Prevalence and Treatment Outcome of Schistosomiasis in Preschool-aged Children; A Systematic Review and Meta-analysis

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Prevalence and Treatment Outcome of Schistosomiasis in Preschool-aged Children; A Systematic Review and Meta-analysis

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CERTIFICATION OF ADDIS ABABA UNIVERISTY SCHOOL OF GRADUAES STUDIES

This is to certify that the thesis prepared by Mahlet Abbay, entitled "**Prevalence and Treatment Outcome of Schistosomiasis in Preschool-aged Children; A Systematic Review and Meta-analysis"** and submitted in partial fulfillment of the requirements for the award of the degree of master of science in Clinical Trial complies with the regulations of the University and meets the accepted standards with respect to originality and quality. Approved by the Board of Advisors.

Advisors: Dr. Girmay Medhin

Signature_____ Date ___ /___ /___

Dr. Solomon M. Abay

Signature _____ Date ___ /___ /___

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LIST OF ABBREVIATIONS AND ACRONYMS

CI……. Confidence Interval

CMA……. Comprehensive Meta-Analysis

CR……...…...Cure Rate

DDIA……...Dipstick Dye Immunosorbent Assay

ECD……...…...…. Early Childhood Development

EPG……..... Egg Per Gram of stool

ERR…… Egg Reduction Rate

FECT……Fecal Concentration Technique

GBD……Global Burden of Disease

KK……Kato Katz

MDA……... Mass Drug Administration

NCP …… National Control Program

NTD…… …Neglected Tropical Disease

PC ……Preventive Chemotherapy

POC-CAA……. Point of Care Circulating Anodic Antigen

POC-CCA…… Point of Care Circulating Cathodic Antigen

PSAC……. …. Pre School Aged Children

PZQ……..... Praziquantel

RCT…….……. Randomized Control Trial

RT-PCR……. Real Time Polymerase Chain Reaction

SAC……...…School Age Children

SEA-ELISA……...Soluble Egg Antigen Enzyme-Linked Immunosorbent Assay

STH ……..…Soil Transmitted Helminths

WHO……... World Health Organization

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ABSTRACT

Background: Schistosomiasis is a parasitic disease caused by worms of the genus Schistosoma. Almost 85% of infected individuals live in Africa. Infection among preschool-aged children (1-5 years) in endemic areas was underestimated and is currently excluded from preventive chemotherapy because of limited data on safety and efficacy, and partly due to a common thought that schistosomiasis is not common in preschool-aged children (PSAC).

Objective: The aim of this study was to review evidences regarding the prevalence of schistosomiasis and its treatment outcome among preschool aged children.

Methods: PRISMA guideline was followed during the conduct and reporting of this systematic review and meta-analysis. A comprehensive search was carried out from PubMed, Cochrane library, Google scholar and HINARI for studies published till April 2020. Extracted data in preliminary table from papers selected for full-text review and passed eligibility criteria. Quality assessment was based on Hoy 2012 tool using 10 criteria addressing internal and external validity. Random-effects model was used to pool measures of effects and to construct 95% confidence interval (CI) around the pooled effect sizes. In addition, subgroup analysis was conducted to improve the outcome.

Results: 38 studies were eligible for final systematic review and meta-analysis. Among the total of 19592 children's participated 18,509 examined and 5,143 were found to be infected with one or more species of schistosomiasis yielding an overall prevalence of 27.7% (95% CI: 22.8-33.5%). And the result shows there is significant variability between studies (Heterogeneity I^2 =98.252 with Chi-square =2002.59, DF 35 and a *P*-value < 0.001). The result of meta regression showed diagnosis method used and study year had contributed significantly to the heterogeneity study results. Regarding treatment outcome, the overall CR was 88.9% (95% CI: 83.5-92.7%) and ERR 97.3% (95% CI: 95.4-98.5%). The result of meta regression showed diagnosis method used and study year had contributed significantly to the heterogeneity of study results.

Conclusion: this systematic review and meta-analysis showed there was a moderate prevalence of schistosomiasis and also good treatment outcome of praziquantel in preschool-aged children; indicating to review strategies to consider these age groups in mass drug administration deworming programs until proper formulation accessible.

Keywords: Prevalence, Schistosomiasis, Treatment outcome, Preschool-aged children

1. INTRODUCTION

1.1. Background

The Tropical Diseases Research arm of the World Health Organization (WHO) classifies schistosomiasis as one of the major neglected tropical diseases (Wang et al., 2016). Schistosomiasis is severe human water-born parasitic disease caused by flukes of the genus *Schistosoma* (Gryseels et al., 2006). It is a major infectious disease leading to a health problem in some parts of Africa, South America and Asia which mainly affects people living in communities where there is poor hygiene (water & environmental sanitation) and poor water source (Teresinha et al., 2018). The disease found in 78 countries and endemic in 52 of them. Since it is a chronic disease which is not easily noticed at an early stage and becomes a threat to development slowly by disabling people during their most productive years (Ekpo et al., 2012).

*Schistosoma hematobium, S. mansoni and S. japonicium are t*he three main species of schistosomes that cause morbidity to humans. These species have similar life cycles. The worms live within the veins of the human host and develop through a succession of stages (Shaker et al., 2014). The parasite lives for an average of 3–10 years, and in some cases for 40 years, in human hosts.

S. mansoni and S. haematobium are the main *Schistosoma* for the majority of human infections; both are found in Africa and in some Middle East Countries. *S. japonicium* is common in Asia mostly in China and somewhat in Philippines and Indonesia. The only species present in Latin America is *S. mansoni* (Colley etal, 2015). Schistosomiasis is ranked second to malaria in terms of mortality (Adenowo et al., 2015). It infects more than 200 million people worldwide and an estimated 700 million people in 76 countries are at risk of infection. Almost 85% of those infected live in Africa; 200,000 deaths annually are attributed to schistosomiasis worldwide (Colley etal, 2015; Shaker et al., 2014).

In schistosomiasis endemic regions the most dominant form is chronic schistosomiasis, resulting from repeated exposure to the infectious larval stage (Colley etal, 2015). Children are often infected at their 2 years of age and many of them remain chronically infected throughout their school-age years (Van Der Werf et al., 2003).

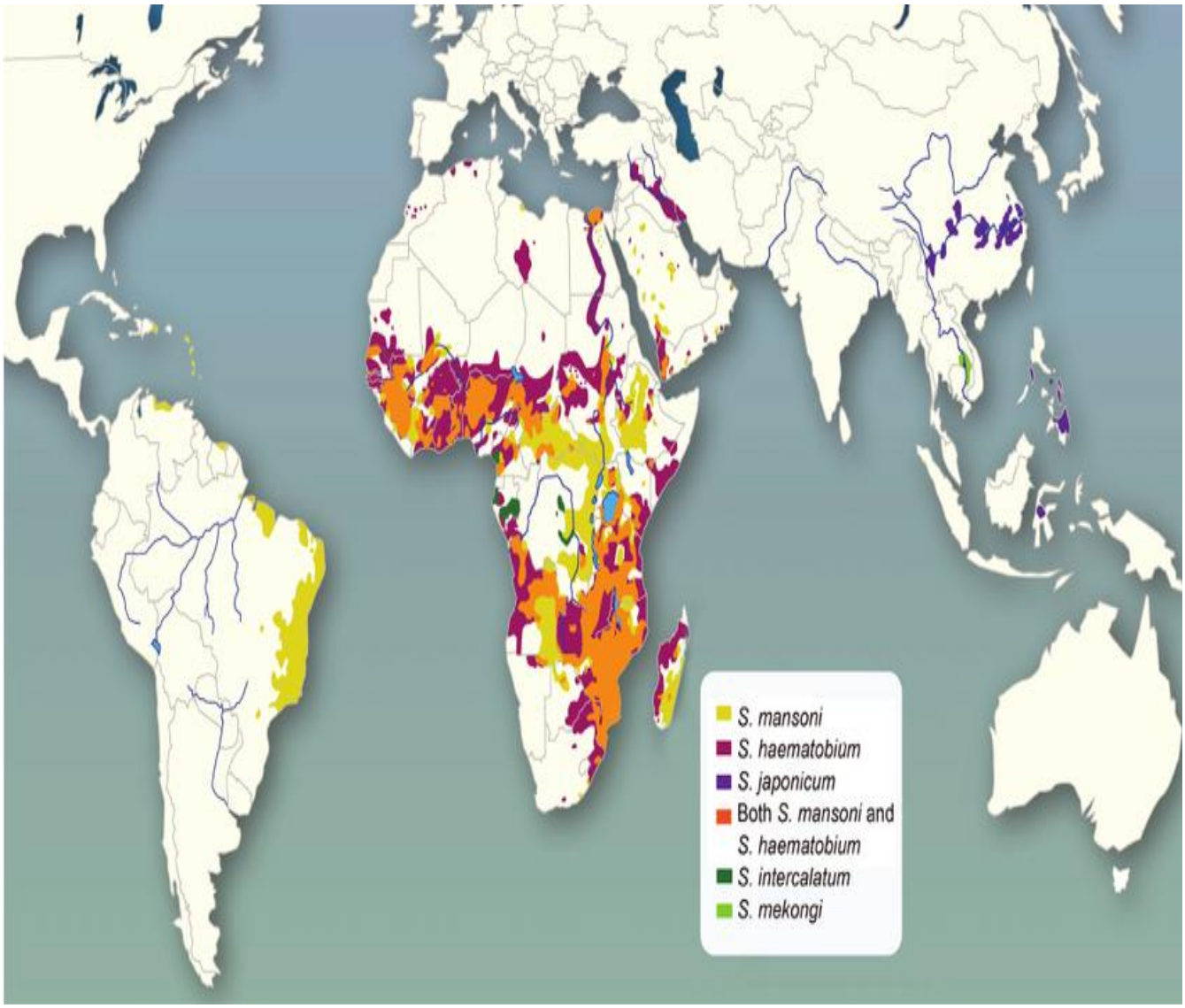


Figure 1: Map of global distribution of Human schistosomiasis.

- ✓ Source: (*Weerakoon 2015 Advances in the diagnosis of human schistosomiasis. Clinical microbiology reviews*)

2. LITRATURE REVIEW

From the estimated greater than 200 million people infected by schistosomiasis; a significant number (around 123 million) are children (Osakunor et al., 2018; WHO, 2010). And according 2017 WHO's report about 10% of those infected are children under 6 years of age. Also PSAC are among the three high‐risk groups mentioned in the report (WHO, 2017).

Schistosomiasis has negative impact on the infected child's future activity and health. Among the health impact include poor growth and cognition (Osakunor et al., 2018). Similarly epidemiologic studies related to morbidity associated to *Schistosoma* infections indicated that it has adverse impacts in growth, fitness, pediatric quality-of-life, deficits in cognitive function, academic achievement, suboptimal child development, malnutrition and vitamin-A deficiency (Ezeamama et al., 2018).

Chronic infection can also result in anemia, intestinal and liver fibrosis, splenomegaly and neurological complications (Gryseels et al., 2006; Strickland, 1994).

The type of morbidity associated with *schistosome* infections in humans and their species-specific symptoms are summarized in Table 1.

Table 1: Common adverse impact and morbidity of *schostosome* infection

S. haematobium	*S. mansoni*	General morbidity
✓ Hematuria	✓ Bloody diarrhoea	✓ Anaemia
✓ Dysuria	✓ Periportal fibrosis	✓ Malnutrition
✓ Genital lesions	✓ Portal hypertension	✓ Stunted growth
✓ Renal failure	✓ Hepatosplenomegaly	✓ Poor memory development
✓ Bladder cancer	✓ Abdominal pain	✓ Cognition impairment
✓ Supra-pubic pain		✓ Decrease physical fitness
✓ Urinary tract infections		✓ Susceptibility to coinfections

2.1. Risk factors for schistosome infection in PSAC

Understanding the risk factors for schistosomiasis in Preschool-aged children (PSAC) is important to design the appropriate control strategy for the disease. The most schistosomiasis affected segment of the population is the poorest that live in remote areas. Among the risk factors that contribute to schistosome infection in PSAC are; access to water (source of all domestic water rely on wall water, families habit of bathing children in the river, washing clothes in infected water, children playing and swimming in the river), irrigation of crops, educational status (illiteracy) of the parents, gender (male are at high risk) (Kabuyaya et al., 2017; M'Bra et al., 2018). These risk factors are summarized in Figure 2 for easy visual observation.

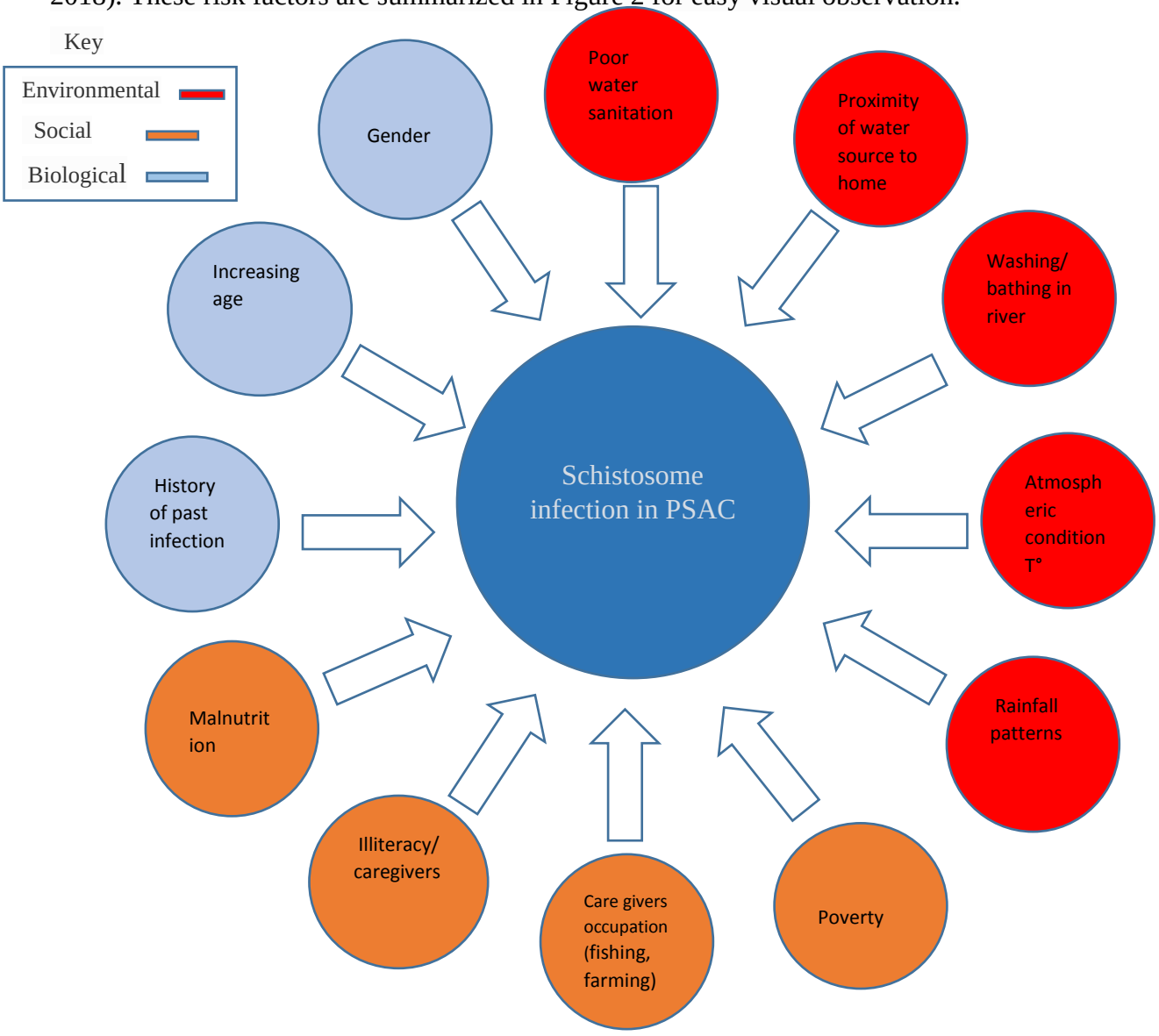


Figure 2: Risk factors for schistosomiasis in preschool aged children

2.2. Diagnosis of schistosome infection

Currently available diagnostic methods for schistosomiasis include stool and urine microscopy (i.e. Kato Katz (KK) and urine microscopy), serum antibodies, antigen detection and the detection of DNA (RT-PCR). Although the last one is less frequently used in the diagnosis of schistosome (Weifeng G et al., 2018).

2.2.1. Urine and Stool Microscopy

Stool Microscopy: -The World Health Organization recommends KK fecal smear method for routine use in prevalence detection as part of procedure in endemic areas. (WHO, 2017) and is a frequently used method for intestinal schistosomiasis worldwide (such as *S. mansoni, S. japonicum,* and *S. mekongi*) (Ajibola et al., 2018). Due to its ease of application and a high diagnostic specificity it has good performance in endemic areas. Its other advantage is being cheap. However, KK test is not an accurate diagnostic method in cases where; part of a population has been previously treated and low egg burden is present in stool, when applied in non-endemic areas and its sensitivity is low (Ba¨renbold et al., 2017).

Fecal concentration technique: - Another approach that is used in stool examination is the fecal concentration technique (FECT). In this method fecal sample is suspended in formalin and ethyl acetate centrifuge. The suspension sediments the parasite material in a pellet which can subsequently be mixed with saline (or stained with iodine) for microscopy. The disadvantage of this methods is being expensive compare to other microscopic tests (Utzinger et al., 2015).

Urine Microscopy: - it is a microscopic examination of parasite eggs in urine samples. About 10 mL of urine sample should be filtered, centrifuged, and the residue should be examined under a microscope for parasite eggs. The number of eggs per 10 mL of urine is used to express infection intensity. This method is used to detect urogenital schistosomiasis and it is the gold standard method to detect *S. haematobium* eggs in endemic areas (Chadeka et al., 2017).

2.2.2. Antigen Based Detection Methods

This is the method of detecting adult worms and egg antigens in serum or urine. The antigens are either circulating anodic antigen (CAA) or circulating cathodic antigen (CCA); (Ajibola et al., 2018) . CAA in urine or serum recently been used in the screening of advanced *S. japonica* in China (Utzinger et al., 2015). The POC-CCA used only for the detection of *S. mansoni* infection in humans. It is rapid antigen-based detection method which is applied to urine samples (Lindholz et al., 2018). Its advantage over KK test includes it has more improved sensitivity and the use of urine samples instead of stool for diagnosis; increases the acceptability by patients and the applicability for prevalence surveys in large populations (Da Silva et al., 2017).

2.2.3. Immunological Analysis Based Detection Methods

This method is relatively simple and it has high sensitivity. The standard is to monitor the antigen and antibody release from schistosome. (Weerakoon et al., 2015) These include enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence (IFAT), indirect hemagglutination (IHA) and Dipstick Dye Immunosorbent Assay (DDIA) (Sulahian et al., 2005). These methods are designed to detect antibodies in the serum of infected people. Among these methods ELISA is the preferred test method with high sensitivity and specificity for diagnosis of schistosomiasis. (Weifeng G et al., 2018)

- Both serological and immunological test methods are helpful for diagnosis of those people living in non-endemic/low transmission areas of schistosomiasis. It helps in showing exposure to infection and the need for treatment and follow-up.

2.3. Treatment of schistosomiasis

Praziquantel is the currently used "gold standard" treatment and drug of choice for all types of schistosomiasis (Vale et al., 2017). It is originally discovered by Merck (Germany) during 1970's for veterinary purposes (Aragon et al., 2009). It is available in tablet formulation (600 mg) with a dose of 40 mg/kg which is safe and effective in adults and school-age children. It is generally a well-tolerated and nontoxic drug with minimal side effects such as nausea, vomiting, hepatomegaly, and headache in some patients (Montero & Ostrosky, 1997; Vale et al., 2017).
However, the concern of this medication for PSAC is that there is no clear evidence of safety on these age group, difficulties of swallowing due to the large, cumbersome and bitter taste of the tablet (Stothard et al., 2013) and risk of choking in Some children during swallowing (Kernell et al., 2018).

2.3.1. Future opportunities /promises

Pediatric PZQ formulation/pediatric PZQ consortium

This PZQ consortium program was an international public-private partnership established in 2012 consists of seven partners including WHO experts (as an observer) that works on a not-for-profit basis with a mission to develop, register and provide access to a suitable pediatric PZQ formulation for treating schistosomiasis in PSAC. And developed an innovative child-friendly formulation available as 150 mg tablet (L-PZQ) (PZQ consortium). It lacks the biologically inactive D-PZQ enantiomer which is also responsible for the bitter taste of the drug (Olliaro et al., 2014). The drug is under clinical trial (it is in phase III b) that is more suitable for younger children, including infants and toddlers (Goran et al., 2019). The formulation is smaller, orodispersible (can be dispersible in water) and have better taste properties compared to the approved PZQ 600 mg tablets. This new formulation if approved it will have benefit for pediatric use both in management and in large scale preventive chemotherapy program (Reinhard-rupp & Klohe, 2017). The phase III trial was under progress in Kenya, Cote Divore and Zimbabwe but currently, the trial is on hold from March 2020 due to the pandemic COVID-19.

3. STATEMENT OF THE PROBLEM

Infection among PSAC (1–5 years) in endemic areas is underestimated in every aspect of prevalence and mass drug administration (MDA). Its burden is recognized only recently and its negative effect on the health and development of PSAC is acknowledged. (Coulibaly et al., 2012) There is an evidence that shows the prevalence of infection in infants and pre-school-aged children (≤6 years old) is increasing in sub-Saharan African countries. (Won et al., 2017)

Studies in Ethiopia (Alemu et al., 2016; Kemal et al., 2019), Mali (Dabo et al., 2011), Niger (Garba et al., 2010), Nigeria (Ekpo et al., 2010), Uganda (Sousa-Figueiredo et al., 2010), Zimbabwe (Wami et al., 2016), Kenya (Verani et al., 2011) and Côte d'Ivoire (Coulibaly et al., 2012, 2013) reported a higher prevalence of both urogenital and intestinal schistosomiases in PSAC ranging from 12% to 65%. Similarly, preliminary results showed that treatment with praziquantel (PZQ) in preschool children had 96% cure rate (CR) and 99% egg reduction rate (ERR) in Ethiopia (Kemal et al., 2019) 100% CR and 100% ERR in Zimbabwe (Wami et al., 2016) , In Gabonese study (Dejon-Agobé et al., 2019) after the 3rd dose of PZQ overall ERR was 95% and CR was 88%, but both ERR (100 *vs* 88%) and CR (90 *vs* 68%) were higher among females than males after the first dose.

PSAC is currently excluded from preventive chemotherapy control campaigns. The focus is still on school aged-children (SAC) and they are treated based on confirmation of infection, however, they are recognized as a vulnerable group (Stothard et al., 2013).

The reasons for the exclusion include:

a. PSAC considered as being at low risk of infection (Verani et al., 2011)
b. Insufficiency of evidence in safety and efficacy of praziquantel for this age group (Won et al., 2017)
c. Lack of a pediatric formulation (Coulibaly et al., 2012).

Since there is no published recommendation on the treatment of schistosomiasis in PSAC with PZQ in population-based control programs, WHO support treatment trials in the area at high risk of schistosomiasis in Mali, Sudan, Uganda, Niger, Zimbabwe and Egypt in 2009 on 3198 children and organize a meeting in 2010 at Geneva to review the result of studies on the treatment of schistosomiasis. The result showed that PZQ in tablet or suspension formulation was safe, effective and acceptable against schistosomiasis. The meeting also recommends systematic review(s) involving PSAC, or well-designed multi-country RCT using a standard protocol to contribute further evidence since the studies reviewed in this report had some limitations of design and methodology (WHO, 2010).

The high prevalence of schistosomiasis in PSAC in different countries especially in Africa and underestimation of the need for preventive and curative efforts in these age group calls for evidence-based policy intervention. Thus, the aim of this study is to systematically review and conduct meta-analysis of existing evidence on the prevalence of schistosomiasis and treatment outcome among PSAC. To the best of our knowledge, this review is the first of its kind in estimating the pooled prevalence of schistosomiasis in PSAC.

4. OBJECTIVE

4.1. General Objective

The main objective of this meta-analysis and systematic review was to generative a conclusive evidence on prevalence and treatment outcome of schistosomiasis in preschool-aged children.

4.2. Specific objectives

The specific objectives were to:

- ✓ Summarize existing evidence in the prevalence of schistosomiases in PSAC
- ✓ Review outcome of medication used to treat schistosomiasis in PSAC.

5. METHODS

This systematic review and meta-analysis followed the preferred reporting item for systematic review and Meta-analysis (PRISMA) guideline (Moher et al., 2009).

5.1. Literature Search methods

Comprehensive literature searches of biomedical databases (PubMed, Science direct, Google Scholar, HINARI) was made to locate studies published till April 2020 supplemented by manual searches to identify relevant studies. The following search terms and their medical subject headings (MESH) terms were used to identify relevant papers: "prevalence" AND "schistosomiasis" OR "bilharzia" AND "preschool aged children" OR "under 7 aged children" AND "treatment outcome" or "efficacy".

The limit of language was English and the limit of study group was human. A manual search for additional related studies using references from retrieved articles was also conducted to identify original articles that might be missed.

The protocol was registered on PROSPERO with registration number "PROSPERO 178102".

5.2. Selection/Eligibility criteria

All population-based studies which reported the prevalence of schistosomiasis and its treatment outcome among preschool aged children using English language were included in the study.

Inclusion criteria:

Studies (papers) that deal with the prevalence of schistosomiasis in preschool-aged children and treatment outcome published in English language till Apr. 2020.

- Studies reported the baseline prevalence of Schistosomiasis in preschool aged children.
- The study design was an observational study (prospective cohort, retrospective cohort, or cross-sectional) and controlled clinical trial which documented the rate or proportion of schistosomiasis prevalence.

Exclusion criteria:

- Papers deal on SAC (prevalence of schistosomiasis in school-age children) and adult human
- Studies of soil-transmitted helminth infections in PSAC where *Schistosoma* coinfection was absent

- Studies which are not primary (such as review articles, conference abstract, editorials), case reports, case series
- Studies that compared the sensitivity and specificity of different test methods used for diagnosis of schistosomiasis and studies not reported either prevalence or incidence of schistosomiasis as an outcome of interest.

Studies were examined for eligibility by reading their titles and abstracts. Relevant abstracts were further assessed for inclusion in the list of full-length articles. During the article selection process, studies that did not have full texts were excluded since it is not possible to assess the quality of each article in the absence of their full texts.

The list of reference of all original articles that were included in the systematic review were manually screened. This helps to identify publications that were missed during the database searches. The search terms used might not be sensitive enough to pick all possible papers.

5.3. Operational definitions/definition of terms

- PSAC: − The term preschool was defined according to the original studies. Children of age below 7 years (children between infancy and school-age) were considered.
- Prevalence: − Proportion of a population with a disease or a particular condition at a specific point in time or over a specified period of time
- Treatment outcome**:** − Evaluation undertaken to assess/ observe the results or consequences of management used in combating disease or illness in order to determine the efficacy(CR), safety (drug resistance, side effects), of the treatment administered.

5.4. Quality assessment of the included studies

Quality assessment was based on Hoy 2012 tool using 10 criteria addressing internal and external validity (Hoy et al., 2012). The items included (1) representation of the population, (2) sampling frame, (3) methods of participants' selection, (4) non-response bias, (5) data collection directly from subjects, (6) acceptability of case definition, (7) reliability and validity of study tool, (8) mode of data collection, (9) length of prevalence period, and (10) appropriateness of numerator and denominator. Each item was assessed as either low or high risk of bias. Unclear was considered as high risk of bias. The overall risk of bias then scored according to the number of risk of bias per study: low (≤ 2), moderate (3–4), and high (≥ 5).

For the included RCT studies quality of studies was assessed by Jaded scale with a description of 3 main characteristics: randomization, blinding, withdrawal, and dropouts. the highest score is 5, and the lowest one is -2. The trial was judged to be of bad quality if the total score is < 3 (Jadad et al., 1996).

5.5. Data extraction

Data extraction was based on preliminary excel table summarizing all included studies. Information extracted from each paper was study author with publication year, study year, study design, setting, sample size, egg positive (prevalence), type of the test method used, PZQ treatment, efficacy (CR and ERR), infection intensity, age of the study participant, gender, species type, follow-up period (if available) and the title of the article.

5.6. Statistical analysis and synthesis

Data entry and analysis were done using Software CMA version 3.0. The variance of schistosomiasis prevalence in each article was computed based on the binomial distribution formula by extracting the sample size from published data (Altman DG, 1997). The summary of the findings is presented in forest plots and tables.

The summary of pooled prevalence of *S. mansoni and S. haematobium* infection with corresponding 95% confidence interval was calculated using random-effects model of DerSimonian–Laird method (Dersimonian & Laird, 1986).

5.7. Subgroup analysis

Subgroup analysis was performed to improve heterogeneity of the outcome. The sub-groups were; year of study (2000-2010 and 2011-2020), Schistosoma species (*S. mansoni* and *S. haematobium*), type and number of laboratory diagnostic method used (Kato Katz, Double Kato Katz, POC- CCA, and SEA-ELISA).

5.8. Heterogeneity and publication bias

The Cochrane Q test and I^2 test statistics (at least 50% considered to be significant) were used to test heterogeneity among the studies (Ioannidis, 2008). The I^2 offers an estimated percentage of the variability in effect estimates, that is due to heterogeneity rather than sampling error or chance differences. The existence of heterogeneity was confirmed using Cochran's Q test ($P < 0.10$ shows statistically significant heterogeneity). I^2 test measures the level of statistical heterogeneity between studies (values of 25 % low, 50 % medium and 75 % high heterogeneity) (Ioannidis, 2008), (Rücker *et al*., 2008).

Begg's Funnel plot were used to detect publication bias. $P < 0.05$ was considered statistically significant publication bias. ("Cochrane Handb. Syst. Rev. Interv.," 2019), (Egger et al., 1997). A potential source of heterogeneity was investigated using subgroup analysis and met-regression.

6. RESULTS

6.1. Identified studies

A total of 857 scientific papers were identified through electronic data based searches. After critically reading the titles and abstracts in light of the eligibility criteria, 788 articles were excluded. Full texts of the remaining 69 articles were evaluated for eligibility and, 38 studies were included in the final analysis (Figure 3).

flow chart diagram describing for the selection of studies for systematic review and meta-analysis on prevalence and treatment outcome of schistosomiasis in PSAC.

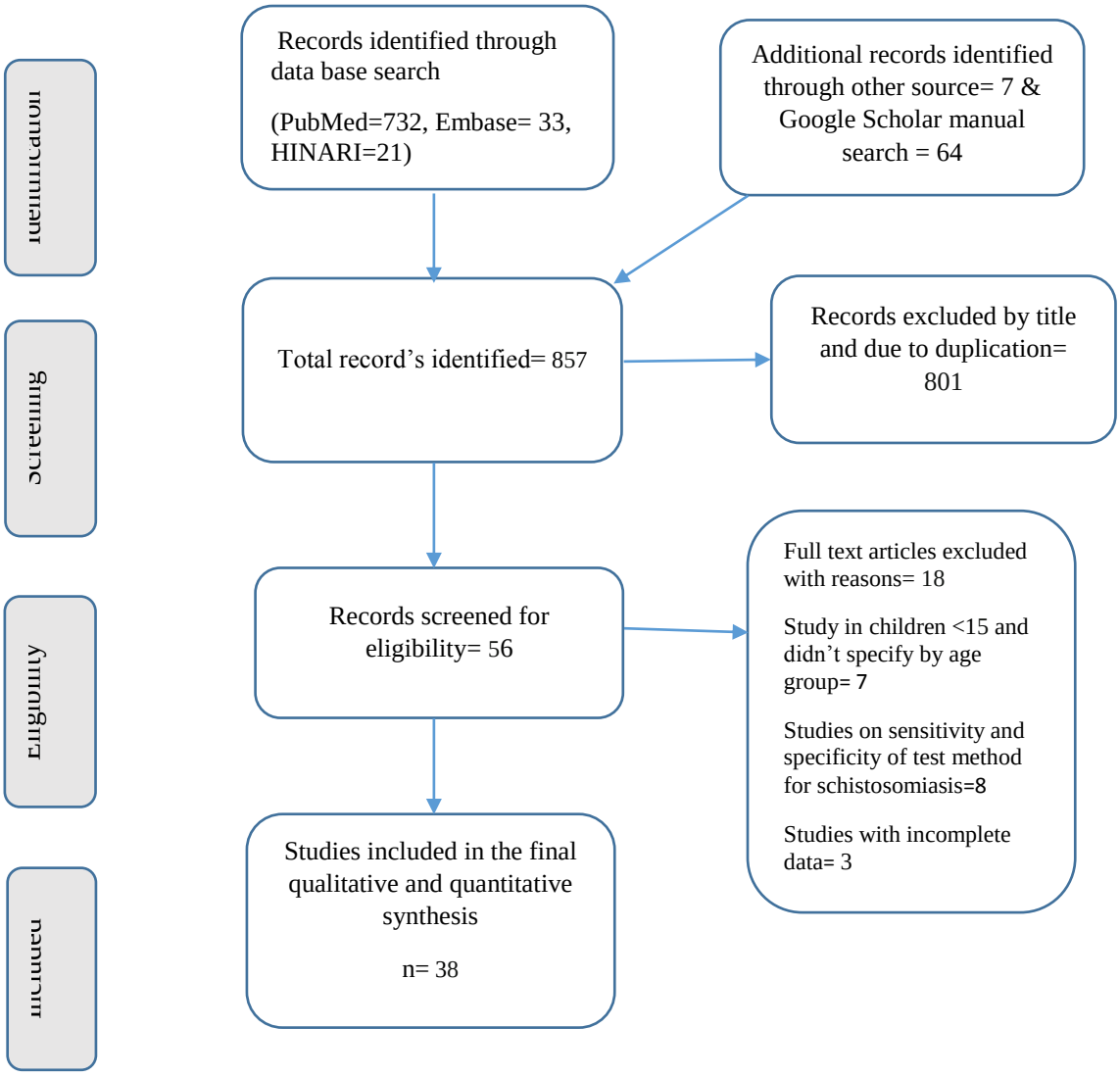


Figure 3: flow chart diagram for the selection of articles used for meta-analysis

6.2. Characteristics of included studies

Thirty-eight studies (all of them from African countries and conducted between 2001 and 2020) were included in this systematic review and meta-analysis with a total of 19,592 children participated in the study (Table 2). The majority of the studies (n=23) were cross-sectional, twelve were Cohort and three were interventional studies (RCT). One RCT and one cohort study used egg positive participants in their intervention to compare treatment outcomes of different doses of Praziquantel without reporting the prevalence of schistosomiasis. Hence the pooled prevalence of Schistosomiasis was based on 36 studies. Of the 38 studies 17 reported about only *S. mansoni*, 13 only *S. haematobium* and 8 both *S. mansoni* and *S. haematobium* infection. Thirty-three out of thirty-eight studies were community-based and the remaining 5 were institutional (school or health centers based). The sample size of the studies ranged from 41 (Rujeni et al., 2013) to 3612 (Won et al., 2017). The highest prevalence (80.1%) reported from Tanzania (Ruganuza et al., 2015), the lowest (0.5%) from Malawi (Poole et al., 2014) and 0.9 % from South Africa (Sacolo-Gwebu et al., 2019).

Table 2: Characteristics of the eligible studies on prevalence and treatment outcome of schistosomiasis

Author	study period	Study region	Study design	Species type	Sample size	Prevalence (%)	Lab test method	Male	Female	PZQ txt	Efficacy CR%	ERR%
Kemal et al 2019	2016	Ethiopia (Erer, Somali region)	Follow-up	*S. m*	236	25	Double kato katz	32/121	27/115	40 mg/kg	96.4	99.4
Gebrehiwot et al 2014	2013	Ethiopia (Wonji)	CS	*S. m*	374	8.3	Single kato katz	10.8/179	6.7/195	na	na	na
Alemu et al 2016	2015	Ethiopia (Dembia district)	CS	*S. m*	401	11.2	Single kato katz	23/218	22/183	na	na	na
Coulibaly et al 2012	2011	Co'te D'ivore (Azaguie district)	Follow-up	*S. m* *S. h*	160	21.9 48.7 13.3	Quadruplicate kato k POC-CCA Urine filtration	19/78	16/82	40 mg/kg 40 mg/kg	88.6 88.9	96.7 98
Nyantekyi et al 2010	2007	Ethiopia (Wondo genet)	CS	*S. m*	288	37.2	Single kato katz	na	na	na	na	na
Wami et al 2016	2012	Zimbabwe (Murewa district)	Follow-up	*S. h*	109	7.34	Urine filtration	na	na	40 mg/kg	100	100
Mutapi et al 2011	2008	Zimbabwe (Mashonoland)	Follow-up	*S. h*	104	20.2	Urine filtration	na	na	40 mg/kg	na	99
Mutsaka-Makuvanza et al 2018	2016	Zimbabwe (Medziwa area)	Cohort	*S. h*	535	13.3	Urine filtration	36/291	35/244	40 mg/kg	83.1	96.8
Coulibaly et al 2013	2011	Co'te D'ivore (Azagui' district)	CS	*S. m* *S. h*	244	42.7 14.3 45 12.4	Quadrplict kato k Single kato katz POC-CCA Urine filtration	na	na	40 mg/kg	na	na
Dabo et al 2011	2008	Mali (Diema district)	CS	*S. h*	338	51.2	Urine filtration	98/189	75/149	40 mg/kg	na	na
Garba et al 2010	2007	Niger (western Sahl zone)	CS	*S. m* *S. h*	282	43.8 55.5	Double kato katz Urine filtration	na	na	40 mg/kg	na	na
Verani et al 2011	2009	Kenya (Usoma)	CS	*S. m*	216	17.6 33.8 36.6	Single kato katz POC-CCA Both	na	na	40 mg/kg	na	na
Davis et al 2015	2012	Kenya (Rusinga island)	CS	*S. m*	201	44.9	Double kato katz	na	na	40 mg/kg	na	na

Author	study period	Study region	Study design	Species type	Sample size	Prevalence (%)	Lab test method	Male	Female	PZQ txt	Efficacy CR% ERR%	
Moyo et al 2015	2012	Malawi (Malengacheanz)	CS	*S. h*	143	13	Urine filtration	12/92	6/51	na	na	na
Ekpo et al 2010	2008	Nigeria (Ilewo-orile)	CS	*S. h*	167	58.1	Urine filtration	52/91	45/76	40 mg/kg	na	na
Sacolo- Gwebu et al 2019	2012	Uganda (Bulisila and Mayuge district)	Cohort	*S. h*	979	37.7 57.1	Double kato katz POC-CCA	na	na	40 mg/kg	56.4	89
Poole et al 2019	2012	Malawi (Chikhiwawa district)	CS	*S. m* *S. h*	208	0.5 9.1 10.7	Single kato katz POC-CCA Urine filtration	na	na	40 mg/kg	na	na
Rujeni et al 2013	2010	Zimbabwe (Mashonlad East)	CS	*S. h*	41	13.2	Urine filtration	na	na	40 mg/kg	na	na
Culibaly et al 2017	2014-2015	Co'te Divore' (district of Azague)	RCT	*S. m*	660	24	Ssingle kato katz	Na	Na	20 mg/kg 40 mg/kg 60 mg/kg Placebo	90.7 94.8 95.8 80.1	Na na na na
Nalugwa et al 2015	2013	Uganda (Lake Victoria)	RCT	*S. m*	1017		Single kato katz	na	na	40 mg/kg	84.3	98.9
Houmsou et al 2018	2014-2015	Nigeria (Taraba state)	Follow up	*S. h*	63		Urine filtrtion	na	na	40 mg/kg	98.1	100
Culibaly et al 2018	2015-2016	Co'te Divore' (district of Adope)	RCT	*S. h*	628	29.6	Urine filtration	79	91	20 mg/kg 40 mg/kg 60 mg/kg placebo	85.7 78 68.3 47.5	98.3 97.6 96.5 na
Kimani et al 2018	2015	Kenya (Kwale)	Cohort	*S. h*	400	20	Urine filtration	47/195	33/195	40 mg/kg	86	96.9
Sakari et al 2017	2014	Kenya (Kirinyaga country)	CS	*S. m*	361	5.54	Single kato katz	na	na	na	na	Na

Author	study period	Study region	Study design	Species type	Sample size	Prevalence (%)	Lab test method	Male	Female	PZQ txt	Efficacy CR%	ERR%
Stothard et al 2011	2009	Uganda (Bugoigo)	CS	*S. m*	242	21.9 42.6 45.9	Double kato katz POC-CCA ELISA-kit	na	na	40 mg/kg	na	na
Ruganuza et al 2015	2013	Tanzania (Musozi village)	CS	*S. m*	386	44.4 80.1	Single kato katz POC-CCA	90/195 159/195	80/188 150/190	na	na	na
Amin et al 2012	2009	Sudan (Gezira state)	Cohort	*S.m* *S. h*	106 498 (Tot=604)	44.3 28.3 (T.P=31)	Single kato katz Urine filtration	na	na	40 mg/kg	na	99.4 96.4
Sousa-Figueir 2008	2006	Zanzibar (Unguja island)	CS	*S.h*	102	3.9	Urine filtration	na	na	40 mg/kg	na	na
Nalugwa et al 2015	2013	Uganda (Shoreline)	CS	*S. m*	3058	1203	Single kato katz	630/1545	573/1513	na	na	na
Opera et al 2007	2005	Nigeria (cross river basin)	CS	*S. h*	126	19.8	Urine filtration	15/71	10/55	na	na	na
Niyituma et al 2017	2015	Rwanda (Bugesra district)	CS	*S. m*	248	0 16.9	Double kato katz POC-CCA	25/129	17/119	Na	Na	Na
Said et al 2017	2015	Tanzania (Dares Salaam)	Cohort	*S. m* *S. h*	310	0 15.2 1	Single kato katz POC-CCA Urine filtration	24/150	23/150	40 mg/kg	Na	Na
Navaratnam et al 2012	2010	Uganda (Buliisa district)	Cohort	*S. m*	549 575 (1124)	27 25.9 (26.4)	Single kato katz	Na	Na	PZQ syrup PZQ tab	80.9 81.7	86.1 89

Table 2: Characteristics of the eligible studies on prevalence and treatment outcome of schistosomiasis (continued)

Author	Study period	Study region	Study design	Species type	Sample size	Prevalence%	Lab test method	Male	Female	PZQ txt	Efficacy CR	ERR
Bosompem et al 2004	2002	Ghana (Okyereko village)	CS	*S. m* *S. h* *S. h*	80	0 11.2 30	Single kato katz Urine filtration Dipstick	na	na	na	na	na
Armoo et al 2020	2017	Ghana (Weija dam; South Ghana)	CS	*S. m*	190 160 190	25.3 24.4 86.3 31.6	Double kato katz PCR (DNA kit) POC-CCA(L.tracce) POC-CCA(w/o L.t)	na	na	na	na	na
Won et al 2017	2012-2014	Kenya (Mbita Subcounty)	Cohort	*S. m*	3612	28% 50%	Single kato katz ELISA-kit	na	na		na	na

CS – Cross Sectional:

RCT- Randomized Control Trial:

S. m – *Schistosoma mansoni*:

S. h – *Schistosoma haematobium*

6.3. Prevalence of schistosomiasis

From the total of 18,509 children examined and reported in the included studies, 5,143 were infected with one or more species of *Schistosoma* parasite according to the Der Simonian-laired random-effect model yielding an overall prevalence of 27.7% (95% CI: 22.8-33.5%). Forest plot derived from the meta-analysis (Figure 4) shows detailed information about an individual study and the pooled prevalence estimate. There was significant variability between studies (Heterogeneity I^2 =98.252 with Chi square =2002.59, degree of freedom 35 and a P-value <0.001).

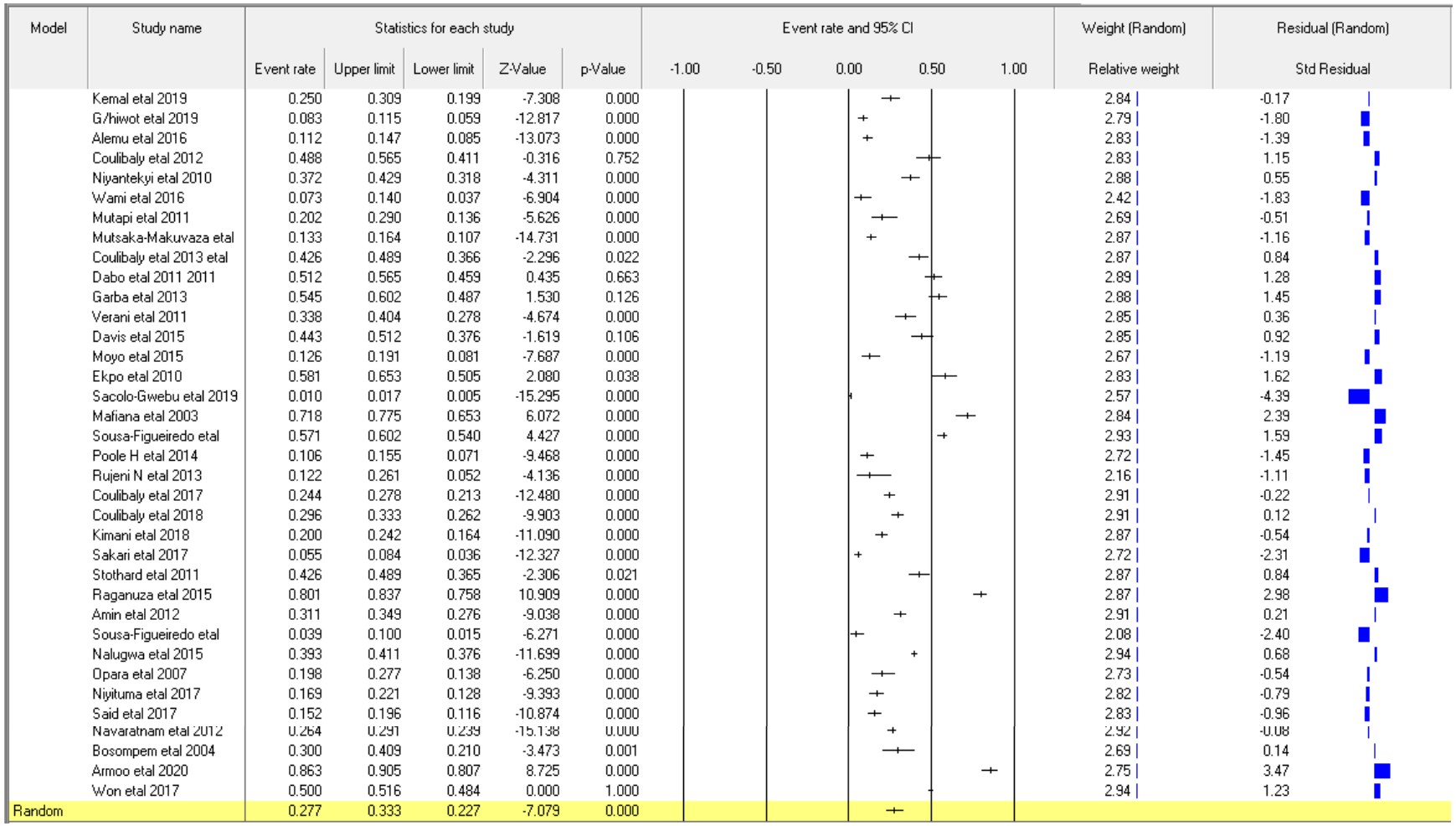
6.4. Treatment outcome

Treatment coverage was reported in twenty-five studies out of the thirty-eight studies (65.8%) positive participants treated with Praziquantel. And only 13 studies assessed efficacy (CR and ERR) of the treatment.

Using data from these 13 studies the overall CR was 88.9% (95% CI: 83.5-92.7%) (Fig 5) and ERR was 97.3% (95% CI: 95.4-98.5%) (Fig.6). Level of Heterogeneity was very high (I^2 =97.17%, Chi square=424.059, degree of freedom=12, and P-value <0.001).

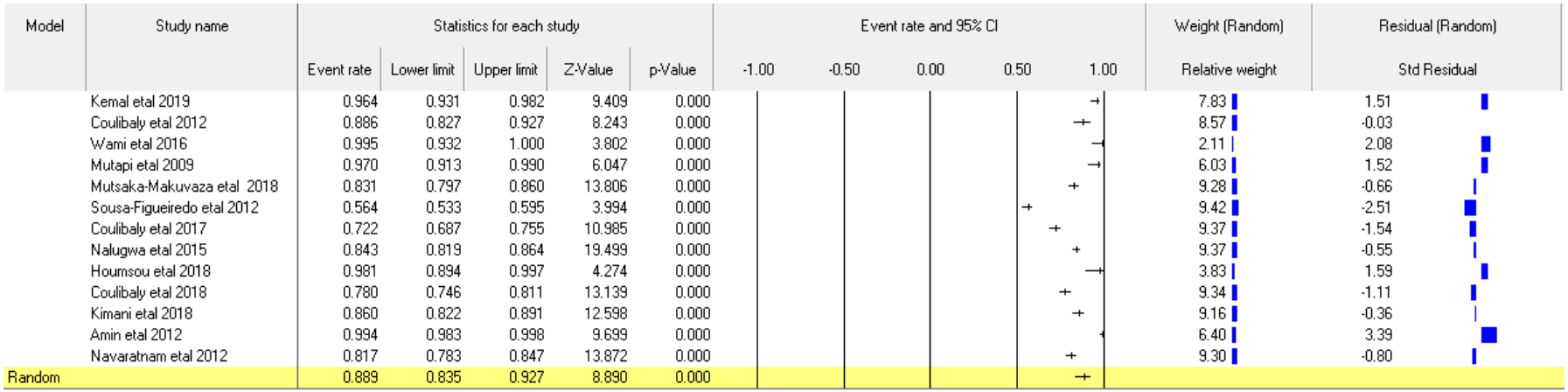
Ugandan preschool-aged children from 1-5 aged (Nalugwa et al., 2015) were randomized to receive PZQ 40 mg/kg single dose or double dose (2 weeks apart). By week 4, no difference was detected between treatment for CR (83.2 and 85.5%, P = 0.390, respectively) or ERR (98.9 and 99.3%, respectively) of both groups.

In 2 RCT studies which is conducted in Côte d'Ivoire (Coulibaly et al., 2017), (Coulibaly et al., 2018) they compared the CR and ERR obtained with three different doses of praziquantel 20, 40, 60 mg/kg and placebo, in PSAC infected with both *S. mansoni* and *S. haematobium.* In both studies, high dose of PZQ (60 mg/kg) had low CR and EER compare to the other doses for both species.



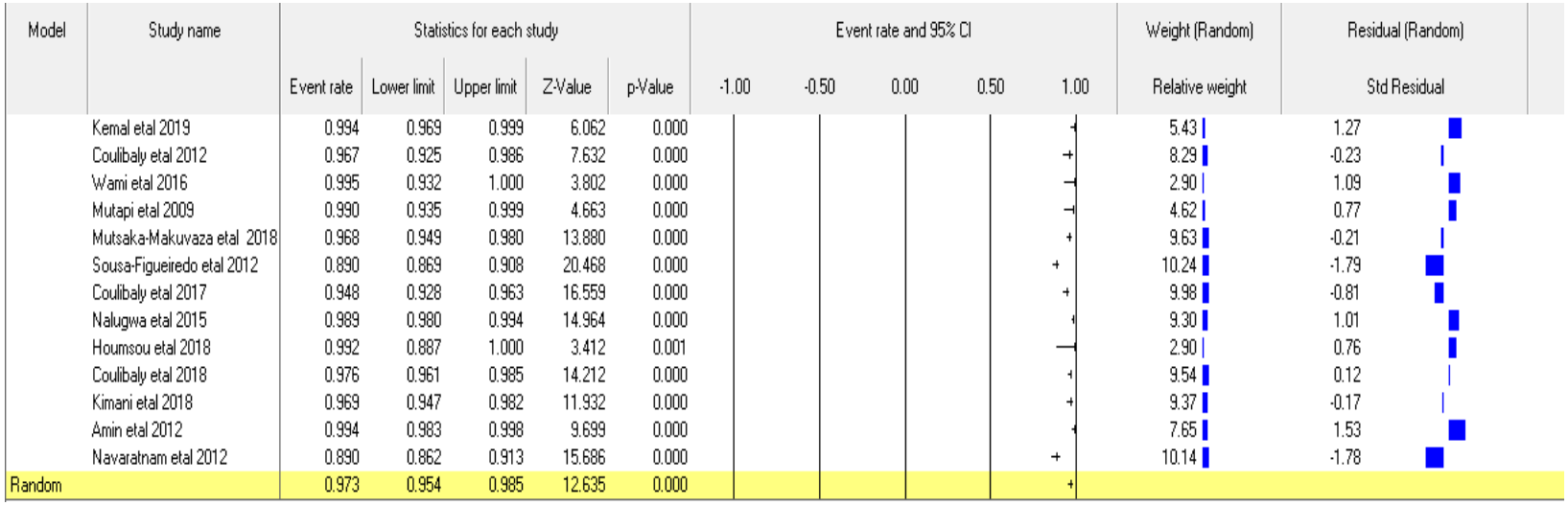
Model	Study name	Statistics for each study					Event rate and 95% CI	Weight (Random)	Residual (Random)
		Event rate	Upper limit	Lower limit	Z-Value	p-Value	-1.00 -0.50 0.00 0.50 1.00	Relative weight	Std Residual
	Kemal etal 2019	0.250	0.309	0.199	-7.308	0.000		2.84	-0.17
	G/hiwot etal 2019	0.083	0.115	0.059	-12.817	0.000		2.79	-1.80
	Alemu etal 2016	0.112	0.147	0.085	-13.073	0.000		2.83	-1.39
	Coulibaly etal 2012	0.488	0.565	0.411	-0.316	0.752		2.83	1.15
	Niyantekyi etal 2010	0.372	0.429	0.318	-4.311	0.000		2.88	0.55
	Wami etal 2016	0.073	0.140	0.037	-6.904	0.000		2.42	-1.83
	Mutapi etal 2011	0.202	0.290	0.136	-5.626	0.000		2.69	-0.51
	Mutsaka-Makuvaza etal	0.133	0.164	0.107	-14.731	0.000		2.87	-1.16
	Coulibaly etal 2013 etal	0.426	0.489	0.366	-2.296	0.022		2.87	0.84
	Dabo etal 2011 2011	0.512	0.565	0.459	0.435	0.663		2.89	1.28
	Garba etal 2013	0.545	0.602	0.487	1.530	0.126		2.88	1.45
	Verani etal 2011	0.338	0.404	0.278	-4.674	0.000		2.85	0.36
	Davis etal 2015	0.443	0.512	0.376	-1.619	0.106		2.85	0.92
	Moyo etal 2015	0.126	0.191	0.081	-7.687	0.000		2.67	-1.19
	Ekpo etal 2010	0.581	0.653	0.505	2.080	0.038		2.83	1.62
	Sacolo-Gwebu etal 2019	0.010	0.017	0.005	-15.295	0.000		2.57	-4.39
	Mafiana etal 2003	0.718	0.775	0.653	6.072	0.000		2.84	2.39
	Sousa-Figueiredo etal	0.571	0.602	0.540	4.427	0.000		2.93	1.59
	Poole H etal 2014	0.106	0.155	0.071	-9.468	0.000		2.72	-1.45
	Rujeni N etal 2013	0.122	0.261	0.052	-4.136	0.000		2.16	-1.11
	Coulibaly etal 2017	0.244	0.278	0.213	-12.480	0.000		2.91	-0.22
	Coulibaly etal 2018	0.296	0.333	0.262	-9.903	0.000		2.91	0.12
	Kimani etal 2018	0.200	0.242	0.164	-11.090	0.000		2.87	-0.54
	Sakari etal 2017	0.055	0.084	0.036	-12.327	0.000		2.72	-2.31
	Stothard etal 2011	0.426	0.489	0.365	-2.306	0.021		2.87	0.84
	Raganuza etal 2015	0.801	0.837	0.758	10.909	0.000		2.87	2.98
	Amin etal 2012	0.311	0.349	0.276	-9.038	0.000		2.91	0.21
	Sousa-Figueiredo etal	0.039	0.100	0.015	-6.271	0.000		2.08	-2.40
	Nalugwa etal 2015	0.393	0.411	0.376	-11.699	0.000		2.94	0.68
	Opara etal 2007	0.198	0.277	0.138	-6.250	0.000		2.73	-0.54
	Niyituma etal 2017	0.169	0.221	0.128	-9.393	0.000		2.82	-0.79
	Said etal 2017	0.152	0.196	0.116	-10.874	0.000		2.83	-0.96
	Navaratnam etal 2012	0.264	0.291	0.239	-15.138	0.000		2.92	-0.08
	Bosompem etal 2004	0.300	0.409	0.210	-3.473	0.001		2.69	0.14
	Armoo etal 2020	0.863	0.905	0.807	8.725	0.000		2.75	3.47
	Won etal 2017	0.500	0.516	0.484	0.000	1.000		2.94	1.23
Random		0.277	0.333	0.227	-7.079	0.000			

Figure 4: Forest plot on prevalence of schistosomiasis in preschool aged children



Model	Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	Std Residual
	Kemal etal 2019	0.964	0.931	0.982	9.409	0.000	7.83	1.51
	Coulibaly etal 2012	0.886	0.827	0.927	8.243	0.000	8.57	-0.03
	Wami etal 2016	0.995	0.932	1.000	3.802	0.000	2.11	2.08
	Mutapi etal 2009	0.970	0.913	0.990	6.047	0.000	6.03	1.52
	Mutsaka-Makuvaza etal 2018	0.831	0.797	0.860	13.806	0.000	9.28	-0.66
	Sousa-Figueiredo etal 2012	0.564	0.533	0.595	3.994	0.000	9.42	-2.51
	Coulibaly etal 2017	0.722	0.687	0.755	10.985	0.000	9.37	-1.54
	Nalugwa etal 2015	0.843	0.819	0.864	19.499	0.000	9.37	-0.55
	Houmsou etal 2018	0.981	0.894	0.997	4.274	0.000	3.83	1.59
	Coulibaly etal 2018	0.780	0.746	0.811	13.139	0.000	9.34	-1.11
	Kimani etal 2018	0.860	0.822	0.891	12.598	0.000	9.16	-0.36
	Amin etal 2012	0.994	0.983	0.998	9.699	0.000	6.40	3.39
	Navaratnam etal 2012	0.817	0.783	0.847	13.872	0.000	9.30	-0.80
Random		0.889	0.835	0.927	8.890	0.000		

Figure 5: Forest plot on cure rate of PZQ 40 mg/kg for schistosomiasis in preschool aged children



Model	Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	Std Residual
	Kemal etal 2019	0.994	0.969	0.999	6.062	0.000	5.43	1.27
	Coulibaly etal 2012	0.967	0.925	0.986	7.632	0.000	8.29	-0.23
	Wami etal 2016	0.995	0.932	1.000	3.802	0.000	2.90	1.09
	Mutapi etal 2009	0.990	0.935	0.999	4.663	0.000	4.62	0.77
	Mutsaka-Makuvaza etal 2018	0.968	0.949	0.980	13.880	0.000	9.63	-0.21
	Sousa-Figueiredo etal 2012	0.890	0.869	0.908	20.468	0.000	10.24	-1.79
	Coulibaly etal 2017	0.948	0.928	0.963	16.559	0.000	9.98	-0.81
	Nalugwa etal 2015	0.989	0.980	0.994	14.964	0.000	9.30	1.01
	Houmsou etal 2018	0.992	0.887	1.000	3.412	0.001	2.90	0.76
	Coulibaly etal 2018	0.976	0.961	0.985	14.212	0.000	9.54	0.12
	Kimani etal 2018	0.969	0.947	0.982	11.932	0.000	9.37	-0.17
	Amin etal 2012	0.994	0.983	0.998	9.699	0.000	7.65	1.53
	Navaratnam etal 2012	0.890	0.862	0.913	15.686	0.000	10.14	-1.78
Random		0.973	0.954	0.985	12.635	0.000		

Figure 6: Forest plot on egg reduction rate of PZQ 40mg/kg for schistosomiasis in preschool aged children

6.5. Subgroup analysis

Sub group analyses were carried out based on test method, type of species and year of study.

6.5.1. Prevalence based on the test method

For the diagnosis of *S. mansoni* 11 studies used different test methods and there was variation in the reported prevalence. The prevalence of *S. mansoni* infection using a single Kato Katz technique varied from 0.5% to 44.4%. Compared to all test methods ELISA-kit had a high detection rate followed by POC-CCA.(Coulibaly et al., 2013), (Sousa-Figueiredo et al., 2012), (Stothard et al., 2011), (Niyituma et al., 2017).

All the 20 studies that reported prevalence of *S. haematobium* used urine filtration method except one study that used additional test method (Dipstick). And the pooled prevalence was 18.0% (95% CI: 12.2-25.6) (Table 4).

6.5.2. Prevalence based on species type

The overall prevalence of *S. mansoni* was 27.4% (95% CI: 22.9-32.5%), whereas that of *S. haematobium* was 18.0% (95% CI: 12.2-25.6) as indicated in (Table 4)

Table 3: Subgroup analysis to compare the prevalence of schistosomiasis by diagnostic methods

Diagnosis Method	# of studies	Prevalence% (95% CI)	I^2	Q	Heterogeneity test	
					DF	P
Double kato katz	7	32.5 (25.8-40.2)	90.94%	55.22	5	<0.001
Single kato katz	16	17.6 (12-21.2)	97.59%	598.99	13	<0.001
ELISA-kit	2	49.1 (45.8-52.4)	0.00%	1.546	1	0.214
SAC (FECT)	1	3.2 (1.8-5.6)	0.00%	0.00	0	1.000
POC-CCA	10	41.9 (27.5-57.9)	98.08%	540.25	9	<0.001
Quadruplicate	2	31.5 (15.0-54.5	94.39%	17.85	1	<0.001
Dipstick	1	30.0 (21.0-40.9)	0.00%	0.00	0	1.000
Urine filtration	20	17.4 (11.6-25.3)	97.53%	769.19	19	<0.001
Overall	59	36.5 (34.1-39.0)	97.94%	2812.69	58	<0.001

Table 4: Subgroup analysis to compare the prevalence of schistosomiasis by specie type

Species	# of studies	Prevalence% (95% CI)	I^2	Q	Heterogeneity test	
					DF	P
S. Mansoni	25	27.4 (22.9-32.5)	98.21%	1908.51	34	<0.001
S. Haematobium	20	18.0 (12.2-25.6)	97. 39%	768.68	20	<0.001
Overall	36	25 (21.3-29.3)	98.01%	2761.11	55	<0.001

6.5.3. Prevalence based on year of study

All included studies grouped by 10 years' difference which is from 2001-2010 &2011-2020. From the included studies 15 studies were conducted from 2001-2010 and 20 studies from 2011-2020. The prevalence of schistosomiasis was higher in the first 10 years 38.0% compare to 2nd 10 years 21.5% and there was statistically significant difference P-value <0.001 (Table 5).

Table 5: Subgroup analysis to compare the prevalence of schistosomiasis by year of the study conducted

Year of study	# of studies	Prevalence% (95% CI)	I^2	Q	Heterogeneity test	
					DF	P
2001-2010	15	38.0 (30.3-46.4)	96.732%	428.42	14	<0.001
2011-2020	21	21.5 (15.6-28.8)	98.707%	1543.74	20	<0.001
Overall	36	29.2 (24.1-35.0)	98.244%	1992.74	35	<0.001

Model	Group by Subgroup	Study name	Statistics for each study					Event rate and 95% CI	Weight (Separate tau)	Residual (Separate tau)
			Event rate	Lower limit	Upper limit	Z-Value	p-Value	-1.00 -0.50 0.00 0.50 1.00	Relative weight	Std Residual
	dipstick	Bosompem etal 2004	0.300	0.210	0.409	-3.473	0.001		100.00	
Random	dipstick		0.300	0.210	0.409	-3.473	0.001			
	double	Kemal etal 2019	0.250	0.199	0.309	-7.308	0.000		16.28	-0.97
	double	Garba etal 2013	0.436	0.379	0.495	-2.138	0.033		17.08	1.27
	double	Davis etal 2015	0.443	0.376	0.512	-1.619	0.106		16.51	1.32
	double	Sousa-Figueiredo etal 2012	0.377	0.347	0.408	-7.622	0.000		18.19	0.63
	double	Stothard etal 2011	0.219	0.171	0.276	-8.180	0.000		16.14	-1.42
	double	Armoo etal 2020	0.253	0.196	0.319	-6.496	0.000		15.80	-0.92
Random	double		0.325	0.258	0.402	-4.331	0.000			
	ELISA-kit	Stothard etal 2011	0.459	0.397	0.522	-1.284	0.199		21.70	-1.00
	ELISA-kit	Won etal 2017	0.500	0.484	0.516	0.000	1.000		78.30	1.00
Random	ELISA-kit		0.491	0.458	0.524	-0.526	0.599			
	POC-CCA	Coulibaly etal 2012	0.488	0.411	0.565	-0.316	0.752		10.00	0.28
	POC-CCA	Coulibaly etal 2013 etal	0.451	0.389	0.514	-1.534	0.125		10.08	0.13
	POC-CCA	Verani etal 2011	0.338	0.278	0.404	-4.674	0.000		10.04	-0.35
	POC-CCA	Sousa-Figueiredo etal 2012	0.571	0.540	0.602	4.427	0.000		10.20	0.63
	POC-CCA	Poole H etal 2014	0.091	0.059	0.139	-9.545	0.000		9.71	-1.96
	POC-CCA	Stothard etal 2011	0.426	0.365	0.489	-2.306	0.021		10.08	0.03
	POC-CCA	Raganuza etal 2015	0.801	0.758	0.837	10.909	0.000		10.09	1.75
	POC-CCA	Niyituma etal 2017	0.169	0.128	0.221	-9.393	0.000		9.97	-1.28
	POC-CCA	Said etal 2017	0.152	0.116	0.196	-10.874	0.000		10.00	-1.41
	POC-CCA	Armoo etal 2020	0.863	0.807	0.905	8.725	0.000		9.83	2.17
Random	POC-CCA		0.419	0.275	0.579	-0.991	0.322			
	quadriplicat	Coulibaly etal 2012	0.219	0.161	0.289	-6.656	0.000		48.96	-1.00
	quadriplicat	Coulibaly etal 2013 etal	0.426	0.366	0.489	-2.296	0.022		51.04	1.00
Random	quadriplicat		0.315	0.150	0.545	-1.589	0.112			
	SAC	G/hiwot etal 2019	0.032	0.018	0.056	-11.610	0.000		100.00	0.00
Random	SAC		0.032	0.018	0.056	-11.610	0.000			
	single kato	G/hiwot etal 2019	0.083	0.059	0.115	-12.817	0.000		7.36	-1.42
	single kato	Alemu etal 2016	0.112	0.085	0.147	-13.073	0.000		7.56	-0.88
	single kato	Niyantekyi etal 2010	0.372	0.318	0.429	-4.311	0.000		7.76	1.72
	single kato	Coulibaly etal 2013 etal	0.143	0.105	0.193	-9.784	0.000		7.40	-0.40
	single kato	Verani etal 2011	0.176	0.131	0.233	-8.641	0.000		7.42	-0.00
	single kato	Sacolo-Gwebu etal 2019	0.009	0.005	0.017	-14.035	0.000		6.17	-4.73
	single kato	Poole H etal 2014	0.005	0.001	0.033	-5.320	0.000		2.15	-3.28
	single kato	Coulibaly etal 2017	0.244	0.213	0.278	-12.480	0.000		7.90	0.70
	single kato	Sakari etal 2017	0.055	0.036	0.084	-12.327	0.000		7.05	-2.08
	single kato	Raganuza etal 2015	0.444	0.395	0.494	-2.193	0.028		7.85	2.24
	single kato	Amin etal 2012	0.443	0.352	0.539	-1.163	0.245		7.31	2.15
	single kato	Nalugwa etal 2015	0.393	0.376	0.411	-11.699	0.000		8.05	1.91
	single kato	Navaratnam etal 2012	0.264	0.239	0.291	-15.138	0.000		7.98	0.89
	single kato	Won etal 2017	0.280	0.265	0.295	-25.497	0.000		8.05	1.03
Random	single kato		0.176	0.133	0.230	-8.995	0.000			

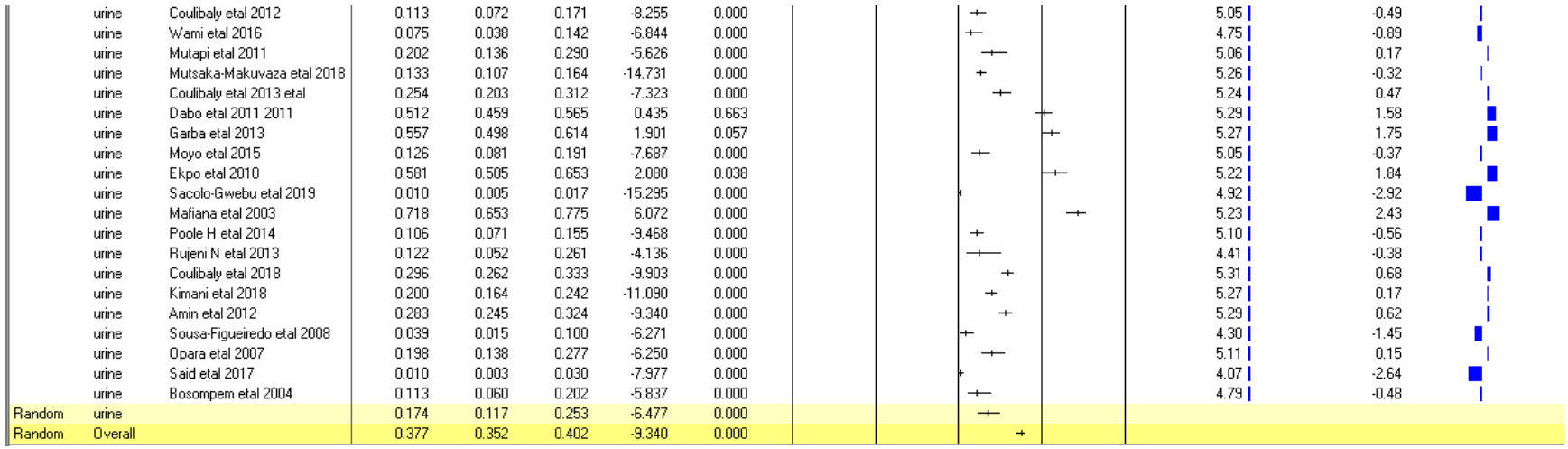


Figure 7: Forest plot of sub group analysis by test method used on prevalence of schistosomiasis in preschool aged children

Model	Group by Comparison	Study name	Statistics for each study					Event rate and 95% CI	Weight (Separate tau)	Residual (Separate tau)
			Event rate	Lower limit	Upper limit	Z-Value	p-Value	-1.00 -0.50 0.00 0.50 1.00	Relative weight	Std Residual
	haematobiu	Coulibaly etal 2012	0.113	0.072	0.171	-8.255	0.000		4.81	-0.53
	haematobiu	Wami etal 2016	0.075	0.038	0.142	-6.844	0.000		4.51	-0.94
	haematobiu	Mutapi etal 2011	0.202	0.136	0.290	-5.626	0.000		4.82	0.14
	haematobiu	Mutsaka-Makuvaza etal	0.133	0.107	0.164	-14.731	0.000		5.02	-0.36
	haematobiu	Coulibaly etal 2013 etal	0.254	0.203	0.312	-7.323	0.000		4.99	0.44
	haematobiu	Dabo etal 2011 2011	0.512	0.459	0.565	0.435	0.663		5.04	1.56
	haematobiu	Garba etal 2013	0.557	0.498	0.614	1.901	0.057		5.03	1.74
	haematobiu	Moyo etal 2015	0.126	0.081	0.191	-7.687	0.000		4.80	-0.41
	haematobiu	Ekpo etal 2010	0.581	0.505	0.653	2.080	0.038		4.98	1.83
	haematobiu	Sacolo-Gwebu etal 2019	0.010	0.005	0.017	-15.295	0.000		4.68	-2.99
	haematobiu	Mafiana etal 2003	0.718	0.653	0.775	6.072	0.000		4.98	2.43
	haematobiu	Poole H etal 2014	0.106	0.071	0.155	-9.468	0.000		4.86	-0.60
	haematobiu	Rujeni N etal 2013	0.122	0.052	0.261	-4.136	0.000		4.19	-0.41
	haematobiu	Coulibaly etal 2018	0.296	0.262	0.333	-9.903	0.000		5.06	0.65
	haematobiu	Kimani etal 2018	0.200	0.164	0.242	-11.090	0.000		5.02	0.13
	haematobiu	Amin etal 2012	0.283	0.245	0.324	-9.340	0.000		5.05	0.59
	haematobiu	Sousa-Figueiredo etal 2008	0.039	0.015	0.100	-6.271	0.000		4.08	-1.50
	haematobiu	Opara etal 2007	0.198	0.138	0.277	-6.250	0.000		4.86	0.12
	haematobiu	Said etal 2017	0.010	0.003	0.030	-7.977	0.000		3.86	-2.69
	haematobiu	Bosompem etal 2004	0.300	0.210	0.409	-3.473	0.001		4.82	0.65
	haematobiu	Bosompem etal 2004	0.113	0.060	0.202	-5.837	0.000		4.55	-0.52
Random	haematobiu		0.180	0.122	0.256	-6.569	0.000			
	mansoni	Kemal etal 2019	0.250	0.199	0.309	-7.308	0.000		2.93	-0.18
	mansoni	G/hiwot etal 2019	0.032	0.018	0.056	-11.610	0.000		2.61	-3.24
	mansoni	G/hiwot etal 2019	0.083	0.059	0.115	-12.817	0.000		2.86	-2.00
	mansoni	Alemu etal 2016	0.112	0.085	0.147	-13.073	0.000		2.91	-1.55
	mansoni	Coulibaly etal 2012	0.488	0.411	0.565	-0.316	0.752		2.91	1.30
	mansoni	Coulibaly etal 2012	0.219	0.161	0.289	-6.656	0.000		2.85	-0.42
	mansoni	Niyantekyi etal 2010	0.372	0.318	0.429	-4.311	0.000		2.97	0.64
	mansoni	Coulibaly etal 2013 etal	0.451	0.389	0.514	-1.534	0.125		2.96	1.10
	mansoni	Coulibaly etal 2013 etal	0.426	0.366	0.489	-2.296	0.022		2.96	0.96
	mansoni	Coulibaly etal 2013 etal	0.143	0.105	0.193	-9.784	0.000		2.87	-1.14
	mansoni	Garba etal 2013	0.436	0.379	0.495	-2.138	0.033		2.97	1.02
	mansoni	Verani etal 2011	0.338	0.278	0.404	-4.674	0.000		2.94	0.43
	mansoni	Verani etal 2011	0.176	0.131	0.233	-8.641	0.000		2.88	-0.80
	mansoni	Davis etal 2015	0.443	0.376	0.512	-1.619	0.106		2.94	1.05
	mansoni	Sacolo-Gwebu etal 2019	0.009	0.005	0.017	-14.035	0.000		2.49	-4.86
	mansoni	Sousa-Figueiredo etal 2012	0.377	0.347	0.408	-7.622	0.000		3.04	0.68
	mansoni	Sousa-Figueiredo etal 2012	0.571	0.540	0.602	4.427	0.000		3.04	1.81
	mansoni	Poole H etal 2014	0.091	0.059	0.139	-9.545	0.000		2.74	-1.81
	mansoni	Poole H etal 2014	0.005	0.001	0.033	-5.320	0.000		1.01	-3.58
	mansoni	Coulibaly etal 2017	0.244	0.213	0.278	-12.480	0.000		3.01	-0.23
	mansoni	Sakari etal 2017	0.055	0.036	0.084	-12.327	0.000		2.76	-2.56
	mansoni	Stothard etal 2011	0.219	0.171	0.276	-8.180	0.000		2.92	-0.42
	mansoni	Stothard etal 2011	0.459	0.397	0.522	-1.284	0.199		2.96	1.15
	mansoni	Stothard etal 2011	0.426	0.365	0.489	-2.306	0.021		2.96	0.96

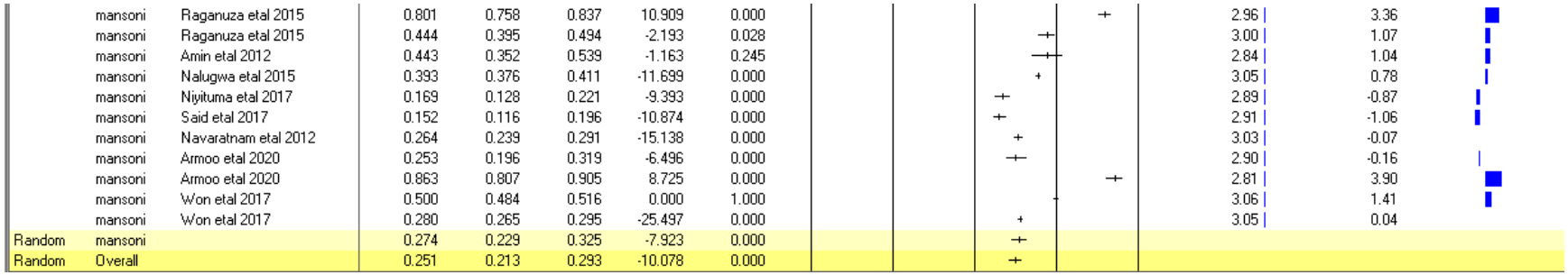


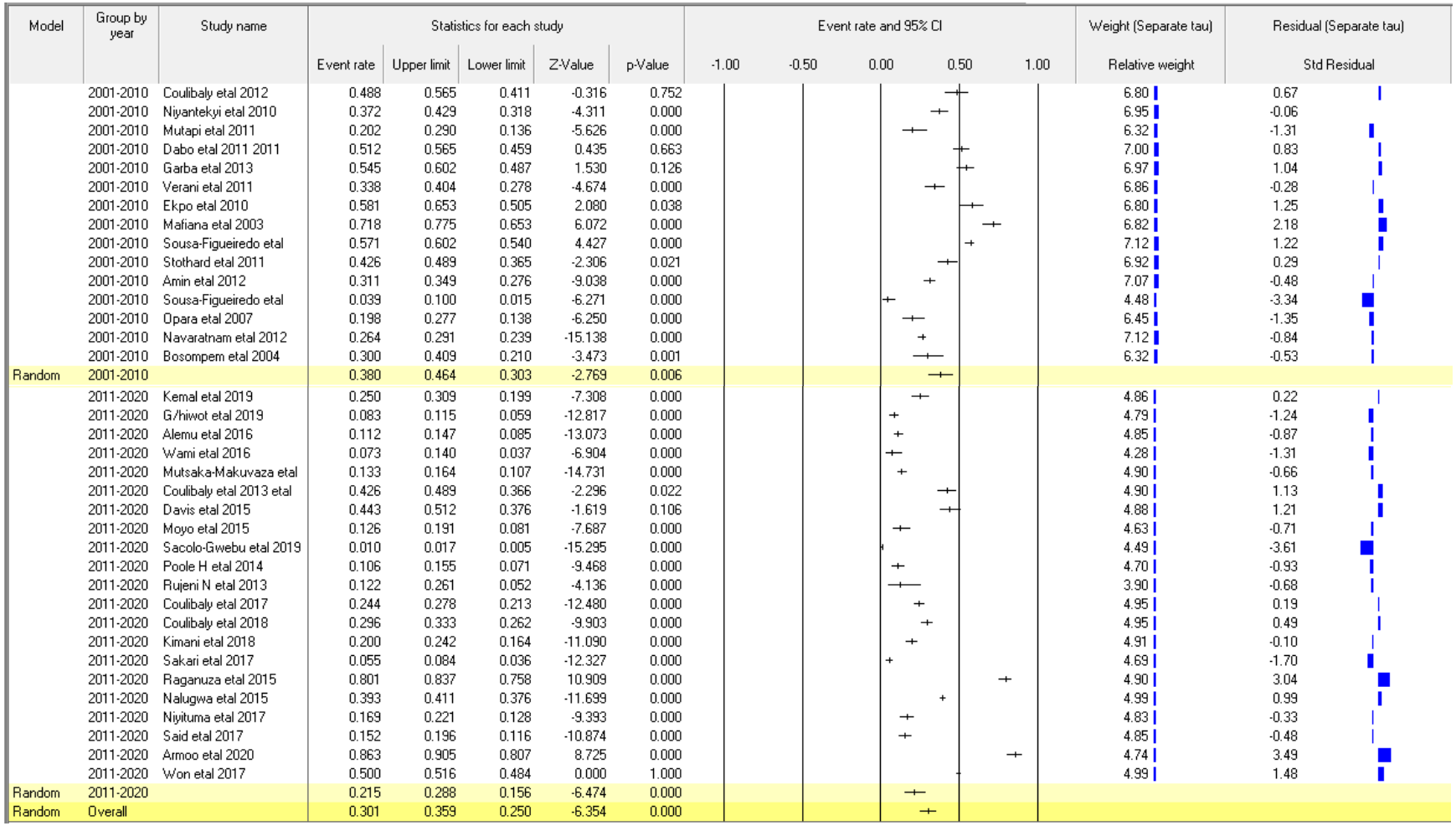
Figure 8: Forest plot of subgroup analysis by type of species on prevalence of schistosomiasis in preschool aged children

6.6. Meta-regression analysis

To understand the trend and source of heterogeneity and pooled the prevalence using CMA.

Table 6: Multivariable meta-regression model

Variables	Coefficient	P-value	95%
Study year category			
2001-2010 (Reference)	-0.5080	0.0198	-0.9353 to -0.0806
2011-2020	-0.7836	0.0061	-1.3438 to -0.2234
Diagnostic method used			
Single kato katz (Reference)	-1.5114	0.000	-1.8699 to -1.1529
Double kato katz	0.7919	0.0370	0.0477 to 1.5362
Quadruplicate kato katz	0.9615	0.1080	-0.2110 to 2.1340
POC-CCA	1.4163	0.000	0.7735 to 2.0591
ELISA-kit	1.6571	0.0050	0.4992 to 2.8150
SAC	-1.6678	0.0510	-3.3427 to 0.0070
PCR (DNA-kit)	0.6067	0.4613	-1.0072 to 2.2206



Model	Group by year	Study name	Event rate	Upper limit	Lower limit	Z-Value	p-Value	Weight (Separate tau) Relative weight	Residual (Separate tau) Std Residual
	2001-2010	Coulibaly etal 2012	0.488	0.565	0.411	-0.316	0.752	6.80	0.67
	2001-2010	Niyantekyi etal 2010	0.372	0.429	0.318	-4.311	0.000	6.95	-0.06
	2001-2010	Mutapi etal 2011	0.202	0.290	0.136	-5.626	0.000	6.32	-1.31
	2001-2010	Dabo etal 2011 2011	0.512	0.565	0.459	0.435	0.663	7.00	0.83
	2001-2010	Garba etal 2013	0.545	0.602	0.487	1.530	0.126	6.97	1.04
	2001-2010	Verani etal 2011	0.338	0.404	0.278	-4.674	0.000	6.86	-0.28
	2001-2010	Ekpo etal 2010	0.581	0.653	0.505	2.080	0.038	6.80	1.25
	2001-2010	Mafiana etal 2003	0.718	0.775	0.653	6.072	0.000	6.82	2.18
	2001-2010	Sousa-Figueiredo etal	0.571	0.602	0.540	4.427	0.000	7.12	1.22
	2001-2010	Stothard etal 2011	0.426	0.489	0.365	-2.306	0.021	6.92	0.29
	2001-2010	Amin etal 2012	0.311	0.349	0.276	-9.038	0.000	7.07	-0.48
	2001-2010	Sousa-Figueiredo etal	0.039	0.100	0.015	-6.271	0.000	4.48	-3.34
	2001-2010	Opara etal 2007	0.198	0.277	0.138	-6.250	0.000	6.45	-1.35
	2001-2010	Navaratnam etal 2012	0.264	0.291	0.239	-15.138	0.000	7.12	-0.84
	2001-2010	Bosompem etal 2004	0.300	0.409	0.210	-3.473	0.001	6.32	-0.53
Random	2001-2010		0.380	0.464	0.303	-2.769	0.006		
	2011-2020	Kemal etal 2019	0.250	0.309	0.199	-7.308	0.000	4.86	0.22
	2011-2020	G/hiwot etal 2019	0.083	0.115	0.059	-12.817	0.000	4.79	-1.24
	2011-2020	Alemu etal 2016	0.112	0.147	0.085	-13.073	0.000	4.85	-0.87
	2011-2020	Wami etal 2016	0.073	0.140	0.037	-6.904	0.000	4.28	-1.31
	2011-2020	Mutsaka-Makuvaza etal	0.133	0.164	0.107	-14.731	0.000	4.90	-0.66
	2011-2020	Coulibaly etal 2013 etal	0.426	0.489	0.366	-2.296	0.022	4.90	1.13
	2011-2020	Davis etal 2015	0.443	0.512	0.376	-1.619	0.106	4.88	1.21
	2011-2020	Moyo etal 2015	0.126	0.191	0.081	-7.687	0.000	4.63	-0.71
	2011-2020	Sacolo-Gwebu etal 2019	0.010	0.017	0.005	-15.295	0.000	4.49	-3.61
	2011-2020	Poole H etal 2014	0.106	0.155	0.071	-9.468	0.000	4.70	-0.93
	2011-2020	Rujeni N etal 2013	0.122	0.261	0.052	-4.136	0.000	3.90	-0.68
	2011-2020	Coulibaly etal 2017	0.244	0.278	0.213	-12.480	0.000	4.95	0.19
	2011-2020	Coulibaly etal 2018	0.296	0.333	0.262	-9.903	0.000	4.95	0.49
	2011-2020	Kimani etal 2018	0.200	0.242	0.164	-11.090	0.000	4.91	-0.10
	2011-2020	Sakari etal 2017	0.055	0.084	0.036	-12.327	0.000	4.69	-1.70
	2011-2020	Raganuza etal 2015	0.801	0.837	0.758	10.909	0.000	4.90	3.04
	2011-2020	Nalugwa etal 2015	0.393	0.411	0.376	-11.699	0.000	4.99	0.99
	2011-2020	Niyituma etal 2017	0.169	0.221	0.128	-9.393	0.000	4.83	-0.33
	2011-2020	Said etal 2017	0.152	0.196	0.116	-10.874	0.000	4.85	-0.48
	2011-2020	Armoo etal 2020	0.863	0.905	0.807	8.725	0.000	4.74	3.49
	2011-2020	Won etal 2017	0.500	0.516	0.484	0.000	1.000	4.99	1.48
Random	2011-2020		0.215	0.288	0.156	-6.474	0.000		
Random	Overall		0.301	0.359	0.250	-6.354	0.000		

Figure 9: Forest plot of subgroup analysis by year of the study conducted

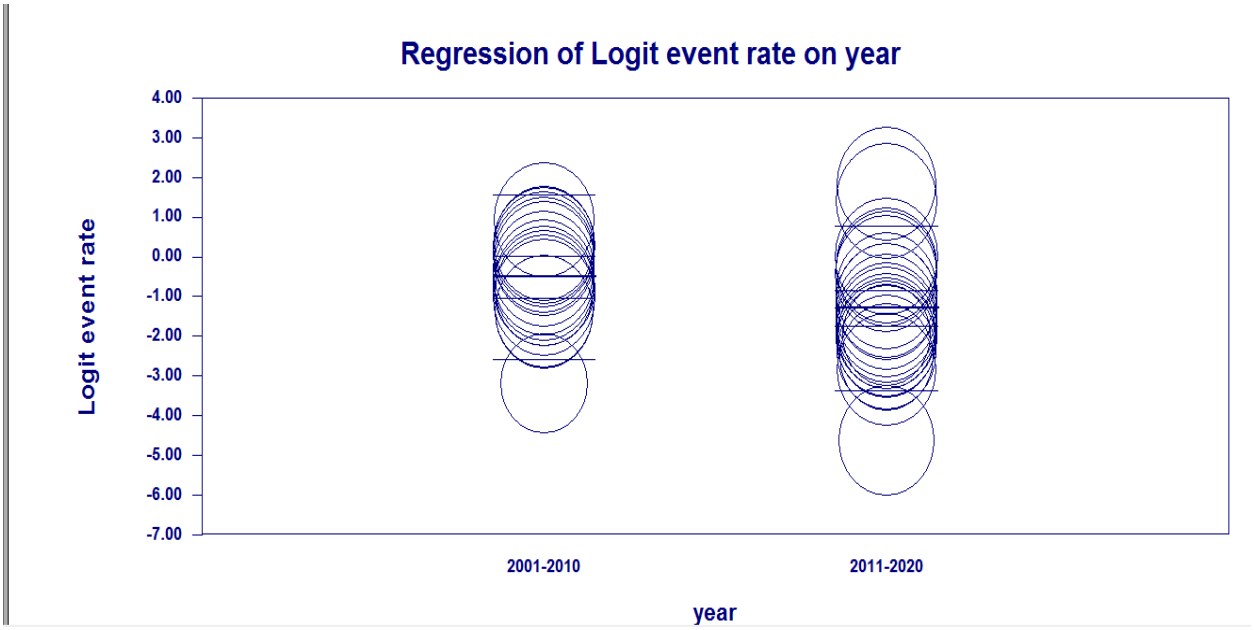


Figure 10: Meta regression scatter plot of study year versus prevalence of schistosomiasis in preschool aged children

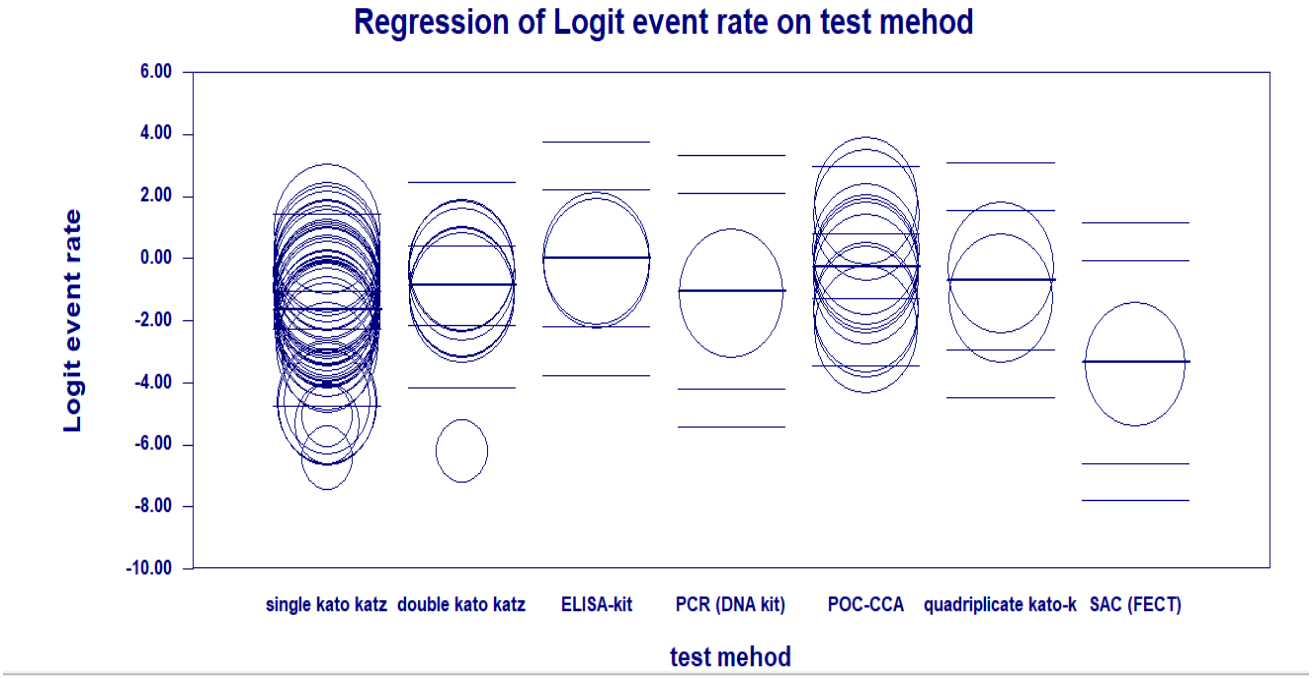


Figure 11: Meta regression scatter plot of test methods used versus prevalence of schistosomiasis in preschool aged children

6.7. Publication bias

The funnel plot which showed the effect estimate against its standard error shows that there is a publication bias (Figure 12).

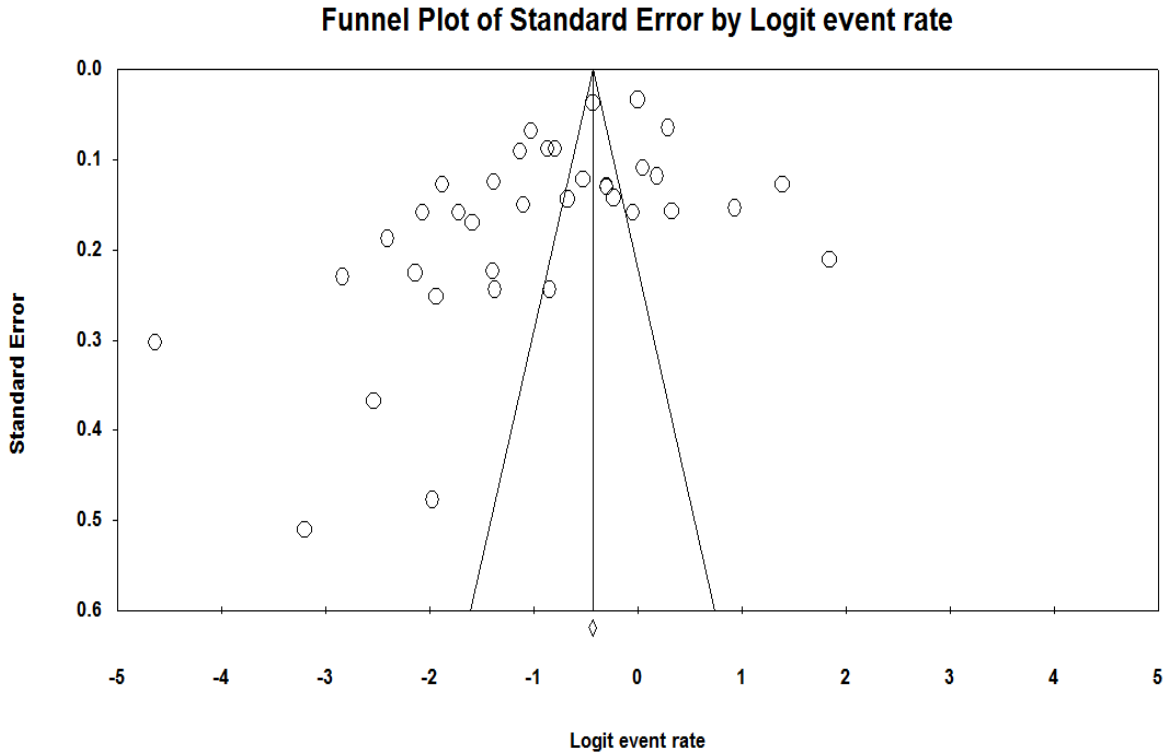


Figure 12: Funnel plots that assesses publication bias

7. DISCUSSION

The aim of this systematic review and meta-analysis was to determine the prevalence and intensity of schistosomiasis and treatment outcome of PZQ in PSAC. Different studies had been carried out in different African countries at different time on the prevalence of schistosomiasis in PSAC, however, there were no summarized data of this parasite infection to our knowledge; so we believe this is the first pooled evidence on prevalence of schistosomiasis in PSAC. The overall prevalence of schistosomiasis was 27.7% considered relatively moderate prevalence; which is between 20 and 50% (Mitchell & Pagano, 2012). The findings are reliable with emerging evidence that the burden of schistosomiasis is high in PSAC. The prevalence reported were all from Africa showing that schistosomiasis is a public health problem in Africa though there was some report on the prevalence of *S. mansoni* infection in Latin America (Teresinha *et al.*, 2018) and *S. Japonium* infection in China's 10-13 years old children (Zhou *et al*., 2005), and in all age (Raso *et al.*, 2009) but not studied specifically on PSAC. Schistosomiasis is the second most parasitic infection counting 34.61% of the reported neglected tropical disease in Brazilian children and adolescents following cutaneous leishmaniasis (48.29%). (Brandão *et al*., 2017) In the present study, schistosomiasis in PSAC had a prevalence ranging from less than 1% to 80%. The variation may be attributed to the difference in socio-ecological setting, hygiene & sanitary facilities, diagnostic methods employed.

The prevalence of *S. mansoni* infection was 27.4 % (95% CI: 22.9%-32.5%) and prevalence of *S. haematobium* infection was 18% (95% CI: 12.2%-25.6%) and higher compared to the study conducted in Côte d'Ivoire in SAC for both *S. mansoni* and *S. haematobium* infection 6.1% and 14% respectively (Angora *et al*., 2019), from Ethiopia meta-analysis of *S. mansoni* 18.7% lower compared to Tanzania study 90.6% (Hussein *et al*., 2020), Ethiopia 35% (Woldegerima et al., 2019) both on SAC & *S. mansoni*, Mozambique aged 5-55 years 60.4% for *S. haematobium*. (Phillips *et al*., 2018), Zambia study for *S. haematobium* age group of 11-15 years 60.7% (Chomba & Mutale, 2014).

The pooled prevalence also had a variation on the results due to the choice of test methods; Studies that compared the prevalence of *S. mansoni* infection based on different laboratory diagnostic methods reported divergent results where higher percentage observed with the more

sensitive test methods. The divergence was common especially with Kato Katz & POC-CCA methods 17.6% vs 33.8% in Kenya (Verani *et al*., 2011), 0 vs 15.2% in Tanzania (Said *et al*., 2017), 44.4% vs 80.1% in Tanzania (Ruganuza et al., 2015), 0 vs 16.9% in Rwanda (Niyituma et al., 2017) and 25.3% vs 86.3% in Ghana (Armoo *et al*., 2020) respectively. Similarly Tanzanian study on antiretroviral therapy in children; Kato Katz 10.7% vs 33.8% POC-CCA (Mazigo *et al.*, 2019). The recommend method by WHO is the Kato Katz fecal smear method (the gold standard) for diagnosis of *S. mansoni* infection (WHO, 2017). However, this test method has limitation in detecting light intensity load parasite and also at the initial/final stage of the disease. In this kind of situation more sensitive diagnostic methods should be considered in detecting the parasite. Other methods such as serological/ immunoassay techniques of antibodies, antigen or DNA (RT-PCR) used to detect the parasite at the initial phase and in cases of light infections; due to this they have higher sensitivity and specificity for diagnosis in certain stages of the disease (Weerakoon *et al*., 2015).

The prevalence of schistosomiasis was higher in the first 10 years compared to 2011-2020. The decline in prevalence was probably due to socio-economic development, improvement in water quality & sanitation use of the community and campaign of a mass deworming program of their older counterparts.

Regardless of age categories, only 12 studies reported the prevalence by age group; and in all of them the prevalence was higher in older children 4-7 years old than their younger counterparts 1-3 years old; The higher prevalence in the older age group was attributed to the frequent visit they had made to the river/lake with their parents/caregivers or by themselves for bathing, fetching, playing and swimming (Dabo *et al*., 2011; Kemal *et al*., 2019; Kimani *et al*., 2018; Moyo *et al.*, 2016; Nyantekyi *et al*., 2010; Olsen *et al*., 2015). And in most of the studies, the river/lake stream was the only source for water supply in the community so that it was particularly impossible to prevent the community from visiting the water streams.

Parents/ guardians understanding of schistosomiasis as a health problem (Coulibaly et al., 2013; Mafiana et al., 2003) and poor knowledge on how the disease is transmitted (Olsen et al., 2015; Sakari et al., 2017) was low, might which contribute to the increase prevalence of schistosomiasis in the children.

The other objective of this meta-analysis was to evaluate treatment outcome of the medication (PZQ) in PSAC. From the thirteen studies that evaluated the efficacy we found high CR and ERR 88.9% and 97.3%, respectively. This was comparable with the Ethiopian SAC study whose CR was 90% & ERR 99.5% (Woldegerima *et al*., 2019). Meta-analysis done on previous studies on PZQ efficacy in PSAC showed that CR of 87.3% and ERR of 97.1% for *S. haematobium* infection and CR of 82% and ERR of 96.4% for *S. mansoni* infection (Zwang & Olliaro, 2017). These rates were higher than the reports from Gabonese study carried out in (6-30 years old participants) with CR of 78% and ERR of 93% (Dejon-Agobé *et al*., 2019). A previous study of meta-analysis on PZQ efficacy in all ages *S. haematobium* infection had CR of 77.1% and ERR of 94.16%, while *S. mansoni* infection had CR of 76.7% and ERR of 86.3% (Zwang & Olliaro, 2014). All studies carried out on treatment of schistosomiasis with PZQ showed a decrease in the disease burden.

The intensity of the infection had also effect on the efficacy of PZQ; those children with light and moderate-intensity would have high ERR &CR compared with heavy intensity participant's; (Mutapi et al., 2011), (Coulibaly et al., 2012), (Nalugwa et al., 2015). Additionally; those with history of previous treatment had also a lower CR and ERR (41.7%, 72.8%) than treatment-naive children (77.6 and 92.1%, respectively) (Sousa-Figueiredo et al., 2012). In Zimbabwe cohort study reinfection was also higher with heavy infection intensity (Mutsaka-makuvaza et al., 2018).

No difference in efficacy was observed in the Ugandan cohort study on egg positive PSAC who randomly received PZQ syrup or crushed tablet with CR of (80.9 for the syrup vs 81.7% for the crushed tablet) and ERR of (86.1 for the syrup vs 89.0% for the crushed tablet) *(Navaratnam et al*., 2012). The syrup formulation PZQ was manufactured in Egypt for school children. This formulation however, used aniseed as flavoring agent which was contraindicated in some children, and had a large packing & storage volume and was expensive compared to the existing tablet and offered no significant advantage over crushed/broken tablet; so WHO general guideline recommends use of crushed tablet until an appropriate pediatric formulation gets available (Stothard et al., 2011, 2013).

Studies conducted in Kenya on morbidity associated before and after treatment indicate; after treating with PZQ there was a decrease in morbidity like malaria and rapid improvement from

organomegaly (hepatomegaly and splenomegaly) which are schistosomiasis- associated hepatic disorder (Davis et al., 2015). MDA of children with PZQ and treating children in addition to reducing the prevalence it can also contribute to reducing the overall burden of disease and improves liver morbidity regression in treated PSAC (Cleland et al., 2014)

Ease of administration, acceptability, accessibility, low cost, relative safety, and less abdominal pain and diarrhea which gets resolved within 24 hours are some of the advantages of treatment with PZQ (Aruleba et al., 2019). Most children, however, have difficulty in swallowing due to its bigger size and bitter taste. To tackle the taste problem in most of the included studies in the present systematic review, the study participants were given orange juice or bread with the medication.

Regular deworming reduces both the morbidity caused by schistosomiasis and the occurrence of severe complications (WHO, 2011). Deworming of PSAC have a positive impact on child growth and decrease the risk of stunting and anemia (Lo et al., 2018). Although young children (PSAC) still do not have satisfactory access to this medication and they are excluded from MDA campaign program. (Sousa-figueiredo et al., 2012) Focus should be considered in solving this unfortunate health inequity.

8. LIMITATIONS OF THE STUDY

The present study has some limitations such as sample size variations, inconsistency of laboratory diagnostic methods, inter country difference in the prevalence and heterogeneity among the studies which was tackled by following a random-mixed effect model to pool data and doing meta-regression on the test method and publication year. Therefore, our finding may not represent/reflect the true burden of the disease.

9. CONCLUSION

The emerging fact from this SR & MA shows there was a moderate level of prevalence of schistosomiasis in PSAC. The prevalence of intestinal schistosomiasis (27.4%) was higher compare to urogenital schistosomiasis (18%). And the disease is still a public health problem in Africa. It can be concluded that the prevalence rate varies with the diagnostic methods employed. Also in this review we have demonstrated treating PSAC affected by schistosomiasis with anti-helminthic drug PZQ is effective though lack of appropriate formulation presents a challenge for this age group.

10. RECOMMENDATIONS

the prevalence rate of schistosomiasis in PSAC was unpredictably high. Also from the review of included studies there was no major safety problem and good efficacy of PZQ observed in these age group indicating to review strategies to consider these age group both in curative and deworming program. Interventions such as protecting of the exposed community to open/infected water to decrease schistosomiasis transmission, giving health education to caregivers on the risk factors of schistosomiasis in PSAC.

There is a need for pediatric formulation with suitable dosing supported by pharmacokinetic and pharmacogenetic evidence. we recommend including these age groups in MDA deworming programs till proper formulation is accessible.

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11. REFERENCE

Adenowo, A., Oyinloye, B. E., Ogunyinka, I. B., & Kappo, A. P. (2015). Africa. *Brazilian Journal of Infectious Diseases*, *19*(2), 196–205. https://doi.org/10.1016/j.bjid.2014.11.004

Ajibola, O., Gulumbe, B., Eze, A., & Obishakin, E. (2018). Tools for Detection of Schistosomiasis in Resource Limited Settings. *Medical Sciences*, *6*(2), 39. https://doi.org/10.3390/medsci6020039

Alemu, A., Tegegne, Y., Damte, D., & Melku, M. (2016). 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*, *16*(1), 1–9. https://doi.org/10.1186/s12889-016-2864-9

Altman DG. (1997). *PRACTICAL STATISTICS FOR MEDICAL The Analysis of Time Series*.

Angora, E. K., Boissier, J., Menan, H., Rey, O., Tuo, K., Touré, A. O., Coulibaly, J. T., Méité, A., Raso, G., N'Goran, E. K., Utzinger, J., & Balmer, O. (2019). Prevalence and risk factors for schistosomiasis among schoolchildren in two settings of Côte d'Ivoire. *Tropical Medicine and Infectious Disease*, *4*(3). https://doi.org/10.3390/tropicalmed4030110

Aragon, A. D., Imani, R. A., Blackburn, V. R., Pauline, M. C., D., M. S., Goronga, T., Webb, T., Loker, E. S., & Cunningham, C. (2009). Towards an understanding of the mechanism of action of praziquantel. *Mol Biochem Parasitol.2009*, *164*(1), 57–65. https://doi.org/10.1016/j.molbiopara.2008.11.007.Towards

Armoo, S., Cunningham, L. J., Campbell, S. J., Aboagye, F. T., Boampong, F. K., Hamidu, B. A., Osei-Atweneboana, M. Y., Stothard, J. R., & Adams, E. R. (2020). Detecting Schistosoma mansoni infections among pre-school-aged children in southern Ghana: A diagnostic comparison of urine-CCA, real-time PCR and Kato-Katz assays. *BMC Infectious Diseases*, *20*(1), 1–10. https://doi.org/10.1186/s12879-020-05034-2

Aruleba, R. T., Adekiya, T. A., Oyinloye, B. E., Mbatha, L. S., Pretorius, A., Kappo, A. P., & Drugs, K. (2019). PZQ Therapy: How Close are we in the Development of Effective Alterna- tive Anti-schistosomal Drugs? *BENTHAM SCINCE*, *19*(4), 337–349. https://doi.org/10.2174/1871526519666181231153139

Ba¨renbold, O., Raso, G., Coulibaly, J. T., K., N. E., Utzinger, J. rg, & Vounatsou, P. (2017). Estimating sensitivity of the Kato-Katz technique for the diagnosis of Schistosoma mansoni and hookworm in relation to infection intensity. *PLoS Neglected Tropical Diseases*, *11*(10), 1–14. https://doi.org/10.1371/journal.pntd.0005953

Brandão, E., Romero, S., Almerice, M., Luciano, F., & Santos, N. (2017). Neglected tropical diseases in Brazilian children and adolescents : data analysis from 2009 to 2013. *Infectious Diseases of Poverty*, *6*(154), 1–10. https://doi.org/10.1186/s40249-017-0369-0

Chadeka, E. A., Nagi, S., Sunahara, T., Cheruiyot, B., Bahati, F., Ozeki, Y., Inoue, M., Osada-oka, M., Okabe, M., Hirayama, Y., Changoma, M., Adachi, K., Mwende, F., Kikuchi, M., Nakamura, R., Dan, Y., Kalenda, J., Kaneko, S., Hirayama, K., … Ichinose, Y. (2017). Spatial distribution and risk factors of Schistosoma haematobium and hookworm infections among schoolchildren in Kwale , Kenya. *PLoS Neglected Tropical Diseases*, *11*, 1–17.

Chomba, C., & Mutale, S. (2014). Factors Characterising High Prevalence Rates of Urinary Schistosomiasis in Mufumbwe District , North Western Province of Zambia. *Global Institution for Research & Education*, *3*(2), 86–95.

Cleland, C. R., Tukahebwa, E. M., Fenwick, A., & Blair, L. (2014). Mass drug administration with praziquantel reduces the prevalence of Schistosoma mansoni and improves liver

morbidity in untreated preschool children. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *108*, 575–581. https://doi.org/10.1093/trstmh/tru097

Cochrane Handbook for Systematic Reviews of Interventions. (2019). In Higgins (Ed.), *Cochrane Handbook for Systematic Reviews of Interventions*. https://doi.org/10.1002/9781119536604

Colley etal. (2015). HHS Public Access; Human schistosomiasis. *Lancet*, *383*(9936), 2253–2264. https://doi.org/10.1016/S0140-6736(13)61949-2.Human

Coulibaly, J. T., N'Gbesso, Y. K., Knopp, S., Keiser, J., N'Goran, E. K., & Utzinger, J. (2012). Efficacy and Safety of Praziquantel in Preschool-Aged Children in an Area Co-Endemic for Schistosoma mansoni and S. haematobium. *PLoS Neglected Tropical Diseases*, *6*(12). https://doi.org/10.1371/journal.pntd.0001917

Coulibaly, J. T., N'gbesso, Y. K., N'guessan, N. A., Winkler, M. S., Utzinger, J., & N'goran, E. K. (2013). Epidemiology of schistosomiasis in two high-risk communities of south cote d'ivoire with particular emphasis on pre-school-aged children. *American Journal of Tropical Medicine and Hygiene*, *89*(1), 32–41. https://doi.org/10.4269/ajtmh.12-0346

Coulibaly, J. T., Panic, G., Silué, K. D., Kovač, J., Hattendorf, J., & Keiser, J. (2017). 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. *The Lancet Global Health*, *5*(7), e688–e698. https://doi.org/10.1016/S2214-109X(17)30187-0

Coulibaly, J. T., Panic, G., Yapi, R. B., Kova, J., Barda, B., Gbesso, Y. K. N., Hattendorf, J., & Keiser, J. (2018). 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*, *16*(81), 1–10.

Da Silva, J., Cristhiany, M., Pinheiro, C., Sousa, M. S., Gomes, S., Maria, I., Castro, N. De, Novaes, A., Júnior, R., Schemelzer, F., & Bezerra, D. M. (2017). Major Article Detection of schistosomiasis in an area directly affected by the São Francisco River large-scale water transposition project in the Northeast of Brazil. *Med Trop*, *50*(5), 658–665. https://doi.org/10.1590/0037-8682-0299-2017

Dabo, A., Badawi, H. M., Bary, B., & Doumbo, O. K. (2011). Urinary schistosomiasis among preschool-aged children in Sahelian rural communities in Mali. *Parasites and Vectors*, *4*(1), 1–7. https://doi.org/10.1186/1756-3305-4-21

Davis, S. M., Wiegand, R. E., Mulama, F., Kareko, E. I., Harris, R., Ochola, E., Samuels, A. M., Rawago, F., Mwinzi, P. M., Fox, L. M., Odiere, M. R., & Won, K. Y. (2015). *Morbidity Associated with Schistosomiasis Before and After Treatment in Young Children in Rusinga Island , Western Kenya*. *92*(5), 952–958. https://doi.org/10.4269/ajtmh.14-0346

Dejon-Agobé, J. C., Edoa, J. R., Honkpehedji, Y. J., Zinsou, J. F., Adégbitè, B. R., Ngwese, M. M., Mangaboula, A., Lell, B., Grobusch, M. P., Mordmüller, B., & Adegnika, A. A. (2019). Schistosoma haematobium infection morbidity, praziquantel effectiveness and reinfection rate among children and young adults in Gabon. *Parasites and Vectors*, *12*(1), 1–11. https://doi.org/10.1186/s13071-019-3836-6

Dersimonian, R., & Laird, N. (1986). Meta-Analysis in Clinical Trials *. *Elsevier Scince*, *188*, 177–188.

Egger, M., Smith, G. D., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple , graphical test measures of funnel plot asymmetry. *Bmj*, *315*(7109), 629–634. https://doi.org/10.1136/bmj.315.7109.629

Ekpo, Laja-Deile, A., Oluwole, A. S., Sam-Wobo, S. O., & Mafiana, C. F. (2010). Urinary schistosomiasis among preschool children in a rural community near Abeokuta, Nigeria. *Parasites and Vectors*, *3*(1), 1–5. https://doi.org/10.1186/1756-3305-3-58

Ekpo, U. F., Oluwole, A. S., Abe, E. M., & Etta, H. (2012). Schistosomiasis in infants and pre-school-aged children in sub-Saharan Africa : implication for control. *Parasitology*, *139*, 835–841. https://doi.org/10.1017/S0031182012000029

Ezeamama, A. E., Bustinduy, A. L., Nkwata, A. K., Martinez, L., Pabalan, N., Boivin, M. J., & King, C. H. (2018). Cognitive deficits and educational loss in children with schistosome infection — A systematic review and meta-analysis. *PLoS Neglected Tropical Diseases*, *12*(1), 1–23. https://doi.org/10.1371/journal.pntd.0005524

Garba, A., Barkiré, N., Djibo, A., Lamine, M. S., Sofo, B., Gouvras, A. N., Bosqué-Oliva, E., Webster, J. P., Stothard, J. R., Utzinger, J., & Fenwick, A. (2010). Schistosomiasis in infants and preschool-aged children: Infection in a single Schistosoma haematobium and a mixed S. haematobium-S. mansoni foci of Niger. *Acta Tropica*, *115*(3), 212–219. https://doi.org/10.1016/j.actatropica.2010.03.005

Goran, E. N., Angbeletchi, N., & Aka, D. (2019). Challenges and Lessons From Conducting A Paediatric Clinical Trial in Sub-Saharan Africa : The Case of the Praziquantel Oral Dispersible Tablets Phase II ^ te d ' Ivoire Study in C o. In *Advances in Parasitology* (Vol. 103). Elsevier Ltd. https://doi.org/10.1016/bs.apar.2018.09.002

Gryseels, B., Polman, K., Clerinx, J., & Kestens, L. (2006). Human schistosomiasis. *Lancet*, *368*(9541), 1106–1118.

Hoy, D., Brooks, P., Woolf, A., Blyth, F., March, L., Bain, C., Baker, P., Smith, E., & Buchbinder, R. (2012). Assessing risk of bias in prevalence studies: Modification of an existing tool and evidence of interrater agreement. *Journal of Clinical Epidemiology*, *65*(9), 934–939. https://doi.org/10.1016/j.jclinepi.2011.11.014

Hussein, R., Id, M., Minzi, O. S., Kinung, S. M., Kamuhabwa, A., & Aklillu, E. (2020). Prevalence and correlates of intestinal schistosomiasis infection among school-aged children in North-Western Tanzania. *PLoS ONE*, 1–17. https://doi.org/https://doi.org/10.1371/journal.pone.0228770

Ioannidis, J. P. A. (2008). Interpretation of tests of heterogeneity and bias in meta-analysis. *Journal of Evaluation in Clinical Practice*, *14*(5), 951–957. https://doi.org/10.1111/j.1365-2753.2008.00986.x

Jadad, A. R., Moore, R. A., Carroll, D., Jenkinson, C., Reynolds, D. J. M., Gavaghan, D. J., & McQuay, H. J. (1996). Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Controlled Clinical Trials*, *17*(1), 1–12. https://doi.org/10.1016/0197-2456(95)00134-4

Kabuyaya, M., Chimbari, M. J., Manyangadze, T., & Mukaratirwa, S. (2017). Schistosomiasis risk factors based on the infection status among school-going children in the Ndumo area, uMkhanyakude district, South Africa. *Southern African Journal of Infectious Diseases*, *32*(2), 67–72. https://doi.org/10.1080/23120053.2016.1266139

Kemal, M., Tadesse, G., Esmael, A., Abay, S. M., & Kebede, T. (2019). Schistosoma mansoni infection among preschool age children attending Erer Health Center, Ethiopia and the response rate to praziquantel. *BMC Research Notes*, *12*(1), 1–6. https://doi.org/10.1186/s13104-019-4246-8

Kernell, J. W., Depaola, R. V, Maglione, A. M., Ahern, L. N., Penney, G., & Addiss, D. G. (2018). Risk of adverse swallowing events and choking during deworming for preschool-

aged children. *PLoS Neglected Tropical Diseases*, 1–18. https://doi.org/10.1371/journal.pntd.0006578

Kimani, B. W., Mbugua, A. K., Kihara, J. H., Ng, M., & Njomo, W. (2018). Safety , efficacy and acceptability of praziquantel in the treatment of Schistosoma haematobium in pre-school children of Kwale County , Kenya. *PLoS Neglected Tropical Diseases*, *9*(Ci), 1–12. https://doi.org/10.1371/journal.pntd.0006852

Lindholz, C. G., Favero, V., Verissimo, C. de M., Candido, R. R. F., de Souza, R. P., dos Santos, R. R., Morassutti, A. L., Bittencourt, H. R., Jones, M. K., St. Pierre, T. G., & Graeff-Teixeira, C. (2018). Study of diagnostic accuracy of Helmintex, Kato-Katz, and POC-CCA methods for diagnosing intestinal schistosomiasis in Candeal, a low intensity transmission area in northeastern Brazil. *PLoS Neglected Tropical Diseases*, *12*(3), 1–16. https://doi.org/10.1371/journal.pntd.0006274

Lo, N. C., Snyder, J., Addiss, D. G., Heft-neal, S., Andrews, R., & Bendavid, E. (2018). Deworming in pre-school age children : A global empirical analysis of health outcomes. *PLoS Neglected Tropical Diseases*, *12*(5), 1–13.

M'Bra, R. K., Kone, B., Yapi, Y. G., Silué, K. D., Sy, I., Vienneau, D., Soro, N., Cissé, G., & Utzinger, J. (2018). Risk factors for schistosomiasis in an urban area in northern Côte d'Ivoire. *Infectious Diseases of Poverty*, *7*(1), 1–12. https://doi.org/10.1186/s40249-018-0431-6

Mafiana, C. F., Ekpo, U. F., & Ojo, D. A. (2003). Urinary schistosomiasis in preschool children in settlements around Oyan Reservoir in Ogun State, Nigeria: Implications for control. *Tropical Medicine and International Health*, *8*(1), 78–82. https://doi.org/10.1046/j.1365-3156.2003.00988.x

Mazigo, H. D., Kirway, L., & Ambrose, E. A. (2019). Prevalence and intensity of Schistosoma mansoni infection in pediatric populations on antiretroviral therapy in north-western Tanzania : a cross- sectional study. *Bmj*, *9*, 1–6. https://doi.org/10.1136/bmjopen-2019-029749

Mitchell, S. A., & Pagano, M. (2012). Effective Classification of the Prevalence of Schistosoma mansoni. *Tropical Medicine and International Health*, *17*(12), 1–15. https://doi.org/10.1111/j.1365-3156.2012.03098.x.Effective

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., Altman, D., Antes, G., Atkins, D., Barbour, V., Barrowman, N., Berlin, J. A., Clark, J., Clarke, M., Cook, D., D'Amico, R., Deeks, J. J., Devereaux, P. J., Dickersin, K., Egger, M., Ernst, E., … Tugwell, P. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*, *6*(7). https://doi.org/10.1371/journal.pmed.1000097

Montero, R., & Ostrosky, P. (1997). Genotoxic activity of praziquantel Genotoxic activity of Praziquantel. *Elsevier Scince*, *387*, 123–139.

Moyo, V. B., Changadeya, W., Chiotha, S., & Sikawa, D. (2016). Urinary schistosomiasis among preschool children in Malengachanzi, Nkhotakota District, Malawi: Prevalence and risk factors. *Malawi Medical Journal*, *28*(1), 10–14. https://doi.org/10.4314/mmj.v28i1.3

Mutapi, F., Rujeni, N., Bourke, C., Mitchell, K., Appleby, L., Nausch, N., Midzi, N., & Mduluza, T. (2011). Schistosoma haematobium treatment in 1-5 year old children: Safety and efficacy of the antihelminthic drug praziquantel. *PLoS Neglected Tropical Diseases*, *5*(5). https://doi.org/10.1371/journal.pntd.0001143

Mutsaka-makuvaza, M. J., Matsena-zingoni, Z., Tshuma, C., Ray, S., Zhou, X., Webster, B., & Midzi, N. (2018). *Reinfection of urogenital schistosomiasis in pre-school children in a*

highly endemic district in Northern Zimbabwe : a 12 months compliance study. 1–16.
Nalugwa, A., Nuwaha, F., Tukahebwa, E. M., & Olsen, A. (2015). Single Versus Double Dose Praziquantel Comparison on Efficacy and Schistosoma mansoni Re-Infection in Preschool-Age Children in Uganda: A Randomized Controlled Trial. *PLoS Neglected Tropical Diseases*, *9*(5), 1–16. https://doi.org/10.1371/journal.pntd.0003796
Navaratnam, A. M. D., Sousa-Figueiredo, J. C., Stothard, J. R., Kabatereine, N. B., Fenwick, A., & Mutumba-Nakalembe, M. J. (2012). Efficacy of praziquantel syrup versus crushed praziquantel tablets in the treatment of intestinal schistosomiasis in Ugandan preschool children, with observation on compliance and safety. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *106*(7), 400–407. https://doi.org/10.1016/j.trstmh.2012.03.013
Niyituma, E., Njunwa, K. J., Mbugua, A. K., Karema, C., Umulisa, I., & Mkoji, G. M. (2017). Intestinal schistosomiasis and the associated transmission factors in pre-school aged children in villages surrounding Lake Rweru in Bugesera District, Rwanda. *Rwanda Journal*, *4*(1), 29. https://doi.org/10.4314/rj.v4i1.4f
Nyantekyi, L. A., Legesse, M., Belay, M., Tadesse, K., Manaye, K., Macias, C., & Erko, B. (2010). 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*, *24*(3), 185–190. https://doi.org/10.4314/ejhd.v24i3.68383
Olliaro, P., Delgado-romero, P., & Keiser, J. (2014). The little we know about the pharmacokinetics and pharmacodynamics of praziquantel (racemate and R -enantiomer). *J Antimicrobe Chemother*, *69*, 863–870. https://doi.org/10.1093/jac/dkt491
Olsen, A., Tukahebwa, M. E., & Nuwaha, F. (2015). Intestinal schistosomiasis among preschool children along the shores of Lake Victoria in Uganda. *Acta Tropica*, *142*, 115–121. https://doi.org/10.1016/j.actatropica.2014.11.014
Osakunor, D. N. M., Woolhouse, M. E. J., & Mutapi, F. (2018). Paediatric schistosomiasis: What we know and what we need to know. *PLoS Neglected Tropical Diseases*, *12*(2), 1–16. https://doi.org/10.1371/journal.pntd.0006144
Phillips, A. E., Gazzinelli-guimarães, P. H., Aurelio, H. O., Dhanani, N., Ferro, J., Nala, R., Deol, A., & Fenwick, A. (2018). Urogenital schistosomiasis in Cabo Delgado , northern Mozambique : baseline findings from the SCORE study. *Parasites & Vectors*, *11*(30), 1–10. https://doi.org/10.1186/s13071-017-2592-8
Poole, H., Terlouw, D. J., Naunje, A., Mzembe, K., Stanton, M., Betson, M., Lalloo, D. G., & Stothard, J. R. (2014). *Schistosomiasis in pre-school-age children and their mothers in Chikhwawa district , Malawi with notes on characterization of schistosomes and snails*. *7*(153), 1–12.
Raso, G., Li, Y., Zhao, Z., Balen, J., Williams, G. M., & Donald, P. (2009). Spatial Distribution of Human Schistosoma japonicum Infections in the Dongting Lake Region , China. *PLoS ONE*, *4*(9), 1–10. https://doi.org/10.1371/journal.pone.0006947
Reinhard-rupp, J., & Klohe, K. (2017). Developing a comprehensive response for treatment of children under 6 years of age with schistosomiasis : research and development of a pediatric formulation of praziquantel. *Infectious Diseases of Poverty*, *6*(122), 17–20. https://doi.org/10.1186/s40249-017-0336-9
Rücker, G., Schwarzer, G., Carpenter, J. R., & Schumacher, M. (2008). Undue reliance on I2 in assessing heterogeneity may mislead. *BMC Medical Research Methodology*, *8*, 2–9. https://doi.org/10.1186/1471-2288-8-79

Ruganuza, D. M., Mazigo, H. D., Waihenya, R., Morona, D., & Mkoji, G. M. (2015). Schistosoma mansoni among pre-school children in Musozi village , Ukerewe Island , North-Western-Tanzania : prevalence and associated risk factors. *Parasites & Vectors*, *8*(377), 1–11. https://doi.org/10.1186/s13071-015-0997-9

Rujeni, N., Nausch, N., Midzi, N., Cowan, G. J., Burchmore, R., Cavanagh, D. R., Taylor, D. W., Mduluza, T., & Mutapi, F. (2013). Immunological consequences of antihelminthic treatment in preschool children exposed to urogenital schistosome infection. *Journal of Tropical Medicine*, *2013*, 2−14. https://doi.org/10.1155/2013/283619

Sacolo-Gwebu, H., Chimbari, M., & Kalinda, C. (2019). 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. *Infectious Diseases of Poverty*, *8*(1), 1–12. https://doi.org/10.1186/s40249-019-0561-5

Said, K., Hella, J., Knopp, S., Nassoro, T., Shija, N., Aziz, F., Mhimbira, F., Schindler, C., Mwingira, U., Mandalakas, A. M., Manji, K., Tanner, M., Utzinger, J., & Fenner, L. (2017). Schistosoma, other helminth infections, and associated risk factors in preschool-aged children in urban Tanzania. *PLoS Neglected Tropical Diseases*, *11*(11), 1–20. https://doi.org/10.1371/journal.pntd.0006017

Sakari, S. S., Wefwafwa, Mbugua, A. K., & Mkoji, G. M. (2017). 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. *Hindawi*, 1–12. https://doi.org/10.1155/2017/1013802

Shaker, Y., Samy, N., & Ashour, E. (2014). *Review Article Hepatobiliary Schistosomiasis*. *2*, 212–216. https://doi.org/10.14218/JCTH.2014.00018.

Sousa-Figueiredo, Betson, M., Atuhaire, A., Arinaitwe, M., Navaratnam, A. M. D., Kabatereine, N. B., Bickle, Q., & Stothard, J. R. (2012). Performance and Safety of Praziquantel for Treatment of Intestinal Schistosomiasis in Infants and Preschool Children. *PLoS Neglected Tropical Diseases*, *6*(10). https://doi.org/10.1371/journal.pntd.0001864

Sousa-figueiredo, J. C., Betson, M., & Stothard, J. R. (2012). Treatment of schistosomiasis in African infants and preschool-aged children : downward extension and biometric optimization of the current praziquantel dose pole. *International Health*, *4*(2), 95–102. https://doi.org/10.1016/j.inhe.2012.03.003

Sousa-Figueiredo, J. C., Pleasant, J., Day, M., Betson, M., Rollinson, D., Montresor, A., Kazibwe, F., Kabatereine, N. B., & Stothard, J. R. (2010). Treatment of intestinal schistosomiasis in Ugandan preschool children: best diagnosis, treatment efficacy and side-effects, and an extended praziquantel dosing pole. *International Health*, *2*(2), 103–113. https://doi.org/10.1016/j.inhe.2010.02.003

Stothard, J. R., Sousa-Figueiredo, J. C., Betson, M., Bustinduy, A., & Reinhard-Rupp, J. (2013). Schistosomiasis in African infants and preschool children: Let them now be treated! *Trends in Parasitology*, *29*(4), 197–205. https://doi.org/10.1016/j.pt.2013.02.001

Stothard, J. R., Sousa-figuereido, J. C., Betson, M., Adriko, M., Arinaitwe, M., Rowell, C., Besiyge, F., & Kabatereine, N. B. (2011). *Schistosoma mansoni Infections in Young Children : When Are Schistosome Antigens in Urine , Eggs in Stool and Antibodies to Eggs First Detectable ? 5*(1). https://doi.org/10.1371/journal.pntd.0000938

Sulahian, A., Franc, Y. J., Izri, A., Verret, C., Delaunay, P., Gool, T. Van, & Derouin, F. (2005). Development and Evaluation of a Western Blot Kit for Diagnosis of Schistosomiasis. *Clin. Diagn. Lab. Immunol.*, *12*(4), 548–551. https://doi.org/10.1128/CDLI.12.4.548

Teresinha, M., Casavechia, G., Alcântara, G. De, Melo, N. De, Claudia, A., Da, B., Fernandes, S., & Castro, K. R. De. (2018). Systematic review and meta-analysis on Schistosoma mansoni infection prevalence , and associated risk factors in Brazil. *Parasitology*, *145*(8), 1000–1014. https://doi.org/10.1017/S0031182017002268

Utzinger, J., Becker, S. L., van Lieshout, L., van Dam, G. J., & Knopp, S. (2015). New diagnostic tools in schistosomiasis. *Clinical Microbiology and Infection*, *21*(6), 529–542. https://doi.org/10.1016/j.cmi.2015.03.014

Vale, N., Gouveia, M. J., Rinaldi, G., Brindley, P. J., Gärtner, F., & Costab, J. M. C. da. (2017). Praziquantel for Schistosomiasis: Single- Drug Metabolism Revisited, Mode of Action, and Resistance. *Antimicrobeal Agents and Chemotherapy*, *61*(5), 1–16. https://doi.org/https://doi.org/10.1128/AAC.02582-16

Van Der Werf, M. J., De Vlas, S. J., Brooker, S., Looman, C. W. N., Nagelkerke, N. J. D., Habbema, J. D. F., & Engels, D. (2003). Quantification of clinical morbidity associated with schistosome infection in sub-Saharan Africa. *Acta Tropica*, *86*(2–3), 125–139. https://doi.org/10.1016/S0001-706X(03)00029-9

Verani, J. R., Abudho, B., Montgomery, S. P., Mwinzi, P. N. M., Shane, H. L., Butler, S. E., Karanja, D. M. S., & Secor, W. E. (2011). Schistosomiasis among young children in Usoma, Kenya. *American Journal of Tropical Medicine and Hygiene*, *84*(5), 787–791. https://doi.org/10.4269/ajtmh.2011.10-0685

Wami, W. M., Nausch, N., Midzi, N., Gwisai, R., Mduluza, T., Woolhouse, M. E. J., & Mutapi, F. (2016). Comparative Assessment of Health Benefits of Praziquantel Treatment of Urogenital Schistosomiasis in Preschool and Primary School-Aged Children. *BioMed Research International*. https://doi.org/10.1155/2016/9162631

Wang, H., Naghavi, M., Allen, C., Barber, R. M., Carter, A., Casey, D. C., Charlson, F. J., Chen, A. Z., Coates, M. M., Coggeshall, M., Dandona, L., Dicker, D. J., Erskine, H. E., Haagsma, J. A., Fitzmaurice, C., Foreman, K., Forouzanfar, M. H., Fraser, M. S., Fullman, N., … Zuhlke, L. J. (2016). Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet*, *388*(10053), 1459–1544. https://doi.org/10.1016/S0140-6736(16)31012-1

Weerakoon, K. G. A. D., Gobert, G. N., Cai, P., & McManus, D. P. (2015). Advances in the diagnosis of human schistosomiasis. *Clinical Microbiology Reviews*, *28*(4), 939–967. https://doi.org/10.1128/CMR.00137-14

Weifeng G, Joseph, W., D, Z., Yumin, Z., & Wei, H. (2018). Advances in diagnosis of schistosomiasis. *Microbiology: Current Research*, *02*(02). https://doi.org/10.4066/2591-8036.18-404

WHO. (2010). Geneva, Switzerland, 13–14 September 2010. *Report of a Meeting to Review the Results of Studies on the Treatment of Schistosomiasis in Preschool-Age Children, Geneva, Switzerland, 13–14 September 2010*, *September*, 13–14. https://apps.who.int/iris/bitstream/handle/10665/44639/9789241501880_eng.pdf?sequence=1

WHO. (2011). *Helminth control in school-age children*.

WHO. (2017). Health Research & Reviews. *WHO*, *4*(3), 26–32. https://doi.org/10.4103/jhrr.jhrr

Woldegerima, E., Bayih, A. G., Tegegne, Y., Aemero, M., & Zeleke, A. J. (2019). Prevalence and Reinfection Rates of Schistosoma mansoni and Praziquantel Efficacy against the Parasite among Primary School Children in Sanja Town , Northwest Ethiopia. *Hindawi*

Journal of Parasitology Resarch, 1–8. https://doi.org/10.1155/2019/3697216
Won, K. Y., Kanyi, H. M., Mwende, F. M., Wiegand, R. E., Goodhew, E. B., Priest, J. W., Lee, Y. M., Njenga, S. M., Secor, W. E., Lammie, P. J., & Odiere, M. R. (2017). Multiplex serologic assessment of schistosomiasis in Western Kenya: Antibody responses in preschool aged children as a measure of reduced transmission. *American Journal of Tropical Medicine and Hygiene*, *96*(6), 1460–1467. https://doi.org/10.4269/ajtmh.16-0665
Zhou, H., Ohtsuka, R., He, Y., Yuan, L., Yamauchi, T., & Sleigh, A. C. (2005). Impact of parasitic infections and dietary intake on child growth in the schistosomiasis-endemic dongting lake Region, China. *American Journal of Tropical Medicine and Hygiene*, *72*(5), 534–539. https://doi.org/10.4269/ajtmh.2005.72.534
Zwang, J., & Olliaro, P. (2017). Efficacy and safety of praziquantel 40 mg / kg in preschool-aged and school-aged children : a meta-analysis. *Parasites & Vectors*, 1–16. https://doi.org/10.1186/s13071-016-1958-7
Zwang, J., & Olliaro, P. L. (2014). Clinical Efficacy and Tolerability of Praziquantel for Intestinal and Urinary Schistosomiasis — A Meta-analysis of Comparative and Non-comparative Clinical Trials. *PLoS Neglected Tropical Diseases*, *8*(11). https://doi.org/10.1371/journal.pntd.0003286

ANNEX

Annex 1 Prisma check list

Section/topic	#	Checklist item	Reported on page#
TITLE			
Title	1.	Prevalence and treatment outcome of schistosomiasis in preschool-aged children	Cover page
ABSTRACT			
Structured summery	2.	Provide a structured summary includingas applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	VII
INTRODUCTION			
Rationale	3.	Describe the rationale for the review in the context of what is already known	1-9
Objectives	4.	Provide an explicit statement of questions being addressed with reference to PICOS	10
METHODS			
Protocol and registration	5	The protocol was registered on PROSPERO with registration number.178102	11
Eligibility criteria	6.	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	11-12
Information sources	7.	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8.	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	11
Study selection	9.	State the process for selecting studies	
Data collection process	10.	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11.	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made	
Risk of bias in individual studies	12.	Describe methods used for assessing risk of bias of individual studies and how this information is to be used in any data synthesis	13
Summary measures	13.	State the principal summary measures (e.g., risk ratio, difference in means)	
Synthesis of results	14.	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis	14
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	14
Additional analyses	16	methods of additional analyses (subgroup analyses and meta-regression),	14

Section/topic		Checklist item	Reported on page #
RESULTS			
Study selection	17.	(PRISMA flow diagram)	15
Study characteristics	18.	For each study, present characteristics for which data were extracted	16-20
Risk of bias within studies	19.	data on risk of bias of each study (publication bias)	33
Results of individual studies	20.	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot	22-23
Synthesis of results	21.	Present results of each meta-analysis done, including confidence intervals and measures of consistency	21
Risk of bias across studies	22.	Present results of any assessment of risk of bias across studies	
Additional analysis	23.	results of additional analyses (summarized table of subgroup analysis and meta regression table and forest plot)	24-32
DISCUSSION			
Summary of evidence	24.	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	34-37
Limitations	25.	limitations at study and outcome level	38
Conclusions	26.	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	39-40
FUNDING			
Funding	27.		40

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