biol Med. 2008;3: 17. doi:10.1186/1751-0473-3-17.
30. Masaku J, *et al.* High prevalence of helminths infection and associated risk factors among adults living in a rural setting, Central Kenya: a cross-sectional study. Trop Med Health. 2017;45(1):15.
31. Dawaki S, Al-Mekhlafi HM, Ithoi I, Ibrahim J, Abdulsalam AM, Ahmed A, *et al.* The Menace of Schistosomiasis in Nigeria: Knowledge, Attitude, and Practices Regarding Schistosomiasis among Rural Communities in Kano State. Kumar N, editor. PLoS ONE. 2015;10: e0143667. doi:10.1371/journal.pone.0143667.

32. Odhiambo GO, Musuva RM, Atuncha VO, Mutete ET, Odiere MR, Onyango RO, *et al.* Low levels of awareness despite high prevalence of schistosomiasis among communities in Nyalenda informal settlement, Kisumu City, Western Kenya. *PLoS Negl Trop Dis.* 2014;8(4):e2784. doi:10.1371/journal.pntd.0002784.
33. Mazigo HD, Waihenya R, Mkoji GM, Zinga M, Ambrose EE, *et al.* Intestinal schistosomiasis: prevalence, knowledge, attitude and practices among school children in an endemic area of north western Tanzania. *J Rural Trop Public Health.* 2010;9:53–60.
34. Mushi V, Zacharia A, Shao M, Mubi M, Tarimo D. Prevalence and risk factors of urogenital schistosomiasis among under-fives in Mtama District in the Lindi region of Tanzania. Webster BL, editor. *PLoS Negl Trop Dis.* 2022;16: e0010381. doi:10.1371/journal.pntd.0010381.
35. Pandey KR, Yang F, Cagney KA, Smieliauskas F, Meltzer DO, Ruhnke GW. The impact of marital status on health care utilization among Medicare beneficiaries. *Medicine.* 2019;98: e14871. doi:10.1097/MD.00000000000014871.

Paper IV

Association of *Schistosoma mansoni* infection with undernutrition and anaemia among preschool children in southern Ethiopia

Tafese Tadele^{1*}, Ayalew Astatkie¹, Birkneh Tilahun Tadesse², Eyasu Makonnen^{3,4}, Solomon Mequanente Abay⁴, and Eleni Aklillu⁵

1. School of Public Health, College of Medicine and Health Sciences, Hawassa University, Hawassa P.O. Box 1560, Ethiopia
2. Department of Pediatrics, College of Medicine and Health Sciences, Hawassa University, Hawassa P.O. Box 1560, Ethiopia
3. Center for Innovative Drug Development and Therapeutic Trials for Africa, College of Health Sciences, Addis Ababa University, Addis Ababa P.O. Box 9086, Ethiopia
4. Department of Pharmacology and Clinical Pharmacy, College of Health Sciences, Addis Ababa University, Addis Ababa, P.O. Box 9086, Ethiopia
5. Department of Global Public Health, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden

***Correspondence:** Tel: +251912144724; E-mail: tafese.gudura@gmail.com (T.T.)

Present address: Hawassa University, P.O. Box 1560, Hawassa, Ethiopia

Abstract

Background: Parasitic infections like schistosomiasis continue causing anaemia and negative effects on the nutritional status of preschool children (pre-SAC). Yet, only limited small-scale studies addressed the association between *Schistosoma mansoni* (*S. mansoni*) infection and undernutrition or anaemia among preschool children (Pre-SAC). Thus, in the current study, the association of *S. mansoni* infection with undernutrition and anaemia was investigated in pre-SAC in southern Ethiopia.

Methods: A cross-sectional study was applied among 565 children selected using a simple random sampling technique. Data was collected using a structured questionnaire and case record format. Fresh stool samples were tested on the same day through double testing using the Kato-Katz technique. Nutritional status was assessed using anthropometric measurements. Haemoglobin concentration was determined using a HemoCue machine and adjusted for altitude. A multivariable logistic regression with a cluster-robust variance estimation method was used to identify the determinants and a p-value <0.05 was fixed statistically significant.

Result: Overall, 24.3% of the pre-SAC were stunted, 6.6% were wasted, and 2.0% were underweight, whereas 28.0% were anaemic. A significant association was detected between *S. mansoni* with soil-transmitted helminths (STH) co-infection (AOR = 4.1, 95% CI: 1.47, 11.11) and stunting relative to those infected only with *S. mansoni*. Besides, adjusted for participants' age, sex, co-infection, education level of caregivers, and household wealth index, *S. mansoni* infection (AOR = 1.9, 95% CI: 1.03, 3.44) had a significant association with anaemia compared to not infected. However, no independent significant association was observed between *S. mansoni* infection and stunting, wasting, or being underweight among pre-SAC.

Conclusions: *S. mansoni* with STH co-infection exhibited higher rates of stunting, while *S. mansoni*-infected pre-SAC had a higher risk of developing anaemia in the study setting. Thus,

praziquantel preventive chemotherapy and STH deworming integrated with nutritional screening and rehabilitation are recommended for pre-SAC.

Keywords: Schistosoma mansoni, Stunting, Wasting, Underweight, Anaemia; Preschool children

Introduction

Schistosomiasis is a main infectious disease leading to health problems in parts of Africa, South America, and Asia [1–3]. It affects mostly the poor and overlooked section of the world [4,5] and more than 252 million people globally. Around 800 million people have a chance of getting the infection in endemic nations [6–8].

Intestinal schistosomiasis presents a significant health threat, predominantly in sub-Saharan Africa [9–12]. Individuals infected with *Schistosoma mansoni* parasites are at risk of acquiring the related morbidity [7,13–15]. The morbidity is mainly initiated by damaging immunologic responses to eggs deposited by adult female worms in the blood vessels surrounding the liver and intestines [16]. *S. mansoni*-linked morbidities such as hepatosplenomegaly, distention of the portal vein, malnutrition, anaemia, diminished physical fitness, and impaired physical and cognitive growth have been evident in children [13,16–19].

Declined food intake, increased nutrient wastage through loss of blood, vomiting, and diarrhea attributed to parasitic infections alter the nutritional status of affected children [4]. Pre-SAC are also furthest at risk of long-lasting infection which can harm growth, development, cognition, iron status, and immaturity of the immune system which further increases defenselessness to infection and future production [1].

In co-endemic communities, schistosomiasis with intestinal helminths plays a critical role in depriving hosts of essential nutrients [20]. Moreover, pre-SAC is a nutritionally susceptible segment of the population, and defects during this early developmental stage may continue for a long [4,21]. *S. mansoni* is responsible for causing blood loss through fecal occult blood further affects iron balance and leads to undernutrition [1].

A previous study conducted in Yemen revealed that *S. mansoni* was an independent risk factor for stunting among SAC [22]. Another study conducted in SAC in Tanzania also reported increased odds of stunting and anaemia among *S. mansoni*-infected children [13], while higher odds of emaciation was detected among *S. mansoni*-infected children from Burkina Faso [23].

To the authors' knowledge, the association between *S. mansoni* infection and undernutrition and anaemia was exhibited insufficiently among pre-SAC. Hence, the extent of the association between *S. mansoni* infection and stunting, wasting, underweight, and anaemia was investigated in the present study among pre-SAC in southern Ethiopia.

Methods

Study design and setting

This was a cross-sectional study conducted between August and December 2021 in the Hawella Tulla district of southern Ethiopia. The study district was confirmed to be prevalent for schistosomiasis based on the burden assessment report of NTDs done in Ethiopia [24]. The district has an average annual rainfall of 1,123mm and a mean temperature of 13-27°C. It is located at an altitude of 1,800m above sea level. The main economic activities around the district include farming of both animals and crops and fishing in Lake Hawassa. A detailed explanation of the study site has been provided elsewhere [25].

Study population

Children aged 4-7 years who lived in the selected *kebeles* (local administrative unit in Ethiopia) of the study district for at least six months were included. In Ethiopia, children are expected to enroll in school at the age of seven years. The age before seven years is considered a pre-school age. On the other hand, by the time the present study was designed, the WHO recommended praziquantel and other schistosomiasis prevention and control interventions for children starting

at four years of age. Hence, the present study focused on the 4-7 years age group. A detailed description of the study's inclusion and exclusion criteria has been provided elsewhere [25].

Sample size determination

OpenEpi sample size calculation software was used to calculate the sample size. It was computed using a comparison of two population proportions of undernutrition and anemia (separately for the four outcomes – stunting, wasting, underweight, and anemia) using the findings of undernutrition and anaemia in previous studies [13,22]. The final largest sample size (n= 620) was calculated using the assumptions, the prevalence of underweight among unexposed with the outcome (24.5%) and exposed with the outcome (39.5%) setting the level of confidence at 95%, power at 85%, the ratio of unexposed-to-exposed at 1, and expected non-response rate at 10% was used.

Sampling procedure

The study participants were recruited using a multistage sampling technique. Of the twelve kebeles of the study district, six were selected to be included in the present study due to the endemicity report of *S. mansoni* infection generated in Ethiopia [24] among SAC. Initially, three kebeles (Tullo, Finchawa, and Chafe Kotijebessa) were selected by using the lottery method. The health extension workers prepared the list of eligible community members through house-to-house enumeration before the initiation of data collection in the selected kebeles. One child was included in the sampling frame using the lottery method whenever there is more than one child in the selected households. Then in each Kebele, a simple random sampling method was applied to enroll the study participants using computer-generated random numbers proportionate to the population size. In cases where the potential respondent was not existing at home during the initial visit, two repeated visits were made, after which the person was considered a non-respondent.

Data collection procedures

The research team collected the required data using a structured questionnaire interview at the homes of study participants. The mothers/ primary caregivers of pre-SAC were interviewed to get information on the children. Stool, blood sample collections, and anthropometric measurements were conducted at the households.

Structured questionnaire

Data on socio-demographic and economic characteristics, and morbidity patterns was collected using a pre-tested, structured questionnaire. The mothers/primary caregivers of the participants were interviewed by eight public health experts who trained on how to apply the questionnaire. The questionnaire was translated into local languages (Amharic and Sidamu Afoo). To ensure proper implementation of the data-gathering procedure regular supervision was conducted by two experienced professionals and the main investigator.

Anthropometric measurements

Height was measured with a locally made stadiometer. Shoes and headdressing of children were removed. Children were guided to stand on the base of the stadiometer with their heads in contact with the vertical board, and both feet together [26]. The child was guided to take a deep breath and stand as tall as possible after proper positioning. Then a precise height was measured in centimeters using a ruler placed on their head. A scale watched at every measurement was used to measure weight. Children removed extra clothing and shoes and then stood in the middle of the scale. The readings in kilograms were recorded with one decimal place [26]. Two readings for height and weight were recorded for each child and the mean of these results was taken.

Nutritional status

Growth and nutritional status were assessed using the WHO Anthro Plus software version 1.0.4 [27] for older age group (6 - 7 years), while WHO Anthro software version 3.2.2 was used for younger age group (4 - 5 years) [28]. Height-for-age Z-score (HAZ), body-mass-index (BMI) for-age Z-score (BAZ) or weight-for-height Z-score (WHZ), and weight-for-age Z-score (WAZ) for each participant were then calculated.

Stool sample collection

A complete explanation of the stool sample collection and processing for both *S. mansoni* and STH has been provided elsewhere [25].

Blood sample collection

A finger prick blood sample was collected from enrolled children by four expert laboratory technologists using a microcuvette. Haemoglobin concentration was determined using HemoCue Hb 301 method (HemoCue AB Angelholm, Sweden). The method is effective and suitable in resource-limited settings [29].

Study variables

Outcome variables

Stunting: A height-for-age Z-score less than minus two standard deviations (SD) of the WHO Anthro /Anthroplus median Child Growth Standards [27,28].

Wasting: A height-for-weight/ body mass index-for-age Z-score less than minus 2SD of the WHO Anthro /Anthroplus median Child Growth Standards [27,28].

Underweight: A weight-for-age Z-score less than minus 2SD of the WHO Anthro /Anthroplus median Child Growth Standards [27,28].

Anaemia: Haemoglobin concentrations were then classified as mild (11.0 – 11.4 g/dL), moderate (8.0 – 10.9 g/dL), and severe anaemia (< 8 g/dL) for 5 to 11 years old children according to the WHO guideline [30], while mild (10.0 – 10.9 g/dL), moderate (7.0 – 9.9 g/dL) and severe anaemia (< 7 g/dL) for children aged 6 to 59 months adjusted for age and altitude according to the WHO Guideline [30].

Exposure variable

S. mansoni infection: It was detected by microscopic examination using Kato-Katz for diagnosing *S. mansoni* infection [31]. If *S. mansoni* infection was detected the *S. mansoni* infection status was recorded as infected or uninfected if no *S. mansoni* infection was detected. The *S. mansoni* infection intensity was categorized as light (1–99 EPG), moderate (100–399 EPG), or heavy (>400 EPG) according to the WHO guideline [32].

Other covariates

The covariates adjusted during the analysis include age, sex, education level of caregivers, household wealth index, and *S. mansoni* with STHs co-infection. The data on a household's assets such as radio, refrigerator, television, bicycle, motorbike, car, phone/cell phone; the household's amenities such as water supply, toilet, flooring, walls/house, roof, electricity, and cooking fuel were used to compute the wealth index of the household. The wealth index was assigned based on the indicator weights computed using the principal component analysis (PCA). The households were grouped into five equal wealth quintiles (WQs) based on their scores. The score was used to order the households. The quintile variable was created using the household score. Then each household member receives the household's quintile category.

Statistical analysis

Data was analyzed using Stata version 14 (StataCorp LLC, College Station, Texas, US). Descriptive analyses were carried out by computing frequencies and proportions for categorical variables, mean with SD, and median with interquartile ranges for continuous variables.

Multivariable logistic regression with cluster-robust variance estimation method was conducted to assess the association of *S. mansoni* infection and various background characteristics with undernutrition and anaemia. The cluster-robust variance estimation method was used as it offers a more precise estimation variance of parameters in clustered data than the standard logistic regression. Variables were comprised in the multivariable model based on a purposeful variable selection approach as recommended in the literature [33]. Accordingly, variables with p-values < 0.25 on bivariable analysis and those that were considered important based on existing literature were encompassed in the multivariable model.

Results from the regression analysis were expressed as adjusted odds ratios (AOR) with their 95% confidence intervals (CI). A p-value of < 0.05 was considered statistically significant.

Results

Sociodemographic characteristics

From the sampled 620 pre-SAC, 565 participated in the survey (91.1% response rate). Two hundred eighty-seven (50.8%) were male participants, while nearly half (51.2%) belonged to the older age group (6 - 7 years) (Table 1).

Table 1. Sociodemographic characteristics of the studied preschool children in southern Ethiopia, August to December 2021

Variable	Category	N (%)
Age groups (years)	4 -5 years	276 (48.9)
	6-7 years	289 (51.1)
Sex	Male	287 (50.8)
	Female	278 (49.2)
Residence	Chefe Kotijebessa	144 (25.5)
	Finchawa	172 (30.4)
	Tullo	249 (44.1)
Wealth index	Poorest	125 (22.1)
	Poorer	124 (22.0)
	Middle	95 (16.8)
	Richer	112 (19.8)
	Richest	109 (19.3)

N: Total number of participants within each category

Parasite infections

The prevalence of *S. mansoni* among pre-SAC was 27.4% (95% confidence interval (CI): 23.7%, 31.1%): 52.3% were lightly infected, 33.5% were moderately infected, and 14.2% were heavily infected. Of the total *S. mansoni*-infected children, 33.5% (52/155) were co-infected with one or more STHs. *S. mansoni* with *A. lumbricoides* (23.2%) double infection was the most predominant followed by *S. mansoni* with *T. trichiura* (3.2%) co-infection, while 3.9% of the participants presented with *S. mansoni*, *A. lumbricoides* with *T. trichiura* triple infection. Of the 52 children with co-infection, 29.6% had light, 38.5% had moderate, and 36.4% children had heavy-intensity intestinal schistosomiasis.

Prevalence of undernutrition (stunting, wasting, and underweight)

Of the total screened children, 24.3% (95% CI: 20.7%, 27.8%) were stunted, 6.6% (95% CI: 4.5%, 8.6%) wasted, and 2.0% (95% CI: 0.8%, 3.1%) underweight (Figure 1).

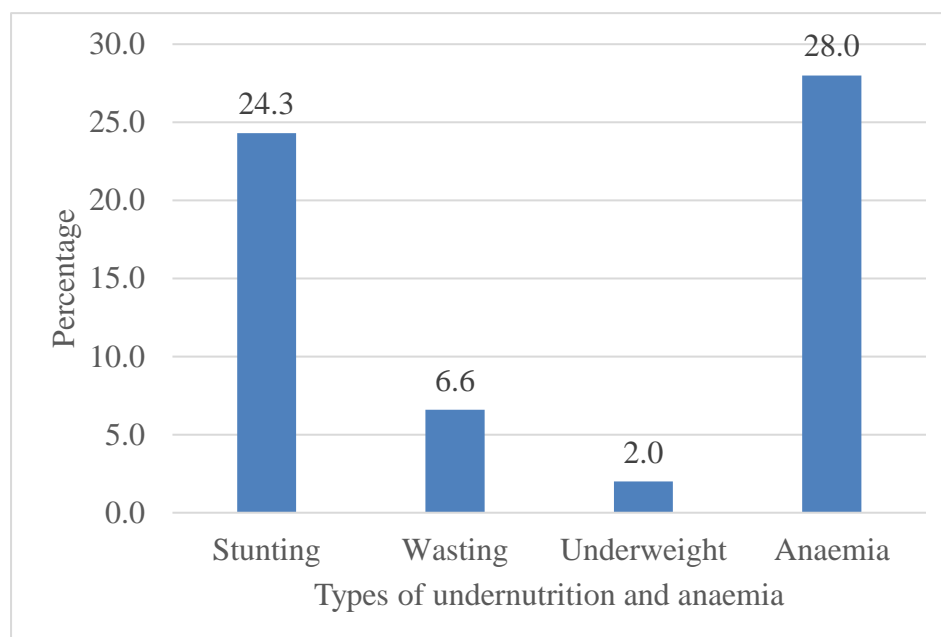


Figure 1. Prevalence of undernutrition and anaemia among preschool children in southern Ethiopia, August to December 2021

Prevalence of anaemia

Of the 565 screened children with complete data on haemoglobin concentration, 28.0% (95% CI: 24.3%, 31.7%) were found to be anaemic (Figure 1). Ninety-five (16.8%) children developed mild anaemia, while moderate anaemia constituted 11.2% (63/565). However, severe anaemia was not detected among the study participants. Out of the 158 children with anaemia, 15.2% of children had moderate-to-heavy intensity intestinal schistosomiasis. The studied population had a median haemoglobin level of 11.8 g/dl (IQR = 11.1–12.5 g/dl).

The mean (\pm SD) haemoglobin concentration for the younger children (4-5 years) was 11.5 g/dl (\pm 1.1), while the older children (6-7years) had a mean (\pm SD) haemoglobin concentration of 12.0 g/dl (\pm 0.90).

Association of *S. mansoni* infection with undernutrition

No independent significant association was observed between *S. mansoni* infection and stunting ($p = 0.50$). However, higher odds of stunting was observed among *S. mansoni* with STH co-infected children (AOR = 4.1, 95% CI: 1.47, 11.11) compared to those having only *S. mansoni* infection (Table 2). *S. mansoni* infection had no significant association with wasting ($p = 0.15$) (Table 3) or underweight ($p = 0.42$) among pre-SAC (Table 4).

Table 2. Association between *Schistosoma mansoni* infection and stunting among preschool children in southern Ethiopia, August to December 2021

Variable	Category	Stunting (HAZ)		COR (95%CI)	AOR (95% CI)
		Stunted	Not stunted		
<i>S. mansoni</i> infection	Not-infected	78 (19.0)	332 (81.0)	1.0	1.0
	Infected	59 (38.1)	96 (61.9)	2.6 (1.74, 3.93)***	1.4 (0.51, 4.06)
Co-infection	<i>S. mansoni</i> only infected	27 (26.2)	76 (73.8)	1.0	1.0
	<i>S. mansoni</i> + STH infected	32 (61.5)	20 (38.5)	6.2 (3.42, 11.31)***	4.1 (1.47, 11.11)**
Age groups (years)	4-5 years	59 (21.4)	217 (78.6)		1.0
	6-7 years	78 (27.0)	211 (73.0)	1.4 (0.92, 2.00)	1.2 (0.56, 2.58)
Sex	Female	52 (18.7)	226 (81.3)	1.0	1.0
	Male	85 (29.6)	202 (70.4)	1.8 (1.23, 2.71)**	1.7 (1.40, 2.09)***
Educational level of caregivers	College and above	10 (11.0)	81 (89.0)	1.0	1.0
	No formal education	69 (27.8)	179 (72.2)	3.1 (1.53, 6.37)**	2.6 (0.43, 16.07)
	Primary education	67 (38.3)	108 (61.7)	3.8 (1.79, 7.92)***	3.8 (2.02, 6.99)***
Household wealth index	Secondary education	46 (31.7)	99 (68.3)	1.4 (0.57, 3.46)	1.3 (0.52, 3.22)
	Richest	27 (24.8)	82 (75.2)	1.0	1.0
	Poorest	30 (24.0)	95 (76.0)	0.96 (0.53, 1.74)	0.7 (0.19, 2.82)
	Poorer	33 (26.6)	91 (73.4)	1.10 (0.61, 1.99)	0.8 (0.34, 1.88)
	Middle	27 (28.4)	68 (71.6)	1.21 (0.65, 2.25)	0.8 (0.37, 1.67)
	Richer	20 (17.9)	92 (82.1)	0.66 (0.34, 1.27)	0.6 (0.38, 1.03)

^a: Reference category; LR: Logistic regression; COR: Crude odds ratio; AOR: Adjusted odds ratio; CI: Confidence interval; p-value <0.001***, p-value <0.05**; +: And

Table 3. Association between *Schistosoma mansoni* infection and wasting among preschool children in southern Ethiopia, August to December 2021

Variable	Category	Wasting (BAZ/WHZ)		COR (95%CI)	AOR (95% CI)
		Wasted	Not-wasted		
<i>S. mansoni</i> infection	Not-infected	23 (5.6)	387 (94.4)	1.0	1.0
	Infected	14 (9.0)	141 (91.0)	1.7 (0.84, 3.34)	2.8 (0.69, 11.63)
Co-infection	<i>S. mansoni</i> only infected	14 (13.6)	89 (86.4)	1.0	1.0
	<i>S. mansoni</i> + STH infected	0 (0.0)	52 (100.0)	a	a
Age groups (years)	4-5 years	20 (7.3)	256 (92.7)	1.0	1.0
	6-7 years	17 (5.9)	272 (94.1)	0.8 (0.41, 1.56)	0.7 (0.61, 0.77) ***
Sex	Female	20 (7.2)	258 (92.8)	1.0	1.0
	Male	17 (5.9)	270 (94.1)	0.8 (0.42, 1.59)	0.7 (0.43, 1.28)
Educational level of caregivers	College and above	11 (12.1)	80 (87.9)	1.0	1.0
	No formal education	16 (6.5)	232 (93.5)	0.5 (0.23, 1.29)	0.5 (0.14, 1.56)
	Primary education	6 (4.1)	139 (95.9)	0.3 (0.11, 0.84) **	0.3 (0.15, 0.56) ***
	Secondary education	4 (4.9)	77 (95.1)	0.4 (0.12, 1.38)	0.3 (0.26, 0.45) ***
Household wealth index	Richest	6 (5.5)	103 (94.5)		1.0
	Poorest	5 (4.0)	120 (96.0)	0.7 (0.21, 2.41)	1.0 (0.30, 3.55)
	Poorer	6 (4.8)	118 (95.2)	0.9 (0.27, 2.79)	1.2 (0.44, 3.24)
	Middle	6 (6.3)	89 (93.7)	1.2 (0.36, 3.72)	1.7 (0.21, 13.61)
	Richer	14 (12.5)	98 (87.5)	2.5 (0.91, 6.64)	2.6 (0.99, 6.97)

COR: Crude odds ratio; AOR: Adjusted odds ratio; CI: Confidence interval; p-value

<0.001***, p-value <0.05**; STH: Soil-transmitted helminths, ^aOR could not be estimated

because it predicts failure perfectly.

Table 4. Association between *Schistosoma mansoni* infection and underweight among preschool children in southern Ethiopia, August to December 2021

Variable	Category	Underweight (WAZ)		COR (95%CI)	AOR (95% CI)
		Under weight	Normal		
<i>S. mansoni</i> infection	Not-infected	7 (1.7)	403 (98.3)	1.0	1.0
	Infected	4 (2.6)	151 (97.4)	1.5 (0.44, 5.28)	1.6 (0.50, 5.26)
Co-infection	<i>S. mansoni</i> only infected	3 (2.9)	100 (97.1)	1.0	1.0
	<i>S. mansoni</i> + STH infected	1 (1.9)	51 (98.1)	1.0 (0.12, 7.86)	1.1 (0.07, 18.22)
Age groups (years)	4-5 years	6 (2.2)	270 (97.8)	1.0	1.0
	6-7 years	5 (1.7)	284 (98.3)	0.8 (0.24, 2.63)	0.6 (0.40, 0.93)
Sex	Female	2 (0.7)	276 (99.3)	1.0	1.0
	Male	9 (3.1)	278 (96.9)	4.5 (0.96, 20.86)	4.5 (2.31, 8.93)***
Educational level of caregivers	College and above	4 (4.4)	87 (95.6)	1.0	1.0
	No formal education	4 (1.6)	244 (98.4)	0.4 (0.09, 1.46)	0.4 (0.13, 1.16)
	Primary education	0 (0.0)	145 (100.0)	a	
Household wealth index	Secondary education	3 (3.7)	78 (96.3)	0.8 (0.18, 3.85)	0.9 (0.37, 2.13)
	Richest	2 (1.8)	107 (98.2)	1.0	1.0
	Poorest	2 (1.6)	123 (98.4)	0.9 (0.12, 6.28)	0.9 (0.09, 9.55)
	Poorer	2 (1.6)	122 (98.4)	0.9 (0.12, 6.33)	0.9 (0.63, 1.29)
	Middle	0 (0.0)	95 (100.0)	a	
	Richer	5 (4.5)	107 (95.5)	2.5 (0.47, 13.17)	2.2 (0.41, 11.85)

CRR: Crude risk ratio, ARR: Adjusted risk ratio, CI: Confidence interval; p-value <0.001***,

p-value <0.05**; ^aOR could not be estimated because it predicts failure perfectly.

Association of *S. mansoni* infection with anaemia

Of the total examined pre-SAC, 34.2% with *S. mansoni* infection had anemia, while 25.6% without *S. mansoni* infection had anemia. Adjusting for other covariates, higher odds of anaemia was detected among *S. mansoni*-infected pre-SAC compared to those not infected with *S. mansoni* (AOR = 1.9, 95% CI: 1.03, 3.44) (Table 5).

Table 5. Association of *Schistosoma mansoni* infection with anaemia among preschool children in southern Ethiopia, August to December 2021

Variable	Category	Anaemia		COR (95% CI)	AOR (95% CI)
		Anaemic	Normal		
<i>S. mansoni</i> infection	Not-infected	105 (25.6)	305 (74.4)	1.0	1.0
	Infected	53 (34.2)	102 (65.8)	1.5 (1.01, 2.25)**	1.9 (1.03, 3.44)**
Co-infection	<i>S. mansoni</i> only infected	35 (34.0)	68 (66.0)	1.0	1.0
	<i>S. mansoni</i> + STH infected	18 (34.6)	34 (65.4)	1.4 (0.77, 2.58)	0.9 (0.58, 1.53)
Age groups (years)	4-5 years	75 (27.2)	201 (72.8)	1.0	1.0
	6-7 years	83 (28.7)	206 (71.3)	1.1 (0.75, 1.56)	0.9 (0.59, 1.37)
Sex	Female	72 (25.9)	206 (74.1)	1.0	1.0
	Male	86 (30.0)	201 (70.0)	1.2 (0.85, 1.77)	1.2 (0.94, 1.66)
Educational level of caregivers	College and above	36 (39.6)	55 (60.4)	1.0	1.0
	No formal education	50 (20.2)	198 (79.8)	0.4 (0.23, 0.65)***	0.3 (0.07, 1.02)
	Primary education	37 (25.5)	108 (74.5)	0.5 (0.30, 0.92)**	0.4 (0.12, 1.58)
	Secondary education	35 (43.2)	46 (56.8)	1.2 (0.63, 2.14)	1.1 (0.25, 4.57)
Household wealth index	Richest	32 (29.4)	77 (70.6)	1.0	1.0
	Poorest	35 (28.0)	90 (72.0)	0.9 (0.53, 1.65)	1.5 (0.73, 2.97)
	Poorer	43 (34.7)	81 (65.3)	1.3 (0.73, 2.22)	1.7 (0.76, 3.77)
	Middle	29 (30.5)	66 (69.5)	1.1 (0.58, 1.93)	1.5 (0.77, 2.90)
	Richer	19 (17.0)	93 (83.0)	0.5 (0.26, 0.94)**	0.5 (0.28, 1.01)

CRR: Crude risk ratio, ARR: Adjusted risk ratio, CI: Confidence interval; p-value <0.001***,

p-value <0.05**

Discussion

We have shown an association between *S. mansoni* infection and undernutrition or anaemia among pre-SAC in the present study. The odds of stunting among children who had *S. mansoni* with STH co-infection was significantly higher than those infected only with *S. mansoni*. Besides, a significant association was detected between *S. mansoni* infection and anaemia among pre-SAC. However, no independent significant association was observed between *S. mansoni* infection and stunting, wasting, or being underweight among pre-SAC in the study area.

Our finding of an association between *S. mansoni* with STH co-infection and stunting agrees with a finding of a Tanzanian study [7] that reported co-infected children had higher rates of stunting than children who were not co-infected. For this association, the effect of *S. mansoni* with STH co-infection could be responsible for the observed increased risk of nutritional deficit evident among pre-SAC who had co-infection compared to those infected only with *S. mansoni*. This finding could be related to repeated exposure to chronic parasitic infections, and impaired immunologic response resulting from heavy-intensity infections [35]. In addition, having intestinal schistosomiasis with other parasitic infections during pregnancy may act as a distant factor leading to the increased odds of stunting among co-infected children [35]. While the mechanism underlying the linkage between *S. mansoni* with STH infection and stunting might not be straightforward, considering the complex nature of stunting the mechanism seems to work vice versa. Repeated chronic *S. mansoni* with STH co-infection may lead to stunting; stunting, in turn, may lead to immunosuppression, thereby decreasing resistance to disease and increasing susceptibility to parasitic infections and together accelerating childhood nutritional deficit.

The present study has revealed no significant independent association between stunting and *S. mansoni* infection. Contrary to our finding, a significant association was reported previously from Yemen [22]. The difference between the present finding and a previous report might be attributed to the variation in the focus of nutritional screening among children. Contrary to Ethiopia, in Yemen nutritional screening has been a bit neglected in schistosomiasis prevalent settings which accounted for the observed 4.1 times higher odds of stunting among *S. mansoni* infected relative to non-infected counterparts [22].

Our study has found no significant association between *S. mansoni* infection and wasting or being underweight among pre-SAC. Contrary to our finding, a previous study conducted in Burkina Faso [23] reported 1.27 times higher odds of emaciation among *S. mansoni*-infected children compared to non-infected ones. The variation between the present and a previous report could be accounted for by the variation in the extent of acute infections, differences in child feeding culture, variation in the knowledge of caregivers, and immunologic differences. Additionally, wasting is an indication of acute nutritional insult results in recent illness, parasitic infections, and failure to gain or lose weight.

Adjusting for other covariates, higher odds of anaemia was observed among *S. mansoni*-infected children relative to those not infected with *S. mansoni* in the current study. A previous study conducted among SAC in Ethiopia also reported higher odds of anaemia among children with *S. mansoni* infection than uninfected [19]. The fact that higher odds of anaemia attributed to *S. mansoni* infection may be explained partly by inflammatory mechanisms that affect the body's ability to use iron needed to make enough red blood cells and partly by occult bleeding caused by *S. mansoni* infection due to perforation of the intestinal mucosa and colorectal polyps through the formation of granuloma, ulcers, haemorrhage, and colonic fibrosis [36]. Other possible justifications for the detected association could be iron-deficiency anaemia related to

extracorporeal blood loss and/or impaired iron absorption and micronutrient deficiencies among *S. mansoni*-infected children compared to not-infected counterparts [37].

The strength of the present study is that it has been conducted among the overlooked pre-SAC population aiming at reducing the possible source of reinfection and accelerating the attainment of the elimination goal of the disease.

The study has, however, some limitations. Firstly, being a cross-sectional survey, the temporal relationship between *S. mansoni* infection and stunting is not clear. Secondly, the study didn't control for the effect of parasitic diseases like malaria and factors related to household food security; thus, those unmeasured confounders might result in an overestimation or underestimation of the magnitude of association between *S. mansoni* infection and undernutrition and anemia.

Conclusion

S. mansoni with STH co-infection is linked with higher rates of stunting, while a significant association was detected between *S. mansoni* infection and anaemia among pre-SAC in rural southern Ethiopia. Thus, regular nutritional screening and provision of preventive treatment against *S. mansoni* infections and STHs with other integrated control interventions are critical. A longitudinal study is recommended to get more evidence on the temporal relationship between *S. mansoni* with STH co-infection and stunting. Moreover, the possibilities of integrated nutritional screening and rehabilitation for families in endemic communities should be considered.

Abbreviation

Pre-SAC: Pre-school age children

SAC: School-age children

STH: Soil-transmitted helminths

WHO: World Health Organization

HAZ: Height for Age Z score

BAZ: Body mass index (BMI) for Age Z score

WAZ: Weight-for-age Z-score

WHZ: Weight-for-height Z-score

BMI: Body mass index

CIs: Confidence intervals

Ethical considerations

This study was conducted as per the Declaration of Helsinki [34]. The Institutional Review Board (IRB) of the College of Medicine and Health Sciences of Hawassa University granted ethical approval for the study (Ref. No: IRB/200/13). A support letter was also obtained from the Sidama Regional State Health Bureau. Before enrolment, participants were explained the purpose and the conduct of the study, and written informed consent was obtained from the mothers/primary caregivers of each study participant. The respondents were assured of confidentiality, which was maintained during and after the study.

Data Availability: The data generated in this study are included in the article, further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

Funding

The data collection for this study was supported by pharmacovigilance infrastructure and post-marketing surveillance system capacity building for regional medicine regulatory

harmonization in East Africa (PROFORMA) (Grant number CSA2016S-1618) and PrazOpt (Grant number TMA2018CDF-2345) projects, which were funded by the European & Developing Countries Clinical Trials Partnership (EDCTP) two program.

Authors' contributions

Conceptualization: T.T., A.A., B.T.T., S.M.A., E.M., and E.A.; Data curation: T.T., A.A., S.M., E.M., and E.A.; Formal analysis, T.T., A.A., S.M.A., and E.A.; Funding acquisition, E.A., E.M., and S.M.A.; Methodology, T.T., A.A., S.M.A., B.T.T.; E.M., and E.A.; Project administration: E.A., E.M., and S.M.A.; Drafted an original manuscript, T.T.; Writing; review & editing, T.T., A.A., B.T.T., S.M.A, E.M., and E.A.

Acknowledgments

We appreciate the staff of Hawassa City Health Department for their continued support throughout the data collection period. We also acknowledge all the participants who were involved in the study.

References

1. Faust CL, Osakunor DNM, Downs JA, Kayuni S, Stothard JR, Lamberton PHL, et al. Schistosomiasis Control: Leave No Age Group Behind. *Trends in Parasitology*. 2020;36: 582–591. doi:10.1016/j.pt.2020.04.012.
2. Maciel PS, Gonçalves R, Antonelli LR do V, Fonseca CT. Schistosoma mansoni Infection Is Impacted by Malnutrition. *Front Microbiol*. 2021;12: 635843. doi:10.3389/fmicb.2021.635843.
3. Hailu T, Yimer M, Mulu W, Abera B. Synergetic Effects of Plasmodium , Hookworm, and Schistosoma mansoni Infections on Hemoglobin Level among Febrile School Age

- Children in Jawe Worda, Northwest Ethiopia. *Journal of Parasitology Research*. 2018;2018: 1–6. doi:10.1155/2018/9573413.
4. Adeniran AA, Mogaji HO, Aladesida AA, Olayiwola IO, Oluwole AS, Abe EM, et al. Schistosomiasis, intestinal helminthiasis and nutritional status among preschool-aged children in sub-urban communities of Abeokuta, Southwest, Nigeria. *BMC Res Notes*. 2017;10: 637. doi:10.1186/s13104-017-2973-2.
 5. Shen Y, King CH, Binder S, Zhang F, Whalen CC, Evan Secor W, et al. Protocol and baseline data for a multi-year cohort study of the effects of different mass drug treatment approaches on functional morbidities from schistosomiasis in four African countries. *BMC Infect Dis*. 2017;17: 652. doi:10.1186/s12879-017-2738-5.
 6. Gebreyesus TD, Tadele T, Mekete K, Barry A, Gashaw H, Degefe W, et al. Prevalence, Intensity, and Correlates of Schistosomiasis and Soil-Transmitted Helminth Infections after Five Rounds of Preventive Chemotherapy among School Children in Southern Ethiopia. *Pathogens*. 2020;9: 920. doi:10.3390/pathogens9110920.
 7. Kinung'hi SM, Mazigo HD, Dunne DW, Kepha S, Kaatano G, Kishamawe C, et al. Coinfection of intestinal schistosomiasis and malaria and association with haemoglobin levels and nutritional status in school children in Mara region, Northwestern Tanzania: a cross-sectional exploratory study. *BMC Res Notes*. 2017;10: 583. doi:10.1186/s13104-017-2904-2.
 8. Cisse M, Sangare I, Djibougou AD, Tahita MC, Gnissi S, Bassinga JKW, et al. Prevalence and risk factors of *Schistosoma mansoni* infection among preschool-aged children from Panamasso village, Burkina Faso. *Parasites Vectors*. 2021;14: 185. doi:10.1186/s13071-021-04692-8.

9. Nalugwa A, Nuwaha F, Tukahebwa E, Olsen A. Schistosoma mansoni-Associated Morbidity among Preschool-Aged Children along the Shores of Lake Victoria in Uganda. *TropicalMed*. 2017;2: 58. doi:10.3390/tropicalmed2040058.
10. Erismann S, Knoblauch AM, Diagbouga S, Odermatt P, Gerold J, Shrestha A, et al. Prevalence and risk factors of undernutrition among schoolchildren in the Plateau Central and Centre-Ouest regions of Burkina Faso. *Infect Dis Poverty*. 2017;6: 17. doi:10.1186/s40249-016-0230-x.
11. Stephenson LS, Latham MC, Ottesen EA. Malnutrition and parasitic helminth infections. *Parasitology*. 2000;121: S23–S38. doi:10.1017/S0031182000006491.
12. Bisetegn H, Eshetu T, Erkihun Y. Prevalence of Schistosoma mansoni infection among children in Ethiopia: a systematic review and meta-analysis. *Trop Dis Travel Med Vaccines*. 2021;7: 30. doi:10.1186/s40794-021-00156-0.
13. Munisi DZ, Buza J, Mpolya EA, Kinung'hi SM. Schistosoma mansoni Infections, Undernutrition and Anaemia among Primary Schoolchildren in Two Onshore Villages in Rorya District, North-Western Tanzania. Gutman J, editor. *PLoS ONE*. 2016;11: e0167122. doi:10.1371/journal.pone.0167122.
14. Njiru J, Muhoho N, Simbauni J, Kabiru E. Effects of Soil- Transmitted Helminths and Schistosoma Species on Nutritional Status of Children in Mwea Irrigation Scheme, Kenya. *JALSI*. 2016;5: 1–8. doi:10.9734/JALSI/2016/25053.
15. Abera B, Alem G, Yimer M, Herrador Z. Epidemiology of soil-transmitted helminths, Schistosoma mansoni, and haematocrit values among schoolchildren in Ethiopia. *J Infect Dev Ctries*. 2013;7: 253–260. doi:10.3855/jidc.2539.

16. Nigo MM, Odermatt P, Nigo DW, Salieb-Beugelaar GB, Battegay M, Hunziker PR. Morbidity associated with *Schistosoma mansoni* infection in north-eastern Democratic Republic of the Congo. Garba A, editor. *PLoS Negl Trop Dis*. 2021;15: e0009375. doi:10.1371/journal.pntd.0009375.
17. Chami GF, Fenwick A, Bulte E, Kontoleon AA, Kabatereine NB, Tukahebwa EM, et al. Influence of *Schistosoma mansoni* and Hookworm Infection Intensities on Anaemia in Ugandan Villages. Bethony JM, editor. *PLoS Negl Trop Dis*. 2015;9: e0004193. doi:10.1371/journal.pntd.0004193.
18. Tandoh MA, Steiner-Asiedu M, Otchere J, Daisie LA, Appawu MA, Wilson MD. Helminthiasis burden and nutritional status of non-enrolled school-aged children in irrigated farming communities in Bongo district, Ghana. 2015; 10.
19. Tarekegn D, Birhanie M, Lemma W. Impact of Intestinal Helminth Infections on Malnutrition and Haematological Indices of School-Age Children in Gondar Town, Ethiopia. : 14.
20. Mwinzi PMN, Odhiambo K, Montgomery SP, Karanja DMS, Secor WE, Muok EM, et al. Mechanism of Anemia in *Schistosoma mansoni*-Infected School Children in Western Kenya. *The American Journal of Tropical Medicine and Hygiene*. 2012;87: 862–867. doi:10.4269/ajtmh.2012.12-0248.
21. Ekpo UF, Oluwole AS, Abe EM, Etta HE, Olamiju F, Mafiana CF. Schistosomiasis in infants and pre-school-aged children in sub-Saharan Africa: implication for control. *Parasitology*. 2012;139: 835–841. doi:10.1017/S0031182012000029.
22. Al-Haidari SA, Mahdy MAK, Al-Mekhlafi AM, Al Murisi WMS, Thabit AAQ, Al-Amad MA, et al. Intestinal schistosomiasis among schoolchildren in Sana'a Governorate,

- Yemen: Prevalence, associated factors and its effect on nutritional status and anemia. Garba A, editor. *PLoS Negl Trop Dis.* 2021;15: e0009757. doi:10.1371/journal.pntd.0009757.
23. Savadogo LGB, Savadogo B, Dianou D, Poda JN. Schistosoma mansoni and Schistosoma heamatobium Infection and Nutritional Status of Children in the Hydro-Agricultural Complex Zone of Sourou, Burkina Faso. *ODEM.* 2014;02: 13–18. doi:10.4236/odem.2014.22002.
24. Federal Democratic Republic of Ethiopia Ministry of Health. National Master Plan for Neglected Tropical Diseases (NTDs) 2013015.pdf. 2013. Available online: http://ec2-18-210-136-214.compute-1.amazonaws.com/sites/default/files/docs/national_ntd_master_plan_ethiopia_2013-2015 (accessed on 4 April 2023).
25. Tadele T, Astatkie A, Abay SM, Tadesse BT, Makonnen E, Aklillu E. Prevalence and determinants of Schistosoma mansoni infection among pre-school age children in Southern Ethiopia. *Pathogens.* 2023;12(7):858. <https://doi.org/10.3390/pathogens12070858>.
26. The Royal children's Hospital. Growth measuring 2 years and over. 2013. Available Online:https://www.rch.org.au/uploadedFiles/Main/Content/childgrowth/Growth_measuring_over2. (accessed on 6 December 2022).
27. World Health Organization, Geneva (2009). WHO Anthroplus Software; Software for assessing Growth and Development of the World's Children and Adolescents. Available at https://www.who.int/growthref/tools/who_anthroplus_manual.pdf. Accessed on 6/11/2019.

28. World Health Organization, . WHO Anthro Software; Software for assessing Growth and Development of the World's Children aged below five years.
29. Nkrumah B, Nguah SB, Sarpong N, Dekker D, Idriss A, May J, et al. Hemoglobin estimation by the HemoCue® portable hemoglobin photometer in a resource poor setting. *BMC Clin Pathol.* 2011;11: 5. doi:10.1186/1472-6890-11-5.
30. World Health Organization, Geneva (2011). Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Available at <https://www.who.int/vmnis/indicators/haemoglobin/en/>. Accessed on 6/11/2019.
31. WHO. Prevention and control of schistosomiasis and soil-transmitted helminthiasis: report of a WHO expert committee. Technical Report Series. Geneva: World Health Organization; 2002. Report No.: 912.
32. World Health Organization. Bench Aids for the Diagnosis of Intestinal Parasites. WHO, 1994. Available online: <http://apps.who.int/iris/bitstream/10665/37323/1/9789241544764> (accessed on 4 April 2023).
33. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. *Source Code Biol Med.* 2008;3: 17. doi:10.1186/1751-0473-3-17.
34. World Health Organization. Declaration of Helsinki. World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. 2001. Available: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2566407/>.
35. Fauziah N, Aviani JK, Agrianfanny YN, Fatimah SN. Intestinal Parasitic Infection and Nutritional Status in Children under Five Years Old: A Systematic Review. *TropicalMed.* 2022;7: 371. doi:10.3390/tropicalmed7110371.

36. Qin X, Liu C-Y, Xiong Y-L, Bai T, Zhang L, Hou X-H, et al. The clinical features of chronic intestinal schistosomiasis-related intestinal lesions. *BMC Gastroenterol.* 2021;21:12. doi:10.1186/s12876-020-01591-7.
37. Oliveira D, Ferreira FS, Atouguia J, Fortes F, Guerra A, Centeno-Lima S. Infection by Intestinal Parasites, Stunting and Anemia in School-Aged Children from Southern Angola. Weber CR, editor. *PLoS ONE.* 2015;10: e0137327. doi:10.1371/journal.pone.0137327.

Annexes

English Version Questionnaire:

001. Name of the kebele _____

002. House code _____

003. Visit number 1 _____ 2 _____ 3 _____

Mother/ Care giver name: _____

Participant ID (Code): _____

1. Site Information

Name of Data collector ID (required): _____

Enrollment Date (required) (DD-MM-YYYY): _____

2. Consent Method (required)

- Self
- Mother/primary caregiver
- Other guardian (specify): _____
- No consent (STOP)

3. Enrollment Location

- Home
- Health Facility
- Village meeting point

Instruction: The questionnaire has multiple choices, fill-in-the-blank spaces, and other (specify) alternatives. Please for multiple-choice questions circle the response of the study participant properly and write the responses of the open-ended questions and specify options in a readable

manner with a dry pen. If the respondent reported I don't know circle 999 under the response column. Some questions may have more than one response.

S. N.	Questions	Responses (Code/s)	Skip	Remark
PART I: Socio-Demographic Characteristics of Respondent (Applicable to mothers/caregivers).				
101	How old are you? (Record the last birth day)	Age in years _____ 999. I don't know		
102	What is your religion?	<ol style="list-style-type: none"> 1. Protestant 2. Orthodox 3. Muslim 4. Catholic 5. Other (specify)_____ 		
103	What is the highest education level you have attained?	<ol style="list-style-type: none"> 1. Not able to read and write 2. Only read and write 3. primary education(Grade 1 – 6) 4. Secondary (Grade 7 – 8) 5. Tertiary(Grade 9 – 12) 6. Other (specify)_____ 		

104	<p>What is your major current occupation? (More than one answer is possible).</p>	<ol style="list-style-type: none"> 1. Farmer 2. Full-time housewife 3. Merchant 4. Governmental employee 5. Private employee 6. Student 7. Housemaid 8. Daily labourer 9. Other (specify)_____ 		
105	<p>What is your marital status?</p>	<ol style="list-style-type: none"> 1. Single \longrightarrow 2. Married 3. Divorced 4. Widowed 5. Separated 	Skip to Q 109	
106	<p>What is the highest education level your husband has attained?</p>	<ol style="list-style-type: none"> 1. Not able to read and write 2. Only read and write 3. primary education(Grade 1 – 6) 4. Secondary (Grade 7 – 8) 5. Tertiary(Grade 9 – 12) 6. Other (specify)_____ 		
107	<p>What is your husband's occupation?</p>	<ol style="list-style-type: none"> 1. Farmer 2. Merchant/trader 3. Governmental employee 4. Private employee 5. Student 		

		6. Deriver 7. Daily labourer 8. Fishing 9. Other (specify)_____		
108	Who is the principal income source for your family?	1. Myself 2. Spouse 3. Family 4. Other sources(specify)_____		
109	Monthly total household income in Eth Birr.	_____		
110	What household assets and basic services do you possess?			
	Television	1. Yes 0 No		
	Gas stove	1 Yes 0 No		
	Telephone	1 Yes 0 No		
	Fridge	1 Yes 0 No		

Radio	<p>1 Yes</p> <p>0 No</p>		
Car	<p>1 Yes</p> <p>0 No</p>		
Motor bicycle	<p>1 Yes</p> <p>0 No</p>		
Bicycle	<p>1 Yes</p> <p>0 No</p>		
What is the common water source for your family?	<p>1 Piped inside dwelling</p> <p>2 Piped outside dwelling</p> <p>3 Communal standpoint</p> <p>4 Personal hand pump or well</p> <p>5 Communal hand pump or well</p> <p>6 River, lake, spring, reservoir, or other(Specify)-----</p>		
Electricity	<p>1 Yes</p> <p>0 No</p>		

	What is the floor material of your house?	<ol style="list-style-type: none"> 1 Sand/soil 2 Smoothed mud or other 3 Smooth cement, or wood 		
	What is the type of latrine your family commonly uses?	<ol style="list-style-type: none"> 1 Flush toilet 2 VIP latrine 3 Traditional latrine with roof 4 Latrine with no roof 5 None or other(Specify) ----- 		
111	Where is your residence?	<ol style="list-style-type: none"> 1 Rural 2 Urban 		
112	What is the distance of your home from lake Hawassa/---pond /---river water body?	<ol style="list-style-type: none"> 1 < 10 minute walking distance 2 30 minute walking distance 3 30 minutes to 1 hour walking distance 4 > 1hour walking distance 		

Part II (A): Characteristics of the child				
Ser. No.	Questions	Responses(Code/s)	Skip	Remark
201	How old is your child? (Record the last birth day)	Age in years _____		
202	Sex of the child	1 Male 0 Female		
203	Weight	_____ kg		
204	Height	_____ cm		
205	Hemoglobin	_____ gm/dl		
206	How often does your child accompany you when performing daily tasks around the water source?	1 Never 2 Some times 3 All the time		
207	Did your child have contact with infested water body while accompanying you?	1. Yes 0. No 999. I don't know		

208	If yes for (Q 207) what is the reason/s of water contact of your child? (More than one response is possible)	<ol style="list-style-type: none"> 1 Playing 2 Swimming 3 Domestic purpose 4 Irrigation(accompany) 5 Fishing (accompany) 6 Waste disposal (accompany) 7 Other(Specify) ----- 		
209	If yes for (Q 207) When was the first exposure of your child to the infested water body?	<ol style="list-style-type: none"> 1. Before the first year 2. During the first year of life 3. 2-7 year of life <p>999. I don't know</p>		
210	If before the first year, how?	<ol style="list-style-type: none"> 1 The baby was taken to a stream 2 Water from stream used to bath child at home. 3 Other (Specify) _____ 		
211	If during the first year of life, how?	<ol style="list-style-type: none"> 1 The child was taken to a stream 2 Water from stream used to bath child at home 3 Other (Specify) _____ 		
212	If 2-7 years of life, how?	<ol style="list-style-type: none"> 1 The child was taken to stream by the mother 2 Water from stream used to bath child 		

		3 A child goes to stream by himself		
213	Does the child infected with <i>S. mansoni</i> ? (Record after lab test)	1 Yes 0 No		

Part Three: Questionnaire to assess KAP of mothers/ caregivers of PSAC towards schistosomiasis.

A Questionnaire to assess mothers/ caregivers knowledge about *S. mansoni* infection

SN	Questions	Responses(Code/s)	Skip	Remark
301	Have you ever heard of schistosomiasis?	1 Yes 1 No 999. I don't remember		
302	If yes to (Q301) from which source did you get the information?	1 Mass media(radio/TV) 2 Health extension worker 3 Book 4 Health institution 5 From neighbors 6 From school 7 Community meetings 8 Relatives and friends		

		9 Research organizations 10 Other specify_____		
303	What are the symptoms/signs of <i>S. mansoni</i> ?		Yes	No
		Headache		
		Nausea		
		Abdominal pain		
		Weight loss		
		General body weakness		
		Blood in stool		
		Poor school performance		
		Recurrent illness		
		Pale face (anemia)		
		Swollen abdomen		
		I don't know		
304	What are the preventive methods of <i>S. mansoni</i> ? (Multiple responses possible) Don't read responses		Yes	No
		Avoid swimming or bathing in river /ponds/streams/lake		
		Avoid crossing river barefoot		
		Crossing river in bridge		
		Avoid washing clothes in ponds/streams		
		Taking anti-schistosomal drugs		
		Kill freshwater snails using chemicals		
		I don't know		

305	What modes of <i>S. mansoni</i> transmission do you know? (Multiple responses possible) Don't read responses		Yes	No		
		During farming activities				
		During fishing				
		Through swimming or bathing in river /ponds/streams/lake				
		During crossing river barefoot				
		During irrigation				
		I don't know				
B Questionnaire to assess mothers/ caregivers attitude about <i>S. mansoni</i> infection						
306	<i>S. mansoni</i> is a serious disease	1 Strongly agree 2 Agree 3 No opinion 4 Disagree 5 Strongly disagree				
307	<i>S. mansoni</i> is a minor infection that may clear over time without treatment	1 Strongly agree 2 Agree 3 No opinion 4 Disagree 5 Strongly disagree				
308	<i>S. mansoni</i> is not preventable	1 Strongly agree 2 Agree 3 No opinion				

		<ul style="list-style-type: none"> 4 Disagree 5 Strongly disagree 		
309	Feces/urine can be a source of infection for <i>S. mansoni</i> infection	<ul style="list-style-type: none"> 1 Strongly agree 2 Agree 3 No opinion 4 Disagree 5 Strongly disagree 		
310	<i>S. mansoni</i> infection can be treated	<ul style="list-style-type: none"> 1 Strongly agree 2 Agree 3 No opinion 4 Disagree 5 Strongly disagree 		
311	<i>S. mansoni</i> infection treatment results in severe, long-term side effects.	<ul style="list-style-type: none"> 1 Strongly agree 2 Agree 3 No opinion 4 Disagree 5 Strongly disagree 		
312	<i>S. mansoni</i> can affect (4 to 7 years) preschool-aged children	<ul style="list-style-type: none"> 1 Strongly agree 2 Agree 3 No opinion 4 Disagree 5 Strongly disagree 		

C Questionnaire to assess mothers/ caregivers practice about <i>S. mansoni</i> infection						
313	Where do you wash the family's clothes most of the time?		Yes	No		
		River				
		Irrigation canal				
		Lake				
		Dam				
		Well at home				
		Unprotected spring				
		Pond				
		Piped inside compound				

Part IV: Assessment of treatment history

401	Have you dewormed your child with praziquantel drug this month?	1. Yes 0 No 999. I don't know		
402	If yes (Q401), where was the place of deworming?	_____		

Amharic Version Questionnaire:

የመጠይቅ ቅፅ

001. የቀበሌ ስም _____

002. የቤት መለያ ቁጥር _____

003. የጉብኝት ብዛት 1 _____ 2 _____ 3 _____

የልጅ እናት/ ተንከባካቢ ስም----- የተሳታፊው መለያ ቁጥር(ኮድ): -----

1. መረጃዎ የተሰበሰበበት ቦታ መረጃ

የመረጃ ሰብሳቢው ስም/መለያ ቁጥር/ኮድ/(አስፈላጊ): _____

መረጃ የተሰበሰበበት ቀን(አስፈላጊ): ቀን/ወር/ዓ. ም) -----

2. ስምምነት የተፈፀመበት ዘዴ(አስፈላጊ)

በግል

የልጅ እናት/ ተንከባካቢ

በሌላ ተንከባካቢ (ይገለፅ): _____

ስምምነት የለም (አቁም)

3. መረጃዎ የተሰበሰበበት ቦታ

ቤት

ጤና ተቋም

በመንደር ስብሰባ ቦታ

የመጠይቁ አሞላል መመሪያ፡

ይህ መጠይቅ ምርጫ፣ ባዶ ቦታ ሙሉ እና ሌላ (ይገለፅ) አማራጮችን የያዘ ነው። ስለሆነም ለምረጫ ጥያቄዎች የተሳታፊውን ምላሽ የሚያሳይ ቁጥር በአግባቡ ይክበቡ። በዕሁፊ እንዲመለሱ ለሚጠየቁ ጥያቄዎች እና ሌላ(ይገለፅ) አማራጮች በሚነበብ መልኩ በደረቅ እስክርብቶ የተሳታፊውን ምላሽ/ሾች ይፃፉ። የተሳታፊው ምላሽ አላውቅም ከሆነ 999ን ያክብቡ። አንዳንድ ጥያቄዎች ከአንድ በላይ ምላሾች ልኖራቸው ሲለምችል የተሳታፊውን ምላሾች በጥንቃቄ ያክብቡ።

ተራ ቁጥር	ጥያቄ	ምረጫና ኮድ	የሚዘለሉ ጥያቄዎች	ምርመራ
ክፊል አንድ ፡ መሰረታዊና ማህበረሰባዊ ጥያቄዎች(በእናቶች/በተንከባካቢዎች የሚተገበር)				
101	ዕድሜዎ ስንት ነው? (የመጨረሻውን ልደት ይመዝግቡ)	ዕድሜ በዓመት _____ 999. አላውቅም		
102	የሚከተሉት ኅይማኖት የቱ ነው?	1 ፕሮቴስታንት 2 ኦርቶዶክስ 3 ሙስሊቶሊም 4 ካቶልክ 5 ሌላ(ይገለፅ)_____		
103	የት/ት ደረጃዎ ምን ያህል ነው?	1 መፃፍና ማንበብ የማይችል 2 መፃፍና ማንበብ የሚችል 3 ከ1ኛ እስከ 6ኛ ክፍል 4 ከ7ኛ እስከ 8ኛ ክፍል 5 ከ9ኛ እስከ 12ኛ ክፍል 6 ሌላ(ይገለፅ)_____		

104	<p>እርስዎ የተሰማሩበት ዋና የስራ አይነት ምንድን ነው? (ከአንድ በላይ ምላሾች ልኖሩ ይችላሉ)</p>	<ol style="list-style-type: none"> 1 ግብርና/አርሶ አደር 2 የቤት እመቤት 3 በንግድ ሥራ 4 የመንግስት ሰራተኛ 5 የግል ድርጅት ሰራተኛ 6 ተማሪ 7 የቤት ሰራተኛ(ተቀጣሪ) 8 የቀን ሰራተኛ 9 ሌላ(ይገለፅ)_____ 		
105	<p>በአሁኑ ጊዜ የትዳር ሁኔታዎ ምንድን ነው?</p>	<ol style="list-style-type: none"> 1 ያላገባች \longrightarrow 2 ያገባች 3 የተፋታች 4 ባለቤቷ የሞተባት 5 ከባሏ ተለይታ የሚትኖር 	<p>ወደ ጥያቄ ቁጥር 109 ሂድ</p>	
106	<p>የባለቤትዎ የት/ት ደረጃ ምን ያህል ነው?</p>	<ol style="list-style-type: none"> 1 መፍናና ማንበብ የማይችል 2 መፍናና ማንበብ የሚችል 3 ከ1ኛ እስከ 6ኛ ክፍል 4 ከ7ኛ እስከ 8ኛ ክፍል 5 ከ9ኛ እስከ 12ኛ ክፍል 6 ሌላ(ይገለፅ)_____ 		
107	<p>ባለቤትዎ/የትዳር አጋሪዎ የተሰማሩበት ዋና የስራ አይነት ምንድን ነው?</p>	<ol style="list-style-type: none"> 1 ግብርና/አርሶ አደር 2 ነጋዴ 3 የመንግስት ሰራተኛ 		

	(ከአንድ በላይ ምላሾች ልኖሩ ይችላሉ)	4 የግል ድርጅት ሰራተኛ 5 ተማሪ 6 ሾፊር 7 የቀን ሰራተኛ 8 ዓሳ አስጋሪ 9 ሌላ(ይገለፅ)_____		
108	የቤተሰባችሁ ዋና የገቢ ምንጩ ማን ነው?(ከአንድ በላይ መልስ ልኖረዎ ይችላል)	1 እኔ 2 የትዳር ጎደኛዬ 3 የቤተሰቦቻችን ድጋፍ 4 ሌላ(ይገለፅ)_____		
109	ጠቅላላ የቤተሰባችሁ የወር ገቢ በአማካኝ ምን ያህል ብር ነው?	_____		
110	ከዚህ በታች የተዘረዘሩት ሀብቶች ወይም ንብረቶች እና መሰረታዊ አገልግሎቶች በቤትዎ አለዎት?			
	ቴሌቭዥን	1 አለ 0 የለም		
	ቡታጋዝ	1 አለ 0 የለም		
	ስልክ መደበኛ/ ተንቀሳቃሽ	1 አለ 0 የለም		
	ፊርጅ	1 አለ 0 የለም		
	ሬዲዮ	1 አለ 0 የለም		

መኪና	1 አለ 0 የለም		
ሞተር ሳይክል	1 አለ 0 የለም		
ብስክሌት	1 አለ 0 የለም		
ቤተሰባችሁ በዋናነት ወ.ሃ የሚያገኘው ክፍት ነው?	1 በቤት ውስጥ ካለ ቧንቧ 2 ከግቢ ውስጥ ካለ ቧንቧ 3 ከጋራ ቦኖ ወ.ሃ 4 ከግል እጅ ፓምፕ/ ጉድጓድ 5 ከጋራ እጅ ፓምፕ/ ጉድጓድ 6 ከወንዝ፣ ሐይቅ፣ ምንጭ፣ ታንክ፣ ወይም ሌላ -----		
ማብራት	1 አለ 0 የለም		
የቤትዎ ወለል በምን የተመረጠ/የተሠራ ነው?	1 አሽዋ/አፈር 2 በጭቃ 3 በስምንቶ/ በእንጨት		
ቤተሰባችሁ በዋናነት የሚጠቀመው የመጠጫ ቤት ዓይነት ምንድን ነው?	1 በወ.ሃ የሚሰራ መጠጫ 2 የተሻሻለ መጠጫ/የአየር ማወጫ ቱቦ ያለው 3 ጣራ ያለው ባህላዊ መጠጫ 4 ጣራ የሌለው ባህላዊ መጠጫ 5 ሌላ-----		

111	መኖሪያዎት የት ነው?	1 ገጠር 2 ከተማ		
112	ቤትዎ ከየትኛውም ወ.ሃ መገኛ ምን ያህል ይርቃል?	1 ከ10 ደቂቃ እግር ጉዞ ያነሰ 2 የ 30 ደቂቃ እግር ጉዞ 3 ከ 30 እስከ አንድ ሰዓት ያህል የእግር መንገድ 4 ከአንድ ሰዓት በላይ ይርቃል		

ክፍል ሁለት (ሀ): የተሳታፊ ልጅ ባህሪያት				
ተራ ቁጥር	ጥያቄ	ምረጫና ኮድ	የሚዘሉ ጥያቄዎች	ምርመራ
201	የልጅዎ ዕድሜ ስንት ነው?(የመጨረሻውን ልደት ይመዝግቡ)	ዕድሜ በዓመት _____ 999. አላውቅም		
202	የልጅዎ የታ	1 ወንድ 0 ሴት		
203	ክብደት	_____ ኪ.ግ		
204	ቁሜት	_____ ሴ.ሜ		
205	ሄሞግሎብን (Hemoglobin)	_____ gm/dl		
206	እርስዎ በወሃ መገኛ አካባቢ ለሥራ ሲሄዱ ልጅዎ አጅቦት ይሄዳልን?	1 በፊውም ሄዶ አያውቅም 2 አዎ አንዳንድ ጊዜ 3 አዎ ሁል ጊዜ		
207	ልጅዎ አጅቦት በሄደ ጊዜ ከወሃ ጋር ንክኪ ነበረው/ራት?	1 አዎ 0 አልነበረውም/ራት 999. አላውቅም		
208	ለጥያቄ ቁጥር 207 መልስዎ አዎ ከሆነ	1 ሲጫወተት/ሲትጫወተት 2 ወሃ ወስጥ ሲዋኝ/ሲትዋኝ		

	<p>ልጅዎ ከወ.ሃ ጋር ንክኪ የሚያደርገው በምን ምክንያት ነው? (ከአንድ በላይ ምላሾች ልኖሩ ይችላሉ) (መልሶቹን አያንብቡላቸው)</p>	<p>3 ለቤት ወ.ሃ ሲቀዳ/ሲትቀዳ 4 ለመስኖ ሥራ አጅቦኝ/ባኝ ሲሄድ/ሲትሄድ 5 ዓሳ ለማጥመድ አጅቦኝ/ባኝ ሲሄድ/ሲትሄድ 6 ወ.ሃ ዳር ቆሻሻ ለመጣል አጅቦኝ/ባኝ ሲሄድ/ሲትሄድ 7. ሌላ-----</p>		
209	<p>ለጥያቄ ቁጥር 207 መልስዎ አዎ ከሆነ ለመጀመሪያ ጊዜ ልጅዎ ከተበከለ ወ.ሃ ጋር ንክኪ ያደረገው መቼ ነው?</p>	<p>1 የመጀመሪያ ልደቱን ሳያከብር 2 በአንድ ዓመት እድሜ 3 ከ2-7 ዓመት ባለው እድሜ 999. አላውቅም</p>		
210	<p>ከአንድ ዓመት በፊት ከሆነ እንዴት ልጋለጥ ቻለ? (ከአንድ ዓመት ዕድሜ በታች ለተጋለጡ ብቻ ይጠየቅ)</p>	<p>1 ህፃኑ ወደ ወ.ሃ ተወስዶ ነበር 2 ቤት ወስጥ ከተበከለ ወ.ሃ ተቀድቶ በመጣ ወ.ሃ ሰውነቱ ይታጠብ ነበር 3 ሌላ(ይገለፅ)_____</p>		
211	<p>በአንድ ዓመት እድሜ ከሆነ እንዴት ልጋለጥ ቻለ?(በአንድ ዓመት ዕድሜ ለተጋለጡ ብቻ ይጠየቅ)</p>	<p>1 ህፃኑ ወደ ወ.ሃ ተወስዶ ነበር 2 ቤት ወስጥ ከተበከለ ወ.ሃ ተቀድቶ በመጣ ወ.ሃ ሰውነቱ ይታጠብ ነበር 3 ሌላ(ይገለፅ)_____</p>		
212	<p>ከ2-7 ዓመት ባለው እድሜ ከሆነ እንዴት ልጋለጥ ቻለ?</p>	<p>1 ህፃኑ ወደ ወ.ሃ ተወስዶ ነበር 2 ቤት ወስጥ ከተበከለ ወ.ሃ ተቀድቶ በመጣ ወ.ሃ ሰውነቱ ይታጠብ ነበር 3 ህፃኑ በራሱ ወደተበከለ ወ.ሃ ሄዶ 4 ሌላ(ይገለፅ)_____</p>		

ክፍል ሶስት : ለሽህተት ማረጋገጫ በሽታ ያለውን የእናቶችን ወይም የተንከባካቢዎችን ግንዛቤ/እውቀት፣ አመለካከት እና ድርግት መፈተሻ መጠይቅ

ሀ. ሽህተት ማረጋገጫ በሽታ አስመልክቶ ያለውን ግንዛቤ/እውቀት መፈተሻ መጠይቅ

ተራ ቁጥር	ጥያቄ	ምረጫና ክፍ	የሚዘሉ ስፍራዎች	ምርመራ
301	ስለሽህተት ማረጋገጫ በሽታ ሰምተው ያወቃሉ?	1 አዎ 0 ሰምቼ አላወቅም 999. አላስታውስም		
302	ለጥያቄ ቁጥር (301) መልሱ አዎ ከሆነ መረጃውን ያገኙት ክፍት ነው?	1 ክሬዲት/ ቴሌቪዥን 2 ክጤና ኤክስፔንሽን ባለሙያ 3 ከመፅሐፍ 4 ክጤና ተቋም 5 ከጎረቤት 6 ከትምህርት ቤት 7 ከሰብሰባ ቦታ 8 ከዘመዶች እና ከገጽቶች 9 ከምርምር ተቋም 10 ሌላ(ይገለፅ)_____		

303	የሽሰቶሶማ ማንሶኒ/ብልሃሪዚያ በሽታ ምልክቶች ምንድን ናቸው?		አዎ	ሰምቼ አላወቅም		
		የራስ ምታት				
		ማቅለሽለሽ				
		የሆድ ህመም				
		የክብደት መቀነስ				
		ድካም				
		ደም አዘል ሰገራ				
		የትምህርት አቀባበል አናሳ መሆን				
		ተደጋጋም ህመም				
		የደም ማነስ በሽታ/ ዓይን ነጭ መሆን				
		የሆድ እብጠት				
		አላወቅም				
304	የሽሰቶሶማ ማንሶኒ/ብልሃሪዚያ በሽታ መከላከያ ዘዴዎች ምንድን ናቸው?		አዎ	ሰምቼ አላወቅም		
		በተበከለ ወንዝ፣ኩራ ወይም ሐይቅ ውስጥ አለመዋኘት/ አለመታጠብ				
		ሽሰቶሶማ ማንሶኒን የሚያስተላልፉ ቀንድ አወጣዎችን በኬሚካል መግደል				
		ፕራዚኪንቲል መድኃኒት መውሰድ				
		በባዶ እግር በተበከለ ውሃ አለማቋረጥ				
		የተበከለ ውሃ ለማቋረጥ ድልድይ መጠቀም				

		በተበከለ ውሃ ልብስ አለማጠብቅ			
		አላውቅም			
305	የትኛውን የሽህተት ማንሰኚ /ብልሃሪዚያ በሽታ መተላለፊያ መንገድ ያወቃሉ?	<p>በግብርና ሥራ ተግባራት ወቅት እንደሚተላለፍ</p> <p>በዓላ ማጥመድ ሥራ</p> <p>በተበከለ ወንዝ፣ ኩሬ ወይም ሐይቅ በመዋኘት /በመታጠብ</p> <p>በባዶ እግር በተበከለ ውሃ በማቋረጥ</p> <p>በመስኖ ሥራ ተግባራት ወቅት</p> <p>አላውቅም</p>	አዎ	ሰምቼ አላውቅም	
ለ. ሽህተት ማንሰኚ በሽታ አስመልክቶ ያላዉን አመለካከት መፈተሻ መጠይቅ					
306	ሽህተት ማንሰኚ/ብልሃሪዚያ አደገኛ በሽታ ነዉ።	<ol style="list-style-type: none"> 1 በጣም እስማማለሁ 2 እስማማለሁ 3 ምንም ሀሳብ የለኝም 4 አልስማማም 5 በጣም አልስማማም 			
307	ሽህተት ማንሰኚ/ብልሃሪዚያ በሽታ	<ol style="list-style-type: none"> 1 በጣም እስማማለሁ 2 እስማማለሁ 			

	ቀላልና ያለመድኃኒት የሚደኑ በሽታ ነዉ።	3 ምንም ሀሳብ የለኝም 4 አልስማማም 5 በጣም አልስማማም		
308	የሽስቶሶማ ማንሶኒ/ብልሃሪዚያ በሽታን መከላከል አይቻልም።	1 በጣም እስማማለሁ 2 እስማማለሁ 3 ምንም ሀሳብ የለኝም 4 አልስማማም 5 በጣም አልስማማም		
309	ሰገራ ለሽስቶሶማ ማንሶኒ/ብልሃሪዚያ በሽታ መንስኤ ልሆኑ ይችላሉ።	1 በጣም እስማማለሁ 2 እስማማለሁ 3 ምንም ሀሳብ የለኝም 4 አልስማማም 5 በጣም አልስማማም		
310	የሽስቶሶማ ማንሶኒ/ብልሃሪዚያ በሽታ ህክምና አለዉ/ልታከም ይችላል።	1 በጣም እስማማለሁ 2 እስማማለሁ 3 ምንም ሀሳብ የለኝም 4 አልስማማም 5 በጣም አልስማማም		
311	ለሽስቶሶማ ማንሶኒ/ብልሃሪዚያ በሽታ ህክምና የሚሰጥ ፕራዚኪንቴል መዲኃኒት ከፊተኛ ለረጅም ጊዜ የሚቆይ የጎንዮሽ ጉዳት ያስከትላል።	1 በጣም እስማማለሁ 2 እስማማለሁ 3 ምንም ሀሳብ የለኝም 4 አልስማማም 5 በጣም አልስማማም		
312	የሽስቶሶማ ማንሶኒ/ብልሃሪዚያ በሽታ	1 በጣም እስማማለሁ 2 እስማማለሁ		

	ዕድሜያቸው ከ4-7 ዓመት ያሉ ልጆችን ልያጠቃ ይችላል።	3 ምንም ሀሳብ የለኝም 4 አልስማማም 5 በጣም አልስማማም		
ሐ. ሽስቶሶማ ማንሶኒ በሽታን አስመልክቶ ያላውን ድረግት መፈተሻ መጠይቅ				
313	የቤተሰብዎን ልብስ ብዙ ጊዜ የሚያጥቡት የት ነው?		አዎ	አይደለም
	ወንዝ			
	በመስኖ ቦይ ውስጥ			
	ሐይቅ			
	ግድብ አከባቢ			
	ግቢ ውስጥ በጉድጓድ ውሃ			
	ባልታጠረ ምንጭ			
	ኩራ			
	ግቢ ውስጥ ካለ ቧንቧ			

ክፊል አራት : መዲኃኒትን የተመለከቱ መጠይቆች

401	ለልጅዎ ፕራዚኪንቲል መዲኃኒት በዚህ ወር ተሰጥቶታልን/ታልን?	1 አዎ 0 አልተሰጠውም/ጣትም 999. አላውቅም		
402	ለጥያቄ ቁጥር (401) መልሱ አዎ ከሆነ የት ተሰጠው/ተሰጣት?	_____		

Sidamu Afi Xa'mo:

001. Xa'mote kiiro _____

002. Qawalete Su'ma _____

003. Minu badooshshi kiiro _____

004. Towanyote kiiro1 _____ 2 _____ 3 _____

Amate/owaante aannohu su'ma:
egeshiishsha "code":

Beeqqasincho banddani

1. Akkawaawette tajje:

Tajje gamba asinohu su'ma "code": _____

Tajje gamba assinoonni barra (barra-agana-dirro): _____

2. Sumuu yinoonni doogo

- Meesi
- Ama/umi deerri owante aannohu
- Wolootu owatano nooro xawisi: _____
- Sumuu yaannohu dino (Urissi)

3. Tajje gamba assinoonni baayicho

- Mine
- Faayyimatte Urrisha
- Olluu gambooshshi bayichcho

Hajajo: Xa'muwwa doorishsha, fanno bayiichcho woshshinanniwanxa xawishsha uyinaanni suudda afidhdhinotte. Ikkinohurra xiinxallote beeqanichchi tummo doorishshu xa'muwarra

amaanynyootunni qooqowaateninna xawishsha uyinaniterranno danchcha angaate бороонни booresattenni nabaawammano garinni xawissi. Tummo qoolanno xa'mamaachchi tummo diafoomo yirro 999 qooqowi tummo uyinanni bayichchira. Mite mite xa'mo mitte ale ikkitaano dawaarro afidhiinotunno heedhdhano dafiirra beqanchu tummo dawarinno garinni qoqoowa hasisanno.

Antete kiiro	Xa'muuwa	Tummo(doorishanna "code")	Kubina ani xa'mo	Buuxo
Gafa Mite: Tummo aanohhu Dagoomi-Baliichchoomu amaanyotte (Amaatanno owaante anoohurano horoosinaanni).				
101	Dirikki Me'eho?	Dirru Kirotenni _____ 999- diroya diafooma/mo		
102	Ati hiite dagaati milaatti?	1 Sidaamu 2 Wolayitu 3 Amarru 4 Oromote 5 Guragete 6 Wolleterro xawissi_____		
103	Ati hiite A'maano harunsaatto/tta?	1 Protestante 2 Orthodoxise 3 Isilamu 4 katolikete 5 Wolleterro xawissi_____		
104	Ateehu rosikki deeri maati?	1 Boreesanna nabaawa didaandemmo/mma 2 Boreesanna nabaawa		

		<p>3 1^{kki} dirimi roso</p> <p>4 2^{kki} dirimi roso</p> <p>5 3^{kki} dirimi roso</p> <p>6 Wolleterro xawissi_____</p>		
105	Tene yanaarra nooheehu qaru loosi maati? (Mite aleeni ikkitinno dawaaro qla dadinaanni).	<p>1 Batto loosirra</p> <p>2 Wo'ma yana mine amaxxa</p> <p>3 Mootimaate looso</p> <p>4 Hallaanynyu looso</p> <p>5 Rosaanchcho</p> <p>6 Manni mini loosaasichcho</p> <p>7 Barru looso</p> <p>8 Looso diafirommo</p> <p>9 Wollehorro xawissi _____</p>		
106	Tene yanarra maatette amanyotikki maati?	<p>1 Caliichchoho →</p> <p>2 Mi'ne amaadomoho</p> <p>3 Minaamma/nna tiroomoho/mate</p> <p>4 Minaamma/nna retiinosiho/sette</p> <p>5 Babbadame herannore</p>	<p>109^{kki} xa'mowa sai</p>	

107	Gashaanikkihu /gashaamakkihu rosu deeri maati?	1 Boreesanna nabaawa didaandemmo/mma 2 Boreesanna nabaawa 3 1 ^{kki} dirimi roso 4 2 ^{kki} dirimi roso 5 3 ^{kki} dirimi roso 6 Wolleterro xawissi_____		
108	Gashaanikiihu/gashaamak kihu qaru loosu dani maati?	1 Baatto loosirra 2 Daadalanicho 3 Mootimaate looso 4 Hallaanynyu looso 5 Rosaanchcho 6 Ofaancho 7 Barru looso 8 Wollehorro xawissi _____		
109	Mini'ne maattera qaru eotte buichcho ayeetti?	1 Aneetti 2 Galiteyaati 3 Maatekketti 4 Wollehorro xawissi _____		
110	Xaphphoomunni wililichchinetti eo birunni me'eete?	_____		

110	Miniine/Wiliilichchine giddo hiikku uduunichchi /jiiro/ mannaho hassiissanno horro afamaanno?	
	“Televisione”	1 Ee 0 Deeni
	Lambda horoonisine sagaale raisinaani udunichchi	1 Ee 0 Deeni
	Biliibillu	1 Ee 0 Deeni
	Qisanno udunnichchi	1 Ee 0 Deeni
	Radoone	1 Ee 0 Dee’ni
	Kaamelu	1 Ee 0 Dee’ni
	Xexxerisu	1 Ee 0 Dee’ni

Shalleette	<p>1 Ee</p> <p>0 Dee'ni</p>		
Mini'ne maate gaanyite horoonsidhanno waayi hiikkoneeti?	<p>1 Mini giddo eessinonni wayi boombeniiti</p> <p>2 Howeete giddo qixxeessinonni wayi boombeniiti</p> <p>3 Duuchu mannira qixxeessinoonni waa xoorshinaani boombeniiti</p> <p>4 Haallanyu xukunni fushshinanni waayi baaleniitti</p> <p>5 Gutu xukunni fushshinanni waayi baaleniitti</p> <p>6 Lagu,Garbu,Buicho,Kuuniso oni waayi woyi w.k.l</p>		
Korreenteete caabichi	<p>1 Ee</p> <p>1 Dee'ni</p>		
Mini'nehu uullaadisi maayinni loosaminno?	<p>1 Shaafunni</p> <p>2 Buushshu woyi sabunni</p> <p>3 Shalaqa simitooti woyi Haqaho</p>		

	Maatenne duucha woyite horoosidhannohu shumaate mini hikkoneeti?	<ol style="list-style-type: none"> 1 Dunaanii waa afiirino shumaate mine 2 Mine minneenna foolu shumate mininni fulanno bombe afiirino 3 Buddunitta mine afiirino shumaate mine 4 Buddunitta mine afiirinokki shumaate mine 5 Shumate mini dinno woyi wolle danna 		
111	Teesookki mamiichoti?	<ol style="list-style-type: none"> 1 Baadiyete 2 Quchumaho 		
112	Waayi bissaawinni minikki geshsha noo xeeritinyi mageeshshiho?	<ol style="list-style-type: none"> 1 TONU daqiqi lekate doogo diikinno 2 Sajuu daqiqi lekate dogo 3 Sajuu daqiqinni mite sa'ate geshsha 4 mitte sa'ate alenni fafaano 		
(A): Qaaquullu Amaanyoote la"ano xa'mo				
A. Kiiro	Xa'muwa	Tumo	Sai/kub bi	Buux o
201	Qaaqqikki diri me"eeho?	Diro kirotenni _____		
202	Qaaqu koo/tee	<ol style="list-style-type: none"> 1 Labbaaaho 		

		1 Meyaate		
203	Xuka	_____ kg		
204	Hojja	_____ cm		
205	“Hemoglobine”	_____ gm/dl		
206	Ati waayi qoxesirra looso loosiraata wooyite qaaqqikki ate ledoo haranonni?	<ol style="list-style-type: none"> 1 Co”onta diharanno 2 Sae sae haranno 3 Duucha woyiitte haranno 		
207	Qaaqqikki ate ledoo hare waayi ledoo xaadinno?	<ol style="list-style-type: none"> 1 Ee 2 Dee’ni <p>999.Diafoomma/mmo</p>		
207	Xa’ mote kiiroo (207) ee yootaro; qaaqqikki waayi ledoo xaadanno koorkaati maati? (Duchcha tumoo heedhdhara dadiitanno) Tummo nabaabooti	<ol style="list-style-type: none"> 1 Daahatte 2 Godo’late 3 Waa dirriate 4 Gorisaho 5 Qulixu’me fushshirate 6 Ishine tugate 		
208	Xa’ mote kiiroo (207) ee yootaro; qaaqqikki umi yannara battaawino waayira regecci yiinohu mamooteti?	<ol style="list-style-type: none"> 1 Ilamikkunni mittu diri alibaanni 2 Ilamikkunni mittu diri gedesaanni 		

		3 2-7 diri mereero 999. Ani diafoomma/mmo		
209	Ilamikkunni mittu diri alibaanni ikkiro, hitto ikke?	1 Qaaqo waayi laga massineenna 2 Mine battawino waayinni qaaqo hayishshineenna 3 Wolehoro xawisi _____		
210	Mittu dirisinni heerenatiro, hiitto ikke?	1 Qaaqo waayi laga massineenna 2 Mine battawino waayinni qaaqo hayishshineenna 3 Wolehoro xawisi _____		
211	2-7 diri merero hereenatiro, hiitto ikke?	1 Qaaqo waayi laga masineenna 2 Lagunni hikkilonni waayinni qaaqo mine hayishshineenna 3 Qaaqo umisiinni waayi lagga hareetti		
Gafa Sase: “Schistosomiasisete” dhibbi anna Ama/owaante aannohu Egenno, laonna Rosicho buunxanni xa’muwa.				
“Schistosomiasisete” dhibbi anna Ama/owaante aannohu Egenno buunxanni xa’muwa				
A.Kiir o	Xa’muuwa	Tummo	Kubbi /sai	

301	Konni alibaani “schistosomiasis” woyi Qereeqeneetenni taraawanno dhibbire macciishshite egenootta/tto?	1. Ee 0. Dee’ni 999.Diafoomma/mmo			
302	Xa’ mote kiirro (301) ee yootaro; Hitteene duduuwu bueniitti maccishotahu?	1 Tuqqu xaadinni(Radoone/TV) 2 Fayyimate halaashshasinne ogeeyewinni 3 Maxaafunni 4 Fayyimate uurrishshanni 5 Olluwiinni 6 Rosu mininni 7 Dagate gambooshshiiwinni 8 Fiixi’yanna Jaalla’yawiinni 9 Xiinixaallote Uurrishshawinni 10 Wolewinnitiro xawisi_____			
303	“Schistosomiasise” woyi Qereqee’netenni daanno dhibbi malaati mati?		E e	Dee’ni	
		Umu damuume			
		Looqqi assa			
		Godowu Xisso			
		Xuka xea			
		Xaphoma biso shaqishsha			

		Mundee karsino cili				
		Rosu jawaante ajja				
		Ganye xissama				
		Mundeete anje				
		Godoowu giddo udiinni darsha				
		Diafoomma/mmo				
304	“Schistosomiasisete” woyi Qereqee’netenni danno dhibba garigaadhinaanni doogo mati?		E e	Dee’ni		
		Haranno waayinni woyi lagunni, xaashshunni, Garbunni, kuusaminno wayinni haayishshirannna woyi daaha aguratenni				
		Waa batesittanno Qeereqee’ne xagichunni shaatenni				
		“Schistosoma manisoni” shaanno xagichcho hoorosiratenni.				
		Haranno waayi giddoonni mullichcho lekaanni fula aguratenni				

		Haranno waa buusu anaanni fulatenni.				
		Imaanna woyi udanna kuusaminoonna daadanno wayayira haayishira aguuratenni				
		Diafoomma/mmo				
305	Hiittenne “Schistosomiasisete” woyi Qereqee’netenni danno dhibbi taraawo doogo egennootta/tto?		E e	Dee’ni		
		Baattote latishshi looso loonsanni woyite				
		Qulixu’me fushshinanni woyite				
		Haranno waa woyi lagu ,xashshu,Gaibu, kuusaminno wayinni haayishshiratenni woyi daahatenni				
		Muliichcho lekkanni daadano waa tayisatenni				
		Goorissu looso loosanni woyite				
		Ani diafoomma/mmo				

“Schistosomiasisete” dhibbi anna Ama/owaante aannohu Lao buunxanni xa’muwa				
306	“Schistosomiasisete” woyi Qereqee’netenni danno dhibbi buutotte dhibaati	<ol style="list-style-type: none"> 1 Lowo geshsha suumu yeemma/mmo 2 Suumu yeemma/mmo 3 Hedo dinooe 4 Suumu diyeemma/mmo 5 Lowo geshsha suumu diyeemma/mmo 		
307	“Schistosomiasisete” woyi Qereqee’netenni danno dhibbi xagisinikinni huranoho.	<ol style="list-style-type: none"> 1 Lowo geshsha suumu yeemma/mmo 2 Suumu yeemma/mmo 3 Hedo dinooe 4 Suumu diyeemma/mmo 5 Lowo geshsha suumu diyeemma/mmo 		
308	“Schistosomiasis” woyi Qereqee’netenni danno dhibbi garigaadhine affanikki dhibaati.	<ol style="list-style-type: none"> 1 Lowo geshsha suumu yeemma/mmo 2 Suumu yeemma/mmo 3 Hedo dinooe 4 Suumu diyeemma/mmo 5 Lowo geshsha suumu diyeemma/mmo 		

309	Cilu/shumma “schistosomiasisete” dhibbinni amadamate kaima ikkitara danditanno	<ol style="list-style-type: none"> 1 Lowo geshsha suumu yeemma/mmo 2 Suumu yeemma/mmo 3 Hedo dinooe 4 Suumu diyeemma/mmo 5 Lowo geshsha suumu diyeemma/mmo 		
310	“Schistosomiasisete” woyi Qereqee’netenni danno dhibbi xagisii’neena huranno dhibbatti	<ol style="list-style-type: none"> 1 Lowo geshsha suumu yeemma/mmo 2 Suumu yeemma/mmo 3 Hedo dinooe 4 Suumu diyeemma/mmo 5 Lowo geshsha suumu diyeemma/mmo 		
311	“Schistosomiasisete” woyi Qereqee’netenni danno dhibbi xagicho adha seeda yannara qarra abbitanno.	<ol style="list-style-type: none"> 1 Lowo geshsha suumu yeemma/mmo 2 Suumu yeemma/mmo 3 Hedo dinooe 4 Suumu diyeemma/mmo 5 Lowo geshsha suumu diyeemma/mmo 		
312	“Schistosomiasisete” woyi Qereqee’netenni danno dhibbi dirinssa	<ol style="list-style-type: none"> 1 Lowo geshsha suumu yeemma/mmo 2 Suumu yeemma/mmo 3 Hedo dinooe 		

	rosoho illinokki qaqullenno gawajaanno	4 Suumu diyeemma/mmo 5 Lowo geshsha suumu diyeemma/mmo			
“Schistosomiasisete” dhibbi anna Ama/owaante aannohu Rosicho buunxanni xa’muwa					
313	Maatte’ne imaana ducha wooyitte mama hayishshatta/tto?		Ee	Dee’ni	
		Harranno waayira			
		Gorsu gadaawirra			
		Gaarbaho			
		Kofote			
		Qaete noo waayi bale waayini			
		Coitte ikkitinokki buichchonni hikkilooni waayinni			
		Kussaminno waayira			
		Howeete giddo qixxeessinonni wayi boombeniiti			

Gafa Shoole: Xagichu adhate buuxo xa'mo

401	Qaaqqikki konni agani giddo “Schistosomiasisete” woyi Qereqee’netenni danno dhibbi xagicho adhe egeenino?	1 Ee 1 Dee’ni 999. Ani diafomma/mmo		
402	Xa’mote kiirro (401) ee yootta/rro, me’e hige adhino?	_____		

Pre-screening form for schistosomiasis

Participant Information

Participant Code _____

Kebele: _____

Treatment Date (DD-MM-YYYY): _____

Ser. No	Questionnaire	Response	Remark
1	Stools exams	1 Yes 0 No 999.NA	
2	Date of stool sample collection	(dd/mm/yy): ____/____/____	
3	Consistency of stools:	1 Formed 2 Soft 3 Loose 4 Watery 5 Bloody 6 Mucus	
4	Result of parasitological exam for <i>S. Mansoni</i> (Kato Katz):	Slide 1: _____ eggs; Slide 2: _____ eggs;	
5	Result of parasitological exam for <i>Hookworm</i> (Kato Katz):	Slide 1: _____ eggs; Slide 2: _____ eggs;	
6	Result of parasitological exam for <i>A.lumbricoides</i> (Kato Katz):	Slide 1: _____ eggs; Slide 2: _____ eggs;	
7	Result of parasitological exam for <i>T.trichiura</i> (Kato Katz):	Slide 1: _____ eggs; Slide 2: _____ eggs;	
8	Egg count (<i>S.mansoni</i>) at screening:	_____ eggs = _____eggs/gram of stool	
9	Infection intensity:	1. Light 2. moderate 3. Heavy	

Pretreatment Stool and blood samples

10	Praziquantel dose (40mg/kg):	_____mg	
	<i>Egg count at Screening:</i>	_____ eggs= _____ eggs/gram of stool	

Blood specimen

Blood specimen collection for safety assessment Day 1 (Time zero)				
11	Hematology(3ml)	Tube code _____		
12	Chemistry(3ml)	Tube code _____		
13	PG blood (3 ml)	Tube code _____		

Blood specimen collection for safety assessment Day 1 (2-hour post-treatment)				
11	PK (Plasma) (2 mL)	Tube code _____		

Blood specimen collection for safety assessment Day 8 (Time zero)				
11	Hematology(3ml)	Tube code _____		
12	Chemistry(3ml)	Tube code _____		

Safety Assessment Form

Participant Information

Participant code _____

Kebele: _____

Treatment Date (DD-MM-YYYY): _____

Physical examination at time zero

1. Blood pressure _____ Systole, _____ Diastole
2. Heart rate _____ Beats/min
3. Respiratory rate _____ per min

Assessment Information

Day 1 (Zero time, 4h post-treatment), Day 2 (24 h post-treatment), and Day 8: All participants should be asked all the questions in Table 1.

Table 1: Reported Symptoms

Record a symptom grade from 0-5 for each day on which the participant experienced symptoms.

For participants reporting ANY symptom, complete every question in Table 1.

Symptom Grading

0 = No adverse event or within normal limits

1 = Mild adverse event, Symptoms causing no or minimal interference with usual social & functional activities

2 = Moderate adverse event, Symptoms causing greater than minimal interference with usual social & functional activities at least 1 day

3 = Severe and undesirable adverse event; Symptoms causing an inability to perform usual social & functional activities requires medical assessment

4 = Potentially life-threatening or disabling adverse event; Symptoms causing an inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death; requires transfer to a medical facility

5= Death

Symptoms/Signs Since you took the medication have you experienced...?		Day 1 [Zero time]	Post-treatment symptoms or signs					
			Day 1; 4 h		Day 2; 24 h		Day 8	
		(Yes=1; No=0)	(Yes=1; No=0)	If Yes (1-5)	(Yes=1; No=0)	If Yes (1-5)	(Yes=1; No=0)	If Yes (1-5)
Fever	ትኩሳት							
Loss of appetite	የምግብ ፍላጎት ማጣት							
Dizziness, giddiness, or fainting	የራስ መቅለል/መሳት							
Confusion	ግራ የመጋባት							
Drowsiness	እንቅልፍ እንቅልፍ የማለት ስሜት							
Headache	ራስ ምታት							
Vertigo	ራስ መዞር							
Cough	ሳል							
Difficulty breathing (wheezing or dyspnea)	ለመተንፈስ መቸገር/ሲር ሲር የማለት							
Nausea	ማቅለሽለሽ							
Vomiting	ማስመለስ							
Diarrhea	ተቅማጥ							

Stomach pain	የጨንፎ ህመም							
Stomachache	የሆድ ቁርጠት							
Itching skin	ቆዳን ማሳከክ							
Other illness or symptoms (specified by the caregiver):	ሌላ ህመም ወይም ምልክት በተንከባካቢ የተገለጸ ካለ							

Table 2: Measurements									
<i>Record the result under the column that corresponds to the day the assessment was taken.</i>									
Measurements		Post-treatment day(s)							
		Day 1, Zero time (Value)		Day 1; 4 h post-treatment (Value)		Day 2; 24 h post-treatment (Value)		Day 8 (Value)	
Temperature [non- axillary]									
Post-Exam Adverse Event Grade (Assign grade of 0-5 for the adverse reactions below based on physical exam. See “Guide to Assigning Adverse Event Severity”									
		Post-treatment day(s)							
		Day 1, Zero time		Day 1; 4 h post-treatment		Day 2; 24 h post-treatment		Day 8	
		(Yes=1; No=0)	If Yes (1-5)	(Yes=1; No=0)	If Yes (1-5)	(Yes=1; No=0)	If Yes (1-5)	(Yes=1; No=0)	If Yes (1-5)
Allergic reaction									
Lymphangitis (streaks of redness, warmth, and swelling in arms or legs)									
Sweating			ማላብ						
Rash (specify the location and brief description):			ሽፍታ ካላ ቦታውን ይግለፁ						
Other illness or symptoms (specify):			ሌላ ህመም ወይም ምልክት ካለ ይግለፁ						

**Baseline and post PZQ treatment LAB tests and results for schistosomiasis positive Day 1
(Pre PZQ-Treatment) and Day 8 (Post PZQ Treatment)**

Participant Information

Participant code_____

Kebele: _____

Treatment Date (DD-MM-YYYY):_____

Hematology and Chemistry lab report (Fill lab report result on Day 1 and Day 8)

Attach a copy of laboratory results

Schistosoma mansoni infection positive

Panel	Parameter (unit)	Day 1	Day 8
Hematology (CBC panel)	WBC		
	Bands or stabs		
	Lymphocytes; abs (%)		
	Monocytes; abs (%)		
	Neutrophils; abs (%)		
	Eosinophils; abs (%)		
	Basophils; abs (%)		
	RBC		
	PLT		
	HGB		
	HCT		
	MCV		
	MCH		
	MCHC		
	CHCM		

	RDW		
	MPV		
Chemistry	ALT		
	AST		
	ALP		
	Albumin		
	Cholesterol		
	Triglycerides		
	Creatinine		
	Total Bilirubin		
	Direct Bilirubin		
	Total Protein		
	Urea Nitrogen		

Post PZQ Treatment Parasitological test & result for efficacy (28th Day Post PZQ Treatment)

Participant Information

Participant Code _____

Kebele: _____

Treatment Date (DD-MM-YYYY): _____

Post Treatment Parasitological Tests and results (For Schistosomiasis Positive only)

Pretreatment Parasitological Tests & Results

Ser. No	Questionnaire	Response	Remark
1	Stools exams	1. Yes 0. No 999. NA	
2	Date of stool sample collection	(dd/mm/yy): ____/____/____	
3	Consistency of stools:	1. Formed 2. Soft 3. Loose 4. Watery 5. bloody 6. Mucus	
4	Result of parasitological exam for S. Mansoni (Kato Katz):	Slide 1: _____ eggs; Slide 2: _____ eggs;	
5	Result of parasitological exam for Hookworm (Kato Katz):	Slide 1: _____ eggs; Slide 2: _____ eggs;	

6	Result of parasitological exam for A.lumbricoides (Kato Katz):	Slide 1: _____ eggs; Slide 2: _____ eggs;	
7	Result of parasitological exam for T.trichiura(Kato Katz):	Slide 1: _____ eggs; Slide 2: _____ eggs;	
8	Egg count (S.mansoni) at screening:	_____ eggs = _____eggs/gram of stool	
9	Infection intensity:	1. Light 2. Moderate 3. Heavy	
	Egg count at Screening:	_____ eggs= _____eggs/gram of stool	



Ref.No. MoSHE//RD/14.1/0994/20

Date: 09 MAR 2020

Addis Ababa University College of Health Science (AACHS)
Addis Ababa

Subject: Letter of Approval

The Ministry of Science and Higher Education (MoSHE) via its National Research Ethics Review Committee has reviewed "**Optimization of Praziquantel Therapy for Schistosomamansoni Infection in Preschool-Aged Children in Ethiopia: Prazopt**" project protocol in an expedited manner. We are writing to advise you that MoSHE has granted full approval to the above named project, for a period of **one year (March 08, 2020- March 07, 2021)**.

All your most recently submitted documents have been approved for use in this study. The study should comply with the international and national scientific and ethical standard guidelines. Any change to the approved protocol or consent material must be reviewed and approved through the amendment process prior to its implementation. In addition, any adverse or unanticipated events should be reported within 24-48 hours to MoSHE. Please ensure that you submit biannual progress report to MoSHE once in six months and annual renewal application 30 days prior to the expiry date.

We, therefore, request you as PI and your esteemed organization to ensure the commencement and conduct of the study accordingly and wish for the successful completion of the project.



Sincerely

Solomon Benyon Tessema
Solomon Benyon Tessema (PhD)
Director General for Science
and Research Affairs

Cc.

- Office of the State Minister (Sector for Science, Research and Community Service)
- Science and Research Affairs Directorate General
- Research Ethics Directorate
- MoSHE
- Dr. Solomon Mequanent (PI)
- AACHS



Ref. No: IRB/200/13

Date: 31/05/2021

Meeting No: 12/2013

Name of Researcher(s): Tafese Tadele, Ayalew Astatkie (Ph.D. Assoc. Prof.), Eyasu Mekonnen (Ph.D., Prof.), Eleni Aklilu (Ph.D.)

Topic of Proposal: Improving control and elimination of Schistosoma mansoni infection in Hawella Tula district, Sidama Regional State, Ethiopia: Targeting pre-school aged children

Dear researcher(s),

The Institutional Review Board (IRB) at the College of Medicine and Health Sciences of Hawassa University has reviewed the aforementioned research protocol with special emphasis on the following points:

- | | | | | |
|--|-----|-------------------------------------|----|--------------------------|
| 1. Are all principles considered? | | | | |
| 1.1. Respect for persons: | Yes | <input checked="" type="checkbox"/> | No | <input type="checkbox"/> |
| 1.2. Beneficence: | Yes | <input checked="" type="checkbox"/> | No | <input type="checkbox"/> |
| 1.3. Justice: | Yes | <input checked="" type="checkbox"/> | No | <input type="checkbox"/> |
| 2. Are the objectives of the study ethically achievable? | Yes | <input checked="" type="checkbox"/> | No | <input type="checkbox"/> |
| 3. Are the proposed research methods ethically sound? | Yes | <input checked="" type="checkbox"/> | No | <input type="checkbox"/> |

Based on the aforementioned ethical assessment, the IRB has:

- | | | |
|---|-------------------------------------|---|
| A. Approved the proposal for implementation | <input checked="" type="checkbox"/> | -Approval period from May. 31/ 2021 to May.30 /2022 |
| B. Conditionally Approved | <input type="checkbox"/> | -Element Approved: Protocol Version No. 1 |
| C. Not Approved | <input type="checkbox"/> | -Follow up report expected in 6 months |

Obligation of the PI:

1. Should comply with the standard international and national scientific and ethical guidelines
2. All amendment and changes made in protocol and consent form needs IRB approval
3. The PI should report SAE within 3 days of the event
4. End of study, including manuscript should be reported to the IRB

Yours faithfully,

Dawit Jember (Asst. Prof.)
Institutional Review Board Chairperson.



Material Transfer Agreement

This Material Transfer Agreement (MTA) has been prepared for use by Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), College of Health Sciences, Addis Ababa University, Addis Ababa (Ethiopia); and Department of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska Institute, Stockholm (Sweden) in all transfer of research material (samples, derivatives, and specimens) related to the protocol.

Provider: Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia

Recipient:

Division of Clinical Pharmacology, Karolinska Institute, Stockholm, Sweden

1. Provider agrees to transfer to recipient's designated (human biological sample) the following research materials (specimen).

Human Blood

The research material will only be used for research purposes as described in the protocol by recipient's investigator in designated laboratory for the research project described below, under suitable containment conditions. This research material will not be used for commercial purposes such as screening, production or sale for which a commercialization license may be required. Recipient agrees to comply with all National and International guidelines rules and regulations applicable to the Research Project and the handling of the Research Material.

- a) Are the Research materials of human origin?

Yes

No

b) If yes, will they be collected according to the details in the protocol and in adherence to National Health Research Ethics Review Committee (NERC) and College of Health Sciences, Addis Ababa University recommendations and their approval?

Yes

No

2. This research material and its derivatives will be used by recipient's investigator solely in connection with the following research project ("Research Project") described with specificity as follows Optimization of praziquantel therapy for Schistosoma mansoni infection in preschool-aged children in Ethiopia: PrazOpt.
3. In all presentations or written publications concerning the research projects, recipient will seek agreement of provider and acknowledge provider's contribution of this research material unless requested otherwise.
4. This research material represents a significant contribution on the part of provider and is considered proprietary to provider. Recipient therefore agrees to retain control over this research Material and further agrees not to transfer the research Material to other people not under her/his direct supervision without advance written approval of provider. The research material will be disposed of as agreed upon per protocol at the end of completion of the project on September, 2024.
5. The provider does not take any responsibility for loss, damage, wastage or spoilage of the research material during or after shipment to the address provided by the Recipient under conditions agreed to in the protocol on shipment of the samples. This Research Material is provided as a service to research community. IT IS BEING SUPPLIED TO RECIPIENT WITH NO WARRANTIES, EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. Provider makes no representations that the use of the research material will not infringe any patent or proprietary right or third parties.

6. The recipient shall notify the provider in writing of any intention, improvement, modification discovery or development to the material or the information made by Recipient or parties, collaborating with Recipient, herein after referred to as "invention". Nothing in this agreement shall, however, be construed as conveying to the provider any rights under any patents or other intellectual property to such invention, other than as explicitly provided herein. At its option the provider shall be entitled to receive sample of any materials derived from the Materials for its own research and evaluation purposes only.
7. The under-signed provider and Recipient expressly certify and affirm that the contents of any statements made herein are truthful and accurate.
8. Any additional terms (use an attached page if necessary):
9. The provider maintains, ownership right of the research material and its derivatives unless stated otherwise.

The provider will retain a copy (aliquot) of every sample sent abroad as much as possible for local research needs.

**Material Transfer Agreement
Signature page**

For Recipient:

Recipient's Investigator


Signature

Prof Eleni Aklillu

Date 2019-06-24

Mailing Address

Dept. of Laboratory Medicine

Karolinska Institutet

Division of Clinical Pharmacology

Department of Laboratory of Medicine, Karolinska Institutet

SE-141 86 Stockholm, Sweden.

+46-73-511 61 31

elen.aklillu@ki.se

Duly Authorized

Signature/ 
Department of Laboratory Medicine
Division of Clinical Pharmacology

For Provider:

Provider's Investigator

Dr Solomon Mequanente Abay

Signature 

Date June 28, 2019

Mailing Address

CDT Africa

P.O. Box: 9086

Tel: +251 941222169

Fax: (+251) 115511079

Duly Authorized

Dr Abebaw Fekadu

Signature 

Date 03 July 2019

Mailing Address for Notices

CDT Africa

P.O. Box: 9086

Tel: (+251) 1118787311

Fax: (+251) 115511079

