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# Malaria: Immune System Modulation in Asymptomatic Parasitaemiain the Perpetuation of an Old Enemy – A Narrative Review

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## Abstract

Malaria infectionis intertwined with poor economic disposition in endemic regions whereasymptomatic malaria parasitaemia serves as the basinfor new infections, and influenced by the inability of the host immune system to adapt to the multi-variable malaria parasites' surface antigen that incapacitates the host immune systems' ability to respond appropriately. This review focused on the immune system modulation during malaria infections enabling parasitaemia to remain asymptomatic. Published literature on the subject matter involving the use of electronic quest engines to access databases for relevant materials, applying the major themes of the subject under review and the extraction of related items for study. A major contributory factor to the failure of malaria control, elimination or eradication strategies is the existence of asymptomatic malaria parasitaemia enabled by the multi-gene locus on the surface antigen that renders naturally acquired immunity insufficient and release of substances by the parasites that interfere with the host immune systems' ability to respond adequately. The consequential creation of equilibrium between the parasites and the host immune system promotes anti-inflammatory reaction over pro-inflammatory responses leading to tolerance of parasitaemia and the attendant symptomless nature of the infection.

***Keywords:*** *Malaria, asymptomatic parasitaemia, cytokines, immune modulation, tolerance.*

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## Introduction

Malaria remains one of the foremost international public health concerns and key agent in serious illness affecting millions of people for generations in Sub-Saharan African and South-East Asian countries [1,2]. A close link between malaria infection and low socio-economic index exists in endemic regions [3-5].The global burden of malaria infection averages 95% in the endemic areas and continues to defy control or elimination and eradication strategies in spite of being preventable, treatable and curable [6]. Malaria burden spiked by almost 5 million cases to 249 million between 2021 and 2022 with 233 million (or 94%) of these cases occurring in the World Health Organization African region [7-9]. Malaria infection comes with high morbidity and mortality rates especially in children under the age of 5 years, with 97% of the exposed population living in Sub-Saharan Africa region [2,6,10,11]. Human malaria typically occur due to four main Plasmodium species:(P. species) – P. falciparum, P. vivax, P. ovale and P. malariae,however, Plasmodium knowlesi known classically to infect primates, latelyreported in human infections in the South-East Asian region [12-14]. Plasmodium falciparum is the most virulent species responsible for 99% of the fatality in malaria infections [9,15]. Over half of the burden of all malaria infections occur in four African countries, with Nigeria in the lead with 31% of the cases, Democratic Republic of Congo 12%, Niger 6% and Tanzania 4% [12,15]. Several global action plans against malaria such as the scale-up or malaria elimination and eradication programme resulted in remarkable fall in the rate of cases and associated deaths, and stagnating in 2015 [16-18]. Attempts at malaria elimination and eradication in the endemic regions continue to meet roadblocks with resurgent spirals in cases of malaria infection and proportionally high mortality ratios mainly in Sub-Saharan Africa where in the year 2020, 95% of all cases and 96% of deaths with almost 80% of mortality affecting children under 5 years occurred. This scenario, attributed to several factors includes resistance to artemisinin-centered combination therapy, ACT and related agents, vector resistance to pyrethroids and insecticides [19-22]. In addition, the COVID-19 pandemic caused critical shortfalls in resource allocation to malaria control strategies in most African regions [9,23] and reversal of gains due to inefficient resource management, climate change leading to heavier rain falls and flooding that facilitates vector multiplication [24].This review highlights the role of asymptomatic malaria parasitaemia and the immune system interference as drivers of unending cycles of malaria infections.

## Methodology

Search of published literature was assisted with the application of electronic exploration engines of databases using key words from the main study theme and their combinations including malaria infection, regions, affected populations, asymptomatic malaria,immune response and immune tolerance. Relevant literature on the subject published between 2000 and 2024 in English language assembled, and reviewed for inclusion**.**

## Asymptomatic malaria parasitaemia

The survival and multiplication of sexual stages of malaria parasites (gametocytes) in the mid-gut of the female anopheles mosquitos eventually results in the development ofhost

infective sporozoites [25]. Asymptomatic malaria often remain undiagnosed, untreated and become the quiet aqueduct the keeps the cycle of malaria infection unbroken [26,27]. Reports indicate that asymptomatic malaria is common in endemic localities and completely independent of the patterns of infection [28-30]. This sustains malaria parasitaemia persistence for extended timesthus,posing major impediments in malaria control and eradication strategies, especially in low endemic settings [29,31,32].

**Malaria infection and immune response**

Studies reveal that the host immune response during malaria parasitaemia could lead to modulation in the control of the degree of parasitaemia under certain regulated conditions. However, the intricacies in the different stages of the malaria parasites life cycle posed prominent obstacles for the development of an effective vaccine until more recently [33,34]. The multiple and complex life cycle of the malaria parasite also throw-up a variety of challenges that demonstrate proof of convergence of facts on immunity cutting across the different stages in malaria parasites development.This is coupled with extensive genetic variation and the influence of age on infection, the balance between immuno-pathogenesis and tolerance to the parasites [33,35-37]. Immunity in malaria entailsboth innate and acquired immune pathways in the control of pathogenesis [38]. These systems involve effector cellsproducing pharmacologically active chemical signaling molecules (cytokines: interleukins,lymphokines, monokines, interferons, chemokines and numerous other molecules) to equilibrate pro-inflammatory and anti-inflammatory mechanisms and prevent hypercytokinemia (cytokine storm) which ultimately can lead to systemic injury, organ failure and fatality[39]. Although, elevated release of cytokines and immune cells hyper-activation may also occur in several other pathogens infection or cancer cells, therapeutic applications, autoimmune disease and monogenic circumstances [40]. Cytokines play critical roles in the immune system in health and disease acting in concert in definite ways as part of the immune response to the presence of pathogens including signaling the activation of B-cells and T-cells, macrophages, mast cells, neutrophils, basophil and eosinophils [41-43].During malaria infection, the host immune defense systems often possess the capacity to resist the establishment of parasitaemia and destroy the parasites. However, malaria parasitesendowments with a number of evasiveschemes enable them toescape phagocytic destruction by the immune system [44-46]. The modification of surface antigen protein and release of biochemical molecules including toxinsthat aid parasite penetration intothe host's red blood cells, intra-cellular nature of the parasites, as well as formation of rosette with uninfected red blood cells shield them from ready destruction [47-49].In addition, there is also the interference with the host immune system's ability to function leading to the inhibition of T-cells' tasks and depression of cytotoxic T-lymphocyte antigen-4, CTLA-4that is critical in T-cell protein regulation [50]. The possession of multi-gene antigenic locus enable the parasites to remodel the variant surface antigen, VSA protein (*var*) initially recognized by the host immune system leading to sterile immunity[51,52]. This thus, shifts the host immune responseto subdued pro-inflammatory response tohigher anti-inflammatory reaction, adduced to be responsible for the maintenance of equilibrium between pro-inflammatory and anti-inflammatory cytokines activation resulting in the absence of symptoms or tolerance accompanying asymptomatic malaria parasitaemia [27,53]. This scenario ultimately leads to insufficiency of the naturally acquired immunity to protect the

host against transient malaria infection [54]. Although, many of the adult population in endemic areas develop immunity due to repeatedexposure that is helpful incurtailingparasitaemia density,consequently, theimmunity so developed affords no protection against subsequent infections [55-57]. This forms the basis of the higher morbidity and mortalityseen in malaria cases in children under the age of five years due to naïve immune systems, in pregnant women and immuno-depressed individuals [60]. Asymptomatic parasitaemia often persists for lengthy phases,subsequently leading to symptomatic malaria due to failure in immune function regulation [29,31].

## Conclusion

The perpetuation of malaria cycle of infection emanates fromasymptomatic malariaparasitaemia in endemic settings. The interference of the parasites with the host immune response systems through a balancing act involving suppression of pro-inflammatory and heightened anti-inflammatory cytokines and the resultant absence of symptoms due to the parasitaemia are key contributory factors in the failure of malaria control, elimination or eradication strategies.Therefore, the design of novel strategies to track and prevent asymptomatic malaria in endemic regions is desirable in winning the war against malaria globally.

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