

# SEASONAL MALARIA CHEMOPREVENTION WITH SULFADOXINE- PYRIMETHAMINE PLUS AMODIAQUINE IN CHILDREN

A FIELD GUIDE

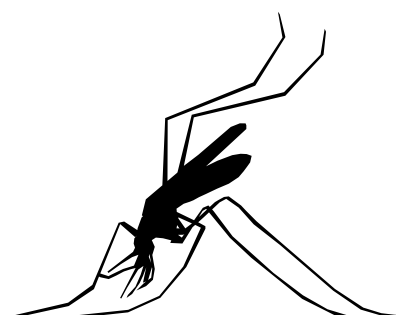




# SEASONAL MALARIA CHEMOPREVENTION

WITH SULFADOXINE-  
PYRIMETHAMINE PLUS  
AMODIAQUINE IN CHILDREN

A FIELD GUIDE  
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# ABBREVIATIONS

AQ	amodiaquine
SMC	seasonal malaria chemoprevention
SP	sulfadoxine–pyrimethamine
WHO	World Health Organization



# 1. BACKGROUND



Malaria remains a major public health problem, with an estimated burden of 216 million clinical episodes and 655 000 deaths worldwide attributable to malaria in 2010.<sup>1</sup> A significant proportion (91%) of reported deaths from malaria occurs in sub-Saharan Africa, where children under 5 years of age bear most of the burden. In 2010, it is estimated that 86% of all malaria deaths occurred in this age group.

Across the Sahel sub-region, most childhood mortality and morbidity from malaria occurs during the rainy season, which is generally short. Giving effective antimalarial medicines at full treatment doses at appropriate intervals during this period has been shown to prevent illness and death from malaria in children.

The interventions currently recommended by the World Health Organization (WHO) for the control of malaria are use of long-lasting insecticidal mosquito nets and/or indoor residual spraying for vector control, prompt access to diagnostic testing of suspected cases and treatment of confirmed cases with effective artemisinin-based combination therapy. In addition to these, other interventions recommended for specific high-risk groups in areas of high transmission include intermittent preventive treatment in pregnancy and infancy.

With the changing epidemiology of malaria, there has been a progressive shift from a 'one size fits all' approach to targeting malaria control strategies to specific populations and/or locations for maximal effectiveness. In line with this approach and on the basis of new evidence, WHO recommends an additional intervention against *Plasmodium falciparum* malaria: seasonal malaria chemoprevention (SMC). This intervention has been shown to be effective, cost-effective, safe and feasible for preventing malaria among children under 5 years of age in areas with highly seasonal malaria transmission.

**SMC is defined as “the intermittent administration of full treatment courses of an antimalarial medicine during the malaria season to prevent malarial illness with the objective of maintaining therapeutic antimalarial drug concentrations in the blood throughout the period of greatest malarial risk.”<sup>2</sup>**

<sup>1</sup> World Health Organization. *World malaria report 2011*. Geneva, 2011. [http://www.who.int/malaria/world\\_malaria\\_report\\_2011/9789241564403\\_eng.pdf](http://www.who.int/malaria/world_malaria_report_2011/9789241564403_eng.pdf).

<sup>2</sup> World Health Organization. *Report of the technical consultation on seasonal malaria chemoprevention (SMC)*. Geneva, 2011. [http://www.who.int/malaria/publications/atoz/smc\\_report\\_teg\\_meetingmay2011.pdf](http://www.who.int/malaria/publications/atoz/smc_report_teg_meetingmay2011.pdf).



## 2. WHO POLICY RECOMMENDATION FOR SEASONAL MALARIA CHEMOPREVENTION<sup>3</sup>



SMC is recommended in areas of highly seasonal malaria transmission throughout the Sahel sub-region. A complete treatment course of sulfadoxine–pyrimethamine (SP) plus amodiaquine (AQ) should be given to children aged 3–59 months at monthly intervals, beginning at the start of the transmission season, up to a maximum of four doses during the malaria transmission season (provided both drugs retain sufficient antimalarial efficacy).

The recommended dosing schedule by age is:

- ❖ infants 3–11 months old: half of a 153mg tablet of AQ base given once daily for 3 days and a single dose of half a 500/25mg tablet of SP; and
- ❖ children 12–59 months: a full tablet of 153mg AQ base given once daily for 3 days and a single dose of a full tablet of 500/25mg SP.

The single dose of SP is given only on the first day, at the same time as the first dose of AQ.

The target areas for implementation are those in which:

- ❖ malaria transmission and the majority (> 60%) of clinical malaria cases occur during a short period of about 4 months;
- ❖ the clinical attack rate of malaria is greater than 0.1 attack per transmission season in the target age group; and
- ❖ SP + AQ remains efficacious (> 90% efficacy).

### Contraindications

SMC should not be given to:

- ❖ a child with an acute febrile illness or to severely ill children unable to take oral medication;
- ❖ an HIV-positive child receiving co-trimoxazole prophylaxis;
- ❖ a child who has received a dose of either SP or AQ during the past month; and
- ❖ a child who is allergic to either SP or AQ.

Breakthrough malaria infections that occur during SMC administration should not be treated with drug regimens containing either SP or AQ.

<sup>3</sup> World Health Organization. *WHO policy recommendation: seasonal malaria chemoprevention (SMC) for Plasmodium falciparum malaria control in highly seasonal transmission areas of the Sahel sub-region in Africa*. Geneva, 2012 [http://www.who.int/malaria/publications/atoz/who\\_smc\\_policy\\_recommendation/en/index.html](http://www.who.int/malaria/publications/atoz/who_smc_policy_recommendation/en/index.html)

### Considerations for deployment of SMC

SMC with SP + AQ should not be implemented in areas with high levels of resistance to SP or AQ.

While there are several potential approaches to implementing SMC, there is presently insufficient evidence to recommend a standard strategy, and individual approaches best suited to the local conditions should be used. If possible, SMC should be integrated into existing programmes, such as community case management and other community health worker schemes.

The results of clinical trials indicate that a high level of protection against uncomplicated clinical malaria is likely to be maintained for only 4 weeks after administration of each treatment course of SP+ AQ; thereafter, protection appears to decay rapidly.

For maximum protection, and to minimize selection of drug resistance, children should receive SMC each month during the transmission period and should take the complete 3-day course each month.

In areas where SMC is deployed:

- ❑ Pharmacovigilance should be strengthened where it exists and should be instituted where it does not.
- ❑ Drug resistance monitoring and system evaluation should be supported or instituted, including systems to assess the number of breakthrough infections and their intervals after the last dose of SMC.
- ❑ Health workers must record and monitor the doses of SP + AQ administered in order to evaluate the impact of the intervention. Existing systems for documenting severe malaria, malaria deaths and confirmed cases of malaria should be strengthened.

Treatment of breakthrough *P. falciparum* infections during SMC should not include either AQ or SP or combinations containing either of these drugs, such as artesunate + amodiaquine. Where SMC is implemented, alternative antimalarial combinations must be made available for the treatment of clinical malaria in the target age group.

Existing systems for recording and reporting confirmed cases of malaria and malaria deaths should be strengthened for evaluation of the impact of SMC.

SMC complements existing malaria control interventions and should therefore be deployed concurrently.

Intermittent preventive treatment in infancy and SMC should not be given concomitantly to the same population. Therefore, in target areas for SMC, intermittent preventive treatment of malaria in infancy should not be used.

### Expected benefits of SMC

The WHO policy recommendation for SMC is based on the results of seven studies conducted in areas of highly seasonal malaria transmission in the Sahel and sub-Saharan Africa between 2002 and 2011. Evidence from these studies suggests that SMC with SP + AQ administered monthly for up to 4 months during the malaria transmission season in children aged 3–59 months:

- ❏ prevents approximately 75% of all malaria episodes;
- ❏ prevents approximately 75% of severe malaria episodes;
- ❏ may decrease child mortality by about 1 in 1000;
- ❏ probably reduces the incidence of moderately severe anaemia;
- ❏ does not result in an increase in clinical malaria cases in the subsequent malaria transmission season after 1 year of SMC, although the consequences of implementing SMC for several years have not yet been evaluated; and
- ❏ no serious adverse events have been reported and are probably rare.



# 3. SEASONAL MALARIA CHEMOPREVENTION



## 3.1 WHAT IT IS

---

SMC, formerly known as ‘intermittent preventive treatment of malaria in children’, is defined as “intermittent administration of full treatment courses of an antimalarial medicine during the malaria season to prevent malarial illness with the objective of maintaining therapeutic antimalarial drug concentrations in the blood throughout the period of greatest malarial risk”. The SMC strategy consists of administering a maximum of four treatment courses of SP + AQ at monthly intervals to children aged 3–59 months in areas of highly seasonal malaria transmission.

## 3.2 WHEN TO IMPLEMENT IT

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SMC should be implemented during the high malaria transmission period, when the incidence of malaria is high. It should be administered to children aged 3–59 months at 1-month intervals (SMC cycle) up to a maximum of four cycles in a year (SMC round). SMC with SP + AQ provides a high degree of protection for up to 4 weeks, and protection decreases rapidly thereafter. It is therefore important to respect a 1-month interval between SMC cycles in order to achieve a high level of protection and to minimize selection for malaria parasites resistant to SP + AQ.

The period of administration of SMC should be chosen to target the period when children are most at risk for malaria attacks. For example, SMC was delivered in August, September and October in field trials in Burkina Faso<sup>4</sup> and Mali;<sup>5</sup> while in Senegal;<sup>6</sup> it was given in September, October and November, covering the period of highest risk for malaria.

<sup>4</sup> Konaté AT et al. Intermittent preventive treatment of malaria provides substantial protection against malaria in children already protected by an insecticide-treated bednet in Burkina Faso: a randomised, double-blind, placebo-controlled trial. *PLoS Medicine*, 2011, 8:e1000408.

<sup>5</sup> Dicko A et al. Intermittent preventive treatment of malaria provides substantial protection against malaria in children already protected by an insecticide-treated bednet in Mali: a randomised, double-blind, placebo-controlled trial. *PLoS Medicine*, 2011, 8:e1000407.

<sup>6</sup> Cissé B et al. Seasonal intermittent preventive treatment with artesunate and sulfadoxine–pyrimethamine for prevention of malaria in Senegalese children: a randomised, placebo-controlled, double-blind trial. *Lancet*, 2006, 367:659–667.

### 3.3 CHOICE OF SULFADOXINE-PYRIMETHAMINE PLUS AMODIAQUINE

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The combination of SP + AQ was chosen for SMC for the following reasons:

- ❖ In clinical trials, SP + AQ conferred greater protection than other drug combinations.<sup>7</sup> The use of the two drugs in combination limits the risk for selection for resistance to either SP or AQ used as monotherapy.
- ❖ SP and AQ retain their efficacy in areas of Sahel and sub-Sahel with seasonal transmission where SMC is appropriate.<sup>8</sup>
- ❖ The SP + AQ regimen is safe, well tolerated and relatively cheap.
- ❖ The combination of SP + AQ does not include artemisinin derivatives. Therefore, artemisinin based combinations can be reserved for treatment of clinical cases in which the rapid action of an artemisinin derivative is most useful.

### 3.4 AREAS SUITABLE FOR IMPLEMENTATION

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SMC is recommended for use in areas with highly seasonal malaria transmission, and it is likely to be most cost-effective where the burden of malaria is highest in children. The suitability of an area for SMC is determined by the seasonal pattern of rainfall, malaria transmission and the burden of malaria. SMC is recommended for deployment in areas:<sup>9,10</sup>

- ❖ where more than 60% of the annual incidence of malaria occurs within 4 months;<sup>11</sup>
- ❖ where there are measures of disease burden consistent with a high burden of malaria in children (Incidence  $\geq$  10 cases of malaria among every 100 children during the transmission season);
- ❖ where SP and AQ retain their antimalarial efficacy.<sup>12</sup>

### 3.5 DRUG RESISTANCE

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The areas in which SMC with SP + AQ is suitable are those in which the efficacy of the combination remains > 90% (see Annex 1). Resistance to SP or AQ will reduce the efficacy of SMC in protecting children against clinical malaria, although the relation between the degree of resistance and the effectiveness of SMC has not yet been clearly defined. There is, however, a threat that deployment of SMC with SP + AQ will increase drug pressure on the malaria parasite and lead to increased resistance to the combination. It is therefore essential to continue to monitor the development of resistance to SP and AQ both *in vivo* and *in vitro*.

### 3.6 SAFETY

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SP + AQ are safe and well tolerated when used at the recommended doses and regimens. Both drugs have been used for decades for malaria treatment, and SP is currently used for intermittent preventive treatment of malaria in pregnancy and in infancy. Both AQ and SP are also used in combination with artesunate as artemisinin-based combination therapy, which is used for the treatment of uncomplicated malaria in many endemic countries. Mild side-effects may occur, of which the commonest is vomiting associated with intake of AQ. Severe side-effects include severe skin reactions and blood dyscrasia, but they are rare. In Senegal, where nearly 800 000 treatment courses of SP + AQ within SMC have been given to children, no serious adverse events attributable to these drugs were observed during intensive pharmacovigilance based on spontaneous reporting.

<sup>7</sup> Sokhna C et al. A trial of the efficacy, safety and impact on drug resistance of four drug regimens for seasonal intermittent preventive treatment in Senegalese children. *PLoS One*, 2008, 3: e1471.

<sup>8</sup> World Health Organization. *Global report on antimalarial drug efficacy and drug resistance 2000–2010*. Geneva, 2010. <http://www.who.int/malaria/publications/atoz/9789241500470/en/index.html>.

<sup>9</sup> Note that that in some countries, eligibility for SMC might apply only to part of the malaria-endemic area.

<sup>10</sup> SMC with SP + amodiaquine is not currently recommended for countries in southern and eastern Africa, even though there are some locations where the transmission pattern would suggest suitability, because of the high level of *P. falciparum* resistance to amodiaquine and/or SP and the absence of adequate data on the efficacy and safety of other antimalarial regimens for potential use in SMC.

<sup>11</sup> In these areas, more than 60% of the average annual rainfall falls within 3 months.

<sup>12</sup> Based originally on assessments of the therapeutic efficacy of SP + amodiaquine in children < 5 years of age in the WHO therapeutic efficacy testing protocol. Methods to assess the continued efficacy of SMC will be developed.



- ❗ **To minimize the risk for overdosing, it is recommended that SP + amodiaquine not be given for SMC to children who received either drug or a combination containing one of the drugs in the past 30 days.**
- ❗ **SP + amodiaquine should not be given for SMC to children with a history of allergy to sulfa-based drugs or to amodiaquine.**
- ❗ **SMC with SP + amodiaquine is not recommended for children with the Human immunodeficiency virus receiving co-trimoxazole prophylaxis against opportunistic infections.**
- ❗ **Pharmacovigilance should be maintained, and existing systems might have to be improved.**

### 3.7 DELIVERY

The method of delivery must be such that > 95% of eligible children receive SMC at monthly intervals during the period of highest malaria risk. This strict timing is best suited for community delivery, in which community health workers reach each household once a month, and a sufficient number of health workers can be deployed in each area to treat all children over a period of 3–4 days; community case management schemes are also suitable, in which health workers living in a village deliver SMC a few days each month. SMC drugs can be dispensed door-to-door or by gathering children at a pre-agreed location in each area of residence. Combining SMC with community case management has particular advantages: there are more opportunities for catching up missed doses; breakthrough cases can be diagnosed and treated, providing information about the effectiveness of SMC; and use of the same person to deliver SMC and to provide diagnoses and treatment is more economical.

SMC can also be delivered in programmes at health facilities, e.g. in outreach clinics of the Expanded Programme of Immunization. Field trials have shown, however, that such programmes are less effective in achieving high coverage.

### 3.8 IMPORTANCE OF ADHERENCE TO THE 3-DAY REGIMEN

SMC provides protection for up to 1 month after each complete (3-day) course. It is therefore important that children receive SMC each month during the main risk period and complete the course each month in order to obtain the maximum degree of protection. Good adherence also reduces the risk for selecting drug resistant parasites. Health workers should give the dose of SP and the first dose of AQ to the children under their direct observation and should advise the children's caregivers on how to give the second and third doses of AQ to the child at home.

Adherence to the full regimen should be one of the main messages in advocacy and behaviour change communication during the launching and promotion of SMC. The importance of adherence should also be stressed in communication activities at each monthly cycle.

### 3.9 LIKELY COST

Evaluation of the cost of delivering SMC in large field trials shows that the greatest costs are for delivering the drugs and the incentives paid to health workers. In The Gambia, the cost of SMC delivery by village health workers was estimated to be US\$ 1.63 per child per year.<sup>13</sup> In Senegal, where SMC was delivered by community health workers paid a daily rate and supervised by the health post nurse, the overall cost at 46 health posts was estimated to be US\$ 0.5 per child per month, or approximately US\$ 1.50 per child per year. The cost of SMC is similar to those of other malaria control interventions.

<sup>13</sup> Bojang KA et al. Comparison of two strategies for the delivery of IPTc in an area of seasonal malaria transmission. *PLoS Medicine*, 2011, 8:e1000409.

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