
**Report of the Technical consultation on Seasonal Malaria Chemoprevention (SMC) /
Chimio-prévention saisonnière du paludisme (CSP)****Background**

Across the Sahel region *falciparum* malaria is a major cause of childhood death. Most of the malaria mortality and morbidity occurs in short rainy season. Giving effective malaria chemoprevention during this period has been shown to prevent illness and death from malaria in children.

Seasonal malaria chemoprevention (SMC) previously referred to as Intermittent preventive treatment in children (IPTc) 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.

A group of researchers who have worked on IPTc established a task force (IPTc Working Group) to collate and summarize data on the efficacy, safety, tolerability, acceptability and affordability of IPTc.

As a first step in the policy making process of the Global Malaria Programme (GMP), the Technical Expert Group (TEG) on Preventive Chemotherapy was convened to review the evidence compiled by the IPTc Working Group. The objective was to formulate recommendations which will be presented to the newly established Policy Advisory Committee of the Department in order to formulate a WHO policy on the role of SMC as a potential in malaria control strategy for children.

The specific objectives of the consultation were:

- To review the current evidence on efficacy, safety and large-scale implementability of SMC, and assess the risks and potential benefits of SMC for use as an additional malaria control strategy in different malaria epidemiological settings.
- Based on this assessment, to advise WHO on the potential role of SMC as a malaria control strategy.
- To identify the critical gaps in knowledge and priority research agendas for the implementation of SMC as a WHO malaria control strategy if recommended.

Eight randomized controlled trials (7 published and 1 unpublished, (Table 1)) in children aged between 3 and 59 months during the rainy season comparing treatment doses of amodiaquine-sulfadoxine-pyrimethamine (AQ-SP) at monthly or two monthly intervals versus no treatment conducted in several

countries in west Africa were included in the analysis for protective efficacy. The end points for the analysis were

1. Uncomplicated clinical malaria (defined as fever or a history of fever plus any level of *P.falciparum* parasitaemia) during the period of drug administration and one month following the last SMC course.
2. Severe malaria (defined as per the WHO definition¹ during the period of drug administration and one month following the last SMC course) (WHO, 2000).
3. Moderate anaemia (Hb < 8g/dL) at the cross-sectional survey at the end of the intervention period (approximately one month following the last SMC course).
4. All-cause mortality during the period of drug administration and one month following the last SMC course.

Table 1 – List of studies included in the analysis of protective efficacy

Study	Site	Drug Regimen
Cisse <i>et al</i> , 2006 ²	Niakhar, Senegal	AS+SP monthly
Dicko <i>et al</i> , 2008 ³	Kambila, Mali	SP bimonthly
Kweku <i>et al</i> , 2008 ⁴	Hohoe, Ghana	AS+AQ monthly
Bojang <i>et al</i> , 2010 ⁵	Basse, The Gambia	SP+AQ monthly SP+PQ monthly DHA+PQ monthly
Dicko <i>et al</i> , 2011 ⁶	Kati Region, Mali	SP+AQ monthly
Konate <i>et al</i> , 2011 ⁷	Bousse District, Burkina Faso	SP+AQ monthly
Sesay <i>et al</i> , 2011 ⁸	Farafenni, The Gambia	SP+AQ monthly
Zongo <i>et al</i> , unpub.	Bobo Dioulasso, Burkina Faso	SP+AQ monthly DHA+PQ monthly

SP: sulphadoxine-pyrimethamine, AS: artesunate, AQ: amodiaquine, PQ: piperaquine, DHA: dihydroartemisinin

Conclusions

The summary of the conclusions of the evidence review by the TEG are as follows:

1. Monthly or bimonthly administered SMC regimens (irrespective of the drug used) showed a protective effect of SMC against clinical malaria of 78% [95%CI: 69% to 84%, $p<0.001$]. A slightly higher protective effect against clinical malaria was found when the analysis was restricted to monthly administered SMC (all drugs) [PE=83%, 95%CI: 78% to 87%, $p<0.001$] or monthly administered SP+AQ only [PE=83%, 95%CI: 72% to 89%, $p<0.001$]. The benefit was observed also in areas with good ITN coverage.
2. Monthly administered SMC using any drug regimen had a protective efficacy (PE) of 61% (95% CI: 15% to 82%, $p=0.02$) against severe malaria, defined as an episode of malaria which met the WHO definition of severe malaria or which resulted in hospital admission. A higher PE against severe malaria was demonstrated using monthly administered SP+AQ alone [PE=77%, 95% CI: 45% to 90%, $p<0.001$].
3. Monthly administered SMC (all regimens) and monthly administered SP+AQ gave a PE against moderate anaemia (Hb <8g/dl) of 20% [95% CI: -5% to 38%, $p=0.11$] and 29% [95% CI: -11% to 54%, $p=0.14$] respectively.
4. There were no serious adverse events reported attributed to SMC in over 900,000 treatment courses. Only a small number of deaths were observed in the eight controlled studies during the intervention period limiting possible evaluation of the effect of SMC against all-cause mortality, although the results are consistent with a protective effect and do not exclude a substantial benefit. Monthly administered SMC and monthly administered SMC using SP+AQ gave a pooled protective efficacy against all cause mortality of 18% (95% CI: -69% to 61%, $p=0.58$) and 34%, (95% CI: -73% to 75%, $p=0.40$) respectively.
5. A high level of protection against uncomplicated clinical malaria (defined as fever or a history of fever with parasitaemia at any density) was maintained for 4 weeks after the administration of each treatment with SP+AQ; thereafter protection decayed rapidly. The cumulative efficacy over 21 days was 91% and over 28 days it was 86%. This duration of protection was also demonstrated for severe malaria (mainly cerebral malaria and severe anaemia)
6. Age based dosing schemes used either a half or whole tablet. There was no association between efficacy and the dose of SP given, however there was an association between AQ dose and malaria incidence, the effect being most marked in children under 2 years of age. There is evidence of a moderate increase in the incidence of vomiting when the

dose of AQ given exceeds the maximum recommended value ($>15\text{mg/kg}$ daily). To ensure maximum efficacy balanced with tolerability, and for effective wide-scale deployment, a dosing scheme using either a half or a whole tablet is ideal. For AQ, a regimen of $\frac{1}{2}$ of a 153mg tablet should be used in infants <12 months old, and a full tablet in those aged 12-59 months. Use of a similar age regimen for SP tablets ensures that the majority of children receive the recommended minimum SP dose of 25/1.25mg/kg.

7. Analysis of the costs of delivering SMC suggest that in areas where the incidence of malaria in children in the target age group is above 0.2 attacks of malaria per transmission season, SMC will be a highly cost-effective intervention as assessed by both the cost of a case and a DALY prevented. In areas where the incidence of clinical attacks of malaria in children is between 0.1 and 0.2 attacks per transmission season, SMC may still be an attractive option although relatively more expensive. At an incidence rate of less than 0.1 clinical attacks per transmission season, SMC is unlikely to be a cost effective intervention.

Recommendations

The committee made the following recommendations -

- A complete treatment course of AQ+SP at monthly intervals to a maximum of four doses during the malaria transmission season should be given to children aged between 3 and 59 months as Seasonal Malaria Chemoprevention in areas of highly seasonal malaria transmission across the West Africa Sahel Sub-Region (where both drugs retain sufficient antimalarial efficacy).
- Target areas for implementation are areas where
 - more than 60% of clinical malaria cases occur within a maximum of 4 months,
 - the clinical attack rate of malaria is greater than 0.1 attack per transmission season in the target age group, and
 - AQ+SP remains efficacious (>90% efficacy^{*})

*(*Note in some countries, the eligibility for SMC deployment might apply only to part of their malaria endemic area).*

- A complete treatment course of AQ+SP should be dosed at monthly intervals to a maximum of 4 doses a year (transmission season). The recommended dosing schedule is AQ - ½ of a 153mg tablet for infants <12 months old, and a full tablet in those aged 12-59 months given once daily for three days; and a single dose of SP - ½ of a 500/25mg tablet for infants and a full tablet for children aged between 12 and 59 months. Administration of at least the first dose of AQ and the SP dose must be directly observed, and efforts to ensure adherence to the full three day course of AQ strengthened.
- For maximum protection and to minimize selection for drug resistance, children should receive preventive treatments each month during the transmission period, and should comply to the complete 3-days treatment course each month.
- Treatment of breakthrough malaria infection during the course of SMC should not include either AQ or SP.

^{*} Based on therapeutic efficacy assessment in children under 5 years of aged using the WHO therapeutic efficacy testing protocol

- Intermittent Preventive Treatment with SP in infancy and SMC should not be administered concomitantly. Therefore in target areas for SMC, IPTi should not be deployed.
- SMC Contraindications:
 - HIV positive children receiving co-trimoxazole.
 - Subject has received a dose of either AQ or SP drug during the past month.
 - Allergy to either drug (AQ or SP).
- Other considerations
 - While there are several potential approaches to implement this strategy, there is presently insufficient evidence to recommend a standard deployment strategy. However, the committee strongly recommends integration into existing programmes, such as the integrated Community Case Management and other Community Health Workers schemes.
 - In areas where SMC is deployed,
 - pharmacovigilance should be strengthened or instituted,
 - 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,
 - the health system needs to record and monitor AQ+SP doses administered in order to evaluate the impact of the intervention. Existing systems to document severe malaria, malaria deaths, and record confirmed cases of malaria should be strengthened.

Research gaps

Although there is evidence to support the initiation of SMC, there are still practical questions concerning the roll out of this additional malaria intervention. The committee did not feel that these questions should limit the imminent roll out and deployment of SMC, but can be incorporated into the implementation of the program. These include:

- Drug related
 - Are there alternative dosing regimens for SMC?

- Pharmacology studies are required to inform optimum dosing, assess the prophylactic responses, evaluate adverse effects, and characterize relevant drug interactions
 - Toxicity studies are needed to determine the risks of AQ related neutropenia and hepatotoxicity from repeat dosing of AQ for SMC
 - Studies of other age groups are needed to inform policies in other regions.
- Health and socioeconomic Impact
 - Implementation research on acceptability, implementation strategies and impact assessment
 - Is there an impact on malaria transmission?
- Monitoring and evaluation
 - How should SMC be evaluated and how can effectiveness thresholds be defined and set to guide starting, stopping, or changing the strategy?

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Annex 1

List of Participants

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**** Declaration of Interest.**

The members of the Technical Expert Group (a standing committee of GMP,) along with other invited participants attending the technical consultation on Seasonal Malaria Chemoprevention reported relevant interests, in accordance with the WHO procedures. All declared interest was discussed before the start of the meeting. All members of the TEG (core and co-opted members) reported no interest relevant to the meeting.

However, of note are the members of the IPTc taskforce (a group of researchers who have undertaken the studies on IPTc) who were invited to the meeting solely to present the results of the studies and clarifications as required to the committee, and where not a part of the review panel. The members of the Task force were thus excluded from the discussions and formulation of recommendations. Sections of the meeting with discussions related to recommendations was conducted exclusively as a closed door section of the TEG and excluded the members of the IPTc Task Force and observers.