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Artemisinin Resistance Mechanisms and Surveillance Strategies in Plasmodium falciparum Malaria Control

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ABSTRACT

Artemisinin-based combination therapies represented the cornerstone of contemporary malaria treatment, yet emerging resistance in Plasmodium falciparum threatens global malaria control achievements. Artemisinin resistance manifested as delayed parasite clearance following treatment, driven primarily by mutations in the Kelch propeller domain of the K13 gene that confer survival advantages during the early ring stage of parasite development. This review examined the molecular mechanisms underlying artemisinin resistance in Plasmodium falciparum and evaluated current surveillance strategies for detecting and monitoring resistance emergence and spread. A comprehensive synthesis of peer-reviewed literature on K13 mutations, resistance phenotypes, molecular surveillance tools, and epidemiological monitoring approaches was conducted. Artemisinin resistance results from K13 mutations that alter protein homeostasis pathways, enhancing parasite capacity to withstand oxidative stress and maintain cellular quiescence during drug exposure. Validated resistance markers include C580Y and other nonsynonymous K13 mutations confirmed through clinical, in vitro, and genetic studies. Molecular surveillance utilizing polymerase chain reaction amplification and sequencing of K13 mutations enabled early detection, while therapeutic efficacy studies measuring parasite clearance kinetics provided functional resistance assessment. Geographic expansion of resistance from Southeast Asia to Africa necessitated intensified surveillance combining molecular marker detection, clinical outcome monitoring, and in vitro susceptibility testing. Surveillance gaps included limited capacity in resource-constrained settings, delayed reporting systems, and incomplete understanding of resistance mechanisms independent of K13 mutations. Integrated surveillance frameworks combining molecular diagnostics, clinical monitoring, and standardized reporting are essential for guiding treatment policy and containment strategies, though strengthening laboratory capacity and real-time data sharing remained critical priorities for effective artemisinin resistance management in malaria-endemic regions.

Keywords: Artemisinin resistance, Kelch 13, Plasmodium falciparum, Molecular surveillance, Parasite clearance.

INTRODUCTION

Artemisinin and its derivatives constitute the most rapidly acting and potent antimalarial compounds available, exerting their effects through a unique mechanism involving endoperoxide bridge activation within parasite-infected erythrocytes [1-3]. Following activation by heme iron or ferrous species, artemisinin generates carbon-centered free radicals that alkylate multiple parasite proteins, disrupting essential cellular processes including protein synthesis, glycolysis, and hemoglobin degradation [4,5]. The drug demonstrates particular efficacy against young ring-stage and mature trophozoite parasites, achieving rapid parasite clearance within 48 to 72 hours in susceptible infections. Artemisinin pharmacokinetics feature rapid absorption, short elimination half-lives of 1 to 3 hours, and extensive metabolism via hepatic cytochrome P450 enzymes, necessitating combination with longer-acting partner drugs to prevent recrudescence and protect against resistance development [6,7]. The biochemical versatility of artemisinin, targeting multiple parasite pathways simultaneously, initially suggested low propensity for resistance evolution, yet clinical and molecular evidence now demonstrates that Plasmodium falciparum can develop sophisticated adaptive mechanisms.

The emergence of artemisinin resistance in Southeast Asia, first documented clinically along the Thailand-Cambodia border in 2008, represents a critical threat to malaria control and elimination efforts globally. Resistance manifests phenotypically as delayed parasite clearance, with significant parasite biomass remaining detectable at 72 hours post-treatment, rather than complete treatment failure when artemisinin-based combination therapies are administered with effective partner drugs [8,9]. However, partner drug resistance, particularly to piperaquine and

mefloquine, combined with artemisinin resistance results in treatment failure rates exceeding 50% in some regions, necessitating therapeutic regimen changes and threatening the limited antimalarial drug arsenal [10,11]. The geographic spread of resistance from initial Cambodian epicenters to neighboring Myanmar, Vietnam, Laos, and Thailand, coupled with independent resistance emergence in eastern India and recent reports from African countries, signals potential for pandemic resistance that could reverse decades of mortality reduction achievements [12,13]. Mathematical modeling suggests that uncontrolled artemisinin resistance spread to high-burden African countries could result in millions of additional malaria deaths over the coming decades [14]. The objective of this review is to critically evaluate the molecular mechanisms underlying artemisinin resistance in Plasmodium falciparum and to assess the effectiveness, limitations, and optimization requirements of current surveillance strategies for detecting, monitoring, and responding to resistance emergence and geographic expansion.

Molecular Mechanisms of Artemisinin Resistance

Artemisinin resistance in Plasmodium falciparum is predominantly mediated by nonsynonymous mutations in the K13 gene, encoding a Kelch propeller domain-containing protein localized to the parasite endoplasmic reticulum and associated with phosphatidylinositol-3-kinase complexes [15,16]. The C580Y mutation in the K13 propeller domain represents the most prevalent resistance-conferring variant in Southeast Asia, accounting for over 50% of resistant parasites in Cambodia and surrounding regions, while other validated mutations including R539T, I543T, and Y493H demonstrate similar resistance phenotypes in clinical and laboratory studies [17,18]. Genome-wide association studies and genetic manipulation experiments confirm that K13 mutations are necessary and sufficient to confer the delayed clearance phenotype, with isogenic parasite lines differing only in K13 genotype demonstrating reproducible resistance differences in ring-stage survival assays [19,20]. The mechanism by which K13 mutations confer resistance involves alterations in protein homeostasis and cellular stress response pathways, particularly affecting phosphatidylinositol-3-phosphate metabolism and autophagy-related processes [21,22].

Recent investigations demonstrate that K13 mutations enhance parasite capacity to enter a quiescent state upon artemisinin exposure during the early ring stage, the developmental phase when parasites are normally most susceptible to artemisinin [23]. This quiescence involves cell cycle arrest, reduced metabolic activity, and decreased hemoglobin uptake, collectively minimizing artemisinin activation and target protein alkylation during the critical drug exposure window [24]. Transcriptomic and proteomic analyses reveal that resistant parasites exhibit dysregulated expression of oxidative stress response genes, unfolded protein response components, and metabolic enzymes compared to susceptible parasites, suggesting multifaceted adaptations to maintain cellular viability during drug pressure [25,26]. K13 protein interactions with components of the endoplasmic reticulum quality control machinery, including the proteasome and ubiquitin ligase complexes, support a model wherein resistance mutations alter protein trafficking and degradation pathways, enhancing cellular resilience [27].

Epistatic interactions between K13 mutations and other genetic loci modulate resistance magnitude and fitness costs, with background mutations in genes encoding ferredoxin, apicoplast ribosomal proteins, and multidrug resistance-associated proteins influencing resistance expression [28,29]. These modifier loci partly explain geographic variation in resistance phenotype intensity despite identical K13 mutations and may influence transmission fitness of resistant parasites. Artemisinin resistance imposes measurable fitness costs in the absence of drug pressure, with resistant parasites demonstrating reduced multiplication rates and competitive disadvantages in mosquito transmission studies, suggesting potential for resistance reversion if drug pressure diminishes [30,31]. However, compensatory mutations that restore fitness while maintaining resistance have been identified in evolved parasite populations, indicating that sustained transmission of highly resistant, fit parasites is biologically plausible [32].

Phenotypic Characterization and Resistance Definitions

Clinical phenotyping of artemisinin resistance relies on measurement of parasite clearance kinetics following artemisinin monotherapy or artemisinin-based combination therapy, with standardized protocols requiring microscopic parasite quantification at defined time intervals post-treatment [33,34]. The parasite clearance half-life, defined as the time required for parasitemia to decrease by 50%, serves as the primary quantitative metric, with half-lives exceeding 5 hours indicating suspected resistance and values above 6.5 hours confirming slow clearance phenotype in multiple studies [35,36]. Day 3 parasite positivity, representing the proportion of patients with microscopically detectable parasitemia 72 hours after treatment initiation, provides an operational resistance indicator with thresholds above 10% suggesting population-level resistance [37,38]. These clinical measures correlate moderately well with K13 mutation prevalence but show substantial individual variation influenced by host immunity, initial parasitemia, and partner drug efficacy [39].

In vitro phenotyping through the ring-stage survival assay quantifies the proportion of early ring-stage parasites surviving brief exposure to pharmacologically relevant artemisinin concentrations, typically 700 nanomolar for 6 hours [40,41]. Survival rates exceeding 1% indicate resistance, with validated resistant parasites demonstrating survival rates of 5 to 20% compared to less than 0.5% for susceptible reference strains [42]. This assay specifically captures the ring-stage quiescence mechanism central to artemisinin resistance but requires specialized laboratory

capacity and fresh parasite isolates, limiting implementation to research settings [43]. Alternative in vitro approaches measuring conventional drug susceptibility through inhibitory concentration assays show poor correlation with clinical resistance, as artemisinin retains potency against trophozoites and schizonts despite ring-stage resistance [44,45].

Ex vivo assays adapting ring-stage survival methodology to patient isolates enable phenotypic surveillance without continuous parasite culture, though technical complexity and the requirement for sufficient parasitemia restrict applicability [46]. Discordance between phenotypic resistance measures and K13 genotype occurs in 5 to 15% of samples, attributable to non-K13 resistance mechanisms, laboratory error, or K13 mutations with uncertain functional significance [47,48]. The World Health Organization defines artemisinin resistance operationally based on clinical endpoints, including delayed parasite clearance or day 3 positivity in areas with validated K13 mutations, recognizing that resistance manifests along a continuum rather than as a binary trait [49]. Harmonization of resistance definitions across surveillance networks remains incomplete, complicating meta-analyses and global resistance mapping efforts [50].

Molecular Surveillance Methodologies

Molecular surveillance for artemisinin resistance centers on detection and geographic mapping of K13 mutations through polymerase chain reaction amplification and Sanger sequencing of the K13 propeller domain from patient samples or routine diagnostic specimens [51,52]. Standardized protocols amplify a 849 base pair fragment encompassing codons 440 to 680, the region containing all validated resistance mutations, with sequencing sensitivities detecting mutations present in greater than 20% of polyclonal infections [53,54]. Next-generation sequencing approaches enable detection of minority variants at frequencies below 5% and characterization of multiclonal infections, revealing cryptic resistance circulation and importation events missed by conventional sequencing [55,56]. Targeted amplicon sequencing balances cost, throughput, and sensitivity for large-scale surveillance, while whole-genome sequencing provides comprehensive resistance marker profiling but remains cost-prohibitive for routine surveillance in most endemic settings [57,58].

Multiplex polymerase chain reaction assays incorporating allele-specific primer designs or restriction fragment length polymorphism analysis enable rapid K13 mutation screening without sequencing, facilitating point-of-care or district-level surveillance where sequencing infrastructure is unavailable [59,60]. Loop-mediated isothermal amplification adaptations further simplify molecular detection, eliminating thermal cycling requirements, though validation for diverse K13 mutations remains incomplete. Molecular surveillance implementation requires standardized sample collection, storage, and transport protocols, as DNA degradation in dried blood spots compromises amplification success rates when samples exceed 3 to 6 months storage at ambient tropical temperatures [61,62]. Quality assurance programs incorporating proficiency panels, replicate testing, and reference laboratory confirmation ensure surveillance data reliability, particularly when capacity-building initiatives expand testing to peripheral laboratories [63].

Surveillance network design considerations include sampling strategies, with sentinel site surveillance providing longitudinal trend detection at fixed locations while cross-sectional surveys enable broader geographic coverage and population-representative prevalence estimation [64,65]. Therapeutic efficacy studies enrolling patients for clinical follow-up enable paired molecular and phenotypic resistance assessment, strengthening causal inference regarding mutation-resistance associations. Molecular surveillance of partner drug resistance markers, including mutations in pfcrt, pfmdr1, plasmepsin 2-3, and pfdhps, provides complementary information on multidrug resistance threats requiring integrated analysis [66,67]. Bioinformatic platforms integrating molecular surveillance data with geographic information systems, treatment policy databases, and epidemiological indicators enable spatiotemporal resistance mapping and predictive modeling to guide containment responses [68,69].

Clinical and Epidemiological Surveillance Approaches

Therapeutic efficacy studies represent the gold standard for surveillance, prospectively enrolling patients receiving artemisinin-based combination therapies and monitoring treatment outcomes through 28 to 42 days post-treatment with standardized parasitological and clinical assessments [70]. The World Health Organization recommends routine efficacy studies in sentinel sites every 2 to 3 years or following policy changes, with sample sizes of 50 to 100 patients per site providing adequate precision for detecting treatment failure rates above 10% [71]. Outcome classification distinguishes adequate clinical and parasitological response from early treatment failure, late clinical failure, and late parasitological failure, with parasite genotyping differentiating recrudescence from new infections in subsequent parasitemia episodes [72,73]. Efficacy studies capture real-world treatment effectiveness under operational conditions, integrating drug quality, adherence, pharmacokinetics, and resistance into composite outcomes, though logistical intensity and cost limit implementation frequency and geographic coverage [74].

Passive surveillance through routine health information systems collects treatment outcome data from standard care delivery, offering broader coverage and continuous monitoring but suffering from incomplete follow-up, inconsistent data quality, and inability to distinguish recrudescence from reinfection [75]. Strengthening passive surveillance requires integration of standardized case report forms, laboratory confirmation of treatment failures, and data

management systems enabling real-time analysis and feedback. Pharmacovigilance networks monitoring adverse events and treatment failures complement efficacy studies, identifying unusual resistance patterns or drug quality issues requiring investigation.

Parasite clearance monitoring, though more resource-intensive than standard efficacy studies, provides sensitive resistance detection during the early emergence phase when treatment failure rates remain low. Nested parasite clearance substudies within efficacy studies or dedicated clearance surveys enroll 30 to 50 patients with intensive parasitemia measurements at 0, 6, 12, 24, 36, 48, and 72 hours post-treatment, calculating clearance half-lives and day 3 positivity rates [76]. Mathematical modeling of clearance curves improves precision and enables mechanistic interpretation of resistance phenotypes. Population-level surveillance tracking day 3 positivity trends identifies geographic resistance hotspots and temporal progression, informing targeted containment interventions.

Health facility surveys assessing antimalarial drug stock availability, prescription practices, and treatment adherence identify health system factors amplifying resistance selection pressure, including monotherapy use, substandard drug quality, and inadequate dosing. Integration of resistance surveillance with malaria epidemiological surveillance, vector control monitoring, and case management quality assessments provides comprehensive program evaluation and identifies synergistic intervention opportunities [77]. Private sector surveillance addressing antimalarial drug distribution, quality, and utilization patterns in informal markets captures resistance drivers often missed by public sector-focused surveillance [78].

Surveillance Gaps, Challenges, and Future Directions

Current surveillance systems face substantial capacity limitations, particularly in resource-constrained African countries where malaria burden is highest but molecular diagnostic infrastructure, trained personnel, and funding for sustained surveillance remain inadequate [79,80]. Reliance on sentinel sites creates geographic blind spots, potentially missing resistance emergence in under-sampled areas until substantial prevalence is achieved and regional spread occurs. Delays between sample collection, laboratory analysis, and data reporting commonly exceed 6 to 12 months in operational surveillance, diminishing opportunities for timely containment responses when resistance is first detected [81,82]. Standardization gaps across surveillance networks, including variable K13 mutation panels, inconsistent phenotypic thresholds, and heterogeneous efficacy study protocols, complicate data aggregation and inter-regional comparisons [83].

The potential for artemisinin resistance mechanisms independent of K13 mutations represents a critical surveillance challenge, as exclusive focus on K13 genotyping may miss novel resistance pathways [84,85]. Slow clearance phenotypes with wild-type K13 have been reported in African sites, raising concerns about either non-K13 resistance or confounding factors including host immunity and concomitant infections [86,87]. Surveillance strategies must balance targeted K13 monitoring for known resistance with hypothesis-free approaches, such as whole-genome sequencing and phenotypic screening, capable of detecting unexpected mechanisms [88]. Partner drug resistance surveillance requires parallel attention, as artemisinin resistance becomes clinically significant only when combined with partner drug failure, yet integrated resistance profiling remains incompletely implemented [89].

Data sharing and transparency represent persistent challenges, with substantial proportions of surveillance data remaining unpublished or inaccessible beyond national programs, limiting global situational awareness and modeling efforts [90]. Establishment of open-access databases and real-time reporting platforms, exemplified by initiatives such as the World Antimalarial Resistance Network and MalariaGEN, improves data accessibility but requires broader participation and standardized data formats [91]. Ethical considerations regarding data sharing, particularly for genomic information, necessitate clear governance frameworks balancing public health imperatives with participant privacy and country ownership.

Future surveillance optimization requires integration of novel technologies, including portable sequencing devices enabling field-based molecular diagnostics, digital health platforms for real-time data capture and transmission, and artificial intelligence approaches for predictive modeling and automated data analysis [92,93]. Expanded surveillance linking parasite genotypes with detailed patient clinical data, pharmacokinetic profiles, and longitudinal outcomes would elucidate resistance mechanisms and transmission dynamics more comprehensively. Surveillance extension to asymptomatic infections, which constitute substantial parasite reservoirs in elimination settings, may reveal cryptic resistance circulation and inform targeted screening strategies [94]. Cost-effectiveness analyses of alternative surveillance approaches remain limited, yet are essential for optimizing resource allocation and demonstrating value to policymakers and funders [95].

CONCLUSION

Artemisinin resistance in Plasmodium falciparum results from molecular adaptations, predominantly K13 mutations, that alter cellular stress responses and enable parasite survival during drug exposure through quiescence mechanisms. Surveillance strategies combining molecular marker detection, clinical parasite clearance monitoring, therapeutic efficacy studies, and in vitro phenotyping provide complementary approaches for resistance detection, characterization, and geographic mapping. Current surveillance reveals established artemisinin resistance across Southeast Asia, emerging threats in South Asia, and concerning signals from Africa, necessitating urgent

intensification of monitoring and containment efforts. Molecular surveillance targeting K13 mutations enables scalable resistance screening, while therapeutic efficacy studies and parasite clearance assessments capture functional resistance under operational conditions and detect treatment failures resulting from combined artemisinin and partner drug resistance. Substantial surveillance gaps persist, including limited capacity in high-burden regions, geographic blind spots, delayed reporting, and incomplete coverage of non-K13 resistance mechanisms and partner drug resistance. Strengthening surveillance requires sustained investment in laboratory infrastructure, workforce development, quality assurance systems, and data management platforms enabling real-time analysis and sharing. Integration of surveillance with malaria control program monitoring, health system assessments, and multisectoral interventions addressing drug quality and appropriate case management maximizes resistance prevention and containment effectiveness. Future surveillance evolution must incorporate emerging molecular technologies, predictive modeling, and hypothesis-free genomic approaches capable of detecting novel resistance mechanisms while maintaining operational feasibility in resource-limited settings where implementation impact is greatest. National malaria programs should establish integrated surveillance systems combining annual molecular screening for K13 and partner drug resistance markers at representative sentinel sites with biennial therapeutic efficacy studies, supported by regional reference laboratory networks ensuring quality assurance and timely reporting to guide evidence-based treatment policy and targeted containment interventions.

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