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Effectiveness of CRISPR-Modified Mosquitoes Versus Insecticide-Treated Nets in Reducing Malaria Transmission: A Review

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ABSTRACT

Malaria remains a major global health challenge, particularly in sub-Saharan Africa, where conventional vector control strategies such as insecticide-treated nets (ITNs) have significantly reduced morbidity and mortality. However, emerging pyrethroid resistance in mosquito populations threatens the long-term efficacy of ITNs, necessitating exploration of novel vector control approaches. This review compared the effectiveness of CRISPR-modified mosquitoes and insecticide-treated nets in reducing malaria transmission to inform integrated malaria control strategies. A narrative review approach was utilised, synthesising evidence from published studies on mechanisms of action, operational feasibility, effectiveness, ecological and ethical considerations, and integration prospects for both interventions. ITNs provide a physical barrier and insecticidal effect, reducing malaria incidence by approximately 50% and all-cause child mortality by 20%. However, widespread pyrethroid resistance undermined their effectiveness. CRISPR-modified mosquitoes, employing gene drive technologies to spread sterility or anti-Plasmodium traits, have demonstrated promising laboratory and semi-field results, achieving near-complete population suppression or high refractoriness rates. Nonetheless, their field efficacy remained unproven, with ecological, evolutionary, and ethical risks necessitating further research. Operationally, ITNs remained more feasible for immediate deployment, whereas gene drives require robust regulatory frameworks, community acceptance, and phased field testing. While ITNs continued as cornerstone interventions in malaria control, CRISPR-modified mosquitoes hold transformative potential if proven safe and effective. Their integration into malaria control programmes, alongside ITNs, could enhance elimination prospects, but deployment must be evidence-based, ethically grounded, and community endorsed to ensure sustainable public health impact.

Keywords: CRISPR-modified mosquitoes**,** Insecticide-treated nets**,** Malaria transmission reduction**,** Gene drive technology**,** Vector control strategies.

INTRODUCTION

Malaria remains one of the world's most devastating infectious diseases, with an estimated 249 million cases and 608,000 deaths reported globally in 2022, disproportionately affecting sub-Saharan Africa [1–3]. Despite significant progress over recent decades through conventional vector control strategies such as insecticide-treated nets (ITNs) and indoor residual spraying, challenges such as insecticide resistance, suboptimal coverage, and operational limitations continue to impede eradication goals. ITNs, primarily treated with pyrethroids, act by physically barring and chemically repelling or killing mosquitoes, thereby reducing human-vector contact and malaria incidence [4]. However, the rise of pyrethroid-resistant Anopheles species in endemic regions threatens the long-term effectiveness of ITNs.

Concurrently, scientific advances have fostered the emergence of novel vector control approaches, notably gene drive technologies using clustered regularly interspaced short palindromic repeats (CRISPR)-Cas systems to genetically modify mosquito populations [5, 6]. These CRISPR-modified mosquitoes are engineered either to suppress vector populations by inducing sterility or to render mosquitoes refractory to Plasmodium infection, effectively reducing transmission potential. Proof-of-concept studies in laboratory and semi-field settings have demonstrated promising outcomes, raising global discourse on their potential role in complementing or replacing traditional interventions such as ITNs. This review compares the effectiveness of CRISPR-modified mosquitoes with insecticide-treated nets

in reducing malaria transmission. It synthesises available evidence on their mechanisms, operational feasibility, field efficacy, ecological safety, ethical considerations, and integration prospects in malaria control programmes. By systematically examining both approaches, this review aims to provide insight for policymakers, researchers, and public health practitioners on optimal vector control strategies as the global health community works towards malaria elimination and eventual eradication. Understanding these comparative dynamics is critical to guide evidence-based decision-making in deploying innovative technologies alongside proven interventions within integrated vector management frameworks.

Mechanisms of Action

i. **Insecticide-Treated Nets:** Insecticide-treated nets function via dual mechanisms: providing a physical barrier and delivering insecticidal action [7]. Pyrethroid-treated nets cause knockdown and mortality upon contact while repelling some mosquitoes due to their excito-repellent effect. Long-lasting insecticidal nets (LLINs) are currently the standard, requiring minimal retreatment and maintaining efficacy for approximately 3 years. By reducing vector density, biting rates, and human-vector contact, ITNs lower entomological inoculation rates (EIR) and malaria incidence in endemic communities.

ii. **CRISPR-Modified Mosquitoes:** CRISPR-modified mosquitoes leverage gene drive technology to bias inheritance of targeted genes throughout populations [8]. Two major strategies are employed: population suppression drives, which spread sterility-inducing or sex-biasing genes to reduce vector populations, and population replacement drives, which insert anti-Plasmodium effector genes conferring refractoriness to infection. Using CRISPR-Cas9-mediated homing endonucleases, these genetic modifications are inherited at super-Mendelian rates, rapidly propagating within mosquito populations to diminish vectorial capacity or competence.

Effectiveness in Reducing Malaria Transmission

i. **Evidence for ITNs:** Multiple randomised controlled trials and meta-analyses have demonstrated that ITNs reduce malaria incidence by approximately 50% and all-cause child mortality by 20% [9, 10]. Large-scale distribution campaigns have yielded substantial declines in malaria prevalence across sub-Saharan Africa. However, pyrethroid resistance has emerged in over two-thirds of endemic countries, leading to reduced mortality and feeding inhibition, threatening the sustainability of ITN-based interventions.

ii. **Evidence for CRISPR-Modified Mosquitoes:** Laboratory and semi-field studies have demonstrated the potential of CRISPR-modified mosquitoes to effectively spread desired traits across populations. In cage trials, gene drives targeting female fertility genes achieved near-complete population suppression within 7-11 generations. Replacement drives expressing anti-Plasmodium effectors have shown up to 99% refractoriness rates in modified mosquitoes [11]. However, no field trials in endemic settings have been conducted, and extrapolation of laboratory success to natural, genetically diverse, and ecologically complex environments remains uncertain.

Operational Feasibility

i. **ITNs:** Operationally, ITNs are well established with defined manufacturing, distribution, and monitoring frameworks integrated into national malaria control programmes [12]. Challenges remain in ensuring universal coverage, promoting consistent usage, and replacing worn nets promptly to sustain protective efficacy.

ii. **CRISPR-Modified Mosquitoes:** Deployment of gene drive mosquitoes requires rigorous risk assessment, regulatory approval, and community acceptance [13, 14]. Mass rearing and targeted releases demand specialised infrastructure and logistical capacity. Additionally, ecological unpredictability, potential for resistance evolution against gene drives, and governance complexities challenge operational feasibility, necessitating robust stakeholder engagement.

iii. **Ecological and Evolutionary Considerations:** CRISPR-based gene drives raise ecological concerns, including unintended off-target mutations, effects on non-target species through ecological interdependence, and potential horizontal gene transfer [15, 16]. Moreover, emergence of resistance alleles that block gene drive spread is a critical evolutionary threat, as observed with naturally occurring resistant alleles in caged populations after multiple generations. Conversely, ITNs pose minimal ecological risk beyond insecticide resistance selection pressure.

iv. **Ethical, Legal, and Social Implications:** ITNs, having been widely adopted for over two decades, are ethically accepted, though their effective use depends on behavioural compliance and socio-cultural factors [17]. In contrast, CRISPR-modified mosquitoes invoke complex ethical considerations around environmental release of self-propagating organisms, consent at community and national levels, intergenerational impact, and potential cross-border effects without recipient country approval. Comprehensive governance frameworks and community-led engagement processes are paramount before deployment.

v. **Integration into Malaria Control Programmes:** Effective malaria control requires integrated vector management (IVM) combining multiple interventions to maximise impact and mitigate resistance [18]. ITNs remain a cornerstone alongside indoor residual spraying, larval source management, and chemoprevention. CRISPR-modified mosquitoes, if proven effective and acceptable, could complement ITNs by targeting residual transmission unaddressed by conventional tools. Mathematical models suggest synergistic reduction in malaria prevalence when gene drives are combined with existing interventions, underscoring the importance of integrated deployment strategies.

Current Research Gaps

While ITNs have an extensive evidence base on field trials and routine programme data, research gaps remain in optimising net durability, insecticide resistance management, and distribution strategies for hard-to-reach populations. Addressing these gaps through multidisciplinary and community-led research is critical to ascertain the safe, effective, and ethical use of gene drive technologies in malaria elimination efforts. For CRISPR-modified mosquitoes, key research gaps include:

i. Field efficacy studies in endemic settings to validate laboratory findings.
ii. Assessment of ecological risks and evolutionary stability in complex environments.
iii. Development of robust regulatory and governance frameworks for responsible deployment [19].
iv. Community acceptance studies to inform social licensing processes [20].
v. Strategies to mitigate resistance evolution against gene drives [21].

Future Directions

The future of malaria vector control lies in leveraging innovations alongside proven interventions. ITNs will continue to play a vital role given their established operational framework and impact, though integrating novel net chemistries and dual active ingredients is necessary to overcome resistance threats. CRISPR-based gene drive mosquitoes represent a potentially transformative tool to achieve local elimination, particularly in settings with persistent residual transmission despite high ITN coverage [22]. Strategic field trials, phased testing, and adaptive management are necessary to refine their deployment within IVM programmes.

Collaborative partnerships involving endemic country governments, affected communities, research institutions, and international agencies are essential to ensure that gene drive research, regulation, and implementation uphold public health goals while safeguarding ecological and social interests. Moreover, establishing cross-border governance mechanisms is critical given the transboundary nature of mosquito populations and gene drive spread.

CONCLUSION

In conclusion, insecticide-treated nets remain a proven, effective intervention in reducing malaria transmission and mortality, though their sustainability is challenged by escalating insecticide resistance. CRISPR-modified mosquitoes offer a promising novel approach by targeting vector populations genetically to suppress or replace malaria transmission capacity. Laboratory and semi-field studies have demonstrated high effectiveness of gene drives in controlled settings; however, critical research gaps persist regarding their field efficacy, ecological safety, evolutionary stability, ethical acceptability, and regulatory governance. A direct comparison reveals that while ITNs are immediately deployable and operationally feasible, CRISPR-modified mosquitoes are still under development, with real-world effectiveness yet to be established. Nonetheless, their integration with existing interventions within an evidence-based, ethically grounded, and community-endorsed framework could revolutionise malaria control and accelerate global elimination targets. Future malaria vector control strategies should thus adopt a cautious but proactive approach towards gene drive technologies, ensuring that rigorous scientific evidence, community participation, and environmental stewardship underpin their potential deployment. As technological innovations converge with traditional public health tools, malaria elimination prospects will depend on strategic, integrated, and ethically responsible utilisation of all effective interventions available.

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