STM JOURNALS

International Journal of
Insects

ISSN: 3049-1649
Volume 3, Issue 1, 2026
January–June
DOI (Journal): 10.37591/IJI

https://journals.stmjournals.com/iji

Review IJI

Investigating Mosquito Innate Immune-Defense Mechanisms Toward Malaria Vaccine Development

Feisal Mohammed*

Abstract

Mosquito-borne diseases weigh heavily on public health across the globe. The mosquito's innate immune system certainly decides whether malaria parasites survive inside the vector, and that sighted it as a logical place to discover new vaccine ideas. In this review, we examine how Anopheles mosquitoes defend themselves against Plasmodium parasites and how those defenses could be turned into tools for malaria control. We focus on three layers of immunity: antimicrobial peptides that attack invaders directly, reactive oxygen species that create a hostile oxidative environment, and physical barriers, like the peritrophic matrix, that block parasites in the midgut. We also consider antioxidant enzymes that mosquitoes use to manage their own oxidative stress during infection, because that balance influences parasite success. Beyond the midgut, mosquito salivary proteins are drawing attention as vaccine targets, though saliva-based approaches come with practical and immunological hurdles. A clearer picture of mosquito immune pathways, the genes that drive them, and the vector's physiology could open faster routes to transmission-blocking vaccines.

Keywords: Mosquito, innate immunity, plasmodium, parasite, malaria vaccine, vector biology

INTRODUCTION

Malaria has not let go of its grip on much of the developing world. The WHO World Malaria Report 2024 estimated 263 million cases and 597,000 deaths in 2023. The WHO African Region carried 94% of those cases and 95% of the deaths. Nigeria alone accounted for 27% of global cases and 31% of deaths. *Plasmodium falciparum* causes the disease, and it remains the most lethal species in humans.

Transmission depends on female *Anopheles* mosquitoes. When a mosquito bites an infected person, it ingests *Plasmodium* gametocytes with the blood meal. Inside the mosquito, those gametocytes undergo fertilization, transform into ookinetes, cross the midgut wall, and later produce sporozoites that invade the salivary glands. At the next blood feed, the mosquito injects sporozoites into a new host.

The mosquito's internal environment often works against the parasite. Immune responses in the midgut lumen, the epithelium, and the hemolymph can eliminate large numbers of developing parasites. Recent work has mapped key players. The complement-like protein TEP1 in *Anopheles* gambiae binds to *P. falciparum* ookinetes and drives their lysis, and when TEP1 is active, infection prevalence can fall by more than 80% [1]. Likewise, midgut catalase expression shapes ROS levels; silencing catalase spikes ROS and can fully block P. falciparum in the development [2]. Results, like these, show that boosting natural mosquito immunity is not just theoretical; it changes transmission outcomes.

Right now, we rely on drugs, insecticide-treated nets, and indoor spraying. Resistance is chipping away at all three. That pressure is why the field is looking harder at the vector itself. *Anopheles*

***Author for Correspondence**
Feisal Mohammed Ashish Kumar
E-mail: Mohammedfeisalsesi@gmail.com

Student, Department of Biochemistry, Chemical society, federal university of Education, Kontagora, Nigeria

Received Date: March 16, 2026
Accepted Date: April 01, 2026
Published Date: April 02, 2026

Citation: Feisal Mohammed. Investigating Mosquito Innate Immune-Defense Mechanisms Toward Malaria Vaccine Development. International Journal of Insects. 2026; 3(1): 50–54p.

mosquitoes are obligate hosts for *Plasmodium* [3]. Infection comes at a cost to the mosquito, forcing it to juggle immunity, reproduction, and basic maintenance [4]. Most parasite killing happens early, in the midgut, through both lumenal factors and epithelial responses [5].

If we want durable malaria control, the strategy must go beyond killing mosquitoes or treating humans after infection. We also need ways to make the mosquito a dead end for the parasite. One avenue is to exploit mosquito biology directly. This paper evaluates the feasibility of using mosquito salivary peptides as a basis for vaccines that stop transmission before it starts.

MOSQUITO INNATE IMMUNITY AND PHARMACOLOGICAL TARGETS

Mosquitoes lack the adaptive immune system we see in humans. They cannot make antibodies or memory cells. Yet they survive in a pathogen-rich world because their innate immune system is fast, broad, and surprisingly effective.

The main weapons are antimicrobial peptides, melanization reactions, phagocytic hemocytes, and bursts of reactive oxygen species. Physical structures help too. The peritrophic matrix forms around the blood meal and acts like a sieve, keeping many parasites away from the midgut cells [6].

The last decade has sharpened our view of these defenses. Transcriptomic studies show that TEP1, LRIM1, and APL1C form a complex that tags *P. falciparum* ookinetes for destruction [1]. That complex is so effective that mosquitoes with intact TEP1 rarely sustain heavy infections. The midgut redox state matters as well. A. gambiae uses catalase and other antioxidant enzymes to keep ROS from damaging its own tissues, but that same control gives *Plasmodium* a window to survive. When researchers knocked down catalase, ROS rose, and *P. falciparum* infections collapsed [2].

Antimicrobial peptides, like defensins and cecropins, are secreted into the hemolymph and gut after infection. They punch holes in bacterial membranes and also damage *Plasmodium* stages. ROS are less specific but potent; they oxidize proteins and lipids in the parasite. The mosquito has to walk a line of enough ROS to kill parasites, not so much that its own cells die.

These pathways give us two kinds of targets. First, immunomodulatory strategies: if we can upregulate TEP1 or defensin expression in wild mosquitoes, we might cut transmission without any gene drive. Second, vector-targeted therapies: compounds that shift the redox balance or disrupt the peritrophic matrix could make the midgut uninhabitable for *Plasmodium* [7]. Both ideas are now moving from lab models toward field thinking.

Mosquitoes face constant microbial pressure, especially during blood feeding [8]. Their innate system, paired with structural barriers, like the PM, often keeps parasitaemia low. The question is how to tip that system further in our favor [9].

MOSQUITO SALIVARY PROTEINS AS VACCINE TARGETS

Mosquito saliva is not just water. It is a cocktail of anti-clotting, anti-inflammatory, and vasodilatory proteins that let the mosquito feed before the host notices. Those proteins enter our skin with every bite, and if the mosquito is infected, sporozoites come with them.

That co-delivery has a consequence: our immune system observes parasite antigens and mosquito proteins at the same time, every time. Researchers noticed this and asked whether we could vaccinate against the saliva itself. The idea is to prime people so that, during a bite, their antibodies bind salivary proteins, trigger local inflammation, and disrupt sporozoite handoff.

There is early evidence that it could work. People naturally exposed to A. gambiae bites develop antibodies to the salivary protein gSG6. In one cohort, higher anti-gSG6 titers correlated with lower risk of *P. falciparum* infection [10]. Animal models go further: mice vaccinated with sand fly or mosquito salivary proteins show reduced pathogen loads after challenge.

The appeal is clear. A saliva-based vaccine might block malaria at the skin, before parasites reach the liver. It could also work against multiple diseases carried by the same mosquito. But the challenges are just as clear. Salivary proteins can be allergenic. Immune responses vary by person and by exposure history. And not all malaria is mosquito-delivered; transfusion and congenital cases would bypass a saliva vaccine entirely.

Still, the field is moving. Current transmission-blocking vaccine candidates mostly target parasite stages like Pfs25 or Pfs230. Adding a salivary component could produce a dual action shot: one antigen to stop the parasite in the mosquito, another to stop it in the skin [7].

MOSQUITO COMPARTMENTS AND PHYSICAL BARRIERS

To transmit malaria, Plasmodium must run a gauntlet through three mosquito compartments: the midgut, the hemocoel, and the salivary glands. Each one throws up different barriers.

The Midgut Compartment

This is where the fight usually ends. When a mosquito ingests gametocytes, they become gametes, fuse, and form ookinetes within 24 hours. To continue, an ookinete must cross the peritrophic matrix, then the midgut epithelium, before emerging into the hemocoel as an oocyst. The PM is acellular but dense. It delays parasites long enough for digestive proteases and immune factors to act. Epithelial cells then produce nitric oxide, TEP1, and other effectors that lyse ookinetes on contact. Midgut-specific immune signaling, especially the IMD pathway, controls a lot of this response [11].

The Hemocoel Compartment

Oocysts that survive grow on the basal side of the midgut, exposed to hemolymph. Here they face hemocytes, mosquito blood cells that can phagocytose or encapsulate foreign bodies. Melanization is common: layers of melanin smother the oocyst and starve it of nutrients. The cuticle protects the mosquito from the outside, but inside the hemocoel, the main defense is cellular and chemical. ROS levels rise during infection, and antioxidant enzymes, like superoxide dismutase and catalase, determine whether that ROS kills parasites or the mosquito [2].

The Salivary Glands

After oocysts rupture, thousands of sporozoites swim through the hemolymph. Only those that invade the salivary glands matter for transmission. The glands are paired, lobed organs, and sporozoites prefer specific lobes. We know less about immunity here, but the glands are not passive. They express antimicrobial peptides and likely produce ROS. How some sporozoites evade those defenses while others are destroyed is an open question, and it is central to saliva-vaccine design.

Mosquito Defense Against *Plasmodium falciparum*

The best-studied defense is oxidative. *A. gambiae* generates a burst of ROS in the midgut after an infected blood meal. That burst can damage ookinetes directly. To survive it, the mosquito leans on a set of antioxidant enzymes: superoxide dismutase converts superoxide to hydrogen peroxide; catalase and glutathione peroxidase then break hydrogen peroxide down to water.

This balancing act is tight. Too little ROS and parasites survive. Too much and the mosquito's own gut cells apoptose, cutting fecundity [12]. *P. falciparum* seems to have adapted to the normal range. When researchers artificially tilt the balance by silencing catalase, the midgut becomes lethal to the parasite [2]. That points to a lever we could pull with small molecules or genetic approaches.

Antioxidant Enzymes and Oxidative Stress

Oxidative stress is not just a side effect of infection; it is a weapon. The mosquito uses it, and the parasite tries to endure it. The enzymes involved, catalase, glutathione S-transferase, glutathione peroxidase, and superoxide dismutase, are conserved and well characterized. Their expression shifts with blood feeding, infection status, and mosquito age. Mapping those shifts gives us time points where the vector is most vulnerable, and therefore, where an intervention might hit hardest.

LIMITATIONS OF MOSQUITO SALIVA-BASED VACCINES

The concept is attractive, but four problems keep coming up. First, efficacy may depend on bite exposure. People in low-transmission areas might not get enough natural boosting to maintain immunity. Second, safety: some salivary proteins are known allergens, and sensitization could worsen bite reactions. Third, immunology: a strong anti-saliva response might increase blood flow to the bite site and, paradoxically, help sporozoites establish. Fourth, coverage: any transmission that skips the skin blood transfusion, needle sharing, or congenital transmission will not be covered. These are not deal-breakers, but they mean saliva vaccines will need careful antigen selection and clinical testing [8].

CONCLUSION

Mosquito-borne diseases remain a defining public health challenge. The mosquito is not a passive syringe; it is an active participant in the *Plasmodium* life cycle, and its innate immune system often determines whether transmission happens. That system peptides, ROS, barriers, and salivary proteins give us concrete targets. Recent data on TEP1, catalase, and gSG6 move the discussion from theory to testable interventions. Understanding these mechanisms in more detail, across diverse *Anopheles* species and ecological settings, is the next step toward vaccines that stop malaria in the mosquito, not just in the human.

Recommendations

We need deeper work on mosquito immune genes and the regulatory networks around them, especially in field strains of *A. gambiae* and *A. funestus*. Vaccine trials should stratify by vector species and biting rates, because a saliva antigen that works in one setting may fail in another [3]. Molecular tools for transient immune boosting in wild mosquitoes deserve more attention; they could bridge the gap between lab results and field use. Finally, any salivary protein advanced to trials must go through strict allergenicity and enhancement screens. The wrong protein could increase infection risk, and that would set the field back. Careful antigen choice, paired with parasite antigens, is the most plausible path forward.

REFERENCES

1. Eldering M, Morlais I, van Gemert GJ, van de Vegte-Bolmer M, Graumans W, Siebelink-Stoter R, et al. Variation in susceptibility of African Plasmodium falciparum malaria parasites to TEP1-mediated killing in Anopheles gambiae mosquitoes. Sci Rep. 2016;6(1):20440.
2. Bahia AC, Oliveira JH, Kubota MS, Araújo HR, Lima JB, Ríos-Velásquez CM, et al. The role of reactive oxygen species in Anopheles aquasalis response to Plasmodium vivax infection. PLoS One. 2013;8(2):e57014.
3. Kumar S, Christophides GK, Cantera R, Charles B, Han YS, Meister S, et al. The role of reactive oxygen species on Plasmodium melanotic encapsulation in Anopheles gambiae. Proc Natl Acad Sci U S A. 2003 [cited 2026 May 1];100(24):14139–44. Available from: https://pubmed.ncbi.nlm.nih.gov/14623973/.
4. Olayemi IK, Ande AT. Life table analysis of Anopheles gambiae (Diptera: Culicidae) in relation to malaria transmission. J Vector Borne Dis. 2009;46(4):295–9.
5. Ghosh AK, Jacobs-Lorena M. Plasmodium sporozoite invasion of the mosquito salivary gland. Curr Opin Microbiol. 2009 [cited 2026 May 1];12(4):394–400. Available from: https://www.sciencedirect.com/science/article/abs/pii/S1369527409000794.
6. Alavi Y, Arai M, Mendoza J, Tufet-Bayona M, Sinha R, Fowler K, et al. The dynamics of interactions between Plasmodium and the mosquito: a study of the infectivity of Plasmodium berghei and Plasmodium gallinaceum, and their transmission by Anopheles stephensi, Anopheles gambiae and Aedes aegypti. Int J Parasitol. 2003;33(9):933–43.
7. Duffy PE. Transmission-blocking vaccines: harnessing herd immunity for malaria elimination. Expert Rev Vaccines. 2021;20(2):185–98.

8. Osta MA, Christophides GK, Kafatos FC. Effects of mosquito genes on Plasmodium development. Science. 2004;303(5666):2030–2.
9. Söderhäll K, editor. Invertebrate immunity. New York: Springer Science & Business Media; 2011.
10. Manning JE, Morens DM, Kamhawi S, Valenzuela JG, Memoli M. Human immune responses to mosquito salivary proteins and their implications for vaccine design. Nat Rev Immunol. 2021;21(12):789–803.
11. Abraham EG, Jacobs-Lorena M. Mosquito midgut barriers to malaria parasite development. Insect Biochem Mol Biol. 2004 [cited 2026 May 1];34(7):667–71. Available from: https://pubmed.ncbi.nlm.nih.gov/15242707/.
12. Ahmed AM, Baggott SL, Maingon R, Hurd H. The costs of mounting an immune response are reflected in the reproductive fitness of the mosquito Anopheles gambiae. Oikos. 2002;97(3):371–7.

