JOURNAL OF CLINICAL IMMUNOLOGY AND MICROBIOLOGY

E-ISSN: 3068-5168
Journal of Clinical Immunology & Microbiology

ATHENAEUM SCIENTIFIC PUBLISHERS

Review Article

Check for updates

Gut Microbiome-Malaria Axis: Mechanism, Clinical Implications and Research Gaps

Kalpana Kuntal[1*], **Nishtha Singh**[2]
[1]Senior Resident, King George Medical University, Microbiology, Lucknow, India
[2]Assistant Professor, Hind Institute of Medical Sciences, Microbiology, Lucknow, India
***Correspondence author**: Kalpana Kuntal, MD, PDCC, Senior Resident, King George Medical University, Microbiology, Lucknow, India;
Email: ktsk221292@gmail.com

Citation: Kuntal K, et al. Gut Microbiome-Malaria Axis: Mechanism, Clinical Implications and Research Gaps. J Clin Immunol Microbiol. 2026;7(1):1-13.

https://doi.org/10.46889/JCIM.2026.7109

Received Date: 25-03-2026
Accepted Date: 08-04-2026
Published Date: 16-04-2026

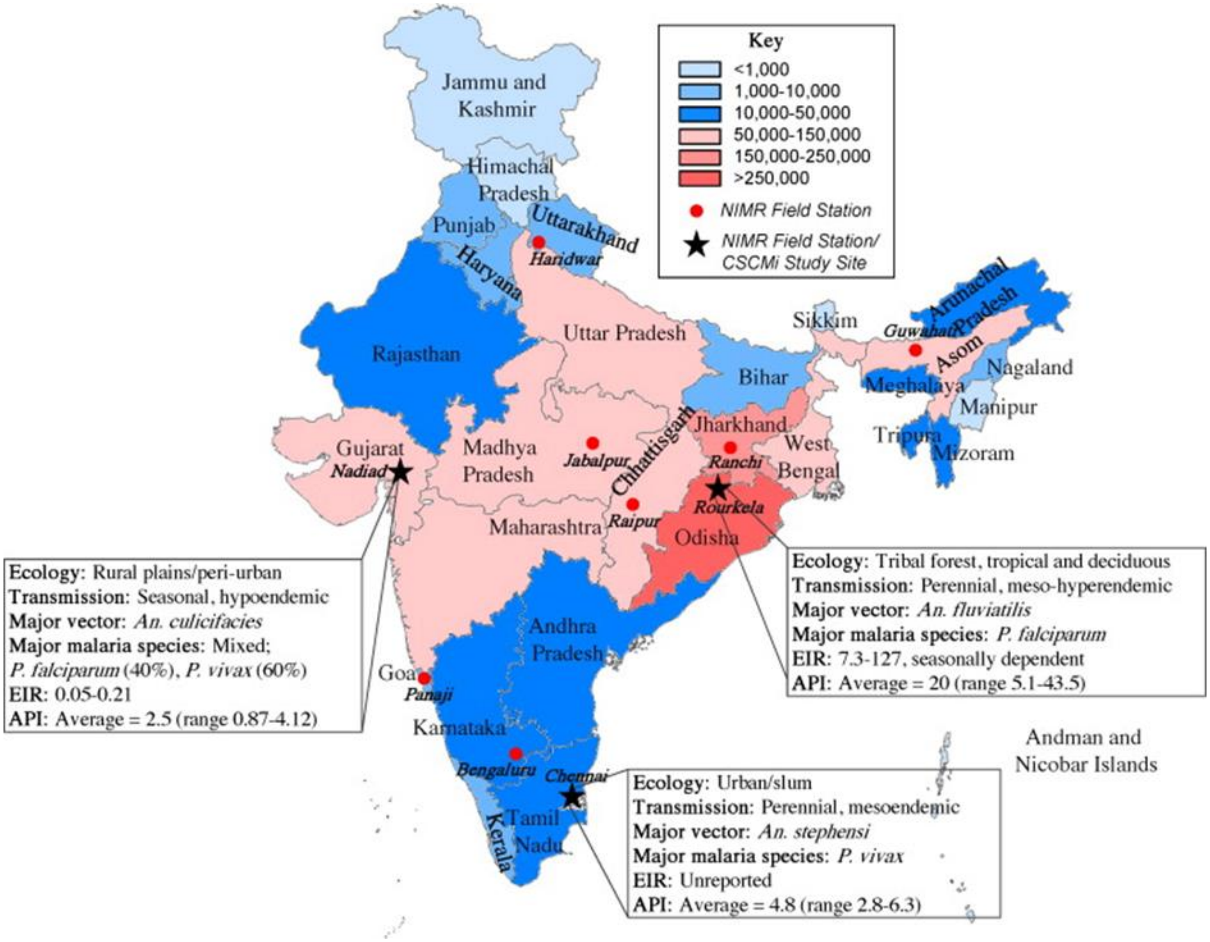
Abstract

The gut microbiome is increasingly recognized as a key modulator of malaria susceptibility, severity and treatment outcomes. Evidence from human cohort studies and integrated multi-omics analyses demonstrates that specific microbial communities influence immune priming, inflammatory responses and drug pharmacodynamics. Enrichment of short-chain fatty acid-producing taxa such as *Bifidobacterium* and *Lactobacillus* is associated with reduced parasitaemia and lower risk of severe disease. Expansion of pro-inflammatory taxa, particularly *Enterobacteriaceae*, correlates with higher parasite burdens and complications. These findings suggest a potential role for the gut microbiome as a predictive biomarker and a target for adjunctive interventions. However, translation into clinical practice is hindered by major research gaps, including the lack of longitudinal human cohorts, limited integration of metagenomic, metabolomic and immunologic datasets and the absence of region-specific microbiome baselines. To date no clinical trials have yet evaluated microbiome-targeted strategies in malaria prevention or treatment. Future progress will require multi-site, context-specific studies that assess both efficacy and safety, with a focus on vulnerable populations in endemic regions. Integrating microbiome science into malaria control could open new avenues for precision public health, complementing existing strategies and improving disease outcomes.

Keywords: Gut Microbiome; Inflammatory Responses; *Bifidobacterium*; *Lactobacillus*

Introduction

Malaria continues to pose a substantial global health challenge, with an estimated 249 million cases and 608,000 deaths reported across 85 endemic countries in 2022. The disease is caused by protozoan parasites of the genus Plasmodium, with *P. falciparum* and *P. vivax* being the most clinically significant species. *P. falciparum*, responsible for the majority of severe and fatal cases, accounts for approximately three-quarters of global infections, while *P. vivax* characterized by its ability to form dormant hypnozoites-contributes to around one-sixth of the global burden. In contrast, the WHO South-East Asia Region accounts for roughly 2% of global cases but exhibits greater species heterogeneity. Here, *P. falciparum* predominates in Myanmar, Indonesia and parts of India, while *P. vivax* is more prevalent in India, Bangladesh and Thailand. Zoonotic P. knowlesi, transmitted from macaques, is of emerging concern in Malaysia and neighbouring countries [1]. India remains the largest contributor to the malaria burden in the South-East Asia Region, accounting for approximately two-thirds of regional cases in 2022 [1]. Fig. 1 shows distribution of malaria species in India. While overall incidence has declined substantially over the past decade, malaria remains endemic in pockets of high transmission. Nationally, *P. falciparum* accounts for ~52% of reported infections and *P. vivax* for ~48%, though species distribution varies considerably by geography [2]. Northeastern states such as Arunachal Pradesh, Mizoram, Meghalaya and Tripura report a predominance of *P. falciparum* infections, often exceeding 90% of confirmed cases [2,3]. Central Indian states-including Chhattisgarh, Jharkhand and Odisha-also show high *P. falciparum* prevalence, particularly in forested and tribal areas where Anopheles vector density is high and healthcare access is limited [4]. In contrast, *P. vivax* predominates in northwestern and western regions such as Rajasthan, Gujarat and parts of Maharashtra, as well as in major urban centres including Delhi, Mumbai and Bengaluru, where transmission is more seasonal and linked to monsoon-related breeding sites [5,6]. In southern states like Andhra Pradesh, Telangana and Tamil Nadu, mixed-species transmission is observed, with *P. vivax* forming the majority [2,5]. Seasonal peaks occur post-monsoon (July-October in most states, extended to November-December in southern coastal regions), with regional differences in vector species composition influencing local epidemiology [2, 3]. Despite substantial reductions in incidence and mortality through intensified vector control, early diagnosis and treatment initiatives, persistent transmission in forested tribal belts, border areas and urban slums remains a barrier to India’s ambitious goal of achieving malaria elimination by 2030 (Table 1) [1-3].



Ecology: Rural plains/peri-urban
Transmission: Seasonal, hypoendemic
Major vector: *An. culicifacies*
Major malaria species: Mixed; *P. falciparum* (40%), *P. vivax* (60%)
EIR: 0.05-0.21
API: Average = 2.5 (range 0.87-4.12)

Ecology: Tribal forest, tropical and deciduous
Transmission: Perennial, meso-hyperendemic
Major vector: *An. fluviatilis*
Major malaria species: *P. falciparum*
EIR: 7.3-127, seasonally dependent
API: Average = 20 (range 5.1-43.5)

Ecology: Urban/slum
Transmission: Perennial, mesoendemic
Major vector: *An. stephensi*
Major malaria species: *P. vivax*
EIR: Unreported
API: Average = 4.8 (range 2.8-6.3)

Figure 1: Distribution of malaria species in India 2023 WHO data.

Region / State	Recent API	Dominant Species (% estimated)	Key Features
Mizoram	~4.6 per 1,000 (2021)	*P. falciparum* (~80-90%)	Persistent high burden, tribal, forested, near international border
Tripura	~2.4 per 1,000	*P. falciparum* dominant	High burden despite small size
Odisha (state-wide)	~0.5 per 1,000 (2022)	*P. falciparum* (~80%)	Heavy contributor of national *Pf* cases (13.5%)
Kalahandi (Odisha district)	>15 per 1,000	*P. falciparum* (~88%)	One of the most endemic districts, high burden year-round
Western India - Goa	API trending toward 0	*P. vivax* (~78%) initially	Now elimination phase; imported cases pose risk

Eastern and Central (aggregate)	Varies; some districts >1 API	*P. falciparum* predominant	Contains >70% of national malaria burden

Table 1: Summary table with API and species insights [7-13].

Why the Microbiome Matters: Immunomodulatory Potential and Metabolic Interactions

The gut microbiome is increasingly recognized as a dynamic immunological organ-one that communicates bidirectionally with the host via molecular, cellular and metabolic signals [14,15]. Its influence extends beyond the gastrointestinal tract, shaping immune cell maturation, trafficking and functional polarization in distant tissues, including the spleen, liver and bone marrow-organs central to malaria pathophysiology [16].

From an immunomodulatory perspective, the microbiota regulates the tone and threshold of innate immunity through modulation of dendritic cell activation, macrophage polarization and the training of monocytes via epigenetic reprogramming [17]. Pattern Recognition Receptor (PRR) ligands derived from commensals such as Lipopolysaccharides (LPS), peptidoglycans and flagellin-act as systemic immune primers, influencing the magnitude of responses to malaria parasites [18]. For example, microbe-derived LPS can enhance TLR4-dependent cytokine production, potentially impacting early control of Plasmodium replication [19].

On the adaptive immune axis, the microbiota shapes CD4$^+$ T helper subset balance, promoting Th1, Th17 or regulatory T cell dominance depending on community structure and metabolite output [20]. This is particularly relevant for malaria, where an early Th1 response aids parasite clearance, but excessive pro-inflammatory cytokine release contributes to severe disease manifestations such as cerebral malaria [21]. Microbiota-driven modulation of B cell maturation and germinal center responses further impacts antibody quality and longevity critical factors in anti-malarial immunity and vaccine efficacy [22].

Metabolically, commensals produce Short-Chain Fatty Acids (SCFAs) like butyrate, propionate and acetate, which not only fuel colonocytes but also act as Histone Deacetylase (HDAC) inhibitors, altering transcriptional programs in immune cells [23, 24]. Bile acid derivatives influence macrophage and natural killer T-cell activity, while tryptophan catabolites modulate Aryl Hydrocarbon Receptor (AhR) signaling, impacting IL-22 production and barrier integrity [25,26]. During malaria, systemic inflammation and hemolysis alter gut physiology, potentially reshaping the microbiota-metabolite landscape in ways that feed back into disease severity and recovery [27].

The microbiome also intersects with host metabolic status in ways that are relevant to malaria outcomes. By regulating iron availability, heme metabolism and redox balance, gut microbes may influence parasite growth kinetics [28]. Microbiota-mediated nutrient competition especially for B vitamins such as riboflavin and folate, which are co-factors in parasite metabolism-may directly affect Plasmodium replication [29].

Finally, gut microbes participate in immune education during early life, setting the baseline immune architecture that determines malaria susceptibility in childhood [30,31].

The Gut Microbiome in Health and Immunity

Composition in Healthy Individuals: Regional and Dietary Influences

In healthy adults, the gut microbiome is dominated by the bacterial phyla Firmicutes and Bacteroidetes, with Actinobacteria, Proteobacteria and Verrucomicrobia contributing variably to functional diversity [32]. High-fiber, plant-based diets common in agrarian societies-are associated with greater microbial diversity and enrichment of Short-Chain Fatty Acid (SCFA)-producing taxa, whereas wetsernized diets, rich in fat and simple sugars, favor bile-tolerant and mucin-degrading organisms [33].

Microbiota-Immune System Cross-talk

The gut mucosa forms both a physical barrier and a dynamic immunological interface. Epithelial tight junctions and an overlying mucus layer physically segregate microbes from host tissues while serving as reservoirs for secretory IgA (sIgA), defensins and other antimicrobial peptides [34].

At the molecular level, Microbe-Associated Molecular Patterns (MAMPs)-including Lipopolysaccharide (LPS), flagellin and peptidoglycan-activate Pattern Recognition Receptors (PRRs) such as Toll-Like Receptors (TLRs), C-type Lectin Receptors (CLRs) and NOD-Like Receptors (NLRs). These signals converge on pathways like MyD88-NF-κB, inducing chemokines and cytokines that tune the magnitude and quality of both innate and adaptive responses [35,36].

Microbiota-derived metabolites further refine immune tone. SCFAs (butyrate, propionate, acetate) promote the expansion of regulatory T-cells (Tregs), dampening excessive inflammation, while ATP and tryptophan-derived indoles influence Th17 and Intraepithelial Lymphocyte (IEL) populations [38, 39]. Importantly, the microbiota actively shapes Innate Lymphoid Cell (ILC) networks, particularly ILC3-mediated IL-22 production, which reinforces epithelial defense and regulates microbial composition [40]. In parallel, T-dependent IgA responses selectively target microbial taxa, maintaining community stability [41]. These feedback loops integrate microbial ecology with host immunity to sustain homeostasis.

Microbiome Shifts in Infection and Inflammation

Infection, systemic inflammation and environmental stressors perturb the microbiome, leading to dysbiosis characterized by reduced diversity, altered taxonomic composition and functional shifts. Barrier integrity often declines, increasing microbial translocation and fuelling further immune activation [42,43].

Antibiotic exposure, while sometimes essential, disrupts SCFA production, destabilizes immune regulation and can hyperactivate macrophage and T-cell responses, paradoxically heightening vulnerability to secondary infections. Dietary patterns modulate these effects: Western diets skew bile acid profiles and dendritic cell homeostasis, whereas fiber-rich diets foster resilience through SCFA-mediated epithelial repair [44]. Perturbations during this critical window can prime the immune system toward hyper-responsiveness or tolerance, influencing susceptibility to infections, including parasitic diseases such as malaria, decades later (Fig. 2) [45].

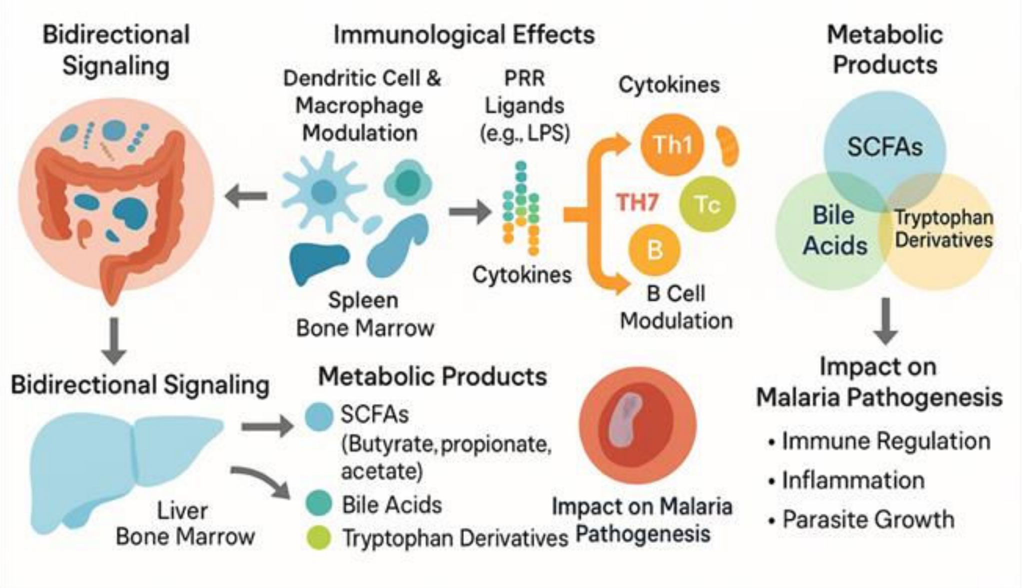


Figure 2: Gut microbiome-immune system cross-talk and links to malaria pathogenesis.

Schematic representation of the pathways through which the gut microbiome influences systemic immunity and malaria outcomes. Microbial composition, shaped by diet, geography and lifestyle, generates metabolites (short-chain fatty acids, bile acid derivatives, tryptophan catabolites) that enter circulation. Microbe-Associated Molecular Patterns (MAMPs) activate Pattern Recognition Receptors (PRRs) on gut epithelial and immune cells within Gut-Associated Lymphoid Tissue (GALT), modulating dendritic cell activation, T-helper subset balance, regulatory T-cell expansion, cytotoxic T-cell (Tc) activity and B cell responses. These processes influence anti-malarial immunity by affecting parasite clearance, inflammatory regulation and antibody production. Plasmodium infection can reciprocally alter microbiota composition and barrier function, creating a bidirectional microbiome-malaria axis.

Mechanistic Links Between the Gut Microbiome and Malaria Pathogenesis

Microbiome → Malaria: Modulation of Immune Priming and Effector Responses

Early parasite control in malaria depends on well-calibrated innate and adaptive immunity. The gut microbiome shapes this through:

a. *Immune Priming Before Infection*

- Baseline innate tone: Microbial ligands (LPS, peptidoglycan, flagellin) engage PRRs (TLRs, CLRs, NLRs) to induce low-level tonic activation in dendritic cells and macrophages. This generates trained immunity in monocytes via epigenetic reprogramming, leading to heightened responsiveness upon Plasmodium exposure [46].
- T/B cell readiness: SCFA-producing taxa (e.g., Faecalibacterium, Roseburia) enhance Treg expansion and IL-10 production, potentially preventing excessive inflammation but risking suboptimal parasite clearance. Tryptophan catabolites and bile acid derivatives modulate Th17 and NK T cell responses, influencing outcomes such as cerebral malaria [47,48].

b. *Effector Responses During Infection* [49,50]

- Liver stage: Microbiome-driven cytokine tone affects Kupffer cell activation and NK/NKT recruitment, impacting early sporozoite clearance.
- Blood stage: Microbiota influence splenic macrophage polarization-M1 phenotypes promote clearance, whereas M2 phenotypes favor repair but may permit higher parasite loads. Microbiota also shape germinal center dynamics, follicular helper T-cell function and B-cell class switching, thereby modulating antibody quality.

c. *Human Evidence*

Cohort studies in Mali and Kenya show pre-season microbiota composition predicts malaria risk: *Bifidobacterium* enrichment is linked to reduced incidence, whereas antibiotic-driven dysbiosis increases susceptibility in children [51].

Malaria → Microbiome: Infection-Driven Dysbiosis and Barrier Disruption

These changes are partly mediated by altered bile acid metabolism and hypoxia-induced epithelial damage. In human severe malaria, increased plasma LPS levels and microbial DNA signatures suggest enhanced gut permeability. This bidirectional relationship-malaria shaping the microbiome-may establish a feedback loop where dysbiosis worsens systemic inflammation and complicates recovery [47,52].

The Vector-Microbiome-Host Triad

The mosquito vector's microbiome can influence parasite load and strain diversity, indirectly altering the immunological challenge faced by the human host. Variability in sporozoite inoculum size and genotype may interact with the host gut microbiome to modulate early immune events, although this axis remains underexplored [49].

Life-Course and Early-Life Immune Education

Dysbiosis during this period-common in low-resource, malaria-endemic areas due to malnutrition and repeated enteric infections-may predispose to either hyper-inflammatory or hypo-responsive states upon Plasmodium exposure in childhood [30, 53, 54]. This life-course perspective, though rarely integrated into malaria research, could explain regional differences in disease epidemiology.

Metabolic Intersections Relevant to Malaria

Competition for B vitamins such as riboflavin and folate between microbiota and Plasmodium may further shape infection dynamics. Polyamines, often enriched in dysbiotic states, can modulate parasite growth and host immune activation [55].

Influence of Co-Infections

Helminth-induced shifts towards Treg-dominated immune profiles may attenuate malaria pathology, while bacterial dysbiosis from repeated gastroenteritis may impair adaptive responses to Plasmodium [56]. Accounting for such co-infection-microbiome-malaria interactions is critical for interpreting field data and designing interventions

Host Genetics × Microbiome Interactions

The mechanistic basis for these interactions-largely unexplored-could represent an underutilized area for precision medicine approaches in malaria (Fig. 3) [57,58].

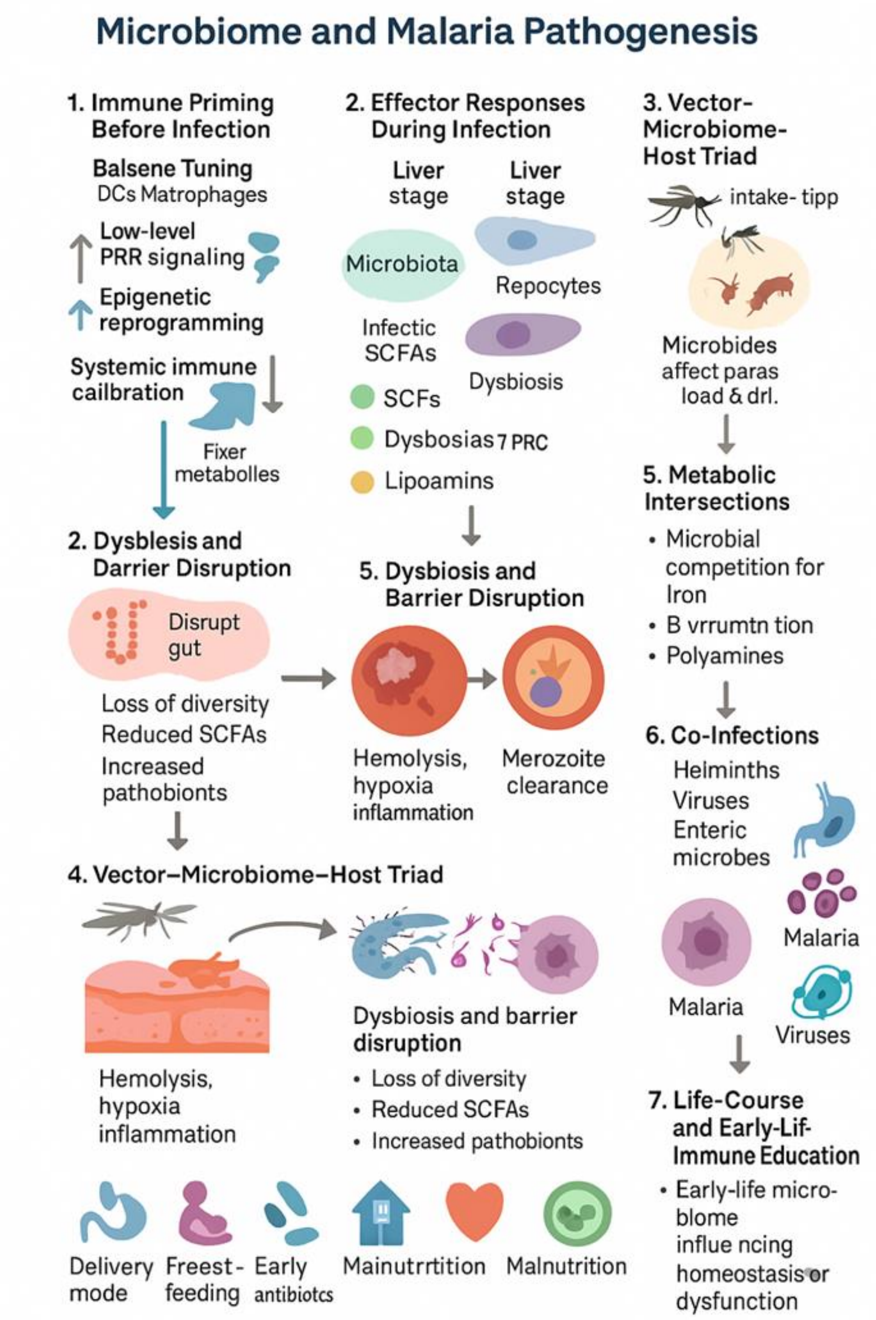


Figure 3: Schematic representation of microbial and malaria pathogenesis.

Microbiome Influence on Malaria Susceptibility and Severity

Evidence from Animal Models (causal signals)

Murine studies provide causal evidence that gut communities tune malaria outcomes. In the landmark vendor-mouse study, genetically similar C57BL/6 mice from different suppliers (distinct gut microbiota) showed large differences in parasitemia, morbidity and mortality after Plasmodium infection; fecal transfers into germ-free recipients recapitulatedresistance vs susceptibility and enrichment of *Lactobacillus*/*Bifidobacterium* reduced parasite burden (yogurt rescue) [50,59]. Mechanistically, the authors argue severity is more likely mediated by immune modulation than direct effects on parasite growth, given similar blood-stage expansion kinetics; resistant mice mounted stronger humoral responses than susceptible mice [60].

Additional rodent work shows malaria itself can remodel the gut (dysbiosis, barrier injury) and alter downstream outcomes (e.g., increased susceptibility to *nontyphoidal Salmonella*), while antibiotic perturbations or FMT change susceptibility and pregnancy outcomes in *P. chabaudi* models-underscoring bidirectionality and context dependence [61-63].

Role in severe malaria syndromes: cerebral malaria and severe malarial anemia

Human causality is unproven; prospective, stage-resolved studies with gut, plasma metabolome and neuroinflammatory readouts are needed [64,65]. Severe malaria studies in human population focuses on complications like cerebral malaria where parasite host interactions involving endothelial protein C binding with PfEMP1 is mainly responsible for pathogenesis (Table 2,3).

Research Priority	Rationale
1. Prospective, age-stratified cohort studies in endemic regions	Stratifying by age allows detection of developmental differences in microbiome-immune interactions that may influence malaria susceptibility. Harmonized endpoints (infection, febrile malaria, cerebral malaria, severe malarial anemia) and standardized confounder panels (diet, antibiotic exposure, HbAS/HLA status, helminth infections) improve comparability across studies and reduce bias.
2. Humanized gnotobiotic validation with functional profiling	Colonizing germ-free mice with stool from deeply phenotyped human donors directly tests causality. Coupling this with shotgun metagenomics and targeted/untargeted metabolomics can map specific microbial taxa and metabolic pathways to protective or pathogenic phenotypes.
3. Mechanism-first biomarker endpoints	Measuring intestinal barrier markers, SCFA, tryptophan and bile acid profiles, GC/Tfh cell activity, monocyte epigenetic "training," and iron-hepcidin axis readouts can reveal whether microbiome effects operate through immune modulation, metabolic shifts or both, guiding targeted interventions.
4. Embedded intervention trials in malaria programs	Integrating randomized trials of dietary fiber, prebiotics, next-generation probiotics or synbiotics into existing malaria prevention or vaccination initiatives enables real-world testing of microbiome modulation on susceptibility, severity and vaccine responsiveness.
5. Contextual modules for vector and co-infection variables	Considering mosquito vector microbiome diversity, vector competence variation and prevalent co-infections ensures that microbiome-malaria findings are interpreted within the broader ecological and epidemiological context, enhancing relevance for region-specific control strategies.

Table 2: Priority research directions to advance understanding of microbiome-malaria interactions.

Study / Year	Design	Sample Size (n)	Age Group	Endpoint	Key Taxa / Metabolites	Limitations
Villarino et al., 2016 [59]	Murine vendor-mouse study; fecal microbiota transfer into germ-free recipients	Multiple cohorts (C57BL/6 from different vendors)	Adult mice	Parasitemia, morbidity, mortality after Plasmodium infection	*Lactobacillus*, *Bifidobacterium* enrichment linked to reduced parasite burden	Species-specific; P. yoelii / P. berghei differ from *P. falciparum*; diet-controlled but not all variables matched
Yooseph et al., 2015 [64]	Murine experimental cerebral malaria (ECM) with antibiotic perturbation	Various experimental groups	Adult mice	Neuroinflammation, blood-brain barrier injury, survival	Loss of commensals; SCFA depletion associated with worse outcomes	ECM not identical to human CM; antibiotics may have off-target effects beyond microbiome
Van Den Ham KM et al, 2024 [51]	Prospective, seasonal; microbiome + metabolomics	181 enrolled; 156 sequenced	6-10 years	Febrile malaria (≥1 episode) vs asymptomatic infection	Susceptible: Eubacteriales taxa, NO-related metabolites; Resistant: Prevotella/Bacteroides,	Association significant only in 10-year-olds; residual

	+ stool-to-mouse transfer				Streptococcus/Veillonella	confounding possible
Mandal RK et al, 2021 [67]	Cross-sectional stool analysis	Not specified	<2 years	Severe malarial anemia vs asymptomatic infection	Differential community structure; lower SCFA producers in SMA	Cross-sectional; cannot determine causality; possible reverse causation

Table 3: Evidence table: Malaria and microbiome studies.

Bidirectional Modulation of Antimalarial Disposition

Antimalarial drugs themselves, particularly those with antimicrobial activity (e.g., doxycycline, primaquine), may reshape gut microbial communities and metabolic outputs, creating feedback loops that influence subsequent dosing or combination regimens. Such bidirectionality, widely described for other drug classes, is highly plausible for antimalarials but has yet to be comprehensively mapped in humans [68-70].

Evidence from Preclinical Malaria Models

Mechanistic hypotheses include microbial sequestration, modulation of gut pH and interference with transporter or metabolic enzyme activity. While limited by small sample size and lack of mechanistic dissection, this work establishes proof-of-principle for microbiome-mediated modulation of antimalarial PK [71].

Antibiotic-Induced Dysbiosis as a Modifier of Antimalarial Outcomes

These perturbations are mechanistically linked to changes in host bile-acid metabolism, epithelial transport capacity and systemic inflammatory tone, all of which can modulate drug absorption, hepatic biotransformation and clearance. In antimalarial therapy, such alterations could plausibly lead to subtherapeutic exposures or altered metabolite ratios, thereby influencing efficacy, toxicity and potentially the selection pressure for resistance [69,71,72]. This remains an untested but high-priority hypothesis.

Barrier Integrity and Intestinal Permeability

Antibiotic-induced depletion of these taxa or malaria-associated enteropathy, may increase permeability, resulting in erratic absorption and altered T_{max}.

Inflammatory damage-common in malaria-endemic areas due to repeated enteric infections-can compound malaria-induced gut pathology, magnifying variability in oral antimalarial bioavailability [59, 73]. (lumefantrine, piperaquine) that depend on bile-mediated solubilization [68- 70].

Perturbations in the Microbiome During Malaria

Changes in Microbiota Diversity and Composition During Acute Malaria

Acute malaria is associated with marked alterations in gut microbiota diversity and taxonomic composition, as reported in both human cohorts and experimental Plasmodium infections. In endemic human populations, acute *P. falciparum* or *P. vivax* malaria correlates with reduced abundance of *Lactobacillus* and *Ruminococcus* and increased representation of Gram-negative pathobionts [64,73]. Proposed mechanisms for these dysbiotic shifts include systemic inflammation, increased intestinal permeability, altered bile acid metabolism and infection-induced anorexia. However, interpretation is complicated by several limitations. Most human studies are cross-sectional, making it difficult to determine whether dysbiosis is a cause or consequence of infection [64,67]. Dietary variation, co-infections such as helminths, antibiotic exposure and host genetics are not consistently accounted for [47, 64].

Persistence of Dysbiosis Post-Treatment and Potential for Relapse Risk

Persistent enrichment of pro-inflammatory or metabolically disruptive taxa may sustain low-grade inflammation and alter host metabolic signalling, potentially impairing immune restoration. This could increase susceptibility to recurrent parasitaemia or recrudescence-particularly for *P. vivax*, in which hypnozoite reactivation is possible and predispose individuals to enteric infections or malnutrition [74].

The potential for direct effects of antimalarial drugs on the microbiome also varies: while some regimens may alter community composition, artemether-lumefantrine showed minimal impact in infants [72,74]. Few studies combine functional metagenomics with compositional profiling, leaving gaps in understanding the metabolic implications of persistent dysbiosis [64,74].

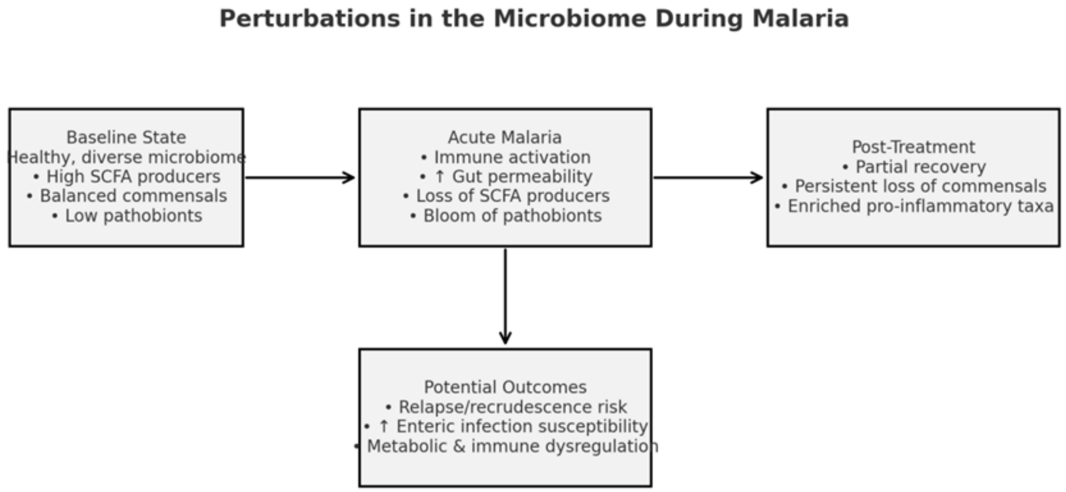


Figure 4: Dynamics of gut microbiome perturbations from acute malaria to post-treatment recovery.

Microbiome as a Predictive Biomarker

Baseline microbiota composition has emerged as a promising biomarker for malaria susceptibility and severity. Prospective cohort studies in Mali and Kenya have linked enrichment of short-chain fatty acid (SCFA)-producing taxa such as *Bifidobacterium* and *Lactobacillus* with reduced incidence of Plasmodium infection, while expansion of pro-inflammatory taxa-particularly *Enterobacteriaceae*-correlates with higher risk of high-density parasitaemia and severe malarial anemia. Notably, the predictive association was significant only in certain age groups (e.g., 10-year-olds in the Malian cohort). Functional validation via gnotobiotic mouse models colonized with stool from high- and low-risk children has confirmed causality in some contexts, with SCFA-related metabolic and immune signatures implicated [51,59,75].

Multi-omics integration-combining metagenomics, metabolomics and immunoprofiling-has revealed specific microbial taxa (e.g., *Bacteroides caccae*, *B. uniformis*) and pathways associated with severe malaria syndromes, suggesting that biomarker panels could include both compositional and functional indicators [76].

Adjunctive and Preventive Interventions

Manipulation of the gut microbiota to enhance host resistance or facilitate recovery represents a feasible adjunct to conventional malaria control.

- Probiotics - Supplementation with targeted strains such as *Lactobacillus* casei or *Bifidobacterium* longum has reduced parasitaemia, modulated systemic cytokine profiles and attenuated cerebral malaria severity in murine models [77-79]. Combined probiotic-drug regimens have achieved complete parasite suppression in experimental settings [77]. The study also found that administering *L. casei* with chloroquine resulted in a greater decrease in parasitaemia count and maximum suppression of parasite growth. further investigation is needed through well-designed clinical trials to confirm the potential benefits of probiotics as an add-on therapy for malaria treatment C
- Prebiotics - Dietary fibers and oligosaccharides that selectively enrich SCFA-producing commensals may promote gut barrier restoration, lower systemic inflammation and improve nutritional status in endemic communities [80]
- Dietary Modulation - Community-level promotion of fermented foods and fiber-rich staples offers a culturally adaptable, low-cost approach to sustaining microbial diversity and resilience [81]
- Emerging evidence suggests that microbiome modulation might also influence malaria transmission dynamics. Skin microbiota composition has been linked to mosquito host-seeking behavior, implying that interventions could target not only host immunity but also vector attraction [82]

Temporal Dynamics and Intervention Timing

Longitudinal studies in humans and non-human primates demonstrate that acute malaria induces rapid, often reversible, dysbiosis-marked by SCFA depletion and barrier disruption-with partial microbiome recovery after treatment [83,84]. The timing of probiotic or dietary interventions relative to infection and recovery phases may be critical for efficacy, underscoring the need for temporal mapping of microbiome shifts in endemic populations.

Risks and Safety Considerations

Severe malaria frequently coincides with gut barrier compromise, raising concerns about bacterial translocation when administering live microbes. This risk is heightened in children with malnutrition or concurrent enteropathy. Therefore, probiotic interventions in acute severe malaria should be restricted to monitored clinical trials with predefined safety endpoints [85].

Methodological and Analytical Rigor

Given the complexity of microbiome-malaria interactions, biomarker development and intervention studies must apply robust analytical pipelines that account for microbial co-occurrence networks, potential confounders and false discovery control. Harmonized study designs, standardized metadata collection and region-specific microbiome reference datasets will be essential for reproducibility and scalability [86].

Conclusion

The gut microbiome is an emerging determinant of malaria susceptibility, severity and treatment outcomes. Findings from human cohorts, animal models and multi-omics investigations highlight its role in shaping immunity, modulating drug responses and influencing vector attraction. Specific microbial patterns-particularly enrichment of short-chain fatty acid-producing commensals and reduction of pro-inflammatory taxa-may serve as predictive biomarkers for malaria risk. Adjunctive strategies such as probiotics, prebiotics and dietary modulation offer promising, low-cost complements to existing malaria control measures. Nevertheless, the field is still in an early stage. Longitudinal, multi-site human studies are needed to establish causality, validate biomarkers and adapt interventions to local contexts. Translating microbiome insights into practice will require rigorously designed clinical trials that assess both safety and efficacy, particularly in vulnerable populations with compromised gut barrier function. A precision public health approach, integrating microbiome-informed strategies into malaria programs, could enhance prevention and improve outcomes in endemic regions.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding Statement

This research did not receive any specific grant from funding agencies in the public, commercial or non-profit sectors.

Acknowledgement

None.

Data Availability Statement

Not applicable.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement

Informed consent was taken for this study.

Authors' Contributions

All authors contributed equally to this paper.

References

1. World Health Organization. World malaria report 2023. Geneva: World Health Organization. 2023.
2. National Vector Borne Disease Control Programme. Malaria situation in India 2022. Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India. 2023.
3. World Health Organization Regional Office for South-East Asia. Malaria elimination in India - 2023 update. New Delhi: WHO SEARO. 2023.
4. Sharma RK, Thakor HG, Saha KB. Epidemiology of malaria transmission in forested tribal villages of India: insights from the Malaria Elimination Demonstration Project. Malar J. 2021;20(1):152.
5. Bhatt RM, Sharma SN, Dash AP. Plasmodium vivax malaria in India. Trends Parasitol. 2020;36(9):800-3.
6. Singh V, Mishra N, Srivastava B. Species distribution and drug resistance patterns of Plasmodium species in India: A multicentre cross sectional study. Lancet Reg Health Southeast Asia. 2022;2:100021.
7. Singh MP, Bharti PK, Rajvanshi H. Malaria elimination: situation analysis of cases in India, Madhya Pradesh and Mandla district. Front Public Health. 2024;12:1363736.
8. National Center for Vector Borne Diseases Control. Malaria elimination-challenges and research priorities. [Last accessed: April 8, 2026].
   https://ncvbdc.mohfw.gov.in
9. Parliament of India, Lok Sabha. Annexure to Unstarred Question No. 4936. [Last accessed: April 8, 2026].
   https://sansad.in
10. NDM Consortium. Malaria elimination: challenges and research priorities. [Last accessed: April 8, 2026].
    https://www.ndmconsortium.com
11. Mishra MM, Sahu N, Mallick G, Pani B. Trend of malaria incidences and its association with rainfall in Kalahandi district of Odisha, India. Indian J Public Health. 2023;67(1):166-9.
12. Sarkar S, Singh P, Lingala MAL, Verma P, Dhiman RC. Malaria risk map for India based on climate, ecology and geographical modelling. Geospat Health. 2019;14(2):767.
13. Mohanty AK, Naik A, Govekar A. Spatiotemporal epidemiology of indigenous and imported malaria cases in Goa, western India. Malar J. 2025;24(1):46.
14. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell. 2014;157(1):121-41.
15. Belkaid Y, Harrison OJ. Homeostatic immunity and the microbiota. Immunity. 2017;46(4):562-76.
16. Rooks MG, Garrett WS. Gut microbiota, metabolites and host immunity. Nat Rev Immunol. 2016;16(6):341-52.
17. Netea MG, Joosten LA, Latz E. Trained immunity: A program of innate immune memory in health and disease. Science. 2016;352(6284):aaf1098.
18. Thaiss CA, Zmora N, Levy M, Elinav E. The microbiome and innate immunity. Nature. 2016;535(7610):65-74.
19. Schuijt TJ, Lankelma JM, Scicluna BP. The gut microbiota plays a protective role in host defence against pneumococcal pneumonia. Gut. 2016;65(4):575-83.
20. Honda K, Littman DR. The microbiota in adaptive immune homeostasis and disease. Nature. 2016;535(7610):75-84.
21. Hansen DS, Schofield L. Regulation of immunity and pathogenesis in malaria. Parasite Immunol. 2010;32(8):572-83.
22. Zeng MY, Cisalpino D, Varadarajan S. Gut microbiota-induced immunoglobulin G controls systemic infection. Immunity. 2016;44(3):647-58.
23. Koh A, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From dietary fiber to host physiology: short-chain fatty acids. Cell. 2016;165(6):1332-45.
24. Trompette A, Gollwitzer ES, Yadava K. Gut microbiota metabolism influences allergic airway disease. Nat Med. 2014;20(2):159-66.
25. Hang S, Paik D, Yao L. Bile acid metabolites control Th17 and Treg differentiation. Nature. 2019;576(7785):143-8.
26. Zelante T, Iannitti RG, Cunha C. Tryptophan catabolites engage AhR to control mucosal immunity. Nature. 2013;501(7468):97-101.
27. Taniguchi T, Miyauchi E, Nakamura S. Plasmodium berghei infection alters gut microbiota in mice. Malar J. 2015;14:94.
28. Raffatellu M. Learning from bacterial competition in the host. Nat Med. 2018;24(8):1097-103.
29. Graziani F, Bustamante L, Sörensen M. Folate metabolism and malaria. Trends Parasitol. 2020;36(2):111-23.
30. Gensollen T, Iyer SS, Kasper DL, Blumberg RS. Microbiota colonization shapes immunity. Science. 2016;352(6285):539-44.
31. Yilmaz B, Portugal S, Tran TM. Gut microbiota elicits protective immune response against malaria. Nature.

2014;515(7528):389-92.

32. Fava F, Rizzetto L, Tuohy KM. Gut microbiota and health. Proc Nutr Soc. 2019;78(2):177-88.
33. Negi S, Das DK, Pahari S. Role of gut microbiota in innate immune memory. Front Immunol. 2019;10:2441.
34. AboNahas HH, Darwish AM, Abd El-Kareem HF. Trust your gut: Microbiome in health and disease. In: Microbiome-gut-brain axis. Singapore: Springer; 2022. p. 53-96.
35. Erturk-Hasdemir D, Oh SF, Okan NA. Symbionts educate the immune system. Proc Natl Acad Sci U S A. 2019;116(52):26157-66.
36. Brown GD. Dectin-1: a signalling pattern-recognition receptor. Nat Rev Immunol. 2006;6(1):33-43.
37. Bouskra D, Brézillon C, Bérard M. Lymphoid tissue genesis induced by commensals. Nature. 2008;456(7221):507-10.
38. Tan TG, Sefik E, Geva-Zatorsky N. Symbiont bacteria induce Th17 cells. Proc Natl Acad Sci U S A. 2016;113(50):E8141-50.
39. Atarashi K, Tanoue T, Ando M. Th17 cell induction by microbes. Cell. 2015;163(2):367-80.
40. Guo X, Liang Y, Zhang Y. Innate lymphoid cells control colonization resistance. Immunity. 2015;42(4):731-43.
41. Sutherland DB, Suzuki K, Fagarasan S. Immunoglobulin A and microbiota mutualism. Immunol Rev. 2016;270(1):20-31.
42. Budden KF, Gellatly SL, Wood DL. Gut-lung axis and microbiota. Nat Rev Microbiol. 2017;15(1):55-63.
43. Dang AT, Marsland BJ. Microbes and the gut-lung axis. Mucosal Immunol. 2019;12(4):843-50.
44. Zheng D, Liwinski T, Elinav E. Microbiota and immunity. Cell Res. 2020;30(6):492-506.
45. Wopereis H, Oozeer R, Knipping K. Early-life microbiology. Pediatr Allergy Immunol. 2014;25(5):428-38.
46. Yap XZ, Lundie RJ, Beeson JG, O'Keeffe M. Dendritic cells in malaria. Front Immunol. 2019;10:357.
47. Mandal RK, Schmidt NW. Gut microbiome and malaria interaction. PLoS Pathog. 2023;19(10):e1011665.
48. Ippolito MM, Denny JE, Langelier C. Malaria and microbiome: systematic review. Clin Infect Dis. 2018;67(12):1831-9.
49. He S, Qi Y. Microbiota and malaria interaction. Front Microbiol. 2025;16:1615846.
50. Waide ML, Schmidt NW. Gut microbiome and Plasmodium severity. Curr Opin Microbiol. 2020;58:56-61.
51. Van Den Ham KM, Bower LK, Li S, Lorenzi H, Doumbo S, Doumtabe D. The gut microbiome is associated with susceptibility to febrile malaria in Malian children. Nat Commun. 2024;15(1):9525.
52. Haroun E, Kumar PA, Saba L, Kassab J, Ghimire K, Dutta D. Intestinal barrier functions in hematologic and oncologic diseases. J Transl Med. 2023;21(1):233.
53. Robertson RC, Manges AR, Finlay BB, Prendergast AJ. The human microbiome and child growth. Trends Microbiol. 2019;27(2):131-47.
54. Tamburini S, Shen N, Wu HC, Clemente JC. The microbiome in early life: implications for health outcomes. Nat Med. 2016;22(7):713-22.
55. Mancio-Silva L, Slavic K, Grilo Ruivo MT, Grosso AR, Modrzynska KK, Vera IM. Nutrient sensing modulates malaria parasite virulence. Nature. 2017;547(7662):213-6.
56. Mutoni JD, Coutelier JP, Rujeni N, Mutesa L, Cani PD. Interactions between malaria, helminthiases and gut microbiota. Microorganisms. 2022;10(4):721.
57. Shah SS, Stone EF, Francis RO, Karafin MS. The global role of G6PD in infection and immunity. Front Immunol. 2024;15:1393213.
58. Davies CS, Worsley SF, Maher KH, Komdeur J, Burke T, Dugdale HL. Immunogenetic variation shapes the gut microbiome. Microbiome. 2022;10(1):41.
59. Villarino NF, LeCleir GR, Denny JE, Dearth SP, Harding CL, Sloan SS. Gut microbiota modulates malaria severity. Proc Natl Acad Sci USA. 2016;113(8):2235-40.
60. Taniguchi T, Miyauchi E, Nakamura S, Hirai M, Suzue K, Imai T. Plasmodium berghei ANKA causes intestinal malaria with dysbiosis. Sci Rep. 2015;5(1):1569.
61. Donnelly E, Van de Water J, Luckhart S. Malaria-induced bacteremia and parasite survival strategies. Curr Res Microb Sci. 2021;2:100036.
62. Feasey NA, Dougan G, Kingsley RA, Heyderman RS, Gordon MA. Invasive non-typhoidal salmonella disease. Lancet. 2012;379(9835):2489-99.
63. Smith CD, Gong M, Andrew AK, Russ BN, Ge Y, Zadeh M. Gut microbiota influences malaria severity and pregnancy outcome. EBioMedicine. 2019;44:639-55.
64. Yooseph S, Kirkness EF, Tran TM, Harkins DM, Jones MB, Torralba MG. Stool microbiota and risk of Plasmodium falciparum infection. BMC Genomics. 2015;16(1):631.

65. Morffy Smith CD, Gong M, Andrew AK, Russ BN, Ge Y, Zadeh M. Gut microbiota influences malaria severity and pregnancy outcome. EBioMedicine. 2019;44:639-55.
66. Sarangam ML, Namazzi R, Datta D, Bond C, Vanderpool CP, Opoka RO. Intestinal injury biomarkers predict mortality in pediatric severe malaria. mBio. 2022;13(5):e01325-22.
67. Mandal RK, Denny JE, LeCleir GR. Stool bacteria correlate with malaria severity in children. Cell Rep. 2021;34(8):108940.
68. Zhao Q, Chen Y, Huang W, Zhou H, Zhang W. Drug-microbiota interactions in precision medicine. Signal Transduct Target Ther. 2023;8(1):1-27.
69. Torres-Carrillo N, Martínez-López E, Torres-Carrillo NM, López-Quintero A, Moreno-Ortiz JM, González-Mercado A. Pharmacomicrobiomics and drug-infection interactions. Int J Mol Sci. 2023;24(23):17100.
70. Wilson ID, Nicholson JK. Gut microbiome interactions with drug metabolism and toxicity. Transl Res. 2017;179:204-22.
71. Ippolito MM, Denny JE, Nenortas E, Shapiro TA, Schmidt NW. Microbiome-drug interaction with lumefantrine. Am J Trop Med Hyg. 2020;103(4):1553.
72. Denny JE, Schmidt NW. Antimalarial drugs do not modify murine gut microbiota. Sci Rep. 2019;9(1):11952.
73. Sriboonvorakul N, Chotivanich K, Silachamroon U, Phumratanaprapin W, Adams JH, Dondorp AM. Intestinal injury and microbiota in malaria. PLoS Pathog. 2023;19(10):e1011661.
74. Mandal RK, Crane RJ, Berkley JA, Gumbi W, Wambua J, Ngoi JM. Longitudinal gut microbiota changes with malaria and treatment. J Infect Dis. 2019;220(4):687-98.
75. Mandal RK, Denny JE, Namazzi R, Opoka RO, Datta D, John CC. Gut bacteria modulate spleen immune responses. Cell Rep. 2021;35(6).
76. Mandal RK, Mandal A, Denny JE, Namazii R, John CC, Schmidt NW. Gut Bacteroides increase susceptibility to severe malaria. Nat Commun. 2023;14(1):6465.
77. van den Nieuwboer M, van Hemert S, Claassen E, de Vos WM. *Lactobacillus* plantarum WCFS1 and host interaction. Microb Biotechnol. 2016;9(4):452-65.
78. Mahajan E, Sinha S, Bhatia A, Sehgal R, Medhi B. Probiotics in malaria therapy in mice. BMC Res Notes. 2021;14(1):246.
79. Fitri LE, Sardjono TW, Winaris N, Pawestri AR, Endharti AT, Norahmawati E. *Bifidobacterium* longum reduces parasitemia in malaria. J Inflamm Res. 2023;16:1393-404.
80. Makki K, Deehan EC, Walter J, Bäckhed F. Dietary fiber and gut microbiota. Cell Host Microbe. 2018;23(6):705-15.
81. Marco ML, Sanders ME, Gänzle M, Arrieta MC, Cotter PD, De Vuyst L. ISAPP consensus on fermented foods. Nat Rev Gastroenterol Hepatol. 2021;18(3):196-208.
82. Verhulst NO, Qiu YT, Beijleveld H, Maliepaard C, Knights D, Schulz S. Skin microbiota affects attractiveness to malaria mosquitoes. PLoS One. 2011;6(12):e28991.
83. Mooney JP, Lokken KL, Byndloss MX, George MD, Velazquez EM, Faber F. Microbiota changes reduce colonization resistance during malaria. Sci Rep. 2015;5(1):14603.
84. Farinella DN, Kaur S, Tran V, Cabrera-Mora M, Joyner CJ, Lapp SA. Malaria disrupts gut microbiome in macaques. Front Cell Infect Microbiol. 2023;12:1058926.
85. Preidis GA, Versalovic J. Targeting the human microbiome in therapy. Gastroenterology. 2009;136(6):2015-31.
86. Weiss S, Xu ZZ, Peddada S. Normalization and microbial differential abundance strategies depend on data characteristics. 2017.

About the journal

Journal of Clinical Immunology and Microbiology is an international, peer-reviewed, open-access journal published by Athenaeum Scientific Publishers. The journal publishes original research articles, case reports, editorials, reviews, and commentaries relevant to its scope. It aims to disseminate high-quality scholarly work that contributes to research, clinical practice, and academic knowledge in the field.

All submissions are evaluated through a structured peer-review process in accordance with established editorial and ethical standards. Manuscripts are submitted and processed through the journal's online submission system.

Manuscript submission: **https://athenaeumpub.com/submit-manuscript/**