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REVIEW ARTICLE

The Role of Microbiome in Malaria Transmission and Severity

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Abstract

Malaria is a public health concern, especially in Sub-Saharan Africa. Several malaria control programs to treat, control, and eradicate malaria have been implemented, however, more than 90% of malaria-related deaths in under five years occur in Africa. With the emergence and spread of artemisinin-resistant P. falciparum, global malaria control now focuses on vaccine development and a search for novel and efficient antimalarial drugs. Although current evidence shows host microbiota play a significant role in malaria transmission and disease severity, little attention has focused on advancing the understanding of the role played by microbiome in malaria infection and the pathogenesis of the disease. This review discusses the interplay between malaria and host microbiomes and their role in malaria transmission and disease severity. Microbiota is known to regulate malaria survival, and fertility, control transmission and modulate immunity against malaria infection. Thus, advancing the study of the interaction between malaria infection and microbiome could broaden the therapeutic advancement and the discovery of new and potent antimalarial drugs to tackle the various aspects of malaria infection and block malaria transmissions.

Keywords

Plasmodium falciparum, Microbiota, Malaria transmission, Disease severity, Novel antimalarial drug discovery, Malaria immunity, Immune escape

Introduction

Malaria is a parasitic disease that affects humans globally [1]. Five causative organisms, *P. falciparum*, *P. malariae, P. ovale, P. vivax* and *P. knowlesi*, infect humans. Malaria kills over 660,000 people annually, mostly children under five years [2]. *P. falciparum* is the most virulent malaria parasite and is predominantly transmitted by the Anopheles gambiae vector in Sub-Saharan Africa [1,3-5].

The transmission of parasites across vertebrate and invertebrate hosts involves a series of complex interactions that allow the parasite to survive, invade and replicate in different cells and tissues. Mosquitoes ingest sexual forms of malaria parasites (macrogametocytes and microgametocytes) that fuse to form gametes in the midgut. The gametes develop into sporozoites that invade the salivary glands. Malaria parasites adapt to the host environmental niche inhabited by a community of microbes (microbiota). The host-microbiota plays a crucial role in the pathophysiology of invading pathogens (Table 1). The symbiotic interactions between microbiota and pathogenic organisms contribute to the acquisition of disease resistance or abiotic stress tolerance in both invertebrate and vertebrate hosts [6]. The microbiota composition of the mosquito's midgut and salivary glands determines the capacity of a mosquito to transmit pathogens and is affected by the mosquito's immunity, longevity, fertility, and metabolism [7-10]. Bacteria inhabit almost every part of the female *Anopheles* mosquito, the vector of malaria [11-13]. Bacteria-malaria parasite interactions either promote or inhibit survival and growth in the midguts of vectors [14,15].

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Table 1: Common microbes involve in vector and host microbiota and infected *Plasmodium* species.

	Vector microbiota		Host microbiota	
	Inhibition	**No Inhibition**	**Skin**	**Gut**
P. falciparum	General microbiota: *Pseudomonadaceae, Enterobacteriaceae, Aeromonadaceae, Comamonadaceae, Moraxellaceae*, *Cyanobacteria*, *Serrratia* Vector specific microbiota*:* *An. Stephensi: Escherichia coli* H243; *Pseudomonas aeruginosa*; *Ewingella americana; E. coli* HS5; *P. aeruginosa*; *Serratia marcescens*; *Xanthomonas malthophila*; *Cedecea lapagei* *An. gambiae: S. aureus, E. coli, Enterobacter* sp.*, Chromobacterium* sp.*, P. putida*; *Pantoea* sp.; *S. marcescens, Serratia*; *Methylobacterium* *An. coluzzii: E. coli*; *S. marcescens*; *Pseudomonas sutzeri*; *Comamonas* spp.; *Enterobacter* spp.; *B. pumilus*	*An. Stephensi: Staphylococcus aureus*; *S. epidermidis*; *E. coli* HB101 *An. gambiae: Bacillus pumilus* *An. coluzzii: Acinetobacter septicus*	*Corynebacteria, Staphylococcus, Propionibacterium, Micrococcus, Pseudomonas, Brevibacterium* species, *Pityrosporum, Pityrosporum*	*Enterobacter*, *Enterococci*, *Bifidobacterium, Bacteroides*, *Clostridium, Firmicute, Bacteroidetes, Proteobacteria, Actinobacteria*, *Verrucomicrobia*
P. vivax	*Enterobacter, Serratia* *An. albimanus: S. marcescens; Enterobacter cloacae; Enterobacter amnigenus*			
P. berghei	*An. gambiae*, and *An. coluzzii: S. aureus*; *E. coli*; *E. cloacae* *An. stephensi: S. marcescens* HB3	*An. stephensi: S. marcescens* HB18		
P. yoelii	*An. gambiae: Pseudomonas aeruginosa*, *Ps. vesicularis* and *Cedecea lapagei*.			

The mosquito feeding patterns, risks and severity of malaria infection are affected by human microbiota [16-20]. The recognition that malaria parasites interact with the host microbes to establish infection and virulence at various stages of the parasite life cycle has attracted the interest of researchers and clinicians. Understanding the specific role played by the host microbiome in malaria transmission and pathogenesis is critical for developing strategies for the prevention, control, and eradication of malaria globally. The review discusses the significance of microbiota in malaria transmission and severity.

The Mosquito Gut Microbiota and Malaria

Microbiota may have several metabolic effects that are often detrimental to invading pathogens. However, changes in the microbiota composition may increase susceptibility to infectious and non-infectious diseases [21]. The clinical manifestations of pathogenic infections may be affected by the host microbiota and the host immune system [22]. Microbiota modulates pathogenic infections by augmenting the innate and adaptive immune system [23] and plays a variety of functions ranging from food supplementation, improvement of digestive systems, toleration of environmental disturbances, protection against parasites, enhancement and maintenance of homeostasis of the host immune system [24]. In the mosquito vector, the microbiotas play a role in nutrition, development, and reproduction [4], such that a change or removal in microbiota composition in mosquitoes could reduce fitness and the phenotype of the mosquito host [25].

Bacteria are the most prominent microbiota found in mosquitoes and are predominantly found in the digestive tract of mosquitoes. *Acetobacteriaceae* are the most dominant bacteria that affect both wild and laboratory-raised colonies of Anopheline and Aedes mosquitoes [26].

The mosquito midgut harbours digestive enzymes and an innate immune system that inhibit disease transmission [27,28], by influencing the susceptibility of the insect to diseases such as *Plasmodium* infection [29-32]. Although the microbiota might protect mosquitoes from pathogenic infections [10,33], organisms such as viruses, helminths and protozoans have devised ways to take advantage of the gut microbiota to spread [34,35]. The *Enterobacteriaceae* and *P. falciparum* infections in mosquitoes suggest possible bacteria-parasite interactions playing a role in malaria parasite development [10,33]. Both laboratory-cultivated and field-collected mosquitoes harbour varieties of bacteria such as *Asaia*, *Enterobacter*, *Mycobacterium*, *Sphingomonas*, *Serratia* and *Chryseobacter* in their midgut [36,37].

Variations in Mosquito Gut Microbiota

Mosquitoes harbour a diverse microbial flora that contributes to the expansion of the mosquito gene pool [33]. The mosquito-microbiota genotypes interaction influences the variations in the specific immunological phenotypes and the adaptation of gut microbes. The mosquito gut microbiota comprises prokaryotes, viruses, and eukaryotic microorganisms that shape diversity in vector competence across diverse mosquito-borne diseases and pathogenic species. *Bacteroidetes, Proteobacteria, Actinobacteria,* and *Firmicutes* are the major microbiota in the midgut of adult mosquitoes [38]. Mosquito populations in different geographical settings exhibit different levels of parasitic diseases or parasite-specific infections, suggesting a possible role of inhabited microbiota in the transmission of parasites [34,39]. The presence of interspecific rivalry, the generation of poisons and inhibitory substances and specific bacterial taxa may render the mosquito midgut inhospitable for some bacteria or malaria parasites. Mosquito bred in different locations exhibits diverse midgut bacteria compositions suggestive of the environmental role in gut microbiota, nutritional status, developmental stages and mosquito species [10]. Mosquito gut microbiota may have been influenced by the consumption of aquatic bacteria by larvae, alkaline (pH range of 8 to 11 & high quantities of carbonate ions) and favours the establishment of a subset of bacterial infections, similar to humans [40-42]. Factors such as redox potential, specific nutrients and proteolytic enzymes in the gut, early colonists, and selective pressures determine the mosquito gut microbiota [43]. The novel bacterial community shaped by maternally transmitted germs may compete with the new colonists. For instance, maternally inherited bacteria compete with *Asaia* in the reproductive tract of the Asian malaria vector, *Anopheles stephensi* [44-48]. Although all mosquito species typically consume blood and nectar, some mosquito species exhibit marked variations in their preferred larval habitats and sugar, and blood meal hosts, which may pre-expose them to different microbes. Such may partially explain the observed differences. The midgut microbiota may enhance parasite infection, showing that *Plasmodium falciparum* development in the *Anopheles gambiae* mosquito depends on complex vector-microbes-parasite interactions [33].

Effects of Mosquito Gut Microbiota on Malaria Transmission

Transmission of malaria depends on the success of the several transitional stages that the malaria parasites go through in the midgut during a series of intricate developmental stages [49,50]. The development from motile ookinetes to oocysts migrates through the midgut epithelium, most oocysts die when resting under the basal lamina of the midgut wall [50]. The microbiota could influence the parasite's development and viability from the ookinete to the formation of oocyst and penetrating midgut epithelial cells [24]. The gut microbiota and the metabolic by-products determine the pathogenic effects of a compromised gut barrier [51]. The microbiota decreases mosquito vulnerability to *Plasmodium* infections by stimulating mosquito immunity, forming a physical barrier and producing reactive oxygen species to inhibit *Plasmodium* infection [9,15]. There are variations in the vulnerability of wild *Anopheles* populations, and these observed variations are associated with the presence or absence of specific gut microbiota [9]. Also, only a few fractions of the natural *Anopheles* population carry specific gut microbiota [9]. The *Anopheles gambiae* and *Anopheles funestus* in the field harbour 16 bacterial species among the 14 genera [52]. The ability of the microbiota to control the malaria parasite infections as well as alter the mosquito lifespan suggests that the gut microbiome could prevent malaria transmission [37,53,54]. Gram-negative bacteria such as *Enterobacter Esp Z*, *Chromobacterium Csp*, and *Serratia marcescens* in the midgut of *Anopheles* mosquitoes inhibit *P. falciparum* development [9,55-57]. Furthermore, *Wickerhamomyces anomalous*, a yeast from the midgut of *Anopheles stephensi*, produces a lethal toxin which suppresses *P. berghei* ookinetes in the presence of 1-3-glucanase *in vitro* [58]. Also, chitinase secreted by *Plasmodium* ookinetes allows the crossing of the peritrophic matrix [57,59]. Thus, barrier or bacteria toxins may put selection pressure on malaria parasites.

The Human Microbiota

Humans harbour complex communities of symbiotic microbes such as bacteria, archaea, viruses, and fungi. The gastrointestinal microbiome contains roughly millions of distinct genes, mostly from bacteria. Factors such as gestational age, diet, antibiotics exposure, probiotics usage and nutritional supplements, hygienic conditions, host genetics, and host immune system

could influence the microbiota. The human microbiome is essential for the immune system, the brain, nutrition, and metabolism [60]. Antimicrobial drugs such as antimalarials or antibiotics may poison gut microbial ecosystems and the normal physiological function of the microbiota [61,62].

The Human Gut Microbiota and *Plasmodium* Infections

The gastrointestinal microbiota constitutes about 70% of all human microbiota. The bacterial population is diverse and has been associated with several disease conditions such as malnourishment and allergies, and has a severe impact on cognitive and physical development [63-65]. The *Enterobacter*, *Enterococci*, *Bifidobacterium, Bacteroides*, *Clostridium, Firmicute, Bacteroidetes, Proteobacteria, Actinobacteria*, and *Verrucomicrobia* dominate the gut microbiota [59,66-68]. The small intestines contain monosaccharides, disaccharides and amino acids and harbour *proteobacteria, Lactobacillales, Enterococcus*, and *Akkermansia*, and the lumen harbours *Enterobacteriaceae* and *Bacteroides*, *Bifidobacterium*, *Streptococcus*, *Enterococcus, Clostridium, Lactobacillus*, and *Ruminococcus* [67,69]. The gut microbiota also includes virus such as bacteriophages (Picornaviridae, Reoviridae, Astroviridae and Caliciviridae) which has a nonpathogenic relationship with the human host [70]. The bacteriophages produce lysogenic and lytic substances for prevalent viral infections in healthy human tissues [70].

The gut microbiota, environmental factors and genetic variations are associated with variabilities in the clinical episodes of *Plasmodium* infections [71]. Frequently, *Bifidobacterium* and *Streptococcus* species isolated from the gut of people with no *P. falciparum* infections, are known to offer resistance to malaria infection. Similarly, *Lactobacillus* and *Bifidobacteria* species protect mice from *P. yoelii* infection. Their protective effects are, however, affected by diet alterations and probiotic administration. The microbiota may alter T cell and B cell responses that could induce resistance to malaria infection [23]. The gut microbiota differentially expresses toxic metabolites in severe malaria in human and animal models that could be detrimental to malaria parasites [72,73]. Blood-stage malaria parasites are more vulnerable to metabolic dysregulation driven by either antimalarials or the microbiota [74].

Malaria and Mammalian Gut Microbiota

Microbiota and bacterial communities influence the severity of malaria [75]. The cardinal symptoms of diarrhoea and abdominal discomforts associated with *Plasmodium falciparum* infection result from pathological alteration of the gut [76]. Malaria infections cause changes in villi and lead to bleeding of mucosal tissues due to rupturing [77]. Human cases of severe *falciparum* malaria increase intestinal permeability [78]. This alteration of the gut environment influences the progression of malaria infection [76]. The severity and disease progression of *Plasmodium* infection in C57BL/6 and BALB/c mice coincides with the extent of alteration in gut microbiota [76]. *P. yoelii* 17XNL and *Heligmosomoides polygyrus* coinfection protect mice from fatal malaria infections [79]. Tomoyo and associates have shown that severe intestinal pathology during malaria is associated with changes in the microbiota [76]. Different bacteria communities modulate malaria infections and disease severity differently. For instance, *Lactobacillus* reduces parasitemia and causes milder cerebral malaria [76]. Hence, the vulnerability of individuals to *Plasmodium* infections, disease subtypes, and mosquito affinity is related to gut microbiome dysbiosis [16,80,81]. Although variations in immune response and host genetics play a role in parasite defence, the current information shows that gut microbiota significantly affects the transmission and development of malaria [22,82].

The Skin Microbiota and Mosquito Attraction

The skin forms the first line of defence against environmental and pathogenic exposures [83]. The skin microbiota varies among individuals and is affected by individual behaviour, genetic makeup, age, sex and environmental factors [84-87]. These factors indirectly influence the choice of mosquitoes to their prospective human hosts for disease transmission [85]. Individuals produce volatile odour substances [88] which are modified by the skin microbiota and vary among individuals and their exposure to mosquito vectors. The skin microbiota produces odour by breaking down substances into by-products such as methyl ketones, carboxylic acids and linear alcohols, and these odours serve as chemical signals to draw mosquito vectors to the host [83,89,90]. The strength of odour is associated with specific bacteria compositions [90-96]. Female mosquitoes use unique olfactory profiles to detect host-derived chemical and physical signals (such as heat and visual cues) to determine hosts of choice [16,97-99]. The vector-host feeding interaction influences the transmission of the disease [100,101].

The various skin microbes have unique metabolic pathways and by-products [83], and early studies showed that *Corynebacteria* distinctively produced apocrine odour from volatile fatty acids, whiles *Staphylococcus* species convert branched-chain amino acid residues into short-chain which are extremely odorous and volatile [102]. Anthropophilic anopheline mosquitoes that transmit malaria to humans exhibit variations in their attraction to different individuals [88]. The unique composition of skin microbiota impacts the distinctive odour profiles of individuals [88]. A previous study reported that female *Anopheles gambiae sensu stricto* is attracted to sweat samples incubated under aerobic conditions [80]. Similarly, female *Anopheles gambiae* is

more attracted to lures made from skin microorganisms from the feet of healthy individuals than the control traps made of sterile agar and clean air with or without carbon dioxide [81]. *Corynebacterium, Staphylococcus, Propionibacterium, Micrococcus, Pseudomonas, Brevibacterium* species and *Pityrosporum* species are possible skin microbes that produce chemoattractants. *Pseudomonas aeruginosa* and *Staphylococcus epidermis* are essential bacteria species that determine the attractiveness of mosquitoes to the host [80,103]. Verhulst, et al. showed that people who are attracted to mosquitoes had a less varied microbiome [89]. Also, individuals with *Pseudomonas* poorly attract mosquitoes [83]. This pattern of intraspecies variations in mosquito attraction is essential for pathogen exposure and transmission. Thus, individuals that attract mosquitoes more frequently have a high risk of contracting a pathogen carried by a mosquito and promoting its spreading [83].

Microbiota and Immunity in Malaria

Microbiota interacts with malaria infections by producing inhibitory bioactive toxins and enzymes or stimulating the host immune system [24]. Surface glycan Gal-13 Gal-4 GlcNAc (-galactosyl) expressed by *Enterobacteriaceae; Klebsiella, Serratia,* and *Escherichia* induces the host to produce anti-galactosyl antibodies that interact with *Plasmodium* sporozoites and inhibits hepatic invasion [104,105]. A study revealed that Malians with high anti-galactosyl immunoglobulin M (IgM) have a low occurrence of *P. falciparum* infection [104]. *Streptococcus, Bifidobacterium, Escherichia* and *Shigella* provide cross-protection against *P. falciparum* infection [82]. Microbe-stimulated antibodies opsonize *Plasmodium*-parasitized erythrocytes and process them for spleen clearance [75]. Also, the recruitment of phagocytic cells by *Bifidobacteriaeceae* could regulate outcomes in malaria [106,107]. The peptidoglycan recognition protein (PGRP) family functions as pattern recognition receptors and effectors for innate immunity and regulates microbial growth and parasite infection in mosquitoes [108]. The host immune response to blood-stage malaria parasites involves RBC sequestration and systemic-induced IL-1β, IL-6, IL-8, IL-12p70, interferon (IFN)-γ, and tumour necrosis factor-α (TNF)-α pro-inflammatory cytokines and chemokines (e.g., interleukin IL-1β, IL-6, IL-8, IL-12p70, interferon (IFN)-γ, and tumour necrosis factor-α (TNF)-α) and innate immune cells such as natural killers (NKs), mast cells, neutrophils, and antibodies. Previous studies showed that the lack of interleukin-21 (IL-21) signalling within the spleen leads to impaired clearance of *Plasmodium* infection. T follicular helper (Tfh) and germinal centre (GC) B cells are critical in developing immune antibodies against *Plasmodium* species.

The disruption of IL-21 inhibits the production of immunity by Tfh cells leading to sustained high parasitemia. The Tfh cell disruption in mice infected with *P. yoelii* is able to self-resolve chronic *P. chabaudi* infection. Impaired Tfh differentiation and inefficient GC responses cause severe malaria infection. IFNγ and IL-10 cytokines affect the humoral immune response to *Plasmodium* and control parasite control and host survival. The spleen germinal centre (GC) activation and coordination of humoral immunity are responsible for clearing *Plasmodium* infection. The clinical presentation of malaria depends on a balance between pro-inflammatory and regulatory cytokines such as IL-10, transforming growth factor beta (TGFβ), and regulatory T lymphocytes, IL-10-producing T lymphocytes immune cells.

The microbiota prevents malaria transmission by inducing anti-α-gal IgM and IgG (IgG2b, IgG3) in the skin to employ an immune complement pathway to inhibit liver invasion and sporozoites transmission. CD8+, CD4+, and T cells in the skin and the liver are adaptive immune factors that target antigens specific to intracellular pathogens and act as initial sterilizing immunity. IFN-γ, TNF, and IL-2 inhibit the early stages of malaria parasites and protect against sporozoites and blood-stage antigens. The NK, NKT, γδT cells and macrophages induced by microbiota in the peripheral blood circulation stimulate nitric oxide and nitric oxide synthase. The gut microbiota downregulates IL-1β, IL-6, IL-8, and IL-12 to control blood-stage malaria parasites. TGF-β and IL-10 regulatory cytokines reduce malaria parasitaemia and Treg, DCs balance the immune system and present parasites to the T cells and the activation of B cells for parasite clearance.

The cross-talk of host-microbiota-malaria immunity can modulate the risk of *Plasmodium* infection, transmission and disease severity. Understanding the immune interaction between the host-microbiota and malaria infection could give insight into an innovative approach to preventing and managing malaria in endemic countries.

Malaria, Antibiotics, and the Microbiome

Sub-optimal antibiotics treatment of microbiota promotes dysbiosis and affects mosquito gut bacteria [109-111]. Notably, the addition of a cocktail of streptomycin and penicillin to mosquito blood meals enhanced insect survival, fertility, and toleration of *Plasmodium* infection [112]. Exposure of high doses of doxycycline to gut microflora resulted in increased *P. falciparum* infection load, similar to the effect of penicillin-streptomycin [112,113]. However, azithromycin or co-trimoxazole treatment is detrimental to both midgut microbiota and the *Plasmodium* infection. Thus, characterizing antibiotic usage could be a novel method for controlling malaria transmission.

A previous study suggested that malaria may predispose to bacteraemia as acute *P. falciparum*

malaria causes widespread immunosuppression and decreases macrophage functionality to phagocytosis-infected parasites [114,115].

Future Perspective

Mosquito-transmitted epidemics like malaria, yellow fever, dengue fever, chikungunya fever and Zika fever cause roughly 350 million illnesses and 500000 fatalities worldwide each year [116]. Considering that the majority of these diseases lack an effective vaccination [117], one of the most effective methods to prevent disease is vector control [118]. Rapid scientific advancement in the study of the microbiome has invented different therapeutic possibilities and revived "primitive techniques" that target the microbiota and may be useful in the fight against infectious diseases. The impact of microbiota and invasive pathogens on mosquito capacity to transmit malaria parasites in contrast to the parasite itself provide new approaches for malaria biocontrol [119]. The application of microbes to prevent the spread of malaria has drawn attention worldwide. A high-tech method based on genetically altered mosquitoes has several advantages over a low-tech one when used as a control strategy. These include mass manufacturing of *in vitro* cultures, the ability to store and transfer products to remote locations, the absence of evolutionary pressure, mosquito population coverage, the absence of side effects, and needless genetic change [120]. The positive outcomes of the microbiota and mosquito-derived microbiota could be used as biological agents against the *Plasmodium* species and/or its mosquito vectors. Also using synthetic microbes to modify the genetic composition of *Anopheles* vectors may help reduce the spread of malaria [119]. Entomopathogenic fungi such as *Beauveria bassiana* (Bals. -Criv.) Vuill. and *Metarhizium anisopliae* Metschn. have been proposed as biological control agents for malaria [121]. Recent research has shown the value and possibility of using permethrin and entomopathogenic fungi together as pesticide resistance prevention measures for vectors *Angambiae s.l*. [122,123].

Conclusion

Understanding the role microbiota play in the transmission, control of malaria infections (symptomatic and asymptomatic) through the modulation of vector and host immunities has become essential with the emergence and spread of artemisinin-resistant *P. falciparum.* The microbiota has been shown to affect malaria survival and fertility, as well as control transmission and alter immunity to malaria infection. Thus, furthering the study of the interaction between malaria infection and microbiome could extend therapeutic progress and the identification of novel and strong antimalarial medications to address the various aspects of malaria infection and block malaria transmissions.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All the data are available in the manuscript.

Competing interests

The authors declare no competing interests.

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Authors' contributions

Conceptualization, KKA; Methodology, KKA, PED; Supervision, KKA; Writing – original draft, PED; Writing – review & editing; KKA, PED.

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