PLOS NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Malaria and helminth co-infections in children living in endemic countries: A systematic review with meta-analysis

Muhammed O. Afolabi[1]*, Boni M. Ale[2], Edgard D. Dabira[3], Schadrac C. Agbla[4], Amaya L. Bustinduy[5], Jean Louis A. Ndiaye[6,7], Brian Greenwood[1]

1 Department of Disease Control, London School of Hygiene & Tropical Medicine, London, United Kingdom, **2** Holo Healthcare Limited, Nairobi, Kenya, **3** Disease Control and Elimination Theme, Medical Research Council Unit The Gambia at London School of Hygiene & Tropical Medicine, Fajara, The Gambia, **4** Department of Health Data Science, University of Liverpool, Liverpool, United Kingdom, **5** Department of Clinical Research, London School of Hygiene & Tropical Medicine, London, United Kingdom, **6** Department of Parasitology, University of Thies, Thies, Senegal, **7** Département de Parasitologie-Mycologie, Université Cheikh Anta Diop, Dakar, Senegal

* Muhammed.Afolabi@lshtm.ac.uk

Check for updates

OPEN ACCESS

Citation: Afolabi MO, Ale BM, Dabira ED, Agbla SC, Bustinduy AL, Ndiaye JLA, et al. (2021) Malaria and helminth co-infections in children living in endemic countries: A systematic review with meta-analysis. PLoS Negl Trop Dis 15(2): e0009138. https://doi.org/10.1371/journal.pntd.0009138

Editor: Jessica K. Fairley, Emory University, UNITED STATES

Received: August 29, 2020

Accepted: January 13, 2021

Published: February 18, 2021

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pntd.0009138

Copyright: © 2021 Afolabi et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the manuscript and its Supporting Information files.

Abstract

Background

Current knowledge on the burden of, and interactions between malaria and helminth co-infections, as well as the impact of the dual infections on anaemia, remains inconclusive. We have conducted a systematic review with meta-analysis to update current knowledge as a first step towards developing and deploying coordinated approaches to the control and, ultimately, elimination of malaria-helminth co-infections among children living in endemic countries.

Methodology/Principal findings

We searched Medline, Embase, Global Health and Web of Science from each database inception until 16 March 2020, for peer-reviewed articles reporting malaria-helminth co-infections in children living in endemic countries. No language restriction was applied. Following removal of duplicates, two reviewers independently screened the studies for eligibility. We used the summary odds ratio (OR) and 95% confidence intervals (CI) as a measure of association (random-effects model). We also performed Chi-square heterogeneity test based on Cochrane's Q and evaluated the severity of heterogeneity using I^2 statistics. The included studies were examined for publication bias using a funnel plot and statistical significance was assessed using Egger's test (bias if p<0.1).

Fifty-five of the 3,507 citations screened were eligible, 28 of which had sufficient data for meta-analysis. The 28 studies enrolled 22, 114 children in 13 countries across sub-Saharan Africa, Southeast Asia and South America. Overall, the pooled estimates showed a prevalence of *Plasmodium*-helminth co-infections of 17.7% (95% CI 12.7–23.2%). Summary estimates from 14 studies showed a lower odds of *P. falciparum* infection in children co-infected with *Schistosoma spp* (OR: 0.65; 95%CI: 0.37–1.16). Similar lower odds of *P. falciparum*

Funding: This work was implemented as part of a career development fellowship awarded to MOA, which is funded under UK Research and Innovation Future Leaders Fellowship scheme (MR/S03286X/1). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

infection were observed from the summary estimates of 24 studies in children co-infected with soil transmitted helminths (STH) (OR: 0.42; 95%CI: 0.28–0.64).

When adjusted for age, gender, socio-economic status, nutritional status and geographic location of the children, the risk of *P. falciparum* infection in children co-infected with STH was higher compared with children who did not have STH infection (OR = 1.3; 95% CI 1.03–1.65).

A subset of 16 studies showed that the odds of anaemia were higher in children co-infected with *Plasmodium* and STH than in children with *Plasmodium* infection alone (OR = 1.20; 95% CI: 0.59–2.45), and were almost equal in children co-infected with *Plasmodium-Schistosoma spp* or *Plasmodium* infection alone (OR = 0.97, 95% CI: 0.30–3.14).

Conclusions/Significance

The current review suggests that prevalence of malaria-helminth co-infection is high in children living in endemic countries. The nature of the interactions between malaria and helminth infection and the impact of the co-infection on anaemia remain inconclusive and may be modulated by the immune responses of the affected children.

Author summary

Updated evidence is needed to guide the planning and implementation of appropriate interventions for control of mixed infections involving malaria and worms affecting children living in endemic countries. We performed a systematic review and meta-analysis to update current knowledge on the magnitude of the burden of dual infections with malaria and worms in children in the developing world. We searched all published articles available in Medline, Embase, Global Health and Web of Science from the database inception until 16 March 2020, without any language restriction. We found 55 eligible studies, and 28 of these studies were included in the meta-analysis. A summary of the evidence synthesis showed that the burden of dual infections involving malaria and worm parasites is high in children and varies significantly across endemic countries. There was a lower risk of *P. falciparum* infection in children infected with soil transmitted helminths (STH) or *S. haematobium or S.mansoni*. Conversely, the odds of anaemia were higher in children who had dual infections with P*lasmodium* and STH parasites than in children with a *Plasmodium* infection alone while the odds of anaemia were almost equal in children who were co-infected with *Plasmodium-Schistosoma* compared to those with a *Plasmodium* infection alone. These findings underscore the need to further understand the epidemiology of malaria-helminth co-infections in order to support implementation of appropriate interventions for control and, ultimately, elimination of the dual infections in children living in endemic countries, especially low and middle-income countries (LMIC).

Introduction

Multi-parasitism, also described as polyparasitism, is the concomitant occurrence of two or more parasite species in a single human host [1]. The parasite species broadly categorised into two groups are macroparasites and microparasites. While macroparasites comprise parasitic

helminths (nematodes and trematodes); microparasites affecting humans are mainly protozoa. Descriptive studies have shown that parasitic helminths (macroparasites) such as soil transmitted helminths (STH) and *Schistosomes*, may co-exist with *Plasmodium* protozoa (microparasites) in children living in resource-poor settings of the world [2–4].

A recent WHO report showed that an estimated 228 million cases of malaria occurred globally, with sub-Saharan Africa (SSA) and Southeast Asia accounting for about 97% of the burden [5]. *Plasmodium falciparum* remains the most prevalent malaria parasite in the WHO African Region, causing 99.7% of the estimated malaria cases in 2018, and 50% in the WHO Southeast Asia Region. Globally, children aged less than five years are the most vulnerable group affected by malaria. In 2018, they accounted for 67% (272 000) of all malaria deaths worldwide [5].

Adding to this very high burden of malaria is the frequent co-existence of parasitic helminths among children living in low and middle-income countries (LMIC) [2]. It is estimated that 1.5 billion individuals are infected with helminths [6], with more than 800 million children in LMIC affected by STH primarily hookworm (*Ancylostoma duodenale* and *Necator americanus*), roundworm (*Ascaris lumbricoides*), and whipworm (*Trichuris trichiura*) [7]. Other important helminths that may co-exist with malaria in children in LMIC include *Schistosoma haematobium* and *S. mansoni* [8].

Schistosomiasis and STH account for a global burden of over 5.2 and 3.3 million disability-adjusted life years, respectively [6] and are associated with anaemia [9, 10], malnutrition [3, 11], and impaired physical and cognitive development [12–14] among preschool-aged children and school-aged children.

An interplay of environmental and host factors has been implicated in favouring mixed infections of parasitic helminths (STH and *Schistosoma* species) with malaria species [15, 16]. Statistical and spatial models also support the geographic overlap and co-endemicity of falciparum malaria and hookworm infections in SSA, suggesting that about 25% of school-aged children are at risk of these two groups of infection [2]. Similar spatial distribution has been documented for the association between malaria and schistosomiasis [11].

This overlap in the endemicity of intestinal helminths and malaria parasites is recognised to be responsible for a high prevalence of malaria-helminth co-infections, with synergistic and antagonistic interactions between helminth and malaria parasites [16–18]. There is some evidence that infections with *Schistosomes* and STH also exert deleterious effects on the course and outcome of clinical malaria [2, 17]. Prominent among the clinical outcomes of malaria-helminth co-infections among children living in LMIC is anaemia [9, 10]. Consequently, in endemic countries where malaria and helminths co-exist, there is potential for these infections to act together to worsen anaemia, a situation previously described as a 'perfect storm of anaemia' [9].

Despite the obvious effects of malaria-helminth co-infections, the nature of the interactions between the two parasites is not clear; existing studies report conflicting findings on the association between malaria and helminths. This may be due to the complexity of multiple pathways involved in the interactions between malaria and helminth parasites during the co-infection [16]. While some studies reported protective effect of hookworms and *S. haematobium* infection against Plasmodium infection [4, 19], other reported increased *Plasmodium* infection in children infected with *S. mansoni* [17].

In 2016, two systematic reviews [7, 8] were published to address the limitations identified in the findings of previous narrative reviews on malaria-helminth co-infections [18, 20]. Consistent with previous reviews, the 2016 review reported an over-estimation of the evidence of the relationship between malaria and helminth parasites making it difficult to conclusively establish the burden of malaria-helminth dual infections and the contribution of helminths to

the interactions in the co-infection [7, 8]. This limitation may be overcome by employing interactive geospatial maps [21–23] to generate real-time epidemiological profile of malaria-helminth co-infections among children in LMIC. This approach has the potential to improve the evidence generated from traditional reviews, which are usually undermined by the methodological limitations of the primary studies included in the reviews.

The objective of this study was to systematically review available data on the burden of malaria-helminth co-infections and the nature of interactions between *Plasmodium* malaria and helminth infections (STH and *Schistosoma spp*) among children living in endemic countries, with a view to establishing how control of malaria and helminth infections might be better co-ordinated in the future.

Methods

Protocol development and registration

We developed and prospectively registered the study protocol on PROSPERO (https://www.crd.york.ac.uk/PROSPERO/) [CRD42020171095]. The systematic review was conducted according to PRISMA guidelines [24].

Eligibility criteria

The PECO framework [25] was used to aid the selection of published articles relevant to the search terms which were eligible for the review, where 'P' stands for the population (children aged 1–16 years living in endemic areas); 'E' for exposure (malaria and helminth co-infection); 'C 'for comparator which is not applicable in the context of this review; and 'O' stands for outcome of interest (anaemia). Epidemiological studies, except case series and case reports, reporting co-infection of *P. falciparum* and/or *P. vivax* with STH (*Ascaris lumbricoides*, hookworm and *T. Trichuria*) and/or schistosomes (*S. haematobium and S.mansoni)*, in children aged 1–16 years living in endemic countries, were included. Unpublished research theses, conference abstracts, grey literature, and studies conducted outside endemic countries were excluded after screening the titles and abstracts were excluded. Also excluded were studies which enrolled only adults or pregnant women, because pathophysiology and immunological effects of malaria and helminth infections differ significantly in children from adults and pregnant women [26]. Further studies were removed after review of the full papers, if they did not meet the eligibility criteria highlighted above.

Definitions

For the purpose of this review, *Plasmodium* infection was defined as microscopic confirmation of asexual *Plasmodium* species with or without clinical features of uncomplicated or severe malaria [27]. *P. falciparum and P. vivax* density was defined as the number of parasites per microliter of blood. STH and *Schistosoma* infections were defined by detection of eggs using FLOTAC, urine filtration or Kato-Katz methods [27]. Kato-Katz thick smears were produced from the stool samples collected from the children and these samples were analysed using light microscopy to determine the egg counts for *S. mansoni* and STH. The numbers of eggs per slide were used to obtain a measure of the number of helminth eggs per gram of faeces (EPG). Anaemia was defined as a haemoglobin concentration below the WHO cut-off values of 11.0 g/dl for children aged 6–59 months; 11.5 g/dl for those 5–11 years; 12.0 g/dl for those 12–14 years [28].

Search strategy

The first author (MOA) searched Medline, Embase, Global Health and Web of Science from each database inception until 16 March 2020, using compound search strategy combining related truncated and non-truncated terms or synonyms tailored to each of the databases. Additional titles and abstracts were obtained through hand search of a list of references of potentially relevant papers. The search was limited to studies conducted in humans, but no language restrictions were applied. The search terms were 'malaria' OR '*Plasmodium*' OR '*Plasmodium falciparum*' OR '*Plasmodium vivax*' AND 'helminth' OR 'Soil transmitted helminth' OR 'geohelminth' OR '*Ascaris lumbricoides*' OR 'Ascariasis' AND 'hookworm' AND '*Trichuris trichuria*' AND 'bilharziasis' OR 'Schistosoma' OR '*Schistosoma mansoni*' OR '*Schistosoma haematobium*' AND 'children' OR 'paediatric' AND 'developing world' OR 'low and mid-income countries'. Details of the complete search strategy are provided in the protocol (S1 File).

After removing duplicates from the search outputs, screening of 133 abstracts was conducted independently for eligibility for full text review by two reviewers (BMA and EDD), using a systematic review app, Rayyan, (https://rayyan.qcri.org/) [29]. Disagreements between the two reviewers on the inclusion of a study for full text review were resolved following discussions with a third independent reviewer.

Data collection

Full text papers for 55 eligible abstracts/titles were retrieved and relevant data were extracted. The following data were extracted: first author and year of publication, country/setting, study title and objectives; confirmation of eligibility for review; methodology—study design, sample size, study duration, data collection with study time points; population of interest; prevalence/incidence and density of *Plasmodium* and helminth co-infection, prevalence of anaemia; authors key discussions, comments, limitations and reviewers' comments, where provided.

Quality and bias assessment

To ascertain the internal and external validity of the included studies, the risk of bias and quality of each study were assessed using a combination of Newcastle Ottawa Scale (NOS) [30] and Effective Public Health Practice Project (EPHHP) tools [31], which are recommended for systematic reviews by The Cochrane Public Health Review Group [32]. Eligible studies were assessed from three angles: selection of the study groups, comparability of the study groups, and the ascertainment of the outcome of interest. Based on these criteria, the overall quality of each study was scored as weak, moderate, or strong. In addition, each study was assessed for selection bias, study design, confounding, blinding, data collection methods, and withdrawals and drop-outs.

Data analysis

Given a very high level of heterogeneity between included studies, meta-analysis was possible in only 28 studies. Data synthesis was performed to estimate pooled effect estimates across studies, allowing for between-study heterogeneity. We adopted Odds Ratio (OR) as a measure of association. We extracted from the papers data about adjusted odds ratio (aOR) of asymptomatic/uncomplicated or severe *Plasmodium* infection and related anaemia along with 95% confidence interval (CI) for children infected with STH or *S. haematobium or S. mansoni*. We extracted raw data for only malaria positive, only STH-positive, only *S. haematobium* or *S. mansoni*-positive, malaria-*S. haematobium* or *S. mansoni*-positive, malaria-and STH-positive,

and intestinal helminth- and malaria-negative and used these data to estimate the pooled prevalence of malaria in the group of children who were malaria positive and STH/*Schistosoma* positive compared to the prevalence in those who were malaria positive and STH/*Schistosoma* negative. We also used the data obtained to calculate the crude odds of asymptomatic/uncomplicated or severe *Plasmodium* infection and related anaemia in children infected with *Schistosomes* or STH compared to those infected with *Plasmodium* parasites only, along with their 95% CI. The log OR and the standard error (SE) of the log OR were estimated using generic inverse variance weighting method [33] and the summary estimate (summary-odds ratio) was estimated. We performed Chi-square heterogeneity test using Cochrane's Q. Moreover, I^2statistic was used to assess the severity of inconsistency (or heterogeneity) across studies. We also examined the studies for publication bias using funnel plots and Egger's test for correlation between the effect estimates and their variances. We used random effects model to estimate the summary Mantel-Haenszel OR of asymptomatic/uncomplicated or severe *Plasmodium* infection in children infected with STH or *Schistosomes* compared to those with *Plasmodium* infection only. We conducted meta-regression to adjust for confounding variables such as age, gender, socio-economic status and nutrition status of the children, as well as study design and geographic location of the study participants. A sensitivity analysis was conducted to assess the robustness of the pooled summary effects by excluding each of the studies from the pooled estimate. Sub-group analyses by helminth types, geographic region and study design were done to compare pooled estimates of the prevalence of the co-infection. All statistical analyses were performed using R software version 4.0.2, R Project for Statistical Computing (https://www.r-project.org/).

Narrative reviews were conducted for 27 studies which did not contain sufficient data that allowed meta-analysis. We adopted a framework consisting of three elements: (i) developing a preliminary synthesis of findings of included studies; (ii) exploring relationships within and between studies; and (iii) assessing the robustness of the synthesis. Studies were grouped together if they compared similar types of outcomes of interest. Content analysis of emerging themes from each group was performed and the summary is presented.

Results

Search results and characteristics of included studies

As illustrated in Fig 1, 3,057 citations were generated from database searches on Embase (n = 814), Global Health (n = 1,430), Medline (n = 577), Web of Sciences (n = 220) and manual search from reference list of potentially eligible titles (n = 16). A total of 2,924 duplicates were removed in two stages. One hundred and thirty-three abstracts/titles were screened for eligibility, following which a further 78 citations were excluded due to reasons such as wrong outcomes/wrong populations (n = 67), duplicates (n = 3), and the full text not available (n = 8). We contacted the authors of these abstracts to ascertain whether the full text papers were available. One author confirmed that a manuscript for the abstract was under development, but no feedback was received from the other authors. The full text papers of the remaining 55 citations were reviewed, 27 of which contained inadequate data for meta-analysis. Narrative reviews were performed on these 27 studies [19, 34–59]; data from the remaining 28 studies [4,14,17,60–84] were included in the meta-analysis.

The characteristics of the 55 studies included in the systematic review are summarised in Table 1. A total of 37,559 children were enrolled in the 55 studies conducted across SSA, Southeast Asia and South America. Forty-three of the studies (78.2%) were cross-sectional, five (9.1%) were longitudinal studies, four (7.3%) were randomised controlled trials (RCT), and three (5.4%) were case-control studies. Thirty-seven studies reported *P. falciparum and*

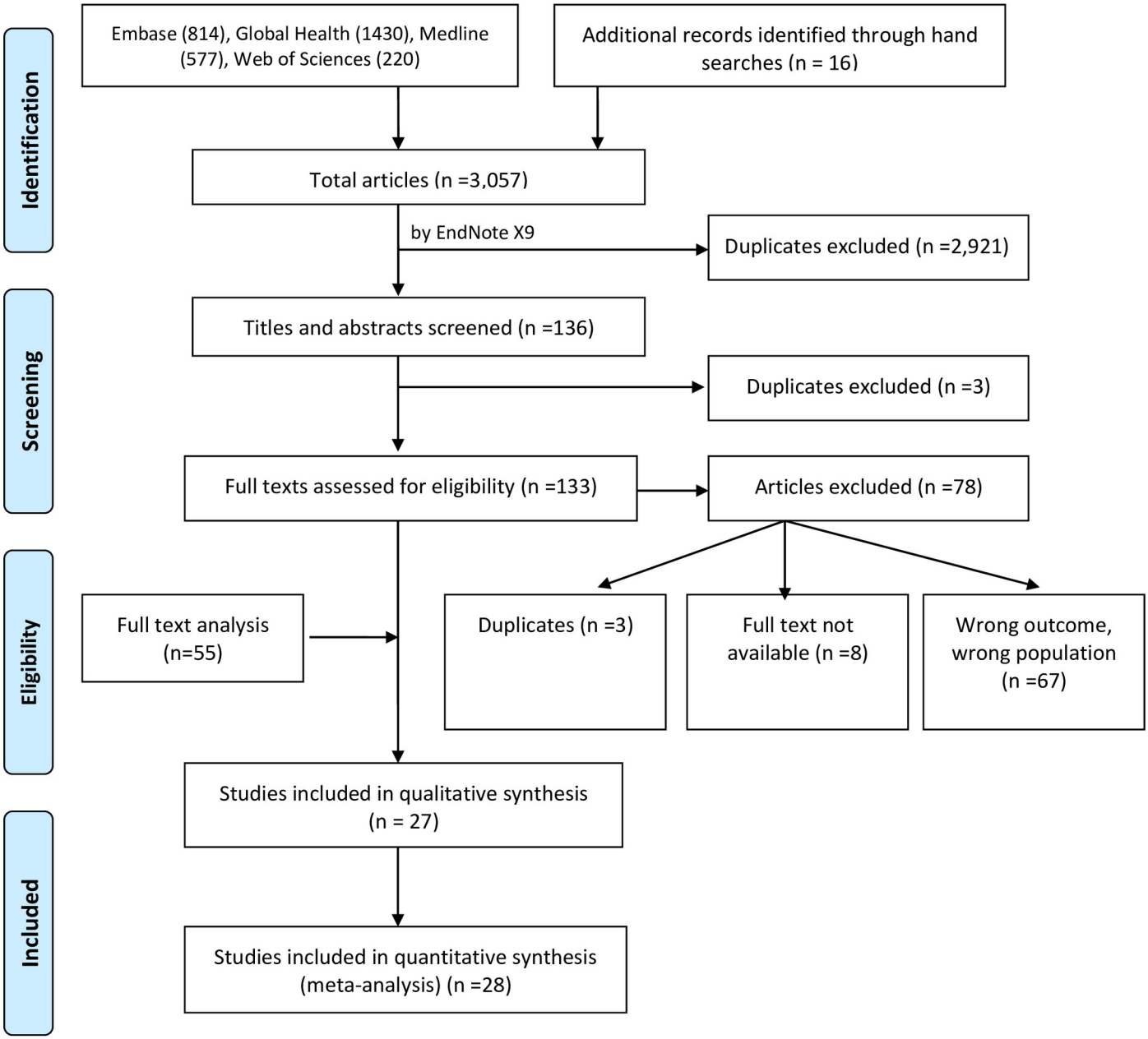

Fig 1. PRISMA flow diagram showing the process undertaken for inclusion and exclusion of studies in the systemic review.

https://doi.org/10.1371/journal.pntd.0009138.g001

STH co-infection; 23 studied *P. falciparum and S. haematobium* co-infection; eight studied *P. falciparum* and *S. mansoni* co-infection and only two reported *P. vivax* and STH co-infection.

Twenty-seven studies compared the odds of asymptomatic/uncomplicated or severe *P. falciparum* infection and 16 studies compared *P. falciparum* density among children infected and uninfected with helminths. Fourteen studies compared the mean haemoglobin concentration or prevalence of anaemia among study participants who had *Plasmodium* and helminth infections and those infected with *Plasmodium* infection only. Most of the studies reported asymptomatic and/or uncomplicated *Plasmodium* infection except three studies [43, 47, 54], which

Table 1. Characteristics of included studies.

SN	Author	Country/year of study	Study design	Sample size	Age range	Co-infection reported	Prevalence of co-infection (%)	Magnitude of outcomes in *Plasmodium*-helminth co-infected participants vs those infected with *Plasmodium* only	Overall quality score
1	Achidi et al, 2008 [60]	Cameroon 2004–2005	Cross-sectional	263	4–12 years	Pf+ STH	65.9	1. Similar Pf prevalence (OR: 1.29; 95% CI 0.60–2.76) 2. Similar Hb levels	Moderate
2	Adedoja et al, 2015 [61]	Nigeria 2012–2013	Cross-sectional	1017	4–15 years	Pf+ HK Pf + Sh	29.2 50.7	1.Higher Pf prevalence 2. Similar Pf risk: Children infected with Sh (RR = 1.3, p = 0.04) and HK (RR = 1.4, p = 0.01) have equal chances of being infected with Pf 3. Higher anaemia risk	Strong
3	Doumbo et al, 2014 [67]	Mali 2011–2012	Longitudinal cohort	616	3 months—25 years	Pf + Sh	8.5	1. Higher Pf prevalence, OR: 3.23; 95% CI: 1.76, 5.90 2. Similar Pf risk (HR) 3. Heavy Sh negatively associated with Pf density but light Sh not associated with Pf density	Strong
4	Akanni et al, 2014 [34]	Nigeria NR	Cross-sectional	292	1–15 years	Pf + STH Pf+ Sm	NR	Lower mean Hb and serum ferritin levels (p>0.05)	Weak
5	Humphries et al, 2013 [36]	Ghana 2010	Cross-sectional	812	6–11 years	Pf+ HK	35.1	Higher Pf density, with OR for HK infection increasing with higher Pf parasite density (OR = 5.50, 95% CI 2.10, 14.41, P< 0.01)	Moderate
6	Humphries et al, 2011 [35]	Ghana 2007	Cross-sectional	132	1–15 years	Pf + HK	51% in 6–10 year olds	1. Higher Pf prevalence (aOR = 2.84, 95%CI = 1.11, 7.26), with highest prevalence of co-infection (51%) in 6–10 year olds. 2. Similar anaemia risk (aOR = 2.34; 95% CI = 0.56, 9.84, p = 0.25)	Moderate
7	Ajayi et al, 2015 [84]	Nigeria 2011	Cross-sectional	370	6 months—14 years	Pf+ STH	42.9	1.Risk of Pf +STH co-infection about two times in children aged 5.5–10 years compared to under-fives (OR = 2.3, 95% CI = 0.19, P = 0.95). 2. Similar anaemia risk (P = 0.93)	Weak
8	Briand et al, 2005 [37]	Senegal 2001–2002	Cross-sectional	523	3–15 years	Pf + Sh	NR	Children lightly infected with Sh had lower Pf densities than non-infected children (β: -0.34, 95% CI: −0.85, −0.10)	Moderate
9	Burdam et al, 2016 [64]	Indonesia 2013	Cross-sectional	533	12–59 months	Pf+ STH Pv + STH	7.1 15.3	1. Higher Plasmodium risk = Pv: OR 3.75 (95%CI, 1.53–9.2), p = 0.004; Pf: OR 2.0 (95%CI, 0.4–10.1), p = 0.402 2. Higher anaemia risk for Pf or Pv + STH (OR 4.0 [95%CI, 1.4–11.3], p = 0.008) and severe anaemia (OR 8.6 [95%CI, 1.3–55.8], p = 0.024).	Moderate
10	Brutus et al, 2006 [38]	Madagascar 1996–1997	RCT	350	4–16 years	Pf+ Al	NR	1. Levamisole treatment effect on Al + Pf = 0.58, 95% CI: 0.10–0.95, p = 0.018 2. Negative interaction between Al and Pf parasite density in children aged ≥5 years	Moderate

(*Continued*)

Table 1. (Continued)

SN	Author	Country/year of study	Study design	Sample size	Age range	Co-infection reported	Prevalence of co-infection (%)	Magnitude of outcomes in *Plasmodium*-helminth co-infected participants vs those infected with *Plasmodium* only	Overall quality score
11	Brutus et al, 2007 [39]	Madagascar 1996–1997	RCT	312	4–16 years	Pf+ Al	NR	1. Levamisole treatment effect on Al + Pf = 0.58, 95% CI: 0.20–0.95, p = 0.003 2. Negative interaction between Al infection and Pf parasite density in 5–14 year old	Moderate
12	Bwanika et al, 2018 [65]	Uganda NR	Case-control	240	7.6 ± 3.0 years	Pf + STH Pf+ Al Pf+ HK	13.3 78.1 21.2	Higher levels of IL-10 (304 pg/ml) expressed compared to Pf only infected children (11.57 pg/ml), P< 0.05	Moderate
13	Carmona_Fonseca et al, 2006 [66]	Colombia 2004–2005	Cross-sectional	93	4–10 years	Pf + Al + HK+ Tt	74–97	1. Similar Pf prevalence. 2. Frequency of associations not increased with increasing parasite loads	Weak
14	Dejon_Agobe et al_2018 [4]	Gabon 2012–2014	Longitudinal survey	739	NR	Pf+ Al Pf+ HK Pf+ Tt Pf+ Sh	23.6 25.6 29.5 9	1.Higher Pf incidence, with a significant delay of time-to first-malaria event only in children aged 6-10-years-old infected with Sh 2. Higher Pf risk	Strong
15	Degarege et al, 2014 [81]	Ethiopia 2010–2011	Cross-sectional	702	NR	Pf + STH	19.4	Similar Pf prevalence and risk of undernutrition	Moderate
16	Deribew et al, 2013 [40]	Ethiopia 2013	cross-sectional	387	6–23 months	Pf+ Sh	2.84	1. Higher Pf prevalence, OR: 2.8; 95% CI: 1.21–6.5 2. Higher anaemia prevalence, OR: 10.12; 95% CI: 1.47–69.94 3. Similar mean Hb difference	Weak
17	Doumbo et al, 2018 [68]	Mali 2011	Cross-sectional	688	3 months-25years	Pf+ Sh	2.18	Higher Pf prevalence	Moderate
18	Elfaki et al, 2015 [69]	Sudan 2008–2009	Cross-sectional	250	6–16 years	Pf+ Sh Pf+ Sm	6.4 4	Higher Pf prevalence	Weak
19	Green et al, 2011 [41]	Uganda 2009	Cross-sectional	573	0.4–6 years	Pf+ Sm Pf + STH	28.7 1.8	Similar prevalence of anaemia and Hb levels	Moderate
				453	2–6 years	Pf+ Sm Pf + STH	20.1 6.3		
20	Kepha et al, 2014 [42]	Kenya 2013	Cross-sectional	5471	5–18 years	Pf+ Al Pf+ HK	7.8 9	Higher Pf risk when adjusted for age and gender	Moderate
21	Kinugh'hi et al, 2014 [71]	Tanzania 2006	Cross-sectional	1546	3–13 years	Pf+ HK Pf+ Sh	15.8 10.2	Similar Pf prevalence (OR: 1.19; 95% CI: 0.86–1.63)	Moderate
22	Kwenti et al, 2016 [43]	Cameroon 2014–2015	Cross-sectional	405	1 week-120 months	Pf + STH	11.6	Similar Pf prevalence	Moderate
23	Salim et al, 2015 [77]	Tanzania 2011–2012	Cross-sectional	992	6 months -9 years	Pf+ HK Pf+ Tt Pf + Sh	1.4 0.1 0.2	Higher Pf prevalence and risk (OR = 1.7, 95% CI = 1.1–2.5	Moderate
24	Matangila et al, 2014 [72]	DR Congo 2012	Cross-sectional	989	4–13 years	Pf+ STH Pf+ Sm	6.4 1.5	1.Similar Pf prevalence 2. Lower anaemia prevalence	Moderate
25	Mazigo et al, 2010 [73]	Tanzania 2009	Cross-sectional	400	8–16 years	Pf+ HK Pf + Sm	2.3 5.5	1. Similar Pf prevalence (aOR: 1.35; 95% CI: 0.49–3.72) 2. Higher Pf prevalence OR: 2.1; 95% CI: 1.03, 4.26	Moderate
26	Mboera et al, 2011 [83]	Tanzania 2005	Cross-sectional	578	7.96 ± 1.4 years	Pf + HK Pf + Sh	5.3 10.9	Higher Pf density (P < 0.001)	Moderate

(*Continued*)

Table 1. (Continued)

SN	Author	Country/year of study	Study design	Sample size	Age range	Co-infection reported	Prevalence of co-infection (%)	Magnitude of outcomes in *Plasmodium*-helminth co-infected participants vs those infected with *Plasmodium* only	Overall quality score
27	Morenikeji et al, 2016 [74]	Nigeria NR	Cross-sectional	173	6–18 years	Pf + Sh	62.3	Similar Pf risk OR: 0.8, 95% CI: 0.3–1.7, P = 0.507	Moderate
28	Nankabirwa et al, 2013 [14]	Uganda 2011	Cross-sectional	740	6–14 years	Pf +Al Pf + HK Pf + Tt	28.9 40 66.7	Similar Pf prevalence	Moderate
29	Njunda et al, 2015 [44]	Cameroon 2012	Cross-sectional	411	0–10 years	Pf + STH	11.9	1.Similar Pf prevalence 2.Similar anaemia prevalence and mean Hb difference	Moderate
30	Nkuo-Akenji et al, 2006 [75]	Cameroon 2004	Cross-sectional	425	0–14 years	Pf+ Al Pf + HK Pf + Tt	7.5 0.2 7.8	1. Similar Pf prevalence (OR: 1.00; 95% CI: 0.65–1.53) 2. Higher Pf density (P < 0.001) 3. Similar anaemia prevalence (OR: 1.19; 95% CI: 0.642.21)	Moderate
31	Nyarko et al, 2018 [45]	Ghana NR	Cross-sectional	404	9–14 years	Pf + Sh	12.9	Similar Pf prevalence	Moderate
32	Obi et al, 1996 [76]	Nigeria NR	Cross-sectional	268	5–15 years	Pf + Sh	21.3	NR	Weak
33	Ojurongbe et al, 2011 [82]	Nigeria 2009	Cross-sectional	117	4–15 years	Pf + Al Pf + HK Pf + Tt	13.3 6.7 3.3	1.Higher Pf prevalence 2. Similar anaemia prevalence	Moderate
34	Tchinda et al, 2012 [78]	Cameroon NR	Cross-sectional	503	3–16 years	Pf + Al	49.6	1.Higher Pf prevalence: OR = 1.61, 95% CI = 1.05–2.44, P = 0.028 2.Higher anaemia risk: OR = 1.64, 95% CI: 0.98–2.75; p = 0.059	Moderate
35	Yapi et al, 2014 [79]	Senegal 2011–2012	Cross-sectional	5104	5–16 years	Pf + STH Pf + Sh	13.5 5.6	Higher Pf risk: IRR = 0.7, 95% CI = 0.6–0.8, P = 0.001	Strong
36	Zeukeng et al, 2014 [80]	Cameroon 2011	Cross-sectional	152	1–14 years	Pf + Al Pf+ HK Pf + Tt	21.1 4.61 8.7	1.Higher Pf prevalence 2.Higher anaemia prevalence	Moderate
37	Njua-Yafi et al, 2016 [46]	Cameroon 2011–2012	Cross-sectional	357	6 months -10 years	Pf + STH	2.9	1.Higher Pf prevalence: OR = 4.45, 95% CI (1.66–11.94), p = 0.003 2.Higher mean Hb levels (p<0.006)	Moderate
38	Le Hesran et al, 2004 [47]	Senegal 2001–2002	Case-control	105	Mean age = 6.6 ±3 years	Pf + Sh	10.3	1.Higher Pf risk: OR = 9.95, 95% CI = 3.03–32.69	Weak
39	Lemaitre et al, 2014 [48]	Senegal 2001–2003	Cross-sectional	523	5–13 years	Pf + Sh	NR	Higher Pf density: OR = -0.28, 95% CI: −0.52, −0.039, P = 0.10	Weak
40	Nacher et al, 2012 [49]	Thailand 1998–1999	Cross-sectional	731	Median age = 17 years	Pf + STH	12.7	Higher Pf risk	Moderate
41	Stefani et al, 2017 [50]	French Guiana 2001–2009	Cross-sectional	91	0–7 years	Pv+ HK Pv + Al	35.5 46.5	Higher Pv relapse: OR = 0.36, 95% CI = 0.94–1.4, p = 0.09	Moderate
42	Lyke et al, 2005 [51]	Mali 2002–2003	Case-control	654	4–14 years	Pf + Sh	44.5	1. Lower Pf incidence in 4–8 y.o 2. Lower Pf density in children ages 4–8 y.o 3. Similar Hb level	Moderate

(*Continued*)

Table 1. (Continued)

SN	Author	Country/year of study	Study design	Sample size	Age range	Co-infection reported	Prevalence of co-infection (%)	Magnitude of outcomes in *Plasmodium*-helminth co-infected participants vs those infected with *Plasmodium* only	Overall quality score
43	Sangweme et al, 2010 [17]	Zimbabwe 2004–2005	Longitudinal cohort	605	6–17 years	Pf+ Sh	30.7	1. Similar Pf prevalence 2. Lower Pf density 3. Similar mean Hb 4. Similar anaemia prevalence	Moderate
44	Adio et al, 2004 [62]	Nigeria 2002	Cross-sectional	243	6 months -15 years	Pf + Al Pf + HK Pf +Tt	26.3 16.5 20.2	1.Higher Pf density 2.Higher anaemia prevalence	Weak
45	Adedoja et al, 2015 [52]	Nigeria 2003	Cross-sectional	154	1–15 years	Pf + Sh	54.4	Higher Pf prevalence	Weak
46	Righetti et al, 2011 [53]	Ivory Coast 2010	Cross sectional	147	5–14 years	Pf + HK Pf + Sh	27.9 8.8	1. Higher Pf prevalence (in 6–8 year-old) (aOR: 7.47–95% CI: 1.84–30.32) 2. Lower anaemia prevalence (OR: 0.23; 95% CI: 0.06–0.83)	Moderate
47	Abanyie et al, 2013 [54]	Nigeria 2006–2007	RCT	690	6–59 months	Pf + Al	42.9	1. Similar Pf prevalence (OR: 1.30; 95% CI: 0.91–1.86) 2. Lower anaemia prevalence (OR: 0.50; 95% CI: 0.28–0.87); severity of malarial anaemia not altered by Pf-Al co-infection 3. Similar Pf density (p = 0.965)	Moderate
48	Roussihon et al, 2010 [55]	Senegal 2000–2005	Longitudinal study	203	1–14 years	Pf+ STH	0.655/child/year; ratio of malaria attack incidence density = 1: 1.723	1.Higher Pf incidence (aOR: 2.69; 95% CI: 1.34–5.39) 2.Incidence of malaria attacks is increased in helminth-infected children	Moderate
49	Kirwan et al, 2010 [56]	Nigeria 2006–2007	RCT	320	6–59 months	Pf + Al	NR	1. Similar Pf prevalence (OR: 1.16; 95% CI: 0.73–1.85) 2. Similar rate of increase in Pf density 3. Similar rate of increase in Hb levels 4. Repeated 4-monthly administration of anti-helminth lowers Pf prevalence, coincided with a reduction in both Al prevalence and intensity	Strong
50	Ateba-Ngoa et al, 2015 [57]	Gabon 2011	Cross-sectional	125	6–16 years	Pf+ Sh	26	1. Similar magnitude between the two groups 2. Higher mean Hb difference: OR = 0.7; 95% CI: 0.21, 1.19 3. Increased immune response due to Pf	Moderate
51	Florey et al, 2012 [58]	Kenya 2006	Cross-sectional	223	8–17 years	Pf + Sh	36.3 15.4	1. Higher Pf prevalence, adjusted OR: 1.79; 95% CI: 1.32, 2.44 2. Children with heavy Pf more likely to have concomitant heavy Sh	Moderate
52	Courtin et al, 2011 [59]	Senegal 2003	Longitudinal survey	203	6–16 years	Pf+ Sh	NR	1. Similar Pf prevalence, OR: 1.62; 95% CI: 0.94, 2.80 2. Similar Pf density 3. Additive effect of S. haem and Pf on the cytokine levels (elevated IL-10)	Moderate

(*Continued*)

Table 1. (Continued)

SN	Author	Country/year of study	Study design	Sample size	Age range	Co-infection reported	Prevalence of co-infection (%)	Magnitude of outcomes in *Plasmodium*-helminth co-infected participants vs those infected with *Plasmodium* only	Overall quality score
53	Kabatereine et al, 2011 [70]	Uganda 2009–2010	Cross-sectional	3569	10–14 years	Pf + Sm Pf + STH	23.51 13.79	Higher Pf prevalence, OR: 2.16; 95% CI: 1.89, 2.47	Moderate
54	Alemu et al, 2012 [63]	Ethiopia 2011	Cross-sectional	108	1–14 years	Pf + STH	30	1.Higher Pf prevalence 2.Higher anaemia prevalence: OR = 13.800, 95% CI = 4.871–39.093, P<0.0001	Moderate
55	Sokhna et al, 2004 [19]	Senegal, 2008	Cross-sectional	512	6–15 years	Pf + Sm	13.3	Higher Pf incidence in children with heavy S. *manson*i egg load compared with uninfected (RR: 2.24, 95% CI:1.20, 4.20)	Moderate

https://doi.org/10.1371/journal.pntd.0009138.t001

reported severe malaria. Seven studies [19, 37, 53, 55, 57, 59, 65] reported antibody and/or cytokine expression in *P. falciparum* malaria-STH/*Schistosoma* co-infections.

Prevalence of *Plasmodium*-helminth co-infections

Overall, the pooled analysis showed that the prevalence of *Plasmodium*-STH co-infections in 22,114 children enrolled in 28 studies evaluating both groups of infection, in 13 countries across Central, East, West and Southern Africa, Southeast Asia and South America was 17.7% (95% CI 12.7–23.2%) (Fig 2). There was statistical heterogeneity (I^2: 98.7%), suggesting a high level of heterogeneity among the included studies, although Egger's regression test did not reach statistical significance (Egger's test = 1.5039, p-value = 0.1388) (Fig 3). In a subgroup analysis, the pooled estimates showed that South America had the highest prevalence of 76.3% of co-infections, followed by Southern Africa (30.7%), West Africa (25.4%), East Africa (16.3%), Central Africa (13.1%) and South-east Asia (7.1%) (S1 Fig). Disaggregated by helminth types, the pooled prevalence of *Plasmodium-Schistosoma* co-infections in 9,803 children was 19.2% (95% CI: 9.6–31.1%); and the pooled prevalence of *Plasmodium*-STH co-infections in 12311 children was 17% (95%CI: 11.4–23.4%); (95% CI: 9.6–31.1%) (Fig 2). In a subgroup analysis of 12 studies reporting co-infection of *Plasmodium* and individual STH types in 6325 children, the prevalence for *P.falciparum-A. lumbricoides* co-infection was 24% (95% CI: 11.3–39.6%), *P.falciparum*-hookworm 12.8% (95% CI: 4.8–23.9%) and *P. falciparum-T.trichuria* 9.9% (95% CI: 2.6–21.4%) (S2A, S2B and S2C Fig, respectively). For *Plasmodium falciparum-S. haematobium* co-infection, the pooled prevalence was 24.4% (95% CI: 11.9–39.6%) and 6.7% (95% CI: 1.8–14.6%) for *Plasmodium falciparum-S. mansoni* co-infection (S3A and S3B Fig, respectively). The funnel plot generated using the cases of *Plasmodium*-helminth co-infections compared with children infected with *Plasmodium* mono-infection and the standard error estimates of the prevalence was asymmetric, in keeping with the high level of heterogeneity between the included studies, but as indicated above, the Egger's regression test was not statistically significant (Egger's test = 1.5039, p-value = 0.1388) (Fig 3).

Interactions of *Plasmodium* and helminths during co-infection

Given a very high level of heterogeneity between the studies, random-effects models were used to calculate the summary odds ratio in this meta-analysis. The overall estimates on 24 studies showed lower odds of asymptomatic/uncomplicated or severe *P. falciparum* infection in children co-infected with STH when compared with those with *Plasmodium* only (summary OR:

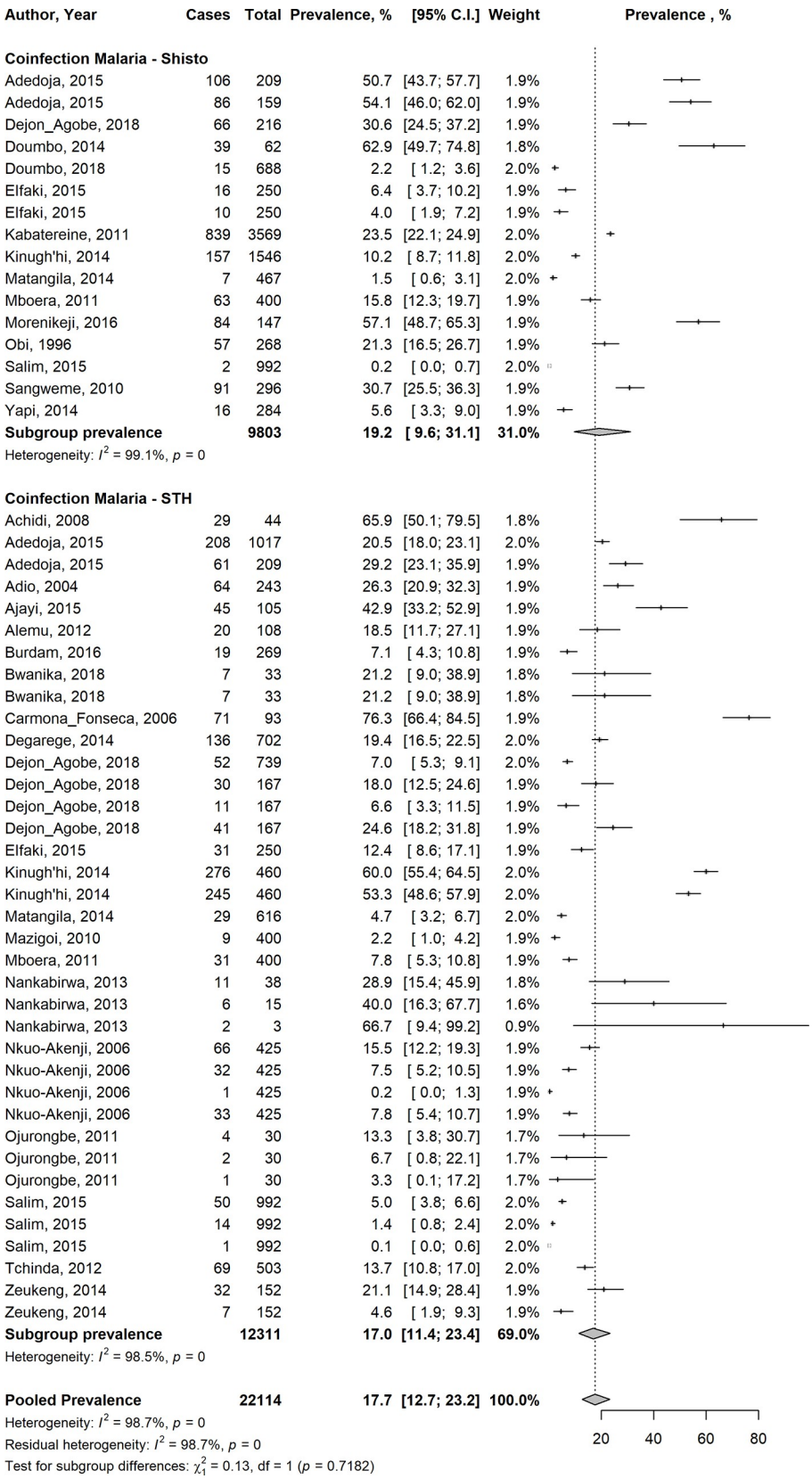

Fig 2. Forest plot showing overall pooled prevalence of *Plasmodium*-helminth co-infections among children living in LMIC in studies which evaluated the prevalence of both groups of infection.

https://doi.org/10.1371/journal.pntd.0009138.g002

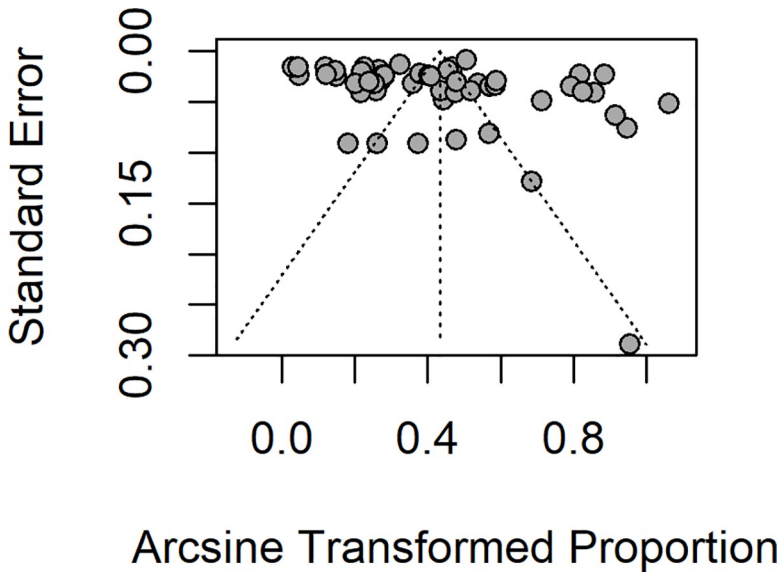

Fig 3. Funnel plot showing distributions of included studies.

https://doi.org/10.1371/journal.pntd.0009138.g003

0.42; 95%CI: 0.28–0.64; I^2 = 96.2%) (Fig 4). Similarly, the overall estimates in 20 studies showed lower odds of asymptomatic/uncomplicated *P. falciparum* infection among children co-infected with *Schistosoma spp*. compared with those with *Plasmodiu*m infection only (summary OR: 0.65; 95%CI: 0.37–1.16; I^2 = 96.8%), although the odds-ratio did not reach statistical significance (Fig 5). Compared with children who had *Plasmodium* infection only, sub-group analyses showed similar lower odds in the summary estimates in children who had co-infection with *Plasmodium*-STH sub-types: *A. lumbricoides* - 0R =: 0.39, 95% CI: 0.12–1.23, I^2 = 96.1%); hookworm–OR = 0.31, 95%CI 0.12–0.80, I^2 = 96.8%); *T.trichuria*–(OR = 0.15, 95% CI 0.03–0.77; I^2 = 97.8%) (S2A, S2B and S2C Fig, respectively). For *Plasmodium-S. haematobium* and *Plasmodium-S. mansoni, the* OR was 0.76, 95% CI: 0.41–1.41; I^2 = 99.1% and OR:0.39, 95% CI: 0.1–1.58, I^2 = 99.0% respectively (S3A and S3B Fig, respectively). When adjusted for age, gender, socio-economic status, nutrition status and geographic locations of the children, the risk of asymptomatic/uncomplicated or severe *P. falciparum* infection in children co-infected with STH was higher compared with children who did not have STH infection (OR = 1.3, 95% CI 1.03–1.65; I^2 = 32.1%). (S4 and S5 Figs).

Risk of Anaemia in *Plasmodium*-helminth co-infections

In 15 studies [35,44,46,52–54,62–64,71,75,78,80,83–84], the odds of anaemia were higher in children who were co-infected with *Plasmodium* species and pooled STH species compared to those who were infected with *P. falciparum* alone (summary OR = 1.20 (95% CI: 0.59–2.45, I^2 = 96.3%) (Fig 6). In contrast, the odds of anaemia were almost equal in six studies [17, 40, 61, 71, 72, 83] involving children who were co-infected with *Plasmodium* species and pooled *Schistosoma* species compared to those who were infected with *P. falciparum* alone (summary OR = 0.97, 95% CI: 0.30–3.14; I^2 = 97.8%) (Fig 7).

Narrative review

Roles of biologic factors on malaria-helminth co-infection. Four studies [42,43,52,58] explored the roles of biological factors such as age and gender in the epidemiology of

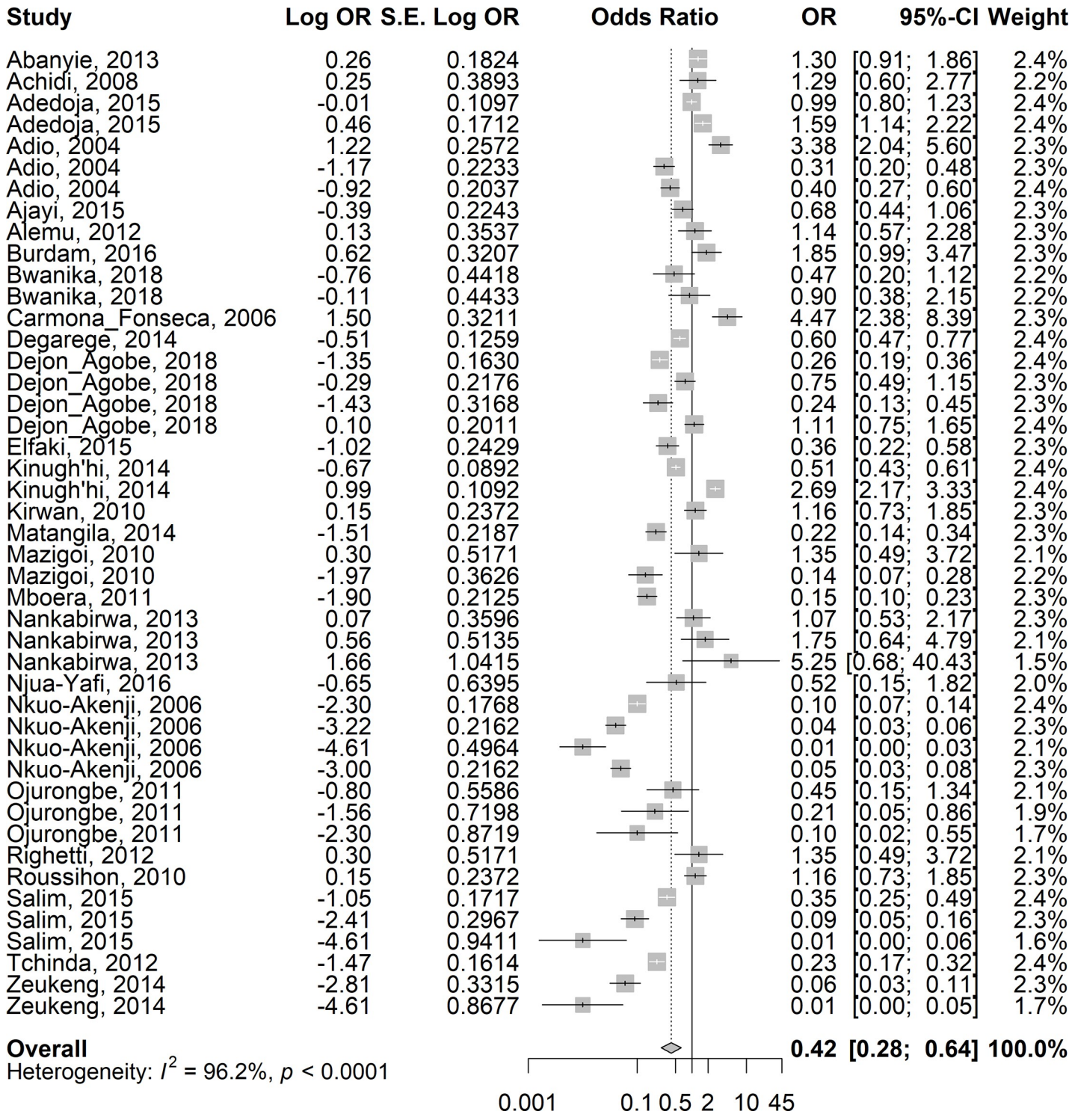

Fig 4. Forest plot showing the risk of asymptomatic/uncomplicated or severe *P. falciparum* infection in children co-infected with STH compared with children who did not have STH infection.

https://doi.org/10.1371/journal.pntd.0009138.g004

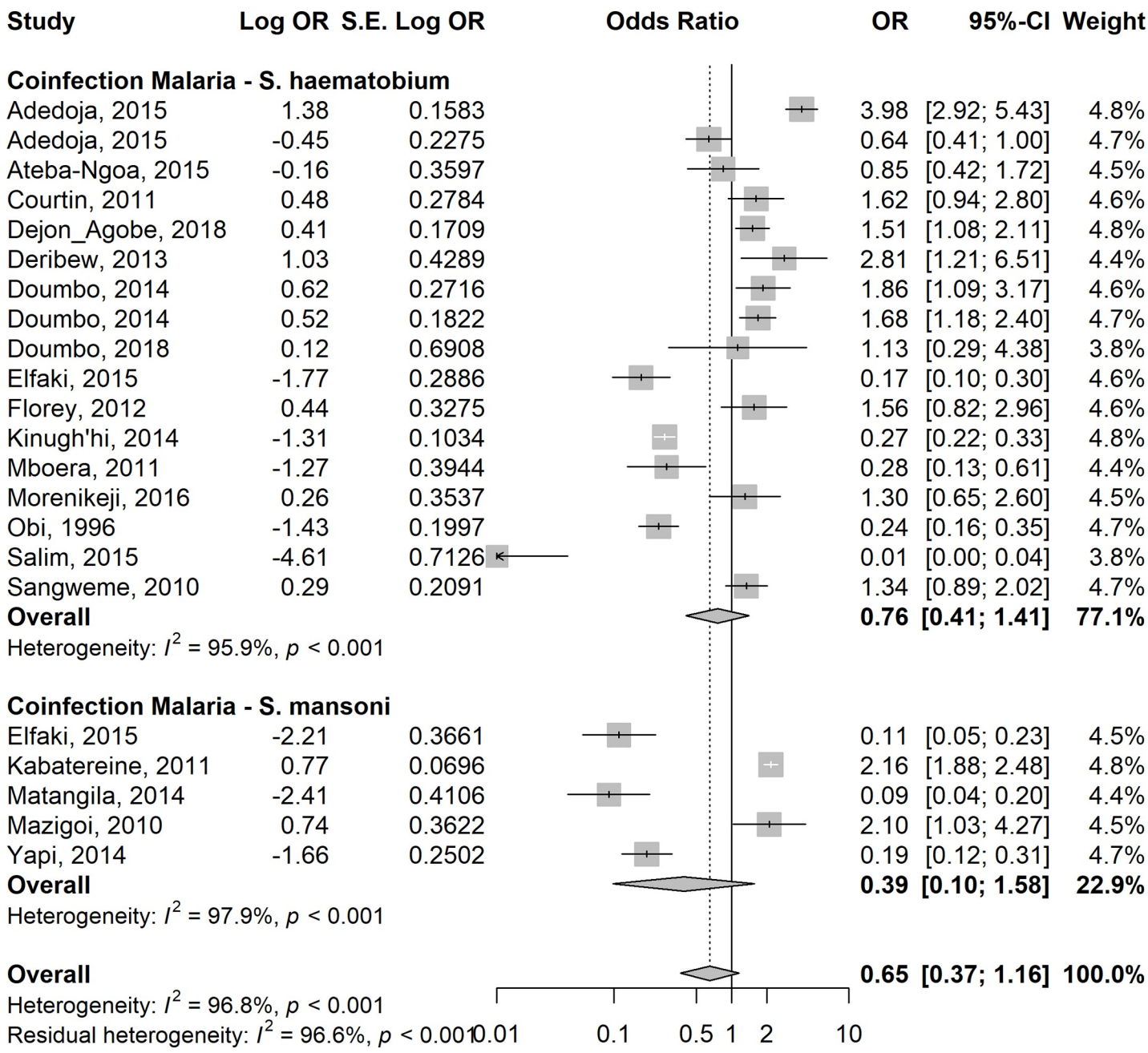

Fig 5. Forest plot showing the risk of asymptomatic/uncomplicated or severe P. falciparum infection in children co-infected with *Schistosoma* spp compared with children who did not have *Schistosoma* infection.

https://doi.org/10.1371/journal.pntd.0009138.g005

Plasmodium-helminth co-infections. The prevalence of hookworm-*Plasmodium* co-infection was significantly higher in boys than girls, but no gender difference was observed in the prevalence of *A. lumbricoides-Plasmodium* co-infection [42, 43]. Children had 9.3 times the odds of co-infection compared to adults (95%CI = 5.3–16.3), with children aged 7–9 years most frequently co-infected with *S. haematobium* followed by the age group 4–6 years [58]. This finding is in agreement with that of another study [52] but conflicts with other findings [85].

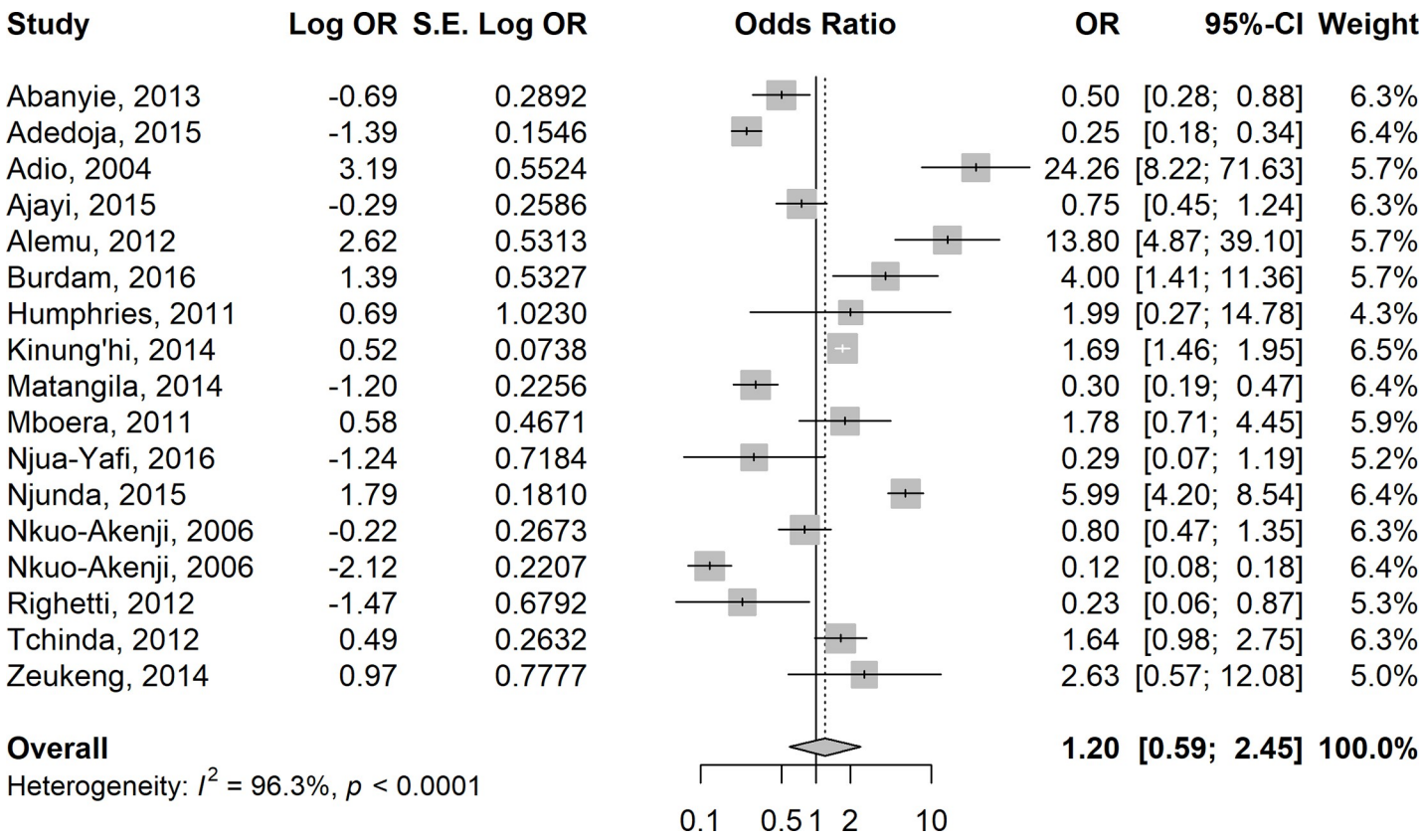

Fig 6. Forest plot showing odds of anaemia in children co-infected with *Plasmodium* species and pooled STH species compared with those who were infected with *P. falciparum* alone.

https://doi.org/10.1371/journal.pntd.0009138.g006

Interactions between malaria and helminth. A Kenyan study [58] reported that the odds of intensity of *S. haematobium* infection increased with increasing *Plasmodium* infection intensity, consistent with similar with findings of studies from Senegal [48], Mali [67, 68],

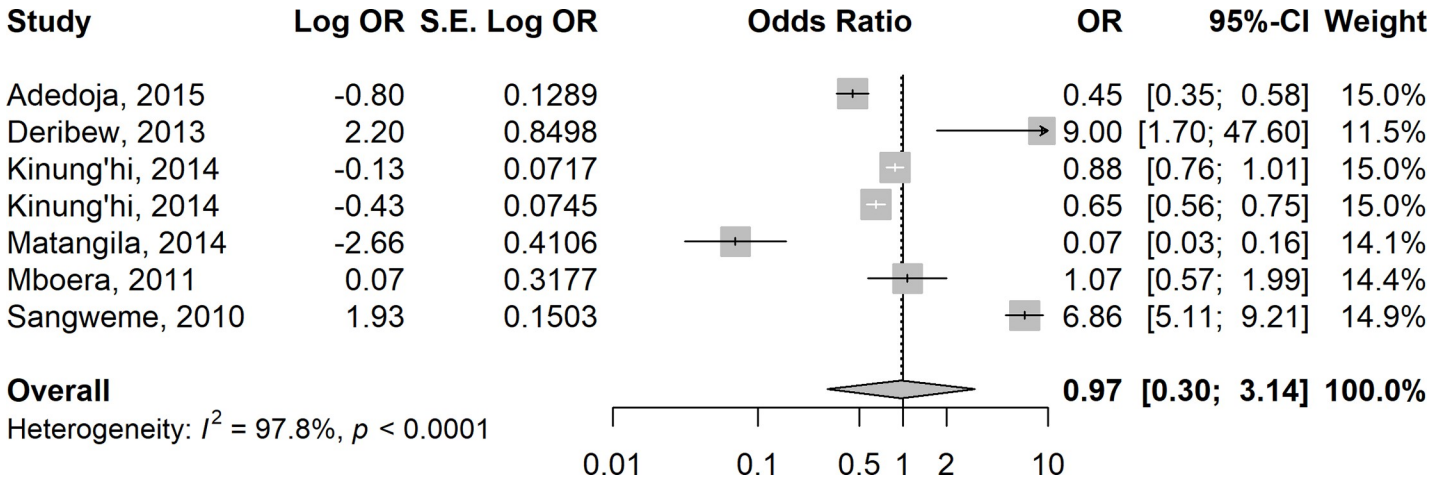

Fig 7. Forest plot showing odds of anaemia in children co-infected with Plasmodium species and pooled Schistosoma spp compared with those who were infected with P. falciparum alone.

https://doi.org/10.1371/journal.pntd.0009138.g007

Thailand [49] and Zimbabwe [17]. These findings conflict with those of two RCTs conducted in Madagascar which reported a negative interaction between *P. falciparum* and *S. haematobium* light infections [38], between *A. lumbricoides* and malaria parasite density [39] and of another study which showed that *S. mansoni* increased susceptibility to malaria [19]. Two studies [43, 47] reported that *A. lumbricoides* exerted a protective impact on the severity and patency of malaria clinical infections [50], in agreement with the findings of another study [56] which showed that administration of anti-helminth drugs lowered the prevalence and intensity of *A. lumbricoides* infections and also the prevalence of *Plasmodium* infection.

Anaemia induced by malaria-helminth co-infection. Seven [34, 35, 40, 44, 46, 53, 54] of the 27 studies analysed for narrative reviews also contributed to the data synthesis for the odds of anaemia in *Plasmodium*-helminth co-infection described above. Four of these studies [34, 35, 40, 46] showed a lower mean haemoglobin values for children with *Plasmodium*-helminth co-infections than children with either *Plasmodium* or helminth infection only. Humphries *et al* in two studies [35, 36] reported that the risk of anaemia was lower in Ghanaian children co-infected with malaria and hookworm than in those with malaria alone, suggesting that hookworm may modulate the pathogenesis of *P. falciparum*. This is similar with findings from Deribew *et al* [40], but deviates from findings of other studies [41, 46, 53, 54].

Immuno-modulating effects of helminths on malaria. Three studies [55, 57, 59] reported the immuno-modulating effect of helminths on the clinical course of malaria. A significant correlation was observed between the occurrence of malaria attacks, hookworm carriage and a decrease in cytophilic IgG1 and IgG3 malaria responses, suggesting that helminth infection might increase malaria morbidity through a Th2 worm-driven pattern of anti-malarial immune responses [55]. This is consistent with a Senegalese study [59] in which higher circulating levels of interleukin-10 in the plasma of co-infected children were associated with decreased anti-plasmodial IgG responses, but disagrees with the findings of another study in which no effect of *S. haematobium* was observed on the innate and adaptive immune response among Gabonese children infected with *P. falciparum* [57].

Quality of the included studies. We assessed the quality of the studies included in this review, and observed that majority of the studies had strong quality in design. Overall rating based on the assessment criteria showed that four studies were of strong quality, 41 studies were of moderate quality and the quality of 10 studies was weak (Table 1). None of the studies was excluded from the review as a result of quality issues.

Discussion

Burden of malaria-helminth co-infections

This systematic review with meta-analysis of 28 studies involving 22,114 children across 13 endemic countries showed an overall prevalence of malaria-helminth co-infection of 17.7%. Expectedly, sub-analysis showed that the prevalence varied according to geographic regions of LMIC, with the prevalence being highest in South America region and lowest in Southeast Asia. The small sample size of the single study which satisfied eligibility for inclusion in this review from South America, is likely to explain the very high prevalence observed in this region. This is in contrast with a low prevalence observed in Southeast Asia region, although the only included study had a relatively bigger sample size. The small number of studies reviewed from outside SSA means that no general conclusions can be made about the frequency of *Plasmodium*-helminth co-infections between continents. The pooled prevalence rates observed among the larger number of studies undertaken in SSA ranged from 13.1 to 30.7%. These are similar findings to those of a previous review [86]. Apart from environmental factors which promote the co-existence of malaria and helminth infections in LMIC, a high

prevalence of co-infection in these settings has been attributed to prevalent infrastructural and behavioural problems such as poor sanitation, lack of toilet facilities, unsafe drinking water, and ineffective public health enlightenment programmes [86].

Nature of interactions between malaria and helminths

Meta-analysis of the 24 studies in this review revealed lower odds of prevalent malaria in children co-infected with either STH or *Schistosoma* spp, but higher odds in children with malaria-STH co-infection when adjusted for confounders. This is similar to the findings of reviews conducted by Dagarege *et al* [7]. Also, narrative reviews conducted as part of this systematic review showed conflicting findings, with positive linear relationship between *Plasmodium falciparum* and *S.haematobium* in Kenyan, Senegalese, Thai and Zimbabwean children [17, 48, 49, 58] but negative interactions reported in Malagasy children [38, 39] and between *P. falciparum and S.mansoni* in another Senegalese paediatric population [19]. These conflicting findings underscore the complexity in the interactions between *P.falciparum* and helminths. The variations may also be influenced by the nature of immune responses elicited by the dual infections. Given the variability in the mechanisms of immune activation by helminths and *Plasmodium* parasites [16], and the fact that helminths downregulate immune responses to *Plasmodium* pathogens [57, 87], previous studies suggested that STH infections increase risk to *Plasmodium* infection and related clinical outcomes [55, 65].

Risk of anaemia from malaria-helminth co-infections

The summary estimates from 16 studies in this review showed that the odds of anaemia were higher in children who were co-infected with *Plasmodium* and STH species than in children infection with *Plasmodium* alone. These findings are consistent with review by Naing *et al* [26], but not with findings of review by Dagarege *et al* [7]. The negative effect of *Plasmodium*-helminth co-infection on anaemia is not surprising considering the different mechanisms by which anaemia is produced in the two infections [2, 63, 88,89].

The pooled estimates from six studies in this review of *Plasmodium-Schistosoma* co-infection showed an equal odd of anaemia in co-infected children compared with uninfected children. This is not in keeping with the finding of a previous review [8], which reported a higher mean haemoglobin concentration in children co-infected with *S. haematobium* and *P. falciparum* than in those infected with only *P. falciparum*. A reason for this difference might be due to the relatively low number of primary studies used in calculating the summary estimates for the mean haemoglobin differences. Nevertheless, the finding of this review supports the postulated mechanisms modulating anaemia in *Schistosoma-Plasmodium* co-infection [40, 55, 59, 74].

Study limitations

This systematic review did not escape from the limitations identified in previous reviews. Most of the primary studies included in this reviews were cross-sectional in design, making it challenging to conclusively establish the prevalence of malaria-helminth co-infections in LMIC. A very high level of heterogeneity was also observed among the included studies, although Egger's test did not reach statistical significance thereby ruling out the possibility of publication bias. Bias may have been introduced given that the primary studies were conducted in widely diverse populations, with significant variations in the study designs and methodologies adopted in implementing these primary studies. Nevertheless, this review has updated the body of knowledge on malaria-helminth co-infection through a comprehensive synthesis of data obtained from studies conducted across LMIC.

Conclusion

In conclusion, we have shown that the prevalence of malaria-helminth co-infection is high in studies which evaluated the prevalence of both groups of infections in children living in endemic countries. The nature of interactions between malaria and helminth infection and impact of the co-infection on anaemia remain inconclusive, and may be modulated by immune responses of the affected children. Findings of this review support our resolve to employ improved tools to quantify the burden of malaria-helminth co-infections. This may generate better understanding of burden of the co-infection, which could be deployed for planning and implementation of appropriate interventions for integrated control and, ultimately elimination of both groups of infections. Exploring the dynamics of immune regulation in malaria and helminth co-infection may also be useful in malaria vaccine development to understand the influence of the dual infection on vaccine immunogenicity [2].

Supporting information

S1 Fig. Forest plot showing pooled prevalence of malaria-helminth co-infection by geographic region.
(DOCX)

S2 Fig. a-b-c: Forest plot showing sub-group analysis of summary estimates of prevalence of *P.falciparum-A. lumbricoides* co-infection, forest plot showing sub-group analysis of summary estimates of prevalence of *P.falciparum*-hookworm co-infection, forest plot showing sub-group analysis of summary estimates of prevalence of *P.falciparum-T.trichuria* co-infection.
(DOCX)

S3 Fig. a-b: Forest plot showing sub-group analysis of prevalence of *Plasmodium-S. haematobium* co-infection in children in LMIC, forest plot showing sub-group analysis of prevalence of *Plasmodium-S.mansoni* co-infection in children in LMIC.
(DOCX)

S4 Fig. Forest plot showing the risk of asymptomatic/uncomplicated or severe P. falciparum infection in children co-infected with STH compared with children who did not have STH infection when adjusted for geographic location of the study participants.
(DOCX)

S5 Fig. Forest plot showing the risk of asymptomatic/uncomplicated or severe P. falciparum infection in children co-infected with STH compared with children who did not have STH infection when adjusted for age, gender, socio-economic status and nutrition status of the children.
(DOCX)

S1 File. Study protocol including the search strategy.
(PDF)

Acknowledgments

We appreciate the support and guidance on the refinement of the search strategy by Jane Falconer and colleagues at the Library and Archive Services of the London School of Hygiene & Tropical Medicine, UK.

Author Contributions

Conceptualization: Muhammed O. Afolabi.

Data curation: Muhammed O. Afolabi, Boni M. Ale, Edgard D. Dabira, Schadrac C. Agbla, Brian Greenwood.

Formal analysis: Muhammed O. Afolabi, Boni M. Ale.

Funding acquisition: Muhammed O. Afolabi, Brian Greenwood.

Investigation: Muhammed O. Afolabi, Edgard D. Dabira, Jean Louis A. Ndiaye.

Methodology: Muhammed O. Afolabi.

Project administration: Muhammed O. Afolabi, Brian Greenwood.

Resources: Brian Greenwood.

Supervision: Muhammed O. Afolabi, Amaya L. Bustinduy, Brian Greenwood.

Writing – original draft: Muhammed O. Afolabi.

Writing – review & editing: Muhammed O. Afolabi, Boni M. Ale, Edgard D. Dabira, Schadrac C. Agbla, Amaya L. Bustinduy, Jean Louis A. Ndiaye, Brian Greenwood.

References

1. Steinmann P, Utzinger J, Du ZW, Zhou XN. Multiparasitism a neglected reality on global, regional and local scale. Adv Parasitol 2010; 73:21–50. Epub 2010/07/16. https://doi.org/10.1016/S0065-308X(10)73002-5 PMID: 20627138.
2. Brooker S, Akhwale W, Pullan R, Estambale B, Clarke SE, Snow RW, et al. Epidemiology of Plasmodium-Helminth Co-Infection in Africa: Populations at Risk, Potential Impact on Anemia, and Prospects for Combining Control. The American journal of tropical medicine and hygiene. 2007; 77(6_Suppl):88–98. https://doi.org/10.4269/ajtmh.2007.77.88 PMID: 18165479
3. Degarege A, Legesse M, Medhin G, Animut A, Erko B. Malaria and related outcomes in patients with intestinal helminths: a cross-sectional study. BMC Infect Dis. 2012; 12:291. Epub 2012/11/10. https://doi.org/10.1186/1471-2334-12-291 PMID: 23136960; PubMed Central PMCID: PMC3519704.
4. Dejon-Agobe JC, Zinsou JF, Honkpehedji YJ, Ateba-Ngoa U, Edoa JR, Adegbite BR, et al. Schistosoma haematobium effects on Plasmodium falciparum infection modified by soil-transmitted helminths in school-age children living in rural areas of Gabon. PLoS neglected tropical diseases. 2018; 12(8): e0006663. Epub 2018/08/07. https://doi.org/10.1371/journal.pntd.0006663 PMID: 30080853; PubMed Central PMCID: PMC6095623.
5. World malaria report 2019. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO. Available from: https://www.who.int/publications-detail/world-malaria-report-2019. Accessed 20 Jan 2020.
6. 2030 targets for soil-transmitted helminthiases control programmes. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO. Available from: https://www.who.int/intestinal_worms/resources/9789240000315/en/. Accessed 20 Jan 2020.
7. Degarege A, Veledar E, Degarege D, Erko B, Nacher M, Madhivanan P. Plasmodium falciparum and soil-transmitted helminth co-infections among children in sub-Saharan Africa: a systematic review and meta-analysis. Parasit Vectors. 2016; 9(1):344. Epub 2016/06/17. https://doi.org/10.1186/s13071-016-1594-2 PMID: 27306987; PubMed Central PMCID: PMC4908807.
8. Degarege A, Degarege D, Veledar E, Erko B, Nacher M, Beck-Sague CM, et al. Plasmodium falciparum Infection Status among Children with Schistosoma in Sub-Saharan Africa: A Systematic Review and Meta-analysis. PLoS neglected tropical diseases. 2016; 10(12):e0005193. Epub 2016/12/08. https://doi.org/10.1371/journal.pntd.0005193 PMID: 27926919; PubMed Central PMCID: PMC5142807.
9. Hotez PJ, Molyneux DH. Tropical anemia: one of Africa's great killers and a rationale for linking malaria and neglected tropical disease control to achieve a common goal. PLoS neglected tropical diseases. 2008; 2(7):e270. Epub 2008/07/31. https://doi.org/10.1371/journal.pntd.0000270 PMID: 18665256; PubMed Central PMCID: PMC2474697.
10. Ezeamama AE, McGarvey ST, Acosta LP, Zierler S, Manalo DL, Wu HW, et al. The synergistic effect of concomitant schistosomiasis, hookworm, and trichuris infections on children's anemia burden. PLoS

neglected tropical diseases. 2008; 2(6):e245. Epub 2008/06/05. https://doi.org/10.1371/journal.pntd.0000245 PMID: 18523547; PubMed Central PMCID: PMC2390851.

11. Sousa-Figueiredo JC, Gamboa D, Pedro JM, Fançony C, Langa AJ, Magalhães RJS, et al. Epidemiology of malaria, schistosomiasis, geohelminths, anemia and malnutrition in the context of a demographic surveillance system in northern Angola. PloS one. 2012; 7(4):e33189–e. Epub 2012/04/06. https://doi.org/10.1371/journal.pone.0033189 PMID: 22493664.

12. Ezeamama AE, Bustinduy AL, Nkwata AK, Martinez L, Pabalan N, Boivin MJ, et al. Cognitive deficits and educational loss in children with schistosome infection-A systematic review and meta-analysis. PLoS neglected tropical diseases. 2018; 12(1):e0005524. Epub 2018/01/13. https://doi.org/10.1371/journal.pntd.0005524 PMID: 29329293; PubMed Central PMCID: PMC5766129.

13. Pabalan N, Singian E, Tabangay L, Jarjanazi H, Boivin MJ, Ezeamama AE. Soil-transmitted helminth infection, loss of education and cognitive impairment in school-aged children: A systematic review and meta-analysis. PLoS neglected tropical diseases. 2018; 12(1):e0005523. Epub 2018/01/13. https://doi.org/10.1371/journal.pntd.0005523 PMID: 29329288; PubMed Central PMCID: PMC5766095.

14. Nankabirwa J, Wandera B, Kiwanuka N, Staedke SG, Kamya MR, Brooker SJ. Asymptomatic Plasmodium infection and cognition among primary schoolchildren in a high malaria transmission setting in Uganda. The American journal of tropical medicine and hygiene. 2013; 88(6):1102–8. Epub 2013/04/15. https://doi.org/10.4269/ajtmh.12-0633 PMID: 23589533.

15. Degarege A, Erko B. Epidemiology of Plasmodium and Helminth Coinfection and Possible Reasons for Heterogeneity. Biomed Res Int. 2016; 2016:3083568. Epub 2016/04/20. https://doi.org/10.1155/2016/3083568 PMID: 27092310; PubMed Central PMCID: PMC4820611.

16. Hartgers FC, Yazdanbakhsh M. Co-infection of helminths and malaria: modulation of the immune responses to malaria. Parasite Immunol 2006; 28(10):497–506. Epub 2006/09/13. https://doi.org/10.1111/j.1365-3024.2006.00901.x PMID: 16965285.

17. Sangweme DT, Midzi N, Zinyowera-Mutapuri S, Mduluza T, Diener-West M, Kumar N. Impact of schistosome infection on Plasmodium falciparum Malariometric indices and immune correlates in school age children in Burma Valley, Zimbabwe. PLoS neglected tropical diseases. 2010; 4(11):e882. Epub 2010/11/19. https://doi.org/10.1371/journal.pntd.0000882 PMID: 21085468; PubMed Central PMCID: PMC2976682.

18. Nacher M. Interactions between worms and malaria: good worms or bad worms? Malar J. 2011; 10:259. Epub 2011/09/14. https://doi.org/10.1186/1475-2875-10-259 PMID: 21910854; PubMed Central PMCID: PMC3192711.

19. Sokhna C, Le Hesran J-Y, Mbaye PA, Akiana J, Camara P, Diop M, et al. Increase of malaria attacks among children presenting concomitant infection by Schistosoma mansoni in Senegal. Malaria journal. 2004; 3:43–. https://doi.org/10.1186/1475-2875-3-43 PMID: 15544703.

20. Adegnika AA, Kremsner PG. Epidemiology of malaria and helminth interaction: a review from 2001 to 2011. Curr Opin HIV AIDS 2012; 7(3):221–4. Epub 2012/03/16. https://doi.org/10.1097/COH.0b013e3283524d90 PMID: 22418449.

21. The Malaria Atlas Project. Available from: https://malariaatlas.org/. Accessed 12 June 2020.

22. Expanded Special Project for Elimination of Neglected Tropical Diseases (ESPEN). Available from: https://espen.afro.who.int/. Accessed 12 June 2020.

23. Global Atlas of Helminth Infections> Available from: http://www.thiswormyworld.org/. Accessed 12 June 2020.

24. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009 Jul 21; 6 (7):e1000097. https://doi.org/10.1371/journal.pmed.1000097 PMID: 19621072

25. Morgan RL, Whaley P, Thayer KA, Schünemann HJ. Identifying the PECO: A framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. Environment international. 2018; 121(Pt 1):1027–31. Epub 2018/09/01. https://doi.org/10.1016/j.envint.2018.07.015 PMID: 30166065; PubMed Central PMCID: PMC6908441.

26. Naing C, Whittaker MA, Nyunt-Wai V, Reid SA, Wong SF, Mak JW, et al. Malaria and soil-transmitted intestinal helminth co-infection and its effect on anemia: a meta-analysis. Trans R Soc Trop Med Hyg. 2013; 107 (11):672–83. https://doi.org/10.1093/trstmh/trt086 PMID: 24123127

27. Basic laboratory methods in medical parasitology. Available from: https://www.who.int/malaria/publications/atoz/9241544104_part1/en/. Accessed 21 July 2020.

28. WHO/UNICEF/UNU. Iron deficiency anemia: assessment, prevention and control: a guide for programme managers. World Health Organization, Geneva. 2011. p. 114. Available from: https://www.who.int/nutrition/publications/en/ida_assessment_prevention_control.pdf. Accessed 21 July 2020.

29. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Syst Rev. 2016; 5:210. https://doi.org/10.1186/s13643-016-0384-4 PMID: 27919275

30. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses 2014. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

31. Effective Public Health Practice Project. Effective Public Health Practice Project. Dictionary for the Effective Public Health Practice Project Quality Assessment Tool For Quantitative Studies. Available from: http://www.ephpp.ca/PDF/QADictionary_dec2009.pdf. Accessed on 15 Jan 2020.

32. Reviews in health promotion and public health. Cochrane Handbook for Systematic Reviews of Interventions. Retrieved from www.cochrane-handbook.org. Accessed 15 Jan 2020.

33. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from: www.training.cochrane.org/handbook. Accessed on 28 April 2020.

34. Akanni EO, Adefioye OA, Akanni RA, Taiwo SS. Iron deficiency anaemia associated with helminths and asymptomatic malaria infections among rural school children in Southwestern Nigeria. Asian Pacific Journal of Tropical Disease. 2014; 4:S590 –S4. https://doi.org/10.1016/S2222-1808(14)60684-8

35. Humphries D, Mosites E, Otchere J, Twum WA, Woo L, Jones-Sanpei H, et al. Epidemiology of hookworm infection in Kintampo North Municipality, Ghana: patterns of malaria coinfection, anemia, and albendazole treatment failure. The American journal of tropical medicine and hygiene. 2011; 84(5):792–800. https://doi.org/10.4269/ajtmh.2011.11-0003 PMID: 21540391.

36. Humphries D, Simms BT, Davey D, Otchere J, Quagraine J, Terryah S, et al. Hookworm infection among school age children in Kintampo north municipality, Ghana: nutritional risk factors and response to albendazole treatment. The American journal of tropical medicine and hygiene. 2013; 89(3):540–8. Epub 2013/07/08. https://doi.org/10.4269/ajtmh.12-0605 PMID: 23836564.

37. Briand V, Watier L, JY LEH, Garcia A, Cot M. Coinfection with Plasmodium falciparum and schistosoma haematobium: protective effect of schistosomiasis on malaria in senegalese children? The American journal of tropical medicine and hygiene. 2005; 72(6):702–7. Epub 2005/06/21. PMID: 15964953.

38. Brutus L, Watier L, Briand V, Hanitrasoamampionona V, Razanatsoarilala H, Cot M. Parasitic co-infections: does Ascaris lumbricoides protect against Plasmodium falciparum infection? The American journal of tropical medicine and hygiene. 2006; 75(2):194–8. https://doi.org/10.4269/ajtmh.2006.75.194 PMID: 16896118.

39. Brutus L, Watier L, Hanitrasoamampionona V, Razanatsoarilala H, Cot M. Confirmation of the protective effect of Ascaris lumbricoides on Plasmodium falciparum infection: results of a randomized trial in Madagascar. The American journal of tropical medicine and hygiene. 2007; 77(6):1091–5. https://doi.org/10.4269/ajtmh.2007.77.1091 PMID: 18165528.

40. Deribew K, Tekeste Z, Petros B, Huat LB. Urinary schistosomiasis and malaria associated anemia in Ethiopia. Asian Pac J Trop Biomed. 2013; 3(4):307–10. Epub 2013/04/27. https://doi.org/10.1016/S2221-1691(13)60068-4 PMID: 23620856; PubMed Central PMCID: PMC3634929.

41. Green HK, Sousa-Figueiredo JC, BasÁÑEz M-G, Betson M, Kabatereine NB, Fenwick A, et al. Anaemia in Ugandan preschool-aged children: the relative contribution of intestinal parasites and malaria. Parasitology. 2011; 138(12):1534–45. Epub 2011/08/08. https://doi.org/10.1017/S0031182011001016 PMID: 21819635

42. Kepha S, Nuwaha F, Nikolay B, Gichuki P, Edwards T, Allen E, et al. Epidemiology of coinfection with soil transmitted helminths and Plasmodium falciparum among school children in Bumula District in western Kenya. Parasites & vectors. 2015; 8:314–. https://doi.org/10.1186/s13071-015-0891-5 PMID: 26063324.

43. Kwenti TE, Nkume FA, Tanjeko AT, Kwenti TDB. The Effect of Intestinal Parasitic Infection on the Clinical Outcome of Malaria in Coinfected Children in Cameroon. PLoS neglected tropical diseases. 2016; 10(4):e0004673–e. https://doi.org/10.1371/journal.pntd.0004673 PMID: 27128975.

44. Njunda AL, Fon SG, Assob JCN, Nsagha DS, Kwenti TDB, Kwenti TE. Coinfection with malaria and intestinal parasites, and its association with anaemia in children in Cameroon. Infectious diseases of poverty. 2015; 4:43–. https://doi.org/10.1186/s40249-015-0078-5 PMID: 26445484.

45. Nyarko R, Torpey K, Ankomah A. Schistosoma haematobium, Plasmodium falciparum infection and anaemia in children in Accra. Ghana Tropical Diseases, Travel Medicine and Vaccines. 2018; 4 (1):3. https://doi.org/10.1186/s40794-018-0063-7 PMID: 29721329

46. Njua-Yafi C, Achidi EA, Anchang-Kimbi JK, Apinjoh TO, Mugri RN, Chi HF, et al. Malaria, helminths, co-infection and anaemia in a cohort of children from Mutengene, south western Cameroon. Malar J. 2016; 15:69. Epub 2016/02/08. https://doi.org/10.1186/s12936-016-1111-2 PMID: 26852392; PubMed Central PMCID: PMC4744422.

47. Le Hesran JY, Akiana J, Ndiaye el HM, Dia M, Senghor P, Konate L. Severe malaria attack is associated with high prevalence of Ascaris lumbricoides infection among children in rural Senegal. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2004; 98(7):397–9. Epub 2004/05/13. https://doi.org/10.1016/j.trstmh.2003.10.009 PMID: 15138075.

48. Lemaitre M, Watier L, Briand V, Garcia A, Le Hesran JY, Cot M. Coinfection with Plasmodium falciparum and Schistosoma haematobium: additional evidence of the protective effect of Schistosomiasis on malaria in Senegalese children. The American journal of tropical medicine and hygiene. 2014; 90 (2):329–34. Epub 2013/12/09. https://doi.org/10.4269/ajtmh.12-0431 PMID: 24323515.

49. Nacher M, Singhasivanon P, Yimsamran S, Manibunyong W, Thanyavanich N, Wuthisen P, et al. Intestinal helminth infections are associated with increased incidence of Plasmodium falciparum malaria in Thailand. J Parasitol. 2002; 88(1):55–8. 4. https://doi.org/10.1645/0022-3395(2002)088[0055:IHIAAW]2.0.CO;2 PMID: 12053980

50. Stefani A, Cheuret M, N'Guyen D, Simon S, Brousse P, Carme B, et al. Interactions between Gastrointestinal Nematodes and Malaria in a Cohort of Children in an Amazonian Village. J Trop Pediatr. 2016; 63(2):144–7. https://doi.org/10.1093/tropej/fmw063 PMID: 27694323

51. Lyke KE, Dicko A, Dabo A, Sangare L, Kone A, Coulibaly D, et al. Association of Schistosoma haematobium infection with protection against acute Plasmodium falciparum malaria in Malian children. The American journal of tropical medicine and hygiene. 2005; 73(6):1124–30. Epub 2005/12/16. PMID: 16354824; PubMed Central PMCID: PMC2738948.

52. Adedoja AA, Akanbi AA, Oshodi AJ. Effect of artemether-lumefantrine treatment of falciparum malaria on urogenital schistosomiasis in co-infected School Aged Children in North Central of Nigeria. International Journal of Biological and Chemical. Sciences. 2015; 9(1):134–40.

53. Righetti AA, Glinz D, Adiossan LG, Koua A-YG, Niamké S, Hurrell RF, et al. Interactions and potential implications of Plasmodium falciparum-hookworm coinfection in different age groups in south-central Côte d'Ivoire. PLoS neglected tropical diseases. 2012; 6(11):e1889–e. Epub 2012/11/01. https://doi.org/10.1371/journal.pntd.0001889 PMID: 23133691.

54. Abanyie FA, McCracken C, Kirwan P, Molloy SF, Asaolu SO, Holland CV, et al. Ascaris co-infection does not alter malaria-induced anaemia in a cohort of Nigerian preschool children. Malar J. 2013; 12:1. Epub 2013/01/04. https://doi.org/10.1186/1475-2875-12-1 PMID: 23282136; PubMed Central PMCID: PMC3544581.

55. Roussilhon C, Brasseur P, Agnamey P, Pérignon J-L, Druilhe P. Understanding human-Plasmodium falciparum immune interactions uncovers the immunological role of worms. PloS one. 2010; 5(2): e9309–e. https://doi.org/10.1371/journal.pone.0009309 PMID: 20174576.

56. Kirwan P, Jackson AL, Asaolu SO, Molloy SF, Abiona TC, Bruce MC, et al. Impact of repeated four-monthly anthelmintic treatment on Plasmodium infection in preschool children: a double-blind placebo-controlled randomized trial. BMC Infect Dis. 2010; 10:277. Epub 2010/09/23. https://doi.org/10.1186/1471-2334-10-277 PMID: 20858280; PubMed Central PMCID: PMC3161357.

57. Ateba-Ngoa U, Adegnika AA, Zinsou JF, Kassa Kassa RF, Smits H, Massinga-Loembe M, et al. Cytokine and chemokine profile of the innate and adaptive immune response of schistosoma haematobium and plasmodium falciparum single and co-infected school-aged children from an endemic area of Lambaréné. Gabon Malaria Journal. 2015; 14 (1):94. https://doi.org/10.1186/s12936-015-0608-4 PMID: 25890010

58. Florey LS, King CH, Van Dyke MK, Muchiri EM, Mungai PL, Zimmerman PA, et al. Partnering parasites: evidence of synergism between heavy Schistosoma haematobium and Plasmodium species infections in Kenyan children. PLoS neglected tropical diseases. 2012; 6(7):e1723–e. Epub 2012/07/24. https://doi.org/10.1371/journal.pntd.0001723 PMID: 22848765.

59. Courtin D, Djilali-Saïah A, Milet J, Soulard V, Gaye O, Migot-Nabias F, et al. Schistosoma haematobium infection affects Plasmodium falciparum-specific IgG responses associated with protection against malaria. Parasite Immunol. 2011; 33(2):124–31. Epub 2011/01/14. https://doi.org/10.1111/j.1365-3024.2010.01267.x PMID: 21226725.

60. Achidi EA, Apinjoh TO, Mbunwe E, Besingi R, Yafi C, Wenjighe Awah N, et al. Febrile status, malarial parasitaemia and gastro-intestinal helminthiases in schoolchildren resident at different altitudes, in south–western Cameroon. Annals of Tropical Medicine & Parasitology. 2008; 102(2):103–18. https://doi.org/10.1179/136485908X252287 PMID: 18318932

61. Adedoja A, Tijani BD, Akanbi AA, 2nd, Ojurongbe TA, Adeyeba OA, Ojurongbe O. Co-endemicity of Plasmodium falciparum and Intestinal Helminths Infection in School Age Children in Rural Communities of Kwara State Nigeria. PLoS neglected tropical diseases. 2015; 9(7):e0003940–e. https://doi.org/10.1371/journal.pntd.0003940 PMID: 26222743.

62. Adio MB, Ndamukong KJ, Kimbi HK, Mbuh JV. Malaria and intestinal helminthiasis in school children of Kumba Urban Area, Cameroon East Afr Med J 2004; 81(11):583–8. Epub 2005/05/05. PMID: 15868968.

63. Alemu A, Shiferaw Y, Ambachew A, Hamid H. Malaria helminth co-infections and their contribution for aneamia in febrile patients attending Azzezo health center, Gondar, Northwest Ethiopia: a cross sectional study. Asian Pac J Trop Med 2012; 5(10):803–9. Epub 2012/10/10. https://doi.org/10.1016/S1995-7645(12)60147-3 PMID: 23043920.

64. Burdam FH, Hakimi M, Thio F, Kenangalem E, Indrawanti R, Noviyanti R, et al. Asymptomatic Vivax and Falciparum Parasitaemia with Helminth Co-Infection: Major Risk Factors for Anaemia in Early Life. PloS one. 2016; 11(8):e0160917–e. https://doi.org/10.1371/journal.pone.0160917 PMID: 27504828.

65. Bwanika R, Kato CD, Welishe J, Mwandah DC. Cytokine profiles among patients co-infected with Plasmodium falciparum malaria and soil borne helminths attending Kampala International University Teaching Hospital, in Uganda. Allergy Asthma Clin Immunol. 2018; 14:10. Epub 2018/03/22. https://doi.org/10.1186/s13223-018-0235-z PMID: 29560020; PubMed Central PMCID: PMC5858126.

66. Carmona-Fonseca J, Uscátegui Peñuela RM, Correa Botero AM. Parasitosis intestinal en niños de zonas palúdicas de Antioquia (Colombia). Iatreia. 2009; 22:27–46.

67. Doumbo S, Tran TM, Sangala J, Li S, Doumtabe D, Kone Y, et al. Co-infection of Long-Term Carriers of Plasmodium falciparum with Schistosoma haematobium Enhances Protection from Febrile Malaria: A Prospective Cohort Study in Mali. PLoS Negl Trop Dis. 2014; 8(9):e3154. https://doi.org/10.1371/journal.pntd.0003154 PMID: 25210876

68. Doumbo SN, Ongoïba A, Doumtabe D, Tran TM, Traoré A, Sangala J, et al. Prevalence of Malaria, Intestinal and Urinary parasite infections in Kalifabougou. Mali Mali Medical. 2018; 33 (1):10–5.

69. Elfaki TEM, Elhassan IM. Prevalence Rate of Malaria/ Helminthiasis Co-Infections in Genaid Irrigated Area, Gezira State, Sudan. Journal of Natural and Medical. Sciences. 2015; 16(1):53–60.

70. Kabatereine NB, Standley CJ, Sousa-Figueiredo JC, Fleming FM, Stothard JR, Talisuna A, et al. Integrated prevalence mapping of schistosomiasis, soil-transmitted helminthiasis and malaria in lakeside and island communities in Lake Victoria. Uganda Parasites & Vectors. 2011; 4(1):232. https://doi.org/10.1186/1756-3305-4-232 PMID: 22166365

71. Kinung'hi SM, Magnussen P, Kaatano GM, Kishamawe C, Vennervald BJ. Malaria and helminth co-infections in school and preschool children: a cross-sectional study in Magu district, north-western Tanzania. PloS one. 2014; 9(1):e86510–e. https://doi.org/10.1371/journal.pone.0086510 PMID: 24489732.

72. Matangila JR, Doua JY, Linsuke S, Madinga J, Inocêncio da Luz R, Van Geertruyden J-P, et al. Malaria, schistosomiasis and soil transmitted helminth burden and their correlation with anemia in children attending primary schools in Kinshasa, Democratic Republic of Congo. PloS one. 2014; 9(11):e110789–e. https://doi.org/10.1371/journal.pone.0110789 PMID: 25372029.

73. Mazigo HD, Kidenya BR, Ambrose EE, Zinga M, Waihenya R. Association of intestinal helminths and P. falciparum infections in co-infected school children in northwest Tanzania. Tanzan J Health Res. 2010; 12(4):283–5.

74. Morenikeji OA, Eleng IE, Atanda OS, Oyeyemi OT. Renal related disorders in concomitant Schistosoma haematobium-Plasmodium falciparum infection among children in a rural community of Nigeria. J Infect Public Health 2016; 9(2):136–42. Epub 2015/07/30. https://doi.org/10.1016/j.jiph.2015.06.013 PMID: 26220794.

75. Nkuo-Akenji TK, Chi PC, Cho JF, Ndamukong KKJ, Sumbele I. Malaria and helminth co-infection in children living in a malaria endemic setting of Mount Cameroob and predictors of anemia. Journal of Parasitology. 2006; 92(6):1191–5, 5.

76. Obi AA Yesufu HM, Fagbenro-Beyioku AF and Obi CL. Concurrent Infections with Schistosomiasis Typhoid Fever and Malaria among Patients in Edo State Nigeria. 1996. Acta Medica et Biologica; 44 (4):215–219.

77. Salim N, Knopp S, Lweno O, Abdul U, Mohamed A, Schindler T, et al. Distribution and risk factors for Plasmodium and helminth co-infections: a cross-sectional survey among children in Bagamoyo district, coastal region of Tanzania. PLoS neglected tropical diseases. 2015; 9(4):e0003660. Epub 2015/04/04. https://doi.org/10.1371/journal.pntd.0003660 PMID: 25837022; PubMed Central PMCID: PMC4383605.

78. Tchinda VHM, Ponka R, Ndzi ES, Madocgne AK, Amédée M, Tchinda MG, Moyou RS. Prevalence of malaria and soil-transmitted helminth infections and their association with undernutrition in schoolchildren residing in Mfou health district in Cameroon. Journal of Public Health and Epidemiology. 2012; 4 (9):253–260. (n).

79. Yapi RB, Hürlimann E, Houngbedji CA, Ndri PB, Silué KD, Soro G, et al. Infection and co-infection with helminths and Plasmodium among school children in Côte d'Ivoire: results from a National Cross-Sectional Survey. PLoS neglected tropical diseases. 2014; 8(6):e2913–e. https://doi.org/10.1371/journal.pntd.0002913 PMID: 24901333.

80. Zeukeng F, Tchinda VHM, Bigoga JD, Seumen CHT, Ndzi ES, Abonweh G, et al. Co-infections of malaria and geohelminthiasis in two rural communities of Nkassomo and Vian in the Mfou health district,

Cameroon. PLoS neglected tropical diseases. 2014; 8(10):e3236–e. https://doi.org/10.1371/journal.pntd.0003236 PMID: 25329479.

81. Degarege A, Animut A, Legesse M, Medhin G, Erko B. Malaria and helminth co-infection and nutritional status of febrile patients in Southern Ethiopia. J Infect Public Health 2014; 7(1):32–7. Epub 2013/09/04. https://doi.org/10.1016/j.jiph.2013.05.007 PMID: 23999346.

82. Ojurongbe O, Adegbayi AM, Bolaji OS, Akindele AA, Adefioye OA. Adeyeba OA Asymptomatic falciparum malaria and intestinal helminths coinfection among school children in Osogbo. Nigeria J Res Med Sci. 2011; 16(5):680–6. PMID: 22091292

83. Mboera LEG, Senkoro KP, Rumisha SF, Mayala BK, Shayo EH, Mlozi MRS. Plasmodium falciparum and helminth coinfections among schoolchildren in relation to agro-ecosystems in Mvomero District. Tanzania Acta Tropica. 2011; 120(1):95–102. https://doi.org/10.1016/j.actatropica.2011.06.007 PMID: 21741929

84. Ajayi IO, Afonne C, Dada-Adegbola H, and Falade CO. Prevalence of Asymptomatic Malaria and Intestinal Helminthiasis Co-infection among Children Living in Selected Rural Communities in Ibadan Nigeria. American Journal of Epidemiology and Infectious Disease. 2015; 3(1): 15–20. https://doi.org/10.12691/ajeid-3-1-3

85. Lyke KE, Dicko A, Dabo A, Sangare L, Kone A, Coulibaly D, et al. Association of Schistosoma haematobium infection with protection against acute Plasmodium falciparum malaria in Malian children. The American journal of tropical medicine and hygiene 2005; 73(6):1124–30. PMID: 16354824.

86. Ojo OE, Adebayo AS, Awobode HO, Nguewa P, Anumudu CI. Schistosoma haematobium and Plasmodium falciparum co-infection in Nigeria 2001–2018: A systematic review and meta-analysis. Scientific African. 2019; 6:e00186. https://doi.org/10.1016/j.sciaf.2019.e00186

87. Winkler S, Willheim M, Baier K, Schmid D, Aichelburg A, Graninger W, et al. Reciprocal regulation of Th1- and Th2-cytokine-producing T cells during clearance of parasitemia in Plasmodium falciparum malaria. Infect Immun. 1998; 66(12):6040–4. Epub 1998/11/24. https://doi.org/10.1128/IAI.66.12.6040-6044.1998 PMID: 9826394; PubMed Central PMCID: PMC108770.

88. Pullan RL, Kabatereine NB, Bukirwa H, Staedke SG, Brooker S. Heterogeneities and consequences of Plasmodium species and hookworm coinfection: a population based study in Uganda. J Infect Dis 2011; 203(3):406–17. Epub 2010/12/27. https://doi.org/10.1093/infdis/jiq063 PMID: 21187338.

89. Haldar K, Mohandas N. Malaria, erythrocytic infection, and anemia. Hematology Am Soc Hematol Educ Program. 2009:87–93. Epub 2009/12/17. https://doi.org/10.1182/asheducation-2009.1.87 PMID: 20008186; PubMed Central PMCID: PMC2933134.