WHO Evidence Review Group on Intermittent Screening and Treatment (ISTp) and ACT Treatment of Malaria in Pregnancy

Malaria Policy Advisory Committee
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Outline

- Background
- Objectives
- Process
- Key Conclusions
- Recommendations
In October 2012, on the advice of the Malaria Policy Advisory Committee (MPAC) after the work of a dedicated evidence review group (ERG), WHO updated the policy for IPTp with sulphadoxine-pyrimethamine (IPTp-SP). The new policy recommends that women living in areas of moderate to high malaria transmission should receive IPTp-SP as early as possible in the second trimester, and at each scheduled antenatal care (ANC) visit thereafter, with SP doses given at least one month apart.

In 2013, the MPAC concluded that there was insufficient data to determine at what level of SP resistance IPTp-SP should be discontinued in the absence of an established and effective alternative and to define the level of Plasmodium falciparum transmission at which IPTp-SP may cease to be cost-effective from a public health point of view.
Background

- **ALTERNATIVES:** several studies have been completed on the efficacy, safety, feasibility, acceptability and cost-effectiveness of alternative interventions to prevent the consequences of malaria in pregnancy, including intermittent screening and treatment of malaria in pregnancy (ISTp).

- During recent years, a growing body of evidence has been accumulated on the clinical safety of the artemisinin derivatives in the first trimester of pregnancy, and of the efficacy of different artemisinin-based combination therapies (ACTs) in treatment of uncomplicated malaria in pregnancy.

- To review these studies and in order to update WHO recommendations, WHO/GMP convened an ERG with specific focus on the efficacy of ISTp compared with IPTp and the safety of artemisinin derivatives in early pregnancy.
Objectives of the ERG meeting

Part 1. To review the available evidence on the efficacy, safety, acceptability and cost-effectiveness of intermittent screening and treatment of malaria in pregnancy (ISTp) using rapid diagnostic tests and different antimalarial medicines as a potential alternative strategy for intermittent preventive treatment of malaria in pregnancy (IPTp).

Part 2. To review the efficacy and safety data on the use of artemisinin-based combination for the treatment of uncomplicated malaria during pregnancy, with specific attention to exposure in the first trimester as compared to quinine, in view of possible revisions of current recommendations for malaria treatment in the first trimester of pregnancy.
Missed opportunities for delivering IPTp in 2013: stagnant increase of IPTp uptake since 2007

Figure 4.1 Proportion of pregnant women attending ANC and proportion receiving IPTp, by dose, among sub-Saharan countries reporting, 2013

Figure 4.2 Proportion of pregnant women receiving IPTp, by dose, by year of pregnancy in survey and by reporting year for NMCP, Africa, 2000–2013

ANC, antenatal care; IPTp, intermittent preventive treatment in pregnancy

Source: National malaria control programme reports, UN population estimates

* Median proportions using household data are based on six-year trend analyses

Source: Demographic health surveys, malaria indicator surveys, multiple indicator cluster surveys and other household survey data, NMCP reports, UN population estimates
Proportion of children aged 2-10 years infected with *P. falciparum*: a) 2000 and b) 2013
ERG areas of review in relation to potential alternatives to IPTp-SP (Part I)

1. Review all available published and unpublished reports on the efficacy, and safety of ISTp compared to IPTp for prevention of the adverse consequences of malaria in pregnancy.

2. Review available reports on the acceptability of ISTp under trial conditions.


4. Review the recent evidence on the effect of submicroscopic infections on maternal and infant outcomes.

5. Review available published and unpublished reports on the impact of SP resistance on IPTp-SP effectiveness.

6. Review results of recently completed clinical trials evaluating the efficacy and safety of DHA-PPQ for IPTp.

7. Based on the evidence reviewed, consider if either ISTp or IPTp with DHA-PPQ could be recommended as a potential alternative to IPTp-SP in some areas with high SP resistance and/or very low transmission.
Current WHO recommendations for treatment of uncomplicated malaria in the 1st trimester of pregnancy

Treating uncomplicated *P. falciparum* malaria in special risk groups

First trimester of pregnancy

Treat pregnant women with uncomplicated *P. falciparum* malaria during the first trimester with 7 days of quinine + clindamycin.

*Strong recommendation, very low-quality evidence*

- ...in the absence of adequate safety data on the artemisinin-derivatives in the first trimester of pregnancy the Guideline Development Group was unable to make recommendations beyond reiterating the status quo.
ERG areas of review in relation to ACT safety in early pregnancy (Part II)

8. Review the evidence of embryotoxicity of artemisinin derivatives from animal studies.

9. Review available published and unpublished reports on exposures to artemisinin derivatives in the first trimester of pregnancy.

10. Review results of recent clinical trials evaluating the efficacy and safety of different ACTs for malaria treatment in the second and third trimester of gestation.

11. Based on the evidence reviewed, consider if the current WHO recommendations on use of ACTs in pregnancy could be updated.
Participants and dynamics of the ERG meeting

<table>
<thead>
<tr>
<th>ERG meeting Part 1 – ISTp</th>
<th>ERG meeting part I2 – ACT Rx</th>
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<tbody>
<tr>
<td>Chairpersons:</td>
<td>Presenters:</td>
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<td>Rapporteur:</td>
<td>Raquel Gonzalez</td>
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<td>Presenters:</td>
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<td>Presenters:</td>
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<tr>
<td>B. Greenwood, J. Gutman, R. Mc Gready, C. Menendez, F. Ter Kuile</td>
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<td>Reviewers:</td>
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<td>Observer: D. Kyabayinze</td>
<td>Observer: S. Duparc</td>
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<td>WHO Secretariat:</td>
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<td>P. Alonso, A. Barette, A. Bosman, G.M. Mbemba, J. Namboze, P. Olumese, S. Schwarte</td>
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</table>
Process

- All participants contributed to the sessions in plenary and in working groups, but only the independent reviewers and WHO Secretariat attended a final closed session to elaborate the recommendations of the meeting.

**DOCUMENT: REPORT**

- The key conclusions emerging from the topics are presented as summarised “Key conclusions”, inboxes, at the end of the respective sections of the report.

- The main conclusions and recommendations of the meeting, reviewed and agreed among the independent reviewers are presented as the last section of the report and summarised at beginning of the document.
Pre-reads, Presentations and Discussions

- ISTp compared to IPTp with SP in West and East Africa
- Acceptability of ISTp under trial conditions
- Cost-effectiveness of ISTp
- Effects of submicroscopic infections on maternal and infant outcomes
- Impact of SP resistance and malaria transmission on IPTp-SP effectiveness
- Evaluation of DHA-PPQ for IPTp
- Embryotoxicity of artemisinin derivatives in animal studies
- Safety of artemisinin exposure in the first trimester of pregnancy
- Efficacy and safety of ACTs in the 2nd and 3rd trimester of pregnancy
- General considerations on antimalarials use in pregnancy
**Key conclusions**

- ISTp (either with SP or AL as treatment) was not inferior to IPTp with SP in preventing third trimester maternal anemia, LBW and placental malaria in studies conducted in areas of low SP resistance in West Africa.

- However, the incidence of outpatient visits and malaria episodes during pregnancy was higher in ISTp group compared to IPTp-SP.

- The results from the trials conducted in West Africa suggest that **IPTp with SP should be continued where SP resistance is low**.

- ISTp with DHA-PPQ was not superior to IPTp-SP in areas of high malaria transmission and high SP resistance of East and Southern Africa and was associated with more malaria during pregnancy and at delivery in all gravidae and lower mean birth weight in paucigravidae.

- **IPTp with SP retains some of its effectiveness in areas of high SP resistance and should be continued in these areas.**
Key conclusions

- Overall, ISTp (either with AS-AQ or DHA-PPQ) was considered to be an acceptable alternative to IPTp with SP both by providers and users in trial conditions.

- Quality of care of ANC services as well adherence to a three-day course of treatment were concerns perceived by pregnant women and health care workers respectively.

- Further research would be needed to confirm these findings in larger studies, other settings and in non-trial conditions.
Cost-effectiveness of ISTp

Key conclusions

- ISTp (with AL) was found to be more expensive and less effective for prevention of MiP than IPTp with SP.

- At the current levels of efficacy of IPTp with SP, it would not be cost-effective to switch from IPTp-SP to ISTp-AL.
Effects of submicroscopic infections on maternal and infant outcomes

Key conclusions

- **Submicroscopic infections**, especially early in pregnancy were associated with maternal anaemia, LBW and prematurity.

- The effects of submicroscopic infections on adverse pregnancy outcomes need to be confirmed in large longitudinal studies and in different settings.

- Malaria infection prevalence is highest at the antenatal booking visit and declines thereafter. The sensitivity of RDTs is also highest at the initial visit, in particular in primigravidae. Thus, the use of RDTs to screen asymptomatic pregnant women for malaria infection is likely to be most beneficial at the first antenatal visit.
Impact of SP resistance and malaria transmission on IPTp-SP effectiveness

Key conclusions

- **IPTp with SP remains effective** in preventing the adverse consequences of malaria on maternal and infant outcomes, including in areas where quintuple mutant haplotypes *Plasmodium falciparum* mutations to SP are highly prevalent.

- The association between *dhfr* 581G mutation and decreased low birth weight in women receiving IPTp with SP compared to non-recipient of SP reported in limited areas from Tanzania has not been observed in other sub-Saharan countries and its potential impact on IPTp-SP effectiveness requires further investigation.

- Further research on the impact of other SP resistance markers on IPTp-effectiveness should be done in sub-Saharan countries where IPTp-SP is used.

- There is currently no evidence of a threshold level of malaria transmission below which IPTp-SP is no longer cost-effective.
Key conclusions

- Recent studies evaluating **DHA-PPQ for IPTp** have found that the drug was more efficacious than SP in reducing maternal malaria infection and anemia at delivery, **incidence of malaria** during pregnancy, **stillbirths** and infant mortality within 6-8 weeks.

- These **promising results** would need to be confirmed in larger RCT involving women in areas with similar malaria transmission and SP resistance and in areas with different malaria transmission and SP resistance levels.

- In addition, the **safety** of administering repeated doses of **DHA-PPQ** (with specific attention to QTc prolongation) requires **further investigations** as well as adherence to the required three-day regimen for each DHA-PPQ treatment dose and the safety of DHA-PPQ co-administration with antiretrovirals in HIV-infected women.
Embryotoxicity of artemisinin in animal studies

Key conclusions

- **Embryo deaths and malformations induced by artemisinin** derivatives have been reported in rats, rabbits and monkeys. The effects are dose and time dependent.

- By extrapolation of animal toxicity findings it is possible to estimate in humans a putative sensitive embryonic period between start of week four to the end of week ten post-conception, or from the start of week six to the end of week 12 post LMP.
Safety of artemisinin in the first trimester of pregnancy

Key conclusions

- Updated evidence on the safety of artemisinin indicates that ACT exposure in first trimester of pregnancy does not increase the risk of miscarriage, stillbirths or major congenital malformations compared to quinine.

- Women treated with an artemisinin anytime during first trimester were at similar or lower risk of miscarriage compared to those treated with oral quinine.

- Based on the available updated evidence, the first line treatment of uncomplicated malaria in the first trimester of pregnancy should be revised to include ACTs as therapeutic option.

- Most of the data of artemisinin exposure in the first trimester of pregnancy are from AL exposure and consequently, more safety data are needed with other ACTs.

- There is a need for continued monitoring and pharmacovigilance of drug exposure in early pregnancy, including more information on congenital malformations.
### Additional information on artemisinin exposure in early pregnancy, performed after the ERG meeting


**Table 1. Number of documented confirmed 1st trimester exposures to artemisinins.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Publication Year</th>
<th>Number of confirmed first trimester exposures</th>
<th>AL</th>
<th>AS*</th>
<th>MAS</th>
<th>AS-SP</th>
<th>Art (IV/IM)</th>
<th>AQAS</th>
<th>DHA-PPQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGready</td>
<td>Thai-Myanmar Border</td>
<td>Updated and not yet published</td>
<td>301</td>
<td>14</td>
<td>188</td>
<td>89</td>
<td></td>
<td>5^</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deen</td>
<td>Gambia</td>
<td>2001</td>
<td>77</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adam</td>
<td>Sudan</td>
<td>2009</td>
<td>62</td>
<td></td>
<td>3</td>
<td></td>
<td>11</td>
<td>48</td>
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<tr>
<td>Manyando</td>
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<td>2010</td>
<td>156</td>
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<td></td>
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<td></td>
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<tr>
<td>Rulisa</td>
<td>Rwanda</td>
<td>2012</td>
<td>96</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Mosha</td>
<td>Tanzania</td>
<td>2014</td>
<td>168</td>
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<td></td>
<td></td>
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<tr>
<td>Poespoprodjo</td>
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<td>Dellicour</td>
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<tr>
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<td>Tinto</td>
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<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>1025</td>
<td>544</td>
<td>188</td>
<td>89</td>
<td>58</td>
<td>40</td>
<td>40</td>
<td>18</td>
</tr>
</tbody>
</table>

*AS for 7 days either as monotherapy n=147; or as a non-fixed combination including AS+Clindamycin n=36; AS + Doxycycline n=3; AS + atovaquone-proguanil n=2;
^ Includes one woman treated with Artemether IM for 6 days.

**Acronyms:** AL, artemether-lumefantrine; AQAS, amodiaquine-artsunate; AS, artesunate; AS-SP, artesunate-sulphadoxine-pyrimethamine; Art, artesunate; DHA-PPQ, dihydroartemisinin-piperaquine; IM, intramuscular; IV, intravenous; MAS: mefloquine-artsunate.
Post-ERG meeting updated analyses

Risk of miscarriage and stillbirth with artemisinin and quinine exposures in early pregnancy.

<table>
<thead>
<tr>
<th></th>
<th>Artemisinin compound # events/ # total</th>
<th>Quinine # events/ # total</th>
<th>Adjusted HR (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Miscarriage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st trimester (2-14 weeks post-LMP)</td>
<td>27/ 604</td>
<td>85/ 595</td>
<td>0.45 (0.27- 0.75)</td>
<td>0.002</td>
</tr>
<tr>
<td>Embryo-sensitive period (6-12 weeks post-LMP)</td>
<td>22/ 406</td>
<td>49/ 333</td>
<td>0.93 (0.55- 1.55)</td>
<td>0.773</td>
</tr>
<tr>
<td><strong>Stillbirth</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st trimester (2-14 weeks post-LMP)</td>
<td>11/ 560</td>
<td>5/ 107</td>
<td>0.81 (0.22, 2.95)</td>
<td>0.745</td>
</tr>
<tr>
<td>Embryo-sensitive period (6-12 weeks post-LMP)</td>
<td>9/ 383</td>
<td>3/ 57</td>
<td>1.69 (0.62, 4.63)</td>
<td>0.309</td>
</tr>
</tbody>
</table>

The upper limit of the 95% CI of the hazard ratio rule out a 1.55-fold or greater increase in risk of miscarriage and a 4.63-fold or greater increase in risk of stillbirth.
## Risk detectable for major malformations

<table>
<thead>
<tr>
<th></th>
<th>Any artemisinin compound*</th>
<th>AL</th>
<th>AS*</th>
<th>MAS</th>
<th>AS-SP</th>
<th>Art (IV/IM)</th>
<th>AQAS</th>
<th>DHA-PPQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st trimester exposures</td>
<td></td>
<td>1025</td>
<td>544</td>
<td>188</td>
<td>89</td>
<td>88</td>
<td>63</td>
<td>40</td>
</tr>
<tr>
<td>Major Malformations (p=0.7%)**</td>
<td>2.1</td>
<td>2.6</td>
<td>4.0</td>
<td>5.9</td>
<td>5.9</td>
<td>7.1</td>
<td>9.5</td>
<td>15.5</td>
</tr>
<tr>
<td>Specific Birth Defect (p=0.1%)</td>
<td>4.6</td>
<td>6.4</td>
<td>12.5</td>
<td>21.5</td>
<td>22.0</td>
<td>28.0</td>
<td>41.0</td>
<td>80.0</td>
</tr>
<tr>
<td>Exposures in embryo-sensitive period ***</td>
<td>615</td>
<td>326</td>
<td>112</td>
<td>53</td>
<td>52</td>
<td>37</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>Major Malformations (p=0.7%)</td>
<td>2.5</td>
<td>3.1</td>
<td>5.1</td>
<td>7.6</td>
<td>7.7</td>
<td>9.5</td>
<td>12.5</td>
<td>25.0</td>
</tr>
<tr>
<td>Specific Birth Defect (p=0.1%)</td>
<td>5.9</td>
<td>8.4</td>
<td>17.2</td>
<td>30.0</td>
<td>31.0</td>
<td>41.0</td>
<td>56.0</td>
<td>120.0</td>
</tr>
</tbody>
</table>

* Treatment categories are not mutually exclusive as some cases were exposed to multiple class of artemisinin treatment.

** Based on major malformations detectable at birth by systematic surface examination observed across studies to date.

*** Estimated at 60% of all 1st trimester exposures based on studies included in the meta-analysis.

**Acronyms:** AL, artemether-lumefantrine; AQAS, amodiaquine-artesunate; AS, artesunate; AS-SP, artesunate-sulphadoxine-pyrimethamine; Art, artesunate; DHA-PPQ, dihydroartemisinin-piperaquine; IM, intramuscular; IV, intravenous; MAS: mefloquine-artesunate.

Minimum level of increase in relative risks for congenital malformations that can be ruled out, according to the number of confirmed exposed pregnancies for each artemisinin treatment type (Power 80% and one-sided $\alpha=0.05$).
Efficacy and safety of ACTs in the 2nd and 3rd trimester of pregnancy

Key conclusions

- Data on **ACTs use for treatment of clinical uncomplicated malaria** in second and third trimesters of pregnancy indicate that they are **safe in terms of pregnancy outcomes and efficacious** to clear *Plasmodium* parasites (especially DHA-PPQ).

- ACTs can be thus considered a safe and efficacious option for treatment of clinical uncomplicated malaria in women in the second and third trimester of gestation.
General considerations on antimalarial use in pregnancy

Key conclusions

- More studies in HIV-infected pregnant women are needed, including evaluation of mother to child transmission and drug interactions between antimalarials and antiretrovirals.

WHO experience

In 2012, WHO recommended the use of efavirenz as first line treatment of HIV infection in pregnancy despite pre-clinical data showing embryotoxicity, based on comprehensive reviews of safety data in pregnant women and programmatic superiority to standard of care. A similar approach could be followed to support an updated WHO recommendation of ACT use in first trimester of pregnancy.
Draft recommendations (I)

- IPTp with SP remains highly cost-effective in preventing the adverse consequences of malaria on maternal and fetal outcomes, and should thus be aggressively scaled-up in line with the current WHO recommendations. IPTp with SP also remains effective in areas where quintuple mutant haplotypes of Plasmodium falciparum to SP are highly prevalent.

- The association between sextuple mutant haplotypes of *P. falciparum* and decreased low birth weight (LBW) reported in limited areas in Tanzania with very high SP resistance in the context of observational studies using retrospective information about the assignment of SP, has not been observed in other sub-Saharan countries in the context of randomised controlled trials with SP, and requires further investigation. In these limited geographic areas with very high SP resistance, the benefits and cost-effectiveness of adding at the first ANC visit a single RDT screening and treatment to the continued provision of IPTp with SP, should be evaluated in pilot studies.
Draft recommendations (II)

- There is currently no evidence of a threshold level of malaria transmission below which IPTp-SP is no longer cost-effective. Therefore, in areas where IPTp with SP is implemented and transmission reduced to low levels as a result of successful control strategies, WHO recommends continued implementation until the area has been targeted for malaria elimination by the national programme.

- Recent studies have shown that intermittent screening and treatment (IST) with RDTs and ACTs of pregnant women at ANC resulted in a higher proportion of maternal infections and clinical malaria during pregnancy and lower mean birth weight compared with IPTp-SP. Further, being less cost-effective than IPTp with SP, ISTp with the currently available RDTs should not be recommended as an alternative to IPT-SP.
Draft recommendations (II)

- Recent studies have shown that IPTp with dihydroartemisinin-piperaquine (DHA-PPQ) did not reduce low birth weight compared to IPTp with SP, but was more efficacious in reducing maternal malaria parasitemia and anemia at delivery, incidence of malaria infection and clinical malaria during pregnancy, stillbirths and early infant mortality within 6-8 weeks. More research is needed to evaluate the impact of DHA-PPQ for IPTp on LBW, safety of repeated doses and adherence to the required three-day regimen.
Draft recommendations (III)

- New evidence from 1025 pregnancies with confirmed artemisinin exposure in first trimester indicate that artemisinins do not increase the risk of miscarriage, stillbirths or major congenital malformations compared to women with malaria treated with non-artemisinin regimens. Moreover, comparison of carefully documented and prospectively collected safety data on women exposed to only artemisinin-based treatment with those collected on women exposed to only quinine in the first trimester of pregnancy showed that artemisinin was associated with a significantly reduced rate of miscarriage compared to quinine. Therefore, the WHO recommendations for the treatment of clinical uncomplicated malaria episodes in women in the first trimester of pregnancy should be updated as follows: “Treat pregnant women with uncomplicated P. falciparum malaria with either the first line ACT for three days or quinine and clindamycin for seven days”. Artemether-lumefantrine (AL) should be the preferred ACT, as most of the available data derive from AL exposure.
Draft recommendations (III)

- Although the evidence regarding the safety of ACTs in early pregnancy has been strengthened by the recent review, there is the need for continued monitoring of drug safety, birth outcomes and neonatal mortality. Moreover, potential drug-drug interactions in HIV-infected pregnant women who are taking antiretrovirals and receive antimalarials as well as the risk of mother to child transmission should also be monitored.