Trends in Parasitology

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Review

Pharmacokinetic considerations in seasonal malaria chemoprevention

Palang Chotsiri [1], Nicholas J. White [1,2] and Joel Tarning [1,2,*]

African children under 5 years of age bear the main burden of global malaria mortality. Seasonal malaria chemoprevention (SMC) with sulfadoxine-pyrimethamine (SP) plus amodiaquine (AQ) given monthly during the rainy season is a highly effective malaria intervention for children aged between 3 months and 5 years living in the Sahel region, a region of intense but seasonal malaria transmission. This intervention is now being considered for other regions of Africa where malaria parasites are more drug resistant. Dihydroartemisinin-piperaquine (DP), an artemisinin-based combination therapy (ACT), has proved to be highly effective and well tolerated in intermittent preventive treatment in pregnant women and children. This combination may be a suitable alternative for SMC. Understanding the safety, pharmacokinetic and pharmacodynamic properties of antimalarial combination therapies is crucial in optimising dosing.

Highlights

In the Sahel region, more than 60% of the annual cases of malaria occur during the rainy season (approximately 3–4 months).

Children under 5 years of age are the population most vulnerable to malaria infections and they are the recipients of seasonal malaria chemoprevention (SMC).

Sulfadoxine-pyrimethamine plus amodiaquine comprise the only World Health Organization (WHO) recommended SMC, but increasing drug resistance threatens its future.

Expanding the deployment of SMC to East and South-East Africa is under evaluation. This region has higher levels of drug resistance than the Sahel.

Alternative SMCs are needed.

A better understanding of the safety, pharmacokinetic and pharmacodynamic properties of potential SMC medicines, and the determinants of preventive efficacy, should guide the choice of drugs, dosing, and dosing intervals.

Malaria seasonality and chemoprevention

Africa has the highest prevalence of malaria in the world. African children under 5 years of age are at highest risk of dying from *falciparum* malaria. Across the Sahel region, malaria is a highly seasonal disease with more than 60% of annual malaria cases in the region occurring during the 3–4 months rainy season [1]. **SMC** (see Glossary) is defined as the administration of repeated treatment courses of antimalarial drugs during the high-transmission season. The optimal number of consecutive antimalarial treatment courses depends on local epidemiology. SMC aims to prevent malaria illness by maintaining sufficiently high antimalarial drug concentrations in the blood throughout the transmission period. As SMC is administered to healthy children, safety and tolerability are paramount – poorly tolerated medicines, such as artesunate-mefloquine, which has predictable central nervous system (CNS) adverse effects at treatment doses, cannot be used [2]. Sulfadoxine-pyrimethamine plus amodiaquine (SPAQ), administered monthly for SMC to children aged between 3 and 59 months in the Sahel region, has been recommended by the World Health Organisation (WHO) since 2012 [3,4]. Approximately 39 million children under 5 years of age live in these areas of seasonal malaria transmission in Africa, resulting in an estimated 33.7 million malaria episodes and 152 000 deaths from malaria each year. In 2020, 33.5 million of the children living across the Sahel region received at least one dose of SMC [5]. Protective efficacy was estimated at 88.2% (95% CI: 78.7–93.8) [6]. Eastern and Southern Africa also have seasonal malaria transmission, and SMC is now under evaluation in these regions, which have different population characteristics and higher levels of drug resistance than West Africa. Therefore, different treatment options and target populations for SMC need to be evaluated in these regions.

Artemisinin-based combination therapies (**ACTs**) are under consideration as alternatives for SMC [7]. The potent artemisinin derivative eliminates most of the malaria parasites in an infection, but the drug is cleared rapidly from the systemic circulation (terminal **half-life** of 1–2 h). The slowly eliminated antimalarial ACT partner drugs have lower potency (in terms of parasite killing), but they

[1]Mahidol-Oxford Tropical Medicine Research Unit (MORU), Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
[2]Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, Oxford University, Oxford, UK

*Correspondence:
joel@tropmedres.ac (J. Tarning).

persist at parasiticidal concentrations for a substantially longer period of time (e.g., piperaquine has a terminal half-life of 20–30 days). This ensures cure of any drug-sensitive malaria infection and it also provides a lengthy post-treatment prophylactic effect. Artemether–lumefantrine is less suitable for SMC because of the substantially shorter terminal elimination half-life of lumefantrine (3–4 days), and its more complicated administration of twice-daily dosing given with food [8,9].

Pharmacokinetics and pharmacodynamics of antimalarial drugs used for SMC

SMC aims to maintain effective antimalarial drug concentrations in the body throughout the high-transmission period to suppress newly acquired infections. Therefore, dosing regimens should be determined by drug-susceptibility of the parasites and the pharmacokinetic properties of the antimalarial drugs (i.e., drug absorption, distribution, metabolism, and elimination). Most antimalarial drugs have been shown to display a nonlinear relationship between bodyweight and exposure, resulting in a higher dose (mg/kg) needed for young children to achieve equivalent drug exposures [10,11]. Age can also have a profound impact on the exposure to drugs due to the enzyme maturation of drug metabolising enzymes during the first 2 years of life [12,13]. Population pharmacometric modelling (see Box S1 in the supplemental information online) which characterises the **pharmacokinetic** and **pharmacodynamic** properties in certain populations (e.g., in young children) can be a valuable guide to optimise drug dosing. Optimal dosing regimens aim to maintain **trough** drug concentrations above the prevailing parasites' **minimum inhibitory concentrations** (**MICs**) for much of the malaria season in all treated subjects. However, for effective chemosuppression with monthly ACTs, it is not essential that blood concentrations exceed the MIC for the entire inter-dosing interval. In the days preceding the next dose, sub-MIC drug levels may still be enough to suppress parasite multiplication sufficiently to prevent symptomatic illness. Any residual parasites exposed to subtherapeutic concentrations at the end of the dosing interval will be exposed to a full antimalarial treatment course during the next cycle, and therefore eliminated (except at the end of the transmission season) (Figure 1). Any asymptomatic initial infections at the start of SMC should also be eliminated by the full ACT treatment regimen. Thus, this strategy of repeated ACT treatments as chemoprevention minimises the risk of symptomatic malaria and resistance development [14]. A breakthrough infection during SMC (an unsuccessful chemoprevention) could occur when blood concentrations are low (altered pharmacokinetics or nonadherence) or when the parasites have a higher MIC level (resistance). Thus, since breakthrough infections could result from a drug-resistant infection, the ACT used for the acute treatment of breakthrough symptomatic malaria should preferably not contain the slowly eliminated antimalarial used for SMC.

The ideal pharmacokinetic and pharmacodynamic properties of antimalarial chemopreventive compounds are shown in Table 1 [15]. The ideal combination therapy for SMC would be two (or more) highly potent antimalarial compounds with different mechanisms of action. These drugs should have long terminal elimination half-lives, allowing for weekly or monthly dosing. Having different mechanisms of action and compatible pharmacokinetic–pharmacodynamic profiles (i.e., similar time above effective drug concentrations) also protects the individual drugs from resistance development. Drug resistance arises as a result of genetic changes, which confer reduced drug susceptibility. This allows the mutated parasites to replicate in the presence of normally suppressive drug concentrations. Drug resistance is more likely to arise *de novo* in patients with high parasitaemia. Drug resistance is substantially less likely to develop during prophylactic therapy since the parasite biomass is low (10^4 –10^5 parasites emerge from the liver during a new infection), compared with the treatment of symptomatic malaria (>10^8 parasites in an adult) [14]. However, if such a rare event would take place, and the resistance conferred was sufficient to allow parasite growth, then exposure to an additional drug with a different mechanism of action would eliminate these parasites and prevent the newly emerged drug-resistant parasites from establishing a patent infection.

Glossary

Allometric scaling: the effect of body-weight on pharmacokinetic parameters (or physiological parameters) by using a power function. For example, drug clearance is proportional to the (body-weight)$^{0.75}$, drug volume of distribution is proportional to the (body-weight)$^{1.00}$, and the half-life is proportional to the (body-weight)$^{0.25}$.

Artemisinin-based combination therapies (ACTs): the recommended first-line treatment for *P. falciparum* infections. ACTs have comprise five regimens: (i) artemether-lumefantrine, (ii) artesunate-amodiaquine, (iii) artesunate-mefloquine, (iv) dihydroartemisinin-piperaquine, and (v) artesunate-sulfadoxine-pyrimethamine.

Forgiveness: reflects the proportion of missing doses that can still maintain the same therapeutic outcome as the ideal dosing schedule.

Half-life: the time interval in which drug concentrations in the systemic circulation are reduced by half.

Intermittent preventive treatment (IPT): a full standard antimalarial treatment administered at the desired intervals regardless of clinical demonstration of malaria disease.

Minimal inhibitory concentration (MIC): the antimalarial blood concentration associated with a parasite multiplication factor of one.

Pharmacodynamics: the wanted or unwanted biological effects associated with the administration of a drug.

Pharmacokinetics: the biological processes involved in the processing of an administered drug, including absorption, distribution, metabolism, and elimination.

Seasonal malaria chemoprevention (SMC): a full standard course of antimalarial treatment given at monthly intervals aiming to prevent malaria infection during the high-transmission malaria season.

Trough concentrations: the drug concentration at the time immediately before a subsequent dose.

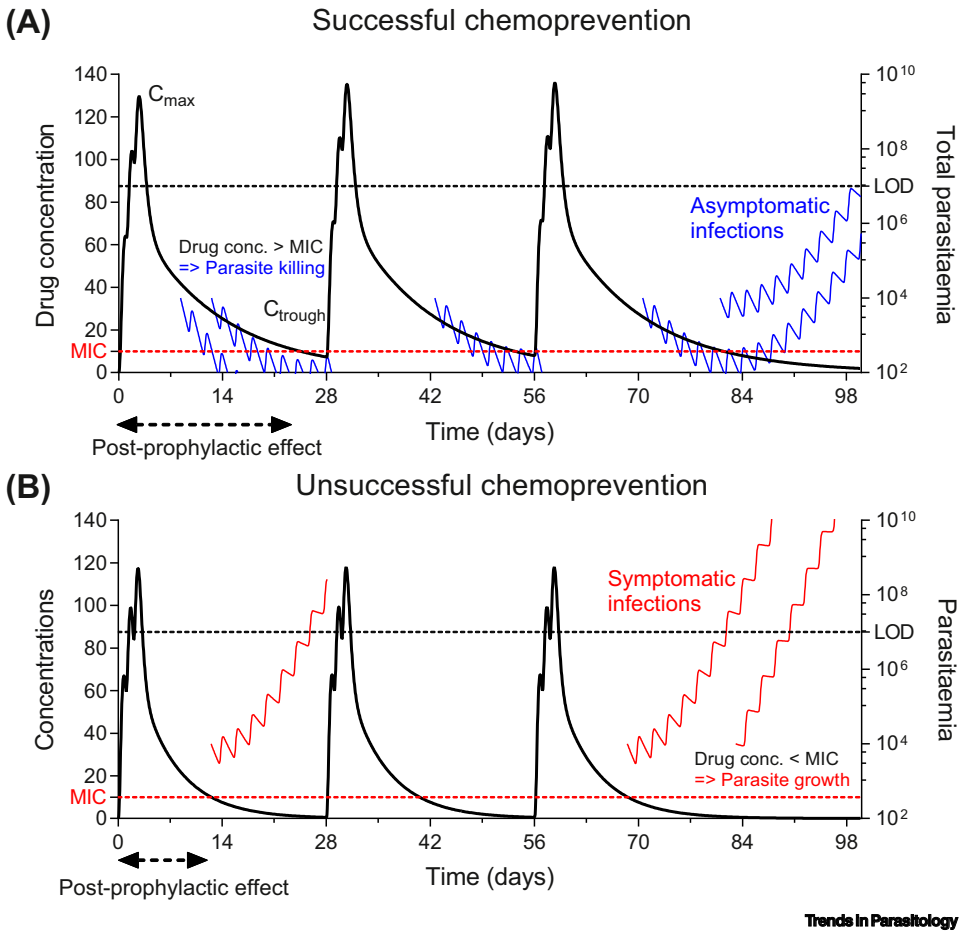

Figure 1. Pharmacokinetic and pharmacodynamic effects of antimalarial drugs in malaria chemoprophylaxis. Black unbroken lines represent pharmacokinetic concentration–time profiles during seasonal malaria chemoprevention (SMC). Maximum drug concentration (C_{max}) and minimum drug concentrations (C_{trough}) are displayed for the first dose cycle in panel A. Blue and red lines represent individual parasitaemias in patients with successful (A) and unsuccessful (B) chemoprevention. The broken black lines represent the microscopy limit of detection (LOD, equivalent to a total parasite biomass of 10^7 parasites in a 6-kg child). The broken red lines represent the minimum inhibitory concentration (MIC). The pharmacodynamic model was implemented according to Cao *et al.* [47].

The currently available ACTs contain a long-acting (i.e., slowly eliminated) antimalarial compound [e.g., sulfadoxine-pyrimethamine (SP), piperaquine, chloroquine, mefloquine, or amodiaquine (AQ)] and allow administration at monthly or weekly intervals due to their long terminal elimination half-life. Use of ACTs in SMC benefits from the artemisinin derivative to eliminate initial and breakthrough infections, and provides long-term antimalarial suppression for sustained protection against new infections. Asymptomatic infections at the beginning of the rainy season are cleared readily (these are substantially easier to treat than the higher biomass infections causing clinical illness) and any newly acquired infections are cleared by the suppressive drug concentrations maintained thereafter. If the prevailing parasites are drug sensitive, then breakthrough infections result from low drug exposures, as a result of under-dosing, poor adherence, vomiting, poor absorption, and/or unusual pharmacokinetic properties. Drugs with low oral bioavailability are more likely to have substantial interindividual variability in drug exposure, which might lead to subtherapeutic concentrations and breakthrough infections.

Table 1. Target pharmacokinetic and pharmacodynamic profile of malaria chemoprotective agents[a] [15]

General consideration	Minimum requirement	Ideal
Dosing regimen	Oral; once per day; <1000 mg	Oral; once per week or month; <100 mg
Onset of action	Slow onset of action (>48 h)	Rapid onset of action (<6 h)
Mechanism of action	Activity against asexual blood stage or liver-stage parasites	Activity against asexual blood stage and liver-stage parasites
Susceptibility to resistance	Low risk for resistance development	Very low risk for resistance development; an orthogonal mechanism to that used in treatment of symptomatic malaria
Clinical protection from infection	>95% protection against primary *Plasmodium* infection	>95% protection against all *Plasmodium* infections (including relapse)
Transmission reduction (i.e., gametocytocidal)	No	>90% transmission reduction
Bioavailability/food effect	>30%, <threefold food effect	>50%, no food effect
Drug–drug interactions	No unmanageable risks	No interaction with other antimalarials, antiretroviral, or tuberculosis medications
Safety – clinical	Acceptable therapeutic ratio based on human volunteer studies between exposure at the human effective dose and NOAEL, dependent on the nature of toxicity	Therapeutic ratio >50-fold based on human volunteer studies between exposure at the human effective dose and NOAEL; benign safety signal
G6PD deficiency status	Measured – no enhanced risk in relevant G6PD-deficient animal models	Measured – no enhanced risk in G6PD-deficiency subjects
Cost of a single treatment	≤US$0.5 for adults, ≤US$0.1 for infants under 2 years	≤US$0.25 for adults, ≤US$0.05 for infants under 2 years
Projected stability of the final product under Zone IVb condition (37°C, 75% humidity)	≥2 years	≥5 years

[a]Abbreviations: G6PD, glucose-6-phosphate dehydrogenase; NOAEL, non-observed adverse event level.

The SMC drugs are given to prevent malaria infections and can therefore be active at any stage of the infection cycle (i.e., pre-erythrocytic or erythrocytic stages), but almost all available antimalarial drugs are active against asexual erythrocytic stages. Some of these drugs are appropriate for chemopreventive administration, depending on parasite sensitivity in the area, first-line malaria treatment in the country, pharmacokinetic properties of the drug, availability of the drug, and price.

SPAQ

Single-dose SP has been used effectively as an antimalarial drug for over 50 years. Recurrence of infection with sensitive parasites is unusual within 1 month of treatment. SP is very well tolerated but increasingly compromised by resistance resulting from sequential acquisition of point mutations in the genes encoding the target enzymes. Sulfadoxine and pyrimethamine are well absorbed following oral administration. They have long terminal elimination half-lives of approximately 8 days for sulfadoxine and 4 days for pyrimethamine. A small fraction of sulfadoxine is metabolised by both phase I (cytochrome P450 (CYP) 2C9 isoenzyme) and phase II (N-acetyltransferase-2; NAT2) processes [16]. Sulfadoxine is primarily eliminated via glomerular filtration, but approximately 70% of the filtered sulfadoxine undergoes tubular reabsorption contributing to its long terminal elimination half-life. Pyrimethamine is metabolised mainly in the liver to several unknown products, and 15–30% is excreted unchanged via urine. The pharmacokinetic properties of sulfadoxine and pyrimethamine are weight- and age-dependent. New-born infants show

approximately 50% of the hepatic and renal function associated with the elimination of both sulfadoxine and pyrimethamine, compared with adults, but they reach 90% of adult activity within their first year of age [17]. This will result in a reduced weight-based clearance and increased drug exposure in infants compared with toddlers. Elimination clearance of both sulfadoxine and pyrimethamine is nonlinearly dependent on body weight (see Figure S1 in the supplementary information online), resulting in a higher bodyweight-normalised clearance in young children compared with older children and adults. This leads to a nonlinear relationship between drug exposure and bodyweight at fixed target doses (mg/kg dose target). As a result, children need a higher mg/kg dose compared with adults to achieve equivalent exposures. The pharmacokinetics are also affected by malnutrition, resulting in 15.6% and 26.7% lower bioavailability for sulfadoxine and pyrimethamine, respectively, in underweight children compared with normal-weight children [18].

Orally administered AQ is well absorbed and metabolised rapidly into its active metabolite, desethylamodiaquine, via the CYP2C8 isozyme [16]. AQ has a terminal elimination half-life of approximately 15 h, while desethylamodiaquine has a terminal half-life of approximately 12 days [19]. The predominantly extrahepatic enzyme CYP1A1 is considered responsible for conversion of desethylamodiaquine to unknown metabolites. Only a small fraction of AQ and desethylamodiaquine is eliminated unchanged in the urine. The pharmacokinetic properties of AQ and desethylamodiaquine are scaled **allometrically** by body weight, and also display an age-dependent enzyme maturation affect on their elimination clearances [20].

In SMC, AQ is provided as a fixed dose strength given once daily for three consecutive days each month (153 mg amodiaquine hydrochloride/day, SPAQ-CO®, Guilin Pharmaceutical Co. Ltd). SP is provided as a fixed single dose (25 mg pyrimethamine/500 mg sulfadoxine, SPAQ-CO®, Guilin Pharmaceutical Co. Ltd) on the first day of AQ treatment. The dosage of SPAQ in children 12–59 months of age is one tablet each of AQ (153 mg) and SP (25/500 mg), and in infants <12 months of age it is one-half tablet of AQ (76.5 mg) and SP (12.5/250 mg). There is no significant interaction between the drugs, and there are few contraindications. Children living with HIV who are receiving trimethoprim-sulphamethoxazole prophylaxis should not receive SP, and those on efavirenz should not receive AQ. This SMC regimen is given for at least three to four monthly cycles during the rainy season to children aged 3–59 months [4]. AQ is less well tolerated than SP. It may be regurgitated or vomited because of its bitter taste. Transient aesthenia is relatively common. The risk of vomiting depends on the dose of AQ. Approximately 26% and 41% of children vomited after receiving AQ doses of ≤15 mg/kg/day and >15 mg/kg/day, respectively, as an **intermittent preventive treatment (IPT**) [21]. However, in a study of almost 500 000 children receiving SPAQ as SMC, only 0.14% of children had reported adverse events, of which vomiting and abdominal pain were the most common [22]. One subject from a large SMC study developed an extrapyramidal syndrome, which may have been related to the SMC drug (probably AQ). AQ prolongs the QT interval, and may cause bradycardia in adults but not in children <12 years of age [23]. Unfortunately, readministration of drugs after vomiting is not possible because of the fixed dose SPAQ package. Recent pooled pharmacokinetic analyses in African children with uncomplicated *falciparum* malaria suggested that an increased dose in young children is needed to achieve an equivalent drug exposure compared with older children and adults for both SP and AQ [18,24]. Under-dosing is unlikely to affect initial parasite clearance but will reduce the period of post-treatment chemoprophylactic effect. This would reduce the duration of suppressive efficacy in the context of high levels of resistance. There are insufficient data on genotyped breakthrough infections with accompanying drug levels to state whether or not the currently recommended doses need adjustment.

Normally, the first dose of monthly SMC (SP with AQ) is a directly observed treatment (DOT), followed by two non-DOT doses of AQ. Children who miss the first DOT dose therefore usually

miss the whole monthly dose. A recent report suggested that only 20% of children took the full course of 4 months of SPAQ doses [20]. A study of intermittent preventive treatment in children in Papua New Guinea suggested that more than half of children skipped at least one dose of AQ [25]. A large observational study in seven African countries showed that the reported full adherence of SPAQ varied from 12.4% [95% confidence interval (CI): 7.9–19.0] in Chad to 91.2% (95% CI: 86.6–94.4) in Burkina Faso during 2016 [6].

In 2020, about 34 million children in 13 African countries received SPAQ as SMC [26]. The overall protective effectiveness of the SMC at day 28 was estimated at 88.2% (95% CI: 78.7–93.4) and the effectiveness between day 29 and day 42 was estimated at 61.4% (95% CI: 47.4–71.8) [6].

DP

The fixed-dose combination of DP is a recommended first-line ACT in the treatment of acute uncomplicated *falciparum* malaria. It has shown excellent efficacy and safety profiles in the treatment of malaria and recently has been evaluated as a chemoprophylactic agent as it provides a long post-treatment prophylactic effect.

The antimalarial contribution of the rapidly eliminated dihydroartemisinin (half-life <1 h) in preventing novel infections during SMC, is minimal. Piperaquine, however, has a multiphasic elimination profile, with a very long terminal half-life of 20–30 days. This allows for monthly dosing, and results in accumulation of trough concentrations with repeated administrations (approximately 100% higher trough concentrations at steady-state compared with the first dosing cycle) [27]. However, piperaquine shows very large between-subject variability in pharmacokinetic parameters, resulting in variation in trough concentrations at the end of each treatment cycle. Piperaquine is a highly lipophilic compound, and a concomitant high-fat meal increases the bioavailability of piperaquine up to 200%, which could explain some of the high within-patient and between-patient variability in exposure when used as SMC. The elimination of piperaquine does not scale linearly with bodyweight, resulting in lower exposures in children compared with adults at standard dosing, so a higher bodyweight-normalised dose (mg/kg) is recommended for young children. Piperaquine is primarily eliminated via CYP3A4. This isoenzyme activity matures during the first 2 years of life, resulting in an additional age-dependent clearance of piperaquine in very young children. A pharmacokinetic analysis showed that approximately 50% of full maturation was reached at a median age of 6.9 months (95% CI: 5.0–8.5) [28]. This results in a higher-than-expected exposure in infants at a fixed mg/kg dose.

Therapeutic concentrations (i.e., above MIC) usually persist for 3–4 weeks after a standard 3-day treatment. DP can be used safely as IPT in children and pregnant women, and several studies have shown high antimalarial protective efficacy of DP, comparable with that of SPAQ [29,30]. DP is not officially recommended as a first-line antimalarial treatment in any African country. There is evidence of emerging artemisinin resistance in some parts of East Africa, but malaria parasites seem to be fully sensitive elsewhere [31]. Piperaquine resistance has not been recorded in the African continent, but is prevalent in the eastern Greater Mekong subregion of Southeast Asia. Although piperaquine prolongs the electrocardiograph QT interval (as does AQ) there is no evidence that either drug is associated with ventricular tachyarrhythmias, notably *torsade de pointes*. Monthly DP has also been shown to be more effective compared with administering DP every other month, that is, 36 weeks preventive efficacy against *Plasmodium falciparum* infections were 99% (95% CI: 96–99%) for the monthly dose and 93% (95% CI: 89–96%) for alternate months [27,32]. A more infrequent dose of once per school term did not show any substantial prophylactic effect [33]. Pharmacometric modelling suggests that a standard 3-day treatment as a loading dose, followed by a single dose of DP once weekly, would improve chemopreventive

efficacy by increasing piperaquine trough concentrations, while reducing safety or tolerability concerns by lowering piperaquine peak concentrations [34]. Weekly dosing would also be more forgiving to poor adherence (i.e., missed or late doses would have less effect on chemoprophylactic efficacy) compared with monthly dosing. However, patient preference of weekly versus monthly dosing would also need to be considered, information that is currently lacking. Monthly or weekly DP is a promising alternative SMC regimen, providing safe and efficacious prophylaxis. Several trials have compared the chemoprophylactic efficacy of monthly DP with SPAQ. However, protective efficacy was comparable in children receiving DP or SPAQ as SMC (i.e., 77% for DP and 83% for SPAQ in Burkina Faso, and 96.4% for DP and 95.7% for SPAQ in Senegal) [29,35]. Weekly DP has not been evaluated prospectively in adults or children. DP was better tolerated than AQ-containing treatments as it was associated with less vomiting, especially in young children [36].

Optimising regimens

The ideal SMC regimen should provide sustained therapeutic concentrations (i.e., chemoprophylaxis) with minimal adverse effects throughout the malaria transmission season. Weekly drug regimens are generally more efficacious and forgiving, but may be operationally challenging. However, weekly administration of SP and AQ, when given as antimalarial chemoprophylaxis in travellers, was associated with unacceptable risks of serious toxicity (severe skin reactions, agranulocytosis, and hepatitis) and should be avoided. Optimal dosing should achieve therapeutic concentrations during the entire inter-dosing interval in at least 95% of the target population. This requires knowledge of the pharmacokinetic profile and especially the terminal blood concentration profiles in different groups of individuals with likely confounders (e.g., nutritional status, age, bodyweight), and information on likely levels of acquired immunity and the prevailing *P. falciparum* drug susceptibilities. These properties can be evaluated against breakthrough infections (i.e., parasitaemia before the next dose) in different groups of individuals. This information is partially available for SPAQ in West Africa where preventive efficacy has been assessed in the context of prevailing molecular markers of SP resistance [6]. Population pharmacokinetic–pharmacodynamic modelling has been conducted to determine an optimal dosing regimen and protective efficacy of DP when given as SMC in children [11]. The most vulnerable age group, the children under 1 year of age, who have the least immunity and often the lowest drug levels after standard dosing, are often under-represented in efficacy assessments. A fixed mg/kg dose throughout all age and bodyweight groups results in subtherapeutic drug exposure in children due to the nonlinear relationship between drug exposure and bodyweight/age. Therefore, optimal dosing should be achieved by dosing according to bodyweight bands or age categories to reach equivalent exposures in all groups of individuals. Methods of assessing the continued efficacy of seasonal malaria chemoprevention are needed but they have not been developed in the 10 years since it was first recommended. Prospective studies in which drug concentrations, breakthrough infections, and drug susceptibility are assessed and analysed by pharmacokinetic–pharmacodynamic modelling are necessary to characterise SMC preventive efficacy and monitor for resistance. Developed models can then be used to evaluate SMC regimens for different levels of resistance, and optimise the dosing in each bodyweight group/age category through large-scale population simulations. Standard methodologies and definitions of resistance (i.e., thresholds for policy change) need to be agreed upon.

Extending the SMC policy to the East and South-East African countries with seasonal malaria transmission (Figure 1) aims to save lives in children under 5 years of age. However, the higher levels of drug resistance there pose a challenge for SPAQ SMC. Neither SP nor AQ have had useful therapeutic activity in treatment in this region in recent years. The SPAQ combination fared better when it was deployed first, but efficacy in the treatment of symptomatic malaria

later declined and was significantly inferior to ACTs [36,37]. The preventive efficacy of SPAQ SMC in East Africa is likely to be substantially better than the treatment efficacy due to the very large difference in total parasite biomass associated with asymptomatic versus symptomatic infections, but whether it will be good enough remains to be seen. In South-Eastern Africa (Malawi, Mozambique), prevailing *P. falciparum* populations have reverted to the wild-type K76 allele in *Pfcrt*, indicating increased susceptibility to 4-aminoquinolines [38], so in these regions SPAQ should, in theory, perform well. However, reintroducing SPAQ in these regions would accelerate the re-emergence of resistant parasites again. If SPAQ preventive efficacy is unsatisfactory, then DP might be the best currently available option for these regions. Recently, SMC combined with seasonal malaria vaccination (i.e., RTS,S/AS01 vaccine) has been shown to enhance the protective efficacy of the SMC regimen in West Africa [39]. The vaccine adds drug-independent antimalarial efficacy, adding to the overall effect and compensating for incomplete adherence.

Challenges for SMC policy

Concerns have been raised that SMC could select for antimalarial drug resistance. In a successful SMC regimen, antimalarial blood concentrations should prevent parasite regrowth, thereby preventing establishment and subsequent transmission of all but the most resistant *de novo* mutant resistant infections [7]. As the initial parasite numbers emerging from the liver are low, the selection probability is also very low (orders of magnitude lower than an established infection). However, if there is already established high-level resistance in the area, and SMC is failing (i.e., the most resistant parasites can establish transmissible infections in the subjects with the least immunity and lowest drug levels) then there will be selection amplifying the spread of resistance. There is a theoretical risk of selection >4 weeks after the last SMC administration, but this should be a time of rapidly declining transmission – so both the probability of infection at that time and subsequent transmission weeks later are markedly reduced. This risk is not different from that associated with mass drug elimination or standard treatment of symptomatic acute malaria infections [14]. However, the overall selection pressure would increase with large SMC programmes, increasing the probability of drug resistance development. Fortunately, this was not seen after implementation of an extensive SMC program in Western Africa, where parasite resistance to SP was uncommon [6].

Different geographic areas have different distributions of population demographic and local epidemiology. The target population and length of SMC should be adjusted according to the geographical epidemiology. Increasing the SMC target population to include children up to 10 years of age in South-East Senegal has been suggested [40]. However, extending the target population for SMC to include different regions and/or children above 5 years of age creates operational and economical challenges.

Successful SMC treatment relies on an accurate understanding of its pharmacokinetic–pharmacodynamic relationship, that is, doses needed to maintain antimalarial drug concentrations associated with prophylactic efficacy throughout the entire season of high malaria transmission. Most MIC values have been estimated from *in vitro* studies, although several studies have tried to determine MIC values indirectly through pharmacokinetic–pharmacodynamic modelling and simulation [11,41–43]. In intermittent preventive trials the likely time point of the start of a blood-stage infection in patients with breakthrough malaria has been back-extrapolated. The predicted antimalarial drug concentrations at that time point have been used to derive *in vivo* MIC values for piperaquine in different regions and populations [11,41]. These indirect MIC calculations might be inaccurate as they depend on several unvalidated assumptions. Controlled human malaria infection (CHMI) studies with subtherapeutic antimalarial doses also provide a method for determining the *in vivo* MIC values, albeit in the absence of induced host defences [44,45].

SMC with SPAQ for children, aged between 3 and 59 months, living in the Sahel region has been recommended by WHO for a decade [3]. Coverage of SMC varies between and within countries. There are several reasons for this, including political and financial factors, logistic issues, and limited accessibility. Maintaining SMC coverage in areas of high malaria transmission needs cooperation from both local and global organisations in order to ensure sufficient antimalarial protective efficacy. WHO recommended in 2012 that 'drug resistance monitoring and system evaluation should be supported or instituted, including systems to assess the number of breakthrough infections and their intervals from the last dose of SMC'. A recent WHO Malaria Policy Advisory Group (MPAG) meeting noted that chemoprevention efficacy has not been monitored accurately [46] and repeated the need for an agreed approach for the monitoring and assessment of SMC. Furthermore, we propose that the general SMC guidelines should be reviewed to cover all populations and regions that might benefit from SMC, as well as reviewing the different antimalarial drug regimens that could be used in different geographical regions.

Concluding remarks

SMC reduces substantially the morbidity and mortality in children living in malaria-endemic regions. SMC with SPAQ has been very successful in the Sahel region, but there are concerns that emerging and spreading SP resistance might limit the usefulness of this drug combination. Recent research has shown that DP could be a promising alternative drug combination for SMC. Developing novel antimalarial agents specifically for SMC is challenged by the high safety requirements for administering drugs to healthy children. Millions of children's lives could be saved by an expansion of the SMC policy throughout the African regions of seasonal malaria transmission, if safety and effectiveness can be ensured. Expanding the target age range to all children under10 years of age might be cost-effective in certain settings. Drug adherence and **forgiveness** to poor adherence of SMC regimens remain an area where more research is needed. Optimising the use of currently available and novel SMC regimens will be a great benefit to children in areas of high malaria transmission but will require better methods of assessment. Several research challenges regarding SMC remain (see Outstanding questions).

Outstanding questions

What are the most promising alternative antimalarial drug combinations for SMC?

What are the optimal drug regimens to maximise efficacy and forgiveness to poor adherence, and how should the efficacy of SMC be monitored?

What is the lower efficacy threshold for policy change?

What is an appropriate study design to determine the clinical MIC value of antimalarial drugs when used for SMC, and how can *in vitro* IC_{50} estimates be translated to the *in vivo* IC_{50} or clinical MIC values?

What are the optimal drug regimens to minimise drug resistance development, and how should drug resistance be monitored in an SMC region?

How rapidly should novel drugs be evaluated for SMC, considering the extremely high tolerability and safety margins needed to treat uninfected/healthy children on a large scale?

How should the individual risk–benefit profile of newly developed antimalarial compounds in SMC be determined?

Should SMC be expanded to the East and South-East African regions of seasonal malaria transmission, and what SMC regimens should be used in these areas considering the prevailing high levels of SP resistance?

Should SMC be expanded to include children between 5 and 10 years of age?

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Declaration of interests

The authors declare no competing interests.

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