**Importance of Genomic Research in Advancing Malaria Treatment in Nigeria: A Mini Review**

 Aderoyeje TG 1,2\*, Erhuanga, OG1

1 Department of Pharmacology and Therapeutics, Faculty of Basic Clinical Sciences, College of Medical Sciences, Edo State University, Iyamho-Uzairue, Edo State.

2 Malaria Research Laboratories, Institute of Advanced Medical Research and Training (IAMRAT), College of Medicine, University of Ibadan, Ibadan, Oyo State.

\*Correspondence author:tope\_forever@yahoo.com; aderoyeje.temitope@edouniversity.edu.ng;  +2348077467765

**ABSTRACT**

**Introduction:**

Malaria remains a critical public health challenge in Nigeria with impact on vulnerable populations, particularly pregnant women and children. The country accounts for 25% of global cases, contributing to high rates of under-five and infant and maternal mortality. Prevalence among pregnant women ranges from 8.4% to 58.1%, leading to severe complications such as high placental parasitaemia and low birth weight. Despite extensive control efforts, malaria infection risk remains at 97% exacerbated by co-morbidities with diseases like HIV/AIDS and Tuberculosis. Inadequate diagnostic methods further complicate eradication efforts, though rapid diagnostic tests (RDTs) have improved accuracy and management. Genomic research has emerged has as a pivotal tool in combating malaria, offering insight into parasite biology, genetic diversity and drug resistance. Techniques such as genetic epidemiology and genetic barcoding enabled detailed tracking of parasite diversity and transmission patterns, aiding the development of targeted interventions. Studies have shown that reduced genetic diversity correlates with lower transmission rates, emphasizing the role of genomic data in understanding malaria dynamics. Additionally, genomic research has facilitated vaccine development by identifying candidate antigens and assessing vaccine efficacy. Innovations like the TriAntiMalTM regimen exemplify the potential for long-term immunity through genomic insights. The identification of genetic polymorphisms linked to drug resistance highlights the need for new treatment strategies, as resistance to existing artemisinin-based combination therapies (ACTs) becomes prevalent.

**Conclusion:**

Overall, integrating genomic data with epidemiological and geographic information systems enhances malaria control programmes, providing a comprehensive approach to understanding clinical features, preventing, and treating malaria. Continued advancement in genomic research is essential for achieving a malaria-free future in Nigeria

**Malaria Epidemiology and Diagnosis in Nigeria**

Nigeria is still wrestling with malaria which has become a significant public health menace. This mosquito-borne disease caused by parasitic protozoans of the genus *Plasmodium* poses a substantial burden on the Nigerian population, especially pregnant women and children 1. Nigeria accounted for about 25% of the total malaria cases globally, 30% of under-five mortality, 25% of infant mortality, and 11% of maternal mortality 2,3,4. The prevalence rate in pregnant women ranges from 8.4% to 58.1% and complications such as high placental parasitemia, fetal complications, low birth weight, and neonatal death are attributed to this high prevalence rate 1,2. Despite the control efforts, the risk of having malaria infection in Nigeria is estimated at 97%, suggesting that the country has a long way to go in its effort to combat malaria and its threat 3.

The problem of malaria infection has been magnified by its co-morbidities with other diseases such as dengue, chikungunya, Zika, tuberculosis, and HIV/AIDS 5. These co-morbidities compound the high childhood and infant mortality rate, and malaria-HIV co-infection in pregnancy affects various biological and clinical outcomes including mother-to-child transmission rate 5. In addition to the current menace of *Plasmodium* infection, recent studies have identified a new species, *P. cynomolgi*, but require further research to determine its prevalence and impact on the African population especially in Nigeria 5,6,7.

Inadequate diagnosis is a major challenge in the effort to eradicate malaria as clinical signs and symptoms are defective resulting in inaccurate diagnosis and unsuitable treatment; laboratory diagnostics such as blood smears using light microscopy are more reliable offering parasite identification, quantification, and therapy response assessment. Nonetheless, implementation is limited, resulting in many undiagnosed or wrongly diagnosed cases 8. To this end, rapid diagnostic tests (RDTs) were introduced due to ease of use, minimal training requirement, and provision of instant results. This solved the challenge of limited implementation of microscopy methods, and improved diagnosis, management, and complications 8.

Despite these efforts, the high prevalence and menace of malaria have remained unresolved, requiring novel approaches for diagnosis, prevention, treatment, and surveillance. Genomic research emerged as a vital tool for combating malaria, offering insights into the parasite’s biology, population dynamics, genetic diversity, drug resistance, drug targets, and host-pathogen relationships 9,10. Genetic epidemiology and genetic barcoding techniques with single nucleotide polymorphisms (SNPs) are examples of genetic approaches allowing researchers to track parasite types, monitor changes in transmission rate, and efficiency of interventions, and characterize genetic diversity with high resolutions 10.

**Role of genomics in diagnosis and malaria therapy**

Furthermore, genetic epidemiology explains the parasite's genetic features underlying transmission patterns such as complexity of infection (COI), diversity, and migration 11. Research showed that an association exists between declines in local malaria transmission rate and reduced parasite genetic diversity stressing the tendency of COI as a proxy for transmission intensity 10. Integrating genomic data with epidemiological and geographic information systems (GIS) data enables researchers to identify hotspots where infection transmission frequently occurs and develop tailored interventions. This leads to better insights into population dynamics, facilitating decision-making for malaria control programs 10.

Genomic research unknots genetic polymorphisms within *Plasmodium* species, explaining variations in chromosome size, gene copy number, and nucleotide alterations; these polymorphisms impact parasite virulence, immune evasion mechanisms, and drug responses. Genomic research also illuminates host-parasite genetic interactions, host immune responses, and adaptation mechanisms 11. *Plasmodium falciparum* genome comprising 14 linear chromosomes and extra-chromosomal DNA circles has been sequenced, allowing for the identification of important structural elements, metabolic pathways, and homology shared among *Plasmodium* parasites 12.

Genomic research identified two types of natural selection in the parasite genome: balancing selection and directional selection. Balancing selection sustains polymorphisms in the parasite’s antigenic genes which are vital for persistence against host immunity. Directional selection is attributed to drug pressure resulting in the rapid rise of drug-resistant variants 12. One key challenge in malaria control is the advent of drug-resistant malaria parasites resulting in antimalarial drug resistance to drugs such as chloroquine, mefloquine, and artemisinin-based combination therapies (ACTs). Genetic research has identified certain genes responsible for resistance such as pfcrt, pfdhfr, and pfdhps driving drug resistance, and justifying the need for immediate treatment substitutes 13. In patients showing artemisinin resistance, Pfmdr1 mutations have been observed to vary, harboring single nucleotide polymorphisms (SNPs), including N86Y and Y184F as most occurring compared to those who showed therapeutic response to artemether-lumefantrine (AL) 13. Furthermore, co-mutations such as N86Y-Y184F significantly contributed to treatment failures in AL 13; studies tracking Pfmdr1 mutations before and after treatment recognized different shifts in the organism’s population under selective drug pressure. However, a marked increase in the occurrence of Pfmdr1 SNPs has been observed, suggesting resistance to AL 13.

Genomic research provides tools for vaccine development through the identification of candidate antigens, predicting T/B cell epitopes, and evaluating vaccine efficacy. Reverse vaccinology and whole-genome sequencing promote conserved epitomes and antigenic targets 11. Also, genomic analyses promote the tailored design of multivalent vaccines for specific parasite populations, enhancing coverage and efficacy in endemic regions. Evidence suggests that the host microbiome influences malaria susceptibility, disease severity, and vaccine efficiency; genomic research reveals the complex interactions between host microbiota, the parasites, and immune responses proffering insights into disease mechanisms and potential therapeutic interventions 9,11. Additionally, genomic research has uncovered the mechanisms underlying the protection, including cytoadhesion of infected red blood cells, and impaired rosette formation. Hemoglobin genotypes such as HbAS and HbAC have been observed to confer protection against severe malaria 9,14.

Genomic research offers a promising approach to understanding the immune response to disease and advancing malaria treatment. A novel approach termed “*in vivo* vaccination,” showed potential complement to conventional vaccine strategies, leveraging humoral, cellular, and innate immunity to confer long-term protection against malaria relapse 15. This approach, exemplified by the TriAntiMalTM regimen, represents a paradigm shift in malaria treatment, offering a one-time treatment regimen with extended immunity periods of up to 14 years in Haiti and two years in Nigeria 15. Polymorphisms in genes encoding interleukins, such as IL12A, IL12B, IL6, IL10, IL18, and IFN-gamma, have been linked to variations in disease susceptibility and severity. For instance, IL12A and IL12RB1 polymorphisms are associated with protection against severe malaria anemia (SMA) in Kenyan children 15,16.

Upregulation of genes encoding defensins, such as DEFA1, DEFB1, DEFB119, and DEFB127, suggests their potential role in combating malaria parasites and conferring immunological memory 15,17,18. While traditionally known for their antimicrobial properties, defensins may play a previously unrecognized role in malaria immunity, offering new avenues for therapeutic exploration. The TriAntiMalTM treatment regimen induces changes in immune gene expression, including upregulation of IFNA1, CD40, and defensin genes, in both children and babies, suggesting a robust immune response against malaria 15,19. Notably, the sustained upregulation of immune regulatory genes, such as DEFA1, long after parasite clearance, indicates the development of immunological memory and potential long-term protection against reinfection 15.

Genomic tools enable the identification of genes associated with drug resistance through linkage and association mappings, including genome-wide association studies (GWAS) 11. Laboratory genetic crosses and whole-genome methods have helped map genetic determinants for specific traits, leveraging the high level of recombination in *P. falciparum* 12. Despite challenges such as low linkage disequilibrium (LD) and population stratification, GWASs are valuable for identifying genetic variants associated with various phenotypes. Sequencing-based approaches show promise for future GWASs in malaria research 12.

In 2019, the Malaria Genomic Epidemiology Network (MalariaGEN) published a comprehensive genome-wide association study (GWAS) of human resistance to severe malaria (SM), using data collected from 11 countries to identify host genetic variants that may confer protection against severe forms of malaria 20. The GWAS analysis identified five replicable associations with genome-wide levels of evidence, including a novel variant on chromosome 6 which is strongly associated with cerebral malaria. These variants collectively accounted for approximately 10% of the estimated heritability of severe malaria. Functional analysis revealed an erythroid-specific transcription start site underlying one of the known associations in ATP2B4, but the causal mechanism at the chromosome 6 locus remained unclear. Advancements in whole genome sequencing (WGS) using next-generation sequencing (NGS) technologies offer improved resolution and coverage of parasite genomes, facilitating the discovery of novel genetic variations relevant for surveillance 21. While large-scale WGS for surveillance purposes may not be practical in resource-limited settings, targeted sequencing approaches hold promise for providing informative genomic data 12,21.

In conclusion, the significance of genomic research in advancing malaria treatment in Nigeria can never be overemphasized. Despite series of control efforts, Nigeria is still battling with a high malaria burden with children, and pregnant women at high predisposition, it is imperative to design innovative approaches to eradicate this public health menace. Genomic research emerged as the crux to unravel the intricacies of parasite biology, transmission dynamics, drug resistance mechanisms, and host-pathogen relationships which proffer insights into targeted interventions. Genomic epidemiology, genetic barcoding techniques, polymerase chain reaction, and genome-wide association studies (GWAS) help researchers track parasite types, monitor transmission patterns, identify drug-resistant variants, and determine genetic determinants of severe malaria. The TriAntiMalTM regimen exemplifies the transformative potential of genomic insights in malaria treatment, offering a paradigm shift towards long-term immunity and protection against relapse. Polymorphisms in immune-related genes not only influence disease susceptibility but also hold implications for immunotherapeutic approaches. Moreover, genomic research holds promise for vaccine development. Targeted sequencing approaches offer a feasible solution for generating informative genomic data in resource-limited settings, thereby enhancing malaria surveillance and control efforts. Importantly, genomic research offers a multifaceted approach to understanding, preventing, and treating this debilitating disease and paving the way towards a malaria-free future for Nigeria and beyond.

**REFERENCES**

* + - 1. Sabina, K. (2017). Prevalence and epidemiology of malaria in Nigeria: a review. *International Journal of Research in Pharmacy and Biosciences*, *4*(8), 10-12.
			2. Bello, F. A., and Ayede, A. I. (2019). Prevalence of malaria parasitaemia and the use of malaria prevention measures in pregnant women in Ibadan, Nigeria. *Annals of Ibadan Postgraduate Medicine*, *17*(2), 124-129.
			3. Nwaneli, E. I., Eguonu, I., Ebenebe, J. C., Osuorah, C. D. I., Ofiaeli, O. C., and Nri-Ezedi, C. A. (2020). Malaria prevalence and its sociodemographic determinants in febrile children hospital-based study in a developing community in South-East Nigeria. *Journal of Preventive Medicine and Hygiene*, *61*(2), E173.
			4. Awosolu, O. B., Yahaya, Z. S., and Farah Haziqah, M. T. (2021). Prevalence, parasite density and determinants of falciparum malaria among febrile children in some peri-urban communities in Southwestern Nigeria: A cross-sectional study. *Infection and Drug Resistance*, 3219-3232.
			5. Obase, B. N., Francis, Z., Forgu, E. L., Honore, A., Bigoga, J. D., and Nsagha, D. S. (2023). The effects of HIV infection on the immune response to malaria among pregnant women in Kumba, southwest Cameroon: protocol for a cross-sectional study. *JMIR Research Protocols*, 12(1), e38213.
			6. Raja, T. N., Hu, T. H., Kadir, K. A., Mohamad, D. S. A., Rosli, N., Wong, L. L., and Singh, B. (2020). Naturally acquired human *Plasmodium cynomolgi* and *P. knowlesi* infections, Malaysian Borneo. *Emerging Infectious Diseases*, *26*(8), 1801.
			7. Kotepui, M., Masangkay, F. R., Kotepui, K. U., and Milanez, G. D. J. (2021). Preliminary review on the prevalence, proportion, geographical distribution, and characteristics of naturally acquired *Plasmodium cynomolgi* infection in mosquitoes, macaques, and humans: a systematic review and meta-analysis. *BMC Infectious Diseases*, *21*, 1-14.
			8. Mac, P. A., Asheadzi, H. F., Gideon, A., Thaker, P., and Airiohuodion, P. (2019). Prevalence of Plasmodium falciparum among Nigerians in Abuja and Central States: A comparative analysis of sensitivity and specificity using rapid diagnostic test and microscopy as tools in the management of malaria. *International Journal of Tropical Diseases*, 1, 014.
			9. Benjamin, G. Y., Benjamin, H. I., Muhammad, H. I. D., and Olayinka, B. O. (2020). Genetic markers associated with antimalarial drug resistance and haemoglobin genotypes among malaria patients in Kaduna State, Nigeria. *Research Square*, 1-13.
			10. Mensah, B. A., Akyea-Bobi, N. E., and Ghansah, A. (2022). Genomic approaches for monitoring transmission dynamics of malaria: A case for malaria molecular surveillance in Sub–Saharan Africa. *Frontiers in Epidemiology*, *2*, 939291.
			11. Su, X., Stadler, R. V., Xu, F., and Wu, J. (2023). Malaria Genomics, Vaccine Development, and Microbiome. *Pathogens*, *12*(8), 1061.
			12. Volkman, S. K., Neafsey, D. E., Schaffner, S. F., Park, D. J., and Wirth, D. F. (2012). Harnessing genomics and genome biology to understand malaria biology. *Nature Reviews Genetics*, *13*(5), 315-328.
			13. Emiliaa, A. E., Victoria, U. C., Christian, M. A., and Okechukwud, N. E. (2016). Prevalence of Pfmdr 1 N86Y and Y184F Alleles is Associated with Recurrent Parasitemia following Treatment of Uncomplicated Malaria with Artemether-Lumefantrine in Nigerian Patients. *Journal of Applied Pharmaceutical Science*, 6(4), 015-021.
			14. Bougouma, E. C., Tiono, A. B., Ouédraogo, A., Soulama, I., Diarra, A., Yaro, J. B., and Sirima, S. B. (2012). Haemoglobin variants and *Plasmodium falciparum* malaria in children under five years of age living in a high and seasonal malaria transmission area of Burkina Faso. *Malaria Journal*, *11*, 1-10.
			15. Thornthwaite, J. T., Olufemi, A. E., Ademola, A. A., and Alli, O. A. T. (2019). DNA Gene Expression to Study Immunologic Mechanisms for the Long-Term Cure of Malaria in Babies and Children in South-Western Nigeria. *Advances in Biological Chemistry*, 9(2), 68-87.
			16. Zhang, L., Prather, D., Eng, J. V., Crawford, S., Kariuki, S., ter Kuile, F., and Shi, Y. P. (2010). Polymorphisms in genes of interleukin 12 and its receptors and their association with protection against severe malarial anaemia in children in western Kenya. *Malaria Journal*, 9, 1-10.
			17. Grishin, D. V., and Sokolov, N. N. (2014). Defensins are natural peptide antibiotics of higher eukaryotes. *Biochemistry (Moscow) Supplement Series B: Biomedical Chemistry*, *8*, 11-18.
			18. Holly, M. K., Diaz, K., & Smith, J. G. (2017). Defensins in viral infection and pathogenesis. *Annual review of Virology*, *4*, 369-391.
			19. Yao, X., Wu, J., Lin, M., Sun, W., He, X., Gowda, C., ... & Su, X. Z. (2016). Increased CD40 expression enhances early STING-mediated type I interferon response and host survival in a rodent malaria model. *PLoS pathogens*, 12(10), e1005930.
			20. Malaria Genomic Epidemiological Network (2019). Insights into malaria susceptibility using genome wide data on 17,000 individuals from Africa, Asia, and Oceania. *Nature Communications*. <https://doi.org/10.1038/s41467-019-13480-z>
			21. Dharia, N. V., Bright, A. T., Westenberger, S. J., Barnes, S. W., Batalov, S., Kuhen, K., and Winzeler, E. A. (2010). Whole-genome sequencing and microarray analysis of ex vivo *Plasmodium vivax* reveal selective pressure on putative drug resistance genes. *Proceedings of the National Academy of Sciences*, *107*(46), 20045-20050.