Efficacy of Different Drugs in Treating Urinary Schistosomiasis: Systematic Review and Network Meta-analysis

Huilong Fang
XiangNan University
Xuli Guo
XiangNan University
Chuwei Tang
XiangNan University
Fuchun Chen
XiangNan University
Ahmed Badr
Menoufia University Faculty of Medicine
Feng Luo
XiangNan University
Junjie Wang (475911403@qq.com)
XiangNan University

Research

Keywords: Urinary schistosomiasis, Praziquantel, Artesunate, Metrifonate

Posted Date: March 11th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-16780/v1

Abstract

Background: Praziquantel is the current pillar for morbidity control of schistosomiasis. Artesunate and its derivatives, widely used for malaria treatment, also display antischistosomal activities. This review compares the efficacy of three drugs, namely praziquantel (PZQ), artesunate, and metrifonate in urinary schistosomiasis.

Methods: Databases were searched for articles comparing the effectiveness of any of the three drugs to other medications or controls in urinary schistosomiasis in children aged 18 or less. Stata software was opted to generate the network meta-analysis. Efficacy (Cure rate and egg reduction rate) was the main outcome measure. Pairwise and network meta-analysis were used to report Odds Ratios (ORs) with either 95% confidence interval (CI) for direct comparisons or 95% credible intervals (CrI) for indirect comparisons.

Results: The SUCRA plot for cure rate revealed that PZQ (SUCRA= 40.4%) was the fourth effective drug after albendazole 400mg (SUCRA= 71.5), metrifonate 5 mg (SUCRA= 62.2%), and metrifonate 10 mg (SUCRA= 59.7). PZQ was only superior to metrifonate 7.5 mg. ORs were PZQ 40 mg (OR 0.48; 95% CI -3.55 to 4.51; p-value 0.816), artesunate 6 mg (OR 0.06; 95% CI -5.67 to 5.79; p-value 0.983), metrifonate 5 mg (OR -1.65; 95% CI -7.52 to 4.21; p-value 0.581), metrifonate 10 mg (OR -1.76; 95% CI -8.86 to 5.34; p-value 0.628), and metrifonate 7.5 mg (OR -2.40; 95% CI -9.78 to 4.98; p-value 0.524). A similar plot for egg reduction rate showed an exclusive superiority of PZQ 40 mg (SUCRA= 94.4%), followed by metrifonate 10mg (SUCRA= 82.3%) and niridazole 25mg plus metrifonate 10mg (SUCRA= 48.6%).

Conclusions: Our network analysis revealed that PZQ 40 mg was the most efficient drug in reducing egg count, whereas albendazole 400mg showed the highest cure rates.

Background

Urinary schistosomiasis is a chronic parasitic infection caused by ***trematodes*** of the***genus Schistosoma*** known as Schistosoma haematobium (SH). SH, also known as “urinary blood fluke”, inhabits and produces eggs in the small venules of the peri-vesical and portal systems. Urinary schistosomiasis is endemic in 53 countries in Africa and the Middle East, where more than 110 million people are infected (1,2). Noteworthy, the prevalence reaches its peak among school-age children to be as high as 46.5% (3,4). A myriad of medications was evaluated for their efficacy in treating SH infection (5–9). Praziquantel (PZQ) is the most commonly used drug worldwide and is the drug of choice for controlling schistosomiasis in endemic regions (10). The reasons for that is its efficacy in reducing egg count at a relatively high rate across different types of schistosomiasis (11). Moreover, PZQ is has shown good safety profiles making it the drug of choice for children and pregnant women (12,13). Additionally, PZQ has a low risk of noncompliance because it is administered as a single oral dose of 40 mg/kg body weight. Noteworthy, recent literature questioned this treatment regimen and suggested that PZQ in multiple dosages is more effective than a single dose (14). In the same context, artesunate, originally an antimalarial treatment, has proved efficacy and tolerability as an antischistosomal therapy (5,15). Two doses of artesunate were more cost-effective compared to single-dose PZQ (16). Nonetheless, PZQ-artesunate combination was safer and more effective as opposed to using either drug (8,17). Metrifonate, a cholinesterase inhibitor, is another selective treatment for SH; it has good efficacy and safety profiles. Although it is economic and causes low recurrence rates, the complicated dose regimen may limit its use (18). The reason for such complexity is the time needed for cholinesterase to return to its normal level, which may take 8-15 days (19). Moreover, three doses of metrifonate are needed to produce the same effect as one dose of PZQ in terms of egg reduction rates (20). Another limitation in using metrifonate is that a prophylactic dose is needed within two years to guard against recurrence (21). Niridazole is also highly effective for treating schistosomiasis, and a single dose of niridazole 25mg/kg daily has a high cure rate (22). However, it has serious side effects in susceptible individuals including central nervous system toxicities and allergic reactions, which limit its use compared to other safe alternatives (23).

In this study, we aim to compare efficacy (cure rate and egg reduction rate) of three drugs, namely praziquantel, artesunate, and metrifonate in cases of SH.

Methods

Search strategy and study selection

The study was conducted following the accepted methodology recommendations of the PRISMA checklist for systematic reviews. On December 18, 2019, we searched PubMed, Cochrane Central, Scopus, Web of Science, and Ovid databases for pertinent English articles using search terms ("Schistosoma haematobium" OR "schistosomiasis haematobia" OR "Bilharzia haematobium" OR "urinary schistosomiasis" OR "urogenital schistosomiasis" OR "vesical schistosomiasis" OR "Bilharziasis haematobium" OR "Bilharzia haematobium") AND (Metrifonate OR "Praziquantel"OR "Artesunate" OR anthelmin* OR treat* OR therapy*). A manual search was done by searching for relevant publications in references of included articles; relevant papers in PubMed and Google Scholar; and primary studies that had cited the included papers. We also hand-searched using each keyword to avoid missing any relevant publications.

Study selection

Three independent reviewers scanned the titles and abstracts to select potentially-relevant articles. We included all original studies reporting treatment of urinary schistosomiasis. There was no restriction on country, language or publication date. We excluded papers if they met the following exclusion criteria: i) in vitro or animal studies, ii) data duplication, overlapping or unreliably extracted or incomplete data, iii) unoriginal work including abstract only articles, reviews, theses, books, conference papers or articles with inavailable full texts (editorials, author responses, letters, and comments), and iv) any previous systematic reviews, meta-analyses and literature reviews on our topic of interest. Three reviewers independently performed an initial eligibility assessment of the retrieved titles and abstracts. Full texts of eligible articles were then retrieved and reviewed for inclusion. In both screening steps, inclusion or exclusion of a

study by all three reviewers was considered conclusive. Conflicts were resolved through discussion among the authors. When necessary, the authors sought the opinion of senior reviewers on disagreements and discrepancies.

Data extraction

Based on a pilot scan and extraction, two authors prepared a data extraction sheet using Microsoft Excel, and three reviewers independently extracted data from included studies. For accuracy, two different authors revised the data, and a third reviewer rechecked them. Disagreements or discrepancies were resolved through discussion and reaching consensus. Papers by the same research group and those studying the same factors were checked for potential duplicate data based on recruitment year, recruitment place, and confirmation from study authors. The outcome of interest was the efficacy of the medications of concern (PZQ, artesunate, and metrifonate), and outcome measurements were opted premised on the most commonly reported data in the included papers, namely cure rates, and egg reduction rates. Not only were these two measures endorsed for being frequently reported but also because they were feasible to assess pre and post-therapy using diagnostic tests. Two independent reviewers extracted and recapitulated data entailing study ID, last name of the first author, publication year, country, total number of participants, percentage of males, age touted as mean (SD), and the administered medication/s (name, dose, number of participants assigned to each drug). Regarding tools of outcome measurement, the extracted data encompassed drug name, the quantitative mean of efficacy, the total number of patients, the dose, the length of the therapeutic course in days, and the diagnostic test used for assessment. Whenever any article reported multiple checkpoints, only the last point was analyzed.

Quality assessment

Two reviewers have independently assessed the risk of bias of the included studies using the National Institute of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-sectional Studies and Case-control Studies. The elements of the quality assessment were indexed either Yes (1), No (0), or others including CD (Cannot Determine), NA (Not Applicable), and NR (Not Reported). Eventually, papers were rated fair, good, or high based on the final score. Having a non-randomized controlled trial included, the Risk of Bias in Non-Randomized Studies of Interventions Tool (ROBINS-I) tool was used for its assessment. This tool includes six categories: confounding bias, participants selection bias, the bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, and bias in the measurement of outcomes. The questions under each category were assigned either Y (Yes), N (No), PY (Probably Yes), or NI (No Information), and so was the case for the overall bias.

Statistical analysis

Odds Ratios (ORs) with 95% confidence interval (CI) for direct comparisons or 95% credible intervals (CrI) for indirect comparisons were used. A network meta-analysis was performed using Stata software (version 14.2, StataCorp, College Station, TX) with random-effects models. To rank the treatments, the surface under the cumulative ranking probabilities (SUCRA) were opted to show which treatment was the best. Heterogeneity was considered significant with either I2>50 or P<0.05 with a subsequent adjustment of the model to small-study effects (incorporation of the heterogeneity) in this case. Inconsistency was also considered significant with either P<0.05, which was further investigated using node splitting methods (of direct and indirect comparisons) whenever indicated.

Results

Search results and screening process

Our search retrieved 2303 studies with only 1434 left after removing duplicates. Title and abstract screening using the criteria aforementioned left only 89 studies eligible for further full-text screening. Following the full-text screening, 20 studies were included in both quantitative and qualitative synthesis. The manual search retrieved no additional relevant studies. **Figure 1** shows a summary of the search and screening process.

Characteristics and quality of included studies

Table 1 summarizes the patient characteristics and the designs of the included studies. Apart from two studies of poor quality, most of the studies were either good or fair in quality (**Table 1**).

Cure rate

For cure rates, six different treatments/doses were compared, and the network plot is showcased in **Figure 2A**. Pooling direct and indirect comparisons showed an advantage of albendazole 400mg (SUCRA= 71.5) over praziquantel (SUCRA= 40.4); different doses of metrifonate (SUCRA= 62.2, 59.7, and 38 for 5mg, 10mg and 7.5mg respectively); and artesunate (SUCRA= 28.2). There was significant heterogeneity (t^2= 2.78, I^2= 71.55%) with no significant inconsistency (P= 0.06). Moreover, adjusting our model to small-study effects (incorporation of the heterogeneity) did not materially alter the relative effectiveness and the ranking of treatments (**Figure 2B**). In the same context, pairwise comparisons of all drugs to albendazole 400mg revealed that albendazole was more effective than any other treatment/dose. However, this difference in cure rates was not statistically significant throughout all comparisons (**Table 2**).

Egg reduction rate

Figure 3A is a network plot of the comparisons of egg reduction among eight different treatments/doses. Pooling direct and indirect comparisons showed an obvious advantage of PZQ 40mg (SUCRA= 94.4), followed by metrifonate 10mg (SUCRA= 82.3) and then niridazole 25mg plus metrifonate 10mg (SUCRA= 48.6) (Detailed SUCRA scores in **Table 3**). There was a significant heterogeneity (t^2= 1.21, I^2= 65.73%) and significant inconsistency (P= 0.007). Moreover, adjusting our model to small-study effects (incorporation of the heterogeneity) did not materially alter the relative effectiveness and ranking of treatments

(**Figure 3B**). In the same context, pairwise comparisons of all drugs to Placebo revealed Praziquantel 40mg-Artesunate 4mg as a combination was the best, followed by Praziquantel 40mg and the Niridazole 25mg-Metrifonate 10mg combination. Interestingly, this difference in cure rate was statistically significant across all drugs when compared to placebo (**Table 3**).

Discussion

This study is, to the best of our knowledge, the first network meta-analysis of its kind to assess the efficacy of all proposed treatments for urinary schistosomiasis in the literature through direct and indirect comparisons between the various treatment modalities. Our network analysis revealed that albendazole (400 mg) achieved higher percentages of cure rate than other treatment modalities. Albendazole is used commonly for treating some human worm infections. Recently, it has been combined with praziquantel for the management of schistosomiasis and other soil-transmitted helminthiases (24,25).

Noteworthy, albendazole has never been investigated as monotherapy for SH, but one study reported the outcomes of a single dose of combined praziquantel and albendazole and concluded that albendazole impacts the effect of praziquantel (26). Olds et al. have reported a failure rate (defined as the continued detection of parasite eggs 45 days after treatment of SH (of 79.6% in patients treated with Albendazole alone (26). This percentage nosedived to 38.5% after adding praziquantel to the therapy (26). Furthermore, they reported a failure rate of 35.1% in praziquantel alone, which is still much better than albendazole alone. Olds et al. had a few limitations: First, they excluded female patients who were liable to pregnancy because albendazole is a known teratogenic. Accordingly, most of their patients were on praziquantel, which might have made their analysis standing in favor of praziquantel. Second, they did not provide any data on the characteristics of their study participants, the intensity of the infection, or the number of patients on each treatment modality. Another trial showed higher cure rates in praziquantel than cure rates of albendazole alone (78% vs 66%) but with statistically insignificant difference. Additionally, the mean post-treatment egg count was lower in patients on praziquantel compared to those on albendazole (2.0±1.2 and 2.7±1.3, respectively) (27). Even though the reports aforementioned indicate that praziquantel is more efficient than albendazole in treating urinary schistosomiasis, albendazole is more readily available and cost-effective (27).

Our finding regarding the efficacy of PZQ is inconsistent with the recommendations in the literature. The World Health Organization recommends that schistosomiasis should be treated with single-dose PZQ of at least 40 mg/kg (28). Similarly, the recently updated review by Kramer et al (8). supports the current evidence of applying 40 mg/kg praziquantel to patients with urinary schistosomiasis. One major limitation to the study by Kramer et al., besides being mostly qualitative review with only minimal meta-analyses, is that all of their included trials were conducted in Sub-Saharan Africa, except for one conducted in Saudi Arabia. So, their conclusions cannot be generalized. On the other hand, our analysis revealed that PZQ held fourth record for cure rates after albendazole, metrifonate (5 mg/kg), and metrifonate (10 mg/kg). Herein, we propose multiple explanations for this finding. The low cure rates of PZQ could be a possibly increasing PZQ resistance in the assessed trials as observed by some authors (29–32). Praziquantel is also kills the adult worms, not the immature stages; therefore, the majority of our patients on PZQ might have been harboring the immature stages at treatment time.

In our analysis, even though praziquantel was ranked fourth in cure rates, it was ranked first in egg reduction rates. There were no data available on egg count reduction in patients on albendazole; thus, it was not included in the analysis. Future studies should assess thoroughly the changes in egg count in patients on albendazole. On the other hand, a combination of niridazole and metrifonate was ranked second in our analysis, but one should keep in mind that both drugs are old, unavailable, and are no longer used in practice. Of note, egg count reduction is not a very sensitive parameter of clinical and parasitological cure, since negative urine examinations is not an indicator of cure. The literature reported that the absence of eggs in the urine is only an occasional finding and does not necessarily exclude infection (33); accordingly, repeated urine examination after treatment is more useful in diagnosing persistent excretion of eggs in the urine and controlling any the possible transmission of the infection. That being said, cystoscopy, in addition to biopsy and histopathological evaluation, is a pivotal indicator of parasitological cure (33). Therefore, extra caution should be given to the interpretation of the data on egg count as they do not necessarily reflect the efficacy of treatments.

Strengths and Limitations

The main strength of our study is being, to the best of our knowledge, the first network meta-analysis to assess the direct and indirect comparisons among different treatment modalities for urinary schistosomiasis in terms of cure and egg reduction rates. Also, unlike the recent Cochrane review of Kramer et al., we assessed the efficacy of albendazole in treating urinary schistosomiasis. However, we encountered several limitations, the biggest of which is the lack of data regarding the egg count reduction in patients on albendazole, and that restricted us from including the egg count networking. Also, the definition of cure differed among the included trials, which impeded us from reaching a sheer conclusion on the best treatment for urinary schistosomiasis. Moreover, the intensity of infection was not reported in most trials; the thing that might have affected the results of egg count reduction to somewhat. Therefore, these issues should be addressed in future work.

Conclusions

Our network analysis revealed that albendazole is the most efficient drug with the highest cure rates in cases of urinary schistosomiasis, whereas PZQ took fourth place. As regards the percentage of egg count reduction, PZQ was superior to other medications.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

Not applicable

Authors' contributions

HF conceptualised the review. All authors screened the articles. XG, CT, AB and FC extracted the data. FL and JW drafted the introduction. HF drafted the methods and results. XG and CT drafted the discussion. All authors reviewed, edited and approved the final manuscript.

Acknowledgements

Not applicable

Abbreviations

PZQ: Praziquantel

OR: Odds Ratio

CI: Confidence Interval

SH: Schistosoma haematobium

PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis

SD: standard deviation

CD: Cannot Determine

NA: not applicable

ROBINS-I: Risk of Bias in Non-Randomized Studies of Interventions Tool

Y: Yes

N: No

PY: Probably Yes

NI: No Information

CrI: credible intervals

SUCRA: surface under the cumulative ranking probabilities

Tables

Table 1

Last name of 1st author/Year/Country	Total Population	Male %	Age; Mean (SD) /Range (N)/Median (Range)	Arm 1 (Drug, Dose and n)	Arm 2 (Drug, Dose and n)	Arm 3 (Drug, Dose and n)	Arm 4 (Drug, Dose and n)	Arm 5 (Drug, Dose and n)	Arm (Dru Dose n)
Al-Waleedi/ 2013 / Yemen	126	51.6	<12 (14)	PZQ, a single oral dose (40 mg/kg body weight), 122	-	-	-	-	-
			12 to <13 (48)						
			13 to <14 (35)						
			14–16 (29)						
Andolina/2010 / Tanzania	178	_	(6-18)	PZQ, 40 mg/kg single dose, 178	-	-	-	-	-
	96		(6-18)	PZQ, 40 mg/kg two doses, 96					
	41		(6-18)	PZQ, 40 mg/kg three doses, 96					
Ben/2017/Nigeria	196	62.2	PZQ: 2–4 (6) /Albend: 2–4 (4)	PZQ, 40 mg/kg body weight single dose, 100	Albend, 400 mg, 96	-	-	-	-
			PZQ: 5–7 (17) /Alabend: 5–7 (20)						-
			PZQ: 8-10 (30) /Albend: 8-10 (26)						-
			PZQ: 11-13 (30) /Albend: 11-13 (28)						-
			PZQ: 14-16 (17) /Albend: 14-16 (18)						-
Coulibal/2012/Côte d'Ivoire	18	50	3.2 (range 5 months- 5 years)	PZQ, 40 mg/kg, 18	-	-	-	-	-
Davis/1969 / Tanzania	43	60.5	5 to 15	7.5 mg Met/ kg	Same patients before receiving ttt	-	-	-	-
	42	71.4		5.0 mg Met/kg					-
	72	73.6		5.0 mg Met/kg					-
	71	74.6		10.0 mg Met/ kg					-
	69	68		7.5 mg Met/ kg					-
	35	85.7		10.0 mg Met/ kg					-
	34	70.6		15.0 mg Met/ kg					-
Doehring/1985/ Congo	6	-	(11-16)	PZQ, 40 mg/kg, 6	-	-	-	-	-
Inyang-Etoh/ 2009/ Nigeria	312	-	(4-20)	PZQ (40 mg/kg) once and Artes (4 mg/kg) daily for three consecutive days, 52	PZQ placebo (40 mg/kg) once and Artes (4 mg/kg) daily for three consecutive days, 52	Artes placebo (4 mg/kg) for three consecutive days and PZQ (40 mg/kg) once, 52	Artes placebo (4 mg/kg) for three consecutive days and PZQ placebo (40 mg/kg) once, 52	PZQ (40 mg/kg) once and no placebo, 52	Artes mg/k daily thre consec days no plac 52
King/ 2002/ Kenya	266	56	(4-23)	PZQ, 40 mg/kg, 145	PZQ, 20mg/kg, 146	-	-	-	-
Mekonnen/2013/Ethiopia	152	80.9	16 (2 to 60 years)	PZQ(40 mg/kg), 1	-	-	-	-	-
Mutapi/2011/Zimbabwe	427	-	-	PZQ(40 mg/kg), 1	-	-	-	-	-
N'Goran/2003/Côte d'Ivoire	354	-	-	PZQ(40	-	-	-	-	-

					mg/kg), 2					
Ojurongbe/2014/Nigeria		245	70.9	-	PZQ(40 mg/kg), 2	-	-	-	-	-
Pugh/1983/Zomba and Malawi		433	-	-	PZQ(40 mg/kg), 1	Niri 25 mg/kg combined with Met 10 mg/kg, 1	Met (10 mg/kg), 1	Niri 25 mg/kg	Placebo	-
Reddy/1975/Nigeria		39	97.4	-	Met (7·5 mg/kg), 1	-	-	-	-	-
SACKO/2009/Mali		603	-	-	Single dose of 40 mg/kg PZQ and a placebo 2 weeks	PZQ(40 mg/kg), 2	-	-	-	-
Senghor/2015/Senegal		237	63.3	8.8 (3.1)	PZQ(40 mg/kg), 1	-	-	-	-	-
Sissoko/2009/Mali		781	64.4	10.45 (2.45)	PZQ(40 mg/kg), 1	100 mg Artes +250 mg sulfamethoxypyrazine/12.5 mg pyrimethamine, 1	-	-	-	-
Stete/2012/Côte d'Ivoire		90	51.1	11.2 (7–15)	PZQ(40 mg/kg), 1	-	-	-	-	-
Tchuentéa/2013/Cameroon	Bessoum	266	64.2	-	PZQ(40 mg/kg), 1	-	-	-	-	-
	Makenene	561	47.6	-	PZQ(40 mg/kg), 1	-	-	-	-	-
	Ouro Doukoudje	150	66.6	-	PZQ(40 mg/kg), 1	-	-	-	-	-
TSWANA/1986/Zimbabwe		187	9	-	Met (10 mg/kg), 1	-	-	-	-	-

PZQ: Praziquantel, Met: Metrifonate; Albend: Albendazole; Niri: niridazole; Artes: artesunate

Table 2

Treatment	OR	Std. Err.	z	P-value	95% LCI	95% UCI
Artes 6mg	0.06	2.92	0.02	0.983	-5.67	5.79
Met 10mg	-1.76	3.62	-0.49	0.628	-8.86	5.34
Met 5mg	-1.65	2.99	-0.55	0.581	-7.52	4.21
Met 7 5mg	-2.40	3.77	-0.64	0.524	-9.78	4.98
PZQ 40mg	0.48	2.06	0.23	0.816	-3.55	4.51

Table 3

Treatment	OR	Std. Err.	z	P-Value	95% LCI	95% UCI	SUCRA
PZQ 40mg + Artes 4mg	5.46	2.07	2.63	0.009	1.39	9.52	26.8
PZQ 40mg	5.41	1.68	3.22	0.001	2.12	8.71	94.4
Niri 25mg + Met 10mg	5.25	2.28	2.3	0.021	0.78	9.73	48.6
PZQ 20mg	4.57	2.69	1.7	0.089	-0.7	9.84	43.7
Artes 4mg	4.5	2.05	2.2	0.028	0.48	8.52	29.6
Met 7.5mg	4.2	2.01	2.09	0.037	0.26	8.14	82.3
Niri 25mg	1.52	2.27	0.67	0.502	-2.92	5.96	31.1

Figures

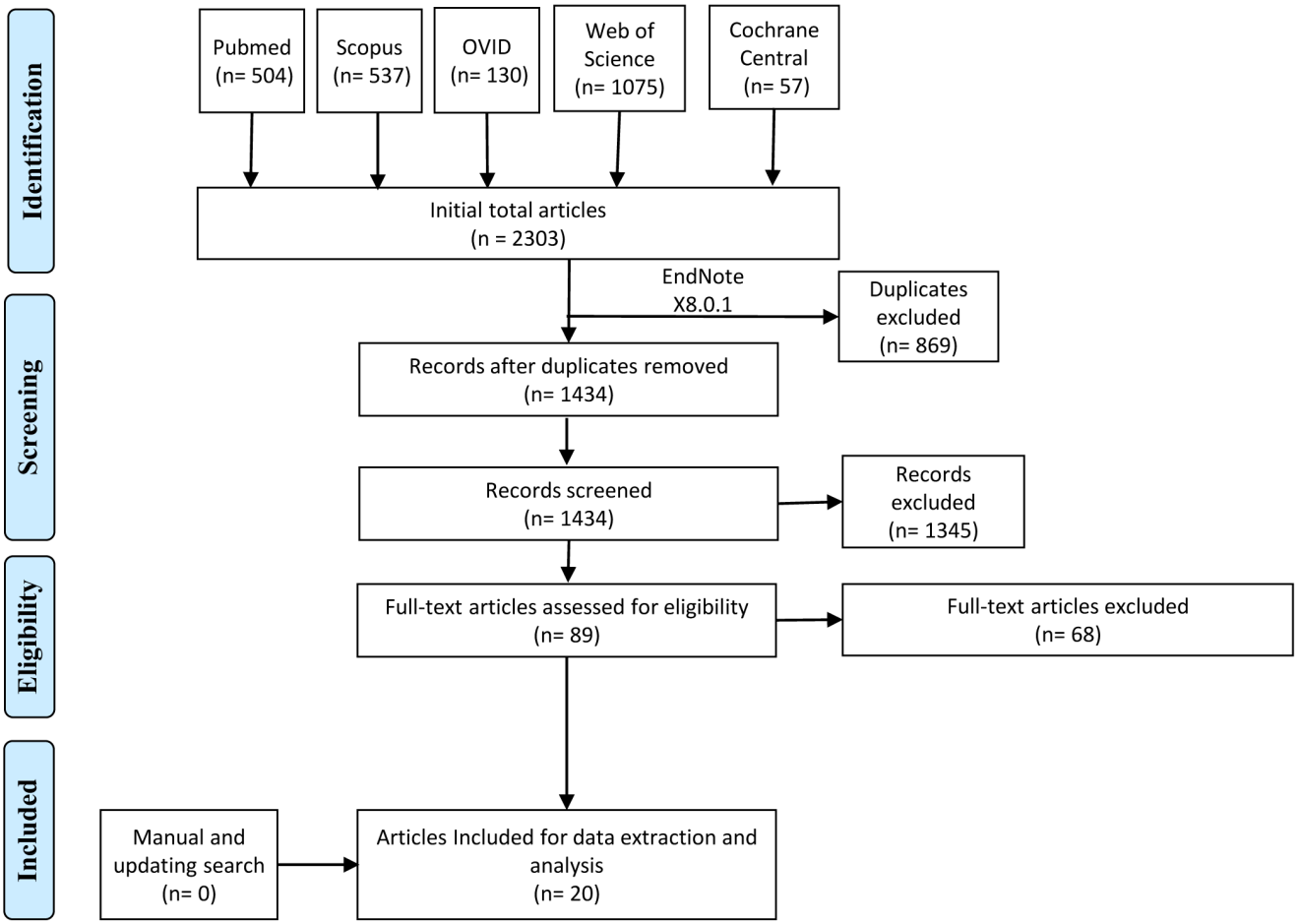

Figure 1

PRISMA flow diagram of the study.

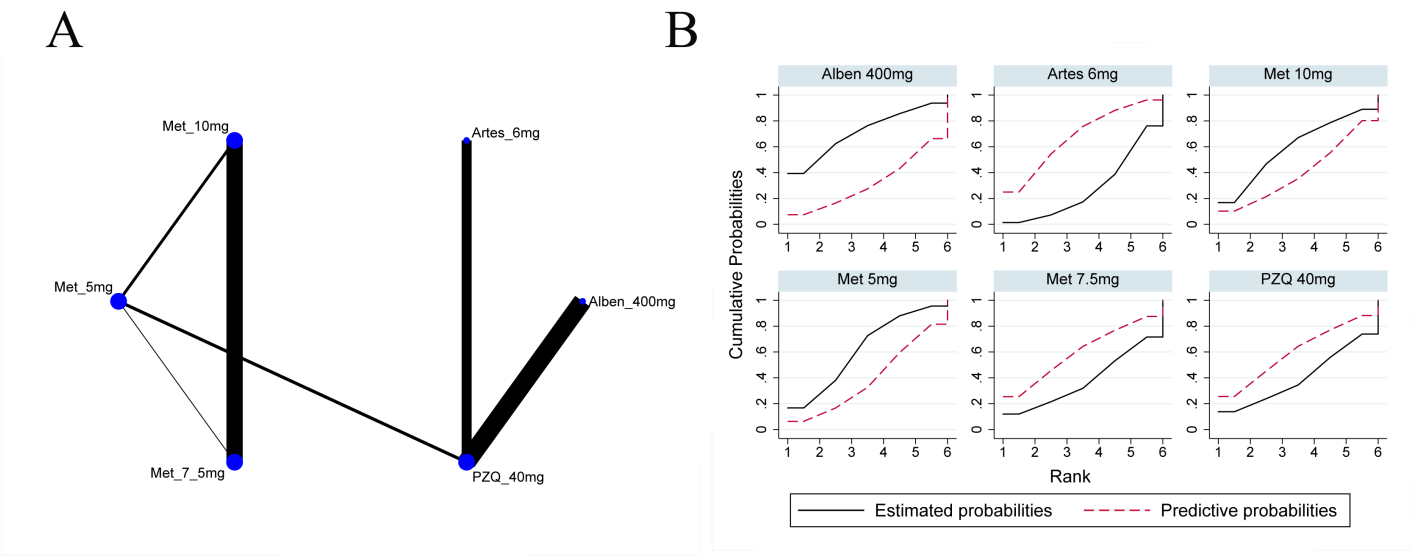

Figure 2

The figure plots the network of eligible comparisons/ drugs as for efficacy, specifically cure rate (A). The thickness of lines reflects the number of articles comparing each pair treatment, and the size of each node is proportionate with the number of participants. (B) is the SUCRA plot for the various treatments;

the SUCRA score is 100%. The more the score, the higher the treatment is ranked in terms of its cure rate. PZQ, Praziquantel; Artes, Artesunate; Met, Metformin; Alben, Albendazole.

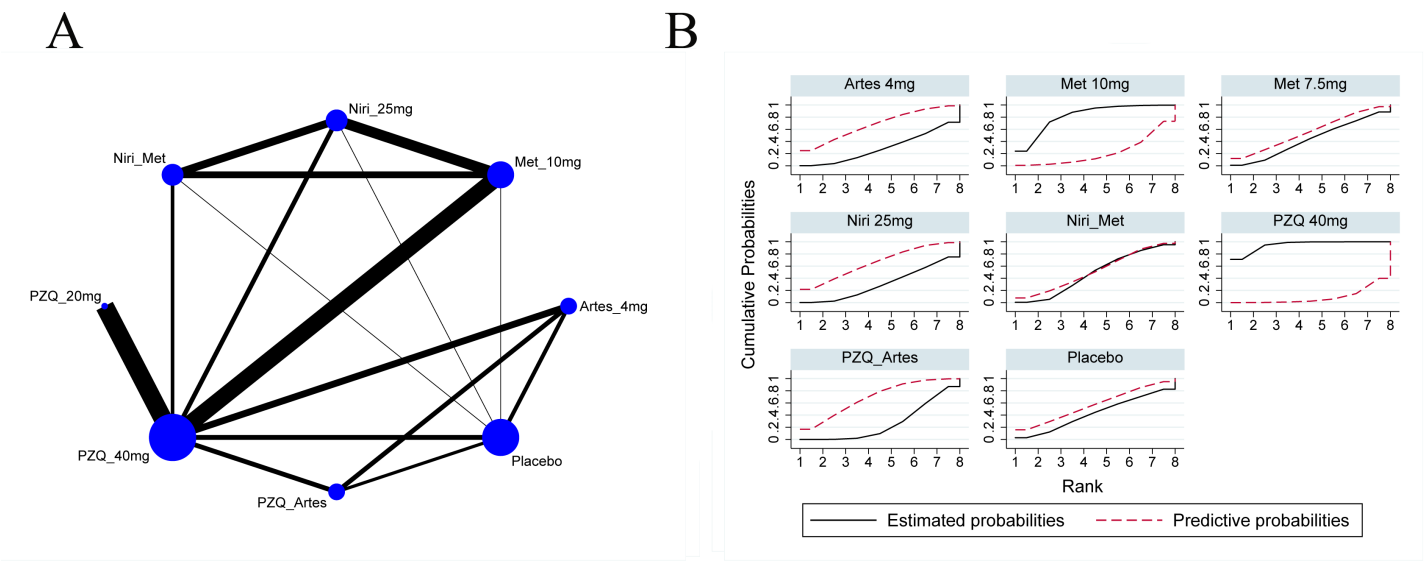

Figure 3

The figure showcases a network of eight drug categories as related to their efficacy (egg reduction rate). the thickness of lines reflects the number of articles comparing each pair treatment, and the size of each node is proportionate with the number of participants. Also, (B) is the Sucra plot for ranking the egg reduction potential of plotted drugs; the SUCRA score is 100%. The more the score, the higher the treatment is ranked in terms of its cure rate. PZQ, Praziquantel; Niri, Niridazole; Met, Metformin; Artes, Artesunate.