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Female *Anopheles* Mosquito Gut Microbiota: Description and Impact on Transmission of *Plasmodium* Parasite

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Abstract

***Malaria, primarily caused by* Plasmodium falciparum, *remains a significant public health concern, particularly in sub-Saharan Africa. While vector control interventions and antimalarial treatments have reduced transmission in some regions, their long-term efficacy is threatened by increasing resistance to insecticides and antimalarial drugs. This review examines the emerging role of mosquito gut microbiota in shaping vector competence and influencing* Plasmodium *development, with the goal of identifying microbiota-based approaches as complementary tools for malaria control. A comprehensive literature review was conducted using peer-reviewed publications from microbiology, vector biology, immunology, and disease ecology. Key focus areas include the structure and diversity of* Anopheles *gut microbiota, their immunomodulatory functions, interactions with* P. falciparum, *and potential applications in paratransgenesis and biological vector control. The mosquito gut microbiota, dominated by genera such as* Serratia, Pseudomonas, Enterobacter, *and* Wolbachia, *plays a pivotal role in modulating immune pathways (Toll, IMD, JAK-STAT), producing antiparasitic metabolites, and forming physical barriers to parasite invasion. Microbial disruption enhances the susceptibility of mosquitoes to* Plasmodium, *while specific bacteria confer resistance. Environmental and genetic factors significantly shape microbiota composition, with consequences for mosquito physiology and vectorial capacity. Symbionts like* Wolbachia *have shown promise in reducing parasite loads and blocking the transmission of diseases. Targeting the mosquito gut microbiota presents a novel and sustainable strategy for reducing* P. falciparum *transmission. Microbiota-based interventions may enhance existing malaria control programs and help counteract the growing challenge of resistance.*

***KEYWORDS:** Mosquito gut microbiota, Plasmodium falciparum, Vector competence, Malaria transmission, Paratransgenesis.*

INTRODUCTION

Malaria is caused by *Plasmodium* parasites, which are transmitted to humans through the bite of an infected female Anopheles mosquito (Mezieobi *et al.*, 2025). WHO estimates 263 million malaria cases occurred globally in 2023, where 94% of all global cases occurred in Africa, and Nigeria is among the five countries with 52% of the global burden and 39·3% of all global malaria deaths in children under 5 years occurring in Nigeria (Venkatesan, 2025).

The Anopheles mosquito species acts as the vector for the human *Plasmodium* parasite in Africa, and the primary vectors include *Anopheles gambiae. arabiensis, An. coluzzi, An. mouchetti, An. funestus, An. melas, An. merus,* and *An. nili,* all of which significantly contribute to malaria transmission across the continent where *An. Plasmodium falciparum, the most abundant and deadliest species, harbors the deadliest form of Plasmodium, which causes falciparum malaria with numerous* symptoms within hours of infection, leading to severe complications such as brain swelling, anemia, and organ failure (Vinayagam *et al.*, 2023).

Four main Plasmodium species that cause malaria in humans: *Plasmodium falciparum*, *P. ovale*, *P. vivax*, and *P. malariae*, with an additional zoonotic species, *P. knowlesi*, also affecting humans (Kalappa *et al.*, 2018). Weakened healthcare systems drive the rise in malaria cases, increased insecticide resistance in mosquitoes, and anti-malarial drug resistance. The World Health Organization considers malaria the most epidemiologically

significant vector-borne disease worldwide (Ezemouka *et al.*, 2020).

Malaria causes severe, life-threatening illnesses that pose substantial health risks, particularly in the most affected regions, such as sub-Saharan Africa, where the highest cases and mortality rates are recorded. Malaria is especially dangerous in children under five and pregnant women, leading to severe neurological and cardiopulmonary outcomes and heightened health risks (World Health Organization, 2020).

Insect gut bacterial diversity is determined by environmental habitat, diet, developmental stage, and phylogeny of the host (Fazal *et al.*, 2023). The gut microbiota of insects not only contributes to nutrition, protection from parasites and pathogens, modulation of immune responses, and communication, but also affects insect growth, development, survival, and fitness. The interaction between disease transmission and the mosquito gut microbiota is dependent on the mosquito species and the specific diseases (Liu *et al.*, 2023).

The mosquito microbiota has been identified as a key component in determining the development of the malaria parasite in the mosquito midgut, as well as in mosquito resistance to the parasite and the cost of parasite infections in terms of survival rates. (Garrido *et al.*, 2023).

One of the primary strategies to combat malaria focuses on targeting the vector, which has significantly reduced malaria cases across Africa and the current vector control efforts mainly use chemical insecticides through insecticide-treated nets (ITNs) with pyrethroids and indoor residual spraying (IRS) with organophosphates and carbamates, where the goal of these conventional methods were to reduce mosquito populations below the threshold needed for disease transmission or to limit human-vector contact (Djihinto *et al.*, 2022). In Africa, the primary malaria vectors include *Anopheles gambiae, An. arabiensis, An. coluzzii,* and *An. funestus*, along with the recently identified urban vector, *An. stephensi* (Sinka *et al.*, 2020). Unfortunately, resistance to these commonly used insecticides is now widespread among natural mosquito populations. Evidence of increasing insecticide resistance in malaria vectors is undermining the effectiveness of vector control programs (Mekuriaw *et al.*, 2019).

The midgut of the mosquito is important not only for digestion and uptake of nutrients but also as the entry site of pathogens including *Plasmodium* parasites and when *Anopheles* mosquitoes ingest *Plasmodium*-infected blood from the host, parasites mate and develop into motile ookinetes within 16–20 h , Ookinetes traverse across the midgut epithelium within 24 h after the feeding and transform into oocysts on the basal side of the midgut. Sporozoites develop and proliferate within oocysts over approximately the next 10 days. The sporozoites released from oocysts then invade the salivary glands, where they await transmission to the next host via a mosquito bite (Kalappa *et al.*, 2018). The early phase of the parasite infection, specifically the invasion into the midgut epithelium, is the bottleneck for the parasite in the mosquito cycle and, therefore, is considered a suitable target for a transmission-blocking strategy of P*lasmodium falciparum* (Mizushima *et al.*, 2023).

Anopheles Gambie Complex

There are over 400 species of Anopheles mosquitoes, with around 30 recognized as significant vectors for malaria transmission. All primary malaria-carrying species are nocturnal, primarily biting between dusk and dawn (WHO, 2019). Female Anopheles mosquitoes lay their eggs in water, where the larvae emerge and develop into adult mosquitoes where the females require a blood meal to nourish their eggs and each species has specific aquatic habitats for egg-laying; for example, some prefer small, shallow pools of fresh water, such as puddles or hoof prints, which are abundant during rainy seasons in tropical areas (WHO, 2019).

Malaria transmission is more intense in areas where the mosquito lifecycle is prolonged, allowing the parasite sufficient time to mature within the mosquito, and where mosquitoes exhibit a strong preference for human blood over that of other animals. The prolonged lifecycle and high frequency of human-biting behavior in African Anopheles species are key factors behind the high malaria burden in Africa, accounting for nearly 90% of global cases (WHO, 2019).

Many species of Anopheles mosquitoes belong to species complexes, groups of closely related species that are often difficult to differentiate morphologically. The Anopheles gambiae complex, for instance, includes at least nine species, three of which are critical malaria vectors in sub-Saharan Africa*: An. gambiae s.s., An. coluzzii, and An. arabiensis.* Remarkably, a new member, *An. fontenillei*, was added to this

complex in 2019 (Loughlin, 2020). In Africa, these Anopheles species are among the most efficient malaria vectors globally (Yawson *et al.*, 2004). This efficiency is attributed to their adaptation to human habitats, their preference for human blood for egg production, and their high susceptibility to the malaria parasite. *Anopheles gambiae*, often referred to as the "African malaria mosquito," is notably the most effective vector of human malaria in the Afro-tropical region (CDC, 2010).

The primary aim of the review was to critically examine the role of mosquito gut microbiota in the development and transmission of *Plasmodium falciparum* and its potential as a novel target for malaria control strategies. Specifically, the study explored the interactions between mosquito-associated microbial communities and *P. falciparum*, and how these interactions influence vector competence, immune responses, and the effectiveness of conventional control methods.

Despite global efforts to reduce malaria incidence through vector control and antimalarial therapies, the disease remains a significant public health burden, particularly in sub-Saharan Africa (Suh *et al.*, 2023). The increasing resistance of mosquitoes to insecticides and of parasites to antimalarial drugs necessitates innovative and sustainable control strategies (WHO, 2023). Recent research suggests that mosquito gut microbiota plays a crucial role in determining vector susceptibility to *Plasmodium* infection and in regulating immune responses (Gabrieli *et al.*, 2021). By understanding the complex interactions between the microbiota, mosquito, and parasite, researchers can identify novel biological control strategies, such as microbiota manipulation or paratransgenesis, which may complement existing interventions and offer long-term, ecologically viable solutions to malaria transmission (Vinagayam *et al.*, 2023)

The study adopts a narrative literature review approach, synthesizing current findings from peer-reviewed articles, scientific reports, and authoritative sources published primarily in the last two decades. Relevant publications were identified through comprehensive searches in scientific databases such as PubMed, ScienceDirect, and Google Scholar using keywords including "mosquito microbiota," "*Plasmodium falciparum*," "vector competence," "paratransgenesis," "*Anopheles* immunity," and "malaria transmission." Emphasis was placed on experimental studies demonstrating the microbiota's influence on *Plasmodium* development, microbial-mediated immunity, and mosquito fitness. Cross-species comparisons were included and where relevant (e.g., *Aedes* or *Culex*), to highlight conserved microbiota-related mechanisms. The review also considered the impact of environmental, genetic, and ecological factors on mosquito microbiome composition and how these affect vectorial capacity.

Mosquito's Gut Microbiota

The gut microbiota of mosquitoes includes a dynamic community of prokaryotic and eukaryotic organisms, primarily acquired from the environment (Wang *et al.*, 2017). Its composition varies widely based on the mosquito's species, diet, developmental stage, and geographical location (Fazal *et al.*, 2023). The mosquito's gut, salivary glands, and reproductive organs are colonized by microbes, including bacteria, viruses, and fungi, with bacteria being the most extensively studied (Pidiyar *et al.*, 2004). This microbiota influences malaria transmission by interacting with *Plasmodium* parasites in the gut and impacting mosquito physiology, notably affecting lifespan and disease transmission (Romoli & Gendrin, 2018).

The presence of these microbes can interfere with *Plasmodium* infection and influence mosquito fitness, which in turn affects the mosquito's capacity to transmit malaria. This natural microbial barrier has gained substantial interest over the past two decades as a potential tool for new malaria-blocking strategies (Romoli & Gendrin, 2018).

The mosquito gut microbiome plays a critical role not only in host development but also in reducing *Plasmodium* infection rates and potentially shortening mosquito lifespans as this may occur through natural processes or be influenced by paratransgenic interventions, suggesting that mosquito-associated microbiota could serve as an innovative approach to malaria control (Vinayagam *et al.*, 2023).

The midgut microbiota plays a particularly crucial role, where dominant bacterial genera such as *Pseudomonas*, *Serratia*, and *Wolbachia* are commonly observed (Wang *et al.*, 2011). Microbiota can impact the development of mosquitoes and influence their ability to transmit pathogens through changes in physiology and immune system regulation (Coon *et al.*, 2016).

The midgut of mosquito's microbiota enhances its resistance to *Plasmodium* infection by forming a physical barrier after a blood meal, which inhibits parasite penetration of the gut wall (Grogan *et al.*, 2021). Additionally, bacteria in the midgut may produce antimicrobial compounds or induce oxidative stress, directly targeting the parasite. This microbial interaction with the mosquito's immune system presents promising pathways for reducing malaria transmission (Singh *et al.*, 2022).

Interactions between the Microbiota, *Plasmodium*, and Mosquito.

Some microorganisms isolated from the mosquito gut produce metabolites that can directly inhibit *Plasmodium*, reducing its infectivity within the mosquito host (Romoli & Gendrin, 2018). Mosquitoes, sand flies, tsetse flies, and triatomines, each with distinct biology, behavior, and ecological niches, host a unique core microbiota. These differences in microbial communities result in varied interactions among microbiota, parasites, and host systems. According to Omondi and Caner (2022), parasite-microbiota interactions generally result in three key outcomes: (i) disruptions in gut microbiota can either increase or decrease parasite survival and disease severity in the host; (ii) parasite infections can reshape the host's microbial composition; and (iii) both microbiota and parasites can influence the host's metabolism and immune responses.

Furthermore, microbiota play crucial roles in vector biology, affecting aspects like innate immunity, reproduction, feeding behavior, and overall vectorial capacity. This influence extends to the pathogenicity and virulence of parasites such as *Plasmodium*, *Leishmania*, and *Trypanosoma cruzi* in mammalian hosts. However, the specific mechanisms through which parasite-microbiota interactions facilitate the development and transmission of these infections are still not fully understood (Omondi & Caner, 2022).

Impact of the Microbiota on the Vectorial Capacity of Mosquito

The concept of vectorial capacity, which measures a vector population's potential to transmit a pathogen, remains central to understanding the dynamics of disease spread. Originally defined by Garret-Jones in 1964, vectorial capacity has evolved to incorporate various environmental, behavioral, and ecological factors affecting mosquito species. Recent studies have highlighted vectorial capacity as an outcome influenced by mosquito behavior, habitat interactions, and the availability of resources, each of which affects the vector's ability to sustain and transmit pathogens (Cansado-Utrilla *et al.*, 2021).

This microbial community affects how mosquitoes carry and transmit diseases by interacting with *Plasmodium* parasites and other pathogens. These interactions can modulate the mosquito's immune system, behavior, and even reproduction, all of which contribute to the vector's ability to spread diseases like malaria (Garrigós *et al.*, 2023).

Recent studies have highlighted the critical role that the composition and dynamics of mosquito-associated microbial communities play in vector competence. For example, certain bacteria within the mosquito gut produce antimicrobial compounds or create physical barriers that hinder parasite development, effectively reducing infection rates. Additionally, microbes like *Wolbachia* can inhibit the transmission of pathogens through pathogen-blocking mechanisms, which have implications for disease control strategies (Wu *et al.*, 2020). These findings underscore the potential of manipulating mosquito microbiota as a novel approach to controlling vector-borne diseases.

Microbial communities can modulate mosquito susceptibility to pathogens. Studies have shown that certain bacteria in the gut can inhibit the establishment of pathogens, thereby impacting the mosquito's vectorial capacity. For instance, *Serratia* species can inhibit *Plasmodium* development in *Anopheles* mosquitoes by producing metabolites toxic to the malaria parasite (Pumpuni *et al.*, 1996). This mutualistic relationship between the microbiota and the mosquito immune system presents an opportunity for biological control strategies that reduce pathogen transmission.

Microbiota Influence on Mosquito Immunity

The microbiota exerts a significant influence on mosquito immune responses. The presence of microbes can stimulate basal immune responses, such as activating Toll, IMD, and JAK-STAT signaling pathways, which are involved in defense mechanisms against pathogens (Xi *et al.*, 2008). For example, *Wolbachia* infection in *Aedes aegypti* mosquitoes can prime the mosquito's immune system, providing cross-protection against other pathogens, such as the

dengue virus, by upregulating antimicrobial peptides (Terradas *et al.*, 2017).

Blood meal, indeed, causes a proliferation of midgut microbiota, which peaks at around 30 hours after the meal in Anopheles gambiae female mosquitoes. Female mosquitoes acquire pathogens together with the blood meal, and the microbes residing in the gut have a profound effect on the outcome of the infection (Scolari *et al.*, 2019).

A specific class of microorganisms can exert the protective role of the microbiota. It is the case of *Enterobacteriaceae* in *Anopheles* mosquitoes, which have a protective effect on *Plasmodium* infection (Boissière *et al.*, 2012).

Relationship between Gut-microbiota and *Plasmodium falciparum*

The relationship between gut microbiota and pathogens transmitted by mosquitoes is not one-way; it is increasingly clear that pathogens can shape the microbial load in the mosquito midgut and the composition of the bacterial population.

For example, during the pre-invasive phase, *Plasmodium vivax* significantly decreases the microbial load, and 16S rRNA gene expression was not detectable before 36 h post-meal, the time frame when ookinetes/early oocysts invade the gut (Sharma *et al.*, 2020).

The relationship between gut microbiota and *Plasmodium falciparum*, the parasite responsible for malaria, is an emerging area of research that explores how microbial populations within the gut influence malaria susceptibility, progression, and immune response. The gut microbiota, a collection of microbes residing in the gastrointestinal tract, plays a significant role in regulating host immunity, metabolic processes, and inflammatory responses, all of which can impact the body's interaction with infectious agents, including *P. falciparum* (Sharma *et al.*, 2020).

Microbial communities can influence pathogen transmission through both direct and indirect interactions. For example, gut bacteria can produce antimicrobial peptides such as Defensin, Cecropin, and gambicin. These antimicrobial peptides stimulate the immune system via the Imd and Toll pathways to upregulate AMP expression, disrupting or inhibiting *Plasmodium* stages (especially ookinetes and oocysts) (Dong *et al.*, 2009). In *Aedes* mosquitoes, the microbiota can also modulate the mosquito's immune system, leading to an enhanced immune response upon pathogen infection. It has also been suggested that microbiota-induced immune priming increases resistance to pathogens, thereby reducing vector competence.

The presence of symbiotic bacteria, particularly *Wolbachia*, has been extensively studied for its inhibitory effects on pathogen replication in mosquitoes. *Wolbachia* strains introduced into mosquito populations can reduce the load of pathogens, such as dengue and malaria, by shortening the mosquito's lifespan or by directly competing with the pathogen for resources. Additionally, Wolbachia may modify the vectorial capacity of *Anopheles* mosquitoes for *Plasmodium* by disrupting parasite development (Caragata *et al.*, 2022).

Host-Microbiota Interactions and Immune Response to Malaria Infection

Interactions between the host and gut microbiota are crucial in shaping immune responses during malaria infection. Studies suggest that gut bacteria may prime the immune system to produce specific cytokines and antibodies that either support or hinder *the clearance of P. falciparum*. For example, gut-derived lipopolysaccharides (LPS) can stimulate the production of inflammatory cytokines, which may help control malaria infection but can also lead to complications if overstimulated (Waide & Schmidt, 2020).

The gut microbiota's interaction with *P. falciparum* appears to influence immune responses at various stages of infection. Some bacteria present in the gut can produce molecules that either enhance or suppress immune activity against *P. falciparum*, potentially impacting how effectively the body controls the infection. Notably, the presence of anti-α-gal antibodies, induced by certain gut bacteria, has been linked to a protective immune response in early stages of stages of ion (Sriboonvorakul *et al.*, 2023).

Commensal bacteria within the mosquito midgut stimulate the production of basal levels of effector molecules that control the proliferation of bacterial populations, as well as Plasmodium parasite populations at the ookinete and oocyst stages of development (Cirimotich et al., 2011). *A. gambiae* mosquitoes are more susceptible to Plasmodium infection when the midgut-commensal bacteria, including *Chryseobacterium*, *Enterobacter*, and *Serratia*

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species, are removed from the midgut via antibiotic treatment before an infectious blood feed, and the resistance phenotype can be recapitulated by the introduction of non native or midgut-isolated bacteria into antibiotic-treated mosquitoes (Cirimotich *et al.*, 2011).

Influence of Gut Microbiota on Malaria Susceptibility and Severity

Gut microbiota composition has been associated with the severity of malaria. Research has shown that certain bacteria, such as *Escherichia coli* and *Klebsiella spp.*, are more prevalent in individuals experiencing severe malaria. These bacteria may exacerbate inflammation and damage the gut barrier's integrity, thereby increasing the translocation of bacterial products into the bloodstream. This disruption may contribute to severe malaria complications, such as acidosis and systemic inflammatory responses (Mandal & Schmidt, 2023).

Additionally, studies in animal models have shown that gut bacteria such as *Bacteroides* and *Firmicutes* may inhibit *Plasmodium* growth. Mice treated with antibiotics to disrupt their gut microbiota exhibited higher parasitemia and lower survival rates, suggesting that a balanced gut microbiome may offer some protection against malaria (Mandal *et al.*, 2023).

The gut microbiome may also affect the efficacy of antimalarial drugs. Some gut bacteria have been observed to metabolize drugs, potentially altering their bioavailability and efficacy. For instance, gut microbiota may degrade or inactivate antimalarial drugs, which could lead to suboptimal treatment outcomes (Hassan *et al.*, 2021). This interaction has important implications for malaria treatment, as a disrupted gut microbiome from diet, antibiotics, or illness could influence the success of antimalarial therapies.

Leveraging the mosquito microbiota for disease control has gained interest. Introducing or enhancing beneficial microbes in mosquito populations can help suppress the transmission of vector-borne pathogens. For instance, genetically engineered *Wolbachia* strains have been introduced to reduce dengue transmission by creating immune environment unfavorable to dengue virus replication (Hughes *et al.*, 2014). This microbiota-based approach presents a promising and sustainable alternative to chemical control methods.

Environmental and Genetic Factors Affecting Mosquito Microbiota

Environmental factors, such as diet, sanitation, and genetic differences between populations, may also influence gut microbiota composition, adding another layer of complexity to the relationship between gut microbiota and *P. falciparum*. For instance, individuals in malaria-endemic regions often have gut microbiota profiles that differ from those in non-endemic areas, potentially contributing to varying immune responses and susceptibility levels of the gut microbiota (Opute *et al.*, 2022).

External factors, such as breeding habitat, diet, and antibiotic exposure, influence the composition of the mosquito microbiota. For example, *Anopheles* mosquitoes breeding in polluted water often harbor different microbiota compared to those in clean environments, which can alter their susceptibility to malaria parasites (Minard *et al.*, 2013). Studies show that antibiotic exposure may significantly reduce microbiota diversity, potentially increasing susceptibility to infections by altering the immune function of the mosquito (Gendrin & Christophides, 2013).

Environmental factors, such as diet, temperature, and habitat, significantly affect the composition of mosquito microbiota, which in turn impacts immune responses. Diets rich in sugar and blood meals alter gut microbiota diversity and density, leading to different immune modulations. Seasonal and geographic variations also play a role, as local environmental conditions can lead to variations in microbiota, ultimately influencing mosquito immunity and susceptibility to pathogens (Muturi *et al.*, 2017).

CONCLUSION

Malaria remains a critical global health challenge, with *Plasmodium falciparum* accounting for the majority of severe and fatal cases, particularly in sub-Saharan Africa. Despite progress achieved through conventional vector control strategies such as insecticide-treated nets and indoor residual spraying, the growing resistance of mosquitoes to insecticides and the parasite to antimalarial drugs necessitates innovative and sustainable approaches. An expanding body of evidence highlights the crucial role of mosquito gut microbiota in shaping malaria transmission. These microbial communities, predominantly composed of bacteria such as *Serratia,*

Enterobacter, *Pseudomonas*, and *Wolbachia*, significantly impact mosquito physiology, immunity, and vectorial capacity. Mechanistically, the gut microbiota can limit *Plasmodium* development through direct antiparasitic metabolites, physical barriers, and immune priming via Toll, IMD, and JAK-STAT pathways. Notably, symbiotic bacteria like *Wolbachia* have demonstrated pathogen-blocking properties and are now being leveraged in field trials aimed at reducing disease transmission. Moreover, the mosquito's gut microbiome interacts dynamically with both parasite and host, influencing not only vector susceptibility but also human immune responses and disease outcomes. The composition of gut microbiota in mosquitoes and humans is further shaped by environmental conditions, diet, and exposure to antibiotics, highlighting the need for context-specific studies.

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