RESEARCH PAPER

Integrated Framework for Model-Informed Antimalarial Dose Optimization

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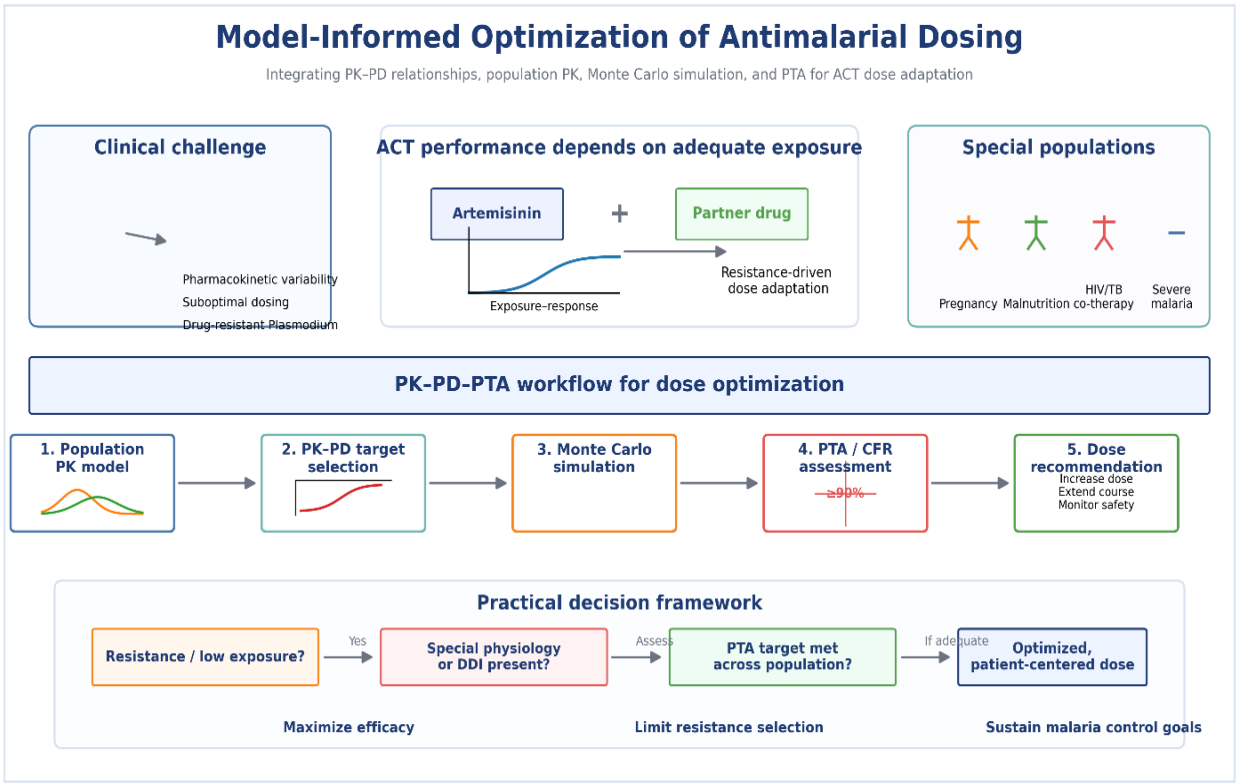
ABSTRACT

Malaria remains a major global health burden, and the long-term effectiveness of antimalarial therapy is increasingly challenged by pharmacokinetic variability, suboptimal dosing, and the emergence of drug-resistant Plasmodium strains. Artemisinin-based combination therapies (ACTs) are the cornerstone of current malaria treatment; however, their success depends on achieving adequate drug exposure across diverse patient populations and clinical settings. This review critically examines the principles of antimalarial dosing with an emphasis on pharmacokinetic–pharmacodynamic (PK–PD) relationships, population PK modeling, Monte Carlo simulations, and probability of target attainment (PTA) as tools for dose optimization.

We synthesize evidence on exposure–response relationships for key ACT components and discuss how artemisinin partial resistance and partner-drug resistance necessitate resistance-driven dose adaptation. Special clinical scenarios, including severe malaria, malnourished children, pregnancy, and HIV– or tuberculosis–malaria co-infection, are highlighted to illustrate how altered physiology and drug–drug interactions influence antimalarial efficacy and safety. Graphical workflows and decision-tree frameworks are used to integrate PK–PD–PTA concepts into practical clinical decision-making.

Collectively, this review underscores that a one-size-fits-all approach to antimalarial dosing is insufficient. Model-informed, resistance-aware, and patient-centered dosing strategies are essential to maximize therapeutic efficacy, limit resistance selection, and sustain the clinical utility of existing antimalarial drugs in support of global malaria control and elimination goals.



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INTRODUCTION

Malaria remains a major global health burden, particularly in tropical and subtropical regions, with Plasmodium falciparum and Plasmodium vivax accounting for the majority of clinical cases and malaria-associated mortality worldwide 1,2. Despite substantial progress in malaria control through vector management, rapid diagnostics, and improved therapeutics, the disease continues to exert a disproportionate impact on low- and middle-income countries, where vulnerable populations such as young children and pregnant women face the highest risk of severe outcomes3. Effective malaria management depends not only on appropriate drug selection but also on the optimization of dosage regimens, which are essential to achieve rapid parasite clearance, prevent recrudescence and relapse, and suppress the emergence and spread of drug-resistant parasite strains 4,5. Inadequate dosing—whether due to underestimation of body weight, altered pharmacokinetics in special populations, poor adherence, or substandard formulations—has been repeatedly implicated in treatment failure and resistance development, particularly in the context of artemisinin-based therapies 6.

Dosage recommendations for antimalarial drugs are shaped by a complex interplay of parasite biology, host factors, and drug-specific pharmacokinetic–pharmacodynamic properties7. Differences in parasite species, life-cycle stages, and intrinsic susceptibility necessitate tailored dosing strategies, while host-related variables such as age, nutritional status, pregnancy, and hepatic or renal function significantly influence drug absorption, distribution, metabolism, and elimination8. Furthermore, regional variations in antimalarial resistance patterns demand continual reassessment of dosing regimens to ensure sustained therapeutic efficacy. The increasing recognition of delayed parasite clearance and reduced drug sensitivity in certain endemic regions underscores the urgent need for precise, evidence-based dosage strategies that balance efficacy with safety 9. Within this context, the present review critically examines current antimalarial dosage regimens, their scientific rationale, and the clinical and operational challenges associated with their implementation, while highlighting emerging considerations for optimizing dosing strategies in the evolving landscape of malaria treatment.

General Principles of Antimalarial Dosage

Antimalarial dosage regimens are designed to achieve rapid parasite clearance while maintaining drug concentrations above the minimum inhibitory concentration (MIC) for a duration sufficient to eradicate both asexual blood stages and, where relevant, dormant hepatic forms10. Weight-based dosing is particularly critical because antimalarial pharmacokinetics show substantial inter-individual variability related to age, nutritional status, pregnancy, and disease severity11. Underdosing has been consistently linked to delayed parasite clearance, treatment failure, and the selection of drug-tolerant parasite subpopulations, especially in regions where partial resistance to artemisinin derivatives has emerged12,13.

Loading doses play a pivotal role in antimalarial therapy by rapidly reducing parasite biomass during the initial treatment phase. Drugs such as artesunate and quinine are administered with higher initial doses to achieve therapeutic plasma concentrations quickly, which is particularly important in severe malaria where high parasitemia correlates with increased mortality14. Rapid parasite reduction not only improves clinical outcomes but also decreases transmission potential by shortening the duration of gametocyte carriage15.

Combination therapy represents a cornerstone principle of modern antimalarial dosing strategies. Artemisinin-based combination therapies (ACTs) pair a fast-acting artemisinin derivative with a longer-acting partner drug, ensuring both immediate parasite clearance and sustained suppression of residual parasites. From a pharmacodynamic perspective, this dual-exposure approach reduces the probability that parasites survive at subtherapeutic drug levels, thereby slowing the development of resistance16. Inadequate dosing of either component, however, compromises this protective effect and has been implicated in the emergence of resistance to partner drugs such as lumefantrine and piperaquine17.

Completion of the full prescribed treatment course is essential for achieving radical cure and preventing recrudescence or relapse. Partial adherence, often driven by rapid symptomatic improvement, results in insufficient drug exposure and persistent low-level parasitemia, which may later rebound clinically or contribute to ongoing transmission18. This issue is particularly relevant for multi-day regimens and drugs with long terminal half-lives, where missed doses can create prolonged subtherapeutic drug concentrations that favor resistant parasite selection.

Dose optimization becomes even more complex in special populations. In pediatric patients, developmental changes in drug absorption, distribution, metabolism, and elimination necessitate carefully defined weight-band dosing rather than age-based estimates11. Similarly, pregnancy alters antimalarial pharmacokinetics through increased plasma volume, altered protein binding, and enhanced hepatic metabolism, often leading to reduced drug exposure at standard doses12. Failure to account for these changes may result in suboptimal efficacy and increased risk of treatment failure.

Renal and hepatic impairment further influence dosing strategies, as several antimalarial agents undergo hepatic metabolism or renal excretion. Although most ACTs do not require routine dose adjustment, drugs such as quinine and amodiaquine demand close monitoring due to their narrow therapeutic indices and potential for cumulative toxicity14,18. Collectively, these considerations underscore the necessity of individualized, evidence-based dosing strategies that integrate pharmacokinetic–pharmacodynamic principles with patient-specific factors to ensure both clinical efficacy and long-term sustainability of antimalarial therapies.

Dosage of Artemisinin-Based Combination Therapies (ACTs)

Artemisinin-based combination therapies (ACTs) constitute the cornerstone of treatment for uncomplicated malaria caused by Plasmodium falciparum 19. The therapeutic rationale behind ACTs is grounded in pharmacokinetic complementarity: a rapidly acting artemisinin derivative achieves swift parasite biomass reduction, while a longer-acting partner drug eliminates residual parasites and prevents recrudescence20. This dual-drug strategy not only improves cure rates but also reduces the probability of resistance development by minimizing parasite exposure to subtherapeutic monotherapy21. WHO guidelines recommend strict adherence to weight-based dosing schedules to maintain therapeutic plasma concentrations above the minimum parasiticidal threshold for an adequate duration22. Variations in dosing accuracy, adherence, or drug quality can significantly influence treatment outcomes and contribute to emerging resistance patterns observed in certain endemic regions21,22.

Artemether–Lumefantrine

Artemether–lumefantrine remains one of the most widely prescribed artemisinin-based combination therapies globally23. Each tablet contains 20 mg of artemether and 120 mg of lumefantrine, and the standard adult regimen consists of four tablets administered at 0, 8, 24, 36, 48, and 60 hours, totaling 24 tablets over three

days24. Artemether, a fast-acting derivative of artemisinin, rapidly reduces parasite load during the initial 48 hours of therapy by targeting asexual blood stages25. Lumefantrine, with its longer elimination half-life, ensures sustained suppression of remaining parasites and reduces the risk of recrudescence26.

The pharmacokinetic profile of lumefantrine is highly dependent on dietary fat intake, as it exhibits poor aqueous solubility and variable oral bioavailability27. Co-administration with fatty food significantly enhances absorption, leading to higher systemic exposure and improved therapeutic outcomes. Failure to administer the drug with adequate dietary fat can result in subtherapeutic plasma concentrations and increased risk of treatment failure27. Clinical studies have demonstrated cure rates exceeding 95% in areas without significant resistance when dosing schedules are properly followed28.

Weight-based dosing is particularly important in pediatric populations, where underdosing has been associated with reduced lumefantrine exposure and higher recurrence rates29. Additionally, vomiting within one hour of administration necessitates re-dosing to ensure adequate absorption24. The safety profile of artemether–lumefantrine is generally favorable, with mild gastrointestinal symptoms and transient headache being the most commonly reported adverse effects. QT prolongation is rare at recommended doses but should be considered in patients with pre-existing cardiac conditions26.

Emerging concerns regarding delayed parasite clearance in Southeast Asia have reinforced the importance of maintaining strict adherence to recommended dosing regimens25,28. Inadequate dosing of either component may accelerate the selection of resistant parasite strains. Therefore, pharmacovigilance and therapeutic efficacy monitoring remain essential components of ACT deployment strategies23,29.

Artesunate–Amodiaquine

Artesunate–amodiaquine is another WHO-recommended artemisinin-based combination therapy widely utilized in sub-Saharan Africa30. The standard dosing regimen consists of artesunate at 4 mg/kg/day combined with amodiaquine at 10 mg/kg/day for three consecutive days31. Artesunate provides rapid parasite clearance through activation by intraparasitic heme iron, generating reactive intermediates that damage parasite proteins and membranes32. Amodiaquine, a 4-aminoquinoline compound structurally related to chloroquine, inhibits heme detoxification within the parasite's digestive vacuole, leading to parasite death33. This combination demonstrates high efficacy in regions where amodiaquine resistance remains limited34. The three-day dosing schedule is designed to maintain adequate drug exposure throughout multiple parasite life cycles, thereby reducing the risk of recrudescence. Weight-band formulations have been developed to improve dosing accuracy and adherence in pediatric populations, where precise mg/kg administration is essential31,34.

However, careful dosing is required due to the potential hepatotoxicity and neutropenia associated with amodiaquine, particularly at higher cumulative exposures or with repeated treatment courses35. Although these adverse effects are uncommon in short-course therapy, pharmacovigilance is critical in high-transmission settings where repeated treatment episodes may occur35. Dose adjustments are generally not required in mild renal impairment but warrant caution in patients with significant hepatic dysfunction36.

The widespread use of artesunate–amodiaquine has contributed substantially to malaria control efforts in Africa30,34. Nevertheless, continuous therapeutic efficacy surveillance is necessary to detect early signs of reduced susceptibility, particularly in regions with historical chloroquine resistance, which may predispose to cross-resistance mechanisms affecting amodiaquine33,36.

Dihydroartemisinin–Piperaquine

Dihydroartemisinin–piperaquine (DHA–PPQ) is a once-daily artemisinin-based combination therapy administered over three days with weight-based dosing37. Dihydroartemisinin, the active metabolite of several artemisinin derivatives, provides rapid parasite reduction, while piperaquine, a bisquinoline compound with an extended elimination half-life, ensures prolonged antimalarial activity38. The long half-life of piperaquine confers an additional post-treatment prophylactic effect, reducing the risk of reinfection in high-transmission settings39.

The simplified once-daily regimen improves patient adherence compared to more frequent dosing schedules, which is particularly advantageous in community-based treatment programs40. High cure rates have been reported in multiple endemic regions; however, the pharmacokinetic properties of piperaquine require careful attention to dosing accuracy to prevent subtherapeutic exposure that may promote resistance development38,41.

One of the primary safety concerns associated with piperaquine is dose-dependent QT interval prolongation42. Although clinically significant arrhythmias are rare at recommended doses, caution is

advised in patients with pre-existing cardiac disease or those receiving concomitant QT-prolonging medications. Electrocardiographic monitoring may be considered in high-risk individuals42.

Recent reports of reduced piperaquine sensitivity in parts of Southeast Asia highlight the importance of maintaining recommended dosing regimens and avoiding underdosing, which may accelerate resistance spread41. Continued pharmacokinetic–pharmacodynamic research is essential to optimize dosing strategies and preserve the long-term effectiveness of DHA–PPQ as a frontline ACT option37,40.

Table 1: Dosage and Clinical Considerations of WHO-Recommended Artemisinin-Based Combination Therapies (ACTs) for Uncomplicated Plasmodium falciparum Malaria

Parameter	Artemether–Lumefantrine (AL)	Artesunate–Amodiaquine (AS–AQ)	Dihydroartemisinin–Piperaquine (DHA–PPQ)	Key References
Drug Components	Artemether (short-acting) + Lumefantrine (long-acting)	Artesunate (short-acting) + Amodiaquine (long-acting 4-aminoquinoline)	Dihydroartemisinin (active artemisinin metabolite) + Piperaquine (bisquinoline)	43,44
Standard Adult Dose	4 tablets (20/120 mg each) at 0, 8, 24, 36, 48, 60 h	Artesunate 4 mg/kg/day + Amodiaquine 10 mg/kg/day	Weight-based once-daily dosing	44,45
Total Duration	3 days (6 doses)	3 days	3 days	43
Pediatric Dosing	Weight-band dosing (5–<15 kg, 15–<25 kg, etc.)	Strict mg/kg dosing; pediatric fixed-dose combinations available	Weight-based dosing with age-adjusted bands	45,46
Mechanism of Artemisinin Component	Generates free radicals via heme interaction → rapid parasite protein damage	Same as AL	Same as AL	47
Mechanism of Partner Drug	Lumefantrine inhibits heme polymerization	Amodiaquine inhibits heme detoxification in parasite vacuole	Piperaquine inhibits heme detoxification; prolonged intracellular persistence	47,48
Half-Life (Partner Drug)	3–6 days	9–18 days (desethylamodiaquine)	~20–30 days	48
Post-Treatment Prophylaxis	Moderate	Moderate	Extended (long piperaquine half-life)	49

Absorption Considerations	Requires fatty meal for optimal lumefantrine absorption	Food improves tolerability; absorption not critical	Absorption improved with food; avoid excess fat due to QT risk	44,49
Peak Parasite Clearance Time	24–48 h	24–48 h	24–48 h	47
Common Adverse Effects	Headache, nausea, dizziness	GI upset, mild hepatotoxicity	Nausea, dizziness	46,48
Serious Safety Concerns	Rare QT prolongation	Hepatotoxicity, neutropenia (rare with short course)	Dose-dependent QT prolongation	48,50
Use in Pregnancy	Safe in 2nd & 3rd trimester	Safe in 2nd & 3rd trimester	Increasing evidence of safety in 2nd & 3rd trimester	45,46
Renal / Hepatic Adjustment	Not routinely required	Caution in significant hepatic disease	Not routinely required	44,50
Resistance Concerns	Reduced lumefantrine sensitivity in some regions	Potential cross-resistance with chloroquine-resistant strains	Piperaquine resistance reported in Southeast Asia	49,50
Adherence Advantage	Well-established regimen	Widely used in Africa	Once-daily dosing improves compliance	43,49
WHO Recommendation Status	First-line in many endemic countries	First-line in Africa	First-line alternative in several regions	43,44

Table 2. Severe Malaria: Parenteral Dosing Comparison (IV/IM) and Transition to Oral Therapy

Parameter	**IV/IM Artesunate (Preferred)**	**IV Quinine (Alternative when artesunate unavailable)**	**IM Artemether (Alternative when IV access not possible / artesunate unavailable)**	**Key References**
Role in severe malaria	First-line therapy for severe malaria in adults and children	Alternative parenteral regimen; requires careful infusion and monitoring	Alternative parenteral regimen (IM only; generally less preferred than artesunate)	51,52

Core dose (adults & children)	2.4 mg/kg per dose IV (or IM if IV not feasible)	Loading: 20 mg/kg quinine salt (dihydrochloride) IV over 4 h (omit if quinine/quinidine/mefloquine taken in previous 24 h)	Loading: 3.2 mg/kg IM on admission	51,53
Timing / schedule	0, 12, 24 h, then every 24 h until oral therapy tolerated	After loading: 10 mg/kg IV infusion (commonly over 2–4 h) every 8 h	After loading: 1.6 mg/kg IM once daily	51–54
Minimum parenteral duration	At least 24 h even if oral intake returns earlier	At least 24 h, then switch to oral when stable	Until oral therapy tolerated (practically ≥24 h in most settings)	52,54
Transition ("step-down") therapy	After ≥24 h and clinical improvement, complete a full 3-day oral ACT (e.g., AL, AS–AQ, DHA–PPQ per policy)	After stabilization, switch to oral therapy to complete full course	After stabilization, complete a full 3-day oral ACT	51,52
Major advantages	Rapid parasite clearance; proven mortality benefit; effective across age groups	Familiar regimen where artesunate unavailable	Useful when IV access is delayed or not feasible	51,55
Key limitations / monitoring	Monitor for delayed hemolysis (rare); ensure correct reconstitution and dosing	Risk of hypoglycemia, hypotension (rapid infusion), arrhythmias; omit loading dose if recent quinine exposure	IM injection; generally less effective than artesunate for mortality reduction; injection-site reactions possible	53–55
Reference dosing sources	WHO operational guidance; CDC clinical guidance	WHO standard quinine regimen (loading + maintenance)	WHO-referenced standard IM artemether regimen	51–56

Comparative Dosing

Comparative dosing considerations among artemisinin-based combination therapies (ACTs) highlight important pharmacokinetic and safety-driven differences that influence regimen selection in clinical practice57. Artemether–lumefantrine is typically administered at a total artemether dose of approximately 1.7–2.0 mg/kg per dose and lumefantrine 10–12 mg/kg per dose, given twice daily over three days (six doses)58. The defining feature of this regimen is the relatively short half-life of artemether (≈1–3 h) paired with a longer lumefantrine half-life of about 3–6 days, which provides sustained antimalarial activity after rapid parasite clearance59. However, lumefantrine absorption is highly dependent on dietary fat, making dosing frequency and administration conditions critical determinants of therapeutic success60. Key safety concerns are generally mild and include gastrointestinal disturbances and headache, while QT prolongation is uncommon at recommended doses61. In special populations, particularly young children and pregnant women, inadequate lumefantrine exposure due to underdosing or poor fat intake can compromise efficacy, necessitating strict adherence to weight-band dosing and counseling on food co-administration60,62.

Artesunate–amodiaquine differs substantially in dosing structure and safety considerations. Artesunate is administered at 4 mg/kg/day, while amodiaquine is given at 10 mg/kg/day, both for three consecutive days63. Amodiaquine has a comparatively long terminal half-life (≈9–18 days, via its active metabolite desethylamodiaquine), ensuring prolonged parasite suppression beyond the short half-life of artesunate64. This extended exposure contributes to high cure rates but also raises safety considerations, particularly hepatotoxicity and rare but serious neutropenia65. These risks become more relevant in high-transmission areas where repeated treatment courses may occur within short intervals65. Pediatric patients benefit from fixed-dose, weight-band formulations that improve dosing accuracy, while in patients with hepatic impairment, caution is required due to amodiaquine's hepatic metabolism63,65. Thus, while artesunate–amodiaquine remains highly effective, its dosing must be carefully managed to balance efficacy with cumulative toxicity risks.

Dihydroartemisinin–piperaquine (DHA–PPQ) represents a distinct dosing paradigm characterized by once-daily administration, typically delivering dihydroartemisinin at approximately 2–4 mg/kg/day and piperaquine at 16–20 mg/kg/day for three days66. The exceptionally long elimination half-life of piperaquine, ranging from 3 to 5 weeks, provides extended post-treatment prophylaxis, reducing reinfection rates in high-transmission settings67. However, this prolonged exposure also creates a wider resistance selection window if subtherapeutic concentrations occur, making precise weight-based dosing essential68. The most notable safety concern is dose-dependent QT interval prolongation, which, although rarely associated with clinical arrhythmias, necessitates caution in patients with pre-existing cardiac disease or those receiving other QT-prolonging medications69. In malnourished children and pregnant women, altered pharmacokinetics may further influence piperaquine exposure, underscoring the importance of dosing accuracy and clinical monitoring67,69.

Across all ACT regimens, special population considerations play a decisive role in dosing optimization and regimen choice57,62. In pediatric patients, developmental changes in hepatic enzyme activity and drug clearance can lead to lower drug exposure at standard mg/kg doses, increasing the risk of treatment failure if weight-band recommendations are not rigorously followed62,70. Pregnancy introduces additional complexity, as increased plasma volume, altered protein binding, and enhanced hepatic metabolism often reduce exposure to both artemisinin derivatives and partner drugs, potentially necessitating closer monitoring or alternative regimens in certain trimesters71. Patients with hepatic or renal impairment require individualized assessment, particularly for regimens involving amodiaquine or quinine-like compounds with narrow therapeutic indices65,72. Collectively, these comparative dosing considerations emphasize that while ACTs share a common therapeutic rationale, their optimal use depends on integrating dose, frequency, partner-drug half-life, safety profile, and patient-specific factors into a coherent, evidence-based treatment strategy 57,72.

Table 3. Extended Comparative Dosing Characteristics of Artemisinin-Based Combination Therapies (ACTs)

ACT Regimen	Dose (mg/kg)	Dosing Frequency & Duration	Partner Drug Half-Life	PK Advantages	Key Safety Concerns	Special Population Considerations	Key References

Artemether–Lumefantrine (AL)	Artemether: 1.7–2.0 mg/kg/dose Lumefantrine: 10–12 mg/kg/dose	Twice daily for 3 days (6 doses)	Lumefantrine: ~3–6 days	Rapid parasite clearance with moderate post-treatment protection	GI upset, headache; rare QT prolongation	Requires fatty food for absorption; underexposure common in children, pregnancy, and malnutrition; strict weight-band dosing required	73–75
Artesunate–Amodiaquine (AS–AQ)	Artesunate: 4 mg/kg/day Amodiaquine: 10 mg/kg/day	Once daily for 3 days	Desethylamodiaquine: ~9–18 days	Strong sustained suppression of residual parasites	Hepatotoxicity, neutropenia (rare); cumulative toxicity	Avoid repeated courses in short intervals; caution in hepatic disease; pediatric fixed-dose formulations improve adherence	76–78
Dihydroartemisinin–Piperaquine (DHA–PPQ)	DHA: 2–4 mg/kg/day Piperaquine: 16–20 mg/kg/day	Once daily for 3 days	Piperaquine: ~3–5 weeks	Excellent post-treatment prophylaxis; high adherence	Dose-dependent QT prolongation	Avoid underdosing; caution in cardiac disease, pregnancy, and malnutrition; ECG monitoring in high-risk patients	79–81
Artesunate–Mefloquine (AS–MQ)	Artesunate: 4 mg/kg/day Mefloquine: total	Once daily for 3 days	Mefloquine: ~14–21 days	Effective in multidrug-resistant malaria	Neuropsychiatric effects, dizziness, vomiting	Contraindicated in epilepsy and psychiatric disorders; avoid in first-	74,80

	8–15 mg/kg					trimester pregnancy	
Artesunate–Sulfadoxine–Pyrimethamine (AS–SP)	Artesunate: 4 mg/kg/day SP: single dose (25/1.25 mg/kg)	Artesunate ×3 days + single-dose SP	Sulfadoxine: ~7–9 days	Simplified dosing; good adherence	Severe cutaneous reactions (rare), hematological toxicity	Ineffective in SP-resistant regions; contraindicated in sulfa allergy	73,77
Pyronaridine–Artesunate (PA)	Artesunate: ~4 mg/kg/day Pyronaridine: ~7–13 mg/kg/day	Once daily for 3 days	Pyronaridine: 13–17 days	High efficacy against *P. falciparum* and *P. vivax*	Transient liver enzyme elevation	Avoid in active hepatic disease; limited data in pregnancy	78,81
Triple ACTs (TACTs)	Standard ACT + additional partner	Once daily for 3 days	Dual long half-life partners	Resistance containment strategy	Additive QT or hepatic risks	Reserved for resistance settings; requires intensive pharmacovigilance	80,81

PK–PD Modeling and Monte Carlo Simulations

Pharmacokinetic–pharmacodynamic (PK–PD) modeling has become a critical tool for optimizing antimalarial dosing strategies, particularly in the context of increasing inter-individual variability and emerging drug resistance82. Population PK modeling enables the characterization of drug concentration–time profiles across diverse patient populations by integrating sparse clinical sampling data with demographic and physiological covariates such as body weight, age, pregnancy status, nutritional state, and disease severity83. For artemisinin-based combination therapies (ACTs), population PK models have been instrumental in identifying factors that contribute to subtherapeutic exposure, including rapid clearance in young children and reduced bioavailability in pregnant women84. By quantifying variability in drug disposition, these models inform evidence-based dose adjustments and weight-band dosing schemes that ensure adequate exposure across vulnerable subpopulations without increasing toxicity risk85.

Exposure–response relationships form the pharmacodynamic backbone of PK–PD modeling and are essential for linking systemic drug exposure to antimalarial efficacy86. Key PK–PD indices, such as the area under the concentration–time curve (AUC), maximum concentration (C_max), and duration of time above the minimum inhibitory concentration (T > MIC), have been correlated with parasite clearance rates and recrudescence risk87. For artemisinin derivatives, rapid attainment of high peak concentrations is associated with swift parasite reduction, whereas for long-acting partner drugs such as lumefantrine and piperaquine, total drug exposure (AUC) and trough concentrations are more predictive of sustained parasiticidal activity88. Defining these exposure–response relationships allows researchers to establish pharmacodynamic targets that

dosing regimens must achieve to ensure clinical cure86,88.

Monte Carlo simulations extend population PK–PD modeling by enabling virtual evaluation of dosing regimens across thousands of simulated patients, capturing the full spectrum of variability observed in real-world settings89.These simulations integrate population PK parameters, variability distributions, and pharmacodynamic targets to predict drug exposure under different dosing scenarios. In antimalarial research, Monte Carlo approaches have been widely used to compare standard dosing regimens with alternative strategies, assess the impact of missed doses, and evaluate the adequacy of dosing in special populations such as children and pregnant women85,89. By simulating large virtual cohorts, these methods provide a robust framework for evaluating regimen performance before implementation in clinical practice.

A key output of Monte Carlo simulations is the probability of target attainment (PTA), which quantifies the proportion of patients in a population expected to achieve predefined pharmacodynamic targets at a given dose82,86. High PTA values are indicative of dosing regimens that reliably maintain drug concentrations above parasiticidal thresholds for sufficient durations, thereby minimizing the risk of datatreatment failure and resistance selection [87]. In the context of ACTs, PTA analysis has revealed that standard dosing may be insufficient in certain high-risk groups, prompting consideration of dose optimization strategies84,88.Consequently, PTA-guided dosing represents a powerful, evidence-based approach for refining antimalarial treatment guidelines, supporting rational dose selection that balances efficacy, safety, and resistance containment82,89.

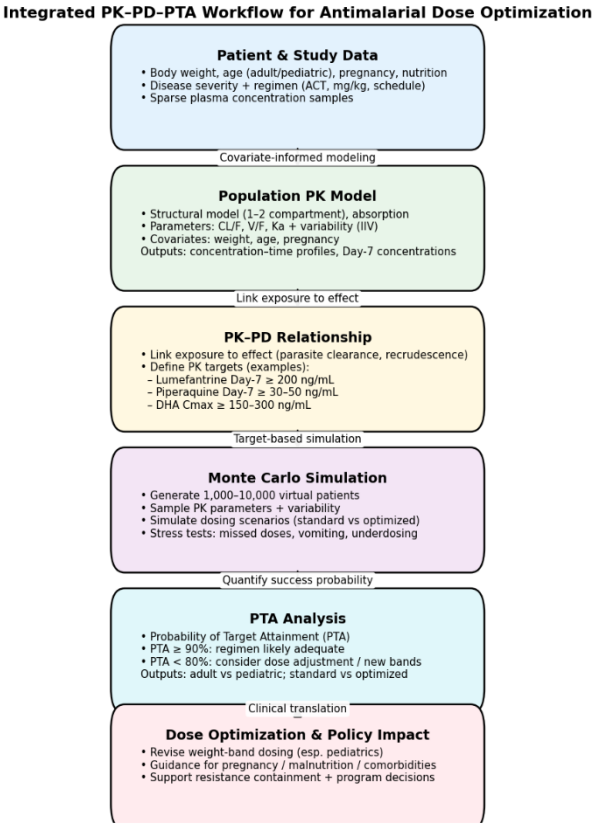

Figure 1. Integrated PK–PD–PTA workflow for antimalarial dose optimization

The schematic illustrates a stepwise framework in which patient and study covariates (e.g., weight, age, pregnancy, nutrition, disease severity) and sparse concentration data are incorporated into a population pharmacokinetic (PK) model to generate exposure profiles (including Day-7 concentrations). These exposure metrics are then linked to pharmacodynamic (PD) outcomes (parasite clearance and recrudescence) to define clinically relevant PK targets (e.g., lumefantrine Day-7 ≥ 200 ng/mL; piperaquine Day-7 ≥ 30–50 ng/mL; DHA C_max ≥ 150–300 ng/mL). Monte Carlo simulations (1,000–10,000 virtual patients) evaluate standard and optimized dosing scenarios under variability and adherence stressors (missed doses/vomiting), followed by probability of target attainment (PTA) analysis to quantify the proportion meeting PD targets. The outputs guide evidence-based dose refinement (weight-band adjustments, pediatric and pregnancy considerations) and support policy decisions for resistance containment.

Resistance-Driven Dose Adaptation

Artemisinin partial resistance represents a major challenge to contemporary malaria control efforts and has fundamentally altered dose optimization strategies

for artemisinin-based combination therapies (ACTs)105.Clinically, partial resistance is characterized by delayed parasite clearance despite adequate drug exposure, often reflected by prolonged parasite clearance half-life rather than outright treatment failure106. This phenotype is associated with reduced susceptibility of early ring-stage parasites to artemisinin derivatives, leading to slower initial parasite biomass reduction107. Under these conditions, standard dosing regimens may still achieve parasitological cure but create a narrower margin of therapeutic success, increasing reliance on the partner drug for complete parasite elimination108. Consequently, resistance-driven dose adaptation emphasizes maintaining robust artemisinin exposure during the early treatment phase while ensuring sustained partner-drug concentrations that compensate for reduced artemisinin killing efficiency109.

Partner drug resistance thresholds have emerged as critical determinants of ACT effectiveness in areas with established artemisinin partial resistance110. For long-acting partner drugs such as lumefantrine and piperaquine, subtherapeutic post-treatment concentrations create a selective window in which resistant parasites can survive and proliferate111. Pharmacokinetic–pharmacodynamic analyses have identified minimum exposure thresholds—such as lumefantrine day-7 concentrations and piperaquine trough levels—that must be exceeded to prevent recrudescence and resistance amplification112. When circulating parasite populations exhibit reduced susceptibility, these thresholds may shift upward, necessitating higher or more sustained drug exposure to achieve the same therapeutic effect110,112. Failure to meet these resistance-adjusted thresholds has been strongly associated with declining cure rates and geographic spread of partner-drug resistance113.

Adaptive dosing strategies under resistance pressure aim to restore therapeutic efficacy while minimizing toxicity and further resistance selection114. Approaches include optimizing weight-based dosing to prevent underexposure in high-risk populations, extending treatment duration, or increasing partner-drug exposure without altering artemisinin dosing109,114. In some settings, the deployment of triple artemisinin-based combination therapies (TACTs), which incorporate an additional long-acting partner drug, has been explored to distribute selective pressure across multiple pharmacological targets113,115. These adaptive strategies are increasingly guided by population PK–PD modeling and probability of target attainment analyses, which allow simulation of alternative dosing regimens under resistance-specific scenarios before clinical implementation112,114.

From a public health perspective, resistance-driven dose adaptation must balance individual-level therapeutic benefit with population-level resistance containment105,116. Escalating doses indiscriminately risks increased toxicity and reduced adherence, whereas inadequate adaptation accelerates the spread of resistant parasite strains116. Therefore, adaptive dosing strategies should be informed by real-time therapeutic efficacy surveillance, molecular resistance markers, and regional PK–PD data110,113. Integrating these data into dynamic dosing guidelines enables context-specific adjustments that preserve ACT effectiveness, prolong the clinical lifespan of existing antimalarials, and support sustainable malaria control in regions facing evolving resistance pressure114,116.

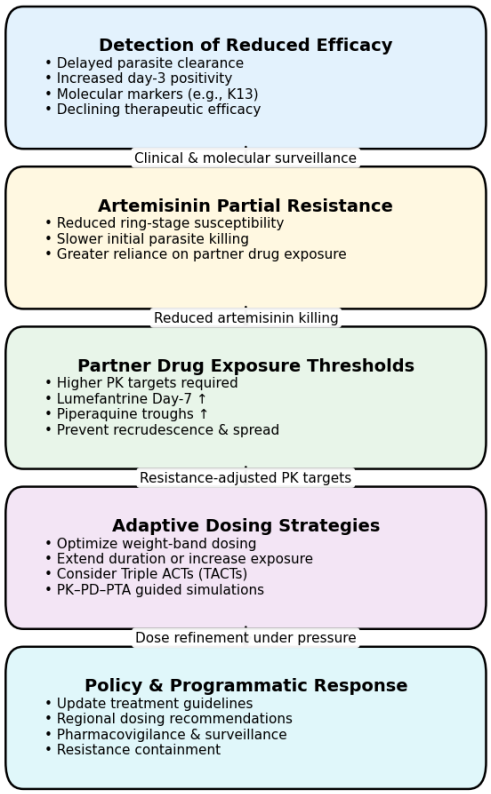

Figure 2. Resistance-driven dose adaptation framework for antimalarial therapies

The flow diagram illustrates the sequential process from detection of reduced therapeutic efficacy through identification of artemisinin partial resistance and resistance-adjusted partner-drug exposure thresholds, leading to adaptive dosing strategies guided by PK–PD–

PTA analyses. The framework culminates in policy and programmatic responses, including guideline updates, regional dosing recommendations, pharmacovigilance, and resistance containment to preserve long-term antimalarial efficacy.

Special Clinical Scenarios

Management of severe malaria differs fundamentally from uncomplicated malaria in terms of dosing strategy, route of administration, and therapeutic urgency90. Severe malaria is characterized by high parasitemia, organ dysfunction, and a markedly increased risk of mortality, necessitating rapid parasite clearance through parenteral therapy91. Intravenous artesunate is the treatment of choice, as it achieves high systemic exposure rapidly and significantly reduces mortality compared with quinine92. In contrast, uncomplicated malaria can be effectively managed with oral artemisinin-based combination therapies (ACTs), where the emphasis is on sustained drug exposure rather than immediate peak concentrations93. Transition from parenteral artesunate to a full oral ACT course is essential once the patient can tolerate oral therapy, as incomplete follow-on treatment increases the risk of recrudescence and resistance selection94.

Malaria in malnourished children presents a particularly complex dosing challenge due to profound alterations in pharmacokinetics and pharmacodynamics95. Protein–energy malnutrition can reduce drug absorption, alter plasma protein binding, and modify hepatic enzyme activity, leading to unpredictable drug exposure96. Studies have demonstrated lower lumefantrine and piperaquine concentrations in malnourished children compared with well-nourished counterparts receiving the same weight-based doses, increasing the risk of treatment failure97. Additionally, malnutrition is often associated with concurrent micronutrient deficiencies and gastrointestinal disturbances, which further compromise oral drug absorption96. These factors underscore the importance of strict weight-band dosing, food-assisted administration, and close clinical monitoring in malnourished pediatric populations95,97.

Co-infection with human immunodeficiency virus (HIV) significantly complicates antimalarial therapy due to overlapping pharmacokinetic pathways and clinically relevant drug–drug interactions98. Many antiretroviral agents modulate cytochrome P450 enzymes and drug transporters involved in antimalarial drug metabolism. Enzyme-inducing agents can reduce exposure to artemisinin derivatives and partner drugs, whereas enzyme inhibitors may increase drug concentrations and toxicity risk98,99. Additionally, HIV-infected individuals often present with higher parasite densities and slower parasite clearance, further increasing dependence on optimal partner-drug exposure100. These interactions necessitate careful selection of ACT regimens, vigilance for reduced efficacy or toxicity, and, in some cases, consideration of alternative dosing strategies99,100.

Tuberculosis (TB)–malaria co-infection poses additional therapeutic challenges, primarily due to the potent enzyme-inducing effects of rifampicin, a cornerstone of TB treatment101. Rifampicin markedly accelerates the metabolism of artemisinin derivatives and partner drugs such as lumefantrine and piperaquine, leading to substantially reduced plasma concentrations and compromised antimalarial efficacy102. Clinical studies have reported higher rates of treatment failure when standard ACT doses are administered concomitantly with rifampicin-based TB therapy103. In such settings, alternative antimalarial regimens, extended dosing strategies, or non-rifampicin-based TB regimens may be required, guided by PK–PD modeling and therapeutic efficacy monitoring104. Addressing these complex co-infection scenarios is essential to ensure effective malaria treatment while maintaining the integrity of TB control programs 101,104.

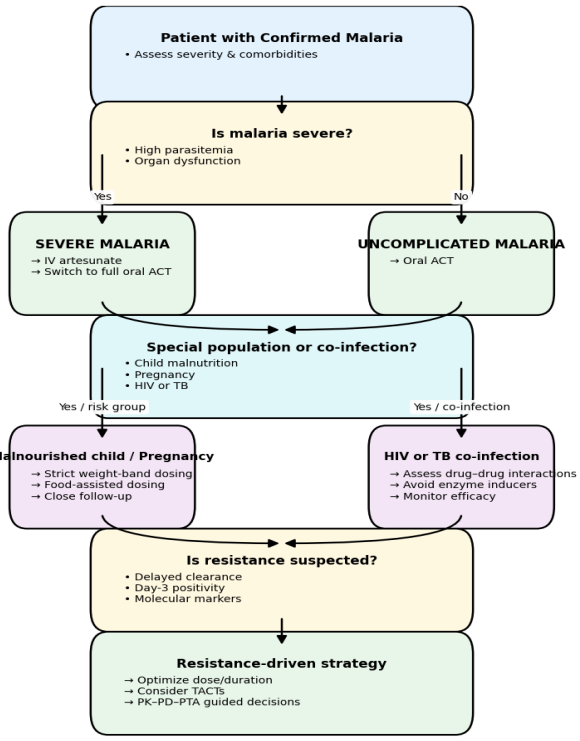

Figure 3. Clinical decision tree for antimalarial treatment in special scenarios

The schematic guides therapeutic decision-making based on disease severity, patient-specific factors

(malnutrition, pregnancy), co-infections (HIV/TB), and resistance indicators. Severe malaria is managed with parenteral artesunate followed by oral ACT, while uncomplicated malaria is treated with oral ACTs. Special populations require dosing optimization and interaction assessment, and suspected resistance triggers PK–PD–PTA-guided adaptive strategies, including dose modification or consideration of triple ACTs.

Conclusion

This review highlights that effective antimalarial therapy, particularly with artemisinin-based combination therapies (ACTs), depends on optimized, context-specific dosing rather than fixed regimens alone. Integration of pharmacokinetic–pharmacodynamic (PK–PD) modeling, probability of target attainment (PTA), and resistance surveillance provides a robust framework to ensure adequate drug exposure, rapid parasite clearance, and prevention of recrudescence. Adaptive dosing strategies are especially critical in the face of emerging artemisinin and partner-drug resistance.

Special clinical scenarios such as severe malaria, malnutrition, pregnancy, and HIV/TB co-infection further emphasize the need for individualized treatment approaches that account for altered drug disposition and drug–drug interactions. Overall, model-informed, resistance-aware dosing strategies combined with vigilant clinical and programmatic monitoring are essential to preserve antimalarial efficacy and support sustainable malaria control and elimination efforts.

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Dr. Karuna Shanker Shukla: Supervision, critical review

Dr. Shweta Sinha: Conceptualization, literature review, manuscript writing

Shadab Mobeen: Helped in literature review and manuscript editing.

Surya Prakash: Assisted in experimental work and data collection

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Ethical Approval

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