Association of anthelmintic treatment with malaria prevalence, incidence, and parasitemia: A systematic review and meta-analysis

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ABSTRACT

A chronic helminth infection can alter host immune response and affect malaria infection. We conducted a systematic review and meta-analysis to find the impact of anthelmintic treatment on malaria prevalence, incidence, and parasitemia. Nine and 12 electronic databases were searched on 28th July 2015 and 26 June 2020 for relevant studies. We performed meta-analysis for malaria prevalence, incidence, parasitemia, and a qualitative synthesis for other effects of anthelmintic treatment. Seventeen relevant papers were included. There was no association between anthelmintic treatment and malaria prevalence or change of parasitemia at the end of follow up period (pooled OR 0.93, 95% CI: 0.62, 1.38, *p*-value=0.71 and SMD -0.08, 95%CI: -0.24, 0.07, *p*-value=0.30 respectively) or at any defined time points in analysis. Pooled analysis of three studies demonstrated no association between malaria incidence and anthelmintic treatment (rate ratio 0.93, 95%CI: 0.80, 1.08, *p*-value=0.33). Our study encourages anthelmintic treatment in countries with high burden of co-infections as anthelmintic treatment is not associated with change in malaria prevalence, incidence, or parasitemia.

Word Count: 166

KEYWORDS

Ascaris, *Trichuris*, hookworm, *Schistosoma*, *Plasmodium*, co-infection, deworming

RUNNING TITLE

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KEY FINDINGS

- Anthelmintic treatment has no impact on malaria in the presence of helminth infection
- No current evidence in literature support association of maternal anthelmintic treatment with offspring malaria incidence
- Deworming should not be halted; it could safely be used in malaria-helminth coinfection

1. INTRODUCTION

Malaria is one of the most serious infectious diseases as according to WHO, about 229 million cases of malaria and 409,000 deaths are documented worldwide in 2019 with 67% (274,000) of all malaria deaths occuring in children aged under 5 years. (WHO, 2020) Helminth infection itself is one of the most common health problems in the world. It is estimated that about two billion cases are infected with schistosomes and soil-transmitted helminths (STH)(WHO Expert Committee on the Control of Schistosomiasis (2001 : Geneva, 2002), with up to one-third of the population of Sub-Saharan Africa affected by STH infections. Because helminth infections are often endemic in the same communities that are exposed to infection with malaria(Booth, 2006), the co-infection of helminths and malaria parasites is frequently observed.(Booth et al., 2008; Hartgers and Yazdanbakhsh, 2006) Examination of 1,546 Tanzanian children found that 276 children have malaria-helminth co-infection.(Kinung'hi et al., 2014) A similar study conducted in southern Ethiopia found 255 (55.7%, n=458) malaria-infected patients were positive for one or more STHs.(Degarege et al., 2010) In addition, another study demonstrated that the rate of helminths co-infection among the malaria patients (n=230) was 67%.(Mulu et al., 2013) The evidence of common comorbidities between helminth and plasmodia infection brings an inquiry about the nature of their relationship and the immune regulation in the host's system.(McSorley and Maizels, 2012)

It has been known that there is a down-regulation of Th1 cytokine along with an up-regulation of Th2 cytokines with helminth infection. Down-regulation of the Th1 response decreases the protective effects of IFN-γ during the liver and blood stages of malaria infection thus favors the production of non-cytophilic antibodies, subsequently, making individuals more susceptible to clinical malaria.(Mwangi et al., 2006; Torre et al., 2002)

Contrasting facts have been found about the relationship between helminth and plasmodia. Evidence about helminth-malaria co-infection in human and its impact on malaria has been reviewed previously. However, most studies were cross-sectional surveys. It is still a controversy, whether the co-infection with a helminth or using anthelmintic treatment has a

protective effect or is a risk factor for malaria disease.(Mwangi et al., 2006) Therefore, we conducted a systematic review and meta-analysis to investigate the association of anthelmintic treatment with malaria prevalence, incidence, and parasitemia in populations co-infected with helminth and malaria.

2. METHODS

2.1 Protocol and registration

The protocol for this review has been registered at PROSPERO International prospective register of systematic reviews (No. CRD 42015025544). Our study was conducted according to the recommendation of the PRISMA statement (Liberati et al., 2009) which is available in Supplementary Data **Checklist S1 (PRISMA 2009 checklist)**.

2.2 Information sources and search strategies

We searched 9 electronic databases on 28th July 2015. The full search strategy in each database is listed in our protocol. In addition, we manually collected studies by screening the references and related articles in PubMed and Google Scholar. The updated search was performed in 26 June 2020 using the same search terms in three new databases: ISRCTN (International Standard Registered Clinical/Social Study Number) registry, WHO International Clinical Trials Registry Platform (ICTRP), and ClinicalTrials.

2.3 Study selection and eligibility criteria

All titles, abstracts, and full texts were reviewed independently by at least two authors after a pilot training with a senior researcher (NTH). Any original studies like randomized controlled trials, controlled trials, or cohort studies in human subjects that reported an association between anthelmintic therapy and malaria prevalence, incidence or parasitemia were included. There were no restrictions regarding publication language, country, patient age, and gender. We excluded articles with the following characteristics: (i) including data that could not be reliably extracted; (ii) including overlapping data sets; (iii) reviews, theses, books, conference papers and articles without available full text (conference, editorial, author response); (iv) case reports, case series, and systematic review studies. The same criteria were applied for the updated search results.

2.4 Data extraction

Each article was extracted by three independent reviewers and was checked by at least another two researchers. The disagreement was resolved via discussion and consensus between the three authors. A data extraction form in an Excel file

was developed by three authors (NTH, KASD, MTE) based on the pilot review, extraction, and calibration of two randomly selected studies. Data extracted from each study are available in our protocol.

Some studies presented data in a graphical format and these data were extracted using Get Data Graph Digitizer version 2.24 (http://getdata-graph-digitizer.com/).

2.5 Quality assessment

We used Cochrane's tool(Higgins et al., 2011) to assess the risk of bias for randomized clinical trials, *Clinical Guidelines Network Cancer Council Australia*(Clinical Guidelines Network Cancer Council Australia, 2014) tool for non-randomized study, and *National Institute of Health* (NIH) tool(National Heart, Lung, n.d.) for the cohort study. All quality assessment was carried out by discussion and consensus after an independent review of each study by two authors.

2.6 Statistical analysis

Meta-analysis was performed using Comprehensive Meta-analysis software version 2 (Biostat, USA, https://www.meta-analysis.com/). Pooled odds ratio (OR) was calculated for malaria prevalence outcome while standardized mean difference (SMD) was used for malaria parasitemia outcome because of different unit of measurement. The corresponding 95% confidence intervals (95%CI) of pooled effect size were also calculated using a fixed-effects or random-effects when there is evidence of heterogeneity.(Borenstein and Higgins, 2013) Evaluation of heterogeneity was conducted using the Q statistic and I^2-test.(Higgins et al., 2003) We used funnel plot and Egger's regression test to assess the presence of publication bias when there were at least ten studies.(Sterne et al., 2000) If publication bias was found, the trim and fill method of Duvall and Tweedie was performed by adding studies that appeared to be missing to enhance the symmetry.(Duval and Tweedie, 2000) The adjusted pooled effect size and its 95%CI were computed after the addition of potential missing studies.

Subgroup analysis was performed to investigate the effect of different anthelmintic used and different category of subjects on the malaria prevalence or parasitemia outcome if there were at least 10 or more studies or data sets in the analysis.(Borenstein and Higgins, 2013) We also performed a sensitivity analysis by removing smallest study, largest study, and pre-post study.

Most of the included studies have multiple time points observation, with different follow up duration. We defined outcome of malaria prevalence and malaria parasitemia with specific follow up period of included studies: 1-4 months, 5-7 months,

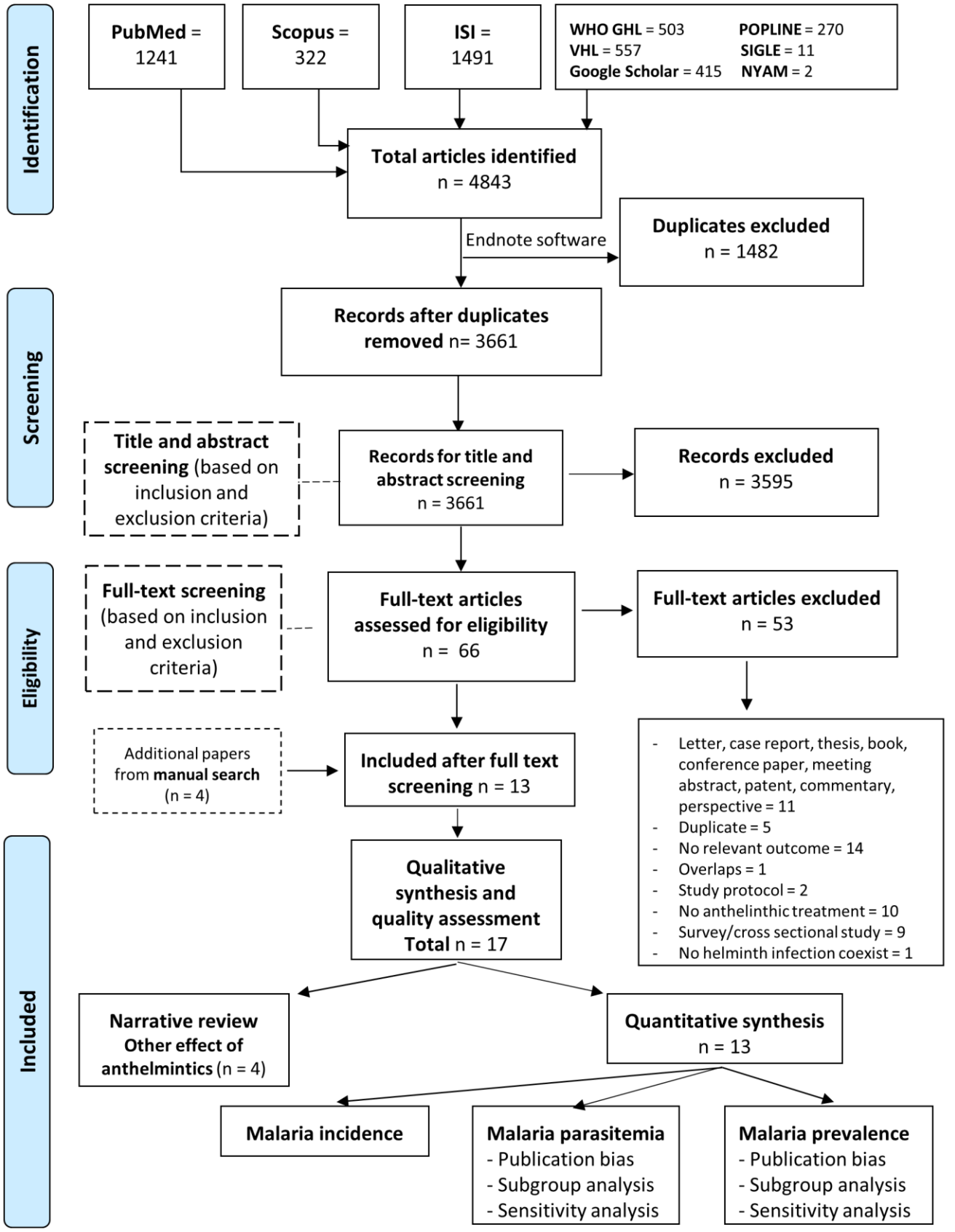
7-9 months, 10-12 months, 13-16 months, 17-20 months, 21-24 months, and at the end of each study follow up period.(J. Higgins and Green, 2011) Parasitemia was measured at baseline using thick and thin blood films as shown in **Table 1**, with effect of anthelmintic treatment on clearance of parasites measured at each of the follow up points as shown in **Table 3**. Studies by Brutus et al in 2006 and 2007 had two data sets and we analyzed both for malaria parasitemia. We analyzed the association with *P. falciparum* only as it was reported in all studies, while *P. malariae,*(Hürlimann et al., 2014) *P. vivax* and *P. ovale* (Wiria et al., 2013) were only reported in one study. There were two studies that recruited the same population (Webb et al., 2011; Ndibazza et al., 2012). We considered them as one dataset if the same outcome was presented in the two studies.

Because most outcomes were reported on log-transformed value for malaria parasitemia outcome, we log-transformed the reported raw data using method 1 described by Higgins, et al.(Higgins et al., 2008) When the published study only reported the mean, the estimated standard deviation (SD) was derived from linear regression of log (published SDs) against log (published means).(Van Rijkom et al., 1998) The published SDs and means were collected from other included studies. In some studies that reported mean with standard error or confidence interval, SDs were calculated using method that has been described elsewhere.(J. P. T. Higgins and Green, 2011)

3. RESULTS

3.1 Characteristics of included studies

The databases search retrieved 4843 citations. Duplicates deletion was performed using EndNote software. A total of 3661 papers were included for initial screening of titles and abstracts. We excluded 3595 papers because they did not meet our inclusion criteria. We performed a full-text review of 66 papers. Fifty three papers were excluded due to one of the reasons listed in **Figure 1**.



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164 **Figure 1. PRISMA flow diagram of study selection process.**

With addition of four studies from manual search of included studies, Therefore, we included seventeen studies. All 17 studies entered qualitative synthesis while only 13 studies entered quantitative synthesis of malaria prevalence, incidence, and parasitemia. (Beasley et al., 1999; Brutus et al., 2006, 2007; Keiser et al., 2010; Kirwan et al., 2010; Ndibazza et al., 2012; Wiria et al., 2013; Kinung'hi et al., 2015; Kepha et al., 2016; Stephenson et al., 1989; Midzi et al., 2011; Hurlimann et al., 2014; Vennervald et al., 2005). Four studies did not have suitable outcome data to perform meta-analysis related to our study objective. We saved these four studies for narrative review of other anthelmintic effects.(Dondorp et al., 2007; Maude et al., 2014; Reilly et al., 2008, Webb et al, 2011). The updated search was performed in 26 June 2020, and 193 papers were retrieved. After duplicates deletion using EndNote, we included 156 citation for the title and abstract screening and none of them met our inclusion criteria.

Overall, we identified nine randomized trials, three non-randomized trials and one cohort study that were eligible for inclusion in the meta-analysis. Most of the included studies for statistical analysis were performed in Africa while only three studies were from Asia (Indonesia, Thailand and Bangladesh). Participants were mostly children. However, there were six studies in which adults were also involved. The duration of the studies ranged from 48 hours up to 45 months. All participants were already infected by *Plasmodium* species (mostly *P. falciparum*) and either STH (*A. lumbricoides, A. duodenale, T. trichiura, S. stercoralis, N. americanus, hookworms*) or *Schistosoma spp* (*S. mansoni or S. hematobium or both*) at the beginning of studies. Malaria was diagnosed microscopically from thin and thick Giemsa-stained blood smears in majority of studies. There were variations in anthelmintic given across included studies. Four studies used levamisole, four studies used albendazole alone, four studies used praziquantel alone, and four studies used a combination of albendazole and praziquantel. Comparator groups used either a placebo or a pre-post design.

184 **Table 1.** Characteristics of included studies

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Author, year of publication	Country of patients	Study design	Duration of follow up/outcome assessment period	Number of participants (total females)	Age mean year(SD)	Intervention	Control	Helminth/malaria Infection at baseline	Diagnostic method for helminth	Diagnostic method for malaria
Stephenson, 1989	Kenya	Non-randomized clinical trial	8 months	312 (116)	Intervention group: 10.5 (2.19) Control group: 10.7 (2.19)	40 mg/kg praziquantel orally, single dose	placebo	*P. falciparum* predominant (up to 98%)[¥], Hookworm, *S. hematobium*	Urine filtration method (*S. hematobium*), Kato-Katz technique (STHs and hookworm)	Giemsa stained thick blood films, Leishman's stained thin blood films
Beasley, 1999	Tanzania	Randomized placebo-controlled trial	4 months	357 (121) (only 250 completed follow up)	Intervention group: 9.85 (2.25) Control group: 9.5 (2.22)	single dose 400 mg albendazole and 40 mg/kg praziquantel orally for 4 months	placebo for 4 months	*P. falciparum, S. hematobium,* STH (hookworm, *A. lumbricoides, T. trichiura*)	Kato Katz technique (intestinal worms), urine concentration (*S. hematobium*)	Thick and thin blood smears stained with Giemsa
Vennervald, 2005	Kenya	Cohort study	24 months	67 (N/A)	(7-18) for the cohort*	a single dose of praziquantel	No control group	*S. mansoni*	Kato-Katz technique	Blood samples (thick and thin films)
Brutus, 2006	Madagascar	Randomized controlled trial	18 months	350 (179)	0-15 and over* for both group	3 mg levamisole orally every 2 months visits	0.5-3 oral tabs of multivitamin treatment every 2 months visits	*P. falciparum, S. mansoni, A. lumbricoides, N. americanus*	Merthiolate iodine formaline/MIF concentration method	Giemsa stain, thick and thin blood smears
Brutus, 2007	Madagascar	Randomized controlled trial	18 months	212 (111)	0-adult* for both group	3 mg levamisole orally every 2 months visits	0.5-3 tabs multivitamin every 2 months visits	*P. falciparum, A. lumbricoides, S. mansoni*	Merthiolate iodine formaline/MIF concentration method for stool samples	Giemsa stain, finger prick thick and thin blood smears
Dondorp, 2007	Thailand	Randomized open label controlled trial	72 hours	21 (2)	Intervention group: 28 (19-39)[§] Control group: 29 (22-35)[§]	adjuvant therapy with a single 150-mg dose of levamisole hydrochloride plus antimalarial treatment of oral quinine salt combined with doxycycline for 7 days	the same antimalarial treatment and no adjuvant therapy	*P. falciparum*	N/A	Blood films (thin films) examined by light microscopy
Reilly, 2008	Zimbabwe	Cohort	6 weeks	117 (64)	6-18 years*	praziquantel	No control group	*S. haematobium, S. mansoni, P. falciparum*	Kato-Katz technique	Thick blood smear

Keiser, 2010	South Cote d'Ivoire	Randomized exploratory open label trial	26 days	26 (12)	9.5 (2.3)	40 mg/kg Praziquantel orally once for 26 days	No control group (pre-post design).	*Schistosoma spp* (*mansoni*, *hematobium*), *P. falciparum*	Urine with filtration method and stool samples with duplicate Kato-Katz technique	Thick and thin blood films stained with giemsa
Kirwan, 2010	Nigeria	Randomized double blind placebo-controlled trial	14 months	1228 (161)	0-4* for both group	200 mg (if 1-year child) or 400 mg (children ≥ 2-year-old) of albendazole orally every four months for 12 months	placebo every four months for 12 months	*P. falciparum* predominant (99.5%)[¥], STH (*hookworm*, *T. trichiura*, *A. lumbricoides*), *S. hematobium*	Stool samples were processed by formol-ether concentration	By microscopy examination of thin and thick blood smears stained with a 3% Giemsa solution.
Midzi, 2011	Zimbabwe	Non-randomized clinical trial	33 months	420[ł] (N/A)	10.3 (2.3)	combined intervention: (1) Basic life skills education in schools, (2) Treatment (Praziquantel 40mg/kg + Albendazole 400 mg single dose) at: baseline, 6, 12, and 33 months follow up, (3) Prompt malaria treatment monitoring	No control group (pre-post design).	*Schistosoma spp* (*haematobium* and *mansoni*), STH (hookworm, *A. lumbricoides*, *T. trichiura*), *P. falciparum*	The urine filtration technique (*Schistosoma*) examined microscopically, Kato Katz and formal ether concentration technique (STH)	Microscopic examination of thick and thin blood films stained with Giemsa
Webb, 2011	Uganda	Randomized, double-blind, placebo-controlled trial	12 months	2507 (all females) (data were available for 2356 women at delivery with 2345 livebirths)	< 20, 20-24, 25-29, 30-34, ≥ 35[†]	either single dose albendazole (440 mg) and single dose praziquantel (40 mg/kg), albendazole and a praziquantel-matching placebo, an albendazole-matching placebo and praziquantel.	an albendazole-matching placebo and a praziquantel-matching placebo.	Hookworm, *S. mansoni*, *P. falciparum*	Kato-Katz technique	Blood samples (thick films) and clinically
Ndibazza, 2012	Uganda	Randomized double blind placebo-controlled trial	45 months	2016 (975)	Intervention group: 1.52 (0.5) Control group: 1.52 (0.54)	[ǂ] 200 mg (From age 15 to 21 months) or 400 mg (from age 2 to 5 years) albendazole treatment orally every 3 months until age 5 years	[ǂ] quarterly matching placebo and followed until age 5 years	*S. mansoni*, *P. falciparum*, STH (hookworm, *T. trichiura*, *A. lumbricoides*), *M. perstans*, *H. nana*, *Trichostrongylus*	Kato-Katz technique (hookworm ova), stool culture (*Strongyloides*)	Leishman stained thick blood films (ring forms or gametocyte)
Wiria, 2013	Indonesia	A household-based cluster-randomized, double blind, placebo-	21 months	4004 (2132)	Intervention group: 25.8 (18.7) Control group: 25.7 (18.7)	400 mg albendazole orally every 3 months	matching placebo every 3 months	STH (*N. americanus*, *A. duodenale*, *A. lumbricoides*, *S. stercoralis*, *T. trichiura*, hookworms, *Plasmodium* spp (*falciparum*, *vivax*,	Stool samples, examined by microscopy (*T. trichiura*) and multiplex real time PCR for hookworms (*A. duodenale*, *N.*	Thick and thin Giemsa stained blood smears, parasitemia examined by microscopy and

		controlled trial						*ovale*)[¥]	*americanus*), *A. lumbricoides*, and *S. stercoralis*	PCR
Hurlimann, 2014	Côte d'Ivoire	Non-randomized clinical trial	5 months	257 (134)	10.6 (5-14)*	400 mg albendazole and 40 mg/kg praziquantel orally	No control group (pre-post design).	*Plasmodium spp* (*falciparum* and *malariae*)[¥], *Schistosoma spp* (*mansoni* and *hematobium*), STH (hookworm, *T. trichiura*, *A. lumbricoides*), intestinal protozoa (*G. intestinalis, E. hystolitica/E. dispar*)	Kato-Katz technique (STH), urine filtration method (*S. hematobium*), SAF-fixed stool with ether concentration technique (intestinal protozoa)	Finger-prick blood samples (for rapid diagnostic test), thick and thin blood films stained with 10% Giemsa
Maude, 2014	Bangladesh	Randomized, open label, controlled trial	48 hours	56 (16)	Intervention group: 30 (25-45)[§] Control group: 28 (21-45)[§]	25 mg levamisole as adjuvant therapy plus an intravenous 150 mg artesunate	intravenous 150 mg artesunate without adjuvant therapy	*P. falciparum*	N/A	Thick and thin blood smears
Kinung'hi, 2015	Tanzania	Randomized open label intervention trial	24 months	765 (392)	3-13* for both group	repeated doses of 40mg/kg praziquantel and 400mg albendazole orally four times a year at three months interval	a single dose of 40mg/kg praziquantel and 400mg albendazol orally once a year	*P. falciparum, S. mansoni, S. hematobium*, hookworm, *T. trichiura*	Kato Katz technique (*S. mansoni* and STH), urine filtration method (*S. haematobium*)	Giemsa stain, thick blood smears and clinical criteria
Kepha, 2016	Western Kenya	Randomized open label equivalence trial	12 months	2346 (1114)	Intervention group: 10.4 (2.5) Control group: 10.5 (2.5)	a single dose of 400 mg albendazole orally every 4 months for 12 months	a single dose of 400 mg of albendazole at month 0 and a single 250 mg dose of vitamin C at 4, 8, and 12 months.	STH (especially, *A. lumbricoides*, *T. trichiura*, hookworms), *P. falciparum*	Kato-Katz technique	Active case finding of clinical malaria; Rapid diagnostic test plus thick and thin blood smears with 2% Giemsa

*Age reported as range.

[¥]Only data of *P. falciparum* were used in analysis.

[ł]Malaria data from this study come only from one study area (Burma Valley). We used the data from this area only for analysis.

[ǂ]Only data from children were used in analysis (offspring of mother which have been given intervention albendazole and praziquantel, or albendazole placebo and praziquantel, or albendazole and praziquantel placebo, or both albendazole placebo and praziquantel placebo).

[†]Age reported as classification range.

[§]Age reported as mean and interquartile range.

193 *3.2 Risk of bias*

194 Overall, the risk of bias in the randomized clinical trials was low in four trials, unclear in seven, and high in one. For all
195 non-randomized studies, the overall risk of bias was high. The overall quality assessment of bias for the two-cohort study
196 was good (low risk). Summary risk of bias can be found in **Supplementary Table 2-4**.

197 *3.3 Effect of anthelmintic treatment on malaria prevalence*

198 Our pooled results demonstrated no association at any time point define in the analysis (**Table 2**).

199 **Table 2.** Effect of anthelmintic treatment on malaria prevalence

Follow up period	No. of study	Intervention (n/N)	Control (n/N)	Heterogeneity		Model	Association with malaria prevalence		Egger's 2-tailed bias *p*-value
				p-value	I^2		*p*-value	Odds ratio (95% CI)	
1-4 months	5	694/2299	655/2286	0.30	17.61	Fixed	0.21	1.10 (0.95, 1.27)	
5-7 months	4	593/2472	686/2499	0.001	92.48	Random	0.37	0.72 (0.35, 1.48)	
7-9 months	5	536/2936	573/2965	0.04	61.34	Random	0.28	0.84 (0.60, 1.16)	
10-12 months	5	706/2680	800/2710	0.001	84.12	Random	0.20	0.77 (0.51, 1.15)	
13-16 months	3	533/1848	526/1868	0.59	0.001	Fixed	0.50	1.06 (0.90, 1.25)	
17-20 months[†]	1	10/803	3/815				0.06	3.41 (0.94, 12.45)	
21-24 months	4	133/1939	113/1942	0.20	35.49	Fixed	0.21	1.19 (0.90, 1.57)	
End of each studies	11	1075/3896	1156/3934	0.00	86.62	Random	0.71	0.93 (0.62, 1.38)	0.97

200 [†]Outcome at this time point only from one study by Wiria et al. 2013

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202 Pooling effect size at the end of each studies (ranging from 1 month to 45 months follow up) also demonstrated no
203 association (OR 0.93, 95%CI: 0.62, 1.38, *p*-value=0.71) (**Figure 2**). Heterogeneity was high (I^2=86.62, *p*-value=0.001).
204 No publication bias was found (Egger's test *p*-value=0.97).

205 Subgroup and sensitivity analysis at the end of each study follow up also demonstrated no association (**Supplementary**
206 **Table 5-7**).

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3.4 Effect of anthelmintic treatment on malaria parasitemia

Our meta-analysis demonstrated no effect on malaria parasitemia at any time point define in the analysis (**Table 3**).

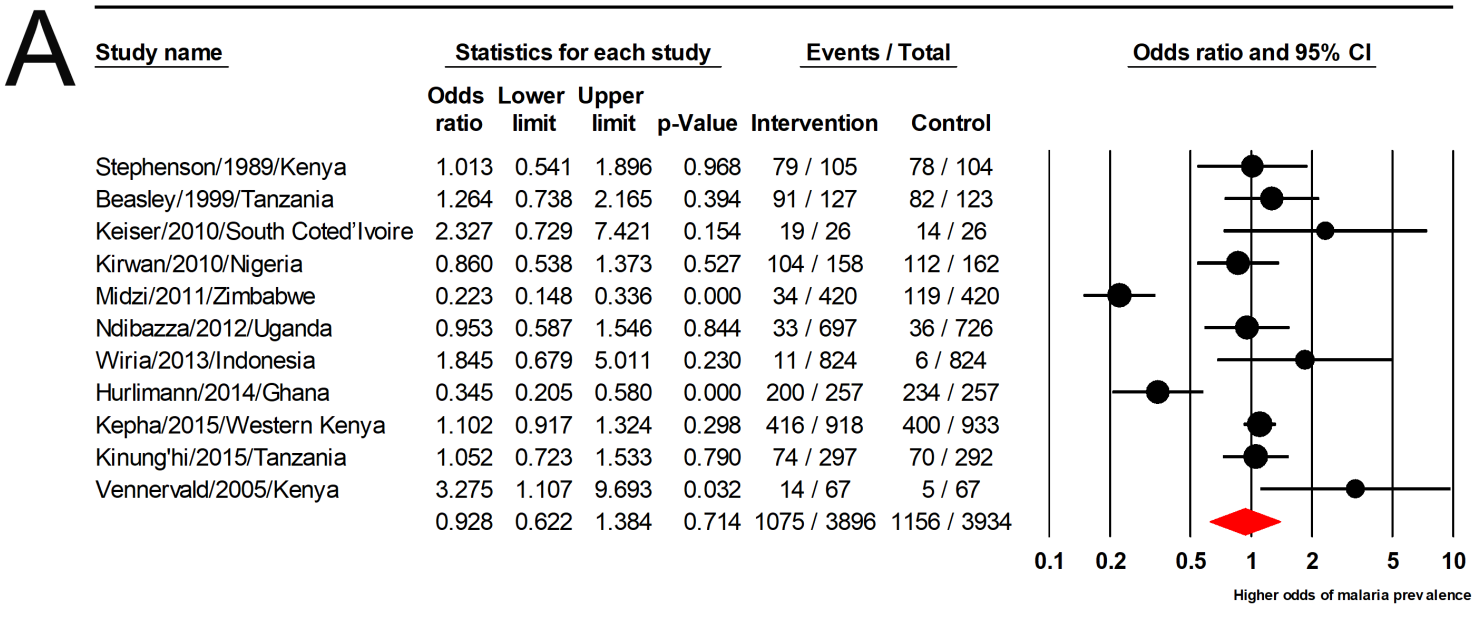
Table 3. Effect of anthelmintic treatment on malaria parasitemia[†]

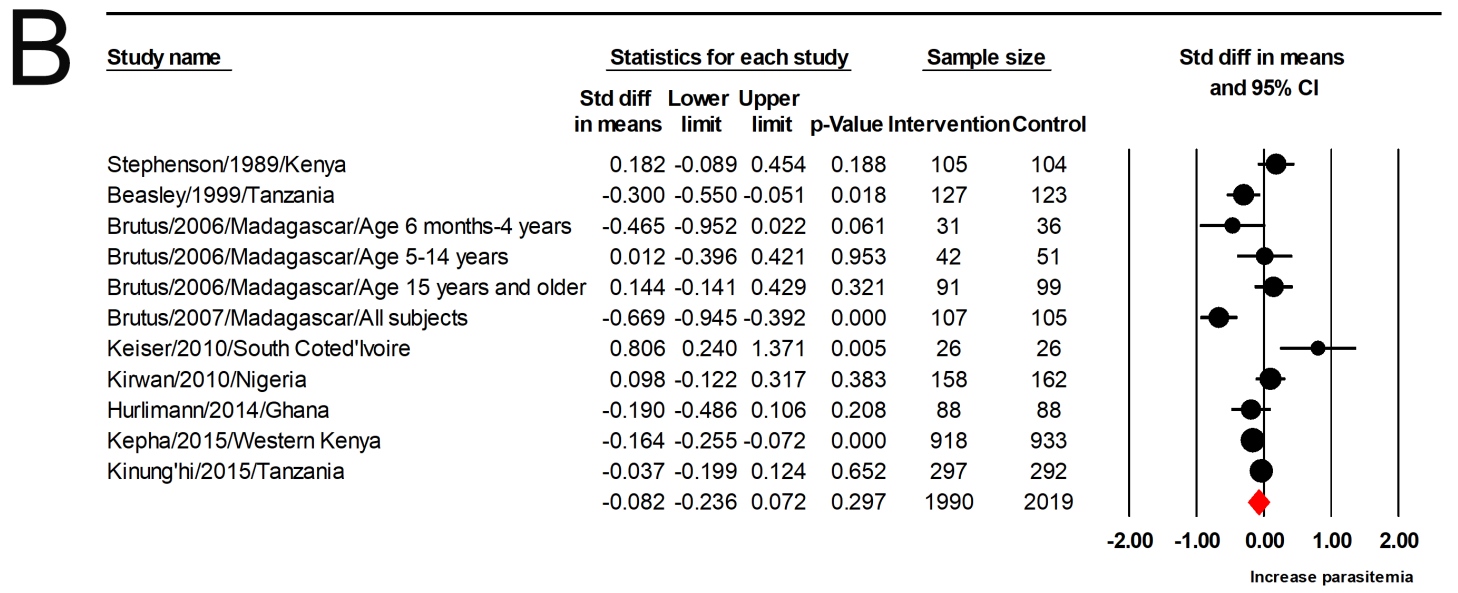
Follow up period	No. of study/No. of datasets[¥]	Intervention (N)	Control (N)	Heterogeneity		Model	Association with malaria parasitemia		Egger's 2-tailed bias *p*-value
				p-value	I^2		*p*-value	Standardized mean difference (95% CI)	
1-4 months[‡]	6/8	1660	1687	0.001	92.81	Random	0.23	0.20 (-0.13, 0.53)	
5-7 months	4/6	1360	1386	0.001	91.27	Random	0.34	0.18 (-0.18, 0.54)	
7-9 months[‡]	5/7	1535	1564	0.001	76.91	Random	0.12	0.15 (-0.04, 0.35)	
10-12 months	5/7	1718	1747	0.001	76.07	Random	0.27	0.10 (-0.07, 0.27)	
13-16 months	4/6	1347	1386	0.001	89.63	Random	0.48	0.11 (-0.20, 0.42)	
21-24 months[*]	1/1	297	292				0.65	-0.04 (-0.20, 0.12)	
End of each studies	9/11	1990	2019	0.001	77.11	Random	0.30	-0.08 (-0.24, 0.07)	

[†]None of included studies has malaria parasitemia outcome at 17-20 months period. Analysis of outcome at 1-4 months, 10-12 months, and 13-16 months was done using Brutus, et al 2006 and 2007 data at 2 months, 10 months, 14 months, respectively.
[‡]Adjustment made for publication bias using trim and fill method by Duval and Tweedie (random effect) did not change the standardized mean difference.
[*]Outcome at this time point only from one study by Kinung'hi et al. 2015
[¥]Study by Brutus, et al 2006 has three data set (subject age 6 months-4 years old, 5-14 years old, and ≥ 15 years old).

Pooled analysis using Brutus et al, 2006 and 2007 data at 4 instead of 2 months for outcome at 1-4 months, 12 instead of 10 months for outcome at 10-12 months, and 16 instead of 14 for outcome at 13-16 months demonstrated no effect in both malaria parasitemia at 1-4 months (SMD 0.15, 95%CI: -0.17, 0.47, *p*-value=0.37) and 13-16 months (SMD -0.16, 95%CI: -0.39, 0.07, *p*-value=0.17). However, small increase was detected for outcome at 10-12 months (SMD 0.21, 95%CI: 0.03, 0.38, *p*-value=0.03).

Pooling effect size at the end of each studies demonstrated no effect (SMD -0.08, 95%CI: -0.24, 0.07, *p*-value=0.30) (**Figure 2**). Heterogeneity was high (I^2=77.11, *p*-value=0.00).





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226 **Figure 2.** Forest plot depicting the effect of anthelminthic treatment on (**A**) malaria prevalence (pooled OR, 95%CI,
227 random-effects model) and (**B**) malaria parasitemia at the end of each study follow up (pooled SMD, 95% CI, random-
228 effects model).

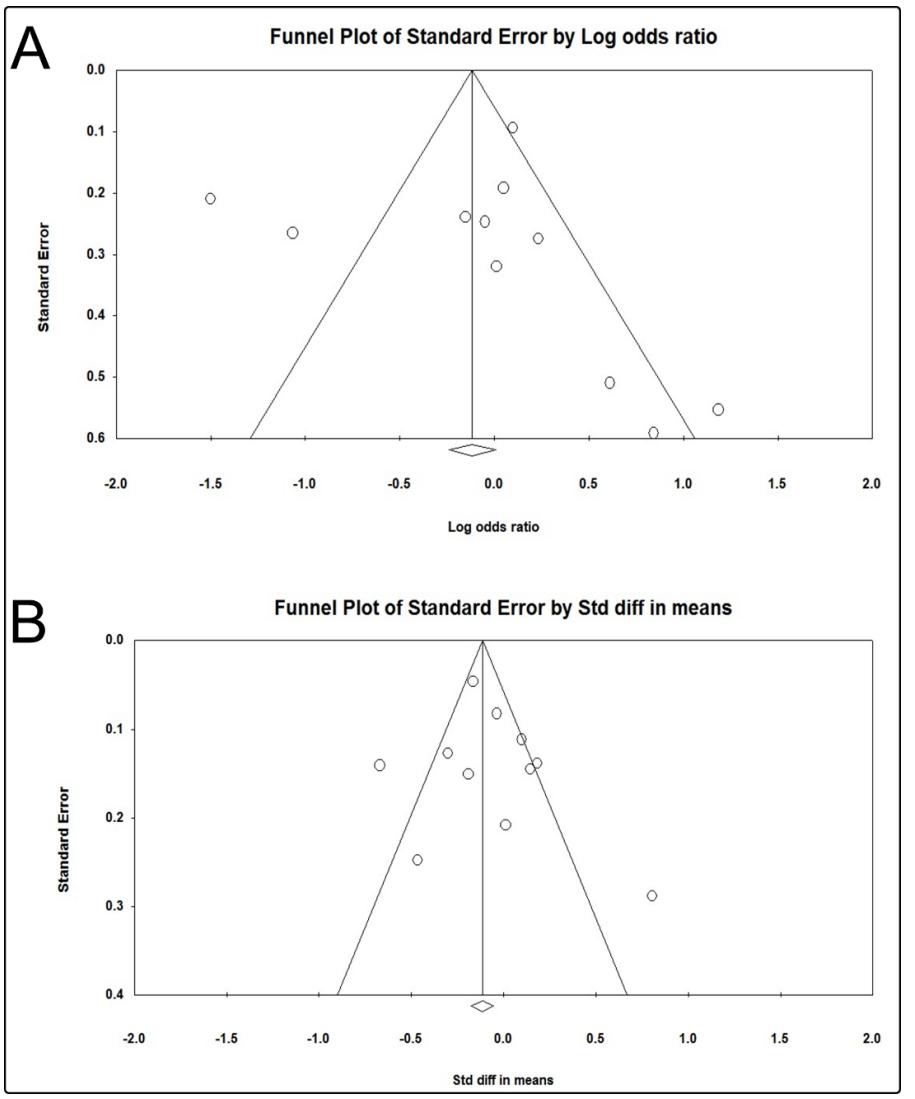

Figure 3. Funnel plot of (**A**) malaria prevalence and (**B**) parasitemia outcome at the end of each study follow up.

Subgroup and sensitivity analysis at the end of each study follow up also demonstrated no effect (**Supplementary Table 5 -7**).

3.5 Effect of anthelmintic treatment on malaria incidence

Pooled analysis of three studies (Kepha et al., 2016; Kinung'hi et al., 2015; Ndibazza et al., 2012) demonstrated no association between malaria incidence and anthelmintic treatment (rate ratio 0.93, 95%CI: 0.80, 1.08, *p*-value=0.33) (**Figure 4**).

3.6 Effect of praziquantel treatment on P. falciparum-specific antibody responses

One study from Zimbabwe reported no association between *P. falciparum*-specific antibody response and anthelminthic treatment after 6 weeks of praziquantel treatment in 117 subjects aged 6-18 years old infected with *S. haematobium* and *P.*

falciparum. Praziquantel treatment had no effect on plasmodia crude antigens or merozoite surface protein -1 (MSP-1) and MSP-2.(Reilly et al., 2008)

3.7 Effect of levamisole hydrochloride as adjunctive treatment on infected red blood cells (iRBCs) by P. falciparum

Two studies investigated the potential effect of levamisole hydrochloride as an adjunctive treatment on the cytoadherence and sequestration of infected RBCs by *P. falciparum.*(Dondorp et al., 2007; Maude et al., 2014) A controlled trial of patients with uncomplicated malaria falciparum conducted by Dondorp et al(Dondorp et al., 2007) found single 150 mg dose of levamisole as adjunctive treatment to quinine (n=12) was associated with marked inhibition of sequestration of *P. falciparum*. Thus, it reduces the impairment of microcirculation occurring with sequestered, parasitized erythrocytes.

The second study was a randomized, double-blind controlled trial,(Maude et al., 2014) conducted with the same concept of the earlier study.(Dondorp et al., 2007) The main difference was the usage of artesunate rather than quinine as antimalarial, and it was conducted in patients with severe malaria (having high parasitemia). The study could not show a beneficial effect when added same single dose of levamisole as adjunctive therapy to intravenous artesunate (n=29) compared to control (n=27). The sequestration ratios for all parasite stages did not differ between treatment groups.

3.8 Effect of maternal anthelmintic treatment during pregnancy on malaria incidence of their offspring

One study investigated the effect of maternal anthelmintic treatment during pregnancy on malaria incidence of their offspring at age 1 year demonstrated no effect on malaria incidence for albendazole (rate per 100 person-years 39.9, 95%CI: 36.6, 43.8, *p*-value=0.67) or praziquantel treatment (rate per 100 person-years 41.0, 95%CI: 37.3, 45.0, *p*-value=0.97) compared to placebo during pregnancy. No effect on malaria incidence of offspring at age 1 year also demonstrated for mother with hookworm or schistosomiasis infection (albendazole hazard ratio 1.01, 95%CI: 0.78, 1.31, *p*-value= 0.48; praziquantel hazard ratio 0.94, 95%CI: 0.62, 1.41, *p*-value= 0.70) compared to mother without hookworm or schistosomiasis infection. (Webb et al., 2011)

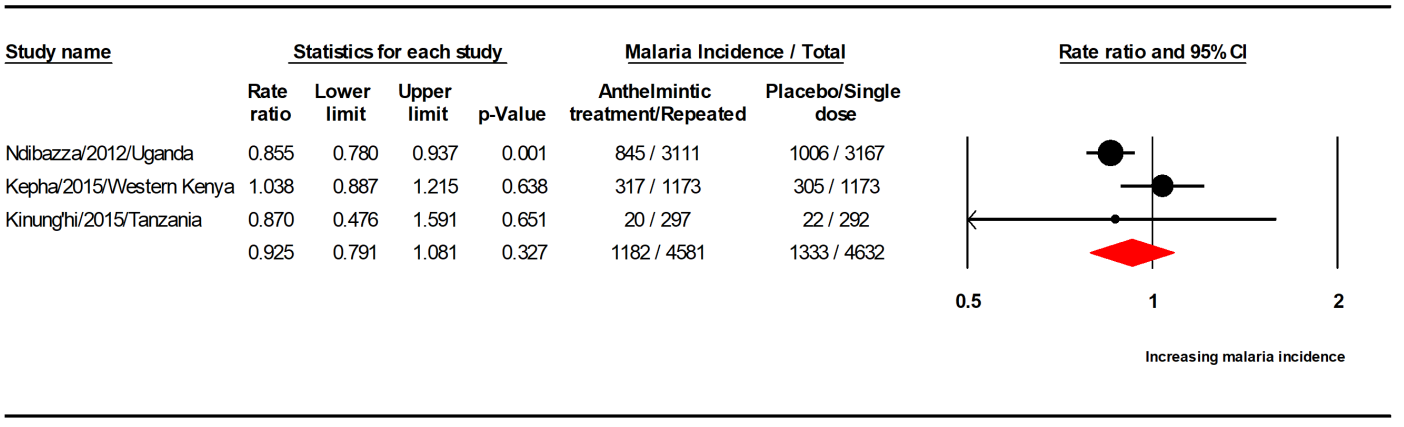

Figure 4. Effect of anthelmintic treatment on malaria incidence. Showing the pooled rate ratio with 95%.

4. DISCUSSION

Our meta-analysis showed no association between anthelminthic treatment and malaria prevalence, incidence or the change of malaria parasitemia at all defined time points. Most of included studies used either praziquantel 40mg/kg orally or albendazole 400 mg orally with few studies using levamisole at different doses (**Table 1**). This is different from the results reported by some systematic review and meta-analysis that there was a positive association of soil-transmitted helminths (STH) or *Schistosoma spp* with asymptomatic/uncomplicated malaria.(Degarege et al., 2016a, 2016b; Naing et al., 2013) There are three explanations as to why we could not find similar findings in our review. First, the duration of existing helminth infection (acute or chronic state) and the timing of when *Plasmodium* infected the host contribute to different mechanism of immune response.(Salazar-Castañon et al., 2014) If *Plasmodium* infection occurs at acute helminth infection, it will increase Th1-immune response, inhibit *Plasmodium* replication, but increase pathology and mortality in the host. While in chronic helminth infection, *Plasmodium* infection will result in shift of host's immune response to Th2, thus increase susceptibility to *Plasmodium* infection, but protect the host from severe malaria.(Salazar-Castañon et al., 2014) Our included studies did not provide helminth infection status at baseline, whether it is an acute or chronic state of helminth infection when malaria infection occurs. Second, anthelmintic treatment may trigger shift of immune responses to Th1 in helminth-plasmodium co-infection leading to decrease plasmodium replication and susceptibility to clinical malaria at early malaria stage. (Salazar-Castañon et al., 2014) Third, different species of helminth infection could lead to

different immune responses to *Plasmodium*. (Salazar-Castañon et al., 2014) We could not perform subgroup analysis based on helminth species because of small number of studies.

For outcome at 10-12 months, using Brutus et al 2006 and 2007 data set at 12 months instead of data set at 10 months yield a small increase of malaria parasitemia. This can be explained by seasonal fluctuations; follow up to 12 months was through humid season, which is peak of parasite densities.(Brutus et al., 2007, 2006)

The study conducted by Reilly et al. found there was no association between antibodies against *P. falciparum* and those against *S. haematobium*. In addition, anthelmintic treatment had an effect only on anti-schistosome responses with none against plasmodia crude antigens. (Reilly et al., 2008)

Dondorp et al,(Dondorp et al., 2007) demonstrated that anthelmintic treatment (levamisole) led to inhibition of sequestration, thus reducing the microcirculation impairment caused by this sequestration. However, the authors did not investigate the relationship in the presence of helminth infection. In their follow up study (Maude et al., 2014) this effect was not shown. Although our current analysis showed no difference when using different anthelmintic, this finding may show that using different anthelmintic in the presence or absence of helminth infection may have different mechanisms and impacts on *Plasmodium* infection.

Anthelmntic treatment on mothers during pregnancy showed no effect on malaria incidence of their offspring ranging from birth to five years of age. The explanation behind this from the theoretical point of view could be helminth infection in early childhood is acute infection and initial Th1-like immune response is associated with low malaria parasite growth.(Salazar-Castañon et al., 2014).For malaria prevalence and parasitemia, our included studies were conducted in infant, children, adult subjects or a mix between them and our subgroup analysis showed no effect of age on the observed association between anthelmintic treatment and malaria prevalence, incidence, or parasitemia. Most of our included studies involving children and adults stated that the effect of anthelmintic treatment on malaria is apparently transient.(Wiria et al., 2013) No effect was observed in children under 5 years,(Brutus et al., 2007, 2006) or adults over 15 years.(Brutus et al., 2007) Therefore, we still consider that our studies could reflect school-age children population (age 5-15 years).

Our study should be interpreted in the light of several limitations. First, we observed significant heterogeneity of data we collected, therefore most of the analysis was conducted using random effect model. Second, for malaria parasitemia outcome, some missing standard deviation were estimated using linear regression and raw scales mean were log-

transformed. Third, some analysis involving baseline data, ignored pre-post correlation but we minimized this bias by excluding pre-post study in the analysis and we observed no different results. Fourth, although we identified some important factors which could affect helminth-malaria co-infection, such as the state of helminth infection and timing of malaria infection, helminth species,(Brooker et al., 2007; Mwangi et al., 2006; Ndibazza et al., 2012; Shapiro et al., 2005) we could not do the analysis for them. Fifth, the risk of bias of included studies should be taken into consideration while interpreting our meta-analysis. Finally, because of the small number of studies, we only performed subgroup analysis for the outcome at the end of each included studies follow up.

5. CONCLUSION

The findings of our systematic review and meta-analysis of latest published trials suggest that anthelminthic treatment has no association with malaria prevalence, incidence, and parasitemia. Plausible explanations include the heterogenous and lack of information regarding the state or duration of helminth infection, helminth species, and malaria infection timing related to helminth infection status. More studies are needed to address the lack of included studies and reduce the heterogeneity in the study by conform design and reporting. Thus, allowing future meta-analysis to conduct subgroup analysis at different time points of anthelmintic treatment effect on malaria outcome, based on helminth species or infection status. More studies also needed to investigate the effect of maternal anthelmintic treatment during pregnancy on malaria incidence of their offspring.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Nguyen Tien Huy, Kenji Hirayama: Conceptualization, Methodology, Validation, Formal analysis, Supervision, Project Administration; **Kadek Agus Surya Dila, Le Khac Linh, Mohamed Tamer Elhady, Amr Ehab El-Qushayri:** Formal analysis; **Kadek Agus Surya Dila, Mohamed Tamer Elhady, Le Khac Linh, Varshil Mehta, Walid Mohamed Attiah Hamad:** Writing-Original Draft; **Nguyen Tien Huy, Kadek Agus Surya Dila, Mohamed Tamer Elhady, Le Khac**

Linh, Varshil Mehta, Walid Mohamed Attiah Hamad, Ahmed Reda Ahmed, Amr Ehab El-Qushayri, Hany Eskarous, Maryan Samson, Nguyen Tran Minh Duc, Nguyen Lac Han: Investigation, Writing-Reviewing and Editing; **Kadek Agus Surya Dila:** Data Curation, Visualization.

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Tables

Figure Legends

ACTA TROPICA

Association of anthelmintic treatment with malaria prevalence, incidence, and parasitemia: A systematic review and meta-analysis

Data source

17 Studies identified

4 Studies for narrative reviews

13 Studies for meta-analysis

12360 participants

Study quality

Low risk
4 RCTs, 2 Cohorts

Unclear Risk
7 RCTs

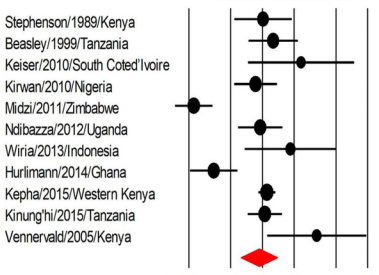
High risk
1 RCT, 3 non-RCTs

Summary

Anthelminthic treatment has no association with malaria prevalence, incidence, and parasitemia at any defined studies time points.

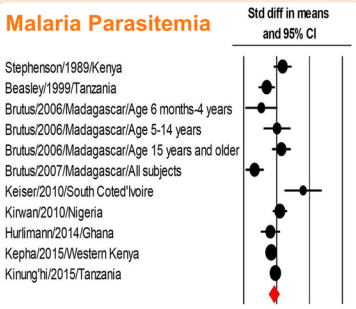
Outcomes

Malaria Prevalence



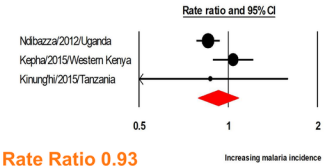
Pooled OR 0.93
95% CI: 0.62, 1.38, p=0.71

Malaria Parasitemia



SMD -0.08
95%CI: -0.24, 0.07, p=0.30

Malaria Incidence



Rate Ratio 0.93
95%CI: 0.80, 1.08, p=0.33

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