

Malaria Policy Advisory Committee

Evidence Review Group on Intermittent Preventive Treatment (IPT) in Pregnancy

Terms of Reference

1. Background:

Malaria infection during pregnancy is a major public health problem, with substantial risks for the mother, her fetus and the neonate. The World Health Organization (WHO) currently recommends a package of interventions for controlling malaria during pregnancy in areas with stable (high) transmission of *Plasmodium falciparum* (WHO, 2004), which includes the use of insecticide treated nets (ITNs), intermittent preventive treatment (IPT) and effective case management of malaria and anaemia.

Current WHO recommendations on Intermittent Preventive Treatment in pregnancy (IPTp)

All pregnant women in areas of stable (high) malaria transmission should receive at least two doses of intermittent preventive treatment after quickening, the first noted movement of the fetus (WHO, 2004)¹. WHO recommends a schedule of four antenatal clinic visits, with three visits after quickening. Intermittent preventive treatment at each scheduled visit after quickening will ensure that a high proportion of women receive at least two doses. Doses should not be given more frequently than monthly. Currently, the recommended drug for intermittent preventive treatment is sulfadoxine–pyrimethamine (SP), because it is safe for use during pregnancy, effective in women of reproductive age and can be delivered as a single dose under observation by a health worker. It is also currently the only antimalarial drug for which there are sufficient data on safety and efficacy to be recommended for IPTp. WHO recommendations on IPTp² are based on the following evidence:

- At least two doses are required to achieve optimal benefit in most women.
- One study of intermittent preventive treatment in HIV-infected pregnant women showed that monthly dosing (most women receiving 3–4 doses) was necessary to achieve optimal benefit.
- HIV-infected pregnant women receiving daily co-trimoxazole should not receive IPTp with SP.
- In settings with an HIV prevalence among pregnant women greater than 10%, if the HIV status of pregnant women is unknown, it is more cost-effective to treat all women with a 3-dose regimen than to screen for HIV and provide the regimen only to HIV-infected women.
- There is no evidence that a third dose carries any additional risk, that more than 3 doses during pregnancy offers additional benefit or that receiving 3 or more doses of SP increases the risk for adverse drug reactions.

¹ WHO (2004). *A strategic framework for malaria prevention and control during pregnancy in the African Region*. Brazzaville. Regional Office for Africa (AFR/MAL/04/01)

² WHO (2007). *Malaria in pregnancy - Guidelines for measuring key monitoring and evaluation indicators*. WHO, Geneva (http://whqlibdoc.who.int/publications/2007/9789241595636_eng.pdf)

Statement of the problem

Preliminary data from observational studies showing reduced effectiveness of SP for IPTp in Malawi have been presented at multiple international scientific meetings. Methods to monitor the effectiveness of IPTp are under assessment by several research institutions, the results of which have not yet been published. There is growing concern over the decreasing effectiveness of the 2-dose regimen of SP for IPTp in many countries facing increasing levels of resistance to SP, especially in Eastern and Southern Africa. A recent study in Tanzania³ showed that IPTp does not improve overall pregnancy outcomes where SP-resistant parasites predominate and may increase the odds of fetal anemia. Moreover, the continued usefulness of this intervention in areas where malaria interventions have successfully reduced malaria transmission has been increasingly questioned in recent years.

2. Questions to be addressed by the ERG on IPTp with SP:

To review these issues, WHO/GMP proposes to convene an Evidence Review Group (ERG) on the effectiveness of SP for IPTp, to review the evidence available as of May 2012, and address the specific questions listed below:

1. What are the key determinants and potential confounders of reduced effectiveness of IPTp with SP emerging from the recent trials?
2. Which levels of transmission intensity and SP resistance (by molecular markers) are associated with loss of effectiveness of IPTp with SP?
3. Is there evidence of harm with the implementation of IPTp with SP in areas with high level of resistance to SP?
4. Should 3-doses or monthly doses of SP for IPTp be recommended in all countries with stable malaria transmission, replacing the current practice of 2-dose SP regimen?
5. Should the policy of IPTp with SP be limited to Africa only or should it be extended to all areas with stable transmission (also outside Africa)?
6. What are the core elements and methods of a simplified protocol to monitor the effectiveness of SP for IPTp?
7. What are the minimum requirements (technical expertise, personnel, laboratory equipment etc) to monitor the effectiveness of SP for IPTp?
8. What data need to be available for review in order to consider a policy of IPTp with an alternative antimalarial medicine (other than SP)?
9. What data are needed to decide if a policy of IPTp should be stopped when transmission has been reduced to a certain level?
10. Which alternative antimalarial medicines will have, in a relatively short term period, sufficient safety and efficacy data to replace SP in IPTp?
11. Based on the review of the evidence available should the current WHO policy recommendations on IPTp be updated?
 - a. If yes, provide specific suggestions

³ Harrington *et al.*, (2011). Intermittent treatment to prevent pregnancy malaria does not confer benefit in an area of widespread drug resistance. [Clin Infect Dis](#) 53: 224-230.

- b. If no, indicate which evidence (scientific and operational) should inform the updating of current WHO recommendations on IPTp
12. What core messages should be addressed by a “WHO interim position statement on IPTp with SP” to Ministries of Health of malaria endemic countries?

The ERG will also be requested to address the following two questions:

13. Based on the review of available evidence, including unpublished reports, which key recommendations (if any) could be proposed for a GRADE assessment?
14. What are the current knowledge gaps (scientific and operational) for effective implementation of IPTp with SP?

3. Suggested timetable:

The report of the assessment made by the ERG with the draft proposed recommendations will be submitted to the Malaria Policy Advisory Committee (MPAC) for review and approval. Based on the timelines of ongoing studies (see ANNEX 1) and the timing of the assessment by the ERG, some of the above questions may have to be prioritized and/or deferred to a later period.

- a. March 2012: identify/contact suitable researcher(s) to present evidence to ERG
- b. March-May: compile and analyse literature and evidence from ongoing studies (MIPc)
- c. May: submission of study reports to ERG members
- d. July: initial meeting of ERG in Geneva
- e. September 2012: present outcome of review to MPAC
- f. Late 2012 and 2013: Depending on the evidence available, the ERG will be asked to meet again to review additional evidence on IPT with SP and with alternative antimalarial medicines, as well as alternative approaches, such as intermittent screening and treatment.

Studies available for review in June 2012:

- i. The 2-dose vs monthly dosing meta-analysis by Kassoum.
- ii. The analysis of individual studies in 8 African countries (currently on-going) as advanced report for submission to WHO (string of tables hopefully draft manuscripts ready for sharing).
- iii. The analysis of the Malawi historical data.

4. Declaration of Interests:

All ERG members to complete a DoI form which will be evaluated, summarized, and published on the MPAC website for public record.

List of relevant ongoing studies and evidence reviews for ERG (to be completed)

IPTp-SP effectiveness studies coordinated by the Malaria in Pregnancy (MIP) Consortium

1. Aggregated meta-analysis of 2 vs 3+ doses of IPTp-SP
 - a. Randomized Controlled Trial (RCT) comparing 2 vs 3 or more doses of IPTp-SP
 - b. Seven trials, six contribute to analysis
 - c. Meta-analysis ongoing (for 1 trial analysis of original data is still ongoing)
 - d. Reporting timeline
 - i. May 2012: Draft completed
 - ii. July 2012: Submit for publication
 - e. Contact Person: Kassoum Kayentao (Malaria Research and Training Centre, Bamako) and Feiko ter Kuile (Liverpool School of Tropical Medicine and MIPc)
2. IPTp-Mon(itoring) study
 - a. Standardized prospective monitoring IPTp-SP effectiveness
 - b. Funding MIPc and US Centers for Disease Control (CDC)- Presidents Malaria Initiative (PMI)
 - c. 3 modules
 - i. In-vivo module
 - ii. Delivery module (different women from in-vivo module)
 - iii. Molecular module
 - d. 8 sites in 6 countries
 - i. Malawi (2x), Uganda, Kenya, Zambia, Mali, Burkina Faso.
 - ii. There is also data from Ghana on the in-vivo module
 - e. Potential limitation identified at ASTMH: All sites are at the extreme ends of the spectrum of resistance; either >80% or 0-5% DHPS 540
 - f. Reporting timeline
 - i. May and Oct 2012: Research groups provide reports of individual studies
 - ii. Oct 2012: Advanced draft of Individual patient data meta-analysis
 - iii. Nov 2012: submit for publication
 - g. Contact Person: Meghna Desai (CDC-KEMRI, Kisumu, Kenya) and Feiko ter Kuile
3. IPTp-AMA (aggregate meta-analysis)
 - a. Historical data; meta-analysis of all published data of IPTp effectiveness
 - i. Older observational studies (1995-2011) reporting prevalence of placental /maternal malaria as a function of the number of doses received
 - b. Reporting Timeline
 - i. Oct 2012: Advanced draft of Individual patient data meta-analysis
 - ii. Nov 2012: submit for publication
 - c. Contact Person: Feiko ter Kuile
4. Historical comparisons from single sites
 - a. (e.g. 12 years' experience in Malawi)
 - b. Reporting Timeline

- i. Oct 2012: submit for publication
- c. Contact Person: Linda Kalilani (College of Medicine, Blantyre, Malawi) and Feiko ter Kuile

IPTp mefloquine comparative studies

A multicenter open-label trial in Benin (from 2005 to 2008)⁴ compared IPTp with SP or 15 mg/kg mefloquine (MQ) in a single intake twice during pregnancy, showing that MQ was more efficacious in preventing placental malaria, clinical malaria and maternal anemia at delivery. Adverse events (mainly vomiting, dizziness, tiredness, and nausea) were more commonly associated with MQ, potentially impairing mefloquine effectiveness for large-scale use.

A multi-center mefloquine versus SP comparative IPTp trial coordinated by CRESIB is being conducted in Africa, expected for completion in January 2013 (Contact Person: Clara Menendez, Barcelona Centre for International Health Research (CRESIB)). In addition to compare the safety, tolerability and efficacy of mefloquine to SP as IPTp for the prevention of malaria in pregnancy for the mother and her infant, the study design includes a comparative arm to determine the safety and efficacy of IPTp with mefloquine among HIV infected women receiving CTX prophylaxis for opportunistic infections.

Review of safety of mefloquine in pregnancy by US-FDA

The US-FDA recent review of the safety of mefloquine in pregnancy has led to the re-categorization of this medicine from a pregnancy category C drug to category B, based on their review of the published data on mefloquine use during pregnancy. The US-FDA review concluded that pregnant women who took mefloquine at various doses for both prevention and treatment of malaria did not have an increased risk of teratogenic effects (birth defects) or adverse pregnancy outcomes compared to the background rate in the general population (http://www.cdc.gov/malaria/new_info/2011/mefloquine_pregnancy.html).

⁴ Briand V *et al.* (2009). Intermittent treatment for the prevention of malaria during pregnancy in Benin: a randomized, open-label equivalence trial comparing sulfadoxine-pyrimethamine with mefloquine. *J Infect Dis.* 200: 991-1001.