Seasonal Malaria Chemoprevention (formally known as Intermittent Preventive Treatment in children) for preventing malaria morbidity in children aged less than 5 years living in areas of marked seasonal transmission

GRADE tables to assist guideline development and recommendations

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Plain Language Summary of Results

Seasonal chemoprevention given to children aged < 5 years in areas of marked seasonal malaria transmission:

• Prevents approximately 75% of all malaria episodes *(high quality evidence)*
• Prevents approximately 75% of severe malaria episodes *(high quality evidence)*
• Probably produces a small decrease in child mortality of around 1 in 1000 *(moderate quality evidence)*.
• Probably reduces the incidence of moderately severe anaemia *(moderate quality evidence)*
• Does not result in an increase in clinical malaria in the following malaria transmission season *(high quality evidence)*
• Does not result in an increase in moderately severe anaemia in the following transmission season *(moderate quality evidence)*
• Probably does not result in rebound increase in mortality in the following malaria transmission season *(moderate quality evidence)*

In addition:

Serious adverse events have not been reported and are probably rare *(moderate quality evidence)*

There is increased vomiting with amodiaquine plus sulfadoxine-pyrimethamine *(high quality evidence)*

These effects are still present even when ITN use is high *(high quality evidence)*

Date: 26 October 2011
Definitions

**Seasonal malaria chemoprevention** (formally known as 'Intermittent Preventive Treatment of Malaria*' (IPT')) is currently defined as ‘the administration of a full curative dose of an antimalarial or antimalarial combination to a selected, target population at specified times without determining whether or not the subject is infected’.

‘Marked seasonality’ is defined by the World Health Organization for the purposes of SCM, as an area where 60% of clinical malaria cases occur within 4 months of the year or less.

**GRADE approach**

In July 2011, we updated the Cochrane systematic review of randomized controlled trials comparing seasonal chemoprevention with placebo, or no seasonal chemoprevention. The results of this review and an assessment of the quality of evidence they provide is presented in five GRADE tables, addressing the following questions:

**In malaria endemic areas with marked seasonality:**

- Does seasonal chemoprevention reduce all-cause mortality and malaria morbidity in children aged less than 5 years? Table 1
- After stopping seasonal chemoprevention is there a rebound increase in all-cause mortality and malaria morbidity during the following malaria transmission season? Table 2
- Is seasonal chemoprevention still effective in settings where ITN coverage is high? Table 3
- Is seasonal chemoprevention still effective where home-based management of malaria is practiced? Table 4
- Is amodiaquine plus sulphadoxine-pyrimethamine (AQ+SP) an effective and safe option for seasonal chemoprevention Table 5

The GRADE system considers ‘quality’ to be a judgment of the extent to which we can be confident that the estimates of effect are correct. The level of ‘quality’ is judged on a 4-point scale. Evidence from randomized controlled studies is initially graded as HIGH and downgraded by one, two or three levels after full consideration of:

- any limitations in the design of the studies, the directness (or applicability) of the evidence, and the consistency and precision of the results.

  **High:** Further research is very unlikely to change our confidence in the estimate of effect.

  **Moderate:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

  **Low:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

  **Very low:** We are very uncertain about the estimate.

In moving from evidence to formulating recommendations the panel should consider the following factors:

- The quality of the evidence
- The balance of benefits and harms
- Values and preferences
- The resource implications

There are two strengths of recommendation:

- **A STRONG recommendation:** Implies that the recommendation can be applied in most settings (with marked seasonal transmission)
- **A WEAK or CONDITIONAL recommendation:** Implies that local policy will require further debate and stakeholder involvement

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Question 1. Does seasonal chemoprevention reduce all-cause mortality and malaria morbidity in children aged < 5 years?

Setting: Areas with marked seasonal malaria transmission

Reference: Meremikwu MM, Donegan S, Esu E, Oringanje C. Seasonal chemoprevention of malaria in children (formerly known as "Intermittent preventive treatment in children"). Cochrane Database of Systematic Reviews [Year], Issue [Issue].

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of events/patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of studies</td>
<td>Design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>Clinical malaria</td>
<td>6</td>
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<td>no serious risk of bias</td>
<td>no serious inconsistency</td>
</tr>
<tr>
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<tr>
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<tr>
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<td>no serious inconsistency</td>
</tr>
<tr>
<td>Serious drug-related adverse event</td>
<td>6</td>
<td>randomised trials</td>
<td>no serious risk of bias</td>
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<tr>
<td>Non-serious adverse event</td>
<td>6</td>
<td>randomised trials</td>
<td>serious</td>
<td>no serious inconsistency</td>
</tr>
</tbody>
</table>

1. The studies were well conducted with allocation concealment at low risk of bias in all studies, and 5 out of 6 studies were blinded and used placebos.
2. There was substantial heterogeneity between these 6 trials. All 6 trials showed a statistically significant benefit but the magnitude of this benefit was variable. Not downgraded.
3. The included trials were conducted in Ghana, Mali (2), The Gambia, Senegal and Burkina Faso, in areas described as 'seasonal malaria transmission'. Most studies were limited to pre-school aged children. Three studies administered monthly AQ+SP, two studies used bimonthly SP, and one study used monthly SP + AS.
4. There was no reason to downgrade for study limitations, inconsistency, indirectness or imprecision.
5. The incidence of malaria in the control groups was 2.25 episodes per child per year in Senegal, 2.4 in Mali, and 2.88 in Burkina Faso.
6. These two trials were well conducted and at low risk of bias.
7. These trials were conducted in areas of seasonal transmission in Mali and Burkina Faso. Both trials compared SP+AQ with placebo in pre-school age children. Of note, LLITN use was high in both the intervention and control groups in both studies.
8. The incidence of severe malaria in the control groups was 37 per 1,000 children per year in Mali, and 32 per 1,000 children per year in Burkina Faso.
9. Downgraded by 1 for imprecision: There were very few deaths in these trials, and none of the trials were adequately powered to detect an effect on mortality. Larger trials are necessary to have confidence in this effect. However, a reduction in death would be consistent with the high quality evidence of a reduction in severe malaria.
10. These control group risks are taken from the sum of events and participants in the included trials.
There was substantial heterogeneity between these 5 trials and the trials from Ghana and the Gambia did not show an effect. Downgraded by 1 for Inconsistency. There was no reason to downgrade for study limitations, directness or precision.

All six trials reported that there was no case of drug-related serious adverse event. One trial reported that four participants were withdrawn from the treatment arm: two cases for non-severe skin rash, one for itching and another for acute respiratory infection. One trial reported skin eruptions with macular hyper-pigmentation which was neither Stevens Johnson syndrome nor any other form of severe skin lesions.

Downgraded by 1 under precision. Trials of this size are underpowered to fully detect or exclude rare serious adverse events. Observation should continue once implemented.

Downgraded by 1 under study limitations. All seven trials commented on observed adverse events. However, the thoroughness of the methods used to collect these data are incomplete in some of these trials. The only adverse event found to be statistically more common with seasonal chemoprevention was vomiting after AQ+SP (see GRADE table 5).
Question 2: After stopping seasonal chemoprevention is there a rebound increase in all-cause mortality or malaria morbidity during the following malaria transmission season?

Setting: Areas with marked seasonal transmission

Reference: Meremikwu MM, Donegan S, Esu E, Oringanje C. Seasonal chemoprevention of malaria in children (formerly known as "Intermittent preventive treatment in children"). Cochrane Database of Systematic Reviews [Year], Issue [Issue].

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<td><strong>Clinical malaria</strong></td>
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<tr>
<td>No of studies</td>
<td>Design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
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<tr>
<td>3</td>
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<td>no serious risk of bias</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
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<tr>
<td><strong>Severe malaria - not reported</strong></td>
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<tr>
<td>0</td>
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<tr>
<td><strong>Death from any cause</strong></td>
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<td>no serious indirectness</td>
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<tr>
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<tr>
<td>1</td>
<td>randomised trials</td>
<td>no serious risk of bias</td>
<td>no serious inconsistency</td>
<td>serious indirectness</td>
</tr>
</tbody>
</table>

1. These trials were well conducted and considered at low risk of bias.
2. Three trials report clinical malaria during the following malaria season when seasonal chemoprevention was not given. These were conducted in Senegal, Mali, and Ghana.
3. There was no reason to downgrade for study limitations, inconsistency, indirectness or imprecision.
4. The incidence of malaria in the control groups was 2.25 episodes per child per year in Senegal, 2.4 in Mali, and 2.88 in Burkina Faso.
5. This trial was well conducted and considered at low risk of bias.
6. This trial was conducted in Ghana. A large reduction in clinical malaria was seen during the intervention period, following seasonal chemoprevention with either bimonthly sulfadoxine-pyrimethamine or amodiaquine plus artesunate.
7. Downgraded by 1 for imprecision: There were very few deaths in these trials, and none of the trials were adequately powered to detect or exclude an effect on mortality. Larger trials are necessary to have confidence that there is no increase.
8. These control group risks are taken from the sum of events and participants in the included trials.
9. Downgraded by 1 for indirectness: Only one trial reports the incidence of moderately severe anaemia during the following transmission season. This trial found no statistically significant benefit on anaemia during the administration of seasonal chemoprevention.
**Question 3: Is seasonal chemoprevention still effective where ITN coverage is high?**

**Setting:** Areas with marked seasonal transmission

**Reference:** Meremikwu MM, Donegan S, Esu E, Oringanje C. Seasonal chemoprevention of malaria in children (formerly known as "Intermittent preventive treatment in children"). Cochrane Database of Systematic Reviews [Year], Issue [Issue].

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<td>Design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
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<tr>
<td>Clinical malaria - (where bed-nets are also used)</td>
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</tr>
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<td>no serious indirectness</td>
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<tr>
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<td></td>
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</tr>
<tr>
<td>2</td>
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<td>no serious inconsistency</td>
<td>no serious indirectness</td>
</tr>
</tbody>
</table>

1 These trials were well conducted and considered at low risk of bias.
2 Two trials compared seasonal chemoprevention with placebo where both groups were also given insecticide treated bed-nets. These trials were conducted in Mali and Burkina Faso. ITN usage was over 99% in both groups in Mali, and 92% in both groups in Burkina Faso.
3 There was no reason to downgrade for study limitations, inconsistency, directness or precision.
4 The incidence of malaria in the control groups was 2.4 in Mali, and 2.88 in Burkina Faso.
5 The incidence of severe malaria in the control groups was 37 per 1,000 children per year in Mali, and 32 per 1,000 children per year in Burkina Faso.
Question 4: Is seasonal chemoprevention still effective where home-based management of malaria is practiced?

Setting: Areas with marked seasonal transmission

Reference: Meremikwu MM, Donegan S, Esu E, Oringanje C. Seasonal chemoprevention of malaria in children (formerly known as "Intermittent preventive treatment in children"). Cochrane Database of Systematic Reviews [Year], Issue [Issue].

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<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
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<td>Clinical malaria - (where home-based management of malaria is used)</td>
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<td></td>
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</tr>
<tr>
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<td>no serious indirectness</td>
<td>serious</td>
</tr>
<tr>
<td>Severe malaria - Not reported</td>
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</table>

- Downgraded by 1 for risk of bias: This trial did not adequately describe the methodology to make judgements about the risk of bias.
- One trial conducted in Ghana compared seasonal chemoprevention with no seasonal chemoprevention in the context of an on-going programme of home-based management of malaria.
- Downgraded by 1 for imprecision: The result is not statistically significant.
- The incidence of febrile episodes (treated presumptively as malaria) in the control group was lower in this trial than seen elsewhere.
Question 5: Is amodiaquine plus sulfadoxine-pyrimethamine an effective and safe option for seasonal chemoprevention?

**Setting:** Areas with marked seasonal transmission

**Bibliography:** Meremikwu MM, Donegan S, Esu E, Oringanje C. Seasonal chemoprevention of malaria in children (formerly known as "Intermittent preventive treatment in children"). Cochrane Database of Systematic Reviews [Year], Issue [Issue].

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<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Amodiaquine plus sulfadoxine-pyrimethamine</th>
<th>Control</th>
<th>Relative (95% CI)</th>
<th>Absolute</th>
<th>Quality</th>
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<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
<td>0.6 episodes per child per year</td>
<td>2.5 episodes per child per year</td>
<td>Rate Ratio 0.23 (0.14 to 0.37)</td>
<td>1.9 episodes fewer per child per year (from 1.6 fewer to 2.2 fewer)</td>
<td>⚫⚫⚫⚫</td>
</tr>
<tr>
<td>Severe malaria</td>
<td>2</td>
<td>randomised trials</td>
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<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
<td>9 episodes per 1000 children per year</td>
<td>35 episodes per 1000 children per year</td>
<td>Rate Ratio 0.25 (0.1 to 0.68)</td>
<td>26 fewer episodes per 1000 children per year (from 11 fewer to 32 fewer)</td>
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<tr>
<td>Death from any cause</td>
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<td>no serious risk of bias</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious</td>
<td>none</td>
<td>6/3498 (0.17%)</td>
<td>10/3512 (0.28%)</td>
<td>RR 0.62 (0.23 to 1.65)</td>
<td>1 fewer per 1000 (from 2 fewer to 2 more)</td>
<td>⚫⚫⚫⚫</td>
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<tr>
<td>Moderately severe anaemia</td>
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<td>no serious risk of bias</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
<td>66/2866 (2.3%)</td>
<td>139/2874 (4.8%)</td>
<td>RR 0.48 (0.36 to 0.63)</td>
<td>25 fewer per 1000 (from 18 fewer to 31 fewer)</td>
<td>⚫⚫⚫⚫</td>
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<td>no serious indirectness</td>
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<td>none</td>
<td>-</td>
<td>-</td>
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<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
<td>387/1814 (21.3%)</td>
<td>131/1730 (7.6%)</td>
<td>RR 2.78 (2.31 to 3.35)</td>
<td>135 more per 1000 (from 99 more to 178 more)</td>
<td>⚫⚫⚫⚫</td>
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</table>

1 The studies were well conducted with allocation concealment at low risk of bias in all studies, and all studies were blinded and used placebos.

2 There was substantial heterogeneity between these 3 trials. All 3 trials showed a trend to favour chemoprevention but the magnitude of this benefit was variable. Not downgraded.

3 Two trials compared seasonal chemoprevention with placebo where both groups were also given insecticide treated bed-nets. These trials were conducted in Mali and Burkina Faso. ITN usage was over 99% in both groups in Mali, and 92% in both groups in Burkina Faso. The third trial was conducted in the Gambia. All were in pre-school age children, and administered monthly SP+AQ.

4 There was no reason to downgrade for study limitations, inconsistency, indirectness or imprecision.

5 The incidence of malaria in the control groups was 2.4 in Mali, and 2.88 in Burkina Faso.
These trials were conducted in areas of seasonal transmission in Mali and Burkina Faso.\(^6\) There was no reason to downgrade for study limitations, inconsistency, indirectness or imprecision.\(^7\)

The incidence of severe malaria in the control groups was 37 per 1,000 children per year in Mali, and 32 per 1,000 children per year in Burkina Faso.\(^8\) Downgraded by 1 for imprecision: There were very few deaths in these trials, and none of the trials were adequately powered to detect an effect on mortality. Larger trials are necessary to have confidence in this effect. However, a reduction in death would be consistent with the high quality evidence of a reduction in severe malaria.\(^9\) These control group risks are taken from the sum of events and participants in the included trials.\(^10\)

All three trials reported that there was no case of drug-related serious adverse event. One trial reported that four participants were withdrawn from the treatment arm: two cases for non-severe skin rash, one for itching and another for acute respiratory infection. One trial reported skin eruptions with macular hyper-pigmentation which was neither Stevens Johnson syndrome nor any other form of severe skin lesions.\(^11\) Downgraded by 1 under precision. Trials of this size are underpowered to detect or exclude rare serious adverse events.\(^12\)