ISSN: 2550-794X

International Digital Organization for Scientific Research IDOSRJSR10.300000
IDOSR JOURNAL OF SCIENTIFIC RESEARCH 10(3):104-108, 2025.
https://doi.org/10.59298/IDOSRJSR/2024/10.3.104108

Transmission-Blocking mRNA Vaccine Platforms against Plasmodium Gametocytes: Opportunities and Challenges for Field Deployment

Nasira A. Sitar

Department of Pharmacy Kampala International University Uganda
Satar.nasira@studwc.kiu.ac.ug

ABSTRACT

Transmission-blocking vaccines (TBVs) targeting *Plasmodium* gametocytes represent a strategic approach to interrupt malaria transmission, complementing existing prevention and treatment measures. This review examined the potential of messenger RNA (mRNA) vaccine platforms to deliver gametocyte and mosquito-stage antigens capable of eliciting functional antibodies that block parasite development in the mosquito vector. A structured literature synthesis and thematic analysis were conducted to integrate current knowledge on gametocyte biology, the immunological basis for transmission blocking, and the specific attributes of mRNA technology relevant to such targets. Key findings indicated that mRNA platforms offer rapid, scalable production, precise antigen expression, and adaptability to conserved gametocyte antigens such as Pfs25, Pfs230, and Pfs48/45. However, challenges included ensuring correct antigen folding, achieving thermostability for deployment in resource-limited settings, and addressing the ultra-cold chain requirements of current lipid nanoparticle formulations. Preclinical data demonstrated promising immunogenicity and functional activity, while early-phase clinical evaluation will require innovative regulatory pathways and well-defined endpoints. Successful field implementation will depend on overcoming logistical constraints, ensuring affordability through regional manufacturing, fostering community acceptance of vaccines with indirect benefits, and integrating TBVs with existing malaria control strategies. Prioritizing research on stable formulations, combination approaches, and field-adapted immunogenicity assays will be essential for realizing the full potential of mRNA-based TBVs in malaria elimination programs.

Keywords: transmission-blocking vaccines, Plasmodium gametocytes, mRNA vaccines, malaria elimination, vaccine deployment

INTRODUCTION

Malaria remains a major global health challenge, with *Plasmodium falciparum* responsible for most severe cases and deaths [1–3]. While significant progress has been made through vector control, case management, and chemoprevention, transmission persistence in high-burden areas necessitates novel interventions. Transmission-blocking vaccines (TBVs) represent an important complementary approach. Unlike conventional malaria vaccines that aim to prevent infection or disease in the vaccinated individual, TBVs target the sexual stages of the parasite specifically gametocytes within the human host [4, 5]. By eliciting antibodies that, when ingested by mosquitoes during blood feeding, inhibit parasite development in the vector, TBVs can reduce onward transmission and contribute to community-level malaria control. Messenger RNA (mRNA) vaccine technology offers a flexible and rapid platform for TBV development [6, 7]. Recent successes in mRNA-based vaccines against viral pathogens have highlighted the potential for high immunogenicity, speed of production, and adaptability to emerging antigenic targets. In the context of malaria, mRNA platforms enable precise delivery of transmission-stage antigens in a form that preserves native epitopes and promotes robust immune responses. Furthermore, the cell-free manufacturing process simplifies scalability and mitigates some biosafety concerns associated with protein subunit or whole-parasite vaccines. However, moving from laboratory innovation to field deployment in malaria-endemic regions presents formidable challenges. Gametocyte biology imposes unique requirements for antigen selection and presentation, mRNA vaccines require sophisticated formulation and delivery systems, and stability concerns complicate

distribution in areas with limited cold-chain infrastructure. Regulatory pathways for TBVs, which have indirect public health benefits, are less established than those for individual-protection vaccines, and community acceptance hinges on clear communication of their collective benefits. This review examines the biological rationale for gametocyte-targeted mRNA TBVs, current antigen and platform strategies, preclinical and emerging clinical evidence, and the operational considerations for large-scale implementation. It emphasizes the opportunities and constraints in translating this promising technology into an effective tool for malaria transmission reduction in real-world settings.

Biology of Plasmodium Gametocytes and Rationale for Transmission Blocking

Gametocytes are the sexual forms of the malaria parasite, representing the only stage capable of infecting mosquitoes [8]. In *P. falciparum*, gametocytogenesis occurs over approximately 10–12 days, progressing through five morphologically distinct stages [9]. Immature gametocytes sequester in the bone marrow and spleen, while mature stage V gametocytes circulate in peripheral blood and can be ingested during mosquito feeding. Within the mosquito midgut, gametocytes rapidly undergo gametogenesis, forming gametes that fuse to create zygotes [10, 11]. These develop into ookinetes, traverse the midgut epithelium, and form oocysts, ultimately releasing sporozoites that migrate to the salivary glands. Interrupting any step from gamete formation to ookinete development can prevent mosquito infection and halt transmission. Transmission-blocking immunity primarily relies on antibodies targeting gametocyte or gamete surface proteins, or antigens expressed during early mosquito-stage development. These antibodies do not protect the vaccinated individual directly but act within the mosquito midgut to neutralize parasites or interfere with fertilization and midgut invasion. The indirect nature of this protection underscores the need for high community coverage to achieve epidemiological impact.

Overview of mRNA Vaccine Technology Relevant to Gametocyte Targets

mRNA vaccines deliver a synthetic transcript encoding the target antigen, typically formulated in lipid nanoparticles (LNPs) for protection and cellular delivery [12]. For gametocyte targets, mRNA vaccines must express conformationally intact antigens to elicit transmission-blocking antibodies. Co-expression of multiple antigens is possible, enabling broader coverage of parasite variability. Formulation with LNPs enhances stability, delivery efficiency, and immune activation through adjuvant-like effects [13]. Once inside host cells, the mRNA is translated into the antigen, which is then processed and presented to the immune system, eliciting both humoral and cellular responses.

Key attributes relevant to TBVs include:

i. **Precision antigen expression**: mRNA allows for codon optimization and inclusion of signal peptides to ensure correct folding and post-translational modifications [14].
ii. **Rapid adaptability**: Antigen sequences can be rapidly modified in response to new data on epitope mapping or parasite variation [15].
iii. **Scalable manufacturing**: Cell-free synthesis facilitates large-scale production without pathogen culture.

Candidate Antigens and Antigen Design Considerations

Codon optimization and incorporation of nucleoside modifications (such as pseudouridine) can improve mRNA stability and translation while reducing innate immune activation that could limit antigen production [16]. Several gametocyte and mosquito-stage antigens have been identified as promising TBV targets:

i. **Pfs25**: A post-fertilization ookinete surface protein; highly conserved and a leading TBV candidate [17].
ii. **Pfs230**: A gamete surface protein essential for fertilization; has large and structurally complex.
iii. **Pfs48/45**: Involved in gamete fusion is also structurally challenging [18].

For mRNA vaccines, antigen design must address size constraints, complex disulfide bonding, and the need for presentation in a native-like conformation. Strategies include:

i. Domain optimization to express only immunogenic, structurally stable regions.
ii. Fusion constructs with carrier proteins to enhance expression and immunogenicity.
iii. Multivalent mRNA formulations combining several antigens to increase functional antibody breadth.

Delivery Platforms and Formulation Issues for Field Use

Lipid nanoparticles are the current gold standard for mRNA vaccine delivery, providing protection from degradation, facilitating cellular uptake, and enhancing immunogenicity [19, 20]. Alternative delivery systems, such as polymer-based nanoparticles or emulsions, are under investigation for improved thermostability and simplified production. However, these must match or exceed the immunogenicity and safety of LNPs before adoption. For malaria-endemic field settings, LNP formulations must be optimized for:

i. **Thermostability**: Standard LNP-mRNA formulations often require storage at −20°C or −80°C [21]. Reformulation with stabilizing excipients or lyophilization can permit storage at 2–8°C or ambient temperatures for limited periods.
ii. **Scalable manufacturing**: Microfluidic mixing technology allows consistent production but requires investment in regional manufacturing capacity to meet demand.

iii. **Dose sparing**: Potent formulations enabling lower mRNA doses can reduce production costs and cold-chain volume.

Preclinical and Early Clinical Evidence for Transmission Blocking mRNA Vaccines

Preclinical studies in rodent malaria models have demonstrated that mRNA-LNP vaccines encoding transmission-stage antigens can elicit functional antibodies that reduce oocyst development in mosquito feeding assays [22]. Immunogenicity is influenced by antigen choice, expression construct design, and delivery system. For *P. falciparum*, early laboratory evidence suggests that mRNA encoding Pfs25 or Pfs230 can induce antibody titers comparable to recombinant protein vaccines, with improved scalability. Functional assays, such as the standard membrane feeding assay (SMFA), show substantial inhibition of parasite development when sera from vaccinated animals are tested. No large-scale clinical trials of mRNA TBVs have yet been completed, but the platform's established safety in licensed mRNA vaccines supports progression to human studies. Planned early-phase trials are expected to evaluate safety, immunogenicity, and functional transmission-blocking activity, with endpoints aligned to WHO-recommended TBV development pathways.

Operational and Field Deployment Challenges and Solutions

i. **Cold-Chain Requirements:** The ultra-cold storage needs of current mRNA-LNP vaccines pose a significant barrier in remote areas [23]. Solutions include development of thermostable formulations, regionalized cold storage hubs, and integration with existing vaccine distribution networks.

ii. **Manufacturing and Cost:** High manufacturing costs could limit access. Technology transfer to facilities in endemic regions, adoption of modular mRNA production units, and economies of scale are potential mitigations.

iii. **Regulatory Pathways:** As TBVs confer indirect protection, regulatory agencies may require novel efficacy endpoints and community-level impact modeling. Early engagement with regulators will be essential to define acceptable evidence for licensure.

iv. **Community Acceptance:** Because TBVs do not directly prevent disease in recipients, sustained community engagement is critical [24]. Educational campaigns should emphasize the public health benefits and role in malaria elimination strategies.

v. **Integration with Existing Interventions:** TBVs should be deployed alongside vector control, case management, and other vaccines. Modeling studies can guide optimal timing and coverage to maximize impact.

Future Directions and Research Priorities

Several priority areas must be addressed to enable successful deployment:

i. **Antigen discovery and optimization**: Continued identification of conserved, immunogenic gametocyte and mosquito-stage antigens, with iterative testing of mRNA constructs for expression and functionality.

ii. **Thermostable formulations**: Research into excipients, lyophilization, and alternative delivery systems to permit storage and transport without ultra-cold infrastructure [25].

iii. **Combination strategies**: Evaluation of mRNA TBVs in combination with pre-erythrocytic or blood-stage vaccines to enhance overall malaria control [26, 27].

iv. **Field-appropriate immunogenicity assays**: Development of simplified, robust assays to assess functional transmission-blocking activity in endemic settings.

v. **Socio-behavioral research**: Understanding community perceptions to inform engagement and acceptance strategies.

vi. **Economic modeling**: Estimation of cost-effectiveness to guide donor and government investment.

CONCLUSION

Transmission-blocking mRNA vaccines targeting *Plasmodium* gametocytes represent a promising tool to interrupt malaria transmission and accelerate elimination in high-burden regions. By harnessing the flexibility, scalability, and immunogenic potential of mRNA technology, these vaccines can deliver key sexual-stage antigens in a format capable of eliciting functional antibodies that neutralize parasites within the mosquito vector. However, translating laboratory success into public health impact requires overcoming substantial challenges. Antigen design must ensure expression of correctly folded, immunogenic targets. Delivery systems must be optimized for thermostability, affordability, and manufacturability under conditions prevalent in malaria-endemic areas. Regulatory pathways need adaptation to accommodate indirect protection endpoints, and community engagement will be critical to secure acceptance of vaccines that do not confer direct personal benefit. Integration with existing malaria control tools, robust monitoring of transmission outcomes, and coordinated investment in regional production capacity will be necessary to achieve scalable, sustainable deployment. With targeted research addressing both scientific and operational barriers, mRNA transmission-blocking vaccines could become a cornerstone of future malaria elimination programs, offering a novel means to reduce transmission and protect entire communities from this persistent disease.

REFERENCES

1. Alum, E.U., Ugwu, O.P.-C., Egba, S.I., Uti, D.E., Alum, B.N.: Climate Variability and Malaria Transmission: Unraveling the Complex Relationship. INOSR Scientific Research. 11, 16–22 (2024). https://doi.org/10.59298/INOSRSR/2024/1.1.21622
2. Obeagu, E.I.O., Alum, E.U., Ugwu, O.P.C.: Hepcidin: The Gatekeeper of Iron in Malaria Resistance. NEWPORT INTERNATIONAL JOURNAL OF RESEARCH IN MEDICAL SCIENCES. 4, 1–8 (2023). https://doi.org/10.59298/NIJRMS/2023/10.1.1400
3. Milner, D.A., Vareta, J., Valim, C., Montgomery, J., Daniels, R.F., Volkman, S.K., Neafsey, D.E., Park, D.J., Schaffner, S.F., Mahesh, N.C., Barnes, K.G., Rosen, D.M., Lukens, A.K., Van Tyne, D., Wiegand, R.C., Sabeti, P.C., Seydel, K.B., Glover, S.J., Kamiza, S., Molyneux, M.E., Taylor, T.E., Wirth, D.F.: Human cerebral malaria and Plasmodium falciparum genotypes in Malawi. Malar J. 11, 35 (2012). https://doi.org/10.1186/1475-2875-11-35
4. de Jong, R.M., Tebeje, S.K., Meerstein-Kessel, L., Tadesse, F.G., Jore, M.M., Stone, W., Bousema, T.: Immunity against sexual stage Plasmodium falciparum and Plasmodium vivax parasites. Immunol Rev. 293, 190–215 (2020). https://doi.org/10.1111/IMR.12828;SUBPAGE:STRING:FULL
5. Peymanfar, Y.: Plasmodium Sexual Stage Parasites Present Distinct Targets for Malaria Transmission-Blocking Vaccine Design. International Journal of Vaccines and Immunization. 2, (2015). https://doi.org/10.16966/2470-9948.109
6. Hayashi, C.T.H., Cao, Y., Clark, L.C., Tripathi, A.K., Zavala, F., Dwivedi, G., Knox, J., Alameh, M.G., Lin, P.J.C., Tam, Y.K., Weissman, D., Kumar, N.: mRNA-LNP expressing PfCSP and Pfs25 vaccine candidates targeting infection and transmission of Plasmodium falciparum. NPJ Vaccines. 7, 1–14 (2022). https://doi.org/10.1038/S41541-022-00577-8;SUBJMETA=1629,2293,250,255,590,631,692,699;KWRD=MALARIA,RNA+VACCINES
7. Cid, R., Bolívar, J.: Platforms for Production of Protein-Based Vaccines: From Classical to Next-Generation Strategies. Biomolecules 2021, Vol. 11, Page 1072. 11, 1072 (2021). https://doi.org/10.3390/BIOM11081072
8. Kuehn, A., Pradel, G.: The Coming-Out of Malaria Gametocytes. Biomed Res Int. 2010, 976827 (2010). https://doi.org/10.1155/2010/976827
9. Usui, M., Williamson, K.C.: Stressed Out About Plasmodium falciparum Gametocytogenesis. Front Cell Infect Microbiol. 11, 790067 (2021). https://doi.org/10.3389/FCIMB.2021.790067/REFERENCE
10. Kuehn, A., Pradel, G.: The Coming-Out of Malaria Gametocytes. Biomed Res Int. 2010, 976827 (2010). https://doi.org/10.1155/2010/976827
11. Bennink, S., Kiesow, M.J., Pradel, G.: The development of malaria parasites in the mosquito midgut. Cell Microbiol. 18, 905–918 (2016). https://doi.org/10.1111/CMI.12604
12. Hou, X., Zaks, T., Langer, R., Dong, Y.: Lipid nanoparticles for mRNA delivery. Nat Rev Mater. 6, 1078–1094 (2021). https://doi.org/10.1038/S41578-021-00358-0;SUBJMETA=1436,152,153,308,565,692,700;KWRD=DRUG+DELIVERY,DRUG+DEVELOPMENT
13. Svensson, M., Limeres, M.J., Zeyn, Y., Gambaro, R.C., Islan, G.A., Berti, I.R., Fraude-El Ghazi, S., Pretsch, L., Hilbert, K., Schneider, P., Kaps, L., Bros, M., Gehring, S., Cacicedo, M.L.: mRNA-LNP vaccine strategies: Effects of adjuvants on non-parenchymal liver cells and tolerance. Mol Ther Methods Clin Dev. 33, (2025). https://doi.org/10.1016/J.OMTM.2025.101427/ASSET/63662427-FE39-4547-BF0F-289ECD342632/MAIN.ASSETS/GR6.JPG
14. Conibear, A.C.: Deciphering protein post-translational modifications using chemical biology tools. Nature Reviews Chemistry 2020 4:12. 4, 674–695 (2020). https://doi.org/10.1038/s41570-020-00223-8
15. Coscolla, M., Copin, R., Sutherland, J., Gehre, F., De Jong, B., Owolabi, O., Mbayo, G., Giardina, F., Ernst, J.D., Gagneux, S.: M. tuberculosis T cell epitope analysis reveals paucity of antigenic variation and identifies rare variable TB antigens. Cell Host Microbe. 18, 538–548 (2015). https://doi.org/10.1016/J.CHOM.2015.10.008/ATTACHMENT/44456B09-3E1D-48CE-B3EE-130DF22B958D/MMC11.PDF
16. Kim, S.C., Sekhon, S.S., Shin, W.R., Ahn, G., Cho, B.K., Ahn, J.Y., Kim, Y.H.: Modifications of mRNA vaccine structural elements for improving mRNA stability and translation efficiency. Mol Cell Toxicol. 18, 1–8 (2022). https://doi.org/10.1007/S13273-021-00171-4/METRICS
17. Ochwedo, K.O.: Functional Analysis of Immune Response to Plasmodium Falciparum Gametocytes Surface Antigens Pfs25, Pfs48/45 and Pfs230. (2022)
18. Ko, K.T., Lennartz, F., Mekhaiel, D., Guloglu, B., Marini, A., Deuker, D.J., Long, C.A., Jore, M.M., Miura, K., Biswas, S., Higgins, M.K.: Structure of the malaria vaccine candidate Pfs48/45 and its recognition by transmission blocking antibodies. Nature Communications 2022 13:1. 13, 1–11 (2022). https://doi.org/10.1038/s41467-022-33379-6

19. Parvin, N., Joo, S.W., Mandal, T.K.: Enhancing Vaccine Efficacy and Stability: A Review of the Utilization of Nanoparticles in mRNA Vaccines. Biomolecules 2024, Vol. 14, Page 1036. 14, 1036 (2024). https://doi.org/10.3390/BIOM14081036
20. Hou, X., Zaks, T., Langer, R., Dong, Y.: Lipid nanoparticles for mRNA delivery. Nat Rev Mater. 6, 1078–1094 (2021). https://doi.org/10.1038/S41578-021-00358-0;SUBJMETA=1436,152,153,308,565,692,700;KWRD=DRUG+DELIVERY,DRUG+DEVELOPMENT
21. Kafle, U., Truong, H.Q., Nguyen, C.T.G., Meng, F.: Development of Thermally Stable mRNA-LNP Delivery Systems: Current Progress and Future Prospects. Mol Pharm. 21, 5944–5959 (2024). https://doi.org/10.1021/ACS.MOLPHARMACEUT.4C00826/ASSET/IMAGES/MEDIUM/MP4C00826_0011.GIF
22. Kunkeaw, N., Nguitragool, W., Takashima, E., Kangwanrangsan, N., Muramatsu, H., Tachibana, M., Ishino, T., Lin, P.J.C., Tam, Y.K., Pichyangkul, S., Tsuboi, T., Pardi, N., Sattabongkot, J.: A Pvs25 mRNA vaccine induces complete and durable transmission-blocking immunity to Plasmodium vivax. NPJ Vaccines. 8, 1–10 (2023). https://doi.org/10.1038/S41541-023-00786-9;SUBJMETA=1629,2293,250,255,590,631,692,699;KWRD=MALARIA,RNA+VACCINES
23. Mata, E., Broset, E., Matute, C., Stoian, A., Adame, S., Alejo, T., López, A., Andrés, B., Heredero, J., de Miguel, D., Giménez-Warren, J., Lampaya, V., Casabona, D., Calvo, A., Quincoces, G., Peñuelas, I., Gamazo, C., Uranga, I., Peña, N., Arias, M., Pardo, J., Moreno, B., Badiola, J., Martínez-Oliván, J., Pérez-Herrán, E.: Preserved efficacy of lyophilized SARS-CoV-2 mRNA vaccine incorporating novel ionizable lipids after one year at 25 °C. npj Vaccines 2025 10:1. 10, 1–19 (2025). https://doi.org/10.1038/s41541-025-01201-1
24. Vogel, G.: The "Do unto others" malaria vaccine. Science (1979). 328, 847–848 (2010). https://doi.org/10.1126/SCIENCE.328.5980.847/ASSET/D1B8F432-8BAE-439E-AC0B-5F7F7C45364C/ASSETS/GRAPHIC/328_847_F3.GIF
25. Choe, J.A., Burger, J., Jones, J., Panjla, A., Murphy, W.L.: Opportunities in Therapeutic mRNA Stabilization: Sequence, Structure, Adjuvants and Vectors. Adv Ther (Weinh). 8, 2400537 (2025). https://doi.org/10.1002/ADTP.202400537;REQUESTEDJOURNAL:JOURNAL:23663987;WGROUP:STRING:PUBLICATION
26. Chen, J., Wang, Q., He, X., Yang, B.: Malaria Vaccines: Current Achievements and Path Forward. Vaccines 2025, Vol. 13, Page 542. 13, 542 (2025). https://doi.org/10.3390/VACCINES13050542
27. Marques-Da-silva, C., Peissig, K., Kurup, S.P.: Pre-Erythrocytic Vaccines against Malaria. Vaccines 2020, Vol. 8, Page 400. 8, 400 (2020). https://doi.org/10.3390/VACCINES8030400

CITE AS: Nasira A. Sitar (2025). Transmission-Blocking mRNA Vaccine Platforms against Plasmodiu Gametocytes: Opportunities and Challenges for Field Deployment. IDOSR JOURNAL OF SCIENTIF RESEARCH 10(3):104-108. https://doi.org/10.59298/IDOSRJSR/2024/10.3.104108