

REVIEW ARTICLE

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The Genomic Arms Race in Mosquito-Borne Diseases: Integrating Entomopathogenic Fungi, Gene Drive, and Symbiont Technologies for Sustainable Vector Control

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Abstract

Mosquito-borne diseases such as malaria, dengue, Zika, chikungunya, and lymphatic filariasis continue to impose enormous health and economic burdens worldwide. The traditional reliance on chemical insecticides has been undermined by the rapid evolution of resistance, ecological concerns, and declining efficacy. Next-generation biocontrol strategies are framed within the concept of a “genomic arms race” between mosquitoes, pathogens, and microbial agents. Entomopathogenic fungi are eco-friendly bioinsecticides with demonstrated efficacy in laboratory, semi-field, and transgenic applications. Symbiont-based approaches, particularly those involving *Wolbachia*, have been evaluated for their ability to reduce vector competence and spread through populations. Parallel advances in CRISPR-based gene drive technologies have provided transformative tools for population suppression and modification, although their deployment is limited by ethical, ecological, and regulatory concerns. An integrated vector management (IVM) framework combining fungi, gene drives, and symbiont-based tools is proposed as the most promising approach for sustainable mosquito management. This multipronged strategy has the potential to reduce disease transmission, delay resistance development, and minimize ecological disruption, paving the way for resilient, eco-friendly solutions against vector-borne diseases.

Keywords: Mosquito management, Entomopathogenic fungi, *Wolbachia*, Gene drive, Vector-borne Diseases, Genomic Arms Race, Integrated Vector Management

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INTRODUCTION

Mosquitoes are among the most important vectors of human and animal diseases, responsible for transmitting malaria, dengue, Zika virus, chikungunya, and lymphatic filariasis. Together, these diseases account for hundreds of millions of cases annually and continue to impose heavy public health and economic burdens worldwide.¹ Malaria alone accounted for an estimated 249 million cases and over 600,000 deaths in 2022, whereas dengue is now considered the most rapidly spreading arboviral disease, with half of the world's population at risk.² Emerging arboviruses, such as Zika and chikungunya, have further highlighted the vulnerabilities of global vector surveillance and control programs.³ Globally, mosquito-borne diseases exert a tremendous economic burden on public health systems and national economies. The cumulative cost attributed to *Aedes* mosquitoes and their associated arboviruses from 1975–2020 is estimated at US\$ 94.7 billion, averaging approximately US\$ 3.29 billion per year, with peaks reaching ~US\$ 20.9 billion in 2013.^{4,5} At a national scale, Brazil's dengue vector control programs have consumed nearly US\$ 1 billion each year, underscoring the immense fiscal pressure of mosquito management in endemic regions.⁶

Historically, vector control has relied heavily on chemical insecticides, which have been applied through indoor residual spraying, space spraying, and insecticide-treated nets.⁷ Although these interventions contributed significantly to malaria reduction in the early 2000s, their long-term effectiveness is now undermined by widespread resistance to insecticides. Resistance to pyrethroids, organophosphates, and carbamates has been documented in major mosquito genera, including *Anopheles* and *Aedes*.^{8,9} This resistance not only reduces the efficacy of control tools but also threatens to reverse the progress in malaria and arbovirus management.¹⁰ Moreover, chemical-based interventions raise environmental and public health concerns, including non-target impacts, bioaccumulation, and community hesitancy toward large-scale spraying.¹¹ The ability to develop resistance to both synthetic and biological insecticides, compounded by ecological pressures, poses a major challenge to

arboviral management in tropical regions.¹² Global climate change is facilitating the expansion of mosquito habitats and prolonging transmission seasons, thereby increasing the potential for the transmission of dengue, Zika, and chikungunya in regions that are not traditionally endemic.¹³

Notably, resistance has extended beyond synthetic insecticides and now encompasses biological larvicides and botanical formulations. Field populations of *Aedes aegypti* L. (Diptera; Culicidae) and *Culex quinquefasciatus* Say (Diptera; Culicidae) have shown reduced susceptibility to the microbial larvicide *Bacillus thuringiensis israelensis* Barjac (Bti) (Bacillales; Bacillaceae) in several regions, linked to repeated exposure and selection pressure.¹⁴ Similarly, tolerance to *Lysinibacillus sphaericus* Meyer and Neide (Bacillales; Bacillaceae) formulations has emerged in African and Asian mosquito populations, driven by midgut receptor mutations that reduce toxin binding efficiency.¹⁵ Furthermore, cases of reduced sensitivity to botanical insecticides, such as neem (*Azadirachta indica*) and pyrethrum-based formulations, have been observed due to adaptive metabolic detoxification mechanisms in *Aedes albopictus* (Skuse) and *Anopheles stephensi* Liston (Diptera; Culicidae).^{16,17}

The limitations of insecticide-based approaches underscore the urgent need for sustainable, evolution-resilient, and environmentally friendly alternatives to vector management. Innovative approaches, such as entomopathogenic fungi (EPF), gene drive technologies, and symbiont-based interventions (e.g., *Wolbachia*), represent promising tools to complement and eventually replace the reliance on chemicals.^{18,19} This review explores these next-generation strategies through the lens of the “genomic arms race”, the co-evolutionary struggle between mosquitoes, pathogens, and microbial control agents, and evaluates their roles in shaping sustainable mosquito-borne disease management.

The genomic arms race: Mosquito-pathogen-microbe interactions

The transmission of mosquito-borne diseases is shaped by a continuous co-evolutionary struggle between mosquito vectors, pathogens, and the microbial agents influencing these dynamics. This interaction, often described

as a “genomic arms race”, involves reciprocal adaptations that determine the vector competence and disease outcomes.

Mosquitoes possess a complex innate immune system that defends against invading pathogens through several key pathways, including Toll, immune deficiency (IMD), Janus kinase/signal transducer and activator of transcription (JAK-STAT), and RNA interference (RNAi).²⁰ These pathways orchestrate antimicrobial peptide expression, melanization, and cellular immunity, which restrict pathogens such as *Plasmodium* and arboviruses.²¹ In response, pathogens have evolved immune evasion strategies, including the suppression of signaling cascades and the exploitation of mosquito midgut microbiota.²² For instance, *Plasmodium* ookinetes secrete proteins to evade melanization, whereas the dengue virus modulates RNAi pathways to enhance replication.²³

Microbial symbionts and entomopathogenic fungi (EPF) play important roles in shaping evolutionary dynamics. Endosymbionts, such as *Wolbachia*, modify host immunity and reduce vector competence by enhancing reactive oxygen species (ROS) production and interfering with pathogen replication.^{18,19} Similarly, gut microbiota have been shown to modulate immune priming and affect susceptibility to infection.²⁴ Entomopathogenic fungi (EPF), such as *Metarhizium anisopliae* (Metchnikoff) Sorokin (Hypocreales: Clavicipitaceae) and *Beauveria bassiana* (Balsamo) Vuillemin (Hypocreales: Cordycipitaceae), are known to activate the Toll and IMD pathways. However, they frequently circumvent host immune defenses by secreting immune-suppressive metabolites.^{25,26}

From the perspective of the pathogen, adaptation to mosquito immunity and microbial competitors is crucial for successful transmission. Arboviruses display high genomic plasticity, which enhances their fitness across multiple mosquito species,²⁷ Similarly, malaria parasites continually evolve antigenic diversity to evade immune recognition in both vertebrate and invertebrate hosts.²⁸ This ongoing interplay forms a triangular evolutionary battlefield among mosquitoes, pathogens, and their microbial associates.

Comprehending these arms race dynamics is essential, as they contribute to the

development of innovative vector management strategies. By exploiting microbial symbionts and EPF, researchers can develop natural antagonists of mosquito vectors and their pathogens. Moreover, genetic technologies such as CRISPR-based gene drives can directly modify mosquito immunity or reproduction, potentially reshaping the evolutionary balance among vectors, pathogens, and microbes.^{29,30}

Entomopathogenic fungi as Eco-friendly Mosquito biocontrol agents

Entomopathogenic fungi (EPF) have emerged as promising and environmentally sustainable alternatives to chemical insecticides for mosquito management. Unlike conventional chemical agents, fungi such as *M. anisopliae* and *B. bassiana* infect mosquitoes through direct contact with their cuticles. The fungal conidia adhere, germinate, and penetrate the hemocoel, where they proliferate by depleting nutrients and releasing insecticidal metabolites, ultimately leading to the death of the host.³¹ This unique infection route reduces the likelihood of resistance development compared with chemical insecticides.^{32,33}

Recent advances in fungal biotechnology have further enhanced their biocontrol potential. Transgenic *Metarhizium* strains engineered to express anti-*Plasmodium* effector molecules or insect-selective toxins exhibit rapid killing and transmission-blocking efficacy in malaria-endemic regions.³⁴ Wang et al. highlighted that engineered fungal systems, when integrated into vector management frameworks, can complement genetic and symbiont-based tools by providing strong short-term suppression.³⁰

The efficacy of EPF is often influenced by environmental conditions, with high humidity favouring spore viability, whereas UV radiation reduces persistence in open environments.³⁵ Recent advancements in formulation science, encompassing oil-based emulsions, nanoparticle carriers, and electrostatic spraying technologies, have effectively addressed these limitations.³⁶ Recent studies have highlighted the potential of diverse *Metarhizium* and *Beauveria* species as sustainable mosquito biocontrol agents (Table). For instance, a transgenic *Metarhizium pingshaense* Chen and Guo (Hypocreales;

Table. The use of EPF strains and their efficacy against mosquito vectors

EPF strain	Country	Formulation	Mechanism	Outcome
<i>M. pinghaense</i> (Transgenic strain)	Burkina Faso	Engineered fungus expressing anti- <i>Plasmodium</i> peptide	Effector proteins blocking parasite development	Rapid mosquito mortality and complete <i>Plasmodium</i> transmission blocking in semi-field trials. ³⁷
<i>M. anisopliae</i> TK-6	India	Solid-state fermentation (rice bran substrate), conidial suspensions (10 ⁵ -10 ⁶ conidia/mL)	Cuticle penetration, spore adhesion, secondary metabolites <i>quinquefasciatus</i> at 10x conidia/mL within 96 hrs. ³⁸	96% larval mortality in <i>Ae. aegypti</i> and <i>Culex</i>
<i>B. bassiana</i> (myco-synthesized AgNPs)	India	Myco-synthesis of silver nanoparticles (36-60 nm), tested against larval instars	Silver nanoparticle toxicity + fungal metabolites	$LC_{50} = 0.79$ ppm; $LC_{90} = 1.09$ ppm; 100% mortality in 1 st -2 nd instars; up to 86.6% in late instars
<i>B. bassiana</i> strain MHK	USA	Laboratory bioassay using conidial suspensions (1 × 10 ⁶ conidia/ml) applied to <i>A. gambiae</i> and <i>Ae. albopictus</i> larvae	Cuticular penetration; hyphal proliferation in hemocoel; production of Beauvericin and Bassianolide toxins	85%-95% larval mortality at 1 × 10 ⁶ conidia/ml; delayed pupation and adult emergence. ³⁹
<i>B. bassiana</i> strain BBPTG4	Mexico	Spore suspension bioassay (1 × 10 ⁶ conidia/mL) against <i>Ae. aegypti</i> adults	Cuticle infection; enzymatic degradation via proteases and chitinases; toxin secretion	$LT_{50} = 7.5$ days for BBPTG4; cumulative mortality > 90% after 10 days. ⁴⁰

Clavicipitaceae) expressing anti-*Plasmodium* peptides demonstrated near-complete blocking of disease transmission in semi-field trials,³⁷ whereas indigenous isolates such as *M. anisopliae* TK-6 from India achieved up to 96% larval mortality in *Ae. aegypti* and *C. quinquefasciatus*.³⁸ *B. bassiana* nano formulations induced over 90% mortality in *Anopheles* and *Aedes* species.^{39,40} These findings reaffirm the adaptability of EPFs and their potential for integration into environmentally sustainable mosquito control programs.

Molecular and immunological responses of mosquitoes to fungal infections

Mosquitoes possess a multilayered immune defense system that is rapidly activated following exposure to EPF such as *M. anisopliae* and *B. bassiana*. Initial recognition occurs via pattern recognition receptors (PRRs) that detect fungal cell wall components, triggering canonical innate immune pathways, such as the Toll, IMD, and JAK-STAT pathways.⁴¹ These cascades lead to the upregulation of antimicrobial peptides (AMPs), including defensins, cecropins, and gambiains, which contribute to fungal growth suppression.⁴² Melanization, mediated by the prophenoloxidase (PPO) cascade, is a critical component of the antifungal immunity of mosquitoes.⁴³ Activation results in the encapsulation of fungal hyphae and the production of cytotoxic intermediates that restrict fungal proliferation.⁴⁴ Experimental silencing of immune-related genes, such as *Relish*, *STAT-A*, and Polyphenol Oxidase (PPO) enzymes, significantly enhances fungal pathogenicity, underscoring the importance of these pathways in defense.⁴⁵

Interestingly, immune responses against fungi often overlap with antiviral and antiparasitic defenses, suggesting a shared evolutionary origin of mosquito immunity.⁴⁶ For example, RNA interference (RNAi)-mediated knockdown of *Dicer-2* and *Argonaute-2* increases fungal susceptibility, linking antiviral RNAi to antifungal defense.⁴⁷ Moreover, fungal infections can dysregulate mosquito physiology by modulating oxidative stress pathways, metabolism, and gut microbiota composition.⁴⁸ Symbiotic bacteria further complicate this interaction. *Wolbachia*-infected *Ae. aegypti* display altered susceptibility to *Metarhizium* infections, likely due to the symbiont-

induced priming of the Toll and IMD pathways.⁴⁸ This complex crosstalk illustrates how mosquito immunity is continuously shaped by interactions among fungi, symbionts, and pathogens.⁴⁹ Collectively, molecular and immunological investigations demonstrate that fungal infections

in mosquitoes are not passive occurrences; rather, they activate intricate host defense mechanisms.

Symbiont-based strategies: *Wolbachia* and microbial interference

Wolbachia, a maternally inherited intracellular bacterium, is a promising symbiont-

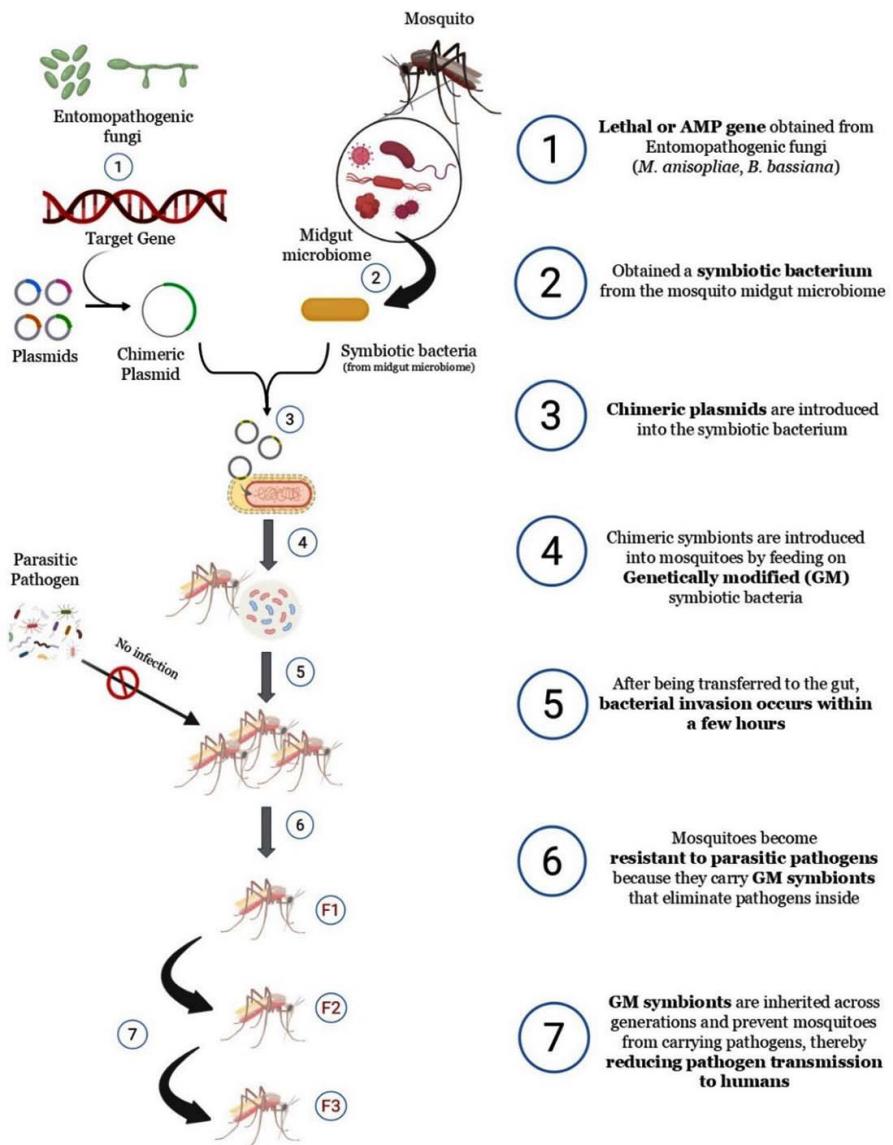


Figure 1. This schematic illustrates the workflow for developing genetically modified (GM) symbionts for mosquito vector control. Antimicrobial or lethal genes are selected from EPF and inserted into plasmids, which are introduced into symbiotic bacteria isolated from the mosquito midgut. These chimeric symbionts are reintroduced into mosquitoes through feeding, colonize the gut within hours, and inhibit pathogen development. Over successive generations (F1-F3), GM symbionts are vertically transmitted, maintaining pathogen resistance and reducing disease transmission potential

based mosquito control tool. Its ability to manipulate host reproduction through cytoplasmic incompatibility enables rapid spread through mosquito populations.¹⁸ Importantly, several strains, including wMel and wAlbB, can block the replication of arboviruses, such as dengue, Zika, and chikungunya, thereby reducing their transmission capacity.⁵⁰ Field deployments have provided robust epidemiological evidence of this efficacy. The Applying Wolbachia to Eliminate Dengue (AWED) trial conducted in Indonesia reported a 77% reduction in dengue incidence in regions where *Wolbachia* was released.⁵¹ *Wolbachia* large-scale releases in Brazil resulted in significant reductions in the incidence of dengue, Zika, and chikungunya, despite its heterogeneous prevalence.⁵² Similarly, city-wide deployments in Colombia have demonstrated stable establishment and reduced arbovirus incidence.⁵³

Recent innovations in symbiont-based mosquito control extend beyond natural *Wolbachia* infections to paratransgenic strategies that utilize genetically modified (GM) symbiotic bacteria.⁵⁴ These bacteria, derived from the mosquito midgut microbiome, can be engineered to express antimicrobial peptides (AMPs) or lethal effector molecules that inhibit or destroy pathogens inside the mosquito.⁵⁵ Once reintroduced, these modified symbionts colonize the gut, establish stable populations, and can be vertically transmitted across generations, providing a self-sustaining and eco-friendly control mechanism. Such approaches have shown potential to disrupt the transmission of arboviruses by blocking pathogen development at the vector stage.⁵⁶ The overall workflow of this paratransgenic system, from gene selection to transgenerational pathogen interference, is illustrated in Figure 1.

At the molecular level, *Wolbachia* infection alters mosquito gene expression, particularly in immune and metabolic pathways, which may underlie its antiviral effects.⁵⁷ The stability of *Wolbachia* has been confirmed in long-term studies, with wMel strain persisting in Australian populations for over a decade without significant loss of viral blocking capacity.⁵⁸ Likewise, wAlbB strain has shown thermal stability and robust blocking capacity across diverse mosquito genetic backgrounds.⁵⁹ These outcomes are consistent with findings from Abbasi, who

highlighted that biological interventions such as *Wolbachia*-based control play a central role within integrated vector management (IVM) frameworks.^{60,61}

Interactions between *Wolbachia* and Entomopathogenic fungi

The interplay between *Wolbachia* symbiosis and EPF adds a crucial layer of complexity to mosquito management. While *Wolbachia* infection generally enhances host immunity and reduces susceptibility to arboviruses,⁶² it may also confer partial protection against fungal pathogens, thereby limiting the effectiveness of fungal biocontrol.⁶³ Laboratory assays have revealed that *Wolbachia*-infected *Ae. aegypti* exhibit reduced mortality when challenged with *B. bassiana*, suggesting antagonistic interactions mediated by immune priming.^{64,65} Conversely, studies have indicated that engineered *M. pingshaense* strains can overcome these defenses by delivering insect-specific toxins, achieving higher virulence even in *Wolbachia*-carrying populations.²⁴

Recent studies have indicated that these interactions are context-dependent. In some *Anopheles* and *Culex* species, *Wolbachia* coinfection does not reduce fungal infection rates, suggesting potential synergism.²⁹ Moreover, fungal infections may suppress *Wolbachia*-induced reproductive advantages, influencing cytoplasmic incompatibility dynamics.⁶⁶ Field studies in Africa and Southeast Asia suggest that combining fungal sprays with *Wolbachia* releases could enhance vector suppression if strain compatibility and environmental parameters are optimized.^{29,61} Future research should focus on the effects of genetic background, host immune trade-offs, and temperature stressors that may shift the balance between fungal virulence and *Wolbachia*-mediated protection.^{67,68} Collectively, these findings position *Wolbachia*-fungus interactions as both a challenge and an opportunity in next-generation integrated vector management.

Gene drive technologies: CRISPR-based vector suppression

Gene drive systems exploit biased inheritance to rapidly spread engineered traits through mosquito populations, surpassing classical Mendelian expectations. With the advent of

CRISPR-Cas9 editing, highly efficient drives have been constructed in *Anopheles* mosquitoes, designed for two primary goals: population suppression and modification.^{69,70} Suppression drives target fertility-associated genes such as double sex, leading to sterile females and population collapse in caged trials.⁷¹ Modification drives aim to introduce refractory traits that block *Plasmodium* or arbovirus development in mosquitoes, thereby reducing the transmission potential.^{72,73}

Recent advancements have augmented the gene drive toolkit by incorporating split-drive systems, temperature-sensitive drives, and localized or self-limiting drives. These innovations enhance biosafety and facilitate controlled propagation within semi-field environments.⁷⁴ These innovations reflect a shift toward reversible and geographically confined drives, addressing early ecological concerns about uncontrollable

spread.⁷⁵ Multiplexing guide RNAs and targeting conserved genomic regions are strategies that have been proposed to mitigate resistance.⁷⁶

In addition to molecular barriers, ecological and ethical considerations are central to gene drive deployment. Field releases raise questions regarding irreversible ecological changes, non-target effects, and community acceptance.⁷⁷ Global policy discussions have emphasized the importance of containment, reversibility, and governance prior to widespread application.^{78,79}

Advances in next-generation CRISPR-based gene drive systems, including self-limiting and Cas12a-based designs, now offer greater precision and control, mitigating some of these earlier concerns.⁸⁰ Such innovations, supported by recent modeling and semi-field studies, suggest that responsibly deployed drives could substantially reduce malaria transmission in

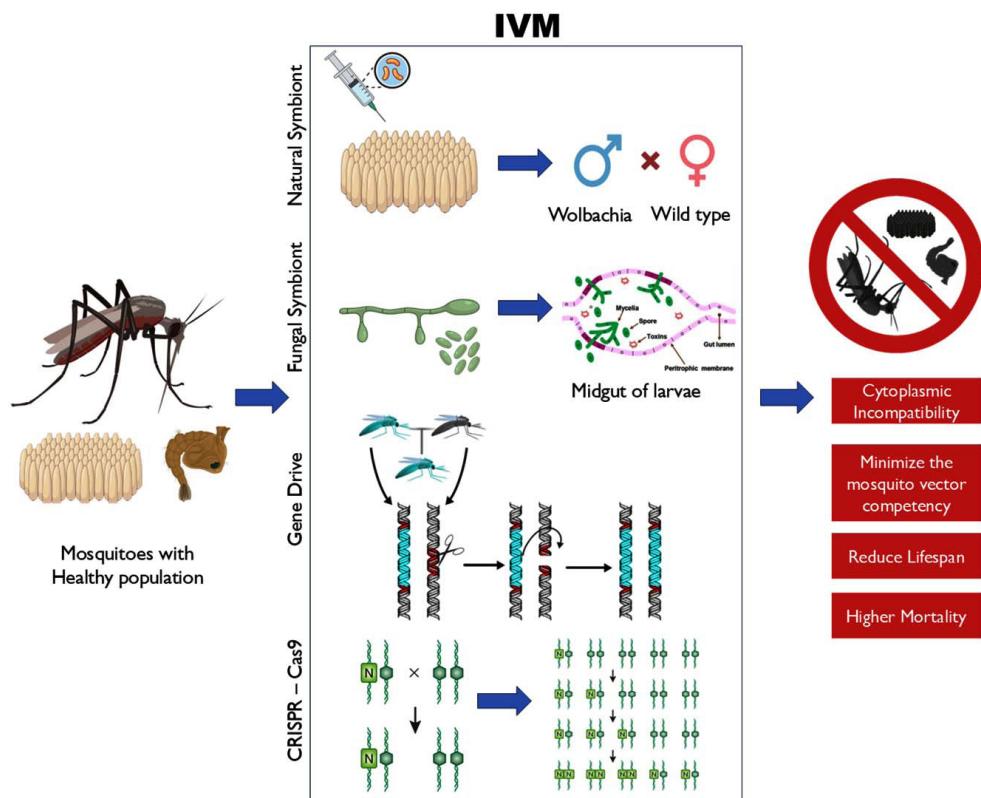


Figure 2. This schematic illustrates the integrated vector management combining EPF, natural symbionts, and gene drives

endemic regions.⁸¹ Although CRISPR gene drives are not yet ready for large-scale release, they remain a transformative tool for rigorous scientific and ethical evaluation.

Integrating fungi, gene drives, and symbionts in vector control

Sustainable mosquito management requires a shift from single-method to integrated strategies. EPF, gene drives, and symbiont-based methods are complementary tools with unique strengths that can overcome the limitations of insecticide-based management strategies. EPF, such as *M. anisopliae* and *B. bassiana*, provide rapid population suppression through direct infection and pathogenicity. Moreover, recent advances have enabled the engineering of fungal strains capable of expressing antiparasitic effectors that target malaria parasites within mosquitoes.⁸² Gene drive systems, particularly CRISPR-based drives targeting fertility or pathogen transmission, offer long-term suppression or modification; however, they face resistance evolution and regulatory concerns.^{83,84} *Wolbachia* spreads through populations by inducing cytoplasmic incompatibility, a reproductive mechanism that prevents uninfected females from producing viable offspring with infected males, thereby favouring the spread of infection.^{85,86}

The integration of these methods offers synergistic potential: fungi provide short-term suppression, gene drives enable self-propagating modification, and *Wolbachia* provides ecological persistence. Studies indicate that combining microbial and genetic tools can reduce the selective pressure on vectors and pathogens, slowing resistance evolution and enhancing sustainability.^{19,87} Moreover, integrated strategies fit within the World Health Organization (WHO) framework of Integrated Vector Management (IVM), enhancing sustainability and social acceptance (Figure 2).^{61,88}

Ethical considerations

The use of advanced biocontrol technologies such as *Wolbachia*, gene drives, and engineered fungi raises important ethical questions. This encompasses ensuring informed consent from the community, clearly communicating potential

risks, and equitably sharing the benefits and responsibilities of these interventions.⁷⁵

Gene drives, in particular, pose challenges because they can spread rapidly through wild populations once they are released. This raises concerns about who has the right to decide when and where such releases should take place, especially in regions that are most affected by mosquito-borne diseases but may have limited regulatory capacity.^{77,89} Examples from *Wolbachia* field programs in Australia, Brazil, and Indonesia show that early community engagement and transparent communication are essential for public acceptance.⁹⁰ The Eliminate Dengue Program (now known as the World Mosquito Program) succeeded largely because it involved local communities in decision-making and used culturally sensitive outreach strategies.⁹¹ These experiences provide useful models for the ethical planning and implementation of future gene drive projects.

Ecological and environmental risks

Ecological risks associated with these biocontrol methods include potential effects on non-target species, disruption of food webs, and unpredictable evolutionary changes. Engineered fungi may persist in the environment longer than anticipated, potentially affecting native microbial communities. Similarly, *Wolbachia* infections can introduce ecological uncertainty through horizontal transfer to other insect species or by changing the natural microbiota.¹⁹

Gene drives pose the greatest ecological concern because they can spread rapidly and permanently alter mosquito populations across ecosystems and national borders. Although molecular safeguards, such as threshold-dependent drives, split drives, and reversal systems have been developed to limit these risks, their reliability in natural settings remains uncertain.⁷⁷ Comprehensive environmental monitoring and adaptive management strategies must accompany any field release to detect unintended ecological consequences and resistance evolution.

Regulatory and governance frameworks

The regulatory oversight of biocontrol technologies remains uneven across regions.

While *Wolbachia* field trials have received approval in several countries, gene drive research is still limited to laboratory and semi-field settings because of biosafety concerns.⁹¹ Coordinated international regulation is essential, as mosquitoes and their genetic modifications can cross national borders.⁹²

Global bodies such as the WHO, Convention on Biological Diversity (CBD), and Cartagena Protocol on Biosafety are working to establish guidelines for safe testing and deployment.⁹³ However, there is currently no globally binding framework that clearly defines standards for gene drive research, risk assessment, or responsibility in the case of cross-border impacts.³⁰ Integrating ethical, ecological, and social considerations into these regulations is vital to ensure transparency, accountability, and public trust.

Ultimately, responsible vector control innovation requires balancing the urgent need for sustainable mosquito management with precautionary principles.^{92,93} Transparent risk communication, participatory decision-making, and iterative policy reviews can help align technological innovations with societal values. Stakeholder engagement, spanning scientists, policymakers, ethicists, and affected communities, will determine whether integrated strategies using fungi, symbionts, and gene drives gain societal acceptance and regulatory approval.

CONCLUSION

Mosquito-borne diseases continue to pose a major global health challenge, intensified by the spread of insecticide resistance and the adaptive resilience of vector populations. Although historically effective, traditional chemical control methods are no longer sufficient on their own. Emerging biological and genetic tools, such as *M. anisopliae* and *B. bassiana*, *Wolbachia*-based symbiont strategies, and CRISPR-based gene drives offer innovative alternatives for sustainable mosquito suppression and disease prevention.

The future of mosquito control depends on the integration of these complementary methods within an integrated vector management framework. For example, EPF can deliver immediate population suppression, whereas

Wolbachia ensures a long-term reduction in vector competence, and gene drives can provide durable genetic modifications for resistance management. Pilot programs could explore sequential or combined field applications, such as releasing *Wolbachia*-infected mosquitoes in areas pre-treated with fungal biocontrol agents to maximize the short- and long-term impact.

To effectively implement these strategies, researchers should focus on optimizing the compatibility between biological and genetic interventions. Policymakers must establish clear biosafety and regulatory guidelines, and public health authorities should prioritize community engagement and transparent risk communication to foster social acceptance. Rigorous ecological monitoring and adaptive management are essential to ensure environmental safety and long-term effectiveness.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors listed have made substantial, direct, and intellectual contributions to the work and approved it for publication.

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ETHICS STATEMENT

Not applicable.

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