Review article

The role of asymptomatic malaria infection in the epidemiology and control of Malaria

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SUMMARY

Despite the recent progress made in the control and eradication of malaria, the disease remains the first endemic especially in sub-Saharan Africa. Malaria often results in a series of clinical presentations, from severe to uncomplicated or mild, and in poorly understood asymptomatic infections. The progress of malaria control interventions has been hindered by the presence of asymptomatic carriage of malaria parasites, its mis-diagnosis, and especially false negative results. This phenomenon has been poorly attributed to the recent mass usage of the substandard Rapid Diagnosis Tests (RDTs) and on the other hand, the global malaria eradication program has focused on symptomatic malaria. Consequently, asymptomatic infection remains undetected and provides a silent natural reservoir that sustains transmission of *Plasmodium* species in the community. Experts have identified the possible intricacies between host, parasites, age, co-infection and/or environmental factors among others to the complexity of asymptomatic infection. Therefore, in order to achieve the recent World Health Organization developed Strategic Framework for malaria elimination from 2016 to 2030 to reduce malaria morbidity and mortality by 90% and eliminate malaria in 35 countries by 2030, it is critical to interrupt the ongoing malaria transmission from the asymptomatic reservoir. Evidence from these studies suggests the strict inclusion of asymptomatic patients in malaria intervention and the adoption of ultrasensitive diagnostics in malaria surveillance and treatment.

Keywords: Malaria transmission, Asymptomatic infection, *Plasmodium* species, Epidemiology

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INTRODUCTION

Malaria is a vector borne disease caused by the parasite of the genus *Plasmodium.* It is transmitted by the bite of an infected female *Anopheles* mosquito. Five species are mainly responsible for human malaria infestation namely; *Plasmodium falciparum, Plasmodium malariae, Plasmodium ovale, Plasmodium vivax* and *Plasmodium knowlesi. Plasmodium falciparum* is the commonest in Africa and is responsible for up to 98% of cases in Nigeria and is associated with severe morbidity and mortality [1,2].

Plasmodium malariae and *ovale* are responsible for 2% of cases while *Plasmodium vivax* is not found among indigenous Nigerians. Pregnant women and children are especially the most vulnerable and susceptible groups to malaria in endemic regions due to low immunity. Each year, approximately 50 million women living in malaria-endemic areas throughout the world become pregnant, of which more than half live in tropical Africa with intense transmission of *P. falciparum* [3]. An estimate of 10,000 of these women and 200,000 of their infants die as a result of malaria [4]. In Nigeria, malaria accounts for 60% of outpatient consultations and 11% of maternal mortality are due to malaria in pregnancy. Malaria in pregnancy is an important cause of anemia, miscarriages, intrauterine growth restrictions, low birth weight, still birth, and other pregnancy-related complications. Seventy percent of pregnant women in Nigeria suffer malaria with maternal and fetal complications. The problem is compounded by high level of resistance to first- and second-line antimalariae drugs as shown by the drug therapeutic efficacy trial conducted in the six geopolitical zones of the country which showed resistance ranging from 23% to 96%[3].

Malaria infections are mainly characterized with different symptoms and signs such as recurrent cycle of fever and chills. Other symptoms include vomiting, shivering, convulsions, and anaemia caused by haemolysis. In some cases, these symptoms are not observed, and the infection is described as asymptomatic in individuals without a recent history of antimalarial treatment [5]. Once an individual is infected with the parasite, immune factors are tasked with reducing parasite numbers, i.e., anti-parasite immunity, and preventing manifestation of clinical symptoms, anti-disease immunity. In asymptomatic individuals, immunity is skewed toward antidisease rather than anti-parasite immunity. The mechanisms behind this phenomenon are still unclear and more studies are required to understand how anti-disease immunity is induced and its potential for application in vaccine development [6].

Asymptomatic Malaria

The asymptomatic parasitaemics are healthy carriers of malaria parasites and serve as reservoir of infection. This is common in malaria-endemic regions of the world particularly Africa. The symptomatic people can be treated during their clinical manifestation but the asymptomatic infections may develop into illness, or remain asymptomatic and untreated [7]. Because asymptomatic infections can serve as a reservoir to mosquitoes, they may be important contributors to transmission and pose a public health challenge [2].

In 2015, a geo-spatial meta-analysis estimated a continent-wide prevalence of

asymptomatic *P. falciparum* in children aged 2 to 10 years of 24% based on microscopy and rapid diagnostic test (RDT) results [9]. Most of the studies of malaria depend on clinical manifestations, severity, and complication because it is the principal cause of malaria-related deaths. Researchers and clinicians have established diagnostic criteria based on the clinical manifestations upon disease onset, which have aided in forming an integrated approach to improving the management and treatment of severe malaria [10].

Furthermore, asymptomatic malaria is prevalent in malaria endemic regions and has become a serious cause for concern as efforts are increasing towards eliminating the parasite. Particularly, subpatent malaria is still transmissible and will complicate elimination of malaria in high transmission regions [11].

In most African countries, the current malaria control methods largely focus on early detection of parasite on suspected individual and treatment, indoor residual spraying and chiefly the advocate and distribution of insecticide-treated bed nets (ITN). However, in these areas, individuals with asymptomatic parasitaemia are mostly neglected and are not identified by early detection and treatment programs, they therefore continue to serve as a source of infection for vector mosquitoes thereby complicating control efforts [3].

Asymptomatic malaria is a new challenge for national strategic plan for malaria prevention and control, a situation in which a human *Plasmodium* reservoir is maintained, with individuals who are not treated because they are not diagnosed, since they are asymptomatic [12]. On the other hand, the diagnosing of such cases becomes difficult because of the low level of parasitemia. Thus, in this area of low endemicity and unstable transmission, healthy residents commonly harbour malaria parasites at low densities, below the detection threshold of microscopy or rapid diagnostic tests. Over time, waves of higher density (although still asymptomatic) parasitemia occur with the sequential emergence of new antigenic variants, generating potentially transmissible densities of gametocytes [13, 14].

Infections with malaria parasites can be asymptomatic in partly immune individuals living in endemic areas. Asymptomatic infections outnumber symptomatic malaria in both high and low transmission settings and as potential reservoirs for transmission can impede efforts to control and eliminate malaria. Infants experience both asymptomatic infections and symptomatic malaria [15]. However, during the first six months of life, infections are reported to be mainly asymptomatic, while between six and twelve months of age the incidence of both asymptomatic and symptomatic malaria infections increase [5]. The low incidence of symptomatic malaria below six months of age has been attributed to presence of fetal hemoglobin and passively acquired maternal IgG [13]. Also, malaria-specific antibodies at birth (in maternal and/or cord blood) have been associated with protection against some malaria parasite antigens but not others [8].

Detection/Diagnosing Asymptomatic Malaria

Diagnosing asymptomatic malaria is not straightforward due to the obvious lack of clinical manifestations and often low level

of parasites [16]. The method for asymptomatic parasitemia diagnosis is also important. For example, microscopy, with a detection threshold of ~50 parasites µl−1, may miss subpatent infections, while others use PCR whose sensitivity can extend to below one parasite µl−1 [17,18]. Studies in Kenya, Uganda and Brazil have reported a significantly high prevalence of asymptomatic parasitemia, as much as 6·7 times higher, using PCR when compared to microscopy [19]. PCR has also helped to identify individuals with low-density parasitemia in low-transmission settings that were previously missed by microscopy [20]. Although the use of PCR is technical and expensive, making it unrealistic in most field studies, it is important in improving the accuracy of diagnosing asymptomatic parasitemia [21].

Interestingly, loop-mediated isothermal amplification (LAMP) has been shown to accurately detect sub-microscopic asymptomatic *Plasmodium* infection. LAMP is cheap and easy to implement in a field setting as it does not require a thermocycler machine like PCR. In addition, several biomarkers such as lactate dehydrogenase, hemozoin and, in particular, Histidine-Rich Protein 2 that is utilized in rapid diagnostic tests (RDTs), have been used to diagnose malaria [22]. Hemozoin is an important metabolite of hemoglobin digestion by the malaria parasite and is associated with pathogenesis as well as inducing immunity to malaria [23]. A hemozoin sensing assay has recently been shown to be 20 times more sensitive than RDTs in diagnosing *Plasmodium* species [24]. It could be applied as a point of care test and more importantly in screening populations for asymptomatic individuals with submicroscopic parasitemia [24]. More efficient diagnostic techniques are needed to effectively detect asymptomatic infections in various settings to improve the quality and reliability of data used in studying asymptomatic infections.

Challenges to combat Asymptomatic Malaria Patients

Asymptomatic malaria infection remains reservoir of infection in the epidemiology of malaria transmission. These have been attributed to some factors including the fact that in such region, many malaria patients with acute symptoms remained undiagnosed. The commonly used diagnostic tests such as Rapid diagnostic Tests (RDT) and microscopic only detect infection with sufficient parasite density (Figure 1). Besides, studies and integration of asymptomatic malaria have been given little or no significant attention in prevention and control programs. The health care-seeking behaviour of these groups of patients, especially in malaria endemic countries makes asymptomatic malaria undetected and untreated.

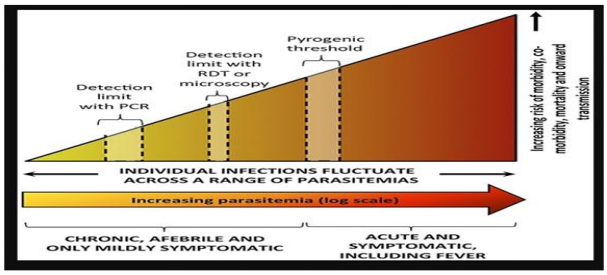

Figure 1: Spectrum of malaria infection: The figure illustrate increasing risks of morbidity, co-morbidity, mortality and onward transmission as density of parasitaemia increases. The test types are unable to detect low-density chronic infections below the threshold indicated and that infections of very low density are undetectable by PCR [25].

Diagnostic Criteria for Asymptomatic Malaria

Studies on different diagnostic criterial used for illustrating and defining asymptomatic *P. falciparum* infection are as summarized in Table 1. These includes thin and thick smear of individual with no history of infection nor treatment and detected infection of patient with no fever nor previous antimalaria treatment in the last two weeks.

Table 1: Examples of diagnostic criteria used to define asymptomatic *P. falciparum* infections as asymptomatic.

Criteria used for identifying asymptomatic malaria cases	Study subjects (sample size)	Follow-up protocol, Duration	References
Positive thick blood smear and afebrile. No history of fever and antimalarial treatment in the previous 1 and 2 weeks, respectively, at the time of mass screening	Children <12 years (13)	No follow-up	26
PCR-detected *P. falciparum* and no fever. No history of antimalarial or immunosuppressive medication in the last 30 days and helminths	Individuals >13 (5)	Bi-weekly and weekly surveillance for *Plasmodium* infection and malaria episode, respectively	27
Thin and thick blood smear and no clinical symptoms	Children 0.5‑6 years (ND)	Follow up for 5 consecutive days	28
Blood smear and no fever	Children 4‑5 years (15)	Follow up for 7 days	29

Factors associated with asymptomatic malaria infection

Immunity

Immunity had been well addressed as the key factors influencing whether a malaria infection produces symptom or not. The immune response of an individual depends on their past exposure and age. An individual with increased and improved immunity will possibly develop potential control over parasite multiplication and decrease parasite density and consequently lessens the severity of symptoms [30,5]. According to Roestenberg *et al.* [32], people with repeated malaria infection exposure over time will develop increased immune control with a resultant decrease in acute symptom. In a national survey in Mozambique, children <10 years of age with low density *P. falciparum* infections (1–499 parasites [p]/μl) had a prevalence of fever of 7.2%, compared with 42.1% among children whose asexual parasite densities were ≥50,000 p/μl [20]. In Brazil, parasite density was compared between symptomatic (age 12-78 years) and

asymptomatic (age 4-56 years, with no fever or malaria symptoms for 7 days prior to blood collection) individuals infected with *P. vivax* and *P. falciparum*; lower asexual parasite densities were found among the asymptomatic individuals for both parasite species, although the difference was much greater for *P. vivax* [19].

According to the report of Lindblade *et al.* [5], some asymptomatic infections may be residual or recrudescent parasitemia remaining after treatment for a clinical episode. For instance, in a low-transmission setting such as Sudan, a higher proportion of people who experienced a clinical episode of malaria during the transmission season from September to December had an asymptomatic infection detected by PCR in the following January than did those without a prior clinical episode (35 vs 8%, respectively), despite having been clinically cured of their symptomatic infection by treatment with chloroquine [32].

It is possible that drug resistant parasites could persist at a low level after treatment, with densities controlled by immunity developed during the initial infection. However, the parasites in these infections were not genotyped to determine whether they were the same clones present during the clinical episode or new infections [5].

Coinfection

Another factor associated with asymptomatic malaria infection is coinfection. This may affect the development of symptoms by altering immune system function. For example, the coinfection of malaria and schistosomiasis is a frequent occurrence, but the effects on malaria immunity and transmission are complex. Some studies suggest that schistosomiasis coinfection favours development of antimalarial immunity [33], whereas others have found lower levels of protective malaria antibodies in *Schistosoma haematobium* carriers [34,35]. Sangweme *et al.* [35] demonstrated in their prospective study that children coinfected with malaria and schistosomiasis were more likely to have detectable gametocytes and higher gametocyte densities than children infected only with malaria, potentially facilitating more intense malaria transmission.

Age and Asymptomatic Malaria

Experts have also mentioned that age is one of the determining factors influencing parasite density in an individual. Bousema *et al.* [36], mentioned that malaria infection with asymptomatic exposure generally increases with age. Infants experience both asymptomatic infections and symptomatic malaria. This could be attributed with the fluctuations in body immunity. Children in malaria endemic area often gain and develop protection from severe disease at a very young age usually by 2-5 years of age followed by a decrease in the rate of symptomatic illness in early adolescence [37]. However, during the first six months of life, infections are reported to be mainly asymptomatic, while between six and twelve months of age the incidence of both asymptomatic and symptomatic malaria infections increase [38]. The low incidence of symptomatic malaria below six months of age has been attributed to presence of foetal hemoglobin and passively acquired maternal IgG. Also, malaria-specific antibodies at birth (in maternal and/or cord blood) have been associated with

protection against some malaria parasite antigens but not others [38].

According to Bousema *et al* [36], areas of high malaria transmission, the proportion of the population that is parasitemic tends to decrease with age, although this relationship may be somewhat muted when molecular assays are utilized. Conversely, the proportion of malaria infections that are asymptomatic generally increases with age, presumably due to acquired immunity and maturation of the immune system.

Roper *et al.* [32] examined the proportion of malaria infections by age (0-4, 5-14 and 15+ years) across five sites that using PCR for diagnosis and found out that there is a consistent positive trend in the proportions of infections that are asymptomatic with age across the five sites, but confidence intervals are wide. The lack of more significant differences by age could be a result of using prevalence rather than incident infections, or the age groupings may be too wide to detect differences between age categories.

In a study to evaluate the risk factor associated with asymptomatic malaria Ligabaw *et al.* [11] observed an association between asymptomatic malaria and the age of the children where the prevalence decreased from 15.1% among children aged 6‑10 years to 4.8% among children aged 11‑15 years ($P < 0.05$). This may be because of increased consciousness about the transmission and information on the prevention mechanism of infection.

Ligabaw *et al.* [11] attributed the high prevalence of asymptomatic *Plasmodium* infection among school children in Sanja Town, Northwest Ethiopia to be the effect of climate change on highland malaria transmission which is strongly dependent on the temperature, because temperature is known to influence transmission intensity through its effects on the population growth of the mosquito vector and on pathogen development within the vector.

Other factors

Besides the above-mentioned factors affecting asymptomatic malaria infection, elevation of C-reactive protein (a biomarker of inflammation), lower platelet counts and haemoglobin levels [39], low birth weight and malnutrition [40]. The aforementioned factors influencing asymptomatic malaria has prompted experts to refer to asymptomatic parasitaemia as “Chronic malaria”[41].

Impacts of Asymptomatic Malaria Infection in Malaria Control

Asymptomatic malaria remained a new challenge for national strategic plan for malaria prevention and control where human *Plasmodium* reservoir is maintained with individuals who are not treated because they are not diagnosed due to lack of symptoms. On the other hand, the diagnosing of such cases becomes difficult because of the low level of parasitaemia. Thus, in this area of low endemicity and unstable transmission, healthy residents commonly harbour malaria parasites at low densities, below the detection threshold of microscopy or rapid diagnostic tests. Also, the waves of higher density (although still asymptomatic) parasitaemia occur with the sequential emergence of new antigenic variants, generating potentially transmissible densities of gametocytes [42]. Asymptomatic infections outnumber symptomatic malaria in both high and low transmission settings and as potential reservoirs for transmission can impede

efforts to control and eliminate malaria. *P. falciparum* infection has been shown to persist asymptomatically in semi-immune individuals for more than 18 months especially in older children making them important reservoirs for sustaining malaria transmission in regions of low and high malaria endemicity. The asymptomatic reservoir contributes to gametocyte carriage (the stage of the life-cycle of the parasites that cause mosquito transmission) to drive and maintain transmission by the local mosquito vectors. Some findings suggest that asymptomatic carriers are more infectious than symptomatic, as they contribute to infections for longer periods of time when they are not treated.

Malaria in areas of unstable transmission usually follows seasonal patterns of transmission as mosquito populations fluctuate, with the prevalence of parasitaemia at a minimum in the cooler dry season. In this time asymptomatic infections of malaria are critical, as this reservoir is likely responsible for sustaining the parasite population from one transmission season to the next [43]. Besides, asymptomatic malaria cases are difficult due to low parasitic density and availabilities of simple diagnostic methods; asymptomatic carriers especially adults are common in endemic areas and, as potential gametocyte carriers, represent an important reservoir for malaria transmission. Many of these individuals can carry microscopically detectable levels of *Plasmodium* asymptomatically and submicroscopic asymptomatic infections below the limit for microscopic detection that can only be detected using molecular techniques [11].

Numerous studies have demonstrated the infectivity of low-density *Plasmodium* infections to mosquitoes in areas of low endemicity [3, 44, 45]. The probability that a mosquito will become infected when feeding on a human host depends on the prevalence and density of mature-gametocyte carriage [45]. Although gametocyte densities are low in asymptomatic carriers, the prevalence of asymptomatic infection is substantially higher than that in individuals with high gametocyte densities (10%-50% vs 0%-2%) [46]. In addition, the duration of infection in asymptomatic carriers is substantially longer than that in symptomatic individuals, who usually seek antimalarial treatment [47].

The contribution of these protracted low-density infections to malaria transmission remains unresolved. According to a report from the World Health Organization Evidence Review Group on Low-Density Malaria Infections, current evidence is insufficient for understanding the contribution of low-density [*Plasmodium*] *falciparum* or [*Plasmodium*] *vivax* infections to onward transmission to human populations. Intervention trials to directly assess the effect of identifying and treating low-density infections are warranted [4].

In a study conducted by Botwe *et al.* [48] on the asymptomatic infections among infants in Ghana, 87 different patterns of alternating asymptomatic infection and symptomatic malaria (over half unique to individuals) were detected among 805 infants with *P. falciparum* parasites, suggesting that although there may be factors facilitating the transitioning from asymptomatic infections to symptomatic malaria, there is no uniform sequence of going between being either symptomatic or asymptomatic.

Given the development of naturally acquired immunity against malaria at intermittent time periods and the observations made, the natural course of malaria in the first year of life may follow the different profiles. Perhaps, each infection time point may have been influenced by factors (placental malaria, decreasing maternal antibodies, use of medications, ITN use or host genetic factors) that could modulate the manifestation of symptoms or morbidity. The modifications resulting out of interactions between the infected child and combinations of such factors is thought to have led to infections which were always accompanied with symptoms for some infants or without symptoms for others through the first year of life [48].

Gametocyte density appears to be a critical factor in determining whether a mosquito develops infection from an infective blood meal. An analysis of 930 transmission experiments showed a largely log• linear positive relationship between gametocyte density and the prevalence of infection in mosquitoes [36]. This suggests that if asymptomatic infections are associated with lower gametocyte densities, asymptomatic infections would be less likely to result in mosquito infections. In a study aimed at demonstrating the viability and contribution of asymptomatic infections to malaria transmission, 1.2% of the mosquitoes feeding on asymptomatic persons (n = 15) versus 22% of the mosquitoes feeding on symptomatic persons (n = 17) developed oocysts in their midguts. Different feeding techniques in the two populations may have affected the comparison but it is likely that the lower gametocyte density among the asymptomatic individuals contributed to the observed differences in mosquito infections [49].

Despite increasing probability of infection with increasing gametocyte density, numerous studies have demonstrated that mosquitoes can become infected by blood from individuals with gametocyte densities as low as five gametocytes (g)/µl, and theoretically as low as 1 g/µ [49]. To look at the relative transmissibility of infections when gametocytes were detectable by microscopy, by PCR or were not detectable, Schneider *et al.* [50] used venous blood from children with and without gametocytes detected by microscopy to feed mosquitoes through membrane feeders. Blood from children with subpatent gametocytes infected half as many mosquitoes as those with patent gametocytemia, but due to the frequency of subpatent gametocytemia in the sample of children, the end result was that both groups contributed equally to the total number of infected mosquitoes.

In this study, children with gametocytemia that was undetectable even by PCR were still found to contribute to almost 10% of the overall number of infected mosquitoes, demonstrating that gametocytes below detection thresholds can still result in malaria transmission. *P. vivax* and other *Plasmodium* species are more efficient at transmitting earlier in the infection and at lower densities than *P. falciparum*, and therefore a greater proportion of individuals infected with these species can transmit without detectable gametocytemia [49].

There may be factors associated with the presence of symptoms that alters infectivity to mosquitoes. In a study by conducted by Botwe *et al.* [48] a significantly smaller proportion of mosquitoes that fed on blood from symptomatic individuals (0.6%) developed oocysts than those that fed on

asymptomatic persons (12%). Although symptomatic individuals were found to have higher asexual but lower gametocyte densities than asymptomatic individuals, the authors concluded that the increased oocyst development in mosquitoes that fed on asymptomatic individuals was not due solely to the higher gametocyte densities, but also to an increased infectivity of these gametocytes. This increased quality of gametocytes has been postulated by others [7] and could be due to a variety of factors, including the stage of development of the gametocytes (for *P. falciparum*, symptoms tend to occur earlier in infection when gametocytes may not have reached a level of maturity to be optimally infective), an inherent property of the parasite strain, a direct effect of symptomatology (i.e., the febrile response may affect the infectivity of gametocytes), or to a more specific host immune response, such as transmission-reducing antibodies [33].

Individuals who receive repeated malaria infections over time eventually achieve increased immune control with a resultant decrease in acute symptoms. Without clinical illness, these infections are silent and remain untreated, resulting in chronic carriage that can last for 6 months or longer. Asymptomatic infections may be associated with a greater probability of gametocyte carriage, although there is also likely to be a lower density of gametocytes in these individuals, and these effects may cancel themselves out with respect to altering the infectivity of asymptomatic infections [5].

However, the proportion of mosquito infections that arise from asymptomatic infections is likely to be high due to a combination of the proportion of asymptomatic infected individuals in the population at any given point in time and the duration of their infections. Evidence summarized in this report suggests that even in areas of low transmission, the contribution of asymptomatic infections to transmission is likely to be substantial, and in areas with seasonal transmission, asymptomatic infections may serve as the source of infections for a new generation of mosquitoes emerging after the start of the rains [5].

Prospects

The World Health Organization (WHO) Framework for Malaria Elimination recognizes the important role of case detection and subsequent treatment as well as broader community level preventive responses around detected cases. In the context of elimination, WHO noted that case detection requires the use of a diagnostic test to identify asymptomatic malaria infections. WHO stresses that a case is a case, regardless of whether it is symptomatic or asymptomatic, as long as the diagnostic process confirms presence of malaria infection [4].

It is important to monitor *Plasmodium* parasitemia in areas where malaria transmission has declined. According to WHO [4], active case detection (ACD) takes place in areas of limited or under-utilisation of health-care services. It may start with initial screening for symptoms, followed by appropriate parasitological laboratory confirmation. In low-transmission settings or as part of a focus investigation, ACD may consist of testing of a defined population group without prior symptom screening (population-wide or mass testing) in order to identify asymptomatic infections. Elimination cannot be achieved until even asymptomatic infections have stopped.

However, the challenge is the expense of community-wide screening [51].

Reactive Case Detection (RCD), according to WHO, takes place in settings with low transmission intensity where the few occurring malaria cases are highly aggregated. When a case is identified, usually through identification of an actual infected patient at a local clinic, the community where the patient comes from is visited and a "net is cast around the index case" where household members and neighbors within a selected radius are tested. In this process asymptomatic cases are also identified.

One of the challenges to asymptomatic cases of malaria detention is inadequacy of existing diagnostic tools. According to the report of McCreesh *et al.* [52] on sub-patent malaria in Namibia, fever history and standard RDTs are not useful to detect asymptomatic cases of malaria. Achievement of malaria elimination may require active case detection using more sensitive point-of-care diagnostics or presumptive treatment such as loop-mediated isothermal amplification (LAMP) using dried blood spots and targeted to high-risk groups [51].

Similarly, Kobayashi *et al.* [53] suggest more sensitive diagnostic tests or focal drug administration may be necessary to target individuals with sub-patent parasitemia to achieve malaria elimination. Responses to detecting asymptomatic cases start at the individual level with prompt treatment of those found through RCD to be infected. Then focused preventive interventions such as distribution of insecticide treated bednets can be provided to those in the cluster or village. Follow-up would be needed for such hot spots.

On a broader basis we have Seasonal Malaria Chemoprevention (SMC) as practiced in Sahelian countries where during the peak transmission (rainy) season intermittent preventive treatment is given to children monthly by community health workers and volunteers. Of course, many of these children would be asymptomatic carriers and SMC could benefit the reduction of parasites in circulation. At present SMC focuses on pre-school aged children, however, reaching school aged children who are also often asymptomatic carriers is also very important [51].

Another intervention being tested for mass drug administration (MDA) use providing the community with ivermectin, a drug that has been highly effective in controlling filarial diseases and also found to kill mosquitoes who take a blood meal from a person who has recently taken it. This strategy is still being tested, but again MDA means all community members, especially those with asymptomatic infection, would be reached [53].

However, treating all asymptomatic infections could have negative consequences, including increased rates of malaria illness. In some studies, individuals with asymptomatic infections were protected against development of malaria illness and clearing asymptomatic infections led to an increased risk of malaria illness [50]. If asymptomatic infections provide protection against malaria illness, treating asymptomatic infections could increase the likelihood of a subsequent infection evolving to disease.

Although, in some populations, particularly children under 3 years of age, evidence suggests that asymptomatic infections can be precursors to malaria

illness. If so, treating and preventing asymptomatic infections could improve long-term health, while simultaneously removing sources of infection in the community [54].

Conclusion

Findings from this study shows that Parasitaemics and in particular asymptomatics are a big threat or challenge to any malaria control programme. For effectiveness, the malaria control programme currently going on in Nigeria and indeed any control programme elsewhere need to take healthy malaria parasite carriers or asymptomatic malaria parasitaemics as reservoirs of infection as serious threat to the success of the programme. The problems it poses needs to be seriously addressed simultaneously with other control strategies.

Recommendations

Symptomatic malaria victims can be forced to seek for treatment and from findings of this review, these are in the minority. That means that the majority of people are public health threat who will continue to be reservoirs of infection and yet have no compulsion to seek for medical treatment. Therefore in any malaria control programme the designers may contemplate including treating the entire population or all the population parasitaemics so as to achieve their desired goal.

Strategies targeting asymptomatic infections are available, but rigorous research efforts to compare the relative effectiveness of different approaches at varying levels of malaria transmission are needed. The approaches that most efficiently and quickly find and eliminate asymptomatic parasite reservoirs may provide the endgame for malaria elimination in many areas.

Thus, for better and complete coverage of malaria control intervention, irrespective of the level of clinical presentation or density, all malaria cases must be treated. There is therefore urgent need for the development of comprehensive strategy that will address the unidentified and control reservoir of malaria infection. Although, the inclusion of asymptomatic malaria patient in malaria control intervention may be challenging with financial and political implication, there is immeasurable health benefit to the public.

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Conflict of Interest

Authors declare no conflict of interest on this Paper.

REFERENCES

1. Lin, J. T., Saunders, D. L.,and Meshnick, S. R. (2014). The role of submicroscopic parasitemia in malaria transmission: what is the evidence?. *Trends in parasitology*, *30*(4), 183-190.

2. Cheaveau, J., Mogollon, D. C., Mohon, M. A. N., Golassa, L., Yewhalaw, D., and Pillai, D. R. (2019). Asymptomatic malaria in the clinical and public health context. *Expert review of anti-*

infective therapy, *17*(12), 997-1010.

3. Nwali, M. I., Umeora, O. U., Joannes, O. B. C., Onoh ,R. C., Ezeonu, P. O., Agwu, U. M., and Agboeze, J. (2014). Prevalence and Parasite Density of Asymptomatic Malaria Parasitemia among Unbooked Paturients at Abakaliki, Nigeria. *Journal of Basic and Clinical Reproductive Sciences*, 3(1), 44-48

4. World Health Organization (2018). Meeting report of the WHO Evidence Review Group on Low-Density Malaria Infections. Document WHO/HTM/GMP/MPAC/2018/10. Geneva:. https://www.who.int/malaria/mpac/mpac-oct2017-erg-malaria-low-density-infections-session2.pdf?ua=1. Accessed 11 December 2018.

5. Lindblade, K. A., Steinhardt, L., Samuels, A., Kachur, S. P., and Slutsker, L. (2013). The silent threat: asymptomatic parasitemia and malaria transmission. *Expert review of anti-infective therapy*, *11*(6), 623-639.

6. Ademolue, T. W., and Awandare, G. A. (2018). Evaluating antidisease immunity to malaria and implications for vaccine design. *Immunology*, 153, 423‐34.

7. Laishram, D. D., Sutton, P. L., Nanda, N., Sharma, V. L., Sobti, R. C., Carlton, J. M., and Joshi, H. (2012). The complexities of malaria disease manifestations with a focus on asymptomatic malaria. *Malaria Journal*, *11*(1), 1-15.

8. Cheaveau, J., Mogollon, D. C., Mohon, M. A. N., Golassa, L., Yewhalaw, D., and Pillai, D. R. (2019). Asymptomatic malaria in the clinical and public health context. *Expert review of anti-infective therapy*, *17*(12), 997-1010.

9. Snow, R. W., Sartorius, B., Kyalo, D., Maina, J., Amratia, P., Mundia, C. W., Bejon, P., and Noor, A. M. (2017). The prevalence of *Plasmodium falciparum* in sub-Saharan Africa since 1900. *Nature* 550:515‐518

10. Siraj, A. S., Santos-Vega, M., Bouma, M. J., Yadeta, D., Carrascal, D. R., and Pascual, M. (2014). Altitudinal changes in malaria incidence in highlands of Ethiopia and Colombia. *Science*, *343*(6175), 1154-1158.

11. LigabawWorku, D. D., Mengistu, E. S.,G., and Mulugeta, A. .(2014). Asymptomatic Malaria and Associated Risk Factors among School Children in Sanja Town, Northwest Ethiopia. *International Scholarly Research Notices,* 1-6

12. Moonen, B., Cohen, J. M., Snow, R. W., Slutsker, L., Drakeley, C., Smith, D. L., ... and Targett, G. (2010). Operational strategies to achieve and maintain malaria

elimination. *The Lancet*, *376*(9752), 1592-1603.

13. Botwe, A. K., Owusu-Agyei, S., Asghar, M., Hammar, U., Oppong, F. B., Gyaase, S., ... and Asante, K. P. (2020). Profiles of Plasmodium falciparum infections detected by microscopy through the first year of life in Kintampo a high transmission area of Ghana. *PloS one*, *15*(10), e0240814.

14. Akindeh, N. M., Ngum, L. N., Niba, P. T. N., Ali, I. M., Ayem, O. L. O., Chedjou, J. P. K., ... and Mbacham, W. (2021). Assessing asymptomatic malaria carriage of Plasmodium falciparum and non-falciparum species in children resident in Nkolbisson, Yaoundé, Cameroon. *Children*, *8*(11), 960.

15. Babiker, H. A., Gadalla, A. A., and Ranford-Cartwright, L. C. (2013). The role of asymptomatic P. falciparum parasitaemia in the evolution of antimalarial drug resistance in areas of seasonal transmission. *Drug Resistance Updates*, *16*(1-2), 1-9.

16. Boldt, A. B., Van Tong, H., Grobusch, M. P., Kalmbach, Y., Ella, A. D., Kombila, M., ... and Velavan, T. P. (2019). The blood transcriptome of childhood malaria. *EBioMedicine*, *40*, 614-625.

17. Vasoo, S. and Pritt, B.S.(2013). Molecular diagnostics and parasitic disease. *Clin Lab Med.* 33:461‑503. doi: 10.1016/j.cll.2013.03.008

18. Agbana, H. B., Rogier, E., Lo, A., Abukari, Z., Jones, S., Gyan, B., ... and Amoah, L. E. (2022). Detecting asymptomatic carriage of Plasmodium falciparum in southern Ghana: utility of molecular and serological diagnostic tools. *Malaria Journal*, *21*(1), 1-11.

19. Idris, Z. M., Chan, C. W., Kongere, J., Gitaka, J., Logedi, J., Omar, A., ... and Kaneko, A. (2016). High and heterogeneous prevalence of asymptomatic and sub-microscopic malaria infections on islands in Lake Victoria, Kenya. *Scientific reports*, *6*(1), 1-13.

20. Barbosa, S., Gozze, A. B., Lima, N. F., Batista, C. L., Bastos, M. D. S., Nicolete, V. C., ... and Ferreira, M. U. (2014). Epidemiology of disappearing Plasmodium vivax malaria: a case study in rural Amazonia. *PLOS neglected tropical diseases*, *8*(8), e3109.

21. Kijogi, C., Kimura, D., Bao, L. Q., Nakamura, R., Chadeka, E. A., Cheruiyot, N. B., ... and Yui, K. (2018). Modulation of immune responses by Plasmodium falciparum infection in asymptomatic children living in the

22. Krampa, F. D., Aniweh, Y., Awandare, G. A., and Kanyong, P. (2017). Recent progress in the development of diagnostic tests for malaria. *Diagnostics*, *7*(3), 54.

23. Ihekwereme, C. P., Esimone, C. O., and Nwanegbo, E. C. (2014).

Hemozoin inhibition and control of clinical malaria. *Advances in pharmacological sciences*, *2014*.

24. Rifaie-Graham, O., Pollard, J., Raccio, S., Balog, S., Rusch, S., Hernández-Castañeda, M. A., ... and Bruns, N. (2019). Hemozoin-catalyzed precipitation polymerization as an assay for malaria diagnosis. *Nature communications*, *10*(1), 1369.

25. Okell, L. C., Bousema, T., Griffin, J. T., Ouédraogo, A. L., Ghani, A. C., and Drakeley, C. J. (2012). Factors determining the occurrence of submicroscopic malaria infections and their relevance for control. *Nature communications*, *3*(1), 1237.

26. Almelli, T., Nuel, G., Bischoff, E., Aubouy, A., Elati, M. and Wang, C. W. (2014). Differences in gene transcriptomic pattern of Plasmodium falciparum in children with cerebral malaria and asymptomatic carriers. *PLoS ONE,* 334-341

27. Tran, T. M., Jones, M. B., Ongoiba, A., Bijker, E. M., Schats, R., Venepally, P., ... and Crompton, P. D. (2016). Transcriptomic evidence for modulation of host inflammatory responses during febrile Plasmodium falciparum malaria. *Scientific reports*, *6*(1), 31291.

28. Boldt, A. B., Van Tong, H., Grobusch, M. P., Kalmbach, Y., Ella, A. D., Kombila, M., ... and Velavan, T. P. (2019). The blood transcriptome of childhood malaria. *EBioMedicine*, *40*, 614-625.

29. Jagannathan, P., Kim, C. C., Greenhouse, B., Nankya, F., Bowen, K., Eccles-James, I., ... and Feeney, M. E. Loss and dysfunction of Vd2 gd T cells are associated with clinical tolerance to malaria.

30. Mabunda, S., Aponte, J. J., Tiago, A., and Alonso, P. (2009). A country-wide malaria survey in Mozambique. II. Malaria attributable proportion of fever and establishment of malaria case definition in children across different epidemiological settings. *Malaria Journal*, *8*(1), 1-7.

31. Roestenberg, M., Teirlinck, A. C., McCall, M. B., Teelen, K., Makamdop, K. N., Wiersma, J., ... and Sauerwein, R. W. (2011). Long-term protection against malaria after experimental sporozoite inoculation: an open-label follow-up study. *The Lancet*, *377*(9779), 1770-1776.

32. Roper, C., Elhassan, I. M., Hviid, L., Giha, H., Richardson, W., Babiker, H., ... and Arnot, D. E. (1996). Detection of very low level Plasmodium falciparum infections using the nested polymerase chain reaction and a reassessment of the epidemiology of unstable malaria in Sudan. *The American journal of tropical medicine and hygiene*, *54*(4), 325-331.

33. Lyke, K. E., Wang, A., Dabo, A., Arama, C., Daou, M., Diarra, I., ... and Sztein, M. B. (2012). Antigen-specific B memory cell responses to Plasmodium falciparum malaria antigens and Schistosoma haematobium antigens in co-infected Malian children. *PLoS One*, *7*(6), e37868.

34. Courtin, D., Djilali-Saïah, A., Milet, J., Soulard, V., Gaye, O., Migot-Nabias, F., ... and Luty, A. J. F. (2011). Schistosoma haematobium infection affects Plasmodium falciparum-specific IgG responses associated with protection against malaria. *Parasite Immunology*, *33*(2), 124-131.

35. Sangweme, D. T., Midzi, N., Zinyowera-Mutapuri, S., Mduluza, T., Diener-West, M., and Kumar, N. (2010). Impact of schistosome infection on Plasmodium falciparum Malariometric indices and immune correlates in school age children in Burma Valley, Zimbabwe. *PLoS neglected tropical diseases*, *4*(11), e882.

36. Bousema, T., and Drakeley, C. (2011). Epidemiology and infectivity of Plasmodium falciparum and Plasmodium vivax gametocytes in relation to malaria control and elimination. *Clinical microbiology reviews*, *24*(2), 377-410.

37. Golassa, L., Baliraine, F. N., Enweji, N., Erko, B., Swedberg, G., and Aseffa, A. (2015). Microscopic and molecular evidence of the presence of asymptomatic Plasmodium falciparum and Plasmodium vivax infections in an area with low, seasonal and unstable malaria transmission in Ethiopia. *BMC infectious diseases*, *15*(1), 1-10.

38. Natama, H. M., Rovira-Vallbona, E., Somé, M. A., Zango, S. H., Sorgho, H., Guetens, P., ... and Rosanas-Urgell, A. (2018). Malaria incidence and prevalence during the first year of life in Nanoro, Burkina Faso: a birth-cohort study. *Malaria journal*, *17*, 1-11.

39. De Mast, Q., Brouwers, J., Syafruddin, D., Bousema, T., Baidjoe, A. Y., de Groot, P. G., ... and Fijnheer, R. (2015). Is asymptomatic malaria really asymptomatic? Hematological, vascular and inflammatory effects of asymptomatic malaria parasitemia. *Journal of Infection*, *71*(5), 587-596.

40. Nankabirwa, J., Wandera, B., Kiwanuka, N., Staedke, S. G., Kamya, M. R., and Brooker, S. J. (2013). Asymptomatic Plasmodium infection and cognition among primary schoolchildren in a high malaria transmission setting in Uganda. *The American journal of tropical medicine and hygiene*, *88*(6), 1102.

41. Wamae, K., Wambua, J., Nyangweso, G., Mwambingu, G., Osier, F., Ndung'u, F., ... and Ochola-Oyier, L. I. (2019). Transmission and age impact

the risk of developing febrile malaria in children with asymptomatic Plasmodium falciparum parasitemia. *The Journal of infectious diseases*, *219*(6), 936-944.

42. Chaumeau, V., Kajeechiwa, L., Fustec, B., Landier, J., Naw Nyo, S., Nay Hsel, S., ... and Corbel, V. (2019). Contribution of asymptomatic Plasmodium infections to the transmission of malaria in Kayin State, Myanmar. *The Journal of infectious diseases*, *219*(9), 1499-1509.

43. Stresman, G. H., Kamanga, A., Moono, P., Hamapumbu, H., Mharakurwa, S., Kobayashi, T., ... and Shiff, C. (2010). A method of active case detection to target reservoirs of asymptomatic malaria and gametocyte carriers in a rural area in Southern Province, Zambia. *Malaria journal*, *9*(1), 1-8.

44. Lin, J. T., Ubalee, R., Lon, C., Balasubramanian, S., Kuntawunginn, W., Rahman, R., ... and Saunders, D. L. (2016). Microscopic Plasmodium falciparum gametocytemia and infectivity to mosquitoes in Cambodia. *The Journal of infectious diseases*, *213*(9), 1491-1494.

45. Vantaux, A., Samreth, R., Piv, E., Khim, N., Kim, S., Berne, L., ... and Ménard, D. (2018). Contribution to malaria transmission of symptomatic and asymptomatic parasite carriers in Cambodia. *The Journal of infectious diseases*, *217*(10), 1561-1568.

46. Imwong, M., Nguyen, T. N., Tripura, R., Peto, T. J., Lee, S. J., Lwin, K. M., ... and Nosten, F. (2015). The epidemiology of subclinical malaria infections in South-East Asia: findings from cross-sectional surveys in Thailand‐Myanmar border areas, Cambodia, and Vietnam. *Malaria journal*, *14*(1), 1-13.

47. Nguyen, T. N., von Seidlein, L., Nguyen, T. V., Truong, P. N., Do Hung, S., Pham, H. T., ... and Hien, T. T. (2018). The persistence and oscillations of submicroscopic Plasmodium falciparum and Plasmodium vivax infections over time in Vietnam: an open cohort study. *The Lancet Infectious Diseases*, *18*(5), 565-572.

48. Botwe, A. K., Owusu-Agyei, S., Asghar, M., Hammar, U., Oppong, F. B., Gyaase, S., ... and Asante, K. P. (2020). Profiles of Plasmodium falciparum infections detected by microscopy through the first year of life in Kintampo a high transmission area of Ghana. *PloS one*, *15*(10), e0240814.

49. Hürlimann, E., Houngbedji, C. A., Yapi, R. B., N'Dri, P. B., Silué, K. D., Ouattara, M., ... and Raso, G. (2019). Antagonistic effects of Plasmodium-helminth co-infections on malaria pathology in different population groups in Côte d'Ivoire. *PLoS neglected tropical diseases*, *13*(1),

e0007086. doi: 10.1371/journal.pntd.0007086

50. Sonden, K., Doumbo, S. and Hammar, U. (2015). Asymptomatic multiclonal *Plasmodium falciparum* infections carried through the dry season predict protection against subsequent clinical malaria. *Journal Infectious Disease,* 212, 608‐616.

51. Peprah, S., Tenge, C., Genga, I. O., Mumia, M., Were, P. A., Kuremu, R. T., ... and Mbulaiteye, S. M. (2019). A cross-sectional population study of geographic, age-specific, and household risk factors for asymptomatic Plasmodium falciparum malaria infection in Western Kenya. *The American journal of tropical medicine and hygiene*, *100*(1), 54.

52. McCreesh, P., Mumbengegwi, D., Roberts, K., Tambo, M., Smith, J., Whittemore, B., ... and Hsiang, M. S. (2018). Subpatent malaria in a low transmission African setting: a cross-sectional study using rapid diagnostic testing (RDT) and loop-mediated isothermal amplification (LAMP) from Zambezi region, Namibia. *Malaria journal*, *17*, 1-11.

53. Kobayashi, T., Kanyangarara, M., Laban, N. M., Phiri, M., Hamapumbu, H., Searle, K. M., ... and Moss, W. J. (2019). Characteristics of subpatent malaria in a pre-elimination setting in southern Zambia. *The American Journal of Tropical Medicine and Hygiene*, *100*(2), 280. doi: 10.4269/ajtmh.18-0399.

54. Portugal, S., Tran, T. M., Ongoiba, A., Bathily, A., Li, S., Doumbo, S., ... and Crompton, P. D. (2017). Treatment of chronic asymptomatic Plasmodium falciparum infection does not increase the risk of clinical malaria upon reinfection. *Clinical infectious diseases*, *64*(5), 645-653.