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Review Article

Asymptomatic plasmodial infection in pregnant women: A global scenario

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ABSTRACT

Though asymptomatic plasmodial infection (API) is well known phenomenon and play an important role in different populations and malaria transmission settings, it has received less attention in malaria intervention strategies. This review was aimed to estimate the prevalence of API in pregnant women across the world. The bibliography records relevant to the study were searched on PubMed and Lilacs, till August 15, 2016, without restriction of language. A total of 78 references were identified, of which 29 met the inclusion criteria. The study of the identified reports revealed that the mean prevalence of API in pregnant women was 10.8% (3382/31186), with wide variation among countries and transmission settings. The reports showed that APIs are very common even in low malaria transmission areas, and most of the APIs are due to submicroscopic plasmodial infection (SPI). More sensitive diagnostic tools are required to address API and SPI in such areas. Every malaria endemic region/country should carry out systematic studies for accurate estimation of frequency for both these events (API and SPI) in different populations for planning appropriate intervention measures.

Key words Asymptomatic plasmodial infection; malaria; *Plasmodium*; pregnancy; submicroscopic plasmodial infection

INTRODUCTION

There are several viral, bacterial, fungal, and parasitic infections of humans that generate asymptomatic infections (AIs). In some cases, AIs do not cause any harm to humans, but in most of the situations they ultimately led to disease. The asymptomatic plasmodial infection (API) has been frequently reported in hyper-endemic regions; however, it has received significant attention only in recent years due to the global goals of malaria elimination and eradication[1]. In October 2007, the call made by Melinda and Bill Gates to make malaria eradication a goal of their Foundation was immediately endorsed by the WHO's General Director which created a momentum to move beyond malaria control to at least achieve the goal of elimination, if eradication is not possible[2]. According to WHO[3], malaria *elimination* means the interruption in local malaria transmission by a specified malaria parasite species in a defined geographic area; therefore, continued measures are required to prevent re-establishment of transmission. On the other hand, malaria *eradication* is the permanent reduction to zero of the worldwide incidence of malaria infection caused by all human malaria parasites species. Intervention measures are no longer needed, after achieving eradication[3].

Malaria control, elimination and eradication are strongly related with asymptomatic and submicroscopic infections. An insightful definition of API is presence of erythrocytic plasmodial stages in a person without fever and other symptoms compatible with malaria, *i.e*. a positive blood diagnostic test in an asymptomatic individual. A list of diagnostic criteria used in different studies, for defining API has been listed by Laishram *et al*[4] in 2012; however, there is no standard definition of API and criteria used in earlier studies are very different[5]. Most definitions of API involve detection of erythrocytic parasites in absence of clinical malaria symptoms (generally fever) during a specified time frame. Some definitions have included parasite density thresholds to define the cases, which means that only a febrile subject with a parasite density above the cut-off is a case of symptomatic malaria, while a febrile subject with lower parasite density than the cut-off is an asymptomatic case[6].

The sensitivity of the diagnostic test used in different studies play a major role in detection of APIs. Microscopy has been the gold standard in malaria research and remains as a point-of-care diagnostic in clinical and epidemiological settings. An expert microscopist can detect 50 parasites/µl. The rapid diagnostic tests (RDTs) detect 100–200 parasites/µl. Polymerase chain reaction (PCR)-based tests improved the detection limit for malaria infection >1 parasite/µl[7]. It may be noted that the rRNA

gene copy number varies from 4 to 8 units per genome in *Plasmodium*[8], hence, parasites/µl and DNA copies/µl are not equivalent units.

Submicroscopic parasite densities (microscopy negative and PCR positive) are common in adults and in chronic infections; studies have reported that microscopy detects only about 54% of all PCR-detectable plasmodial infections[9–10]. There is a relationship between submicroscopic plasmodial infections (SPI) and API; most of SPI are API and *vice versa,* and most of patients with microscopic infections have symptoms (no API). The available information about API is scarce, and the global elimination and eradication goals require this event is well known in different populations (children, adults, pregnant women, *etc.*) and malaria transmission settings. It has been reported that the API is much more common in pregnant women than in non-pregnant women or men[11]. In addition, API on pregnant women caused by *P. falciparum* are evidently associated with maternal anaemia[12-13]. Moreover, SPIs affect health of both pregnant women and babies; when SPI is present, problems such as maternal anaemia and low birth weight newborns have a mean frequency of 42 and 16%, respectively[9, 14-15].

This study was aimed to estimate the prevalence of API in pregnant women across the world through review of the existing scientific literature. For data compilation, references were searched on PubMed and Lilacs (a comprehensive database of scientific and technical literature of Latin America and the Caribbean), till August 15, 2016, without restriction of language. The PubMed search included two search methodologies; the first method was based on the MeSH protocol, wherein the MeSH term *Malaria* was searched as major topic (*i.e.* "Malaria"[Majr]), followed by the MeSH term *Pregnancy*, and following expressions in quotes: "asymptomatic malaria", "asymptomatic malaria parasitaemia", "subclinical malaria", "subpatent malaria", "hidden malaria", "unapparent malaria", "subclinical infection", while the second search was performed without the MeSH protocol, using the words *Malaria* and *Pregnancy* and the expressions "asymptomatic infections", "subclinical infection" and "subclinical malaria". On Lilacs, the keywords pregnancy and malaria were combined with asymptomatic, subclinical, subpatent, unapparent and hidden. Table 1 summaries the search strategies and results, for both PubMed and Lilacs.

Table 1. Search strategies for compiling data on API, and results (August 15, 2016)

Search terms					References	
					Found	Selected
In PubMed with MeSH protocol						
Malaria [Majr]	AND	Pregnancy	AND	"asymptomatic malaria"	35	24[a]
				"asymptomatic malaria parasitaemia"	9	0[b]
				"subclinical malaria"	3	
				"subpatent malaria"	4	0[a]
				"hidden malaria"	3	
				"unapparent malaria"	0	
				"subclinical infection"	0	
In PubMed without MeSH protocol						
Malaria	AND	Pregnancy	AND	"asymptomatic infections"	19	3[a]
				"subclinical infection"	0	
				"subclinical malaria"	3	0[b]
Found in the list of references of other report					1	1
Report obtained from one of the authors					1	1
Total					78	29
In Lilacs						
Pregnancy	AND	asymptomatic	AND	malaria	3	0[a,b]
		subclinical			1	0[b]
		subpatent			0	
		unapparent			0	
		hidden			0	

[a]References unselected, did not meeting the inclusion criteria; some of them were about subjects different to asymptomatic infections, others were literature reviews, studies in non-pregnant subjects, and having no information about prevalence of asymptomatic infection; [b]All included in a previous list.

Inclusion criteria for the references

Only those references/studies were included for this review, which met the following criteria:

(i) references reporting the malaria prevalence data or elements to calculate it;
(ii) those related to studies involving pregnant women; and
(iii) those reporting the use of the malaria diagnostic tests.

Data of the references included were compiled in Microsoft Excel and the statistical analysis was performed with SPSS 10.0.

A total of 78 references were found on PubMed, out of which only 27 met the inclusion criteria[11-14, 16-38]. An additional study/reference[39] was found in the list of references of another report[40], which was not included in this review, as it did not mentioned about data related to calculation of API prevalence. Another study[41] included was obtained from one of its authors.

On Lilacs, four references were found, but two of them were already obtained on PubMed search, and the other two did not meet the inclusion criteria.

A total of 29 reports were analyzed in this review; 72.4% (21/29) were carried out in Africa, 17.2% (5/29) in Asia and 10.3% (3/29) in South America (Table 2). The malaria diagnostic tests used in most of the studies were thick blood smear and/or qPCR. The mean prevalence of API for pregnant women calculated on the basis of 29 reports was 10.8% (3382/31186) (Table 2); the highest mean prevalence was detected in Nigeria [44.4% (1690/3804; 13 studies], and the mean prevalence in other seven African countries (Cameroon, Ghana, Burkina Faso, Democratic Republic of Congo, Uganda, Ethiopia, and Madagascar; eight studies) was 21.7% (593/2738). In Thailand, Bangladesh and Saudi Arabia, the mean prevalence of API was 3.3% (754/22627; five studies), and the mean prevalence in South America was 22.1% (171/775; three studies).

The prevalence of API had high variation even within the countries and with the same diagnostic test. Number of studies per year varied from 1 to 5, with a mean of 2.6 and median of 3; apparently, the number of studies decreased over time, and there was a significant negative correlation in prevalence and time in years (rho = – 0.506; $p = 0.005$; $n = 29$).

Table 2. Prevalence of asymptomatic plasmodial infection in pregnant women per country, 2001–2016

Year	Reference	Country	No. of positive cases	Total studied	% Prevalence
2001	Anorlu *et al*[16]	Nigeria	197	477	41.3
2002	Onyenekwe *et al*[32]	Nigeria	139	229	60.7
2002	Onyenekwe *et al*[33]	Nigeria	189	246	76.8
2002	Sule-Odu *et al*[35]	Nigeria	141	564	25
2009	Nwagha *et al*[28]	Nigeria	73	125	58.4
2009	Ogbodo *et al*[30]	Nigeria	163	272	59.9
2009	Okusanya *et al*[31]	Nigeria	50	150	33.3
2011	Anyaehie *et al*[17]	Nigeria	470	990	47.5
2011	Balogun *et al*[18]	Nigeria	37	77	48.1
2011	Isah *et al*[20]	Nigeria	7	245	2.9
2012	Umeh *et al*[37]	Nigeria	156	237	65.8
2013	Nwaneri *et al*[29]	Nigeria	22	85	25.9
2015	Iwalokun *et al*[21]	Nigeria	46	107	43
Total (Nigeria)			1690	3804	44.4
2010	Thévenon *et al*[36]	Cameroon	24	44	54.5
2010	Wilson *et al*[38]	Ghana	268	746	35.9
2012	Douamba *et al*[13]	Burkina Faso	48	201	23.9
2013	Kizito *et al*[22]	Uganda	57	711	8
2014	Matangila *et al*[24]	DR Congo	98	332	29.5
2015	Nega *et al*[27]	Ethiopia	30	341	8.8
2015	Maiga-Ascofaré *et al*[23]	Madagascar	174	1242	14.1
2016	Francine *et al*[12]	DR Congo	68	363	18.7
	Other		593	2738	21.7
Total (African countries)			2284	6542	34.9
2012	Rijken *et al*[34]	Thailand	336	3779	8.9
2012	McGready *et al*[25]	Thailand	317	17613	1.8
2013	Nasr *et al*[26]	Saudi Arabia	62	120	51.7
2014	Khan *et al*[11]	Bangladesh	21	526	4
2016	Shannon *et al*[41]	Bangladesh	18	589	3.1
Total (Asian countries)			754	22627	3.3
2005	Branch *et al*[39]	Peru	114	593	19.2
2012	Arango *et al*[14]	Colombia	50	57	87.7
2014	Hristov *et al*[19]	Brazil	7	125	5.6
Total (South American countries)			171	775	22.1
Grand Total			3382	31186	10.8

DISCUSSION

Asymptomatic plasmodial infections play an important role in different populations and malaria transmission settings, however, it has received significant attention only in recent years, mainly due to the global goals of malaria elimination and eradication[1]. The global frequency of API in pregnant women analyzed on the basis of this review was 10.8% (3382/31186). In general, studies on this subject are limited across the world; around 45% of reports included in this review were carried out in Nigeria, and another 26% of studies were from other seven African

countries. Reporting of studies related to the prevalence of API in pregnant women was much less from Asia, Pacific and America.

Submicroscopic infection rate estimated in general population of South America was 10%; however, it varies from country to country[9]. For example in Brazil data ranged from 0.7 to 39.5%; in Africa, submicroscopic infection in non-pregnant subjects ranged from 12 to 21%, across the Eastern, Central or Western regions of Africa (calculated on basis of a study carried out by Okell *et al*[9]).

According to Laishram *et al*[4], two classes of immune response develop in the APIs: 1) an antidisease immunity that allows one to carry parasite loads without symptoms, and 2) an antiparasite immunity that may be responsible for the suppression of parasite loads after a certain age, which is likely a factor of exposure-related clinical immunity. In addition, exposure-related immunity may be achieved much earlier in life for individuals who live in low transmission regions due to predictably low parasite genetic diversity and few overlapping infections[4]. APIs can maintain and perpetuate the transmission to anophelines. In a recent study Sutherland[42] observed that that certain human communities living under moderate-to high- intensity malaria transmission in both African and Asian settings may sustain patterns of *Plasmodium* spp infections similar to those of the great apes or the macaques of Borneo, in that multispecies, low-density, asymptomatic parasitaemia is observed in a significant proportion of individuals.

Le Port *et al*[43] in their study reported that in high transmission areas, the number of *P. falciparum* asymptomatic carriers, *i.e*. individuals harbouring parasites without clinical signs, is very high. The consequences and significance of such asymptomatic infections have been studied in diverse situations, but results have been contradictory. According to few authors, long-term asymptomatic carriage may represent a form of tolerance to the parasite in children building up their immune response, therefore, the asymptomatic carriage of parasites would protect these children from developing either a mild malaria attack or a more severe one, by keeping their immunity effective[43]. These problems of AIs, APIs, consequences and meanings of APIs, immunological measurements and others, are related to the so-called, "Genetic Theory of Infectious Diseases", which has gained some support among clinicians and geneticists, but has also encountered resistance among microbiologists and immunologists[44].

Diagnosis of API is difficult because there are no clinical manifestations and parasite density remains very low[45]. PCR-based tests are most appropriate for finding such low densities of parasites[46]. The most accepted definition of API is presence of erythrocytic parasites in peripheral thick blood smears, an axillary temperature < 37.5°C and absence of clinical malaria symptoms, however, it varies among studies[5]. Several studies defined API at admission moment only, but other ones followed up the subjects till 60 days[4, 47]. Definition of clinical malaria symptoms is another complex issue; some studies considered only fever, while others included other nonspecific symptoms[4]. The detection of *P. falciparum* gametocytes is another topic for consideration in API, because these cells do not cause disease and can be carried by infected individuals for up to 55 days post-clearance of asexual stages[48], therefore, gametocytes may or may not be detected in subjects with API[49].

Significance of the plasmodial submicroscopic reservoir (PSR) to malaria elimination depends on its size, and recent studies have shown that PSR is large in low transmission areas[50]. Consequently, it is essential to know the magnitude of both events, asymptomatic and submicroscopic plasmodial infections, since submicroscopic infections are a big component of asymptomatic infections, as observed in this study.

Traditionally, malariologist have focused on patients (symptomatic subjects) with positive microscopy, but it is now understood that it is just a small part of the large number of infected individuals. Accurate estimation of PSR needs diagnostic test more sensible than microscopy and RDTs. The current antimalarial strategies are not enough for the elimination and eradication goals[5, 51-52], and require shifting from passive surveillance to active surveillance, as well as additional intervention measures to deal with the asymptomatic and/or submicroscopic infections[51-53]. Specifically in the case of pregnancy-associated malaria, accurate diagnostic tools with very high sensitivity and specificity are required for a regular antenatal screening in endemic areas. Every country with malaria transmission must carry out a systematic work to know its frequency of API and SPI in different endemic areas and populations [children (infants, preschool and school), adults, pregnant women, *etc*.].

In conclusion, APIs are very common even in low malaria transmission areas, and most of APIs are due to SPI. Additional diagnostic tools with more sensitivity and specificity are required to address the API and SPI infections. Every malaria endemic region/country should carry out systematic studies for accurate estimation of frequency for both API and SPI in different populations for planning appropriate intervention measures. This information might serve as a key to malaria elimination and eradication programmes.

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