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Efficacy of Praziquantel Treatment for *Schistosoma mansoni* Infection Among Children in Ethiopia: Systematic Review and Meta-analysis

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Abstract: *Background:* Schistosomiasis is a chronic neglected tropical disease of poverty caused by blood dwelling trematodes of Schistosoma species. Praziquantel (PZQ) is the current drug of choice for the treatment of human schistosomiasis. The existence of Praziquantel resistance by Schistosoma species is a threat and an alarm for strict monitoring and periodic evaluation of its efficacy. *Method:* We searched PubMed, PubMed Center, Google Scholar, Web of Science, Google, Science Direct, MEDLINE and proceedings of a professional association to identify studies published in English and assessed the efficacy of Praziquantel against *Schistosoma mansoni* infection in children. Studies reporting the efficacy of Praziquantel in both adult and children as study participants and studies which investigated the efficacy of Praziquantel combined with other antischistosomal drugs were excluded. *Result:* Since there was significant heterogeneity, the random effect model was used. A total of 9 papers involving 1,412 participants, that assessed the cure rate and 8 papers that assessed egg reduction rate of Praziquantel were included in the meta-analysis. The pooled cure rate of Praziquantel was 86.65% with 95% CI; 83.4-93.9. There was high heterogeneity (I^2=93.4%). Subgroup analysis showed slightly higher Cure rate of Praziquantel in Amhara regional state compared to Oromia regional state (88.58% vs 84.79%). The egg reduction rate was 87.95% and 99.85% using geometric and arithmetic mean of egg count respectively. The prevalence of *Schistosoma mansoni* decreased from 55.77% to 11.29% after administration of Praziquantel. *Conclusion:* According to the result of this review, standard dose of Praziquantel was effective against *Schistosoma mansoni* infection among children in Ethiopia. The cure rate of Praziquantel was slightly higher in Amhara regional state compared to Oromia regional state. The drug showed a great reduction in egg count and intensity of infection.

Keywords: Praziquantel, *Schistosoma mansoni*, Efficacy, Ethiopia

1. Introduction

Schistosomiasis is a chronic neglected tropical disease of poverty caused by blood dwelling digenetic trematodes of the Schistosoma species. The disease is responsible for a major public health problem and imposed a socioeconomic burden in developing countries. It is endemic in 78 countries, of which most of them are resource-limited [1]. It is a serious public health problem with 200 up to 209 million people being infected. Globally approximately 779 million people are living in an area with active transmission of schistosomiasis [2]. In 2016 about 190 million people were already infected with schistosomiasis [3]. In 2016 About 237.2 million people in 51 countries require preventive chemotherapy for schistosomiasis [4]. Clinically schistosomiasis can have different forms that can be varied according to endemicity and immune response. The manifestation can begin with cutaneous rash, hypersensitivity reactions, abdominal pain, dry cough, general fatigue, myalgia, diarrhea,

abdominal tender and cardiac and central nervous involvement may rarely occurred at sever stage of the infection [5]. Poor sanitations like open field defecation, improper latrine utilization, poor waste management and poor personal hygiene are major concerns in developing countries. Children in those countries spent most of their time by swimming or bathing in contaminated water, thus increasing the chance of acquiring schistosomiasis [6]. Praziquantel (PZQ) is a pyrazinoquinoline derivative that is recommended by WHO as preventive chemotherapy for schistosomiasis with a 40 mg/kg standard dose. Due to its high efficacy and safety PZQ replace other anti-schistosomal drugs, and it leads to a great reduction in schistosomiasis and soil transmitted helminthes [7]. Different factors such as species of the parasite, stage of the parasite, and intensity of infection affect the therapeutic efficacy of Praziquantel for treating schistosomiasis [8]. Praziquantel can be given at different does and can be administered as a single or repeated dose. A repeated standard dose of a 40 mg/kg PZQ was reported to have achieved enhanced efficacy compared to a single dose [9]. Praziquantel at standard dose is fairly effective for treating *Schistosoma mansoni* with cure rate (CR) ranging from 79.4% to 88.6% [9]. In schistosomiasis endemic countries, PZQ mass chemotherapy has been implemented as part of school based or community based campaign in order to control morbidity associated with schistosomiasis and to reduce its transmission [10–13]. Scholars had reported the presence of *Schistosoma mansoni* resistance to PZQ mainly in endemic areas such as Africa [7]. Studies in Egypt and Senegal had reported the resistance of *Schistosoma mansoni* infection to PZQ [14, 15]. The existence of drug resistance of Schistosoma species to PZQ is a threat. It is also alarm for adequate monitoring during mass drug administration and periodic evaluation of its efficacy. It is also indication for developing new alternative drugs.

Ethiopia is among schistosomiasis high burden countries with 37.3 million people living at risk of infection; of this about 3.4 million and 12.3 million are pre-school and school age children respectively [16]. In Ethiopia Schistosomiasis is a major public health problem. It occurs in two clinical forms; intestinal schistosomiasis that is caused by *Schistosoma mansoni* and urogenital schistosomiasis by *Schistosoma hematobium*. *Schistosoma mansoni* is endemic in Ethiopia with pooled prevalence of 18.3%in the total population [17]. Ethiopia had a long term plan to eliminate schistosomiasis related morbidity by 2020 and to reduce the prevalence of heavy infection below 1%. The country had also planned to treat 8.9 million school age children for schistosomiasis by 2015/16 and had treated 6.66 million school age children this indicate 74.8% achievement [16]. Even though the achievement is good the prevalence is still higher in school children. Assessing the drug efficacy, reinfection rate and selecting the most effective drug is mandatory to eliminate the disease associated morbidity as well as to reduce the prevalence of the disease below 1%. Therefore this systematic review provides the overall (pooled) efficacy of Praziquantel for treating *Schistosoma mansoni* infection among preschool and school age children at country level (Ethiopia).

2. Method

2.1. Literature Search

The search period for this study was from July 1 to September 28, 2020. Systematic searching of literatures (published, unpublished and ongoing research) was carried out by using systematic electronic search on PubMed, PubMed center, Google scholar, Web of Science, Google, Science Direct, MEDLINE. Besides proceedings of professional association like Ethiopian medical laboratory association and Ethiopian public health association were searched. Searching of citation of the searched articles was also carried out. The search was conducted using key words and MESH terms; efficacy, Praziquantel, schistosomiasis, *Schistosoma mansoni*, school age children, pre-school children, children and Ethiopia.

2.2. Inclusion and Exclusion

Studies that reported the cure rate and/or egg reduction rate of Praziquantel for *Schistosoma mansoni* infection were included in this meta-analysis. Studies in which Praziquantel was administered at 40mg/kg in a single standard dose and involving pre-school and school age children were also included in this meta-analysis. Studies conducted in a language other than English language were excluded. Studies that reported efficacy of Praziquantel in both adult and children as study participants; studies that reported efficacy of Praziquantel combined with other anti schistosomal drugs; studies that assessed efficacy of Praziquantel in schistosomiasis and other coinfection as well as studies that assessed efficacy of Praziquantel against *Schistosoma hematobium* were also excluded.

2.3. Data Extraction and Quality Assessment

The authors (Habtye B. and Yonas E.) screened the title, abstract and full text of all identified literatures and identified potentially eligible studies. All included studies were added to Excel and extracted by Habtye B. then crosschecked by Yonas E. Missing or unclear outcome data were asked from the investigators. Study characteristics and variables like cure rate, egg reduction rate, study method, sample size; study site; mean or median age, gender, study group, region of origin and publication year of the study were extracted from eligible studies by using Microsoft excel. The primary out come this review and meta-analysis was the cure rate (CR) and egg reduction rate (ERR) of PZQ at a dose of 40mg/kg for *Schistosoma mansoni* infection treatment.

The two reviewers independently assessed the quality of the searched studies included in the review using Jaded scoring criteria [18]. The quality score was cross-checked and differences were resolved by rechecking the quality score

by the two investigators together and through discussion.

2.4. Data Analysis

Statistical analysis of this meta-analysis was conducted by using STATA version 12. The efficacy of Praziquantel was assessed in terms of cure rate CR and egg reduction rate (ERR). Cure rate was defined as the proportion of children who are negative to *Schistosoma mansoni* after treatment given but who were positive at baseline to the number of positive children before treatment. The egg reduction rate was defined as the proportional reduction in the mean eggs per gram of post treatment vs. pre-treatment calculated using either geometric or arithmetic mean and reported separately. The pooled CR and the pooled ERR were calculated and reported using forest plot. The confidence interval for both out comes (CR and ERR) was set at 95% (95%CI). Since there was heterogeneity of efficacy estimate from the studies, the summary outcome (CR and ERR) was calculated by using Random effect meta-analysis with inverse-variance weight [19]. The heterogeneity of the studies was assessed using I^2 statistics as measured by Higgins and Thompson [20, 21]. I^2 statistics is the reliable and preferred test for measuring heterogeneity across studies. I^2 value <25% indicate homogeneity of studies while values 25%-75% and ≥ 75% indicate moderate and very high heterogeneity across studies [20]. Publication bias was assessed by visual inspection of funnel plot and eggers test statistic with p-value ≤ 0.05 indicating the presence of publication bias [22, 23].

2.5. Ethical Consideration

This systematic review and meta-analysis was conducted in accordance with the PRISMA guidelines [24]. This study is systematic review and meta-analysis, therefore ethical permission is not required.

3. Result

3.1. Literature Search Result and Characteristics of Included Studies

In this systematic review and meta-analysis, a total of 276 articles were found from systematic literature search. After screening the title, abstract and full text of the searched literatures, 13 studies met the eligibility criteria. Four studies were excluded as the two studies assessed PQZ efficacy in schistosomiasis and helminths co-infection and two other studies assessed PZQ against *Schistosoma hematobium* with different study participants. Finally 9 studies were included in the meta-analysis (Figure 1). Of the included studies eight of them also assessed the ERR of PZQ and reported using geometric and arithmetic mean. The included studies were conducted between 2002 and 2020. The included studies were conducted in four Ethiopian national regional states where schistosomiasis is known to be endemic. Eight of them assessed PZQ efficacy among school age children and one study use pre-school children as study participant. The studies involve 1,412 children as study participants. In all studies, the standard dose given to each child was 40mg/kg. The post treatment assessment time was 3-6 weeks later. Four of the included studies performed post-treatment assessment after 4 weeks of the drug administration while two studies assessed after 3 weeks. One study assessed post treatment efficacy after 6 month and two studies did not indicate the post treatment assessment time. All studies used Kato–Katz thick smear as diagnostic method. The estimated cure rate of PZQ ranges from 73.60% - 99.10%. There was no uniform reporting method for the ERR. Five studies used geometric mean to report ERR and reported ERR as 68.2% - 99.5%, while two studies used arithmetic mean and reported 99.5% and 99.9% ERR (Table 1).

Table 1. *Summary of characteristics of included studies.*

Author/s/Reference	publication year	study area /region/	Sample size	Reporting methods for ERR	CR (%)	ERR (%)
Tadesse Dejenie, *et al* [25]	2010	Tigray regional state	225	NA	91.11	NA
Makida Kemal, *et al* [26]	2019	Somali Regional state	59	Geometric mean	96.4	NA
Mitiku Bajiro, *et al* [27]	2016	Oromia Regional State	120	Arithmetic mean	99.1	99.4
Getinet Degu, *et al* [28]	2002	Amhara Regional state	148	NA	94	99.9
Birehanu Reta, *et al* [29]	2013	Amhara Regional state	187	Geometric mean	82.89	97
Birehanu Erko, *et al* [30]	2012	Oromia Regional State	144	Geometric mean	73.6	79.46
Samuel Haile, *et al* [31]	2012	Oromia Regional State	204	Geometric	80.9	68.2
Eden Woldegerima, *et al* [32]	2019	Amhara Regional state	80	Arithmetic mean	90	99.51
Addisu Tesfie, *et al* [33]	2020	Amhara Regional state	245	Geometric mean	86.9	99.5

NA=not available; CR=cure rate; ERR=egg reduction rate

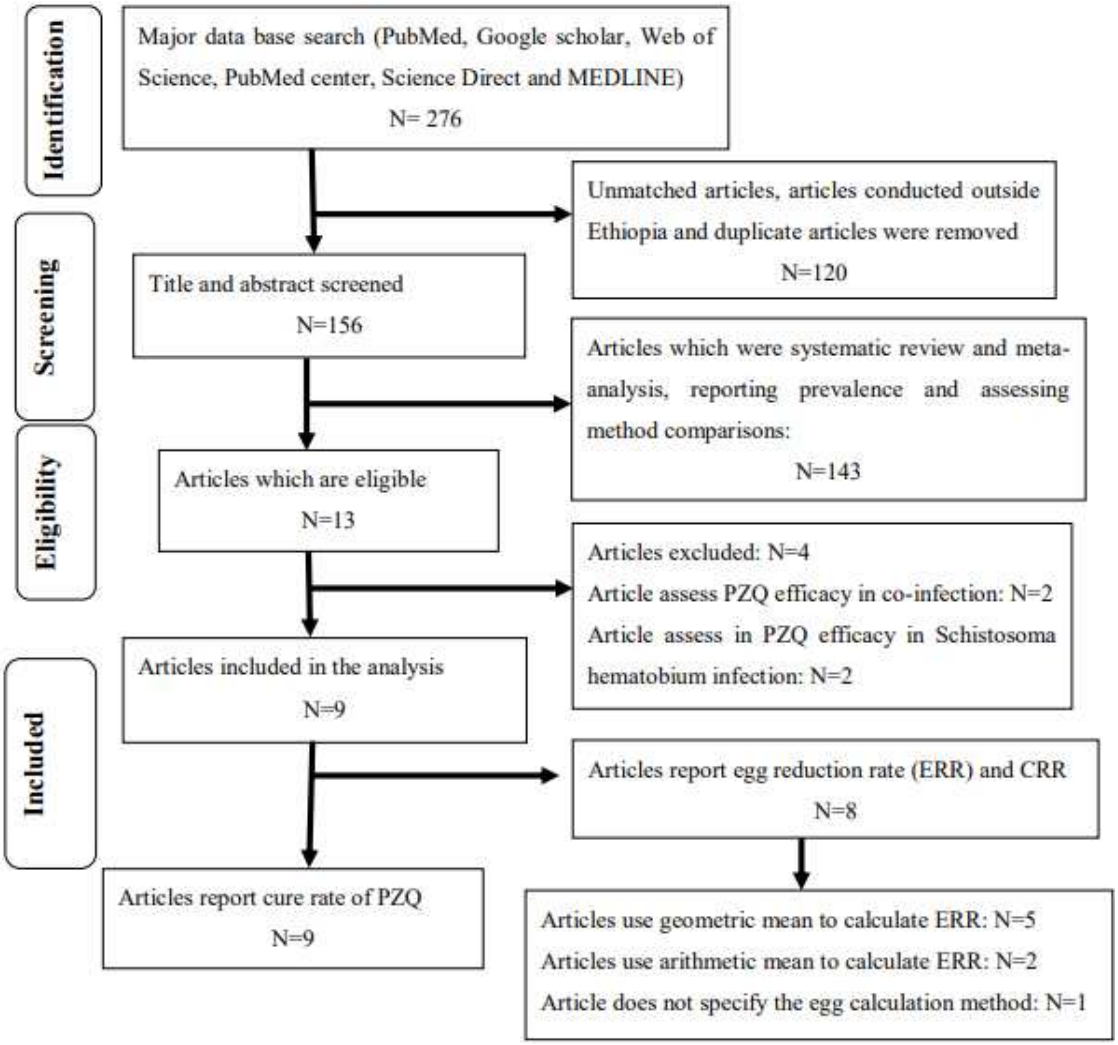

Figure 1. *Flow diagram showing article selection process.*

The authors also assessed the intensity of infection and the pre/post prevalence of *Schistosoma mansoni* infection. According to the reviewed articles, the intensity of infection in most of the study participants were low ranging from 22.52% - 70%. But in one study the participants were in a status moderate and heavy infection only. The drug had reduced the prevalence of *Schistosoma mansoni* infection among children from (24-74.9%) to (3.39%-26.3%) (Table 2).

Table 2. *Pre and post treatment prevalence of Schistosomk a mansoni and intensity of infection*

Author/s/	Pre/post treatment prevalence (%)	Intensity of infection (%)		
		Low	Medium	High
Tadesse Dejenie, *et al*	67.95/8.66	50.94	38.49	10.57
Makida Kemal, *et al*	25/3.39	40.70	50.30	0
Mitiku Bajiro, *et al*	24.00/0.90	70	30%	20
Getinet Degu, *et al*	50.80/6.08	NA	NA	NA
Birehanu Reta, *et al*	70.47/17.11	22.52	41.89	35.59
Birehanu Erko, *et al*	74.90/26.30	26.30	31.30	42.40
Samuel Haile, *et al*	67.60/19.12	35.30	38.70	26%
Eden Woldegerima, *et al*	35/10	0	86.20	13.80
Addisu Tesfie, *et al*	83.30/13.10	26.50	37.30	36.30

Cure rate of Praziquantel against Schistosoma mansoni infection

3.2. Meta-analysis of Cure rate of Praziquantel

The pooled cure rate of PZQ against *Schistosoma mansoni* infection was 86.65% with 95% CI (83.4-93.9). There was high heterogeneity among studies with $I^2$of 93.4% (figure 2).

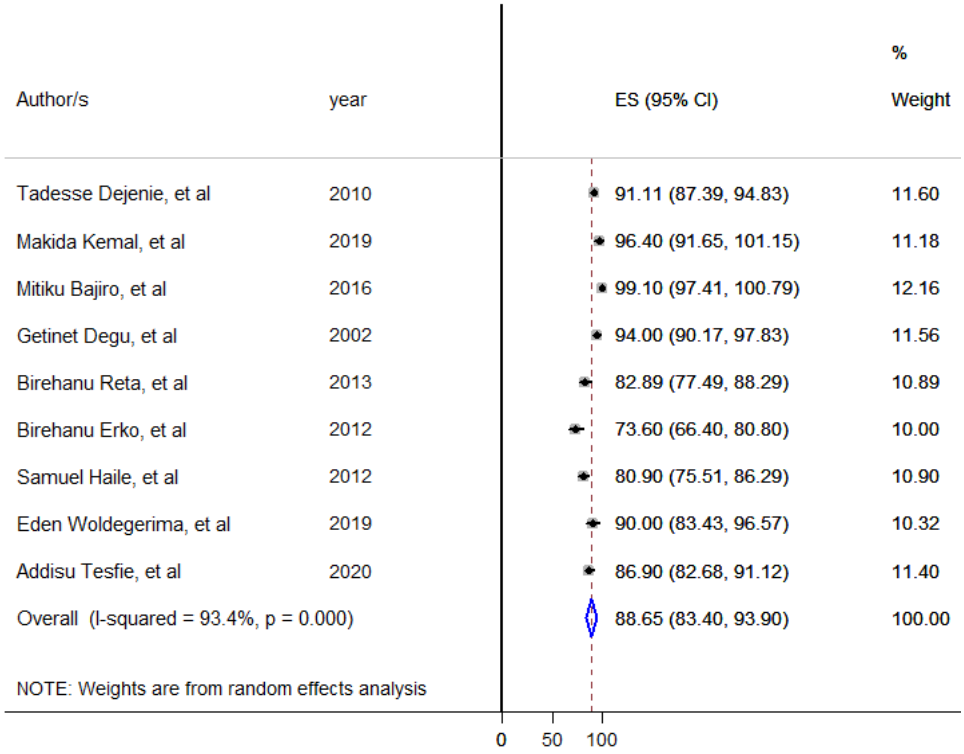

Figure 2. *Forest plot showing pooled efficacy (cure rate) of 40mg/kg PZQ against Schistosoma mansoni infection among pre-school and school age children.*

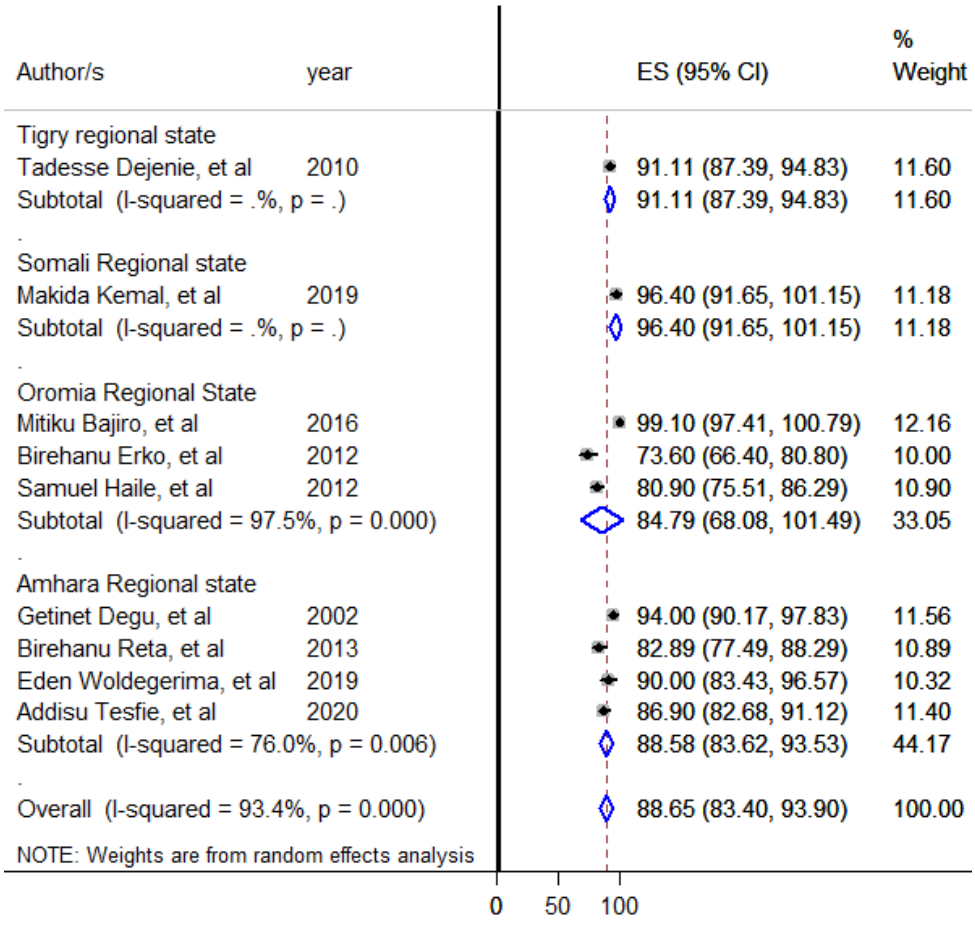

Figure 3. *Forest plot showing subgroup analysis of cure rate of PZQ by the different regional states of Ethiopia.*

3.3. Subgroup Analysis

Since there was substantial heterogeneity, subgroup analysis was done by the region where the studies were conducted. The articles were from four different regional state of Ethiopia. But subgroup analysis was done for only two regional states. The remaining two regional states had only one published article for each as a result meta-analysis cannot be done. The overall cure rate of PZQ was higher in Amhara regional state compared to the cure rate in Oromia regional state. The pooled cure rates were 88.58% and 84.79% in Amhara and Oromia regional state respectively. Heterogeneity was also high after subgroup analysis. It was 97.5% in Oromia regional state but, in Amhara regional state the heterogeneity was moderate with I^2 value of 76% (figure 3).

3.4. Publication Bias

Publication bias was assessed by visual inspection of the symmetry of the funnel plot and by the egger's test statistics. The funnel plot does not show symmetry (Figure 4) and eggers test statistics showed the presence of publication bias with p-value of 0.002. Therefore, trim and fill meta-analysis has been done to in order to account for the publication bias. The pooled cure rate of PZQ was found to be 86.63 which is similar to the frist one.

3.5. Meta-analysis of Egg Reduction Rate (ERR)

Due to high heterogeneity, random effect meta-analysis was done to assess the pooled ERR of PZQ against *Schistosoma mansoni* infection. Reporting the ERR of PZQ was different depending on the method used to calculate ERR. The pooled ERR by using geometric mean was 87.95% (95%CI; 81.69%, 94.21%) with high heterogeneity (I^2=97%). The pooled ERR by using arithmetic mean it was 99.85% (95%CI; 99.32%, 100.38%) with no heterogeneity.

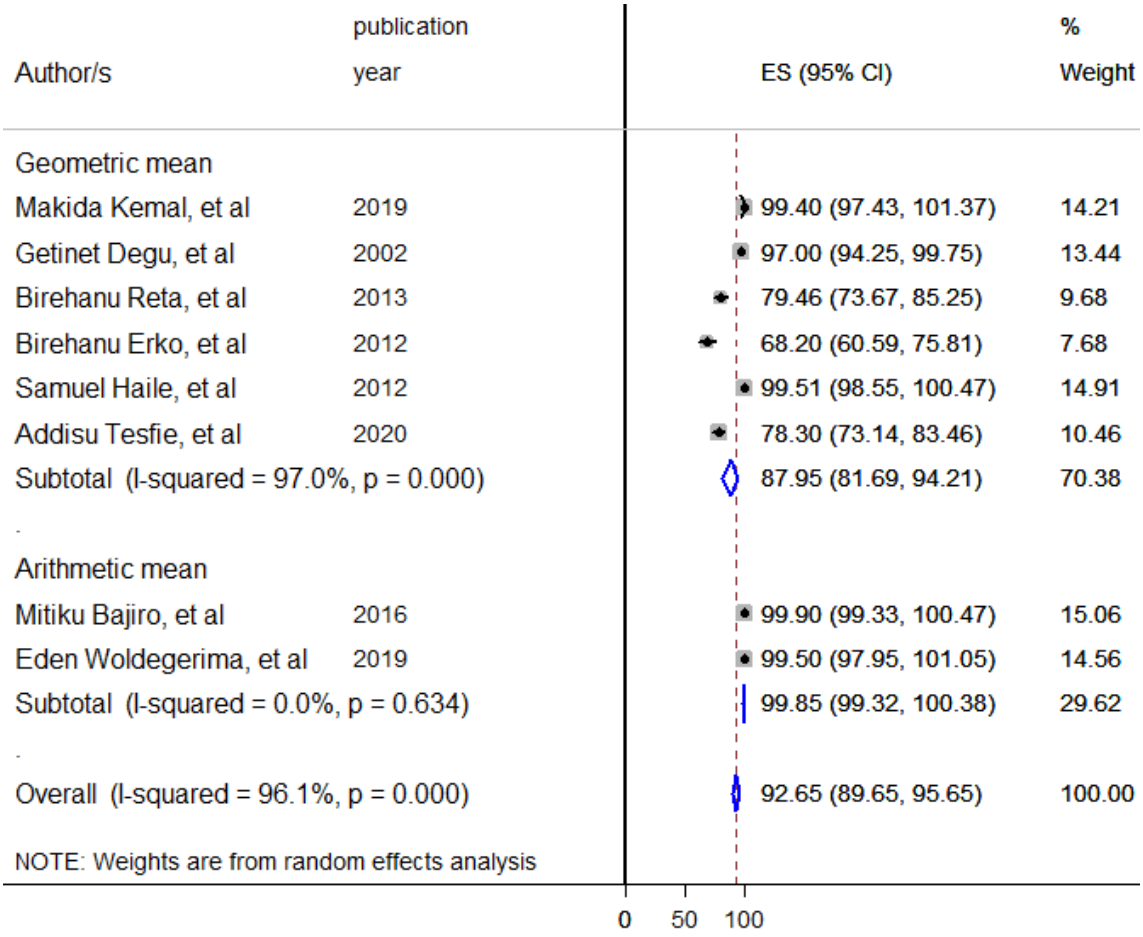

Figure 4. *Forest plot showing egg reduction rate of PZQ by the two reporting methods.*

Pre-treatment and post treatment prevalence of Schistosoma mansoni

According to the reviewed articles the pooled prevalence *Schistosoma mansoni* before administration of standard dose of 40mg/kg PZQ was 55.77%. After administration of the drug the prevalence reduced to 11.28% (Figure 5).

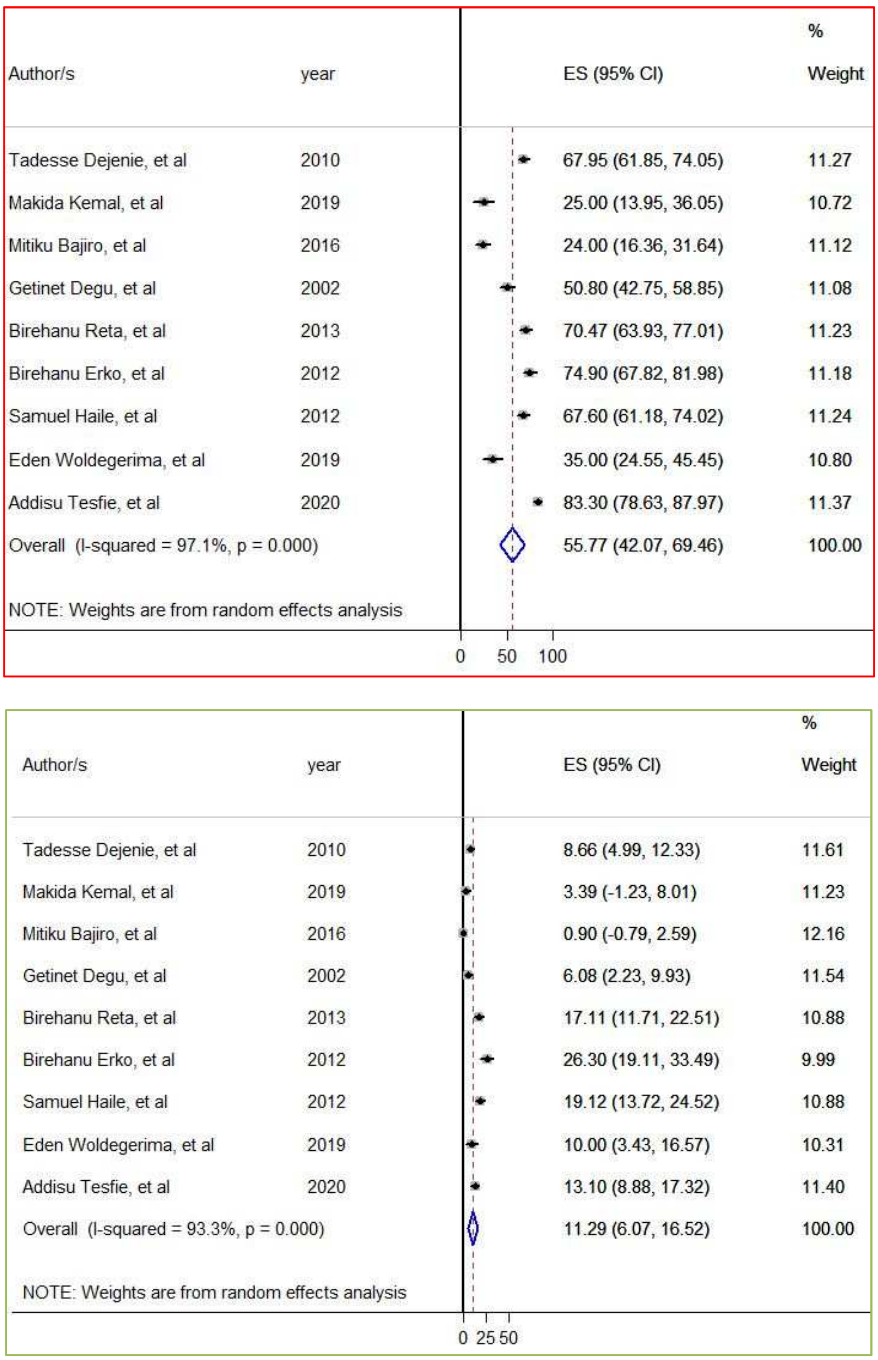

Figure 5. *Forest plot showing the pooled prevalence of Schistosoma mansoni during pre-PZQ treatment in the left panel and post-PZQ treatment.*

4. Discussion

Praziquantel is antihelminthic pyrazinoisoquinoline derivatives discovered in 1972 and developed in 1975 as a broad spectrum drug against helminthic Cestodes and trematodes by E. Merck and Bayer AG, Germany [34]. It is the WHO recommended antischistosomal drug that causes death of the parasite by rapidly contracting the worm muscle and leading to lose of worm movement, bleb formation and vacuolization of tegument which later on results in rupture of the vacuole and blebs. It exhibit stage specific killing mechanism [9]. A standard dose of 40mg/kg PZQ showed a good protective efficacy for both pre-school and school age children with CR of 72% (95% CI; 54.8–85.8) and 69% (95% CI; 53.4–81.8) respectively [35].

This systematic review was conducted in order to estimate the pooled cure rate and egg reduction rate of PZQ against *Schistosoma mansoni* infection among pre-school and school age children from 2002 [28] up to 2020 [33]. In this systematic review and meta-analysis, the cure rate of PZQ against *Schistosoma mansoni* infection among children ranges from 73.6% to 99.1% with an overall pooled CR of 86.65% with 95% CI of 83.4%- 93.9%. In this review, the CR is at the top and slightly better than previously reported reviews 63% -85% by Wegner et al [36]. According to our

review a single dose 40mg/kg PZQ give excellent protection against acute schistosomiasis and its protection rate is higher than review and meta-analysis done by Liu R et al, which reported 52% (95% CI: 49%-55%) protective rate [37]. The difference in efficacy may due to difference period of assessment between the first doses and follow up, the stage of the parasite present in the host, immune status of the participants. The drug effectively reduces the prevalence of the diseases from 55.77% to 11.29%.

Subgroup analysis was also done for the two national regional states of Ethiopia. The pooled cure rate was higher Amhara regional state as compared to Oromia regional state (88.58% vs 84.79%). Significant heterogeneity was observed even after performing subgroup analysis.

Egg reduction rate is also currently recommended as another method of assessing efficacy of drug [38]. In the reviewed articles, researchers used either geometric mean or arithmetic mean of the egg count. Meta-analysis of articles that used geometric mean to report ERR showed a 87.95% (95%CI; 81.69%, 94.21%) pooled ERR of PZQ against *Schistosoma mansoni* infection, while in those that used arithmetic mean of egg count the pooled ERR was 99.85% (95%CI; 99.32%, 100.38%). Praziquantel showed significant egg reduction rate indicating promising protective capacity against *Schistosoma mansoni* infection. Its high cure rate and egg reduction rate found in this meta-analysis can prove the great role of PZQ to achieve the goal of controlling schistosomiasis associated morbidity by the year 2020 and to eliminate schistosomiasis from the public health problem by the year 2025 set by the WHO [39].

5. Conclusion

This systematic review and meta-analysis showed PZQ administered at standard dose (40mg/kg) had promising efficacy against *Schistosoma mansoni* infection among children in Ethiopia. The review indicated treatment of *Schistosoma mansoni* infection with PZQ will result in high CR and ERR. The cure rate of PZQ was higher in Amhara national regional state than Oromia national regional state. The drug also showed high reduction in egg count and intensity of infection. The drug showed variable efficacy with great variation from study to study and to area this indicates the need for periodic evaluation of the drug at regional as well as national level in order to achieve the goal of eliminating morbidity and mortality of children associated with schistosomiasis.

Abbreviations

CR: Cure Rate; *ERR:* Egg Reduction Rate; *PZQ:* Praziquantel; *WHO:* World Health Organization.

Funding Source

There was no specific funding for this systematic review and meta-analysis.

Availability of Data and Materials

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Author's Contribution

Habtye B. and Yonas E. searched, analyzed and interpreted the data. Habtye B. and Yonas E. wrote the first draft of the manuscript. Habtye B. revised the manuscript. All authors read and approved the final version of the manuscript.

Declaration of Interest

The authors declared that they have no competing interest.

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