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Recent advances in malaria treatment: Innovations in drug development, resistance management, and future strategies

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Abstract
Malaria remains one of the most significant parasitic diseases worldwide, with nearly 249 million cases and over 600,000 deaths reported in 2022, predominantly in sub-Saharan Africa and Southeast Asia. Despite major advances in control strategies, the emergence and spread of drug-resistant *Plasmodium falciparum* and *Plasmodium vivax* continue to threaten progress. Artemisinin-based combination therapies (ACTs) remain the cornerstone of treatment for uncomplicated malaria; however, resistance linked to *kelch13* mutations and declining efficacy of partner drugs such as piperaquine and mefloquine underscore the fragility of current approaches. For *P. vivax*, relapse due to dormant hypnozoites presents an additional challenge, with primaquine and tafenoquine providing radical cure but limited by safety concerns in glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Recent advances in malaria therapeutics include the development of triple artemisinin combination therapies (TACTs), which combine an artemisinin derivative with two partner drugs and have shown high efficacy against multidrug-resistant strains. Novel chemical entities such as cipargamin, ganaplacide, MMV390048, artefenomel, and DSM265 are progressing through clinical trials, targeting unique parasite pathways and offering promise for overcoming existing resistance. In parallel, major breakthroughs have been achieved in vaccine development. The RTS, S/AS01 vaccine, the first malaria vaccine to be recommended for large-scale use, demonstrates modest but impactful protection, while the newer R21/Matrix-M vaccine has shown higher efficacy in phase II trials and is undergoing large-scale evaluation. Whole sporozoite vaccines and monoclonal antibodies such as CIS43LS further expand the immunological toolkit.

Innovative strategies, including long-acting injectable prophylaxis, AI-driven drug discovery, and CRISPR-based gene-drive mosquito control, represent a paradigm shift in integrated malaria management. Together, these advances mark an important turning point in the global fight against malaria. Sustained investment, equitable access, and continuous surveillance are critical to translating these innovations into meaningful progress toward elimination.

Keywords: Malaria, artemisinin resistance, Triple ACTs, antimalarial drugs, vaccine development

Introduction

Global Burden of Malaria

Malaria continues to represent a significant global health challenge. Fig 1. According to the World Health Organization (WHO), there were an estimated 249 million malaria cases and 608,000 deaths in 2022, with the majority occurring in sub-Saharan Africa [1]. Children under five and pregnant women remain the most vulnerable groups. While large-scale interventions such as insecticide-treated nets, indoor residual spraying, and improved diagnostics have reduced mortality over the past two decades, progress has plateaued due to emerging resistance in both parasites and vectors [2, 3].

Historical Context of Malaria Therapy

Quinine, derived from the bark of the cinchona tree, was the first effective treatment for malaria and laid the foundation for antimalarial drug development [4]. The mid-20th century witnessed the widespread use of chloroquine, which was inexpensive, safe, and highly effective until resistance emerged in Southeast Asia and South America in the 1950s and later spread to Africa [5].

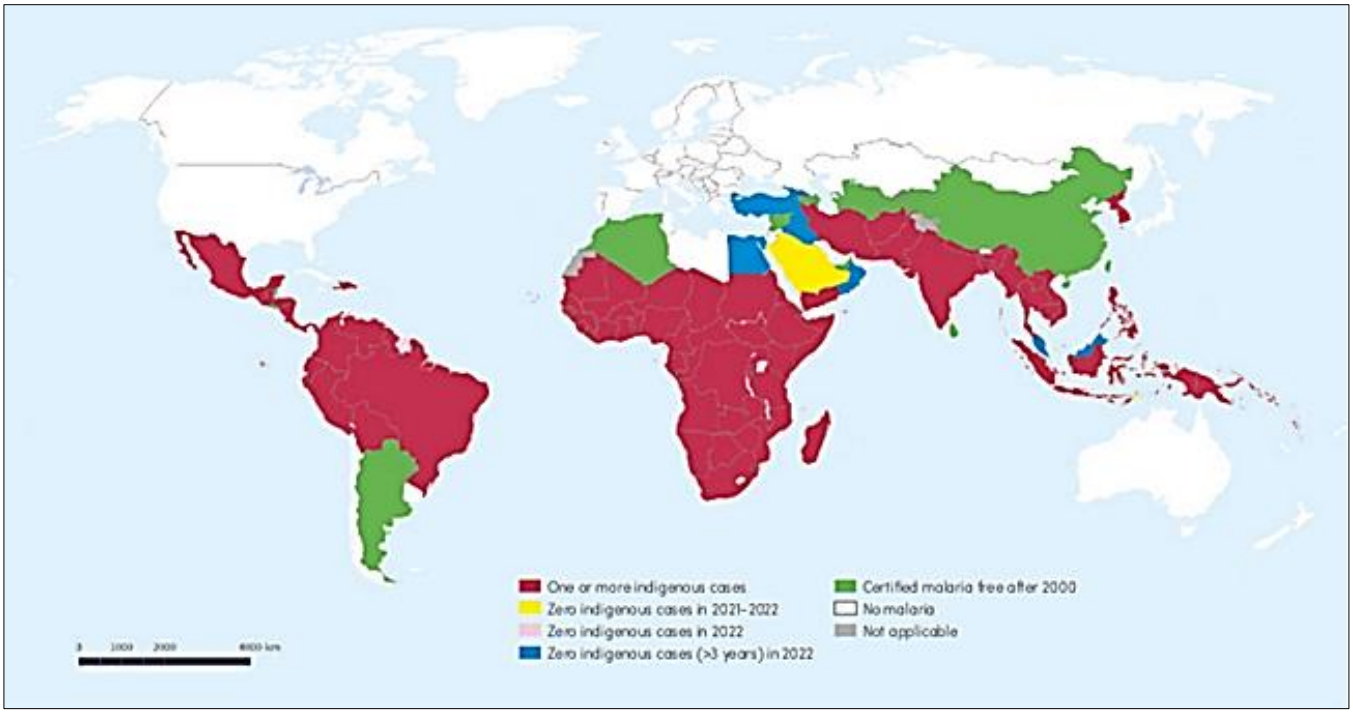

Fig 1: Countries with indigenous cases in 2000 and their status by 2022 [1]

Sulfadoxine-pyrimethamine (SP) was introduced as a replacement but was also quickly undermined by resistance mutations in dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHPS) genes [6]. The discovery of artemisinin, a sesquiterpene lactone isolated from *Artemisia annua* by Tu Youyou in the 1970s, revolutionized malaria therapy [7]. Artemisinin derivatives, including artesunate, artemether, and dihydroartemisinin (DHA), rapidly became the cornerstone of artemisinin-based combination therapies (ACTs), which are now recommended as first-line treatment for uncomplicated *P. falciparum* malaria worldwide [8].

Current Challenges in Malaria Treatment

Despite the success of ACTs, the emergence of artemisinin resistance in the Greater Mekong Subregion has raised major concerns. Resistance manifests as delayed parasite clearance and is strongly associated with *kelch13* propeller domain mutations [9]. Furthermore, resistance to partner drugs such as piperaquine and mefloquine threatens the efficacy of ACTs [9, 10]. For *P. vivax*, relapse due to dormant liver hypnozoites remains a major obstacle. Radical cure requires the use of primaquine or the newer long-acting analogue tafenoquine, but both carry risks of hemolysis in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency, limiting their safe use [11].

Rationale for Recent Advances

The development of novel drugs and combination regimens is a global priority to counteract resistance. In addition, non-chemotherapeutic approaches such as vaccines, monoclonal antibodies, gene drives for vector control, and long-acting prophylactic agents are increasingly recognized as vital tools for integrated malaria control. The convergence of pharmacology, molecular parasitology, immunology, and genomics has therefore ushered in a new era of translational research targeting malaria elimination [12]. This review critically examines the current therapeutic landscape, recent pharmacological innovations, vaccine developments, and future perspectives in malaria treatment.

Current Antimalarial Therapies

Antimalarial therapy has historically evolved in response to the relentless development of resistance in *Plasmodium* species. The classical quinoline derivatives, such as chloroquine, amodiaquine, mefloquine, lumefantrine, and halofantrine, remain important in understanding the pharmacology of malaria drugs. These compounds act by interfering with heme detoxification within the parasite's digestive vacuole, leading to accumulation of toxic free heme that ultimately damages parasite membranes and proteins [13]. Chloroquine was once hailed as a miracle drug due to its low cost, excellent tolerability, and high efficacy, but resistance spread rapidly from Southeast Asia and South America into Africa, driven primarily by mutations in the *pfcrt* gene, particularly the K76T substitution, and additional modulation by *pfmdr1* polymorphisms [5, 14]. Although chloroquine has lost efficacy in most regions for *P. falciparum*, amodiaquine is still used in seasonal malaria chemoprevention in Africa, and lumefantrine remains an essential ACT partner drug [1]. The 8-aminoquinolines represent a unique drug class, as they are the only agents effective against dormant liver hypnozoites of *P. vivax* and *P. ovale*. Primaquine has been the standard of care for radical cure for decades, but the introduction of tafenoquine, a long-acting analogue requiring only a single dose, has been transformative for compliance and relapse prevention. Both drugs, however, pose risks of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, which is highly prevalent in malaria-endemic regions. Thus, integration of point-of-care G6PD testing is critical before deployment of tafenoquine at scale [11]. Antifolate drugs also played a significant role in malaria therapy. The fixed-dose combination of sulfadoxine pyrimethamine (SP) inhibits folate metabolism by targeting dihydropteroate synthase (DHPS) and dihydrofolate reductase (DHFR), while atovaquone-proguanil (Malarone) combines mitochondrial cytochrome bc1 complex inhibition with DHFR blockade. Although SP has been rendered ineffective in most regions due to stepwise mutations in

pfdhfr (N51I, C59R, S108N, I164L) and *pfdhps* (A437G, K540E), it continues to be recommended for intermittent preventive treatment in pregnancy (IPTp) and infants in high-transmission regions [6, 15]. Atovaquone-proguanil remains effective against multidrug-resistant *P. falciparum*, but its high cost has limited widespread use, making it primarily a drug of choice for travellers [16]. The greatest revolution in malaria therapy has been the introduction of artemisinin derivatives, including artesunate, artemether, and dihydroartemisinin [7]. Their rapid parasite clearance, combined with low toxicity, made them the backbone of artemisinin-based combination therapies (ACTs). The WHO currently recommends ACTs as first-line therapy for uncomplicated *P. falciparum* malaria worldwide, with regimens including artemether lumefantrine, artesunate amodiaquine, artesunate mefloquine, and dihydroartemisinin piperaquine [1, 8]. Importantly, these combinations pair artemisinin derivatives with long-acting partner drugs to ensure parasite eradication and reduce the likelihood of resistance emergence. However, despite their success, the spread of artemisinin resistance and declining efficacy of partner drugs underscore the fragility of this therapeutic success [17].

Mechanisms of Antimalarial Resistance

The major classes of antimalarials are associated with specific genetic mutations in *Plasmodium* that confer resistance. These include cytochrome b (CYTb) for atovaquone resistance, kelch13 (K13) protein for artemisinin resistance, dihydropteroate synthetase (DHPS) and dihydrofolate reductase (DHFR) for antifolate resistance, chloroquine resistance transporter (CRT) for chloroquine resistance, multidrug resistance protein 1 (MDR1) and multidrug resistance-associated protein 1 (MRP1) for quinoline and multidrug resistance, Na^+/H^+ exchanger protein (NHE) implicated in quinine and amodiaquine tolerance, and ATPase sodium efflux pump (ATP4) linked to resistance against novel spiroindolones such as cipargamin [18]. Drug resistance in *Plasmodium* parasites is underpinned by well-characterized genetic mutations. Chloroquine resistance is primarily mediated by the *pfcrt* gene encoding a digestive vacuole transporter, where the K76T mutation alters chloroquine accumulation, while *pfmdr1* mutations further modulate responses to multiple drugs [13]. Mefloquine resistance arises from increased copy number of *pfmdr1*, which reduces drug sensitivity [17]. Resistance to sulfadoxine pyrimethamine is driven by point mutations in *pfdhfr* and *pfdhps*, which alter enzyme binding affinity and progressively reduce efficacy [6]. Atovaquone resistance is associated with single-point mutations in the mitochondrial cytochrome b gene, particularly Y268S/N, which prevents drug binding [16]. Of greatest concern is artemisinin resistance, which first emerged in the Greater Mekong Subregion. It manifests clinically as delayed parasite clearance and is strongly associated with mutations in the *kelch13* propeller domain, including C580Y, R539T, and Y493H [9]. Additional modulators such as *pfmdr2* and *pfatp6* have also been implicated. Partner drug resistance compounds the threat: piperaquine resistance correlates with amplification of the *plasmepsin 2-3* gene cluster, while mefloquine resistance is linked to *pfmdr1* copy number increases [11, 1] Molecular surveillance of these markers has become integral to global malaria control efforts, alowing timely detection of emerging resistance hotspots [1]. Table 1.

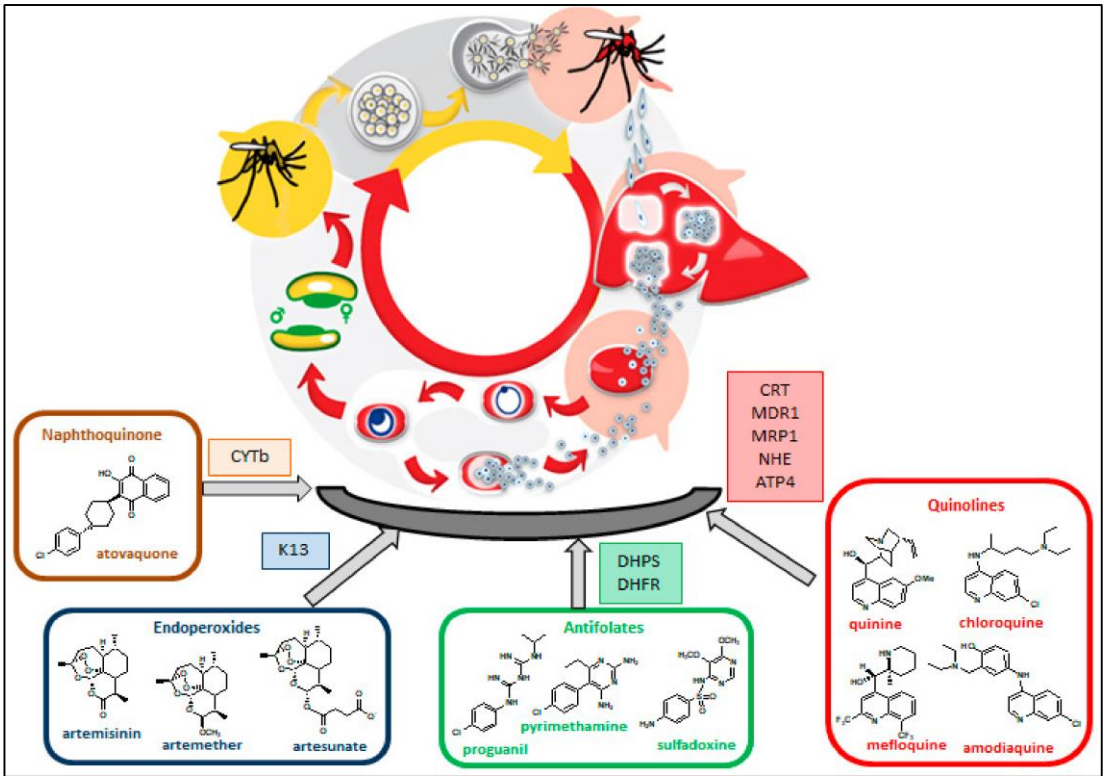

Fig 2: The major classes of antimalarials and the corresponding target mutations responsible for resistance. (CYTb Cytochrome b; K13 kelch 13 protein; DHPS dihydropteroate synthetase; DHFR dihydrofolate reductase; CRT chloroquine resistance transporter; MDR1 multidrug resistance protein 1; MRP1 multidrug resistance-associated protein 1; NHE Na^+/H^+ exchanger protein; ATP4 ATPase sodium efflux pump). (18)

Table 1: Antimalarial Drug Classes, Mechanisms, and Resistance Markers

Class	Example Drugs	Mechanism of Action	Resistance Marker(s)	Clinical Notes
Quinolines	Chloroquine, Amodiaquine	Inhibit heme detoxification	*pfcrt* (K76T), *pfmdr1* mutations	Resistance widespread
Arylamino alcohols	Mefloquine, Lumefantrine	Hemozoin interference	*pfmdr1* gene amplification	Used in ACTs
8-Aminoquinolines	Primaquine, Tafenoquine	Kill hypnozoites via ROS and mitochondria	G6PD deficiency limits use	Prevents relapse
Antifolates	SP, Atovaquone-Proguanil	Inhibit folate metabolism, mitochondrial ETC	*pfdhfr*, *pfdhps*, cytochrome b	SP in IPTp
Artemisinins	Artesunate, Artemether	Free radical-mediated protein damage	*kelch13*, *plasmepsin 2-3* amplif.	First-line ACTs

Recent Advances in Therapy

To overcome resistance, several innovative strategies are being pursued. One promising approach is the development of triple artemisinin-based combination therapies (TACTs). These regimens incorporate an artemisinin derivative with two long-acting partner drugs to reduce the probability of resistance evolution. For example, dihydroartemisinin piperaquine combined with mefloquine has demonstrated cure rates exceeding 90% in Cambodia, compared to <50% for DHA-piperaquine alone [19]. Similarly, artemether lumefantrine plus amodiaquine is under investigation in Africa. TACTs, although logistically more complex, may represent an important stopgap against multidrug resistance. Alongside combination strategies, novel drug scaffolds are advancing through the development pipeline. Cipargamin (KAE609), a spiroindolone that inhibits the PfATP4 Na^+-ATPase, has demonstrated rapid clearance of parasitemia in Phase II trials, even in resistant strains [12, 20]. Ganaplacide (KAF156), an imidazolopiperazine, is active against both blood-stage and liver-stage parasites and is being evaluated in combination with lumefantrine in Phase IIb trials [12]. MMV390048, a selective PI4K inhibitor, has shown activity against all parasite stages, making it a particularly attractive candidate for elimination campaigns [21]. Artefenomel (OZ439), a synthetic ozonide with a longer half-life than artemisinin, has been tested in single-dose regimens, raising hopes for simplified therapy [22]. DSM265, a dihydroorotate dehydrogenase (DHODH) inhibitor, was the first agent in its class but has shown limited efficacy as monotherapy, necessitating exploration of combinations [23]. The Medicines for Malaria Venture (MMV) continues to drive global drug discovery, with over 20 compounds in preclinical or clinical pipelines. These include novel scaffolds targeting epigenetic regulators, mitochondrial metabolism, and protein translation [24]. Importantly, drug development is increasingly guided by genomic surveillance and structural biology, ensuring that compounds are designed to circumvent known resistance pathways.

Advances in Malaria Vaccines and Immunotherapeutics

The development of a malaria vaccine has long been considered the "holy grail" of malaria elimination. The RTS,S/AS01 (Mosquirix) vaccine, the first to receive regulatory approval, is based on the *Plasmodium falciparum* circumsporozoite protein (CSP) fused with hepatitis B surface antigen, formulated with the AS01 adjuvant. Phase III trials across seven African countries demonstrated a vaccine efficacy of ~39% against clinical malaria over four years, with higher efficacy when combined with seasonal chemoprevention [25]. Despite modest efficacy, RTS,S is being deployed in large-scale pilot programs in Ghana, Kenya, and Malawi, marking a historic milestone [26].

More recently, the R21/Matrix-M vaccine, also targeting CSP but with a higher antigen-to-carrier ratio and novel saponin-based adjuvant, has shown efficacy of up to 77% in phase II trials in Burkina Faso [27]. Phase III trials are ongoing across multiple African countries, and results will determine its scalability and integration into immunization programs. Beyond CSP-based vaccines, whole sporozoite vaccines such as the PfSPZ vaccine (radiation-attenuated sporozoites) and genetically attenuated parasite (GAP) vaccines are being evaluated. PfSPZ trials have shown sterile protection in some controlled human malaria infection (CHMI) studies, but logistical challenges with intravenous administration limit field applicability. In addition to traditional vaccines, monoclonal antibodies (mAbs) targeting CSP epitopes are emerging as promising prophylactic tools [28]. The human mAb CIS43LS has demonstrated >70% protection in controlled trials lasting up to six months, suggesting potential for seasonal or traveler prophylaxis. This could complement, or in some cases substitute, chemopreventive regimens in high-risk groups. Table 2.

Table 2: Malaria Vaccine Candidates and Clinical Outcomes

Vaccine Candidate	Target Antigen/Stage	Efficacy (%)	Clinical Trial Phase	Limitations
RTS,S/AS01 (Mosquirix)	CSP (sporozoite)(31)	~39% over 4 years	Phase III, implemented in pilots	Modest efficacy, requires 4 doses
R21/Matrix-M	CSP (sporozoite)	Up to 77% (Phase II)	Phase III ongoing	Durability not fully established
PfSPZ vaccine	Whole sporozoite	>50% in CHMI	Phase II	IV administration limits scalability
GAP vaccines	Genetically attenuated sporozoite	Early promising results	Phase I/II	Still experimental
CIS43LS (mAb)	Passive antibody targeting CSP	>70% (up to 6 months)	Phase II	Requires repeated infusions

Innovative Vector Control and Gene-Editing Approaches: Vector control has historically focused on insecticide-treated bed nets (ITNs) and indoor residual spraying (IRS), both of which have contributed substantially to declines in malaria incidence. However, the spread of pyrethroid resistance in *Anopheles* mosquitoes has diminished their effectiveness. As a response, next-generation nets treated with pyrethroid piperonyl butoxide (PBO) or dual active ingredients such as chlorfenapyr are being deployed, showing improved efficacy in resistant settings. A paradigm-shifting advance is the application of gene-drive technology using CRISPR-Cas9 systems to modify mosquito populations.(29)(30)Gene drives can propagate traits such as sterility or refractoriness to *Plasmodium* through wild populations, reducing transmission at scale. Early trials in laboratory colonies of *Anopheles gambiae* have demonstrated near-complete population suppression, though ecological safety, ethical considerations, and regulatory frameworks remain under discussion. In addition, symbiont-based control strategies, such as the introduction of *Wolbachia* bacteria into *Anopheles* populations, are being explored. Wolbachia has already shown remarkable success in suppressing dengue transmission in *Aedes aegypti*, and its role in malaria transmission is a topic of ongoing investigation.

Long-acting Prophylaxis and Emerging Strategies

Chemoprevention is a critical component of malaria control, particularly for vulnerable populations such as pregnant women, infants, and children in seasonal transmission areas. Traditional regimens require frequent dosing, posing compliance challenges. Recently, long-acting injectable formulations of antimalarials have gained attention. Agents such as atovaquone and new diarylquinolines are being reformulated for extended plasma half-life, allowing monthly or even seasonal administration. Depot injections of antimalarial drugs, analogous to long-acting antibiotics or antivirals, could transform prevention strategies. This is especially relevant for military personnel, humanitarian workers, and populations in highly seasonal transmission areas. Additionally, advances in nanoparticle and liposomal drug delivery promise enhanced stability, bioavailability, and targeted delivery of antimalarial compounds. Another frontier is the application of artificial intelligence (AI) and machine learning in antimalarial drug discovery. AI-driven modeling of compound-target interactions has accelerated the identification of novel scaffolds and optimized lead molecules against resistant parasite strains. Integrating genomic surveillance data with AI-based drug development could enable rapid adaptation of therapies to emerging resistance patterns.

Discussion

The landscape of malaria treatment is rapidly evolving, reflecting a dual imperative: preserving the efficacy of existing therapies and investing in next-generation interventions. ACTs remain the backbone of malaria management, but the spread of artemisinin and partner drug resistance threatens decades of progress. TACTs and novel scaffolds such as cipargamin and ganaplacide are critical stopgap solutions, yet their global rollout will require robust pharmacovigilance, affordability, and integration into national treatment policies.

Vaccines represent a parallel revolution. While RTS, S has proven that malaria vaccination is feasible at scale, the higher efficacy of R21 and the promise of sporozoite-based vaccines suggest that more durable and scalable solutions may soon be available. The integration of monoclonal antibodies further expands the immunoprophylactic toolbox, offering flexible protection strategies for different populations. Vector control innovations, particularly gene-drive technologies, hold potential to reshape transmission dynamics permanently, but require careful ethical and ecological evaluation. Likewise, long-acting injectables and AI-driven drug discovery reflect how technological convergence is being harnessed against malaria. However, these innovations must overcome challenges of cost, delivery, and health system capacity in endemic regions.

Conclusion

Malaria treatment has entered a transformative era, driven by scientific innovation across pharmacology, immunology, and vector biology. ACTs remain the cornerstone of therapy but face erosion from resistance, underscoring the urgency of novel strategies. Advances such as TACTs, new chemical scaffolds, highly efficacious vaccines like R21, and long-acting prophylactic tools highlight a robust pipeline of interventions. Coupled with genomic surveillance, AI-guided drug discovery, and gene-drive mosquito control, these tools hold the potential to shift malaria from a global health crisis to a disease on the path to elimination. Coordinated global investment, equitable access, and adaptive policy frameworks will determine whether these advances translate into real-world progress toward eradication.

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