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Review article

Prevalence of asymptomatic *Plasmodium falciparum* infection in pregnant women in Nigeria: a systematic review and meta-analysis

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ABSTRACT. Asymptomatic *Plasmodium falciparum* infection during pregnancy is a major cause of foetal and maternal morbidity and mortality. The current study estimated the prevalence of asymptomatic *P. falciparum* infection among pregnant women in Nigeria. We systematically searched the PubMed, Web of Science, Google Scholar and AJOL databases for studies that estimated the prevalence of asymptomatic *P. falciparum* infection in pregnant women up to December, 2019, and identified additional studies from reference lists. Twenty-seven studies which fulfilled eligibility criteria were included in final systematic review and meta-analysis. The prevalence of asymptomatic *P. falciparum* infection of individual study varied from 2.1% to 95.4%. Most surveys were performed in the southern parts of Nigeria. We observed a high degree of heterogeneity in most pooled estimates ($I^2 > 75\%$; $p < 0.01$). The pooled estimate of asymptomatic *P. falciparum* infection prevalence across studies for the entire period was 34.3% (95% CI: 24.0–46.3), ranging from 34.7% (95% CI: 22.8–48.9) in primigravida to 28.5% (95% CI: 15.8–45.8%) in the first trimester. Studies conducted from 2000–2009 (51.3%; 95% CI: 29.1–73.0), southern Nigeria (41.8%; 95% CI: 28.2–56.7), rural areas (52.1%; 95% CI: 19.4–83.0), and median sample size ≥ 246 (41.5; 95% CI: 25.9–58.9), had the highest pooled prevalence. Asymptomatic *P. falciparum* infection is considered high in pregnant women in Nigeria. This results, therefore, emphasize the need to actively diagnose and treat asymptomatic malaria infection during all antenatal care visits.

Keywords: prevalence, asymptomatic *P. falciparum*, pregnant women, Nigeria, meta-analysis

Introduction

Malaria is an important public health problem in tropical and subtropical countries of the world. Immuno-compromised individuals, children under 5 years of age, as well as pregnant women are at risk of the infection [1]. Asymptomatic infection with *Plasmodium* species has been documented in a substantial proportion of individuals in sub-Saharan Africa among whom pregnant women are at greater risk [2–4]. In pregnant women, asymptomatic malaria goes unnoticed and untreated, hence it increases the risks of adverse pregnancy consequences such as stillbirth, miscarriage, preterm delivery and low birth-weight babies [5–7], furthermore, asymptomatic carriers of *Plasmodium* gametocytes serve as infection source for the malaria vector mosquitoes [8,9].

The susceptibility of pregnant women to malaria parasites has been linked to the level of antibodies to placental sequestrated parasites, the vascular nature of the placenta during pregnancy and gestational age in pregnancy [10,11]. Moreover, primigravidae and secundigravidae women have been found to be more susceptible to *P. falciparum* infection because of the presence of anti-adhesion antibodies against CSA-binding parasites associated with protection that develops after successive pregnancies [12,13].

In Nigeria, malaria remains one of the most

terrible public health problem causing about 60% of all outpatient attendances, 30% of all hospital admissions and 11% maternal mortality [14], similarly, many studies have also reported high prevalence rates of malaria in pregnancy in various parts of the country ranging from 20% to 70% [15]. Hence, pregnant women (obviously in the high-risk group for malaria infection) need special protective measures to ensure their survival and improve birth outcomes.

Considering, the wide variation in the reportage of the prevalence of malaria in pregnancy in Nigeria. It is therefore imperative to closely assess the prevalence and distribution of asymptomatic *P. falciparum* parasitaemia among pregnant women in Nigeria, such data is needed to complement the effort of Nigeria government other agencies like the Roll Back Malaria programme, WHO, UNICEF, and many other non-governmental agencies in the fight against malaria. This present study presents a systematic review and meta-analysis of available population-based studies on the prevalence of asymptomatic malaria among pregnant women in Nigeria.

Materials and Methods

Study area. Nigeria, the most populous country in Africa, with a total territory of 923,768 square km and an estimated population of 194,615,054 as at January 2018 [16], lies between latitude 4° and 14°N and longitudes 2° and 15°E. The country is grouped into six geopolitical zones (North West, North East, North Central, South West, South-south, and South East), 36 states, a Federal Capital Territory and 774 Local Government Areas [16]. Annual rainfall varies from 600–1,000mm in the North and an annual average of 1,300–1,800 mm in the South. Rainfall is highest in the northern parts of Nigeria between the months of June and September and from March to November in the Southern parts which usually coincides with the peak in the incidence of malaria [17].

Literature search. This systematic review and meta-analysis study was implemented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. An extensive literature search was conducted up to December, 2019 on PubMed, Web of Science, Google Scholar and African Journals OnLine (AJOL) and cross-checking of references of studies that resulted through the search of databases pertaining to the prevalence of asymptomatic malaria in Nigerian pregnant women using the following keywords and their combinations: "asymptomatic malaria", "*Plasmodium falciparum*", "healthy women", "prevalence", "frequency" "epidemiology", "pregnant women", and "Nigeria". None of the authors of original studies were contacted for additional information and no attempt was made to retrieve unpublished articles. The full text of all the included articles was downloaded and obtained through an online mechanism. A study was considered eligible only if: (a) it was published in English, (b) it was carried out within Nigeria, (c) it was asymptomatic parasitaemia (with *P. falciparum*), (d) it used peripheral blood, (e) the sample size and positive cases were clearly stated. Studies without these characters were all excluded.

Data analysis. Data were analysed using the 'meta' packages of the statistical software R (version 3.2.1). Random effect model with DerSimonian–Laird method was utilized for estimation of pooled measures by calculating the pooled estimate and confidence intervals, based on the weighted least square (weighting is given by the reciprocal sum of between and within study variances) [19]. To minimize the effect of studies with extremely small or extremely large prevalence estimates, the variance of the study-specific prevalence was stabilized with logit transformation before pooling the data within a random-effects meta-analysis model. Heterogeneity was evaluated by the χ^2 test on Cochrane's Q statistic [20], which was quantified by H and I^2 values. The I^2 statistic estimates the percentage of total variation across studies due to true between-study differences rather than chance. In general, I^2 values greater than 75% indicates the presence of substantial heterogeneity [21]. The source of variation among studies was assessed with subgroup analysis using grouping variables such as study region, median sample size, residency and year study was conducted.

Literature search results

A total of 327 research articles were retrieved by electronic search, of these, 317 non-duplicate papers were assessed and 274 records excluded based on titles and abstract. The remaining 43 full-text articles were retrieved and evaluated, of which 16 studies were excluded from the inclusion criteria. The remaining 24 articles were retrieved for full text detail analysis. Three additional articles were

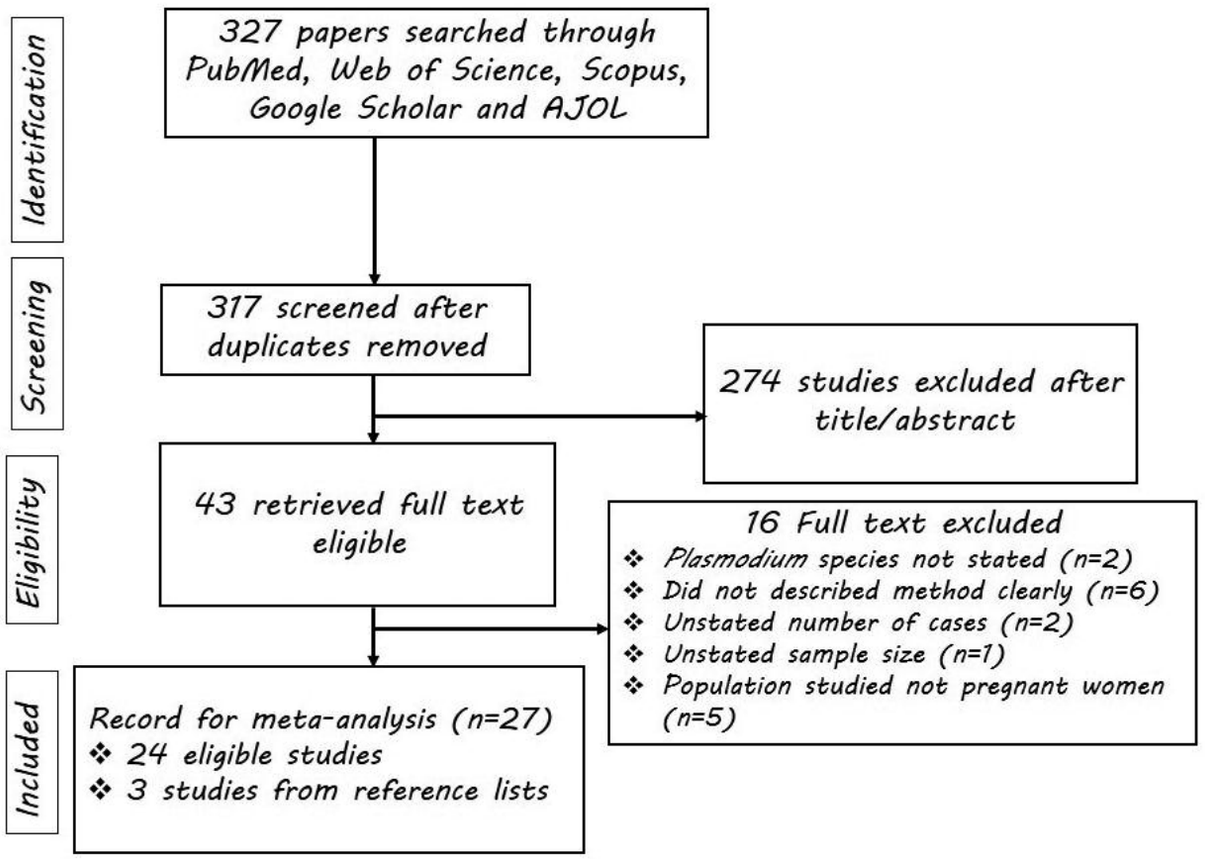

Figure 1. Flow chart of selection of studies

retrieved from reference list of published articles (Fig. 1). Finally, a total of 27 studies involving 8,025 pregnant women with 2,837 cases of asymptomatic *P. falciparum* parasitaemia were included in the meta-analysis.

All the included articles were cross-sectional in design. Most data were collected after 2010 (70.4%) and were from urban areas (88.9%). The sample size ranged from 77 to 1,084 individuals (mean: 297.2; standard deviation [SD±]: 215.1; median: 246). Prevalence of asymptomatic *P. falciparum* parasitaemia varied from 2.1% to 95.4%. Asymptomatic *P. falciparum* infection analysis from the databases revealed many states in the northern regions of the country with little or no data, while the southern parts showed areas of active on-going research work on asymptomatic *P. falciparum* among pregnant women (Fig. 1).

Overall prevalence of asymptomatic *P. falciparum* infection

Pooled prevalence estimates for the 27 studies included in the meta-analysis are presented in Figure 2 and 3, from different states in Nigeria. Substantial heterogeneity was observed in most pooled estimates (I^2>75% and p<0.01). The pooled prevalence of asymptomatic *P. falciparum* infection for the entire period, using the random-effect model was 34.3% (95% CI: 24.0–46.3), ranging from 34.7% (95% CI: 22.8–48.9) in primigravidae, 26.7% (95% CI: 15.5–41.9) in secundigravidae to 28.8% (95% CI: 19.8–40.0) in multipara pregnant women (Fig. 4, 5, and 6). Pooled prevalence according to gestational age revealed a wide variation in prevalence. Estimated prevalence for the first, second and third trimester was 28.5% (95% CI: 15.8–45.8), 33.6% (95% CI: 16.8–55.9), and 24.8% (95% CI: 15.1 –38.0), respectively (Fig. 7, 8 and 9).

Subgroup analysis of asymptomatic malaria

Subgroup analysis for the 27 studies included in the meta-analysis is presented in Table 1. Substantial heterogeneity was observed in most subgroup analysis pooled estimates. Information about regional distribution was available for 27 studies. Prevalence estimates for regions ranged

Table 1. Pooled prevalence estimates for asymptomatic malaria in Nigerian pregnant women stratified according to sub-groups

Variable	N studies	Total individuals	Positive cases	Prevalence % (95% CI)	I^2 (%)	Measure of heterogeneity (Cochran's Q)	P-value
Overall prevalence	27	8025	2837	34.3 (24.0-46.3)	98.6	1897.88	<0.01
Geopolitical zones							
southern	20	6213	2354	41.8 (28.2-56.7)	98.9	1681.63	<0.01
northern	7	1812	483	17.1 (6.8-36.6)	96.9	194.18	<0.01
Survey year							
2000-2009	7	2846	1007	51.3 (29.1-73.0)	99.0	731.85	<0.01
2010-2019	20	5179	1830	27.9 (17.3-41.8)	98.4	1154.97	<0.01
Study setting							
urban	24	7462	2535	32.3 (21.8-44.9)	98.7	1794.44	<0.01
rural	3	563	302	52.1 (19.4-83.0)	94.3	34.99	<0.01
By median sample size							
<246	13	2097	629	27.2 (15.1-43.9)	96.8	373.48	<0.01
≥246	14	5928	2208	41.5 (25.9-58.9)	99.1	1512.53	<0.01
Diagnostic methods							
Microscopy	27	8025	2837	34.3 (24.0-46.3)	98.6	1897.88	<0.01
RDT	6	1226	271	14.2 (3.6-42.5)	98.5	326.08	<0.01
PCR	4	1166	162	16.6 (6.5-36.2)	97.1	105.60	<0.01

Explanations: CI - confidence interval; I - inconsistency or variation

between 41.8% (95% CI: 28.2–56.7) in the southern regions to 17.1% (95% CI: 6.8–36.6) in the northern regions. Sub-analysis by survey year revealed wide variations in prevalence. Prevalence was higher for studies conducted between 2000–2009 (51.3%; 95% CI: 29.1–73.0) than for studies conducted between 2010–2019 (27.9%; 95% CI: 17.3–41.8)

Pooled asymptomatic *P. falciparum* malaria prevalence was higher in surveys conducted in rural areas (52.1%; 95% CI: 19.4–83.0) and with sample size ≥246 (41.5; 95% CI: 25.9–58.9). Among the studies, combination of three different diagnostic methods were utilized to evaluate asymptomatic *P. falciparum* infection among pregnant women. They were staining (microscopy), Rapid Diagnostic Test (RDT), and PCR. The most commonly used diagnostic methods for asymptomatic *P. falciparum* among the pregnant women were microscopy (27 studies), followed by RDT (6 studies), and PCR (four studies).

Meta-regression analysis shows that prevalence estimates decrease significantly with the study year (p=0.0329). This was portrayed graphically in the meta-regression plot (Fig. 10).

Discussion

Asymptomatic *P. falciparum* infection during pregnancy is a major cause of foetal and maternal morbidity and mortality especially in sub-Saharan Africa and reinforce the importance of routine testing for asymptomatic *P. falciparum* infection in all pregnant women.

Our findings corroborate evidence of high prevalence of asymptomatic *P. falciparum* infection in Gabon and Democratic Republic of Congo (DRC) [48,49], and low prevalence in Democratic Republic of Congo (DRC), South Ethiopia, and Bangladesh [4,51,50]. The prevalence obtained in this study represents a considerable level of risk to the mother and foetus. This results, therefore, emphasize the need to actively diagnose and treat asymptomatic malaria infection during all antenatal care visits [52].

This review identified a higher prevalence of asymptomatic *P. falciparum* malaria in primi-

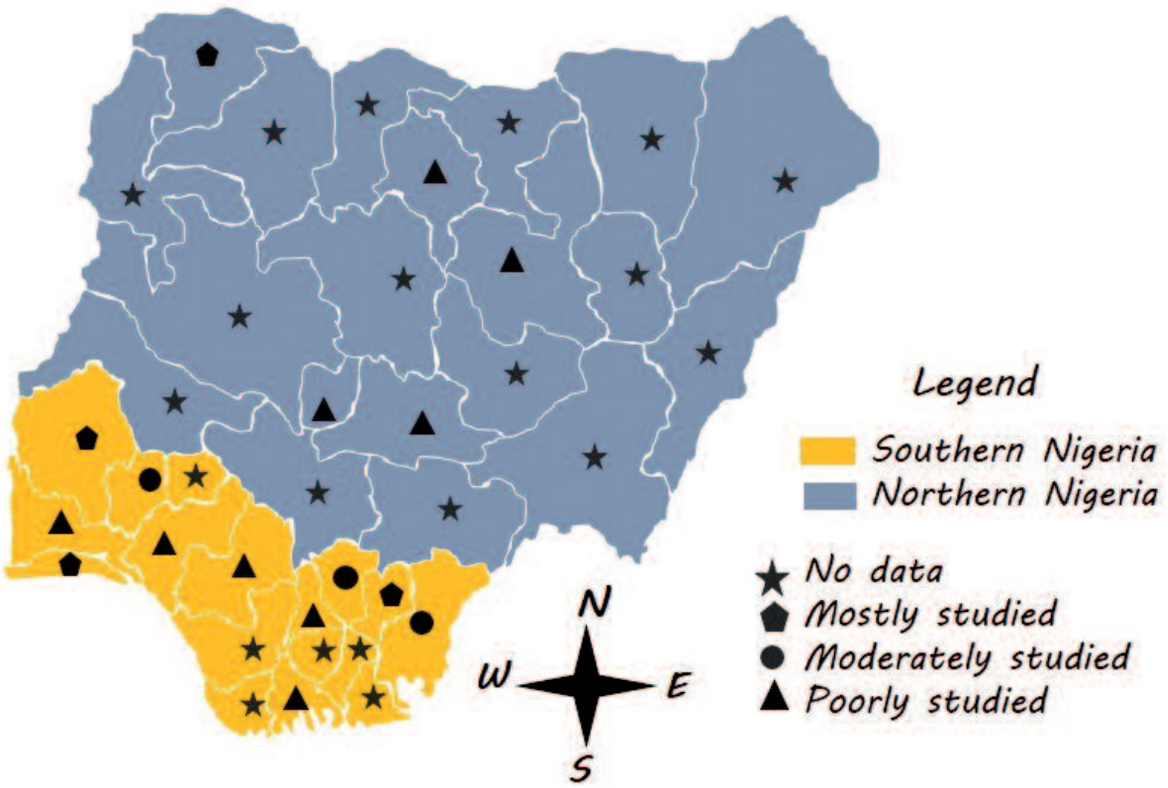

Figure 2. Map showing regions and intensity of the studies

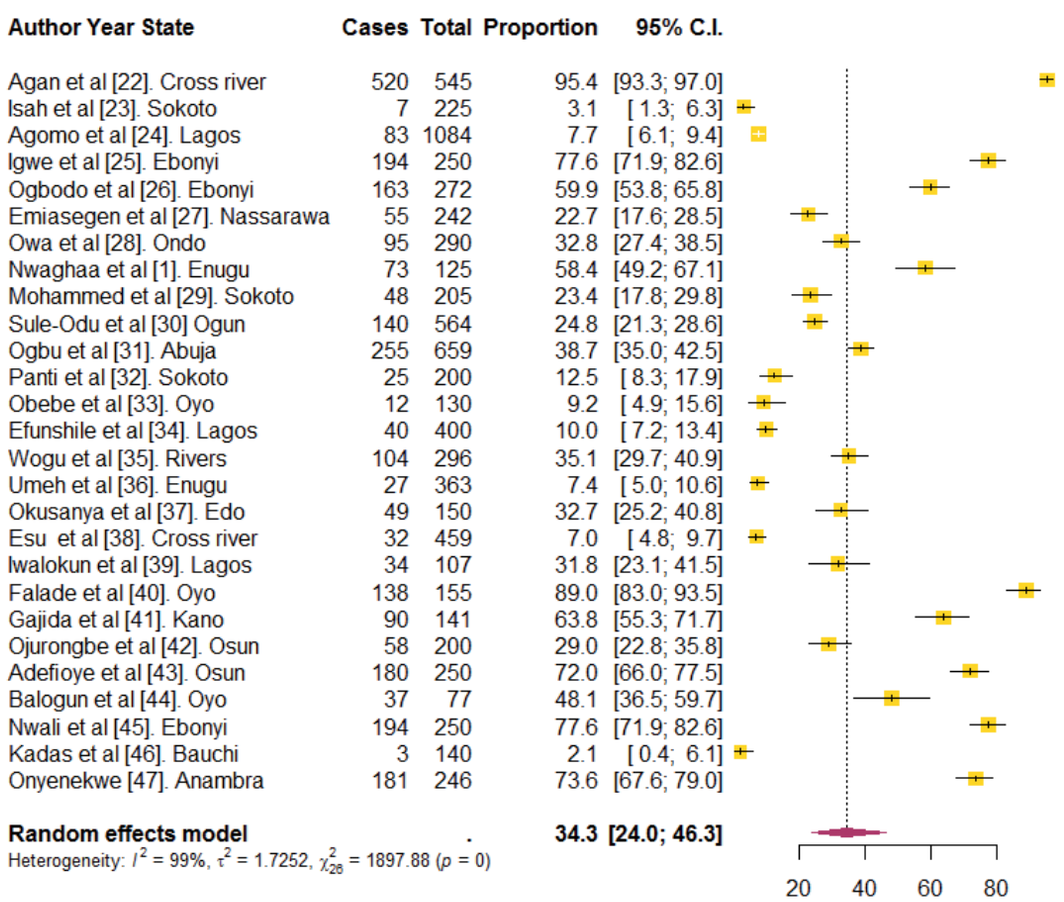

Figure 3. Forest plot of overall prevalence of asymptomatic malaria by microscopy

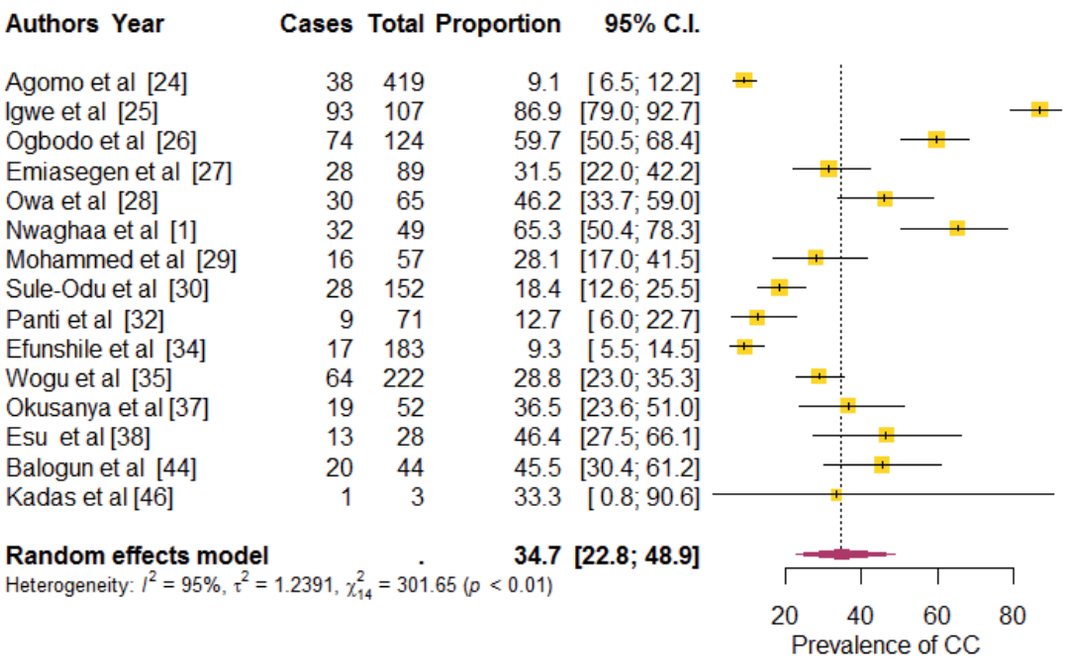

Figure 4. Forest plot of 15 studies showing the prevalence of asymptomatic malaria among primigravidae pregnant women by microscopy

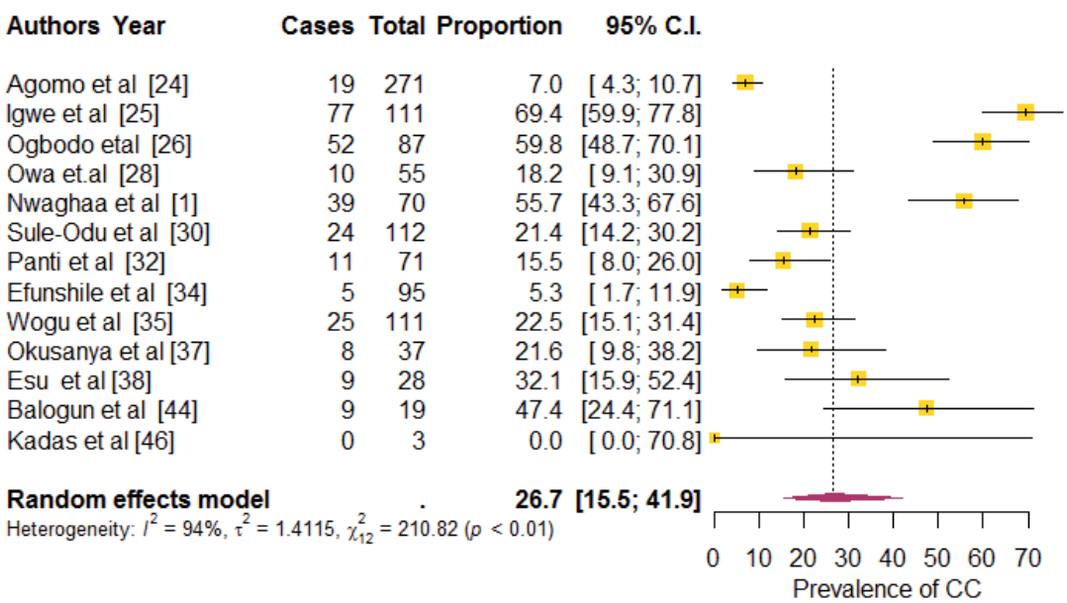

Figure 5. Forest plot of 13 studies showing the prevalence of asymptomatic malaria among secundigravidae pregnant women by microscopy

gravidae and women in their first and second trimester. This finding is similar to what was found by several investigators across the African continent [5,53,54]. This might be due to the characteristic pregnancy-induced immunosuppression common among primigravidae, especially in the first 24 weeks [11,47], hence, primigravidae women in the early stage of pregnancy should be placed more under surveillance.

The review revealed a 23.4% decline in the prevalence of asymptomatic *P. falciparum* parasitaemia within a period of nine years among pregnant women. This may be attributed to the collaborative effort of different partners (WHO, Global Fund, UNICEF, USAID, and World Bank) in the fight against malaria elimination and the increase in financing by the Nigeria government in the last few years [17]. In addition, the increasing number of pregnant women studied in the last few years in this review may be attributed to increased

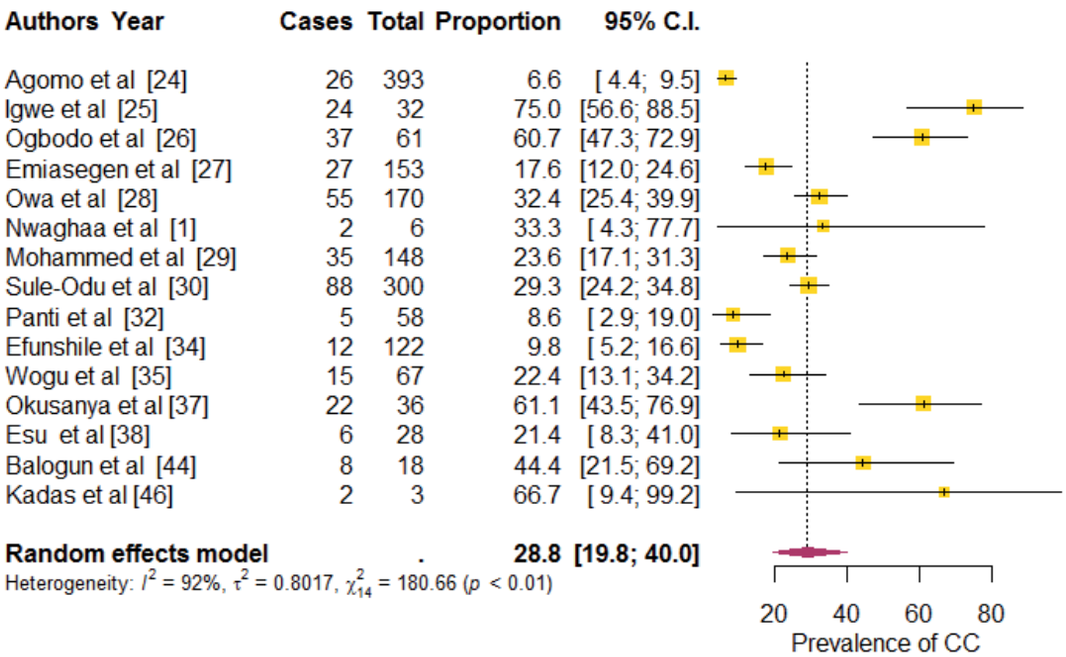

Figure 6. Forest plot of 15 studies showing the prevalence of asymptomatic malaria among multipara pregnant women by microscopy

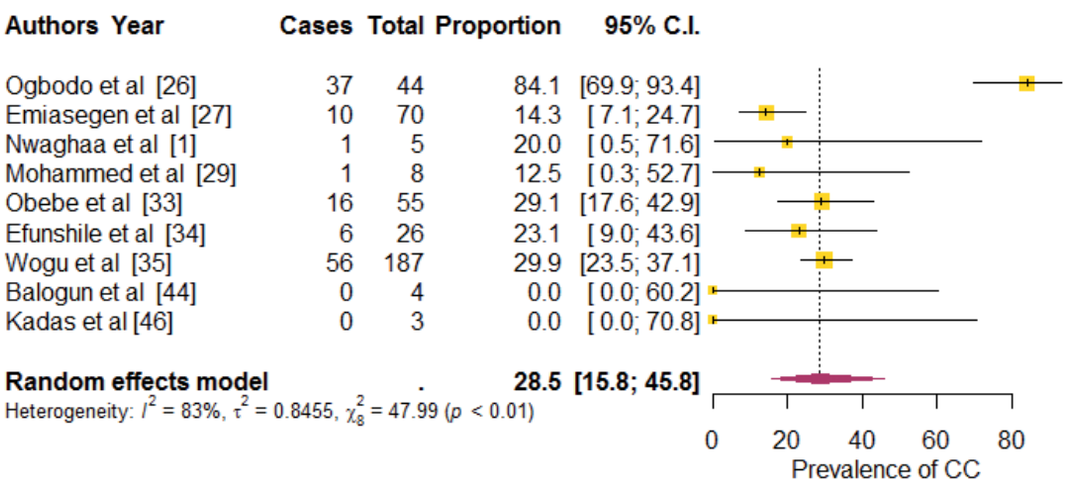

Figure 7. Forest plot of 9 studies showing the prevalence of asymptomatic malaria among pregnant women in their first trimester by microscopy

awareness of the public health threats posed by malaria among pregnant women.

The high level of tropical rainfall and the forested nature in the southern parts (South-south, South-west, and South-east) of Nigeria which may provide breeding sites for mosquitoes [55], may explain the higher prevalence of malaria in this region. This suggests that this region may be more endemic for malaria in Nigeria. However, the north-south prevalence difference presented in this review needs to be better understood to determine if it is related to the accessibility to resources which are able to detect more malaria cases, or the ongoing conflict in the northern region. Addressing the elimination of malaria in delicate conflict/post-conflict regions is an important challenge, as they often have the highest disease burdens and minimum resources to cope with.

The preponderance of asymptomatic *P. falciparum* infection in the rural areas despite lower total cases examined when compared to urban residents is significant. The characteristic of rural areas could be attributed to the higher prevalence. These communities are often geographically isolated and highly mobile, have low levels of literacy, experience language barrier, endure a lack

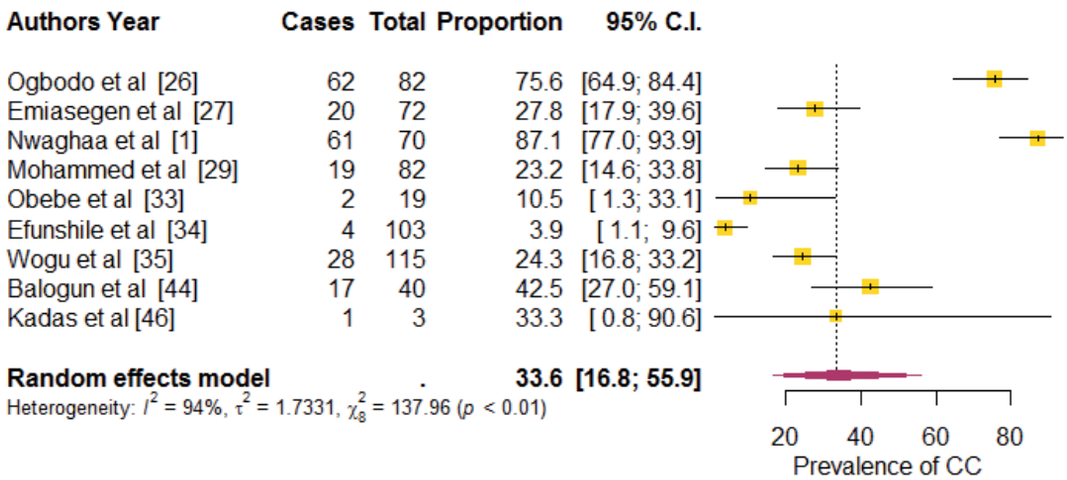

Figure 8. Forest plot diagram of 9 studies showing the prevalence of asymptomatic malaria among pregnant women in their second trimester by microscopy

of health care services and experience high levels of human-mosquito interaction [56–58]. Other probable factors may include low-cost treatment with herbal medicines and difficulty in detecting sub-clinical infections, that allows malaria' to be maintained continuously in the area [8,59]. The implication of this finding is that rural population influx into urban and peri-urban areas can contribute to the epidemiology of malaria in the urban areas [60,61].

Importantly, our analysis reported a limited, molecular-based studies in the country. The use of molecular techniques for malaria research is quite expensive in developing countries, this is complicated by the limited access to reagents and consumables. These and other constraints that include the absence of skilful man power might have contributed to the low number of research conducted on *asymptomatic malaria* with molecular techniques.

Asymptomatic reservoirs of malaria parasites are known to be common, yet are difficult to detect. In addition, different studies recognize the fact that asymptomatic individuals may act as a reservoir for infection, re-infection and malaria resurgence [62,63]. In the strategic plan of the Federal Ministry of Health 2014–2020, resources for malaria elimination programmes have improved in the last few years. However, the identification of these symptomless group in this review can be a silent menace to the national elimination programme, therefore, developing an active case detection system to identify these asymptomatic reservoirs is critical to the elimination of malaria in Nigeria. Apart from the existing intermittent preventive treatment (IPT) and the insecticide-treated bed net

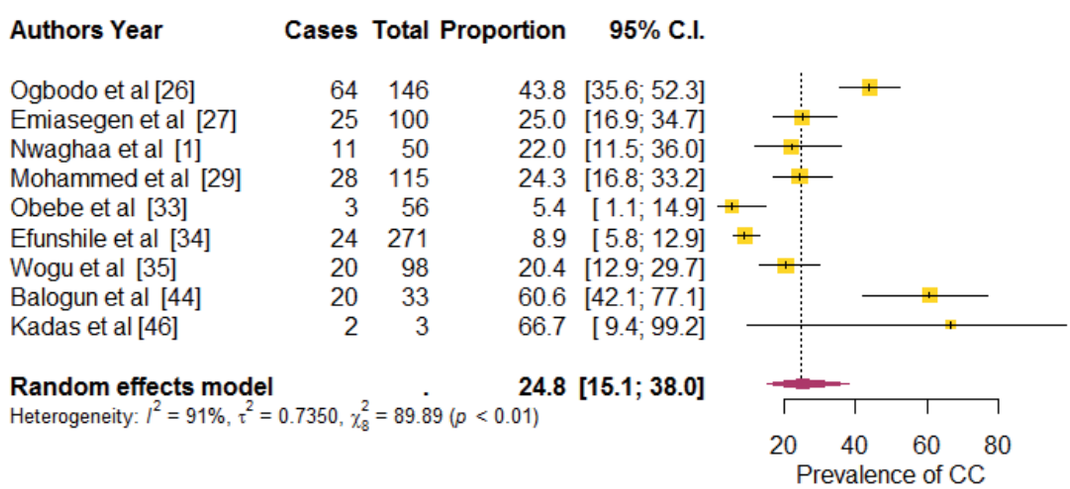

Figure 9. Forest plot of 9 studies showing the prevalence of asymptomatic malaria among pregnant women in their third trimester by microscopy

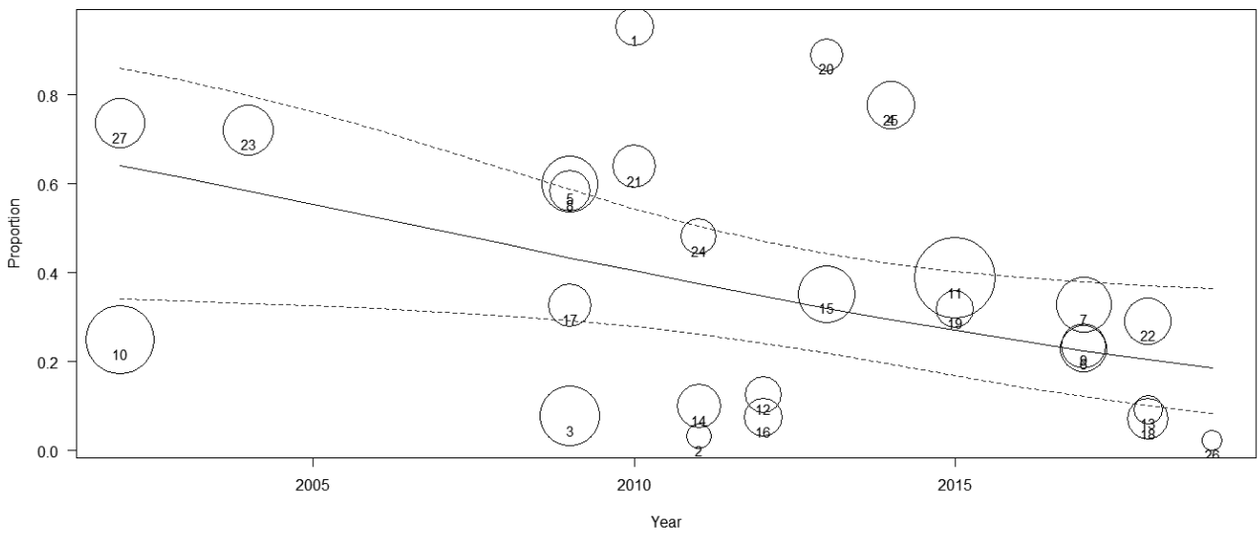

Figure 10. Meta-regression analysis

(ITN) prevention measures for pregnant women in Nigeria, steps are also required to introduce new ultra-sensitive diagnostic tools, reduce hunger, boost nutrition, housing and electricity. This will go a long way in reducing maternal and perinatal morbidity and mortality.

This study has certain limitations. Included studies were cross-sectional providing only snapshots of the situation at a particular moment in time. Other studies which would have added to our understanding of asymptomatic *P. falciparum* infection in Nigeria were excluded for incomplete information. The study revealed high heterogeneity among studies which may be due to variations in sample populations and methods of diagnosis employed by the various studies. Moreover, the lack of information and data from some regions made it difficult to generalize the findings.

Despite the discussed limitations, the results of this study clearly call to action on research and surveillance of asymptomatic malaria in Nigeria

In conclusion, the pooled prevalence of asymptomatic *P. falciparum* among pregnant women in Nigeria is considerably high. Sub-clinical cases must therefore, be taken into consideration in malaria control programme.

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