Addition of amodiaquine + sulfadoxine-pyrimethamine for seasonal malaria chemoprevention in the WHO Model List of Essential Medicines for children

General items

1. Summary statement of the proposal for inclusion, change or deletion.

This proposal suggests the addition of amodiaquine + sulfadoxine-pyrimethamine used in combination for seasonal malaria chemoprevention (SMC) in the WHO Model List of Essential Medicines (EML) for children.

SMC is a full therapeutic course of antimalarial medicine delivered to children less than 6 years of age regardless of whether the child is infected with malaria. SMC reduces the morbidity and mortality of malaria in children with the highest risk of malaria.

WHO recommends that “In areas with highly seasonal malaria transmission in the sub-Saharan region of Africa, provide seasonal malaria chemoprevention (SMC) with monthly amodiaquine + SP for all children aged < 6 years during each transmission season”.

2. Relevant WHO technical department and focal point (if applicable).

WHO Global Malaria Programme (WHO/GMP).
Focal Point: Dr. OLUMESE, Peter, e-mail: olumesep@who.int

3. Name of organization(s) consulted and/or supporting the application.

N/A

4. International Nonproprietary Name (INN), Anatomical Therapeutic Chemical (ATC) code of the medicine and International Classification of Disease (ICD) 11.

- INN: Sulfadoxine-pyrimethamine; Amodiaquine

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5. Dose forms(s) and strength(s) proposed for inclusion; including adult and paediatric (if appropriate).

- Sulfadoxine-pyrimethamine + amodiaquine is available as co-packaged dispersible tablets at a strength of
  - Sulfadoxine/pyrimethamine + Amodiaquine 500mg/25mg + 153mg
  - Sulfadoxine/pyrimethamine + Amodiaquine 250mg/12.5mg + 76.5mg

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

Listing is requested for a new indication for preventive use. SP and amodiaquine are already listed in the Model List of Essential Medicines for treatment of malaria. This will be included in the section 6.5 Antiprotozoal medicines under chapter 6.5.3.2.

7. Treatment details (requirements for diagnosis, treatment and monitoring).

An implementation field guide was developed by WHO to assist countries in the adoption and implementation of SMC²

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).

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; or a full tablet of 76.5mg of AQ daily for 3 days and a single dose of 250/12.5mg 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).

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.

Co-administration of other medication.

- Children receiving a sulfa-based medication for treatment or prophylaxis, including co-trimoxazole (trimethoprim–sulfamethoxazole), which is widely used as prophylaxis against opportunistic infections in HIV-infected infants

² WHO 2013, Seasonal malaria chemoprevention with sulfadoxine-pyrimethamine plus amodiaquine in children: A field guide
Monitoring.
As SMC relies on community health workers, simple, user-friendly recording tools should be designed and adapted to the country context. For instance, pictorial aids are helpful. Data can be presented in tables, bar charts and figures to show stakeholders how the programme is performing globally, by region and district, and highlight areas in which adjustments are required to improve performance. If resources are limited, representative sites in various locations can be selected to monitor the impact of the SMC strategy. Various data collection instruments can be used to record information for SMC programme monitoring, including registers, tally sheets, SMC implementation cards, children’s health cards and survey data collection tools. The monitoring tools should be integrated with existing tools.

SMC with SP + AQ may increase drug pressure on the malaria parasite population, which could lead to selection of drug-resistant parasites and the spread of resistance to SP and/or AQ. Therefore, monitoring the estimated efficacy of SP and AQ during SMC is important. Unfortunately, there is currently no recommended way of estimating the efficacy of SP + AQ. A baseline assessment of resistance would be helpful, and surveys should be carried out at 2–3-year intervals in representative locations with techniques such as molecular markers of resistance to SP and in vitro assays of the sensitivity of P. falciparum to AQ and SP. Indirect methods, such as monitoring the impact of SMC with SP + AQ on the prevalence of malaria infection or clinical malaria over time, might also be useful for detecting declining efficacy of SP + AQ, which could lead to surveys of markers of resistance or in vitro assays for confirmation.

8. Information supporting the public health relevance.
Malaria is one of the leading causes of illness, death, and lost economic productivity globally. The vast majority of malaria cases and deaths in Africa occur in young children. 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.

The objective of preventive treatment is to prevent malarial illness by maintaining therapeutic drug levels in the blood throughout the period of greatest risk.

Evidence supporting the recommendation (see Annex 4, A4.21 Guidelines for the Treatment of Malaria 3rd ed 2015)

The main benefits and other considerations are given below. A detailed Grade table summary is provided thereafter:
In a systematic review SMC was directly compared with no prophylaxis in seven trials with a total of 12,589 children. All the trials were conducted in West Africa, and six of seven trials were restricted to children < 5 years.

In comparison with no chemoprophylaxis, SMC:
- Prevented up to 75% of malaria episodes (rate ratio, 0.26; 95% CI, 0.17–0.38; six trials, 9321 participants);
- Prevented up to 75% of severe malaria episodes (rate ratio, 0.27; 95% CI, 0.10–0.76; two trials, 5964 participants); and
- May be associated with a reduction in mortality (risk ratio, 0.66; 95% CI, 0.31–1.39; six trials, 9533 participants).

These effects remained even when use of insecticide-treated nets was high (two trials, 5964 participants).³

The relevant GRADE table as included in the third edition of the WHO Guidelines for the treatment of malaria are displayed below (MTG, Annex 4, A4.21)

A4.21 Does seasonal malaria chemoprevention (SMC) reduce malaria morbidity and mortality to a greater extent than no intervention?

<table>
<thead>
<tr>
<th>Balance of desirable and undesirable effects</th>
<th>Desirable</th>
<th>Undesirable</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMC prevents up to three quarters of malaria episodes (high-quality evidence).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMC prevents up to three quarters of severe malaria episodes (high-quality evidence).</td>
<td></td>
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<tr>
<td>SMC may cause a small reduction in mortality (moderate-quality evidence).</td>
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<tr>
<td>The current regimen of amodiaquine + sulfadoxine-pyrimethamine causes vomiting in some children (high-quality evidence).</td>
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</tbody>
</table>

Recommendation

In areas with highly seasonal malaria transmission, provide SMC with monthly amodiaquine + sulfadoxine-pyrimethamine for all children ≤ 6 years during each transmission season.

Strength of recommendation

<table>
<thead>
<tr>
<th>For intervention</th>
<th>No recommendation</th>
<th>Against intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>Conditional</td>
<td>Strong</td>
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<tr>
<td>Strong</td>
<td></td>
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</tr>
</tbody>
</table>

Remarks

The target areas for implementation are those where:
- malaria transmission and most clinical malaria cases occur during a short period of about 4 months;
- the clinical attack rate of malaria is > 0.1 episode per child during the transmission season; and
- amodiaquine + sulfadoxine-pyrimethamine remains efficacious (> 90% efficacy). SMC should not be given to children with severe current illness, who are already taking co-trimoxazole or with a known allergy to amodiaquine or sulfadoxine-pyrimethamine.

Overall quality of evidence for all critical outcomes

<table>
<thead>
<tr>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
<th>Very low</th>
</tr>
</thead>
</table>

Rationale for the recommendation

The Guideline Development Group endorsed the previous recommendation for SMC made by the WHO Technical Expert Group on Preventive Chemotherapy in May 2011, subsequently reviewed and endorsed by the WHO Malaria Policy Committee, in January 2012.
### Seasonal malaria chemoprevention (SMC) versus placebo to reduce malaria morbidity and all-cause mortality

**Patient or population:** Children aged < 5 years  
**Settings:** Areas with seasonal transmission  
**Intervention:** Regular full treatment doses of antimalarial medicines (amodiaquine + sulfadoxine–pyrimethamine, artesunate + sulfadoxine–pyrimethamine or sulfadoxine–pyrimethamine alone) every 1–2 months during the malaria transmission season  
**Comparison:** Placebo  

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Illustrative comparative risks (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Importance of outcome to decision-making</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
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<tr>
<td>Placebo</td>
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</tr>
<tr>
<td>Clinical malaria</td>
<td>2.5 episodes per child per year$^3$</td>
<td>0.7 episodes per child per year (0.4 to 1.0)</td>
<td>Rate ratio 0.26 (0.17 to 0.38)</td>
<td>9321 (6 studies)</td>
<td>⚫⚫⚫⚫ High$^1$</td>
</tr>
<tr>
<td>Severe malaria</td>
<td>35 episodes per 1000 children per year$^4$</td>
<td>9 episodes per 1000 children per year (4 to 27)</td>
<td>Rate ratio 0.27 (0.1 to 0.76)</td>
<td>5964 (2 studies)</td>
<td>⚫⚫⚫ High$^2$</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>3 per 1000 per year</td>
<td>2 per 1000 per year (1 to 5)</td>
<td>Risk ratio 0.66 (0.31 to 1.39)</td>
<td>9533 (6 studies)</td>
<td>⚫⚫⚫ Moderate$^4$</td>
</tr>
<tr>
<td>Moderately severe anaemia</td>
<td>67 per 1000 per year</td>
<td>47 per 1000 per year (35 to 65)</td>
<td>Risk ratio 0.71 (0.52 to 0.98)</td>
<td>8805 (5 studies)</td>
<td>⚫⚫⚫ Moderate$^4$</td>
</tr>
<tr>
<td>Serious drug-related adverse events</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>9533 (6 studies)</td>
<td>Moderate[^7]</td>
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</tr>
<tr>
<td>Non-serious adverse events</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>9533 (6 studies)</td>
<td>Moderate[^8]</td>
</tr>
</tbody>
</table>

The assumed risk is based on the sum of events and participants in the control groups in the trials, unless stated otherwise in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI, confidence interval; SMC, seasonal malaria chemoprevention.

[^1]: The trials were conducted in children aged < 5 years in Burkina Faso, the Gambia, Ghana, Mali (two) and Senegal. In three studies, amodiaquine + sulfadoxine–pyrimethamine administered monthly, in two studies sulfadoxine–pyrimethamine was given every 2 months, and in one study sulfadoxine–pyrimethamine + artesunate was given monthly. Two studies, in which insecticide-treated nets were also distributed, showed that the benefits remained even when use of bednets was > 90%.

[^2]: There was no reason to downgrade for study limitations, inconsistency, indirectness or imprecision.

[^3]: The incidence of malaria in the control groups was 2.88 episodes per child per year in Burkina Faso, 2.4 in Mali and 2.25 in Senegal.

[^4]: The incidence of severe malaria in the control groups was 32 per 1000 children per year in Burkina Faso and 37 per 1000 children per year in Mali.

[^5]: Downgraded by 1 for imprecision. There were very few deaths in these trials, and none of the trials had adequate power to detect an effect on mortality. Larger trials are necessary for this effect to be established confidently. A reduction in the number of deaths would be consistent with the high-quality evidence of a reduction in severe malaria.

[^6]: There was substantial heterogeneity among these five trials, and the trials in the Gambia and Ghana did not show an effect. Downgraded by 1 for inconsistency. There was no reason to downgrade for study limitations, indirectness or precision.

[^7]: No drug-related serious adverse events were reported. Downgraded by 1 for precision, as trials of this size have inadequate power to fully detect or exclude rare, serious adverse events.

[^8]: Downgraded by 1 for study limitations. All seven trials reported observed adverse events; however, the adequacy of the methods used to collect these data is unclear in some trials. The only adverse event found to be statistically more common with SMC was vomiting after amodiaquine + sulfadoxine–pyrimethamine.

Adverse events.
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.

Despite the known side effects associated with sulfonamides, SP for intermittent preventive treatment in infancy is generally very well tolerated. Studies showed no evidence of any adverse effects of SP-IPTi on infants’ serological responses to vaccines (DTP, polio, hepatitis B, Haemophilus influenzae B, yellow fever or measles). A rebound effect in terms of greater susceptibility to malaria after termination of SP-IPTi, although reported in some studies, was not found in the pooled analysis.

Surveillance of molecular markers of SP resistance should accompany SP-IPTi, in particular the distribution and prevalence of Pf dhps 540 mutations, which is a surrogate measure of SP efficacy.

Contraindications. SMC is contraindicated in:

- individuals with known hypersensitivity to pyrimethamine, sulfonamides and related compounds and/or amodiaquine
- children receiving a sulfa-based medication for treatment or prophylaxis, including cotrimoxazole (trimethoprim–sulfamethoxazole), which is widely used as prophylaxis against opportunistic infections in HIV-infected infants

Caution. If skin eruptions, cytopenia or a bacterial or fungal super-infection occurs, use of SP should be discontinued. Caution is advised in repeated administration of SP to patients with blood dyscrasias and those with renal or hepatic failure, in whom the drugs accumulate.

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

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.13 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.

Regulatory information

12. Summary of regulatory status and market availability of the medicine.
Sulfadoxine-pyrimethamine and amodiaquine tablets are currently available on the market from three and have been prequalified by the WHO prequalification Programme.

13. **Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).**


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