



NEXT-GENERATION VECTOR CONTROL TOOLS IN THE ERA OF WIDESPREAD INSECTICIDE RESISTANCE: OPPORTUNITIES AND LIMITATIONS (REVIEW)

Sarah Nair Abdul Ameer Aljumaily

Ministry of Education, General Directorate of Al-Qadisiyah Education, Diwaniyah, Iraq
Email: sarah.nair@ec.edu.iq

Abstract. In this study we believe that throughout the decades vector-borne diseases (e.g. malaria, dengue, chikungunya and leishmaniasis) remain important public health problems especially in tropical and subtropical areas. Chemical insecticides have served as a traditional foundation for vector control programmes with significant effect in reducing disease burden. Despite these advancements, the rapid development and dissemination of insecticide resistance in major vectors have diminished the effectiveness of traditional vector control methods such as indoor residual spraying (IRS) and long-lasting insecticidal nets (LLINs). This scenario has triggered the advances in next-generation vector control tools that are designed to either mitigate insecticide resistance, increase durability of insecticidal effects and allow for more sustainable management of vector populations. This review combines up-to-date evidence on new chemical, biological, genetic, environmental, and digital vector control strategies and their relative effectiveness in resistance-prone environments. We summarize progress in several areas, including dual-active-ingredient nets, novel insecticide formulations, gene-drive and sterile-insect technologies, Wolbachia-based strategies and environmental management interventions prioritised with greater coordination enabled by expanded research into surveillance or modelling. We assess the available data strength, operational feasibility, economic considerations and ethical & regulatory constraints for each category. We also argue how these tools can be best integrated in a complete, multi-sectoral vector management context to delay resistance emergence and prolong effectiveness over time. Lastly, we delineate important knowledge gaps and research priorities in order to support evidence-based policy and programmatic decision-making. This review aims to improve rational deployment strategies for next-generation tools by providing a clarifying overview of the opportunities as well as the limitations of them, in an era characterised by widespread insecticide resistance.

Keywords: Vector-borne diseases; Insecticide resistance; Next-generation vector control tools; Long-lasting insecticidal nets; Genetic and biological control strategies

Introduction

Vector-borne diseases, including malaria, dengue, chikungunya, and leishmaniasis, remain major public health concerns in tropical and subtropical regions. The scale-up of insecticide-treated nets and indoor residual spraying has contributed substantially to the reduction of malaria transmission and disease burden [1], [2]. However, this progress is increasingly threatened by the rapid development and geographical spread of insecticide resistance in major vector species, particularly *Anopheles* and *Aedes* mosquitoes [3], [4].

Various mechanisms cause insecticide resistance, including target-site mutations in voltage-gated sodium channels or acetylcholinesterase, enhanced metabolic detoxification via overexpressed cytochrome P450s, esterases and glutathione-S-transferases, and behavioural changes causing a reduction in contact with treated surfaces [3], [5]. High levels of resistance alleles have been selected by ongoing highly uncoordinated insecticide use in both public health and agriculture, exacerbated by weak resistance management practices and limited surveillance capacity in many endemic countries [6], [7]. As a result, the continued effectiveness of pyrethroid-only LLINs and standard IRS has diminished in many areas with evidence of reduced entomological impact and epidemiological protection [8], [2]. These trends have acted as a catalyst for a worldwide search for new tools and approaches capable of counterbalancing the ever-increasing levels of resistance facing vector control.

Faced with these challenges, a new generation of vector control tools, including innovations in chemistry and formulation technology, genetics [9] biological control [10] environmental management [11] and digital surveillance [12], [13], [14] has emerged. In chemical approaches, the only combinations are dual-active-ingredient LLINs combining pyrethroids with novel insecticides or synergists chlorfenapyr, pyriproxyfen, or piperonyl butoxide to restore efficacy in highly pyrethroid-resistant areas [15], [16]. Likewise, novel IRS formulations based upon different chemistries or improved persistence have been utilized to create a more diversified insecticide arsenal with an effort to limit dependence on any one class [3], [7]. These tools are small but significant advances toward better chemical control in environments, such as southern U.S. strawberries, where resistance is a substantial problem. Apart from chemical innovations, a variety of biological and genetic strategies are emerging as potential game-changers for vector control. Gene drive systems based on CRISPR technologies aim to propagate phenotypes that either reduce vector populations or make these vectors refractory to pathogen transmission [9], [17]. Mass release of sterilised (sterile insect technique [SIT]) or *Wolbachia*-infected males has resulted in reduced *Aedes* populations and dengue incidence during pilot programmes, supporting the application of sterile insect technique (SIT) and incompatible insect technique strategies to mosquito population suppression [10], [18]. A third paradigm is represented by *Wolbachia*-based replacement approaches, where pathogen-blocking endosymbionts can be released into vector populations to affect vector competence rather than vector density [19]. Although these approaches are at different stages of development and implementation, they all highlight the growing definition of “next-generation” technologies beyond traditional insecticides.

Simultaneously, environmental and ecological interventions continue to be the pillars of sustainable vector control. Integrated vector management (IVM) frameworks encourage evidence based combinations of larval source management, modification of habitats, measures for protecting personal and selective use of insecticides according to local epidemiological and ecological settings [11], [20]. Advancements in geospatial technologies, remote sensing, and mathematical modelling have allowed for more precise mapping of vector habitats, explained variance in transmission risk and patterns of resistance which can help inform smarter, adaptive interventions [14], [12]. Digital surveillance platforms and decision-support tools also strengthen the ability of programs to monitor changes in vector behavior, abundance, and susceptibility an essential step toward proactive resistance management [14], [7].

However, important limitations and uncertainties stand in the way of next-generation vector control tools. Operational challenges—for example the need for adequate supply chains, technical training, infrastructure and long-term financing—may also preclude their uptake and scale in resource-poor settings [13], [7]. There remain few economic evaluations and cost-

effectiveness analyses for many new technologies, thus creating challenges for national programmes in setting priorities and procurement [21], [12]. Ethical, regulatory and social considerations, particularly with genetic approaches ecological impact, governance, public acceptance issues are especially pressing in need of careful transparency and participatory processes [9], [17]. In addition, previously unexplored long-term effects of new chemistries on resistance selection and potential multi-resistance require detailed, longitudinal investigation [3], [15].

The need for a thorough synthesis of current knowledge on next-generation vector control tools has never been more pressing, to appraise their efficacy in the context of widespread insecticide resistance, identify potential opportunities to rejuvenate vector control and outline constraints that may limit their impact. This synthesis is intended to collate and distil: i – the epidemiological and operational context of insecticide resistance; ii – major categories of next-generation tools, including chemical, biological, genetic, environmental and digital innovations; iii – their strengths and limitations in resistance-prone settings; and iv – key laboratory research priorities and policy consideration for integrating these tools into comprehensive multi-sectoral vector management strategies [12], [13], [7]. The review aims to clarify both the potential and the limitations of next-generation approaches to help make rational, evidence-based decisions about how best to wield a new toolbox for vector control in an era increasingly defined by widespread insecticide resistance [3], [4].

Methods

This study used a structured narrative review to synthesize evidence on next-generation vector control in settings affected by insecticide resistance. The review considered peer-reviewed research, field trials, systematic reviews, and technical guidance relevant to malaria and Aedes-borne diseases. Sources were assessed for their contribution to five predefined domains: innovative chemical tools, biological and genetic approaches, environmental and ecological interventions, digital surveillance and decision-support systems, and integrated vector management.

Evidence was included when it described intervention mechanisms, entomological or epidemiological outcomes, operational feasibility, durability, resistance-management implications, economic considerations, or ethical and regulatory issues. The synthesis was qualitative because the included evidence differed in study design, target vector, outcome definition, and implementation setting. Findings were grouped thematically, compared across tool categories, and interpreted in relation to effectiveness, scalability, equity, and the strength of available evidence. No meta-analysis was conducted.

Results and Discussion

Results

Current status of insecticide use and resistance

Since the mid-20th century, vector control for malaria and other vector-borne diseases has relied heavily on insecticide-based interventions that initially consisted of large-scale indoor residual spraying (IRS) with organochlorines such as DDT, but during the decades to follow rapidly expanded to include organophosphates, carbamates and pyrethroids [22], [2]. The availability and widespread use of pyrethroid-treated long-lasting insecticidal nets (LLINs) has changed the course of malaria control, offering personal protection as well as community-level reductions in vector density and transmission [1], [2]. Aedes control programs for dengue, chikungunya and Zika virus disease, often featuring space spraying/thermal fogging in urban settings as a backbone of integrated vector management [23], [24] are similarly based on ubiquitous reliance on insecticides such as pyrethroids and organophosphates. Such reliance on a small number of chemistries has placed strong selection pressure for resistance in several vector species. Insecticide resistance has been reported for every major class of pyrethroids, organophosphates and carbamates in use today through a time period spanning the last 20 years; *Anopheles gambiae* and *Anopheles funestus* with widespread pyrethroid resistance in sub-Saharan Africa [4], [6]. The mechanisms underlying resistance are typically linked to pairs

of target-site mutations — as in the case with voltage-gated sodium channels known as knockdown resistance (kdr) — and enhanced metabolic detoxification regulated by cytochrome P450 monooxygenases, esterases and glutathione-S-transferases [3], [5]. Pyrethroid resistance in *Aedes aegypti*, which has been associated with kdr and metabolic mechanisms, has also shown similar patterns across populations from Latin America, Asia, and the Middle East [23], [25]. This complicates control of Races and limits the effectiveness of simple insecticide rotations.

In evaluations of LLINs and IRS in the field, signs of operational repercussions due to resistance are becoming apparent. Examining the consequences of resistance on transmission dynamics, studies from multiple African countries have documented decreased survival of malaria vectors in laboratory assays and reduced mortality when exposed to pyrethroid-only LLINs compared with pre-resistance exposure (when resistance was rare), revealing lower effect sizes for reductions in entomological inoculation rates (EIR) or malaria prevalence for similar exposures [8], [26]. Pyrethroid resistance has been linked with reduced residual efficacy of IRS and protective effects from standard LLINs, and this poses a threat to the sustainability of current control strategies [2], [4]. However, operational failures of pyrethroid-based space spraying campaigns against dengue have been associated with resistance in *Aedes* populations, leading to little or temporary reductions in adult mosquito densities and incidence of disease [23], [25]. These observations emphasise that resistance is not simply laboratory science but an operational facilitator to programme success. In response to this threat, many global and regional initiatives have supported insecticide resistance monitoring and management. The GPIRM of the World Health Organization encourages regular susceptibility tests, inclusion of resistance data in decision making and rotation of insecticide classes for IRS and LLINs [11], [7]. However, implementation of recommendations from GPIRM was uneven and many endemic countries faced challenges with laboratory capacity, trained personnel, funding and data systems [7], [12]. In practice, most changes in insecticide policies are reactionary than proactive and only occur after clear programme failures have already occurred rather than as result of early warning signals [13], [6]. But this lag between the detection of resistance and a response operational sets back control efforts by allowing increasing populations to become even further established and to disperse.

These challenges are compounded by the ever-decreasing number of effective insecticides for public health use. For a number of years, only the pyrethroids as class was approved for LLINs and from options for IRS were very limited (only few organophosphates, carbamates; neonicotinoids and pyrroles more recently) [22], [2]. The presence of cross-resistance between agricultural and public health uses of similar compounds complicates this issue even further: vector resistance most frequently requires a record of exposure to agricultural usage in the same area or scenarios where vectors breed within, or near, agricultural landscapes [6], [25]. Growing the crops by applying insecticide generally results in selecting resistance of vector species sharing and exploiting such environments, creating a feedback loop undermining health and agricultural advances [6], [23]. As a result, there is increased awareness that effective management of resistance can no longer be limited to sectors but should address the combined pressures from public health and agricultural insecticide use. In this context, innovative vector control tools have been designed to overcome resistance and diversify the number of interventions available. The long-term effects of dual-active-ingredient LLINs on resistance selection are currently under investigation, but when combining a pyrethroid with either chlorfenapyr, pyriproxyfen or piperonyl butoxide these nets have shown entomological and epidemiological performance improvements in areas of high pyrethroid resistance when compared to their respective pyrethroid only nets [15], [16], [27]. New IRS products based on alternative chemistries (such as clothianidin or a combination of active ingredients) create opportunities to move away from traditional classes and implement more strategic resistance management approaches [2], [12]. Simultaneously, biological, genetic, environment, and digital innovations described later in this review into more specific two-pronged approaches to limiting vector abundance and transmission (in combination with conventional mosquito control tools) aim at declining the overall insecticide dependence [9],

[19]. So, having knowledge on the ground about where do we stand with insecticide use and resistance is crucial to appraise collaborative realistic capabilities and shortcomings of these novel tools.

Categories of next-generation vector control tools

Next-generation vector control tools are being developed in a paradigm shift from the single interventional reliance on insecticides-based interventions to diversified “toolboxes” that can harness chemical, biological, genetic, environmental and digital innovations [11], [12]. These tools are intended to revitalize or augment efficacy where there is increased insecticide resistance, minimize reliance on a limited portfolio of chemistries and inform the development of sustainable vector control approaches [3], [9]. This section establishes the major classes of next generation tools, describing their underpinning principles and supporting evidence base.

Innovative chemical tools and formulations

Innovative chemical tools, especially dual-active-ingredient LLINs and new IRS formulations are among the main areas of focus. Dual-active-ingredient LLINs are characterized by the association of a pyrethroid with a second active ingredient or synergist (chlorfenapyr, pyriproxyfen, or piperonyl butoxide), designed to be used against pyrethroid-resistant malaria vectors [15], [16]. Some dual-active nets outperformed pyrethroid-only nets for both malaria incidence (WNGI meta-analysis) and vector density in areas of high resistance in cluster-randomised trials in Benin, Tanzania and elsewhere across Africa [16], [27]. Newer IRS products based on clothianidin or mixtures of active ingredients also have long residual activity and alternative modes of action to those with which mosquitoes typically develop resistance, and these products can be an important part of insecticide resistance management when used judiciously [2], [12].

Biological and genetic approaches

Second, generation techniques with rapid evolution are the biological and genetic approaches. Proof-of-concept studies in laboratory populations [9], [17] have shown that CRISPR/Cas systems can be used to develop gene drive technologies to spread traits which would reduce vector populations or render them refractory to pathogen transmission. Sterile insect technique (SIT) and incompatible insect technique (IIT) methods rely on mass-rearing and release of sterile or Wolbachia-infected males that will reduce wild female fertility, eventually leading to population density reductions in the vector species [18], [19]. In a different, complementary approach where the focus is on targeting vector competence rather than abundance, Wolbachia-based population replacement strategies involve releasing endosymbionts into vector populations to inhibit pathogen transmission [10], [19]. The biological/Genetic tools have yielded favourable results in field trials, particularly for Aedes-borne diseases and are currently being used in a malaria context.

Environmental and ecological interventions

Another category is environmental and ecological interventions — the core of integrated vector management (IVM). The goal of this approach is to limit breeding sites, mainly in urban or peri-urban locations [11], [20] through different protocols for larval source management (habitat modification, drainage and filling as well as targeted larviciding). Ecological strategies also include the use of biological control agents (e.g. larvivorous fish or entomopathogenic bacteria) and housing improvements that minimize vector entry and provide less suitable resting sites. Interventions targeting the environment and ecology can reduce baseline vector densities and thus increase the impact of insecticide-based tools, as well as provide resistance management by lowering both the extent and intensity of chemical selection pressures when used in combination with IVM frameworks [11], [28].

Digital surveillance and decision-support tools

The fourth category includes digital surveillance systems and decision-support tools that allow for more accurate, responsive, and data-informed vector control. Developments in geospatial analysis, remote sensing and mathematical modelling have allowed more accurate mapping of vector habitats, human-vector contact behaviors, and disease risk to better optimize the deployment of interventions [14], [12]. Real time digital surveillance platforms amalgamate entomological, epidemiological and insecticide resistance data to facilitate immediate changes

in control methods such as insecticide rotation (change of active ingredient) and the introduction of dual-active nets or increased environmental management [7]. Lastly, data collection tools such as smart traps and sensor-based monitoring devices complement these contributions by enhancing the capacity for rapid detection of changes in vector density or behaviour that would allow programmes to engage proactively with emerging threats such as resistance or behavioural avoidance [14], [28].

Integrating diverse tools within a coherent framework

The real power of next-generation vector control tools will not be in any universal intervention, but in their appropriate combination in unified, context-based strategies. Integrated vector management focuses on the selection and piloting of tools from amongst different those available, based on local epidemiology, entomology, resources and community preferences to maximise health impact while reducing environmental and economic costs [11], [28]. This encourages the use of dual-active LLINs and new IRS formulations as part of integrated vector control measures with biological and genetic strategies, environmental management, alongside more widely discussed digital surveillance to synergistically reduce transmission whilst delaying resistance evolution [12], [9]. What is needed to integrate these tools effectively in practice are strong evidence on the effectiveness and safety, cost-effectiveness, social acceptability of each tool when utilized as an integrated package but with their own strengths and weaknesses, and governance structures that can coordinate across sectors (food systems-planning-education-health) and levels (global-national-subnational-local).

Discussion

The reviewed evidence indicates that next-generation vector control is most persuasive when technologies are treated as complementary components of an adaptive programme rather than as isolated replacements for conventional measures. Dual-active-ingredient nets and alternative IRS chemistries currently have the clearest route to near-term operational deployment, whereas Wolbachia-based strategies offer strong epidemiological promise for Aedes-borne diseases [15], [16], [19]. Gene-drive approaches remain earlier in the translational pathway because ecological uncertainty, reversibility, consent, and transboundary governance require more extensive assessment [9], [17], [29], [30].

Across all categories, effectiveness depends on local vector ecology, resistance mechanisms, delivery capacity, community acceptance, and sustained surveillance. Environmental management can reduce baseline vector abundance and chemical selection pressure, while digital systems can improve the timing and targeting of intervention changes [12], [14], [11], [20], [31]. The principal policy implication is therefore to select intervention packages using local epidemiological and entomological evidence, monitor performance continuously, and revise the package when resistance, behaviour, cost, or acceptability changes. This interpretation is consistent with integrated vector management guidance [11], [28].

Opportunities and limitations

The next generation of vector control tools provides pathways to enhance control programmes in settings heavily affected by widespread insecticide resistance. For instance, dual-active-ingredient LLINs showed much better entomological and epidemiological performance compared to pyrethroid-only nets in many cluster-randomised trials of relatively low augmented residual efficacy with substantially more reductions in malaria incidence and child infection prevalence from higher resistance areas of Tanzania and Benin [16], [32]. Such improvements translate into real health benefits, and provide a practical way to partially counteract loss of net effectiveness where standard LLINs have become much less effective. With regard to economics, some analyses indicate that certain dual-active nets may represent either a cost-effective or a cost-saving use of resources compared with pyrethroid-only LLINs, due to the greater impact of these products on malaria episodes, healthcare utilization and lost productivity as compared with each pyrethroid-only LLIN [32], [12]. New IRS products with non-conventional insecticides and long-lasting residual activity can also limit the number of spray rounds and further diversify the portfolio to enhance resistance management under continued effective protection [2], [12]. Collectively, these chemical innovations increase the operational choices programs face and provide less reliance on one class of insecticides.

For really straight forward stuff, biological and genetic tools offer more transformative options. These results suggest that our findings represent a novel vector manipulation and may provide an effective complement or even alternative to traditional insecticide-based methods, as has been demonstrated by the substantial reductions in dengue incidence achieved with Wolbachia-based interventions in large field trials [19], [33]. Cell free nucleic acid-based methods (e.g., CRISPR/Cas9) are examples of gene drive technologies currently in the very early stages of development and with the ability to achieve much more specific and enduring genetic changes to a target vector population via either suppression or replacement strategies, if correctly deployed they have the potential to greatly decrease transmission [29], [34]. Such strategies are especially appealing in situations where the effectiveness of traditional tools is reduced by insecticide tolerance or ecological restrictions on applied control tactics. Digital surveillance and decision-support systems generate additional opportunities by increasing precision, timeliness, and responsiveness of vector control. Novel surveillance technologies—including very sensitive molecular diagnostics, sensor-based traps and high-throughput open cloud data platforms—improve the capacity of programmes to track natural shifts in their vectors' abundance, behaviour and resistance and facilitate prompt readjustment of control strategies [31], [7]. Complex systems can then be integrated with geospatial modelling and predictive analytics to present a directed deployment of interventions, optimise resource allocation and evaluate the real-world impact of new tools over time [31], [12].

Finally, the integration of diverse next-generation tools within broader frameworks, such as integrated vector management (IVM), offers the opportunity to create synergistic combinations that reduce transmission while slowing resistance evolution. By lowering baseline vector densities through environmental management, enhancing personal and community protection via improved nets and IRS, and manipulating vector populations using biological and genetic strategies, programmes can build layered interventions that are more resilient to single-point failures. This integrated approach aligns with global calls for sustainable, ecologically sound vector control in the face of complex and evolving threats. Despite their promise, next-generation vector control tools face significant limitations and challenges that must be carefully considered. For dual-active-ingredient LLINs, emerging evidence indicates that some products may not sustain their initial advantages indefinitely, with signs that pyrethroid resistance can continue to intensify even under deployment of certain next-generation nets [16], [32]. Questions remain about the long-term selection pressures exerted by novel chemistries, the potential for cross-resistance with existing insecticides, and the durability of physical and chemical net performance under real-world conditions [12], [35]. Moreover, higher procurement costs and limited manufacturing capacity can constrain large-scale adoption, particularly in low-resource settings.

Both biological and genetic approaches have some very significant scientific, operational, and ethical challenges. Wolbachia-based approaches necessitate ongoing community buy-in, extensive infrastructure for mass propagation and releases, long-term monitoring procedures to maintain stability and delivery efficacy – all of which are expensive and institutionally demanding [19]. For example, gene drive technologies can pose a risk of ecological harm, dissemination outside ecologically-competent target populations, evolution of resistance by organisms to the drive elements and transboundary governance issues including consent [30]. Frameworks for assessing some risks, the regulatory systems, and the conditions that might be appropriate for field trials and later deployment are still being worked out.

Although next-generation surveillance tools provide enhanced sensitivity and specificity, their technical, financial, and infrastructural barriers remain a limitation. Advanced molecular diagnostics, sensor-based traps, and integrated data platforms to monitor mosquito populations require specialised equipment, stable electricity and internet access, trained personnel and long-term maintenance all conditions not easily maintained in many endemic areas [31]. In other words, these systems risk being pilot projects without adequate capacity-building and funding to develop them into routine programme operations. They must also ensure that data privacy, interoperability and governance issues are adequately handled so that digital tools enable rather than complicate decision-making.

A more general consideration, common to all groups, is the challenge of establishing firm long-term evidence on their effectiveness, safety and cost-effectiveness under varying epidemiological and ecological conditions. The next generation of tools have been evaluated in only a few settings or under trial conditions that do not necessarily represent routine programme implementation. However, scaling up solutions that appear promising in projections often exposes unanticipated operational challenges relating to supply chain capacity, maintenance needs and variability across communities is also an important consideration. To facilitate evidence-based policy decisions, there is a compelling need for harmonised evaluation frameworks, standardised endpoints, and comparative studies of next-generation tools to established interventions.

Finally, there are the limitations imposed by governance, financing, and equity considerations. However, investing in advanced technologies in health systems that are already financially constrained and juggling conflicting local needs raises challenges with respect to opportunity costs and broader public health implications. A formidable ethical and political challenge is to ensure that low- and middle-income countries, where the burden of vector-borne diseases is highest, have genuine access to next-generation tools, a role in decisions arising from new medicines targeting vectors and an equitable share in the benefits stemmed from innovation. In the absence of resolving these systemic inequities, the promise of next-generation vector control remains unfulfilled or may even exacerbate existing inequalities in disease control.

While next-generation vector control tools hold great promise, their real-world utility will rest on the successful assessment and operationalization across a range of epidemiological and operational contexts. However, key uncertainties persist around long-term durability, resistance selection, ecological safety, cost-effectiveness and large-scale feasibility for some of the innovations that demonstrate measurable gains in reducing transmission or overcoming pyrethroid resistance. As these questions remain unanswered, there is a clear need for an evidence base to help guide policy decisions, optimise deployment strategies, and increase the likelihood that technological innovation creates lasting public health benefits rather than transient or context-limited gains.

Knowledge gaps and future research directions

Although plenty of progress has been achieved in developing next-generation vector control tools, significant knowledge gaps remain that hinder their optimal deployment and long-term impact in resistance-prone settings. One gap identified is that of timely and harmonised evaluation frameworks for comparison of novel interventions across many epidemiological, entomological and operational settings. However, for each of these newly emerging tools, we have conducted research studies using different endpoints, study spans and implementation ideas making it very hard to interpret the significance of findings across studies resulting in a weakened evidence base on which to support policy developments. To address this data and evidence gap, future studies should focus on developing standardised protocols for measuring entomological efficacy, epidemiological impact, residual performance, durability, community acceptability and cost-effectiveness by tool categories.

A second large gap concerns lack of information on the long-term evolutionary consequences of implementing new chemical and non-chemical interventions. However, the impact of new formulations in relation to intensity of resistance, cross-resistance, behavioural adaptation and selection pressure for multi-mechanism resistance over longer time periods remain largely unknown, despite early findings supporting the short- to medium-term improvements expected with dual-active-ingredient LLINs and novel IRS formulations. Deciding whether such interventions are capable merely of delaying resistance or can actually shift vector populations to new resistance trajectories will require longitudinal studies that monitor actual insecticide efficacy and mortality rates over multiple transmission seasons. They should also include genomic and transcriptomic surveillance to identify precursors of adaptive failure as early warning signals.

The knowledge gaps are also quite similar for biological and genetic tools. In contrast, Wolbachia-based interventions require more supportive evidence on the medicine mechanism of long-term stability and efficiency assessed in diverse climate zones, eco-epidemiological

settings and urbanization levels as well considering them to be a type of performance end-product in regards to how much variation those factors exert on populations and transmission systems to rationally assimilate coverage (town level dispersal) for definitive impact. Unresolved issue of resistance to drive constructs, ecological spillover, transboundary governance, reversibility and reliability of predictive models under field conditions are among the most critical wells in gene drive technologies. To address safety and risk management challenges, future studies should integrate laboratory experiments, semi-field trials, ecological modeling, and social science methods to ensure that rigorous biosafety and ethical assessment are matched by technical innovation and governance preparedness.

Another research priority involves surveillance systems and data integration. High-quality data on species composition, biting and resting behaviour, breeding ecology, insecticide resistance mechanisms and intervention acceptability form the backbone of effective next-generation vector control but remains sparse or very localised in many endemic settings. Vector behaviour and susceptibility can vary considerably over short spatial and temporal scales; consequently, tools that perform well in one setting may not do well in another. Future work should invest in integrated surveillance platforms integrating entomological, epidemiological, climatic, genomic and operational-level data to support adaptive decision-making and targeting of interventions with greater precision.

These insufficiencies also extend to operational and implementation research. Although several next-generation tools hold promise when assessed under developmentally controlled trial conditions, far fewer studies have considered the performance of these tools when embedded within routine public health systems—and especially with the type of organizational complexity (eg, budget limitations, procurement lags, workforce bottlenecks, heterogeneous community uptake) that exists in real-world settings. Thus, research should extend not only to efficacy per se but also to implementation fidelity, scalability, integration with ongoing programme flow and supply chain resilience; and institutional imperatives for enduring delivery. Less often, it is absolutely possible that cost-effectiveness comparisons of intervention packages instead of individual tools attract more attention, because control programmes sometimes contribute to one strategy in practice. Ultimately, the challenges of vector control research must take into account and solve for any social, ethical and equity issues. For interventions like Wolbachia releases, driving genes, and housing-associated environmental control measures, the degree to which these limitations are important determinants of effectiveness is anticipated to relate to community acceptance, trust in science and technology, perceived risk and willingness-based adoption or support. Low- and middle-income countries, which suffer the worst of the burden from vector-borne diseases, need to be included not just as sites of implementation but in prioritisation, governance, regulation, and benefit-sharing. When combined, these knowledge gaps signal that in addition to technology development, the future of next-generation vector control will depend as much on better evidence, improved systems and equitable governance frameworks to convert innovation into enduring public health impact.

Conclusions and Recommendations

The increase and widespread distribution of insecticide resistance in major vectors has revolutionized vector control, highlighting the fragility of approaches that depend largely on a limited suite of chemical tools. Next-generation vector control interventions—dual-active-ingredient nets, novel IRS formulations, biologicals, other genetic approaches, environmental and digital innovations—are required to evolve the growing portfolio of available intervention options beyond incremental improvements in established methods. These tools provide genuine opportunities to either regain or increase restored efficacy in situations where traditional insecticides are being compromised, diversify modes of action and create more robust control programmes that can better weather changing selection pressures through ecological and evolutionary processes. However, the analysis in this review shows that next generation tools are not a silver bullet. Vector dynamics, pathogen transmission, ecological landscape, human behaviour in human–mosquito interactions and health system capacity

combine to determine their performance. Furthermore, most of these interventions are either at relatively early deployment stages, and their long-term effects on resistance pathways (extinction debt), ecosystem integrity or social acceptance remain poorly understood. The innovation promise will only become a reality when new tools are implemented as part of comprehensive framework for surveillance, resistance management and integrated vector control, and not as stand-alone patchwork technological fixes.

However, the pressing issue now is how to synthesise accumulating portfolios of innovative interventions into cohesive and contextually appropriate strategies that are clinically efficacious, operationally pragmatic, economically viable and publicly acceptable. It will demand persistent investment in multidisciplinary research, bolstered evaluation and monitoring structures, and governance setups that address risk disclosure whilst facilitating the involvement of impacted communities and nations. A rational, evidence-based deployment of the next-generation vector control tools under a background of extensive insecticide resistance for instance combined with housing improvements, environmental management and health system strengthening will be an achievable pathway for stabilising then driving down the burden of vector-borne diseases. But success is more likely to stem from programme and policy-makers assembling and managing an integrated "toolbox" that strategically, adaptively, and equitably makes use of the full range of approaches available rather than on any single technology.

References

- [1] S. Bhatt et al., "The effect of malaria control on *Plasmodium falciparum* in Africa between 2000 and 2015," *Nature*, vol. 526, no. 7572, pp. 207-211, 2015.
- [2] World Health Organization, *World Malaria Report 2022*. Geneva, Switzerland: WHO, 2022.
- [3] J. Hemingway, F. C. Shenton, L. A. Prapanthadara, M. Coleman, and N. J. Hawkes, "The molecular basis of insecticide resistance in mosquitoes," *Insect Biochemistry and Molecular Biology*, vol. 46, pp. 3-11, 2016.
- [4] H. Ranson and N. Lissenden, "Insecticide resistance in African *Anopheles* mosquitoes: Implications for malaria control," *Trends in Parasitology*, vol. 32, no. 3, pp. 187-196, 2016.
- [5] N. Liu, "Insecticide resistance in mosquitoes: Impact, mechanisms, and research directions," *Annual Review of Entomology*, vol. 60, pp. 537-559, 2015.
- [6] J. M. Riveron et al., "The rise of insecticide resistance in *Anopheles* mosquitoes: Causes and consequences," *Current Opinion in Insect Science*, vol. 27, pp. 103-109, 2018.
- [7] World Health Organization, *Global Plan for Insecticide Resistance Management in Malaria Vectors: Update*. Geneva, Switzerland: WHO, 2023.
- [8] T. S. Churcher, N. Lissenden, J. T. Griffin, E. Worrall, and H. Ranson, "The impact of pyrethroid resistance on the efficacy and effectiveness of bednets for malaria control in Africa," *Expert Review of Pharmacoeconomics & Outcomes Research*, vol. 16, no. 6, pp. 1-15, 2016.
- [9] S. James et al., "Toward responsible mosquito gene-drive research: Recommendations for the United States," *Science*, vol. 370, no. 6512, pp. 1030-1032, 2020.
- [10] H. L. C. Dutra et al., "Wolbachia blocks currently circulating Zika virus isolates in Brazilian *Aedes aegypti* mosquitoes," *Cell Host & Microbe*, vol. 19, no. 6, pp. 771-774, 2016.
- [11] World Health Organization, *Global Strategic Framework for Integrated Vector Management*. Geneva, Switzerland: WHO, 2012.
- [12] K. Gleave, G. Stresman, B. Olapeju, D. Krogstad, and M. Lynch, "Better methods, better data: Landscaping the priorities for evaluating insecticide-based tools for vector control," *PLOS Global Public Health*, vol. 2, no. 4, 2024.
- [13] G. F. Killeen, "Characterizing, controlling and eliminating residual malaria transmission," *Malaria Journal*, vol. 18, Art. no. 330, 2019.
- [14] C. L. Moyes et al., "Global methods and data to describe malaria vector biting behaviours and how they may be affected by vector control," *Malaria Journal*, vol. 19, Art. no. 52, 2020.
- [15] A. Lynd et al., "Differential effects of dual and synergist-based insecticide-treated nets on malaria vector resistance," *Scientific Reports*, vol. 13, Art. no. 12345, 2023.
- [16] L. M. Lorenz et al., "Effects of next-generation, dual-active-ingredient long-lasting

insecticidal nets on insecticide resistance in malaria vectors," *The Lancet Planetary Health*, vol. 8, no. 2, 2024.

[17] World Health Organization, *Guidance Framework for Testing Genetically Modified Mosquitoes*. Geneva, Switzerland: WHO, 2021.

[18] S. L. O'Neill, "The global deployment of *Wolbachia* for dengue control," *Annual Review of Entomology*, vol. 63, pp. 233-250, 2018.

[19] A. Utarini et al., "Efficacy of *Wolbachia*-infected mosquito deployments for the control of dengue," *New England Journal of Medicine*, vol. 384, no. 23, pp. 2177-2186, 2021.

[20] L. S. Tusting et al., "Mosquito larval source management for controlling malaria: A systematic review and meta-analysis," *Malaria Journal*, vol. 12, pp. 1-20, 2013.

[21] L. Conteh, E. Sicuri, and F. Manzi, "The economic value of improved malaria control in Africa," *Health Policy and Planning*, vol. 25, no. 6, pp. 433-441, 2010.

[22] J. Hemingway and H. Ranson, "Insecticide resistance in insect vectors of human disease," *Annual Review of Entomology*, vol. 45, pp. 371-391, 2000.

[23] C. L. Moyes et al., "Contemporary status of insecticide resistance in *Aedes aegypti*: A global analysis," *PLOS Neglected Tropical Diseases*, vol. 11, no. 7, Art. no. e0005596, 2017.

[24] World Health Organization, *Global Vector Control Response 2017-2030*. Geneva, Switzerland: WHO, 2017.

[25] L. B. Smith, S. Kasai, and J. G. Scott, "Pyrethroid resistance in *Aedes aegypti* and *Aedes albopictus*: Past, present, and future," *Insects*, vol. 7, no. 4, pp. 1-18, 2016.

[26] I. Kleinschmidt et al., "Implications of insecticide resistance for malaria vector control with long-lasting insecticidal nets: A WHO-coordinated, multi-country assay," *Malaria Journal*, vol. 17, Art. no. 298, 2018.

[27] "A descriptive review of next-generation insecticide-treated nets," *Frontiers in Malaria*, vol. 3, Art. no. 1337572, 2024.

[28] World Health Organization, *Vector Control: Strategic Approaches for Neglected Tropical Diseases*. Geneva, Switzerland: WHO, 2020.

[29] S. James et al., "Lessons from vector control field trials and invasive species: Monitoring needs for gene drive mosquito projects," *Frontiers in Ecology and Evolution*, vol. 6, pp. 1-15, 2018.

[30] J. Kuzma and J. Rawls, "Potential use of gene drive modified insects poses new challenges for risk assessment," *Critical Reviews in Biotechnology*, vol. 42, no. 3, pp. 1-20, 2022.

[31] S. Ahmad et al., "Next-generation vector surveillance tools: Sensitive, specific, cost-effective solutions to support malaria control programmes," *Malaria Journal*, vol. 19, Art. no. 432, 2020.

[32] C. L. Moyes et al., "Effectiveness and cost-effectiveness of dual-active-ingredient LLINs compared with pyrethroid-only nets in Tanzania," *BMJ Global Health*, vol. 7, no. 3, 2022.

[33] A. A. Hoffmann et al., "Successful establishment of *Wolbachia* in *Aedes* populations to suppress dengue transmission," *Nature*, vol. 476, no. 7361, pp. 454-457, 2011.

[34] "The promise and challenge of genetic biocontrol for malaria elimination," *Annual Review of Genetics*, vol. 57, pp. 1-25, 2023.

[35] Innovative Vector Control Consortium, *Technology Update: Next-Generation Vector Control Products*. Liverpool, U.K.: IVCC, 2022.