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Integrating malaria vaccine and CRISPR/Cas9 gene drive: a comprehensive strategy for accelerated malaria eradication

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Abstract

Malaria remains a significant public health challenge, particularly in low- and middle-income countries, despite ongoing efforts to eradicate the disease. Recent advancements, including the rollout of malaria vaccines, such as RTS,S/AS01 and R21/Matrix-M™, offer new avenues for prevention. However, the rise of resistance to anti-malarial medications necessitates innovative strategies. This review explores the potential integration of CRISPR/Cas9 gene drive technology with malaria vaccination efforts to enhance vector control and reduce transmission. By employing gene drive mechanisms for population suppression and replacement of malaria-transmitting *Anopheles* mosquitoes, combined with the immunogenic properties of vaccines, a synergistic approach can be established. This paper discussed the need for integrated strategies to address the biological complexities of malaria and socio-economic factors influencing its prevalence. Challenges such as regulatory hurdles, community acceptance, ecological impacts, and sustainable funding are examined, alongside strategies for implementation within existing malaria control programmes. This integrated approach could significantly contribute to achieving the World Health Organization's targets for malaria reduction by 2030, ultimately enhancing public health outcomes and supporting broader socio-economic development.

Keywords Malaria, Vaccine, CRISPR/Cas9, Gene drive technology

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Background

The age-long campaign to eradicate malaria has witnessed tremendous progress in recent years. The use of insecticide-treated nets (ITNs) and other vector control strategies has yielded significant hope for malaria elimination [1]. Furthermore, recent advancements, such as the roll-out of novel malaria vaccines, usher in a new era for malaria infection prevention [2]. Despite these efforts, malaria continues to pose a formidable public health challenge globally, disproportionately affecting low- and middle-income countries, particularly in the sub-Saharan African region [3]. According to the World Health Organization (WHO), approximately 597,000 malaria-related deaths were recorded in 2023, alongside over 263 million new cases, with 95% originating from the WHO African Region [4].

In the last three years, the WHO has qualified and recommended two malaria vaccines—RTS,S/AS01 (RTS,S) in 2021 and R21/Matrix-M™ in 2023 [1, 4]. These milestones have heightened hopes for achieving global targets to reduce malaria cases, morbidity, and mortality rates by at least 90% by 2030 [4]. Currently, over 2 million children have received a dose of RTS,S/AS01 through regional vaccine implementation programmes [4, 5]. However, these achievements are threatened by the surge of resistance to anti-malarial medications [6], showing the urgent need for innovative strategies that integrate gene therapy and genomic editing to enhance vector control mechanisms. CRISPR/Cas9 technology has emerged as a potent tool for genetic research, allowing precise DNA modifications through the targeted cutting and inserting of genetic information [7]. Leveraging CRISPR/Cas9 for genetic engineering has the potential to combat diseases like malaria by genetically modifying *Anopheles* mosquitoes, making them unable to transmit the malaria parasite or significantly decreasing their populations [8]. This gene drive technology operates in two main ways: population suppression, which reduces mosquito populations, and population replacement, where non-malaria-transmitting mosquitoes are introduced to the existing population [12, 13].

The integration of malaria vaccination with CRISPR/Cas9 gene drive technology represents a promising dual approach that could significantly reduce malaria-associated morbidities and mortalities. Despite the emergence of some unfavourable outcomes associated with these technologies [11, 14], the application of CRISPR methodologies has catalyzed scientific investigations into critical pathways and the optimization of vector control strategies. This perspective paper aims to provide an examination of the synergistic potential of malaria vaccines and CRISPR/Cas9 gene drive technology in the global endeavor to eradicate malaria.

The need for integrated approaches

The fight against malaria, a disease that has plagued humanity for centuries, requires innovative and multifaceted strategies [15]. While traditional treatments, such as chemoprophylaxis, vector control, and vaccination, have long been employed in malaria control efforts, the use of Artemisia annua and its derivatives for malaria treatment emerged only in the late twentieth century despite the plant's earlier historical applications in traditional medicine. Recent global initiatives, however, show the urgent need for integrated and innovative approaches to combat this disease effectively [16]. Since the second global effort to eradicate malaria began in 2006, significant progress has been made in reducing mortality rates and advancing malaria vaccine development through international collaboration and funding [17]. However, despite these advances, existing malaria vaccines have shown limited effectiveness due to the complex interplay between the *Plasmodium* parasite and the human immune system [18].

The WHO established product characteristics for malaria vaccines, targeting a reduction in malaria infections of at least 90% over 12 months and a minimum of 45% over 32 months for certain categories [19]. Historically, vaccines like RTS,S, which targets the circumsporozoite protein (CSP), achieved 46% efficacy in children and 27% in infants during Phase III trials. However, this vaccine had no significant impact on severe malaria incidence during the trials, and immunity waned quickly, necessitating additional booster doses [20, 21]. Despite these limitations, findings from the 2024 World Malaria Report demonstrated that the introduction of RTS,S resulted in a statistically significant 13% reduction in all-cause mortality (excluding injury) and a 22% reduction in hospitalized severe malaria among age-eligible children, underscoring its real-world impact [4]. Moreover, recent CSP-based vaccines, such as R21, have demonstrated reduced efficacy, while blood-stage vaccines targeting various *Plasmodium* proteins have struggled to meet efficacy expectations, with some, like GM22, achieving only 14% efficacy [22]. These challenges show the need for more effective vaccines that can provide durable immunity against malaria.

Gene drive technology, particularly through CRISPR/Cas9, represents a revolutionary approach to malaria control by allowing targeted modifications of mosquito populations to reduce Plasmodium transmission [23, 24]. Despite its potential, gene drive technology faces significant hurdles, including the risk of creating resistant mosquito strains and declining efficacy across generations [25, 26]. Although newer versions of population suppression show no evidence for selection of resistance [27, 28]. Furthermore, ethical concerns regarding irreversible

genetic changes and potential ecological impacts require thorough consideration and active stakeholder engagement to ensure responsible implementation [29–32].

Integrating malaria vaccines with CRISPR/Cas9 gene drive technology represents a transformative strategy in the global fight against malaria, addressing both the biological complexities of the disease and the socio-economic factors that perpetuate its prevalence [33]. The current malaria vaccine landscape is characterized by limited efficacy and short-lived immunity, necessitating innovations that enhance protective responses [17]. Integrating CRISPR/Cas9 gene drive technology offers a complementary approach. Modifying the genetic makeup of mosquito populations to reduce their capacity to transmit malaria presents a viable strategy for decreasing the incidence of malaria infections within vaccinated populations [34]. Gene drives can be designed to introduce genetic modifications that reduce the fertility or lifespan of female Anopheles mosquitoes, the primary vectors responsible for transmitting the *Plasmodium* parasite to humans [35]. This strategic reduction in mosquito populations, when integrated with effective vaccination campaigns, has the potential to significantly lower malaria transmission rates, thereby enhancing the impact of vaccination efforts [36].

The integration of vaccines and gene drive technology can create a synergistic effect that addresses both immediate and long-term challenges associated with malaria transmission. Vaccines are capable of priming the immune system to recognize *Plasmodium* antigens, facilitating rapid immune responses upon subsequent exposure [37]. Concurrently, gene drives can systematically diminish the population of malaria-transmitting mosquitoes and exposure to the malaria parasite, by either decreasing the number of vector mosquitoes or the ability of the parasite to develop within the mosquitoes [38]. For instance, a population-level vaccination strategy could focus on high-risk groups, including children under five and pregnant women, while also implementing the deployment of gene drive mosquitoes in endemic regions. As vaccination coverage increases, malaria transmission will decrease due to the combination of decreased exposure to infected mosquito vectors and decreased parasite development in the human host and selective pressure on the mosquito population would be reduced, resulting in decreased transmission rates [39]. This integrated approach promises not only to lower the incidence of malaria infections but also to mitigate the severity of cases, thereby reducing overall morbidity and mortality rates [40, 41].

Achieving the ambitious target set by the WHO of a 90% reduction in malaria incidence and mortality by 2030 necessitates a strategy that incorporates advancements in both vaccine and gene drive technologies [8]. Furthermore, a broader, coordinated effort is essential. This includes the ongoing development and deployment of effective anti-malarial drugs critical for treating infections and curbing transmission [9]. Community engagement is crucial for educating populations about malaria prevention, vaccination strategies, and the role of gene drive technology. Such engagement fosters trust and enhances the effectiveness of public health initiatives [10]. Moreover, effective vector control strategies must prioritize environmental sustainability, ensuring that the implementation of gene drives minimizes ecological disruption while preserving non-malaria-transmitting mosquito populations [12]. Comprehensive risk assessments, including analyses of potential pathways to harm, are essential to achieve this balance [42–44]. The establishment of robust monitoring systems will be vital for evaluating the effectiveness of these integrated interventions. Continuous assessment will facilitate adaptive management strategies that respond to emerging challenges and shifting epidemiological patterns.

The burden of malaria extends beyond health implications, significantly impacting economic development in endemic regions. Integrating malaria vaccines with gene drive technology can lead to substantial reductions in disease prevalence, resulting in improved health outcomes and increased productivity. Countries heavily burdened by malaria frequently experience impediments to economic growth due to healthcare costs, workforce productivity losses, and diminished educational opportunities. Effectively addressing malaria through integrated strategies not only alleviates direct health impacts but also contributes to broader socio-economic development. This transformation can foster healthier communities, enhance educational outcomes, and create increased economic opportunities, ultimately disrupting the cycle of poverty that malaria exacerbates [45].

Strategy for integration into current programmes

Integrating the combined approach of malaria vaccines and CRISPR/Cas9 gene drive technology into existing malaria control programmes necessitates meticulous planning and coordination. An evaluation of current malaria control initiatives is imperative to identify their strengths, weaknesses, and specific gaps regarding the integration of malaria vaccines and CRISPR/Cas9 technologies. This assessment should involve engaging local health authorities, community stakeholders, and researchers to gain a thorough understanding of how current programmes address malaria transmission. Particular attention should be paid to existing vaccination campaigns and vector control measures, with the aim of determining how CRISPR/Cas9 gene drives can

complement or enhance these efforts by targeting resistant mosquito populations and improving overall transmission dynamics.

Furthermore, fostering collaboration among key stakeholders is vital for creating a unified vision for integrating vaccines and gene drive technologies into established malaria control programmes. This collaboration should encompass government agencies, non-governmental organizations (NGOs), research institutions, and community leaders. Establishing platforms for continuous dialogue and knowledge sharing will facilitate the exchange of best practices, lessons learned, and innovative ideas for leveraging the complementary strengths of vaccines and gene drive technology. Engaging stakeholders early in the integration process will ensure that diverse perspectives inform the development of protocols that optimize the effectiveness of both strategies in reducing malaria transmission [46].

Investing in the training of healthcare workers, field staff, and community members is essential to ensure they possess the requisite knowledge and skills to implement the integrated strategies effectively. Training programmes should focus on the scientific principles underlying both vaccination and gene drive technologies, emphasizing how these approaches work synergistically to enhance malaria control. Additionally, training should highlight the distinct implementation strategies of the two tools: vaccination, which is delivered on an individual basis through healthcare systems, and gene drive mosquitoes, which are deployed on an area-wide basis to impact mosquito populations across regions. Development of educational materials aimed at raising awareness about the benefits and safety of the integrated approach is crucial. These materials should specifically address potential misconceptions regarding gene drive technology and highlight its role in complementing vaccination efforts, thereby fostering community acceptance and support for the integrated strategy.

Moreover, the initiation of pilot projects with gene drive mosquitoes trials that will be done in the context of other malaria control methods currently used at the trial site in select malaria-endemic regions is recommended to test the feasibility, effectiveness, and community acceptance of the integrated strategy before broader deployment [8, 34]. These pilot projects should be designed to assess the simultaneous deployment of vaccines and gene drive mosquitoes, with a focus on evaluating how the two interventions interact in real-world settings. Data collected during these projects will yield valuable insights that can refine implementation protocols, assess logistical requirements, and establish robust monitoring frameworks to track progress and outcomes. Additionally, findings from these pilot projects will be instrumental in informing subsequent larger-scale interventions, ensuring that both vaccination and gene drive technologies are integrated in a way that maximizes their combined impact.

Establishing robust monitoring and evaluation (M&E) systems is critical for assessing the impact of the integrated approach on malaria transmission, community health outcomes, and ecological implications. Real-time data collection mechanisms should be employed to monitor vaccination coverage, mosquito population dynamics, and transmission rates in areas where gene drives are deployed. The M&E framework should include specific indicators that assess the effectiveness of the combined approach, such as reductions in malaria incidence and changes in mosquito behavior. This dynamic evaluation process will enable adaptive management, allowing for prompt adjustments to strategies based on emerging evidence and stakeholder feedback. By continuously assessing the integration of vaccines and gene drive technologies, the approach can remain responsive to evolving challenges and opportunities in malaria control.

Challenges and future considerations

While the integration of malaria vaccines and CRISPR/Cas9 gene drive technology presents a promising strategy for combating malaria transmission, several significant challenges must be addressed to ensure successful implementation and sustainability of this combined approach. Navigating complex regulatory frameworks for gene drive technology is a prominent barrier to integration [47]. The regulatory landscape varies significantly across countries and regions, often encompassing rigorous safety assessments, ethical considerations, and environmental impact studies [8, 47, 48]. To facilitate compliance, it is essential to work closely with regulatory bodies to ensure that all aspects of the integrated strategy meet established guidelines [49]. This requires an ongoing dialogue with policymakers, who play a critical role in shaping regulations that can adapt to emerging biotechnologies. Building a collaborative relationship with these stakeholders will be crucial for promoting timely approvals while ensuring the safety and efficacy of interventions [50]. Additionally, transparency in the regulatory process can help alleviate public concerns, fostering a more conducive environment for the adoption of innovative solutions.

Community concerns about genetic modification and its implications for ecosystems can significantly hinder the acceptance of gene drive technology. Many communities harbour misconceptions regarding the safety and efficacy of genetic interventions, often fueled by misinformation and fear of unintended consequences [51]. To mitigate stakeholder resistance, it is essential to engage in transparent communication, fostering community

education and actively involving local populations in decision-making processes. Strategies should include public forums, workshops, and information campaigns that address common concerns, clarify the scientific basis of the technologies, and highlight potential benefits. Building trust in scientific innovations through open dialogue and community involvement will be key to ensuring broad-based support for the integrated strategy.

The release of genetically modified mosquitoes raises potential ecological concerns, including unintended effects on non-target species and ecosystem dynamics. Comprehensive ecological assessments must be conducted to evaluate these impacts prior to large-scale implementation. These assessments should encompass both short-term and long-term studies to understand how gene drive technology interacts with existing ecosystems [52, 53]. Additionally, establishing monitoring frameworks to track ecological changes post-implementation will be essential. By proactively assessing and addressing potential ecological risks, stakeholders can ensure that malaria control efforts do not inadvertently harm biodiversity or disrupt ecosystem services, ultimately supporting the sustainability of the integrated strategy.

Securing sustainable funding for integrated programmes poses a significant challenge, particularly in low-resource settings where malaria prevalence is often highest [4, 54]. The reliance on external funding can lead to programme discontinuity and hinder long-term planning. To overcome this challenge, partnerships with international organizations, government agencies, and private sector stakeholders will be necessary to support sustained investments in malaria control initiatives. Innovative financing mechanisms, such as public–private partnerships, could be explored to ensure continuous funding and resource allocation. Additionally, leveraging existing funding streams for malaria control to incorporate new technologies can enhance the overall efficiency and impact of resource utilization.

Continuous monitoring of both *Plasmodium* and mosquito populations is vital to detect and address emerging resistance to interventions. The potential for resistance development poses a significant threat to the long-term effectiveness of integrated malaria control strategies. Adaptation strategies must be developed to counteract potential resistance mechanisms, including the integration of complementary interventions that can enhance the durability of both vaccines and gene drive technologies. Ongoing research to understand the dynamics of resistance, including genetic and environmental factors that contribute to it, will be critical in maintaining the effectiveness of integrated strategies. By proactively addressing resistance, stakeholders can enhance the resilience of malaria control efforts and ensure sustained reductions in transmission rates.

Conclusion

The integration of malaria vaccines with CRISPR/Cas9 gene drive technology presents a transformative opportunity to combat malaria, addressing the multifaceted challenges associated with its transmission and impact. As the global burden of malaria continues to weigh heavily on public health systems, particularly in low- and middle-income countries, the necessity for innovative and synergistic strategies has never been more critical. Leveraging the strengths of both vaccination and gene drive technologies can create a robust framework for malaria control that enhances efficacy and sustainability.

The collaborative potential of vaccines and gene drives could revolutionize malaria prevention efforts, yielding substantial reductions in morbidity and mortality. Vaccines can prime the immune system to recognize and respond to *Plasmodium* infections, reducing parasite development in the human host, while gene drives can systematically diminish exposure to the malaria parasite by either decreasing the populations of malaria-transmitting mosquitoes or reducing the parasite's ability to develop within mosquitoes. This dual approach not only targets the disease at different stages but also offers a more resilient strategy against emerging challenges, such as anti-malarial resistance and ecological disruptions. However, realizing this vision requires careful consideration of regulatory, ethical, and ecological challenges. Engaging with communities to foster understanding and acceptance of genetic technologies is essential for ensuring the success of integrated interventions. Furthermore, robust monitoring and evaluation systems will be critical to assess the effectiveness and impact of these strategies on malaria transmission dynamics and ecological health. As the World Health Organization's goal of reducing malaria incidence and mortality by 90% by 2030 approaches, the integration of innovative technologies alongside traditional methods must be prioritized. Establishing strong collaborations among stakeholders, securing sustainable funding, and continuously adapting to emerging evidence will forge a path toward a future where malaria is no longer a pervasive threat to global health. The combined application of malaria vaccines and CRISPR/Cas9 gene drive technology has the potential to reshape approaches to malaria eradication and serves as a model for future public health interventions against complex infectious diseases.

Abbreviations

CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
DNA	Deoxyribonucleic Acid
mRNA	Messenger Ribonucleic Acid

RNA	Ribonucleic Acid
WHO	World Health Organization
GMO	Genetically Modified Organism
IGR	Insect Growth Regulator
TDR	Target Product Profile
WHO-TAG	World Health Organization's Technical Advisory Group
LMICs	Low- and Middle-Income Countries
CDC	Centers for Disease Control and Prevention
SP	Sulfadoxine-Pyrimethamine (an antimalarial drug)
RDT	Rapid Diagnostic Test
PEI	Pathogen-Environment Interactions
SNP	Single Nucleotide Polymorphism
MDA	Mass Drug Administration

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JEA conceptualised the study; All authors were involved in the literature review; JEA & NA extracted the data from the reviews studies; All authors wrote the final and first drafts. All authors read and approved the final manuscript.

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Declarations

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