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REVIEW

Antimalarial treatment in infants

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ABSTRACT

Introduction: Malaria in infants is common in high-transmission settings, especially in infants >6 months. Infants undergo physiological changes impacting pharmacokinetics and pharmacodynamics of anti-malarial drugs and, consequently, the safety and efficacy of malaria treatment. Yet, treatment guidelines and evidence on pharmacological interventions for malaria often fail to address this vulnerable age group. This review aims to summarize the available data on anti-malarial treatment in infants.

Areas covered: The standard recommended treatments for severe and uncomplicated malaria are generally safe and effective in infants. However, infants have an increased risk of drug-related vomiting and have distinct pharmacokinetic parameters of antimalarials compared with older patients. These include larger volumes of distribution, higher clearance rates, and immature enzyme systems. Consequently, infants with malaria may be at increased risk of treatment failure and drug toxicity.

Expert opinion: Knowledge expansion to optimize treatment can be achieved by including more infants in antimalarial drug trials and by reporting separately on treatment outcomes in infants. Additional evidence on the efficacy, safety, tolerability, acceptability, and effectiveness of ACTs in infants is needed, as well as population pharmacokinetics studies on antimalarials in the infant population.

KEYWORDS
Malaria; treatment; infants; pharmacodynamics; pharmacokinetics

1. Introduction

WHO reported 602.000 malaria deaths in 2020 in the sub-Saharan African region, with under five years olds accounting for 80% of these deaths. Children are therefore a key population targeted to reduce the impact of malaria [1]. The age group 'children under five' includes a heterogeneous group of neonates, infants, toddlers, and pre-school children. These subgroups have distinct susceptibilities to infection and exhibit a spectrum of clinical presentations and treatment responses. Yet, epidemiological reports and treatment guidelines frequently fail to make evidence-based recommendations taking these diverse characteristics into account. This is especially true for infants (children under one year), on whom we focus in this review.

1.1. Epidemiology and pathophysiology of malaria in infants

Infants can become infected with malaria *in utero* by trans-placentally transmitted parasites or through an infective mosquito bite after birth. They exhibit relative resilience against malaria through several mechanisms. Maternal immunoglobulins are acquired by the fetus via trans-placental transfer; fetal hemoglobin inhibits cytoadherence of infected red blood cells, and lactoferrin and secretory IgA from breast milk inhibit parasite growth [2–4]. These innate and acquired protective mechanisms limit parasitemia during infections and result in no, or only mild, symptoms [2,4,5].

Despite relative resilience of infants against malaria infections, clinical manifestations can happen at any age. They increase after the age of six months, when protective factors wane and infants have only limited acquired immunity against malaria [3–6]. Health benefits of malaria control measures such as intermittent preventive treatment and the protective effect of sickle cell trait become apparent around this same age [3,7]. A recent birth cohort study (N = 1264) in a high-transmission setting in Ghana showed microscopy positivity for malaria occurring in infants of all ages and increasing from birth to 12 months. *P. falciparum* infection was most frequently microscopically detected for the first time in children with a median age of seven to eight months. Infections were rare and predominantly asymptomatic up to five months of age, while infants from six to 12 months of age had both asymptomatic and symptomatic infections [4]. Other studies have shown similar results [3–6,8–11]. Peak prevalence of infection shifts to a younger age group when transmission intensity increases, with seasonality of transmission attenuating this effect [2,5,12]. A cross-sectional survey in West Africa (N = 6761) found an average of 11.8% of children under six months old

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Article highlights

- Evidence on treatment of malaria in infants is limited.
- Recommended treatment for severe and uncomplicated malaria, including artesunate and artemisinin-based combination therapy (ACTs), respectively, are generally safe and effective in infants.
- Infant physiology is distinct from that of older age groups, influencing pharmacokinetics and pharmacodynamics of antimalarial drugs. This increases risk of under- and overdosing of antimalarials.
- There is a need for additional trials that report on drug efficacy and safety and provide population pharmacokinetic studies in infants.

across different transmission settings with parasitemia as determined by microscopy, while infection rates in high transmission areas were 21.7%. Besides fever, children with malaria infection were at significant risk of having anemia [5].

The term neonatal malaria is used when a child endures a malaria episode (not asymptomatic parasitemia) during the first 28 days of life [13]. A recent meta-analysis by Danwang *et al*. reported that the overall prevalence of clinical neonatal malaria occurring between day seven and day 28 of life in the 28.083 neonates included was 12.0% (95% CI 1.4–30.3; 12 studies), with substantial heterogeneity [13]. Congenital malaria is the result of malaria parasite transmission through the placenta before delivery. It is generally defined as the presence of asexual parasites in cord blood or in the infants' peripheral blood smear in the first week of life [14]. Reported prevalence of light-microscopy proven clinical congenital malaria is highly variable, depending on malaria endemicity and seasonality, study population characteristics and study protocol-related factors [15,16]. Prevalence ranged from 46.7% in a high-transmission setting in Nigeria to zero in a low transmission setting in Colombia [15]. While data on neonatal and congenital malaria is limited, our understanding of this phenomenon and its risk factors is progressing. Alonso et al. recently evaluated the impact of maternal HIV infection on cord blood levels of placental transfer of antimalarial antibodies. They found lower maternally transferred antibodies in HIV-exposed infants. As a consequence, these infants likely have increased susceptibility to malaria [17]. Other factors associated with higher risk of congenital malaria include prematurity and being small-for-gestational-age.

To conclude, infants have relative protection against malaria in the first months of life, but infection can occur at any age and can progress to febrile illness and anemia. Infants older than six months are at increased risk, as they have waning maternal antibodies and fetal hemoglobin, while not yet having developed partial immunity themselves. Adequate anti-malarial treatment for infants is therefore vital.

1.2. Anti-malarial medication in infants

Infants undergo physiological and anatomical changes during their first year of life, impacting the pharmacokinetic (PK) and pharmacodynamic (PD) properties of medication [18–22]. Distinct gut transit times, intestinal absorption surface areas and activity of drug-metabolizing gut enzymes in infants affect drug dissolution and absorption [20–22]. Distribution volumes depend on body composition, with infants having relatively higher fat levels, lower protein-binding capacity and more extracellular water as compared to older children and adults. This can result in higher free fractions of protein-bound drugs and larger distribution volume of hydrophilic and lipophilic drugs [20–22]. Drugs principally eliminated by the kidney can exhibit a prolonged elimination half-life because of immature renal clearance processes. Levels of enzyme expression influencing drug metabolism and clearance vary due to maturation of enzyme systems, and hepatic clearance and first-pass effect can be increased in infants because of increased liver blood flow and other unknown mechanisms [20–22]. Finally, accurate dosing can be challenging in infants as they are more likely to vomit or regurgitate after having received treatment [7]. Thus, simple dosing formulas based on body weight and allometric scaling (e.g. relative body size) applicable in older children with body composition similar to that of adults may not be applicable in neonates and infants. For this group, dosing and dosing interval should be established by empirical PK data describing age-related bioavailability, volume of distribution and clearance of the specific drug [20–22]. Yet, current weight-based dosing of malaria treatments is often based on studies in older children. This results in the advice to monitor infants closely, as they are at increased risk of treatment failure [7]. Also, WHO advises to dose infants with uncomplicated malaria weighing <5 kg with the same dosage of artemisinin-based combination therapy (ACT) as children weighing 5 kg, simply because evidence on dosing in lighter children is lacking [7]. Additionally, antimalarial treatment is mostly calibrated in semi-immune, older populations. Infants who are out of the maternally transferred immunity window have little-to-no immunity and may therefore, in some cases, need higher doses or extended dosing regimens [23–26].

Improving our understanding of infant physiology and its effects on malaria drug concentrations to inform infant dosing schedules and pediatric formulations is important to ensure adequate treatment of infants with malaria. This article summarizes available evidence on safety, efficacy, and tolerability of antimalarial treatments in infants and highlights knowledge gaps that should be addressed. Malaria chemoprophylaxis strategies for infants living in endemic areas and for traveling infants originating from non-malarious are not included in this review. Also, the influence of malnutrition on PK and PD of anti-malarials are reviewed elsewhere [27].

2. Treating infants with severe malaria

This section will focus on treatment of severe *P. falciparum* malaria in infants >28 days old. Neonatal malaria and treatment of non-falciparum malaria are discussed below.

2.1. Artesunate

Artesunate (IV or IM) is recommended by WHO as the drug of choice for severe malaria [7]. It was found to prevent more deaths in adults and children with severe malaria and had a superior safety profile when compared to parenteral quinine. The AQUAMAT trial conducted among 5425 children with

severe malaria <15 years contributed to the evidence on superiority of IV artesunate over IV quinine. It included mainly children around three years of age and the article does not mention age ranges, or number of infants included [28]. Almost all other studies comparing artesunate and quinine, including the SEAQUAMAT trial, excluded infants [29]. One smaller study (n = 109) on IV quinine vs. IM artesunate that mentions age range and included a minority of infants (median age around six years and age range starting at ~four months) concluded that artesunate was at least as effective as quinine and resulted in faster parasite clearance [30]. No direct comparison of artesunate vs. quinine has been conducted in infants specifically. However, given the findings in other age groups and favorable PK and PD properties of reliable absorption, high bioavailability, and rapid parasitological response, it can be assumed that artesunate is the most effective treatment in infants as well [23,26,31].

Population PK studies on IV and IM artesunate including infants (average age around three years and both including infants older than six months) inferred, that children with lower body weights had a larger apparent volume of distribution, as well as higher body weight-normalized elimination clearance values resulting in lower plasma concentrations of artesunate and its active metabolite dihydroartemisinin [32,33]. This caused the WHO to increase the recommended dose of artesunate in children <20 kg to 3 mg/kg/dose [7]. However, outcomes of population PK studies depend on methodology. As the US Food and Drug Administration (FDA) used a different enzyme maturation effect and submodel, they continue to recommend the original 2.4 mg/kg/dose in small children [34]. These different recommendations reflect our limited knowledge on influence of infant hepatic enzyme maturation on malaria drug concentration. The FDA's strategy is supported by the fact that 90% of children in the AQUAMAT study were <20 kg body weight and were successfully treated with the standard 2.4 mg/kg dose, as were infants and young children in Kremsner et al [28,35]. Moreover, no studies found a clear relationship between parasite clearance and PK parameters, showing that PK/PD of artesunate remain incompletely understood [34,36]. Simplified artesunate IV and IM dosing regimens (three injections of 4 mg/kg at 0, 24, and 48 h) have been tested in children and infants and found to be non-inferior, with similar reduction in parasitemia compared to control regimen [35,36]. Moreover, IM administration was highly effective and led to consistent artesunate plasma concentrations [35]. There are no obvious reasons to reject implementation of simplified intramuscular regimens for management of severe malaria in African children as the higher single daily dose suggested obviates the need for modeling and inferential studies [35,36]. WHO's choice to recommend higher doses for infants and small children also takes into account that artesunate treatment is generally safe and well tolerated and aims to minimize risks of suboptimal drug exposure in patients with severe malaria [31,33]. Post-treatment hemolysis occurred in 7–9% of African children treated with artesunate, with 1% requiring blood transfusion on day 14 [37,38]. One study reported young age to be a risk factor for post-treatment hemolysis, showing the importance of follow-up hemoglobin measurements in infants after artesunate treatment [38].

Following initial PK studies that defined the safety and pharmacokinetics of rectal artesunate [39], pre-referral treatment with rectal artesunate has been evaluated in 8050 African infants and children (seven to 72 months of age). Lower mortality was observed in the group receiving rectal artesunate compared to placebo (RR 0.74 95% CI 0.59–0.93), while a higher mortality was observed in older children and adults receiving rectal artesunate (RR 2.21 95% CI 1.18 to 4.15). This while follow-up care-seeking behavior and parasitemia levels at hospital presentation were similar in all treatment and age groups. The difference is speculated to be either due to chance, smaller sample size in adult studies, population differences or to a different dose-response of unknown nature in young children and infants [40–42]. In essence, the fact that different results were seen in older children and adults confirms equipoise and the value of a placebo control. Based on these results, rectal artesunate as pre-referral treatment is recommended in children under six years old, when IM artesunate is not directly available [7].

2.2. Artemether

IM artemether is the second choice of treatment for severe malaria when artesunate is unavailable [7]. It was found to be less effective than artesunate in adults and additional trials comparing these drugs in children were therefore deemed unethical [43]. Treatment with IM artemether resulted in similar mortality rates compared to quinine (RR 0.97, 95% CI 0.77 to 1.21) in 1659 children (six months – 15 years) compared in a meta-analysis. However, coma resolution time, fever clearance time and parasite clearance time were shorter in the artemether group. Serious adverse events between treatment groups were similar [43]. The small studies adding to the review that included a limited number of infants reported comparable efficacy and safety of IM artemether and quinine [43–46].

Artemether is oil-based and absorbed more slowly and erratically then IM and IV artesunate. In studies on the disposition of intramuscular artemether in children with severe malaria, including infants and children over five months, highly variable bioavailability was observed for this reason [7,47,48]. Some children had an inadequate therapeutic response and severely ill children with respiratory distress had the lowest bioavailability of artemether, likely due to decreased peripheral perfusion resulting in decreased absorption rates [47]. Specific age- or bodyweight-related PK differences were not observed [48].

Rectal artemether has been proposed as an alternative to IM artemether. Aceng and colleagues compared rectal artemether to IV quinine for the treatment of cerebral malaria in children in a randomized single-blind trial (N = 103, including infants older than six months). This resulted in higher mortality in the quinine group (RR 1.29 95% CI 0.84 2.01), though treatments may be comparable as the CI includes 1. Other clinical and parasitological outcomes were similar, demonstrating rectal artemether to be safe and effective in children over six months [49].

Table 1. Treatment of severe malaria in infants.

Medication	Advantage	Disadvantage	Research need
Artesunate (IV, IM, rectal)	• Reliable absorption • Fast parasite clearance	• Most evidence in children >6 months • Optimal dose for children <20 kg unclear • Safety of rectal artesunate to be confirmed in infants <6 months	• Additional PK studies on artesunate in infants specifically • Consensus on sub-model for enzyme maturation in population PK studies
Artemether (IM, rectal)	• Fast parasite clearance	• Erratic absorption, especially in severely ill infants • Most evidence children >6 months • Safety of rectal artesunate to be confirmed in infants <6 months	• As artesunate is the preferred treatment no current research priorities
Quinine (IV, IM, rectal)	• No increased number of side-effects observed in infants	• Lower quinine plasma levels in infants (but within therapeutic range)	• As artesunate is the preferred treatment no current research priorities

2.3. Quinine

Quinine can be used as treatment for severe malaria when artesunate and artemether are unavailable [7]. Before synthetic artemisinins were invented and proven to be more effective, quinine was the treatment of choice. Detailed information on pharmacokinetics of quinine in children and infants is therefore available, and has been reviewed comprehensively [50].

The standard dosing regimen for severe malaria (20 mg/kg salt IV loading dose over four hours followed by 10 mg/kg IV every eight hours for seven days) has been applied in trials that included a small number of infants, resulting in good clinical outcomes [31,43,51,52].

Outcomes of treatment with IM quinine, IV quinine, and rectal quinine in patients older than six months were similar in terms of efficacy and safety [51–54]. PK studies in young children and infants (four months to eight years in Hendriksen et al.) as well as the recent review of Saeheng and colleagues found body weight to be an important co-variate influencing pharmacokinetics, with lower body weight resulting in lower quinine C_{max} and half-life values because of differences in clearance and volume parameters [55,56]. However, these values were still within therapeutic margins when body-weight dosing was applied. Furthermore, the observed fluctuations in plasma quinine levels were unrelated to mortality, so dose adjustments for infants do not seem necessary [55–57]. Similarly, Krishna et al. found in their population PK study on IM quinine in children (1–10 years old) predictable quinine PK profiles [58]. A malaria episode itself is associated with a reduction in systemic clearance and volume of distribution, resulting in higher plasma quinine levels in patients with malaria compared to healthy subjects that fall when a patient recovers from malaria [50,59]. There are no reports on this effect being more pronounced in infants [55–57].

Plasma levels of quinine do vary from person to person [55,57]. This, in combination with infants having variable weights-for-age and maturation processes influencing PK, may render them prone to quinine adverse effects such as cardiotoxicity and hypoglycemia when high peak plasma levels occur. However, no severe adverse events were reported for rectal, IM and IV quinine in infants and children, although most studies focussed on efficacy and PK parameters rather than safety [51–54]. When adverse effects did occur, they were unrelated to plasma quinine levels [55,56]. In terms of tolerability, IM injections have the disadvantage of being painful when insufficiently diluted. IV and rectal routes of administration are well tolerated [54,55].

To summarize, existing studies including infants point to artesunate, artemether, and quinine all being viable treatments for infants with severe malaria, with artesunate having the benefit of being rapidly and reliably absorbed, achieving short parasite clearance times and having a favorable safety profile. Treating with IV or IM artesunate, when these are not available with IM artemether, and, as a third choice, with IM or IV quinine as recommended by WHO for children seems the best strategy for infant as well [7]. Findings on the treatment of severe malaria in infants are summarized in Table 1.

3. Treating infants with uncomplicated malaria

3.1. Artemisinin-based combination therapies

Six ACTs are recommended for treatment of uncomplicated *P. falciparum* malaria: artemether + lumefantrine (A-L), artesunate + amodiaquine (A-AQ), artesunate + mefloquine (A-MQ), dihydroartemisinin + piperaquine (DHA-P), artesunate + sulfadoxine-pyrimethamine (A-SP) and artesunate + pyronaridine (A-PYR) [7]. This section summarizes which factors to consider when prescribing these anti-malarials to infants. However, we cannot make recommendations on superior or inferior ACT treatments applicable to all settings. This because national ACT protocols depends on local resistance patterns to the artemisinin partner drug. For example, piperaquine resistance has been reported in the Greater Mekong sub-region and increasing treatment failure due to sulfadoxine-pyrimethamine resistance is becoming apparent in Sudan, Somalia and North-East India [60].

3.1.1. Efficacy

ACT therapeutic efficacy studies conducted in high transmission settings usually include children six to 59 months, as per WHO protocol on surveying antimalarial drug efficacy, resistance and response [60,61]. Most studies thus include a small number of infants, but do not analyze or report on infants separately. ACT drug efficacy rates in children under five years including infants >6 months are reassuringly high. For example, the overall average efficacy rates of A-L, AS-AQ, and DHA-

PPQ in malaria-endemic African countries were 98.0%, 98.4%, and 99.4%, respectively [60]. Yet, it is possible that associations between younger age, PK parameters, and clinical and parasitological response are not detected when infants are not studied separately, and treatment failure rates are low.

The artemisinin component of the ACT reaches peak plasma levels fast, and has a short half-life (for the active metabolite dihydro-artemisinin or DHA ~ 45 min). This short elimination half-life only allows maximum efficacy of an artemisinin component over the three days of a treatment course [25,62,63]. Oral artemether and artesunate co-administered with lumefantrine or mefloquine, respectively, led to highly variable drug plasma parameters of artemisinins in infants and children [63,64]. Consistent with findings for IV artesunate, there was no correlation between artemether or DHA C_{max} and parasite clearance time or clinical parameters [63]. Early treatment failures, generally defined as a subject developing signs of severe malaria during the first three days of treatment, substantial parasitemia increase on day two or three, or persisting parasitemia and fever on day three, may be a sign of inadequate artemisinin dosing, or possibly artemisinin partial resistance [60]. However, in practice, they are often the result of a patient being classified as treatment failure for developing severe malaria after enrollment because initial inclusion criteria were disregarded, or the patient already had borderline severe anemia when included [60]. Early treatment failures in a range of clinical studies (mean N ~ 400 per study), including infants older than six months were reassuringly low (zero to 0.8%) [65–69]. Moreover, while there were concerns about under-dosing of parenteral artesunate in infants, the opposite seems true for oral artemisinins. Guidi et al. described how in African children and infants (6–59 months), relative bioavailability of oral artesunate was increased in younger children [63]. Correspondingly, in African infants weighing <5 kg (mean age 99 days SD 51.8 days in Tiono et al., artemether and (to a lesser extent) DHA exposure rates at hours one and two after drug administration were two to three-fold higher than seen in heavier children [70]. Similar findings are reported for infants and children weighing five to 10 kg [71]. The trend of increased drug concentration with decreasing weight was observed in young infants and children <5 kg included in the study of Tiono et al. as well, and is thought to be the result of immature CYP33A4 enzyme activities causing a decreased first-pass metabolism of artemether and decrease UGT enzymes activity leading to decreased DHA metabolism [63,70]. The higher artemisinin concentrations were well tolerated, but the implications of surpassing preclinical safety margins of artemisinins in infants has not been further explored [70].

ACT longer-acting partner drugs, including lumefantrine, mefloquine, amodiaquine, sulfadoxine-pyrimethamine, piperaquine, and pyronaridine are principally responsible for eliminating residual parasites at the end of the treatment course [25,61]. Failure of long-acting compounds result in late treatment failure due to recrudescence of the original parasite with the same genotype (as determined by PCR) that was incompletely cleared because of parasite resistance or suboptimal plasma drug levels [60]. For three longer-acting ACT partner drugs, lower body weight resulted in decreased drug levels in young children and infants when weight-based dosing was extrapolated from studies in older subjects. This is a result of increased clearance rates and distribution volume in infants.

First, lumefantrine plasma levels on day seven are repeatedly found to be lower in young children and infants (generally <15 kg; six months to two years) when compared to older patients [72–74]. Lumefantrine doses of <60 mg/kg were associated with an augmented risk of recrudescence in Asian infants and young African children with malnutrition [75]. Some trials reported no correlation between PK and PD parameters such as cure rates [71,72,74,76]. At the same time, Kloprogge et al. and Tchaparian et al. found that lower lumefantrine day seven concentrations increased the recrudescence risk [72,73]. Dose-limited absorption preclude the possibility of simply increasing the lumefantrine dose in infants to achieve adequate plasma lumefantrine levels. An extended treatment regimen (A-L bi-daily for five days) or an intensified regimen (A-L three times daily for three days) is one proposed solution. Testing the efficacy and safety of an extended or intensified A-L regimen in infants, who have limited immunity as well as possible suboptimal lumefantrine levels, is advisable. Similarly, measuring day seven lumefantrine concentrations in the context of clinical trials will provide valuable information on efficacy.

Secondly, the recommended piperaquine dose for infants and children <25 kg has been adjusted in the WHO malaria treatment guidelines (to 60 mg/kg total dose) because several studies including infants older than six months found the dose suggested by the manufacturer (40 mg/kg total dose) resulted in low piperaquine plasma levels and subsequent increased risk of treatment failure [77–81]. Further studies on treatment efficacy, piperaquine concentration, safety, and tolerability are needed to assess this adjusted regimen in infants [74,82].

Thirdly, SP has been systematically under-dosed in young children, likely contributing to SP resistance [83]. Current guidelines recommend the double dose of the one originally deployed for children [7]. Efficacy studies specifically on curative treatment with A-SP in infants is lacking, but current response rates to this ACT in studies in children under five years including infants seem sufficient [84–86], though increasing treatment failures likely due to resistance are also reported [61,87–90].

PK and efficacy studies on the use of other longer-acting ACT compounds in infants are limited. Pyronaridine efficacy and safety trials included infants; although this subgroup was relatively under-represented as compared to other age groups [91–93]. The recent study by Tona et al. included 130 infants. It reported a relatively lower, but still overall high cure rate in this age group (efficacy in infants 96.9, 95% CI 92.3–99.2, efficacy in older children and adults 98.6%, 95% CI 98.-98.9) [92]. Causality of this difference remains unclear.

Mefloquine pharmacokinetics is primarily impacted by body weight, justifying weight-based dosing [94]. However, studies including infants over six months revealed a negative correlation between mefloquine concentration and body weight, resulting in higher concentrations of mefloquine in infants and young children. This likely because of decreased mefloquine elimination due to incomplete organ maturation [63,95,96]. Guidi et al. also found increased absorption of

mefloquine in younger age groups and speculated this to be the result of breast milk being the more appropriate nutrition to be co-administered with mefloquine as compared to food given to older children [63]. High plasma mefloquine levels may be problematic, as increased mefloquine dosing is associated with risk of vomiting, and vomiting is linked to treatment failure [96–98].

Most studies on artesunate-amodiaquine, including those in infants and young children, show high cure rates [99–101]. PK data on amodiaquine given in combination with artesunate is contradictory. A recent study in 308 children from Ghana including nine infants found higher amodiaquine AUCs in infants and C_{max} decreasing with age due to a slower apparent clearance in infants [102]. A study from Zanzibar (N = 212) including infants three months and older reported the opposite; namely a negative correlation between age and weight-normalized clearance, resulting in amodiaquine under-dosing in infants [103]. A systematic review on amodiaquine efficacy and safety including 6179 African children found children under five years to have an increased risk of treatment failure, which may be linked to decreased background immunity, but which could also be a sign of under-dosing [104]. Anyorigiya et al. also found a link between low amodiaquine levels on days three and parasite recurrence (including treatment failure and recurrent infection) [102].

As long as there is a therapeutic level of the ACT longer-acting partner drug in the patients' circulation, recurrent malaria infections with susceptible parasites can be prevented. This post-treatment prophylactic effect reduces the malaria burden in the community by limiting the spread of malaria infection, prevents new malaria episodes, and allows for hematologic recovery [7,105]. Multiple studies including infants found that the ability of the ACT longer-acting compound to prevent re-infection correlates with drug half-life. As a result, DHA-P has the longest post-prophylactic effect resulting in the fewest re-infections on day 28 and day 42. As lumefantrine has the shortest half-life, re-infections occur more frequently in children treated with A-L when compared with DHA-AP and in some cases A-MQ and A-AQ (see Table 2) [8,65,74,106–109]. Preventing re-infection and hence possibly a new clinical malaria episode and enabling patients to regain normal hemoglobin levels could be of additional benefit for the vulnerable infant population. Yet, a study in infants (n = 351) in Uganda showed A-L was associated with a significantly higher risk of recurrent malaria on day 28 (HR 3.45; 95% CI 2.21–5.39) compared to DHA-P, while the overall incidence of malaria in the cohort that was followed-up for one year was similar (4.82 vs 4.61 treatments per person-year) [110]. In older children, no significant difference in mean hematocrit on days 42 or 63 of follow-up was reported when comparing ACTs [111]. This is speculated to be due to overwhelming risk of recurrent malaria in high transmission settings combined with DHA-P offering relatively longer but still limited post-prophylactic protection [110]. More studies in infants with long-term follow-up are needed to further determine whether malaria incidence and hematological parameters differ depending on long-acting ACT compound and their half-life. Also, the individual benefits of the post-treatment prophylactic effect must be weighed against the increased risk of resistance developing for the partner drug during the elimination phase, as newly infecting parasites are exposed to sub-therapeutic drug levels [107].

Table 2. Elimination half-lives of longer-acting artemisinin partner compounds [61,112].

Lumefantrine	21.7 to 79.2 hours
Pyrimethamine; sulfadoxine	2.8 to 3.4 days; 4.1 to 8.9 days
Amodiaquine; desethyl-amodiaquine	3.3 hours; 9 days
Chloroquine	4.5 to 9.7 days
Mefloquine	8.5 to 19.3 days
Pyronaridine	12 to 14 days
Piperaquine	12 to 28 days

3.1.2. Safety, tolerability, and acceptability

ACTs are generally safe and well tolerated by patients from all age groups, with most adverse events likely relating to malaria rather than anti-malarial treatment [108,111,113]. For example, Bassat et al. randomized 1553 children (6–59 months of age, mean age 2.4 years SD 1.14 years) to be treated with A-L or DHA-P and found gastro-intestinal tolerability, QTc prolongation, and other adverse events to be similar in both groups [108]. Other primary evidence and systematic reviews in children under five including a minority of infants reported equally comparable safety profiles for ACTs [109,111,114,115]. The only exception may be A-MQ, as it is reported to lead to more CNS-related adverse events such as sleep disturbance, dizziness, and anxiety in children and adults [105,111]. However, three studies including young African children and a small number of infants reported low incidence of neurological and neuropsychiatric adverse effects for A-MQ, justifying the use of A-MQ in infants and young children [116–118].

Drug tolerability problems, such as nausea and vomiting, negatively impact adherence and increase treatment failure. Reduced malaria drug tolerability is observed in young children and infants. They generally seem more likely to vomit during a malaria episode and are at increased risk of vomiting after receiving ACT treatment. For example, a systematic review and pooled analysis including safety data of 5024 patients found that vomiting after A-L treatment occurred in 11% of infants as opposed to 4% of older patients [75]. More frequent occurrence of vomiting in infants compared to older children was reported for DHA-P and A-PYR as well [77,92]. When comparing frequencies of gastro-intestinal adverse events, most studies find A-L is best tolerated; closely followed by, or comparable to DHA-P, A-PYR, A-AQ, and A-SP [82,91,119–122]. A-MQ was reported to lead to increased rates of vomiting compared to other ACTs, although now that it is given in split dose (15 mg/kg followed by 10 mg/kg 12 hours later) and co-administered with artesunate, tolerability has improved [82,96,111,118,123]. Vomiting has led to increased rates of treatment failure in infants and children, at least in the case of A-MQ [97]. Notably, most trials determine efficacy as their primary outcome measure and are therefore not powered to compare ACT safety and tolerability in general, or across age groups.

ACT in liquid and sometimes flavored formulations are hypothetically easier to administer to infants than bitter-tasting tablets, potentially enhancing tolerability and acceptability. Dispersible and granule formulae of A-L, A-MQ, DHA-P, and A-PYR have been tested in infants and children, usually in comparison with crushed tablets given with food or water [113,124,125]. Pediatric formulations showed consistent non-inferiority in terms of safety and efficacy compared to regular treatments [64,91,113,124–128]. Moreover, there is evidence of pediatric formulations resulting in better tolerability in infants and young children. In a recent systematic review including children <14 years, drug-related vomiting appeared to be less common in the dispersible ACT arms (RR 0.75, 95% CI 0.56 to 1.01; 1197 participants) and in the suspension ACT arm (RR 0.66, 95% CI 0.33 to 1.32; 267 participants), though both analyses were underpowered [124]. Correspondingly, a network meta-analysis concluded the number of children needed to be treated with pediatric ACT to prevent drug-related vomiting in one patient was 22 [113]. Findings in studies including infants were similar [64,91,127,129]. It is possible that the tolerability benefit of pediatric formula is more pronounced in infants as they are generally more prone to vomiting. Also, pediatric ACTs are likely to be more acceptable and therefore may result in better adherence, especially under real-life circumstances where drug administration is not supervised [130,131]. Further investigation of pediatric formulations, in infants specifically, focusing on efficacy as well as tolerability and acceptability, is recommended.

In summary, ACT treatments are generally effective and safe in infants, but PK properties of oral artemisinins and longer-acting ACT compounds in infants are incompletely understood. Infants are at risk of under-dosing and treatment failure, for example, when being treated with the current artemether-lumefantrine formulation. Conversely, artemisinin and possibly mefloquine dosing resulted in higher peak plasma levels, surpassing safety margins. Moreover, infants are at increased risk of treatment failure due to higher rates of drug-related vomiting, especially when not treated with pediatric formulations. Main findings on ACTs and other treatments for uncomplicated malaria in infants are summarized in Table 3.

3.2. Oral quinine

Oral quinine is no longer recommended for treating uncomplicated malaria in children as ACTs have a superior safety, tolerability, and efficacy profile. In practice, quinine monotherapy is used during ACT stock-outs [7]. As mentioned, quinine elimination is faster in young children, and clearance rates are higher in uncomplicated malaria compared to severe malaria. This results in lower C_{max} values in young children and infants with uncomplicated malaria, but they were within the therapeutic range [56,59]. The long duration of the standard quinine monotherapy treatment regimen of seven days presents a challenge to completion of therapy, and is considered undesirable (as any treatment for uncomplicated malaria requiring more than three days). However, shorter quinine treatment regimens led to unacceptably high treatment failure rates in infants and children [59,132,133]. Oral quinine also has a tolerability disadvantage, as it has a very bitter taste [50]. A three-day regimen of quinine plus clindamycin has been found safe and effective in adults and children, with for example a PCR corrected cure rate of 94% at 28 day follow-up in Gabonese children three to 12 years old [134–136]. Finally, access to clindamycin is often limited in low-resource settings.

3.3. Treating non- falciparum malaria: ACTs, primaquine, and chloroquine

Most malaria-related deaths are caused by *P. falciparum*, while severe malaria in *P. vivax, P. ovale,* and *P. malariae* infection is a relatively rare complication [137–139]. Yet, these *Plasmodium* species do cause febrile illness and anemia, with infants being especially at risk of anemia caused by *P. vivax* [140,141]. Other complications include nephrotic syndrome (in the case of *P. malariae*) [142]. They should therefore be treated with effective anti-malarial treatment.

3.3.1. Treating blood-stage infection

For blood-stage *P. vivax, P. ovale, P. malariae,* and *P. knowlesi*, either chloroquine or ACTs (except A-SP due to resistance) are recommended treatment options, depending on local resistance patterns to artemisinin partner drugs [7]. Generally, ACTs with a longer half-life (such as DHA-P and A-MQ) performed at least as well as chloroquine [111,143], while DHA-P may provide extra post-treatment prophylactic effect up to six weeks, irrespective of primaquine treatment for radical cure [144]. Specifically, in infants (older then three months), chloroquine and DHA-P were found efficacious as treatment for *P. vivax* malaria [145,146]. Chloroquine PK studies mainly focus on children under five years rather than infants specifically. Yet, they all report chloroquine concentration diminished with lower age, with significantly lower chloroquine concentration and higher relapse rates in young children and infants [147–150]. Higher chloroquine clearance in children compared to adults is thought to be the likely cause [148,150]. Increasing the dose from the currently recommended 25 mg/kg to 30 mg/kg reduced the risk of early recrudescence of *P. vivax* by 40% in children under five years [147]. After studying chloroquine pharmacokinetics in young children and infants, Ursing et al. concluded that even doubling the dose to 50 mg/kg is required for children under two years of age to reach peak plasma levels compared to that of older children and adults, and that these doses were well tolerated [149,151]. Thus, infants are likely under-dosed when receiving chloroquine treatment; increasing the risk of treatment failure. Increasing the dose may be necessary; however, additional studies on efficacy and safety of chloroquine specifically in infants are necessary.

3.3.2. Hypnozoite eradication

To eradicate *P. vivax* or *P. ovale* hypnozoites, 14-day primaquine treatment of 0.25 mg/kg a day in temperate strains and 0.5 mg base/kg in East Asia and Oceania is necessary [7]. Primaquine PK studies found two-to-three-year-old children to have lower levels of plasma primaquine compared

Table 3. Oral treatment of uncomplicated malaria in infants.

Medication	Advantage	Disadvantage	Research need
– ACTs – general	• High efficacy of ACTs in infants and older children • Generally safe and well tolerated	• Most studies in infants over six months and >5 kg • Because infants are at higher risk of vomiting and sub-optimal dosing and have limited immunity, they are at higher risk of treatment failure • Limited studies comparing ACTs and ACT pediatric formula in infants	• Clear reporting of mean age, SD, age range and number of infants included in anti-malarial drug studies • Reporting on oral antimalarial treatment outcomes in infants separately • Including infants in anti-malarial efficacy and resistance monitoring studies • Population PK studies on oral anti-malarials in infants • Per-patient meta-analyses on efficacy and safety of oral antimalarials in infants • RCTs on efficacy safety, tolerability, acceptability, and effectiveness of ACT pediatric formula in infants
Artemisinins	• Generally effective in infants, reflected in low rates of early treatment failure	• Most studies in infants over six months and <5 kg • Evidence of increased plasma levels in infants (especially when <5 kg), enhancing risk of toxicity	• PK studies in infants <6 months including safety analysis
Lumefantrine	• Generally well tolerated by infants and young children	• Evidence of low lumefantrine levels in infants, risking treatment failure. Intensified or extended treatment regiments may be warranted • High re-infection rates in high-transmission settings because of relatively short half-live	• Additional PK and efficacy studies in infants • Efficacy and safety of extended or intensified drug regimens in infants
Amodiaquine	• Relatively long half-life leads less re-infection compared to AL, at least within 42 days post-treatment	• Conflicting evidence on PK properties of amodiaquine in children	• Additional PK and efficacy studies in infants
Mefloquine	• Long half-life leads to less re-infection, at least within 42 days post-treatment	• High plasma mefloquine levels reported in infants, increasing risk of toxicity • Possibly increased gastro-intestinal side-effects	• PK studies in infants including safety analysis
Piperaquine	• Long half-life leads to less re-infection, at least within 42 days post-treatment	• Previously under-dosed in infants, recommended dose recently increased	• Efficacy and safety studies of piperaquine adjusted dosing regimen in infants • Benefit of post-treatment prophylactic effect (in terms of anemia, hospital admissions) should be investigated in infants in high-transmission areas
Sulfadoxine-pyrimethamine	• Generally adequate treatment response in infants and children	• Previously under-dosed in infants, recommended dose recently increased	• Efficacy and safety studies of piperaquine-adjusted dosing regimen in infants
Pyronaridine	• Found safe and effective in infants	• Slightly lower efficacy of A-PYR in infants	• Additional safety and efficacy studies in infants when additional data of studies in older populations becomes available
Quinine	• Longer treatment duration	• Lower quinine levels observed in infants, but still within therapeutic range	• Not recommended as primary treatment, only used in case of ACT stock-out
Chloroquine	• Relatively long half-life, preventing re-infection and recrudescence	• Evidence of under-dosing in infants, increasing risk of treatment failure	• Additional PK and efficacy studies in infants • Efficacy and safety of increased drug dose in infants
Primaquine	• Only approved treatment for hypnozoites in infants >6 months	• Evidence of under-dosing in infants, increasing risk of treatment failure • No evidence of safety in infants <6 months • Can only be given when G6PD deficiency is ruled out • 14 days treatment course	• Additional PK and efficacy studies in infants • Efficacy and safety of increased drug dose in infants
Tafenoquine	• Single-dose therapy • Recently proven safe and effective in children >1.6 years	• Not licensed for use in children and infants • Not yet studied in infants	• PK, safety, and efficacy studies in infants, with attention to tolerability of pediatric drug suspension

to older children due to increased clearing and volume of distribution [152,153]. Correspondingly, Taylor et al. recommended a higher primaquine dose (0.6–1 mg/kg/day) for small children weighing 6–7 kg when determining optimal tablet strength based on extensive weight-for-age data [154]. Increasing the primaquine dose is associated with increased gastro-intestinal side-effects and risk of hemolysis (when G6PD deficiency cannot be excluded) in children and the safety of a changed dosing regimen should therefore be tested in infants before implemented [155,156].

Tafenoquine is a novel 8-aminoquinoline with potential to replace primaquine for therapy. The tafenoquine dosing

scheme might be favorable as radical cure can be provided with a single dose. However, the G6PD deficiency problem applies to this novel compound as well, meaning tafenoquine is only approved for patients with G6PD activity of >70% [157,158]. While the drug is not licensed for use in children yet, the results of the first PK safety and efficacy study of single-dose tafenoquine including young children (>1.6 years old) were published earlier this year. It showed adequate drug levels when using a weight-based dosing schedule, 94.7% (95% CI 84 · 6–98 · 3) 4-months recurrence-free efficacy and limited adverse events, besides increased post-dose vomiting in children receiving dispersed tafenoquine tablets [159].

4. Treatment of malaria in neonates

With symptomatic malaria being rare in neonates, few studies report on appropriate management of malaria in this age category, and no established treatment protocols exist.

Newborns in endemic areas exhibit some resilience against malaria due to the protective factors described above, and may be able to clear infection without specific treatment. There is no consensus on how to manage low-density, asymptomatic parasitemia in neonates [16]. As evidence is lacking, WHO guidelines recommend to treat children lighter than 5 kg, including neonates, as children of 5 kg and above [7]. Case reports describe infants with low parasitemia and no or mild symptoms successfully being treated for *P. falciparum* malaria with oral quinine (10 mg/kg every eight h, in some cases plus clindamycin) and oral chloroquine (no route of administration or dosing mentioned) for *P. vivax* malaria [16,160,161]. As for ACTs, efficacious treatment with oral DHA-P, A-L, and A-AQ is described in studies in infants less than 5 kg, most of them including neonates. No serious adverse events were observed [70,162,163]. In case of *P. vivax* congenital infections (in neonates under seven days old), it should be taken into account that sporozoites do not pass through the placenta into the fetal circulation. Infection occurs via placental breaches from maternal trophozoite-containing erythrocytes. This means there is no extra-erythrocytic phase, and treatment with primaquine is therefore not necessary [16,161,164]. Treatment with primaquine to prevent relapse of *P. vivax* and *P. ovale* malaria is necessary in children becoming infected after the first week of life, but is contra-indicated in children under six months because of insufficient safety data [7,155]. Guidelines do not specify how to eradicate hypnozoites in infants <6 months [7]. A pragmatic approach would be to provide follow-up as far as feasible, and to administer primaquine treatment once children are >6 months old.

Several case reports, case series, and retrospective observational studies describe how neonates (<28 days old) presented with symptoms such as fever, irritability, hepatosplenomegaly, anemia, jaundice, and poor feeding due to either falciparum or vivax malaria acquired congenitally or soon after birth [16,160,163,165,166]. These more severe cases were mostly treated with IV artesunate in dosing regimens recommended for older children, namely 2.4 mg/kg at zero, 12, and 24 hours [163,165]; or, in one case, with an increased dose of artesunate of 4 mg/kg at the same time points [166]. Treatment at earlier points in time included IV quinine [167]. These respective treatments resulted in clinical recovery, and no adverse events were observed [160,161,163,165–168].

Apart from this empirical evidence, no specific PK or PD information on anti-malarial treatment in neonates exists. IV treatment has a theoretical benefit of bypassing the absorption phase (as opposed to oral, IM, or rectal medication), which in ill, vulnerable patients with unknown absorption parameters seems prudent. The beneficial clinical properties of artesunate observed in older populations are likely to apply to neonates as well. Whether the WHO recommendation of a higher dose of IV artesunate (3 mg/kg) should apply to neonates seems questionable, as this recommendation is based on data from older children [32,33]. Plasma protein-binding capacity in neonates is generally lower compared to infants, increasing the free fraction of protein-bound drugs such as artesunate and renal excretion is generally lower due to immaturity of the renal system [20–22]. This means that although higher weight-based dosing seems relevant when looking at distribution of artesunate and DHA based on increased body water of neonates, other age-related mechanisms including protein-binding capacity and renal excretion influence drug distribution and elimination as well, and could potentially increase dihydro-artemisinin plasma levels. It therefore remains unclear if higher dosing currently recommended for all infants <20 kg should apply to neonates.

In short, limited evidence is available on the treatment of severe malaria in the first four weeks of life. However, anecdotal evidence suggests neonates can be treated safely and effectively with artesunate, quinine, ACTs, and chloroquine using the same dosing regimens as in older infants. As in older infants, IV artesunate treatment seems favorable to use in ill children due to its PK profile.

5. Conclusion

The evidence base on treatment of malaria in infants stems mainly from trials conducted in children and infants older than six months. Studies carried out in infants specifically are limited, and findings are rarely disaggregated per age category.

Treatment of severe malaria with artesunate (IV, IM, rectal), quinine (IV, IM, rectal) or artemether (IM or rectal) is effective and safe in children and infants (above six months). The general benefits of artesunate, including reliable absorption, fast parasite clearance and a favorable safety profile likely extend to infants and have been demonstrated in the small number of trials conducted which included infants. Infants have a large apparent volume of distribution and high body weight-normalized clearance, resulting in lower observed artesunate plasma levels. Yet, opinion on optimal artesunate dosing in infants and young children differs, due to incomplete understanding of enzyme maturation systems and limited PK data of infants.

Higher apparent clearance and larger volume of distribution in infants resulting in lower plasma drug levels led to systematic under-dosing of sulphadoxine-pyrimethamine and piperaquine. Adjusted doses are now recommended as per

WHO guideline. Current dosing regimens of lumefantrine, chloroquine, and primaquine likely result in insufficient drug exposure in infants, increasing risk of treatment failure in this vulnerable population, while oral artemisinins and mefloquine plasma levels were higher in infants, augmenting risk of drug toxicity. Vomiting while on ACT treatment occurs more frequently in infants and is related to treatment failure. Pediatric formulations can potentially increase tolerability and acceptability of anti-malarials; however, their benefit remains relatively unexplored in infants specifically. Currently, neonates are pragmatically treated as children >5 kg, with acceptable efficacy and safety according to case reports.

6. Expert opinion

6.1. General considerations

Applying malaria treatment in infants as in older patient groups is generally found to be safe and effective. However, as treatment failure rates are low and most studies do not focus on infants, or regard them a separate subgroup, the likelihood of detecting an association between age, drug levels and clinical and parasitological response is limited.

While it is vital that a dosing regimen results in an anti-malarial blood concentration above the minimum parasitical concentration in order to accomplish cure, there is evidence of infants receiving sub-therapeutic doses of lumefantrine, chloroquine, and primaquine because their distinct PK parameters are not taken into account when weight-based dosing schedules are created. Sub-optimal drug exposure due to inadequate dosing, as well as increased risk of vomiting makes infants prone to treatment failure. Meanwhile, concentrations of oral artemisinins and mefloquine may be higher in infants, risking exposure to toxic drug concentrations and decreasing drug tolerability. Identifying optimal dosing regimens for infants to achieve correct exposure to anti-malarials is necessary to ensure cure. Also, exposure of malaria parasites to sub-therapeutic drug levels in infants drives drug resistance [60]. Moreover, as infants lack background immunity, they may be more susceptible to dose–response effects and therefore at higher risk of treatment failure when infected with parasites relatively resistant to the artemisinin partner drug. Thus, the understanding of PK properties of anti-malarials in infants needs to be broadened, as well as the link between PK parameters, therapeutic response, and adverse events.

6.2. Inclusion of, and reporting on infants in anti-malarial drug trials

Ethical concerns and the conviction that infants are not at substantial risk of clinical malaria seem to have limited the inclusion of infants in clinical studies. This significantly limits our grasp of pharmacokinetics and pharmacodynamics of anti-malarial medication in infants. Evidence on safety and efficacy of anti-malarials in infants should be expanded in order to safely treat this vulnerable population. Currently, the majority of anti-malarial safety and efficacy studies carried out in high transmission settings include infants and children above six months, and report on age distribution using mean and SD. As the currently approved ACTs and severe malaria treatment are already prescribed to infants off-label and found safe in older populations, we suggest to include younger infants (under six months) in efficacy and safety studies. Researchers are encouraged to give special consideration to the infant sub-group and report findings in infants separately whenever possible, to enable interpretation of study results for infants specifically. Including these suggestions in the WHO protocol on Methods and Techniques for Assessing Exposure to Antimalarial Drugs in Clinical Field Studies and Therapeutic Efficacy Studies would help raise awareness on, and offer practical guidance for, how to address the knowledge gap on treatment of infants with severe malaria. Systematically excluding infants from drug efficacy studies, will mean to continue protecting infants from research instead of protecting them by evidence-based treatment concepts obtained from clinical research. Including them under strict safety protocol and reporting findings according to age groups wherever sample size allows will help to improve anti-malarial treatment in infants. When choosing to disaggregate data collected on infants, comparing of the outcomes with earlier drug efficacy studies will still be possible. Also, additional post-marketing registries where data on safety and efficacy on anti-malarial use in infants are aggregated would improve our knowledge on treatment of this vulnerable group.

The distinct metabolic features of infants and their influence on anti-malarials are increasingly recognized. While piperaquine and SP were marketed without proper dosing adjustments for infants; the most recently approved ACT, A-PYR, has been tested specifically in infants. Similarly, for the new anti-malarial KAF-156/lumefantrine, a safety review on children under five has been completed and a trial on a cohort with children above two years of age is now planned [169,170]. The recent study on tafenoquine in young children reflects similar appreciation for employing PK population modeling to determine optimal pediatric doses [159]. For A-L, additional data on PK parameters in infants <5 kg is underway [171].

6.3. Selecting ACTs and ACT dosing

Current ACT dosing regimens are often based on central tendency of drug concentrations in older populations. Extrapolation of doses recommended in adults and older children and deriving PK-PD relations from studies in immune patients therefore might result in treatment errors. Choice of ACT prescribed to infants is currently based on local parasite resistance as well as data from studies focussing on older children and adult studies. Head-to-head, blinded RCTs on ACTs in infants do not exist. Thus, it is not known if, for example, the benefit of the long half-life of AS-MQ leading to potentially less anemia and hospital admissions outweighs the risk of increased vomiting, when compared to, for example, A-L. A per-patient network meta-analysis aggregating efficacy, safety, and tolerability data of ACTs in infants or an RCT conducted in infants in a high-transmissions setting with an extended follow-up period would help in this regard. Further standardization and quality control of anti-malaria drug trials would aid the pooling of infant data from individual

studies assessing anti-malarial drugs. Where there are specific concerns on under-dosing of ACTs in infants and improved dosing schedules are suggested, it is important to directly compare this new dosing regimen to the currently recommended one.

The use of pediatric formulations should be further investigated in infants, addressing not only efficacy but also tolerability, acceptability, and effectiveness. Having at least two ACTs available in pediatric formulations in clinical practice would enable treating infants with treatment failure with another formula that is easy to administer, and would diversity ACT treatment use, slowing down local ACT resistance.

6.4. Population PK modeling

Current PK data on anti-malarials in infants is limited, and studies often have inadequate power to determine relevant co-variates and optimize dosing in the infant subgroup. PK studies usually involve intensive sampling of a small population in the beginning. This provides basic information on the drugs PK properties to guide sparse sampling within a broader population, knowns as population PK studies.

In population PK studies, sparse sampling can be used to obtain information on PK in a subset of the population, such as infants. This sparse data can then be analyzed with a non-linear mixed effects model and has the potential to determine demographic factors influencing PK. Drug concentrations are also increasingly determined at one point in time, such as day seven long-acting anti-malarial drug concentrations. This works well for vulnerable populations where intensive sampling is not possible because of practical and ethical constrains, such as infants [61]. Population-based PK modeling can integrate data from multiple patients, so the burden of sample taking is shared and can integrate data from samples taken at different time points, so blood sampling can for PK analysis coincide with sample taking for clinical purposes [23,26,33]. Additionally, population PK studies can help us identify covariates influencing PK parameters relevant to anti-malarial dosing in infants. With increasing laboratory capacity in endemic areas, regular PK measurements will become possible and enable us to identify optimal treatment and dosing of anti-malarials for infants [61]. This would help gather more data on the influence of weight and age on PK, informing what allometric scaling should be used in infants. It should also be taken into account that although blood spot sampling is often mentioned as a new technique enabling large-scale population PK studies, artemisinin derivates present a challenge in this regard. They are difficult to sample as they are quickly absorbed and have a short half-life, and cannot be analyzed with blood spots [26].

As population-based PK modeling predicts mean population PK parameters using a large number of virtual populations, it uses mathematical modeling taking into account prior knowledge. It is therefore important to evaluate existing PK models to determine what maturation models best reflects infant physiology. For example, the sub-models on infant enzyme maturation chosen should be the same, as to prevent conflicting recommendations as seen in artesunate dosing for children <20 kg [34].

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