



# *Schistosoma haematobium* and *Plasmodium falciparum* co-infection in Nigeria 2001–2018: A systematic review and meta-analysis



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## ABSTRACT

Malaria and schistosomiasis continue to contribute a big burden to infectious disease prevalence in the tropical areas, mainly in sub Saharan African countries. We previously reported high levels of schistosome specific antibody IgG3 in children coinfected with malaria and schistosomiasis. The aim of the current study was to examine the current co-infection rates of these diseases in Nigeria. Published and unpublished studies on co-infection of human urogenital schistosomiasis and malaria carried out in Nigeria between 2001 and August 2018 were retrieved through literature searches in PubMed, Google Scholar, AJOL, and university theses repositories. The filtered and relevant articles were reviewed and combined in a meta-analysis. Studies involving children reported higher rates of coinfection. The fourteen research articles involving 6,559 individuals were combined in a meta-analysis. Our analyses revealed an estimated 15% co-infection for the country, though with wide variability depending on location. In addition, there are few and well-designed research publications in Nigeria on prevalence and mechanism of malaria and schistosomiasis coinfection.

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## Introduction

Malaria and schistosomiasis remain causes of high morbidity and mortality in the tropics and sub-tropics of Africa [1]. According to the World Health Organization (WHO), both parasitic diseases are endemic to Sub-Saharan Africa with more than 194 million malaria cases, and an estimated 91.4% requiring preventive chemotherapy. In 2016, more than 100,000 malaria deaths were reported in Nigeria with *Plasmodium falciparum* responsible for all malaria cases [2]. Infected individuals exhibit mild symptoms ranging from fever, fatigue, chills to severe complications including cerebral malaria, austere anaemia or renal failure [3].

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Schistosomiasis is caused by five identified *Schistosoma* species and is ranked second to malaria as a neglected tropical disease. In Nigeria, *Schistosoma haematobium* and *Schistosoma mansoni* are responsible for almost all the cases of schistosomiasis, causing urogenital and intestinal schistosomiasis, respectively [4]. People infected with *Schistosoma spp* (*S. haematobium* or *S. mansoni*) display various symptoms and pathologies including anaemia, growth retardation (prevalent among school aged children), dysuria, nutritional deficiencies, haematuria [5], hepatosplenomegaly, pelvic discomfort, infertility (in prolonged cases in females) and bladder cancer [6].

Several epidemiological and immunological studies have indicated high rates of co-infection with soil transmitted helminths and *Plasmodium falciparum* in conditions of poverty, where they frequently overlap [7]. Schistosomiasis and malaria exhibit almost similar distribution patterns, making schisto-malaria coinfection a predominant occurrence in malaria endemic countries [2]. Studies conducted in Nigeria have reported conflicting results about whether *Schistosoma* coinfection with *Plasmodium falciparum* regulates the outcome of malaria infections, by altering the pathophysiological and immune responses of the disease [8]. Morenikeji et al. [9] reported higher anti-*Schistosoma* IgG production during co-infection with malaria among school aged children. Anumudu et al. [10] found high levels of schistosome specific antibody IgG3 in children coinfecting with malaria and schistosomiasis.

There is little information about the prevalence of *Schistosoma* co-infection with *Plasmodium falciparum* in Nigeria. Hence, the main objective of this systematic review and meta-analysis is to estimate the current prevalence of *Schistosoma* and *Plasmodium falciparum* co-infection in Nigeria.

## Materials and methods

Searches were conducted for all publications on schistosomiasis co-infection with *Plasmodium falciparum* in relevant academic research databases including Google scholar, PubMed, Elsevier, Biomed, PLoSOne, Science Direct and African journal online (AJOL) published between 2001 and August 2018. Relevant postgraduate theses on schistosomiasis and malaria coinfection were also included in the study.

The search terms used were “co-infection” OR “concomitant” OR “Mixed infection” OR “concurrent” with “schistosomiasis” OR “Bilharziasis” OR “Neglected tropical disease (NTD)” OR “helminths” OR “Schistosoma” combined with “*Plasmodium falciparum*” OR “malaria” and “Nigeria”. The search was limited to human infections.

### Inclusion criteria

All epidemiological and immunological studies conducted in Nigeria, published in English, which reported prevalence of *S. haematobium* and/or *S. mansoni* with *Plasmodium falciparum* co-infection were included in this review. All study designs including cross-sectional, longitudinal and observational were included. In addition, studies involving school aged children, adolescent and adults were included if they were published within the stipulated time frame. Unpublished studies, conference papers and reviews on *Schistosoma* co-infection with *Plasmodium falciparum* that had data on prevalence were also included in our study. Any soil transmitted helminth co-infection with *Plasmodium falciparum* studies which had prevalence data on *Schistosoma* co-infection with *P. falciparum* were included.

### Exclusion criteria

Studies were excluded if after full review, crucial prevalence data on *Schistosoma* and *Plasmodium falciparum* co-infection were missing. Moreover, studies outside of the stipulated time range of this work, and those written in languages other than English or those without prevalence data on a specific Nigerian population, were excluded.

### Outcome measures

The primary outcome measured was the prevalence of *Schistosomiasis* and *Plasmodium falciparum* co-infections. Studies included in this review indicated the species of *Schistosoma* involved with *P. falciparum* co-infection.

## Data collection

After screening individual articles for eligibility for inclusion in our study, information about the author, year of study, study area (classified based on the geo-political zone), sample size, study design, age range, *Schistosoma* species investigated, the prevalence of *Schistosoma* and *Plasmodium falciparum* were coded using Microsoft Excel, and data were analyzed using R and MedCalc.

## Results

The search yielded a total of 157 articles aggregated from Pubmed ( $n=4$ ), African Journal online database ( $n=5$ ), Google Scholar ( $n=144$ ) and other sources ( $n=4$ ). Screening and Assessment of the articles revealed 32 duplicate articles. Subsequently, a total of 125 articles were reviewed and 103 were excluded for irrelevance. Afterwards, the remaining 22 full text articles were examined, eight lacked some component data and 14 were finally included in the meta-analysis (Fig. 1).

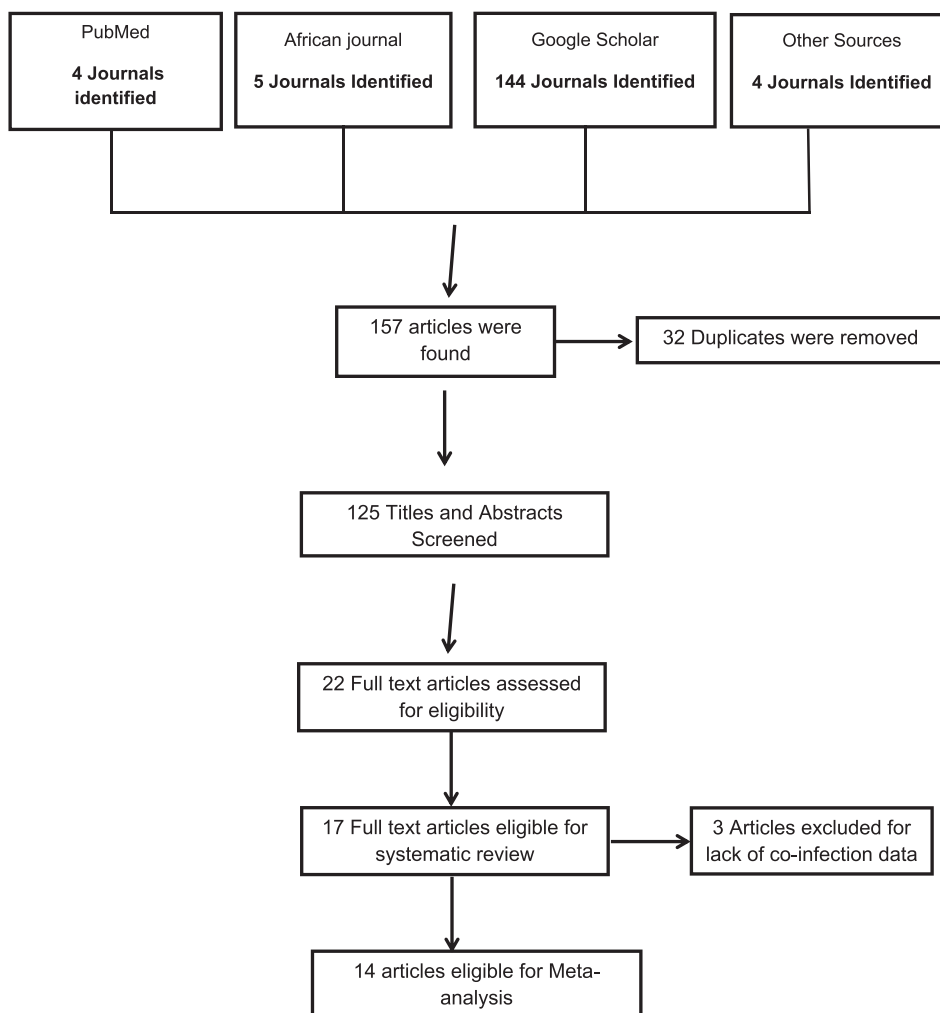


Fig. 1. Flow Diagram of the studies reviewed.

The attributes of the cross-sectional studies included in this work are shown in the table of summaries (Table 1). Only one study involved *S. mansoni* and *P. falciparum* co-infection.

#### Overall prevalence

From the literature search, the reported overall prevalence of schistosomiasis and *Plasmodium falciparum* co-infection in Nigeria ranged from 3.4% to 77% (Table 1). Subgroup analysis according to the geopolitical zone of the study population especially school aged children revealed a diverse prevalence of schistosomiasis and *Plasmodium falciparum* co-infection. Those reporting highest prevalence (77.0%) were carried out in southwestern Nigeria compared with lower rates from studies performed in the South and North central zones. More data have been noted in the south west, 10 out of 17 (Table 1). By the year of article publication, the highest prevalence (77%) was recorded in 2005 and the lowest (6%) in 2012. The study reporting the lowest co-infection prevalence (3.4%) involved adults or pregnant women.

#### Meta-analysis

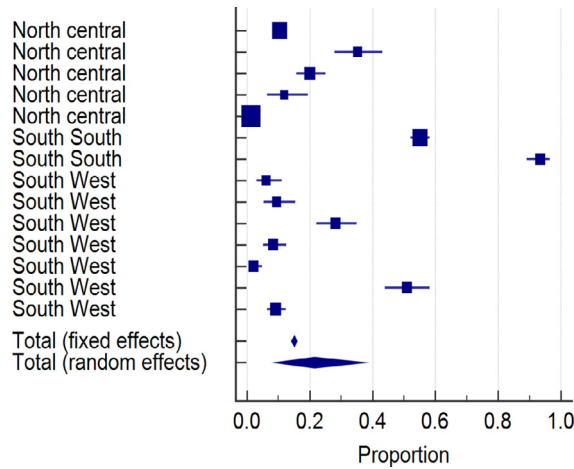
A meta-analysis of combined data from 14 studies reporting on co-infection of malaria and schistosomiasis in Nigeria was carried out. First, the overall content of the meta-analysis was examined to search for systemic bias. The possibility of systemic publication bias did not reach statistical significance (Egger regression  $p=0.354$ , Begg's rank correlation  $p=0.063$ ).

There was significant heterogeneity in the reports of research studies covered ( $p < 0.001$ ) which may be observed from the distribution patterns of individual study effect and asymmetry in the funnel plot (Figs. 2 and 3).

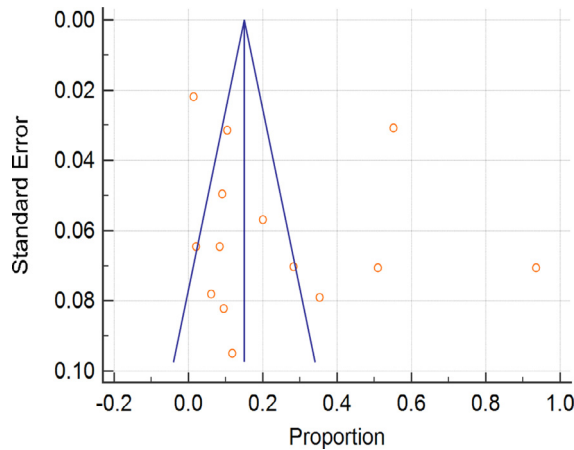
The confidence interval analysis showed that the robust estimates of coinfection prevalence reports ranged from 0.6% to 90% (95% CI) across all studies (Table 2). Such a wide range in estimates of co-infection cases may be highly reflective of

**Table 1**Summary of *Schistosoma* and *Plasmodium falciparum* co-infection studies in Nigeria 2001–2018.

| S/N | Authors                | Year  | Study Area       | Geo-Political Zone | Study Design    | Sample Size | Age Range  | Population Category | Mean Age | Schistosoma Species   | Co-infection Prevalence | No. with co-infection |
|-----|------------------------|-------|------------------|--------------------|-----------------|-------------|------------|---------------------|----------|-----------------------|-------------------------|-----------------------|
| 1   | Adedoja et al. [19]    | 2015a | Kwara            | North Central      | Cross sectional | 1017        | 4–15years  | School Children     | 9.52     | <i>S. haematobium</i> | 10.4%                   | 106                   |
| 2   | Adedoja et al. [20]    | 2015  | Kwara            | North Central      | Cross sectional | 159         | 1–15years  | School Children     | 8.35     | <i>S. haematobium</i> | 54.4%                   | 56                    |
| 3   | Adedoja et al. [23]    | 2017  | Kwara            | North Central      | Cross sectional | 309         | 4–15years  | School Children     | 9.7      | <i>S. haematobium</i> | 25.1%                   | 62                    |
| 4   | Anumudu et al. [10]    | 2012  | Ibadan & Akure   | South West         | Cross sectional | 163         | ---        | School Children     | ---      | <i>S. haematobium</i> | 6.0%                    | 10                    |
| 5   | Arinola, O.G [21]      | 2005  | Ibadan           | South West         | Cross sectional | 147         | 6–14years  | School Children     | ---      | <i>S. haematobium</i> | 77.0%                   | 14                    |
| 6   | Atanda O.S [22]        | 2014  | Ijaka Oke        | South West         | Cross sectional | 202         | 6–14years  | School Children     | 11.5     | <i>S. haematobium</i> | 34.1%                   | 57                    |
| 7   | Dakul et al. [7]       | 2001  | Jinduut          | North Central      | Cross sectional | 110         | 5–15years  | School Children     | 10.3     | <i>S. haematobium</i> | 11.8%                   | 13                    |
| 8   | Egwunyenga et al. [12] | 2001  | Jos              | North Central      | Cross sectional | 2104        | ---        | Pregnant Women      | ---      | <i>S. mansoni</i>     | 3.4%                    | 28                    |
| 9   | Elenwo et al. [24]     | 2014  | Rivers           | South              | Cross sectional | 1060        | 0–83years  | All Age group       | ---      | <i>S. haematobium</i> | 55.1%                   | 584                   |
| 10  | Eleng I.E [13]         | 2015  | Ijaka Isale      | South West         | Cross sectional | 173         | 6–15years  | School Children     | 11.4     | <i>S. haematobium</i> | 57.1%                   | ---                   |
| 11  | Morenikeji et al. [25] | 2014  | Yewa North       | South West         | Cross sectional | 202         | 6–18years  | School Children     | 11.5     | <i>S. haematobium</i> | 28.2%                   | ---                   |
| 12  | Morenikeji et al. [9]  | 2015  | Yewa North       | South West         | Cross sectional | 173         | 6–18years  | School Children     | 11.4     | <i>S. haematobium</i> | 57.1%                   | ---                   |
| 13  | Okafor et al. [26]     | 2007  | Rivers           | South              | Cross sectional | 200         | 0–14years  | School Children     | ---      | <i>S. haematobium</i> | 75.0%                   | 187                   |
| 14  | Oladele et al. [8]     | 2014  | Eggua & Omi-Adio | South West         | Cross sectional | 240         | 5–15years  | School Children     | ---      | <i>S. haematobium</i> | 16.0%                   | 20                    |
| 15  | Olayinka P.I [27]      | 2018  | Yewa North       | South West         | Cross sectional | 240         | 10–70years | All Age group       | ---      | <i>S. haematobium</i> | 8.5%                    | 5                     |
| 16  | Ologunde et al. [28]   | 2015  | Ise Ekiti        | South West         | Cross sectional | 200         | 4–15years  | School Children     | ---      | <i>S. haematobium</i> | 51.0%                   | 102                   |
| 17  | Oloyede et al. [29]    | 2017  | Ibarapa          | South West         | Cross Sectional | 408         | 1–50years  | All Age group       | 28.35    | <i>S. haematobium</i> | 17.1%                   | 37                    |



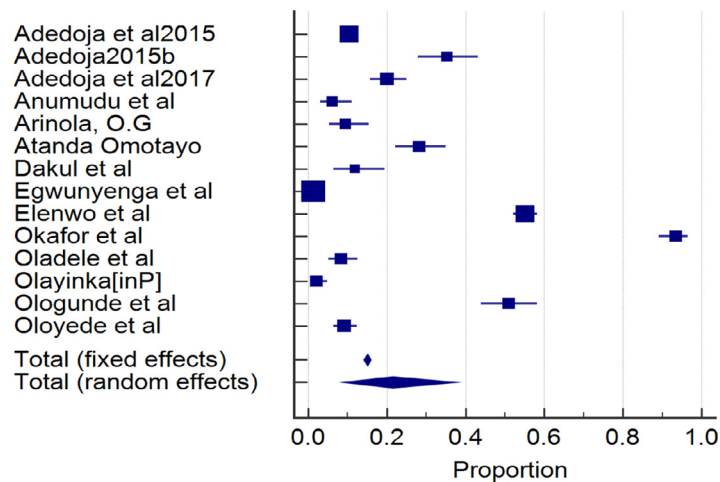
**Fig. 2.** Forest plot showing the real proportion in the prevalence of *P. falciparum* malaria co-infection with *S. haematobium* and greater effect in south-south region.



**Fig. 3.** There was significant heterogeneity in the research studies ( $p < 0.001$ ) which may be observed from the asymmetry in the funnel plot, although systemic publication bias did not reach full statistical significance (Egger regression  $p = 0.354$ , Begg's rank correlation  $p = 0.063$ ).

**Table 2**  
Confidence Interval analysis of estimates of co-infection.

| Study                         | Sample size | Proportion (%) | 95% CI                  |
|-------------------------------|-------------|----------------|-------------------------|
| Adedoja et al. 2015           | 1017        | 10.423         | 8.612 to 12.466         |
| Adedoja et al.2015b           | 159         | 35.220         | 27.821 to 43.181        |
| Adedoja et al. 2017           | 309         | 20.065         | 15.744 to 24.970        |
| Anumudu et al. 2012           | 163         | 6.135          | 2.981 to 10.993         |
| Arinola, O.G 2005             | 147         | 9.524          | 5.305 to 15.463         |
| Atanda O. 2014                | 202         | 28.218         | 22.126 to 34.962        |
| Dakul et al. 2015             | 110         | 11.818         | 6.445 to 19.361         |
| Egwunyenga et al.2001         | 2104        | 1.331          | 0.886 to 1.918          |
| Elenwo et al. 2014            | 1060        | 55.094         | 52.042 to 58.118        |
| Okafor et al. 2007            | 200         | 93.500         | 89.141 to 96.494        |
| Oladele et al. 2014           | 240         | 8.333          | 5.164 to 12.577         |
| Olayinka P. 2018              | 240         | 2.083          | 0.680 to 4.795          |
| Ologunde et al. 2015          | 200         | 51.000         | 43.852 to 58.118        |
| Oloyede et al. 2017           | 408         | 9.069          | 6.466 to 12.283         |
| <b>Total (fixed effects)</b>  | <b>6559</b> | <b>14.993</b>  | <b>14.138 to 15.879</b> |
| <b>Total (random effects)</b> | <b>6559</b> | <b>21.400</b>  | <b>9.025 to 37.273</b>  |



**Fig. 4.** Forest plot showing the difference in the prevalence of co-infection in the range of 0.09 to 0.39 (diamond shape) but more likely close to 0.15 (if studies are assumed to have similar effect size).

location of study in the country as well as age group and social stratum targeted. However, the actual proportion of co-infection was in the range of 0.09 to 0.39 (diamond shape) but with expected mean of 0.15 (or 15%) (if studies are assumed to have similar effect size) (Figs. 2 and 4). The greatest effect on the co-infection data was exerted by the two studies in the south-south region which contributed high proportions (Figs. 2 and 4). Higher levels of heterogeneity were contributed by Ologunde et al. [28] and Okafor and Elenwo [26] compared to other studies, because co-infection was reported relative to the sample sizes of their study population (Fig 5).

## Discussion

In the current study, we performed a combined analysis of more than 6000 individuals from 14 retrieved research articles on co-infection of malaria and schistosomiasis in Nigeria. Estimated co-infection rate was 15% (1SD=9%–39%). There was wide variability in the reports of the co-infection and sample sizes across the studies. Extreme co-infection rates may reach as high 96.4% in small-sized, child-focused studies. The low level of co-infection research across the country retrieved was surprising, and almost 60% (10/17) of those retrieved were carried out in the southwest. An overview of the studies retrieved from the literature search showed that studies involving children had higher co-infection rates. This finding of a higher prevalence of *P. falciparum* infection among children infected with *Schistosoma* could result from social or environmental factors. In some of the children-based reports, more than one-third of the analysed study population had both schistosomiasis and malaria. There are previous reports on co-infection dynamics in children. The different intensities of *Schistosoma* and *P. falciparum* co-infection have been surmised to be based on the age of the host and intensity of *Schistosoma* infection [11]. School aged children co-infected with *S. mansoni* may be more susceptible to *P. falciparum* infection because anaemia associated with *Schistosoma* infection may cause hyperventilation of carbon dioxide and increased lactates, making infected individuals more attractive for mosquitoes and thus increasing their risk for *Plasmodium* infection [12].

Despite the fact that concomitant parasitic infections are a common occurrence in different regions of the world, the small number of research articles retrieved was surprising, especially since schistosomiasis and malaria are among parasitic infections with high prevalence in Sub-Saharan Africa [13]. The high level of co-infection of these two has been attributed to similar factors: poor sanitation, lack of toilet facilities, unsafe drinking water, and ineffective public health enlightenment programme. Therefore, WaSH (safe water, Sanitation and Hygiene) strategies remain valuable against these highly prevalent tropical pathologies.

Three cross-sectional studies included in our work investigated the modulating effect of *Schistosomiasis* infection on the parasitaemia level of *Plasmodium falciparum*. *Schistosoma* co-infection with *Plasmodium* in a patient can alter the development of acquired immunity associated with the resistance or pathology of schistosomiasis activating varied cytokine responses. The type of immune responses depends on the *Schistosoma* species, host age, worm burden and *Plasmodium* spp. involved. *Schistosoma* infection induces helper T cell (Th2) responses which alter cellular responses against malaria parasites [14]. Adedoja et al. [15] found higher levels of IL-10 among children with only schistosomiasis and there was no significant association between pro-inflammatory cytokines in co-infected children. Similar results were found in Kenya [16] and in Senegal [17].

The concomitant infection of two parasites may modulate the effects of each other within their host. This has been reported extensively in different studies where pre-existing infection alters the effect of other (reviewed in [4]). Conversely, *Schistosoma haematobium* exerts a persistent stimulatory effect on the host immune system, protecting children against

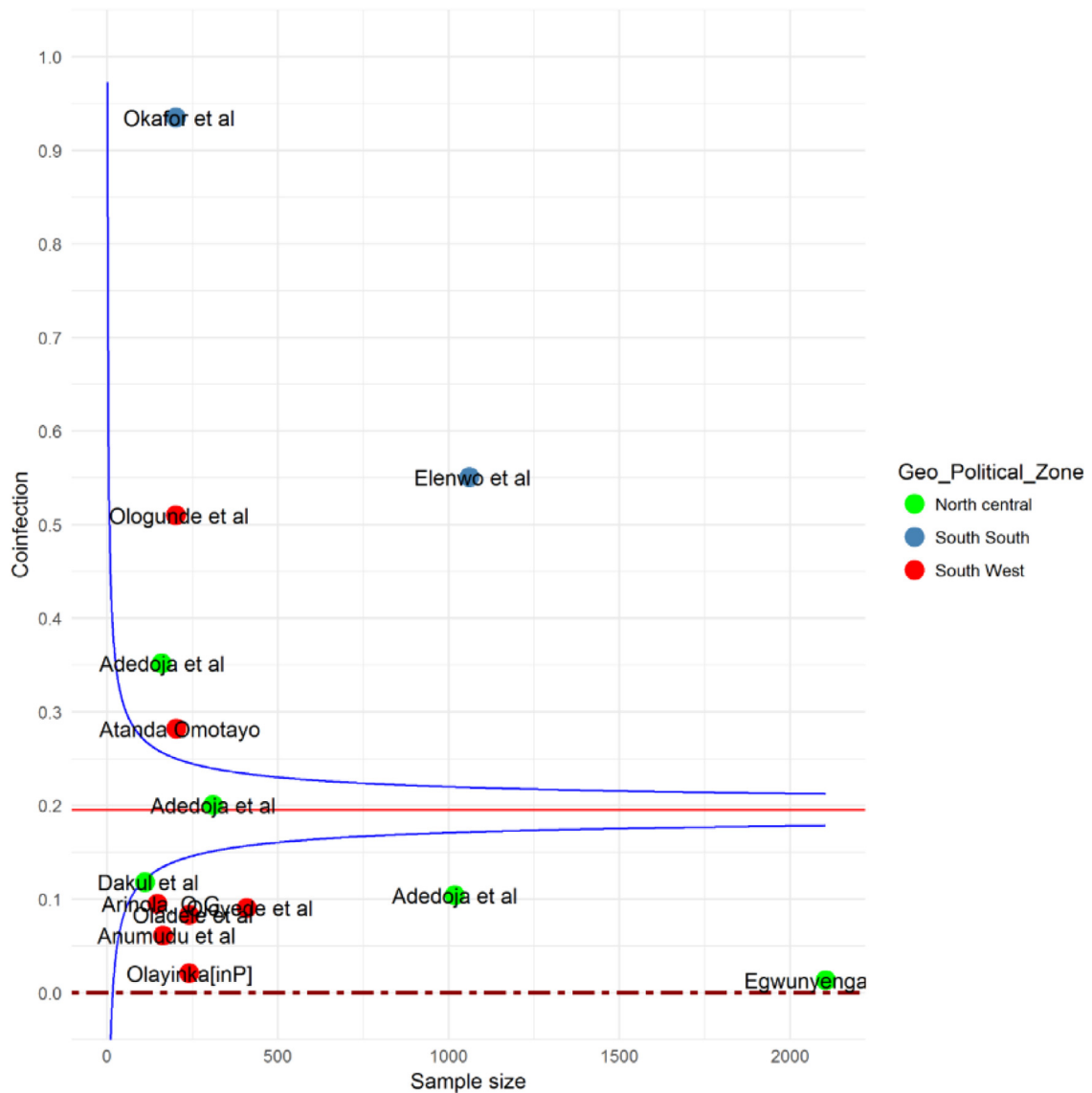


Fig. 5. Higher levels of heterogeneity were contributed by Ologunde et al. [28] and Okafor and Elenwo [26] compared to others.

uncomplicated *P. falciparum* malaria [18]. This modulation effect has not been widely studied in Nigeria. In some studies, proxies for modulation were used, and often not correctly.

Bustinduy et al. [16] studied age-stratified profiles of IL-6, IL-10 and TNF- $\alpha$  cytokines in *Schistosoma haematobium*, *Plasmodium falciparum* and other chronic parasitic co-infections in Kenyan children. They correlated these cytokine levels with schistosomiasis and interactions with concurrent co-infections. After controlling for sex, malaria, anaemia, wasting, stunting and other cytokines, it was shown that IL-6, IL-10 and TNF- $\alpha$  levels were higher among children infected with *S. haematobium*, regardless of *S. haematobium* co-infection status. Morenikeji et al. [9] showed that anti-Schistosoma IgG produced during co-infection with *Plasmodium* spp. among infected individuals in Ijoun, Nigeria, were higher than in malaria mono infection but not in *S. haematobium* mono infection; while Anumudu et al. [10] reported high levels of schistosome specific antibody IgG3 in children co-infected with malaria and schistosomiasis in Ibadan.

Co-infection of the two endemic parasitic diseases has socio-economic and health impact on the population according to authors. Higher prevalence of schistosomiasis and malaria co-infection recorded in some articles included in this review was attributed to poverty, lack of potable water, limited access to health care, lack of protective clothing, poor hygiene, poverty and poor sanitary conditions. The geographical harmony of socio-economic and climatic conditions was also indicative of the overlap in the distribution of *Schistosoma* and *P. falciparum* co-infection; indeed, socio-economic factors were not greatly improved in the communities through the period of studies included in this review. In this review, we find that school



aged children are more prone to schisto-malaria co-infection with severe anaemia, probably due to high worm load and low immunity [1,8,9,22,25,28]. Females had higher co-infection rates than males and this was attributed to daily exposures to water contact related activities including fetching water and swimming [19]. In addition, the poor socio-economic status of the people encourages poor nutrition, and lack of adequate medical attention complicates the infections [24]. When lower prevalence of co-infection was reported, authors indicated that this may reflect increased health awareness and improved sanitary conditions due to gradual urbanization [29] or it may be just the reality faced in rural Nigerian communities. Indeed, the co-infection studies reported indicate that a greater impact is due to prevailing social factors, which could be more visible within certain societal demographics.

Studies also reported the impact of coinfection on the overall host responses. Inyang-Etoh et al. [30] indicated that schistosomiasis can have a negative effect on host response to malaria, including increased susceptibility to plasmodium infection and increased severity of disease especially among children. These co-infected school aged children also had malnutrition, impaired cognitive development, splenomegaly and fatigue [8] resulting in poor school performance and overall physical work capacity. Lower haemoglobin levels were seen among pregnant women with co-infection than in those with single infection of *S. haematobium* or *P. falciparum* [12,29]. Co-infection with these two parasites could aggravate renal related disorders due to excess haematuria and proteinuria [9] inducing kidney complications. In treatment, modulation may even occur such that treatment of schistosomiasis may reduce the risk of malaria infection [11,22]. At the moment, there is no treatment policy for the co-infection, and often the sufferers don't even count on the co-infection when treating the individual infections. However, Oloyede et al. [29] suggested that artemether-lumefantrine, an antimalarial may be a possible treatment against schistosomiasis in uncomplicated *P. falciparum* co-infected individuals, as it also reduces the intensity of *Schistosoma*, severe anaemia and parasitemia [7,19,29]. Morenikeji et al. [9] emphasized the possibility of re-infection with *S. haematobium* among the same individuals following mass chemotherapy for schistosomiasis carried out five years previously. Schistosomiasis influences the production of anti-inflammatory cytokines in children co-infected with malaria. Low levels of circulating T reg memory cells in co-infected children makes them susceptible to opportunistic infections [7]. To summarize, co-infection elicits immune and other molecular responses, thus treatment or preventive strategies need to be developed.

## Conclusion

In essence, there has been attention on eliminating malaria and schistosomiasis, and there is research showing that co-infection modulates immunity. However, only 22 relevant research studies reporting their co-infection in Nigeria could be retrieved. Such a paucity of research into the dynamics of co-infection needs to be addressed, for a holistic understanding, and rapid elimination of these two highly-prevalent diseases.

## Declaration of Competing Interest

The authors declare that there is no conflict of interest regarding this research work.

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