

Review Article

Insecticide resistance in *Anopheles* mosquitoes: mechanisms, epidemiological impact and implications for malaria control in Sub-Saharan Africa

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ABSTRACT

Malaria remains among the most formidable public health challenges confronting Sub-Saharan Africa, with the region bearing 94% of the estimated 265 million global cases recorded in 2024. The emergence and proliferation of insecticide resistance in *Anopheles* mosquitoes threatens to reverse decades of hard-won progress in malaria control. Kenya's experience exemplifies this crisis, with malaria cases surging 27% from 3.3 million in 2023 to 4.2 million in 2024, a trend partly attributable to intensifying resistance patterns. This review synthesizes contemporary evidence on insecticide resistance mechanisms operating in *Anopheles* vectors throughout Sub-Saharan Africa, examining the epidemiological context of malaria transmission, the diversity of vector species, and the multifaceted nature of resistance including target-site modifications, metabolic detoxification, cuticular alterations, and newly identified sequestration mechanisms. Current surveillance indicates that 90% of malaria-endemic nations report resistance to at least one insecticide class, while 32% demonstrate resistance across all four major insecticide classes. Documentation of intense pyrethroid resistance exceeding ten-fold diagnostic concentrations in Uganda, coupled with sporozoite infection rates reaching 20.41% in resistant populations, underscores the operational significance of this phenomenon. Environmental contaminants originating from agricultural pesticides and extractive industries constitute additional resistance drivers that operate independently of public health interventions. This review identifies critical knowledge deficiencies in resistance characterization at subnational scales and emphasizes the imperative for integrated resistance management frameworks incorporating molecular surveillance networks, genomic technologies, and evidence-informed insecticide deployment strategies. Comprehending the intricate relationships between resistance mechanisms and epidemiological outcomes proves essential for maintaining the effectiveness of existing vector control approaches and guiding the strategic deployment of next-generation interventions across malaria-endemic regions.

Keywords: *Anopheles* mosquitoes, Insecticide resistance, Malaria transmission, Vector control, Sub-Saharan Africa, resistance mechanisms

INTRODUCTION

Malaria continues to impose a catastrophic burden on global public health, with an estimated 265 million cases and approximately 579,000 deaths documented in 2024.¹ The African Region shoulders a disproportionate share of this burden, accounting for 94% of cases and 95% of mortality. Within this vulnerable population, children younger than five years represent the demographic at greatest risk, comprising over 75% of all malaria-associated deaths regionally.² Despite being both preventable and treatable, the disease caused by *Plasmodium* parasites transmitted through the bites of infected female *Anopheles* mosquitoes has demonstrated remarkable persistence.³

Vector control interventions, principally long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS), have constituted the foundation of malaria control programs throughout Sub-Saharan Africa.⁴ These tools contributed substantially to reductions in malaria morbidity and mortality during the past two decades. However, the intensive and sustained deployment of insecticides has generated powerful selection pressures, resulting in widespread resistance throughout *Anopheles* populations.⁵ Surveillance data from 2024-2025 reveals that 90% of malaria-endemic countries now report resistance to at least one insecticide class, with 32% demonstrating resistance across all four major classes.²

Alarming contemporary trends

Epidemiological surveillance in the region reveals troubling patterns in malaria transmission. Monitoring data from Kenya indicates that malaria incidence rates showed a modest increase from 235.5 to 237.6 cases per 1,000 population at risk between 2023 and 2024, though the total case numbers remain subject to varying reports across different sources. Investigations conducted in Uganda have demonstrated alarming levels of pyrethroid resistance in *Anopheles funestus* mosquito populations, with resistance intensity reaching ten times the diagnostic concentration and sporozoite infection rates peaking at 20.41% in March 2022 among resistant mosquito groups.⁶ Environmental contamination has emerged as a significant driver of insecticide resistance development across Ghana and adjacent territories, with petroleum spills, mining operations releasing heavy metals including mercury and zinc, along with agricultural pesticide use contributing to resistance selection pressure in vector populations. Genomic investigations have identified previously unrecognized taxonomic entities within the *Anopheles gambiae* species complex that exhibit distinctive insecticide resistance characteristics, presenting additional challenges for surveillance programs and vector control strategies.⁷

The operational implications of insecticide resistance extend beyond entomological observations to measurable impacts on disease transmission and control program

effectiveness.⁸ High-intensity resistance patterns documented across multiple countries indicate that standard vector control tools are experiencing operational failure in numerous settings.^{9,8} This deterioration in tool efficacy translates directly into increased malaria transmission, case burdens, and associated mortality, threatening to undermine the substantial investments and progress achieved over recent decades.¹⁰

Objectives and scope

This review brings together the latest research from 2024-2025 on malaria patterns, mosquito behaviour, and how mosquitoes develop resistance to insecticides, focusing particularly on what this means for malaria spread and control efforts across Sub-Saharan Africa. It's crucial to understand how resistance in mosquitoes affects disease outcomes so that health officials can create better control strategies and ensure that current and future mosquito control methods continue to work effectively.¹⁰ The review examines important questions about the different ways mosquitoes become resistant to insecticides, the genetic changes that cause this resistance, how this resistance affects malaria spread, and what practical strategies are needed to manage and control resistance over the long term.

METHODS

A systematic literature search was conducted across PubMed, Web of Science, Scopus, and Google Scholar for publications from January 2020 through January 2025. The search employed Medical Subject Headings (MeSH) terms and keywords including *Anopheles*, insecticide resistance, malaria, Sub-Saharan Africa, vector control, pyrethroid resistance, metabolic resistance, *kdr* mutation, cytochrome P450, resistance mechanisms, target-site mutations, detoxification enzymes, and vector surveillance, combined using Boolean operators (AND, OR).

Inclusion and exclusion criteria

Studies were included if they were published in English between 2020 and 2025, focused on insecticide resistance in *Anopheles* mosquitoes, and were geographically relevant or applicable to Sub-Saharan Africa. Priority was given to 2024-2025 publications to capture recent evidence on resistance evolution and epidemiological impacts. The review incorporated original research articles, systematic reviews, meta-analyses, policy documents, and technical reports from the World Health Organization (WHO), United States President's Malaria Initiative (PMI), and national malaria control programs.

Studies were excluded if they focused exclusively on non-*Anopheles* vectors, did not address resistance mechanisms or epidemiological consequences, lacked sufficient methodological detail for quality assessment, or

presented data solely from regions outside Sub-Saharan Africa without relevance to the African context.

Data extraction and synthesis

Data were extracted systematically using a standardized form developed for this review. Information collected included study location, *Anopheles* species investigated, resistance mechanisms identified, insecticide classes evaluated, resistance intensity levels, epidemiological outcomes, and implications for vector control strategies. Due to substantial heterogeneity in study designs, methodologies, and outcome measures, a narrative synthesis approach was used to integrate findings. Thematic analysis organized evidence into key domains: epidemiology of malaria transmission, vector biology and species diversity, molecular and biochemical resistance mechanisms, genomic insights into resistance evolution, epidemiological impacts on disease transmission and control effectiveness, and strategic approaches for resistance management.

RESULTS

In 2024, the African region accounted for 94% of the global malaria burden, with approximately 265 million cases reported.² Five nations account for the vast majority of regional malaria cases. Nigeria leads with just over a quarter of all cases at 25.8%, followed by the Democratic Republic of the Congo at 13.3%, Uganda at 5.0%, Ethiopia at 4.7%, and Mozambique at 3.9%.² Malaria transmission across Kenya demonstrates significant geographic variation, with the Lake Victoria basin experiencing the highest disease burden at 19% prevalence. Counties around the lake show varying transmission intensities: Busia and Siaya exceed 30% prevalence, while Bungoma, Kakamega, Kisumu, and Migori range between 10% and 30%. Some counties classified as very low transmission zones report case numbers that appear inconsistent with their designation. Kisii County illustrates this discrepancy, recording 35,000 to 36,000 confirmed cases annually at 22.8% prevalence despite its low-transmission classification.¹¹ Malaria transmission across Kenya demonstrates significant geographic variation, with the Lake Victoria basin experiencing the highest disease burden at 19% prevalence. Counties around the lake show varying transmission intensities, with Busia and Siaya exceeding 30% prevalence, while Bungoma, Kakamega, Kisumu, and Migori range between 10% and 30%. Some counties classified as very low transmission zones report case numbers that appear inconsistent with their designation. Kisii County illustrates this discrepancy, recording 35,000 to 36,000 confirmed cases annually at 22.8% prevalence despite its low-transmission classification.^{11,12}

Climate change and emerging transmission patterns

Climate change and increasingly extreme weather patterns have expanded mosquito breeding habitats across

the region, creating favourable conditions for vector proliferation.¹³ The 2024 El Niño rainfall events precipitated a marked spike in vector-borne diseases including malaria due to widespread flooding, inadequate drainage infrastructure and humanitarian displacement of populations.¹³ A malaria outbreak investigation in Marsabit County during early 2024 revealed a 345% surge in cases during epidemiological weeks one through six compared to the previous year, rising from 210 to 934. Microscopic examination identified 94.9% as *Plasmodium falciparum*, 2.7% as *Plasmodium vivax*, and 2.4% as *Plasmodium ovale*. The outbreak followed unusually heavy rainfall in November 2023, which created favourable mosquito breeding conditions in this normally arid region.¹⁴

Changing precipitation patterns, elevated temperatures and prolonged wet seasons create a conducive environment for *Anopheles* mosquito breeding and survival.^{13,15} These climate-driven changes compound the resistance challenge not only by expanding vector populations geographically and temporally but also by potentially enhancing their physiological resistance capacity. Temperature-dependent modulation of detoxification pathways has been demonstrated to enhance cytochrome P450 enzyme activity and expression in mosquitoes, thereby augmenting metabolic resistance to pyrethroids and neonicotinoids at elevated temperatures.^{16,15}

Diversity and distribution of *Anopheles* mosquitoes

In East Africa, *Anopheles arabiensis*, *Anopheles gambiae sensu stricto*, and *Anopheles funestus* serve as the principal malaria vectors, each exhibiting distinct ecological preferences and behavioural characteristics.^{17,18} Recent investigations conducted in Western Kenya during 2024 revealed that *An. arabiensis* dominates urban environments at 96.2% relative abundance and peri-urban areas at 96.8%, while *An. gambiae sensu stricto* demonstrates greater abundance in rural settings at 82.7%.¹⁹ *An. funestus* remains the dominant vector in numerous regions across the continent, with at least 11 recognized sibling species within the *An. funestus* group displaying varying resistance profiles across Africa.^{17,20}

Recent whole-genome sequencing analyses conducted in Tanzania unveiled a previously unrecognized cryptic taxon within the *An. gambiae* complex, designated the Pwani molecular form. This newly identified form displays distinctive insecticide resistance profiles characterized by moderate amplifications of carboxylesterase genes including *Coeae2f* and the *Coeae2g-Coeae6g* cluster, which are associated with organophosphate detoxification capacity.^{5,13} This finding highlights that there is more genetic variation and behavioural differences among major mosquito species than previously recognized, and it shows that monitoring programs for insecticide resistance need to consider these

hidden mosquito species because they may react differently to the same control methods.^{9,21}

The invasive threat of *Anopheles stephensi*

The Asian malaria vector *Anopheles stephensi*, first detected in Djibouti in 2012, has progressively spread throughout the Horn of Africa and was recently documented in Nigeria and Ghana during 2024.²² Whole-genome sequencing analyses of Ethiopian *An. stephensi* populations reveal substantial genomic differences from South Asian source populations, with evidence of natural selection operating on genetic loci associated with resistance to neonicotinoids, ivermectin, DDT, and pyrethroids.²² This invasion poses significant threats to malaria control because *An. stephensi* demonstrates exceptional adaptation to arid conditions and urban environments where traditional African vectors are typically less prevalent.²² The species' capacity to exploit water storage containers ubiquitous in urban settings creates novel transmission dynamics that may circumvent existing control strategies designed primarily to target traditional rural-adapted vectors.²²

The mechanisms of insecticide resistance

Anopheles mosquitoes develop resistance to insecticides through several key mechanisms that can work alone or in combination. These include alterations at the insecticide target site, enhanced metabolic breakdown of chemicals, reduced penetration through the mosquito's outer layer, and changes in behaviour. Recent studies have uncovered an additional mechanism where chemosensory and odorant-binding proteins trap and isolate insecticides within the mosquito's body.²³

Target-site resistance involves genetic mutations that alter the molecular structure of insecticide binding sites, thereby preventing insecticidal compounds from exerting their intended neurotoxic effects.^{24,25} The most operationally significant mutations occur in two key target genes that are routinely monitored in resistance surveillance programs.

Voltage-gated sodium channel mutations

Mutations in the voltage-gated sodium channel gene, particularly the *kdr* (knockdown resistance) mutations L1014F, L1014S, V402L, I1527T and N1575Y, confer cross-resistance to both pyrethroid insecticides and DDT.²⁵⁻²⁷ Recent investigations conducted in Ghana during 2025 documented varying frequencies of these mutations across distinct bioclimatic zones, with L995F and P1874L emerging as additional variants that contribute to the resistance phenotype.²⁸ In Western Kenya during 2024, urban *An. arabiensis* populations exhibited high frequencies of the *Vgsc*-1014F and *Vgsc*-1575Y mutations, which were strongly associated with high-intensity deltamethrin resistance.¹¹ The widespread distribution of *kdr* mutations across geographically

diverse populations suggests intense and sustained selection pressure from both public health vector control programs and agricultural insecticide applications.²⁹

Mutations in the acetylcholinesterase gene, particularly the G119S substitution in the *ace-1* gene, confer resistance to organophosphate and carbamate insecticides by reducing the enzyme's sensitivity to these compounds.²⁷ Investigations conducted in the Republic of Korea during 2025 identified *ace-1* resistance alleles in four distinct *Anopheles species*, with agricultural pyrethroid usage serving as a significant selective pressure even for non-pyrethroid resistance mechanisms.³⁰ Gene duplication events at the *ace-1* locus have been documented to produce extreme resistance phenotypes when combined with point mutations.³¹ The presence of these mutations in geographically diverse populations across multiple continents suggests widespread selection pressure from both public health interventions and agricultural insecticide use.^{32, 27}

Metabolic resistance, widely considered the most potent and geographically widespread resistance mechanism, involves overproduction or enhanced catalytic activity of detoxification enzymes that metabolize insecticides before they reach their target sites.^{33,34} This mechanism confers broad-spectrum, cross-class resistance capacity that can protect mosquitoes from multiple insecticide classes simultaneously.^{33,34}

Cytochrome P450 enzymes represent the primary enzyme family associated with insecticide resistance in *Anopheles* mosquitoes, demonstrating capacity to metabolize endogenous hormones, xenobiotic compounds and plant secondary metabolites through diverse biochemical reactions including N-dealkylation, hydroxylation, desulfuration, and epoxidation.³⁵ *Anopheles* mosquitoes carry more than 100 P450 genes that are grouped into different families, and certain families have undergone significant expansion over time in ways that are linked to the development of insecticide resistance.³⁶

Recent research conducted in Uganda during 2024 identified a rapidly-selected 4.3 kilobase transposon-containing structural variation associated with cytochrome P450-mediated pyrethroid resistance in *An. funestus*, with CYP6P9a and CYP6P9b enzymes playing critical functional roles in metabolizing pyrethroid insecticides.³⁷ Genomic selection scans from Tanzanian populations revealed strong selection sweeps in the *Cyp6aa/p* gene cluster located on chromosome 2R across all populations within the *An. gambiae* species complex.³⁸ Biochemical enzyme assays conducted in Nigerian, *An. gambiae* populations during 2024 demonstrated elevated cytochrome P450 activity in deltamethrin-resistant populations, with enzyme activity ratios of 2.07-fold compared to susceptible reference strains.³⁹ Temperature modulation significantly enhances P450 catalytic activity, with elevated ambient temperatures increasing metabolic

resistance capacity through enhanced enzyme expression and activity.⁴⁰

Multiple specific P450 genes have been functionally validated as resistance determinants through transgenic expression studies and RNA interference knockdown experiments. CYP6P3 and CYP6M2 show significant elevation in multiple pyrethroid-resistant populations from Southern Benin and Nigeria. CYP6Z1 and CYP6M7 have been positionally cloned and demonstrated to metabolize DDT and pyrethroids efficiently. The highly polymorphic nature of these genes, combined with their directional selection under insecticide pressure, creates a continuously evolving resistance landscape.⁴¹

Glutathione S-transferases (GSTs) catalyse conjugation reactions with reduced glutathione, facilitating detoxification and excretion of insecticidal compounds and their metabolites. Unlike carboxylesterases, GST-based resistance typically involves transcriptional upregulation of multiple enzyme isoforms from one or more GST classes, without substantial evidence of gene amplification events.⁴² The GSTe2 gene serves as a valuable molecular marker allowing tracking of metabolically-based resistance in major malaria vectors, with a single diagnostic mutation enabling resistance monitoring across populations.⁴³

Investigations conducted in West Africa during 2025 documented moderate but significant roles for GSTs in lambda-cyhalothrin resistance, with biochemical synergism tests employing GST inhibitors confirming GST involvement alongside cytochrome P450s and esterases in the overall resistance phenotype.⁴⁴ In Nigerian *An. gambiae* populations, GST enzyme activity showed varied patterns across collection sites, with consistently higher activity detected in deltamethrin-exposed mosquitoes compared to unexposed controls.¹⁵

Carboxylesterases hydrolyse ester bonds present in insecticide molecules, converting them into alcohols and carboxylic acids that lack insecticidal activity, thereby detoxifying pyrethroids and organophosphates.⁴⁵ Resistance mechanisms involving esterases include gene amplification events, which increase total enzyme quantity available for detoxification, or point mutations that alter substrate specificity and catalytic efficiency.⁴⁶ Recent genomic research documents substantial amplification of the Coeae1f/Coeae2f and Coeae2g-Coeae6g gene clusters in *An. arabiensis* populations from Tanzania, with these amplifications strongly associated with pirimiphos-methyl detoxification capacity in areas where this organophosphate is deployed through IRS campaigns.²⁵

Biochemical enzyme assays conducted in Western Kenya during 2024 revealed markedly elevated esterase activity in urban mosquito populations, with enzyme activity ratios of 3.72-fold for alpha-esterases and 1.36-fold for beta-esterases compared to susceptible reference strains.¹¹

These findings demonstrate that esterase-mediated resistance has become widespread geographically and can reach high intensity levels that substantially compromise insecticide efficacy in operational settings.⁴⁷

Penetration or cuticular resistance involves structural or biochemical modifications to the mosquito cuticle that reduce the rate of insecticide penetration into the insect body.²² Changes in cuticular hydrocarbon composition mediated by alterations in CYP4G enzyme expression, which synthesizes cuticular hydrocarbons, modify cuticular properties and substantially reduce insecticide penetration rates.²² This mechanism was first comprehensively elucidated in 2016 in *An. gambiae* and has subsequently been documented in multiple insect species across different orders.²² Recent transcriptomic investigations demonstrate increased expression of numerous cuticular protein genes in resistant strains, with physically thickened cuticles providing moderate, cross-class protection against multiple insecticide classes.^{10, 22}

Recent research has identified a novel resistance pathway in which mosquitoes produce elevated levels of olfactory proteins, such as chemosensory proteins and odorant-binding proteins, that bind to insecticidal compounds and prevent them from reaching their target sites within the mosquito.¹⁵ Transcriptomic studies comparing pyrethroid-resistant and susceptible *Anopheles gambiae* populations showed that resistant mosquitoes consistently produce higher levels of CSP6 and sensory appendage protein 2 genes. Laboratory experiments using genetically modified mosquitoes confirmed that increased SAP2 production causes pyrethroid resistance by binding strongly and selectively to these insecticides.¹⁵

Computer modelling studies paired with genetic mutation experiments pinpointed specific amino acid residues in odorant-binding protein structures that enable selective insecticide capture, providing molecular-level confirmation of this sequestration mechanism. This newly discovered resistance pathway complicates control strategies and may help explain instances where conventional resistance mechanisms, such as target-site mutations and elevated metabolic enzymes, fail to fully account for the observed levels of resistance in mosquito populations.¹⁵

Cross-resistance develops when mosquitoes that become resistant to one type of insecticide gain protection against chemically different insecticide classes, which limits available control options and complicates management efforts.^{4,43} Investigations in Ghana during 2025 found that ongoing exposure to environmental pollutants from mining operations, automotive activities, and agricultural pesticide use creates persistent selection pressure for resistance that occurs separately from public health insecticide applications.⁴

In Obuasi, Ghana, nearly two decades of intensive indoor residual spraying campaigns using sequential rotations of

different insecticide classes, beginning with organophosphates from 2006 to 2017, transitioning through pyrethroids, neonicotinoids, and their combinations from 2018 to 2023, and later adopting meta-diamides, coupled with widespread mining pollution, resulted in extreme resistance patterns in local mosquito populations.⁴ Bioassays revealed high-intensity resistance to pirimiphos-methyl, with only 1.7% mosquito mortality occurring even at ten times the standard diagnostic dose, indicating that this organophosphate has become operationally ineffective regardless of concentration. These results demonstrate that effective resistance management must extend beyond public health insecticides to address broader environmental exposures that sustain selection pressure throughout the region.^{4,42}

Whole-genome sequencing offers comprehensive analysis of complete genomic landscapes, simultaneously revealing population ancestry, ongoing natural selection, and insecticide resistance markers throughout the entire genome without predefined targets.^{5,37} Recent whole-genome sequencing studies in Tanzania revealed distinct population genetic structures and species-specific resistance patterns, with the newly identified Pwani molecular form exhibiting unique carboxylesterase gene amplifications not found in *An. gambiae sensu stricto* or *An. arabiensis* populations.⁵

Genome-wide selection scans using integrated haplotype scores and cross-population extended haplotype homozygosity detected distinct selection peaks near the Cyp6aa/p metabolic resistance locus on chromosome 2R across all populations within the *An. gambiae* species complex.⁵ Additional selection signals appeared at the ace-1 locus, CYP4G cuticular resistance locus, and several esterase gene clusters, indicating simultaneous multi-locus adaptation to insecticides across the genome.^{5,37} These genomic signatures of selection serve as powerful molecular tools for monitoring resistance evolution as it occurs and detecting emerging resistance mechanisms before they become widespread enough to undermine control efforts.^{5,37}

A rapidly selected 4.3 kilobase transposon-containing structural variation linked to cytochrome P450-mediated resistance was identified in *An. funestus* populations from Uganda, demonstrating how mobile genetic elements can accelerate resistance evolution by creating novel regulatory environments.³ Copy number variations affecting detoxification genes, particularly esterases and cytochrome P450s, represent major evolutionary drivers of resistance phenotypes.¹³ Gene amplification provides immediate fitness advantages under intense insecticide pressure by increasing the total quantity of detoxification enzymes without requiring functional mutations that alter their catalytic activity.¹³

The Coeae1f/Coeae2f and Coeae2g-Coeae6g gene clusters show elevated copy numbers in Tanzanian *An. arabiensis* populations, demonstrating species-specific

patterns that correlate with distinct insecticide exposure histories.¹³ Gene duplication events at the ace-1 locus combined with the G119S mutation produce extreme resistance levels, with heterozygous individuals carrying both resistant and susceptible alleles that partially offset the fitness costs associated with resistance.

MicroRNAs and long non-coding RNAs control detoxification gene expression by regulating messenger RNA stability and translation efficiency at the post-transcriptional level. In permethrin-resistant insect populations, miR-33 down regulates voltage-gated sodium channel transcript levels, reducing the number of available permethrin binding sites and enhancing resistance. Upregulation of miR-932 represses CPR5 gene expression in resistant insects, altering cuticular properties and reducing insecticide penetration. This regulatory layer adds complexity to resistance mechanisms and may explain phenotypic variations not fully accounted for by genomic mutations alone.²³

Insecticide resistance directly affects vectorial capacity, which measures how efficiently mosquito populations transmit malaria parasites under field conditions. Investigations in Uganda during 2024 found sporozoite infection rates of 20.41% in pyrethroid-resistant *An. funestus* populations, significantly exceeding rates typically observed in susceptible populations.³ This finding suggests that resistant mosquitoes survive insecticide exposure at rates that undermine control efforts while maintaining or potentially enhancing their ability to transmit malaria.^{3,31}

Resistant mosquito populations exhibit altered life history traits including changes in longevity, fecundity, blood-feeding behaviour, and vertebrate host preference.^{31,39} Some resistance mechanisms carry fitness costs in insecticide-free laboratory environments, including reduced survival, decreased fecundity, or altered developmental rates.³¹ However, other resistance mechanisms show no fitness costs or may confer fitness advantages under certain environmental conditions.^{21,31} Understanding these fitness trade-offs is essential for predicting how resistance spreads and persists when insecticide pressure is absent, which guides strategic decisions about insecticide rotation policies and resistance reversal approaches.³¹

In Western Kenya, Uganda, Tanzania, and Ghana, mosquitoes have shown high-intensity resistance depicting survival rates exceeding 10% when exposed to ten times the diagnostic insecticide concentration. This demonstrates that conventional LLINs and IRS formulations are failing operationally in these regions.^{3,4,11,29} This failure has directly increased malaria transmission and case numbers, as demonstrated by Kenya's 27% rise in malaria cases between 2023 and 2024, despite sustained high coverage of vector control measures.²

Field trials have shown that standard pyrethroid-only nets provide reduced protection in areas with high resistance levels.^{32,43} The link between resistance intensity and its epidemiological consequences does not follow a linear pattern. When resistance levels are modest, achieving high coverage with bed nets can compensate for the reduced efficacy. However, when resistance reaches high intensity, the protective benefits are compromised regardless of how extensively nets are distributed and used.^{32,46}

Despite these challenges, next-generation vector control tools show substantial potential for restoring effectiveness against resistant mosquito populations. In both controlled experimental settings and field trials, nets incorporating piperonyl butoxide, such as PermaNet 3.0 Top and Olyset Plus, as well as those using chlorfenapyr like Interceptor G2, have achieved mortality rates above 80% even when tested against mosquitoes with high levels of pyrethroid resistance.^{3,33,34,45,46} These findings demonstrate that innovative vector control technologies using synergists or novel active ingredients can restore effectiveness even in areas with high resistance. However, their long-term performance requires ongoing monitoring.^{33,46}

DISCUSSION

This review synthesizes contemporary evidence showing that insecticide resistance in *Anopheles* mosquitoes has reached crisis levels throughout Sub-Saharan Africa, with serious implications for malaria control and public health. The simultaneous operation of multiple resistance mechanisms within mosquito populations, and sometimes within individual insects, poses significant challenges for vector control programs that have traditionally depended on a narrow range of insecticide classes.¹ Ninety percent (90%) of malaria-endemic countries have reported resistance to at least one insecticide class, while 32% show resistance across all four major classes available for public health use.¹ This widespread resistance threatens to undermine the significant progress made through intensive vector control efforts over the past two decades.^{30,35}

The epidemiological consequences of widespread resistance are already evident across the region. Kenya experienced a 27% increase in malaria cases between 2023 and 2024, despite maintaining high coverage of vector control interventions. This surge has been partly attributed to intensifying resistance patterns.² This demonstrates that resistance is not merely a laboratory or entomological concern but directly increases human illness and death. Sporozoite infection rates exceeding 20% in resistant mosquito populations indicate that these insects maintain high vectorial capacity under field conditions, potentially offsetting any fitness costs associated with their resistance mechanisms.^{3,31}

Mechanistic complexity and cross-Resistance

The diverse mechanisms underlying insecticide resistance present both challenges and opportunities for management strategies. Target-site mutations like *kdr* and *ace-1* variants serve as easily detectable molecular markers widely used in surveillance programs, though they capture only part of the resistance picture. Metabolic resistance mediated by cytochrome P450 monooxygenases, glutathione S-transferases, and carboxylesterases provides broader protection that can extend across multiple insecticide classes through overlapping substrate specificities.¹⁸

The recent identification of sequestration resistance mediated by chemosensory and odorant-binding proteins represents a significant shift in understanding. This reveals that insects can repurpose proteins originally evolved for chemical communication and environmental sensing to neutralize insecticides through high-affinity binding. This mechanism may explain cases where traditional resistance markers like target-site mutations and metabolic enzyme overexpression fail to accurately predict resistance, underscoring the need for surveillance approaches that integrate molecular markers with bioassay testing.^{15,29}

Environmental contaminants from agricultural pesticides, mining activities, and industrial sources create persistent selection pressure that operates independently of public health interventions. This has important implications for resistance management, indicating that strategies focused solely on judicious deployment and rotation of vector control insecticides will be insufficient without addressing broader environmental pressures. Multi-sectoral approaches engaging agricultural, mining, environmental protection, and industrial regulation sectors are essential for effective landscape-level resistance management.^{4,42}

Genomic insights and hidden diversity

The discovery of previously unrecognized cryptic taxa within the *An. gambiae* species complex, such as the Pwani molecular form identified through whole-genome sequencing,⁵ reveals that vector populations harbor greater genetic and phenotypic diversity than traditional morphological and molecular methods detected. These cryptic species display distinct resistance profiles and may respond differently to control interventions, complicating surveillance and control efforts. Conventional identification methods based on morphological characteristics or limited molecular markers cannot detect this hidden diversity, requiring broader adoption of genomic approaches in operational surveillance programs.⁵

Whole-genome sequencing has revealed the genomic architecture underlying resistance, identifying strong selection sweeps at multiple loci including the Cyp6aa/p cluster, ace-1, CYP4G, and esterase genes. The identification of rapidly-selected structural variations like transposon-containing elements demonstrates that resistance can evolve through diverse genetic mechanisms beyond single-nucleotide polymorphisms. These genomic signatures provide molecular tools for developing early warning systems capable of detecting emerging resistance at low frequencies before it compromises control interventions.^{5,37}

Climate change as a resistance amplifier

The interaction between climate change and insecticide resistance represents an underappreciated threat to malaria control sustainability. Temperature-dependent enhancement of cytochrome P450 catalytic activity indicates that climate warming may directly augment metabolic resistance in mosquito populations, independent of insecticide selection pressure. Additionally, climate-driven habitat expansion brings vectors into new geographic areas where populations may lack acquired immunity, potentially amplifying transmission and disease severity.^{8,42}

The 345% increase in malaria cases during the 2024 Marsabit outbreak following intense El Niño precipitation illustrates how climate extremes interact with factors like insecticide resistance to create explosive transmission scenarios. As climate change increases the frequency and intensity of extreme weather events, malaria control programs must develop adaptive strategies that account for these complex interactions between climate variability, vector ecology, and resistance dynamics.^{8,9,42}

Management implications and promising tools

Despite the challenges documented in this review, several promising management approaches and technologies offer hope for sustaining effective malaria control. Next-generation vector control tools including piperonyl butoxide-based nets that synergize pyrethroids, chlorfenapyr formulations with novel modes of action, and neonicotinoid-based IRS formulations demonstrate substantial efficacy against highly pyrethroid-resistant populations in laboratory and field settings.^{3,33,34,45} These tools exploit fundamentally different biochemical pathways and can restore mortality to effective levels even when pyrethroid resistance has reached high intensity.^{3,46}

However, early molecular signals suggesting possible cross-resistance mechanisms affecting neonicotinoids²⁴ and documented clothianidin resistance in certain *An. gambiae* populations²⁵ provide important cautionary notes regarding over-reliance on any single new insecticide class. The substrate promiscuity characteristic of certain cytochrome P450 enzymes, whereby single enzyme

isoforms can metabolize chemically diverse substrates, and resistance to newly deployed insecticide classes may emerge more rapidly than historical experience would suggest.²⁶ Continuous, intensive resistance monitoring for all deployed insecticides remains absolutely essential for early detection of emerging resistance.^{24,29,35}

Biological control approaches including deployment of entomopathogenic fungi represent potentially innovative alternatives or complements to chemical insecticides. Recent research demonstrates that fungal infections can paradoxically reverse insecticide susceptibility in resistant strains through alterations in energy metabolism and downregulation of detoxification gene expression.²⁷ This synergistic interaction between biological and chemical control could potentially restore susceptibility to conventional insecticides and provides a conceptual template for integrated strategies combining multiple modes of action with non-overlapping resistance mechanisms.²⁷

Chemoprevention strategies including seasonal malaria chemoprevention pilots implemented in Kenya's Turkana County demonstrated 70% to 75% reductions in malaria cases among children under five years during 2024.²⁸ providing an important alternative or complement to vector control in areas experiencing intense resistance. However, chemoprevention effectiveness depends critically on maintaining antimalarial drug efficacy and achieving high population coverage, both of which face challenges from potential antimalarial resistance evolution and implementation difficulties in resource-limited settings.²⁸

Critical knowledge gaps

Despite substantial recent scientific advances, major knowledge gaps continue to impede optimal resistance management and strategic planning. Resistance surveillance data remain heavily concentrated in limited geographic areas, with many malaria-endemic transmission zones lacking even basic resistance monitoring. Resistance intensity levels, operationally defined by mortality rates at multiples of diagnostic concentrations, remain poorly characterized across most endemic regions, substantially limiting capacity to predict operational control failure and guide intervention selection.^{29,35}

The fitness costs imposed by various resistance mechanisms under realistic field conditions with variable temperatures, diverse pathogen exposures, nutritional stress, and other environmental challenges remain inadequately understood.³¹ Laboratory studies provide valuable initial insights into potential fitness trade-offs, but field environments present fundamentally different selective landscapes that may impose qualitatively different fitness consequences.³¹ Understanding fitness costs under field conditions proves essential for

predicting whether resistance alleles will persist, increase, or decline in frequency when insecticide pressure is reduced or eliminated, thereby informing strategic decisions about insecticide rotation policies and resistance reversal approaches.³¹

Many mosquito populations possess multiple resistance mechanisms simultaneously, yet the interactions and combined effects of these mechanisms on operational tool efficacy remain largely unclear. Do multiple resistance mechanisms act in an additive, synergistic, or antagonistic manner? How do different mechanistic combinations affect mosquito responses to various insecticide classes and formulations? Answering these fundamental questions requires integrated research approaches combining molecular characterization, biochemical analysis, and phenotypic testing methodologies.

Finally, next-generation tools including gene drive technologies, novel insecticide chemistries, spatial repellents, and attractive toxic sugar baits require urgent field evaluation specifically in high-resistance settings representative of contemporary operational challenges.²⁴ While laboratory efficacy data provide encouraging preliminary evidence, field performance under operational conditions with highly resistant vector populations will ultimately determine their practical utility for sustained malaria control.²⁴

Toward integrated resistance management

Effective, sustainable resistance management requires integrated approaches operating coherently at multiple organizational and temporal scales. At the molecular surveillance level, comprehensive monitoring systems must simultaneously track both well-established resistance markers and emerging novel mechanisms, employing state-of-the-art genomic approaches to detect resistance determinants before they spread to high frequencies that compromise interventions.^{5,29,35,37} Phenotypic bioassay testing remains absolutely essential to validate molecular predictions and detect resistance mechanisms not captured by currently known molecular markers.²⁹

At the operational programmatic level, evidence-based insecticide rotation policies rigorously guided by high-quality local resistance data can potentially reduce selection pressure and restore susceptibility to previously compromised insecticide classes.²⁴ However, rotation strategies must explicitly account for complex cross-resistance patterns to ensure that sequentially deployed insecticides target fundamentally different biochemical pathways and resistance mechanisms.^{4,49} Strategic deployment of next-generation tools including dual-active ingredient insecticidal nets and novel insecticide formulations specifically in high-resistance areas can restore control efficacy where standard tools have failed.^{33,46}

At the integrated vector management level, comprehensive programs combining multiple complementary control methods targeting different mosquito life stages and behavioural patterns can substantially reduce dependence on chemical insecticides while maintaining effective transmission suppression.⁴⁰ Larval source management, environmental modification, biological control agents, and judicious selective insecticide deployment, implemented in strategic combination, create multiple independent barriers to malaria transmission that collectively reduce selection for resistance while maintaining epidemiological effectiveness.^{24,40}

At the policy and governance level, multi-sectoral approaches explicitly addressing agricultural pesticide use, industrial pollutant releases, and mining contaminants prove essential for reducing pervasive environmental selection pressures that operate independently of public health interventions.^{4,42} This necessarily requires coordination across government sectors that are rarely integrated with health ministries, presenting substantial governance and coordination challenges but offering considerable potential benefits for long-term resistance management sustainability.⁴

Limitations

This review possesses several important limitations that warrant explicit acknowledgment. The available evidence base remains geographically uneven, with certain regions including West Africa intensively studied while others including large areas of Central Africa lack even basic resistance characterization data.^{29,35} Publication bias may systematically favour studies documenting resistance over those finding sustained susceptibility, potentially creating an overly pessimistic view of the overall situation. The exceptionally rapid pace of resistance evolution means that findings from earlier in the review period (2020-2023) may not accurately reflect current situations in 2025, as resistance patterns can shift dramatically within just a few years.^{29,36} Finally, the profound complexity of resistance mechanisms and their potential interactions substantially limit capacity to make definitive quantitative predictions about future resistance trends and their epidemiological consequences.

CONCLUSION

Insecticide resistance in *Anopheles* mosquitoes represents an existential threat to sustained malaria control throughout Sub-Saharan Africa, with the potential to reverse decades of hard-won progress and substantial investments in disease reduction. The rapid evolution and geographic spread of multiple resistance mechanisms including target-site mutations, metabolic enzyme amplification, cuticular modifications, and novel sequestration pathways demands urgent, coordinated responses at local, national, and international scales. Environmental contaminants from agricultural, mining,

and industrial sources, combined with climate change impacts, emerge as critical additional drivers creating selection pressures that extend well beyond deliberate public health insecticide deployments.

Recent data from 2024-2025 document deeply alarming trends: intense resistance persisting at ten times diagnostic concentrations, sporozoite infection rates exceeding 20% in resistant populations indicating maintained vectorial capacity, and surging malaria case burdens despite high intervention coverage. However, promising tools including piperonyl butoxide-based nets, chlorfenapyr formulations, neonicotinoid-based indoor residual spraying, entomopathogenic fungal biocontrol agents, and seasonal malaria chemoprevention offer realistic hope for sustaining effective control even in high-resistance settings.

Preserving the long-term efficacy of vector control in Sub-Saharan Africa requires comprehensive molecular and phenotypic surveillance systems integrated into national malaria control programs. These systems must inform evidence-based insecticide rotation policies, while next-generation tools should be strategically deployed in high-resistance areas. Effective control also depends on integrated vector management approaches that combine multiple complementary methods and multi-sectoral strategies that address agricultural pesticides, industrial pollutants, and mining contaminants. Success demands sustained political commitment, adequate financing mechanisms, and collaboration across national borders to prevent resistance spread and achieve malaria elimination. While the window for effective action continues narrowing, coordinated efforts leveraging emerging tools and technologies can sustain effective malaria control despite widespread resistance.

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