REVIEW ARTICLE

Progress in the Study of Epidemiologic Characteristics and Influencing Factors of Asymptomatic Malaria Infection in Africa

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ABSTRACT

Malaria is caused by protozoan parasitic *Plasmodium* infections. *Plasmodium falciparum* is common in Africa; *P ovale*, *P malaria* and *P vivax* infections are less prevalent and globally confined, contributing to major causes of global mortality and morbidity, particularly in children in sub-Saharan African countries. In 2018, the total incidence of malaria increased from 221 million to 229 million, with an estimated 503 000 deaths reported. Sub-Saharan Africa has the highest number of cases of malaria and highest mortality rate compared with other countries, like southeastern Asia, east Pacific, western, and America with an estimated 213 million cases. In addition, continuous exposure to *Plasmodium* parasites results in the production of partial immunity to guard against more problems, resulting in asymptomatic carriers.

The diagnosis of asymptomatic malaria is not simple because of the apparent absence of clinical factors and sometimes low levels of parasites. The most basic concept appears to be parasitemia and a lack of malaria signs, primarily fever (axillary temperature <37.5° C). Thus, a better awareness of asymptomatic malaria epidemiology in affected countries will help improve strategies to reduce the local burden of malaria and its health consequences. Therefore, the objective of this study was to determine the magnitude of asymptomatic malaria pathology and related risk factors with epidemiologic characteristics in individuals on the African continent. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

In several areas of the world, despite a vast number of national and foreign initiatives to tackle the continuing spread of malaria, it remains a significant public health issue. Malaria in tropical and subtropical regions is one of the most common human parasitic diseases, and has particular socio-economic, public health, and quality of life significance in sub-Saharan Africa and Southeast Asia.[1,2] Different calculations were made to estimate the global malaria burden. Upwards of 216 million malarial illnesses and 655 000 deaths were recorded by the Global Health Organization in 2010, with 106 malaria-prone countries worldwide at risk, 91 percent of which were in sub-Saharan Africa, 3% in the Eastern Mediterranean Region, and 6% in Southeast Asia.[3] While great success has been reported in combating the disease, studies have shown limited success in reducing global malaria cases from 2014 to 2018. In 2018, the incidence of total malaria increased from 221 million to 229 million, with an estimated 503 000 deaths reported. Sub-Saharan Africa has the highest number of cases of malaria and highest mortality rates compared with other countries, like southeastern Asia, east Pacific, western, and America with an estimated 213 million cases of malaria.[4] Furthermore, 74% of Kenya's population is confirmed to be at risk for malaria and the most heavily affected areas are the coastal areas and the west of the world.[4] Malaria is caused by protozoan parasite *Plasmodium* infections. In Africa, *P falciparum* is common, while *P vivax*, *P ovale* and *P malaria* infections are less prevalent and globally limited.[5,6] *P falciparum* malaria remains a major cause of global death and morbidity, especially among children in sub-Saharan Africa.[7,8]

Plasmodium parasites are transmitted by *Anopheles* mosquitoes, with *A funestus*, *A arabiensis* and *A gambiae sensu stricto* being the most prevalent in Africa.[9] In addition, continuous exposure to *Plasmodium* parasites results in partial immunity, which guards against more problems and

thus results in asymptomatic carriers.[10] Studies from Kenya, Uganda and Brazil have shown that asymptomatic parasitemia is 6 to 7 times more prevalent than polymerase chain reaction (PCR) when contrasted with microscopy.[11-13] Many asymptomatic disorders have few to no signs and thus go undetected and untreated. The level of asymptomatic parasitemia is inversely correlated with a clinical disease-prone community.[14] More specifically, asymptomatic individuals are significant sources of infection.[15] Although the use of PCR is difficult, costly and impractical in most field trials, it is necessary to increase the precision of asymptomatic parasitemia diagnoses.[16] However, scientists and clinicians have developed diagnostic recommendations based on the initiation of clinical events in malaria that helped develop an organized approach to strengthening serious malaria management and treatment.[17] Diagnosis of asymptomatic malaria is not simple because of the apparent absence of clinical events and sometimes low levels of parasites.[18] Thus, a better awareness of asymptomatic malaria epidemiology in affected countries will help improve strategies to reduce the local disease burden and health effects of malaria.[19] Therefore, the objective of this study is to determine the magnitude of asymptomatic malaria pathology and related risk factors and epidemiologic characteristics among individuals on the African continent.

LITERATURE SELECTION

Potentially important English-language only studies were culled from ScienceDirect, Medline, PubMed, Public Library of Science, Mendeley, SpringerLink and Google Scholar. Many keywords were used to scan the literature including "sepsis," "epidemiology of malaria," "malaria-associated hyper inflammation," "mechanism of the pathogenesis of asymptomatic malaria," "involvement of epidemiological characteristic of asymptomatic malaria in African continent," "prevalence of asymptomatic malaria," "asymptomatic malaria and anti-inflammatory immunity," "asymptomatic malaria and antibodies," "factor influencing asymptomatic malaria," "immunosuppressive pathway via Plasmodium falciparum in African continent" and "innate and adaptive immunity in asymptomatic malaria." Reference lists of collected papers were also screened for related articles not found with the initial search strategy.

EPIDEMIOLOGIC CHARACTERISTICS OF ASYMPTOMATIC MALARIA

Recent declines in the incidence of clinical malaria show that asymptomatic parasite carriers are essential to maintaining transmission.[20-24] In addition, there are claims that asymptomatic carrier parasites are more dangerous than symptomatic carrier parasites.[25] The most basic concept appears to be parasitemia and the lack of malaria signs, primarily fever (axillary temperature <37.5° C).[26-28] Healthy individuals can carry asexual and sexual blood parasites (gametocytes), which are essential for transmission.[29] Individuals with persistent asymptomatic infections may contribute to the spread of viruses in the subsequent years.[29] Research performed in Mali showed that targeting asymptomatic infections in any chronically symptomatic patient is unlikely to have an impact on clinical malaria prevalence rates.[30] Moreover, malaria transmission results in Africa such as in The Gambia, Mali and Senegal suggest that more than 25% of people with sub-microscopic gametocytes are capable of contaminating mosquitoes.[31] A 2012 study from Laos showed that 20% (175 out of 888) of officially stable individuals had *Plasmodium* infections.[31] Asymptomatic parasitemia is associated with a greater risk for fever caused by malaria in children up to 18 months of age.[32] Older children in areas where malaria is prevalent, however, acquire parasite-specific immunity to the *Plasmodium* parasite that helps reduce the volume and occurrence of asymptomatic parasite carriers in clinical malaria episodes.[33-35] Moreover, schoolchildren with asymptomatic malaria may not be out of school because of a clinical malaria episode but may be a significant reservoir of disease transmission.[15,36,37] Patients with non-specific signs, such as fever, rigors, and chills, would not require hospital admission. In a minority of patients, extreme malaria can present as fever, diminished awareness, serious anemia, respiratory failure, convulsions, and hypoglycemia, among other symptoms.[38] Often such signs are not observed and patients with no recent history of antimalarial care have been diagnosed with infection.[29]

One important concern remains: Why do *P falciparum* infections sometimes remain asymptomatic in people with little or poor immunity without producing large parasite densities? A new theory is that it may be that parasites that are less virulent in low-endemic settings are not subject to strong competition from virulent strains, thereby remaining low-density, asymptomatic, undetected and untreated, enabling further transmission over a long period.[39] However, another hypothesis is that whenever a parasite is present, immune factors are needed to reduce parasite numbers—antiparasite immunity—and antidisease immunity is needed to avoid signs of clinical complications.[40] Immunity in asymptomatic individuals is adversely affected by antidisease immunity rather than antiparasite immunity. The reasons for this phenomenon remain unknown, and further investigations are needed to clarify how antidisease immunity is triggered, which is explored in the next section of this study (see Figure 1).

MOLECULAR EXPLORATION OF PATHOLOGY OF ASYMPTOMATIC MALARIA

The occurrence and longevity of asymptomatic infections is a dynamic phenomenon linked to degrees of defensive immunity with recurrent malaria exposure and immune system maturity.[41] At the genome level, variations in host gene expression can account for numerous clinical manifestations during host-parasite interactions.[42] Specifically, gene pathways that control and augment cytokine signals, as well as immunoglobulin output, have been shown to be involved.[43] In several studies, an elevated incidence of febrile or cerebral malaria was correlated with an aggressive

pro-inflammatory response, whereas asymptomatic infection was associated with a poor response.44-46 *P falciparum* infections are distinguished by the co-circulation of many *P falciparum* clones in acute and chronic infections in malaria-endemic regions, especially in sub-Saharan Africa.[47-48] This is considered the anomaly mechanism of injury (MOI). The distribution of some genotypes of MSP 1 was correlated with different clinical malaria manifestations. Msp1 K1 and MAD20 were associated with asymptomatic malaria with minimal chance of fever in young Nigerian children.[49] Other findings show that high MOI in children with asymptomatic infection is associated with an increased rate of febrile malaria in infants, with a lower risk in older children.[50,51] Thus, MOI and *P falciparum* genetic variations are significant alternative markers in determining the severity of malaria transmission in various endemic regions. The conventional *P falciparum* characterization approach utilizes gel electrophorese entangled polymer chair reactions (PCRs) to identify polymorphisms in msp1, msp2 and rich protein in glutamines (GLuRP).[52] However, the use of molecular genotyping of polymorphic anti-genetic markers msp1, msp2 and GLuRP for studies of parasite diversity is criticized for providing high immune selection involving these genes.[53-56]

People in areas in which malaria is endemic are often asymptomatic and clinically resistant to diseases from numerous genetically complicated *P falciparum* infections over time.[57] Children with repeated episodes of malaria often have a modified immune system,[58,59] which is attributed to enhanced development of B cells, interleukin (IL)-10, activation of neutrophils and CD8 + T cells.[60] Immune responses are regulated by cytokines that control inflammation such as tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), IL-12, thus providing defensive immunity.[61] However, overstimulation of the immune system results in additional cytokine output and immune cell activation, which further inhibits the host defensive mechanism to parasitemia.[62,63] Also, anti-inflammatory cytokines like transforming growth factor beta (TGF-β), IL-10 and IL-27 are active in the dampening of pro-inflammatory cytokines to reduce disease intensity.[61,64] The existence of anti-inflammatory cytokines, particularly IL-10, prevents the clearance of parasites, impedes the production of anti-parasite immunity and promotes the development of asymptomatic infections.[65,66] The risk of an infection being asymptomatic rises with age, as frequent malaria exposure contributes to partial antidisease immunity.[67] Furthermore, increased IL-10 levels have also been correlated with asymptomatic infections in pregnant women.[68] In research in young Ugandan children, CD4 + T cytokines were found to be affected by previous malaria infection exposure. CD4 + T cells in more exposed children had higher levels of IL-10, while less exposed children had higher TNF-α levels and, therefore, inflammation. The activation of pro-inflammatory cytokine (TNFα, IL-1β and IFN-γ) development was reported in a malaria transcriptomic analysis with the least activation of asymptomatic cytokines.[27] Also, studies have shown that elevated regulatory T cell levels were related to increased parasitemia, the expression of TGF-β and clinical symptoms[69-71] while lower levels can reduce the risk of developing symptoms, resulting in immunity to antidisease.[72] Thus, antibodies against malaria tend to be short-lived since malaria infection cannot produce a sufficient B-cell response to the antigen.[73] In comparison, a report on Swedish travelers formerly treated for malaria preserved long-lasting B memory cells for 16 years with no exposure afterwards.[74] In asymptomatic patients, higher immunoglobulin G antigen-specific titers were found compared with patients with other findings.[75,76] In Gabonese children with symptomatic infection with *P falciparum*, elevated antigen-specific antibody responses have been associated with high IFN-α and IL-10 levels, suggesting a protective immune system response.[77] Thus, asymptomatic infections were correlated with a lack of TNF-α development.[44] On the other hand, a 2014 study explored the high activity of Vδ2+ γδ T cells due to the low level of pro-inflammatory cytokines[78] and increased immunoregulatory gene expression possibly dampening the effects of associated infections.

FACTORS INFLUENCING ASYMPTOMATIC MALARIA

Various factors including age, sex, education level, use of mosquito netting around the bed, the vector-host ratio during the wet season and recurrent exposure to malaria have been correlated with risk factors in different studies.[79] The gender variation in asymptomatic malaria may be attributable to samples from various seasons and socio-economic classes, prior access to prevention and recovery and the presence or absence of mosquito reproductive sites.

The investigators suggested that men are more vulnerable to asymptomatic infections than women. Furthermore, various studies have shown that the gender distribution of asymptomatic malaria was 9.8% male and 5.1% female.[80] The incidence in males was 48.1% and in females 41.4% compared with the findings from a 2012 study carried out in Cameroon.[81] Age is one of the most important variables in malaria-endemic areas linked to the defensive immune response. Many previous studies have shown that adults are asymptomatic parasite carriers because they are highly protected due to frequent exposure to malaria parasites, whereas viruses are symptomatic in young children while their protection against malaria continues to grow.[29,82,83] Thus, discovering that schoolchildren (younger than age 15 years) had an elevated risk of asymptomatic malaria infections appears to refute African results. However, this observation did reinforce the findings of earlier studies that schoolchildren have an increased risk for acute *P vivax* malaria.[84,85]

The results of vector-based prevention interventions were noteworthy and the data revealed that not sleeping under mosquito nets resulted in a more than 5 times higher probability of developing asymptomatic infections.[86] Moreover, in many villages in which the inhabitants did not use mosquito nets, there was an increased chance of developing asymptomatic *Plasmodium* infection compared

with individuals who used mosquito nets. Of note, seasonal heterogeneity in small cities was clearer, due to different vector ecology and efforts to monitor this in small cities and encampments.[85] Moreover, the materials used for house construction, which are reflective of families' socioeconomic position, also demonstrated major effects on asymptomatic infections; residents of wood or bamboo houses were found to have almost double the risk of *Plasmodium* infections (see Figure 2).[87-89]

The transmission of malaria is influenced by 2 key variables: vector density and gametocyte infectivity. Effective vector-based malaria prevention strategies such as the utilization of indoor residual spraying and mosquito netting, especially long-lasting insecticide-treated netting, are therefore essential for reducing malaria occurrence.[90] In addition, hidden asymptomatic infections, which provide a reservoir for local malaria transmission, are one of the key challenges to achieving this goal. Any asymptomatic pathogens may be critically charged with drug-resistant genes.[91]

CONCLUSION

In areas in which malaria is hyper-prevalent, anti-mosquito initiatives only function effectively because of the reservoir that has developed in susceptible people who do not even realize they bear the parasite. In high-transmission zones, asymptomatic rather than symptomatic malaria prevails. In sub-Saharan Africa, 24 million people are reported to have asymptomatic malaria infections, including 38% to 50% of school-age children in West Kenya. Of the 219 million malaria infections noted globally in 2017, more than 90% were in sub-Saharan Africa. The number of asymptomatic malaria reports, particularly with *P falciparum*, underscores the underlying problem facing the malaria elimination program in Africa. Besides vector management and the care of symptomatic and asymptomatic cases, active and inactive case identification must be utilized to eliminate malaria. Accurate monitoring via molecular assay and valid serologic methods in asymptomatic individuals and submicroscopic cases of malaria, particularly in areas with seasonal and low transmission rates, can be very helpful. This suggests that the burden of asymptomatic malaria needs to be further measured using a more adaptive approach, taking into account the various age groups and the extent of malaria transmission to improve the elimination and worldwide eradication of malaria.

CONFLICT OF INTEREST

All the investigators state that they have no conflict of interest.

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