Proposal for a second meeting of the WHO Evidence Review Group on Intermittent Preventive Treatment of malaria in pregnancy (IPTp) to be held on 9-11 July 2013, Geneva, WHO

Background

The Malaria Policy Advisory Committee has reviewed the policy on intermittent preventive treatment (IPTp) with sulfadoxine-pyrimethamine (SP) in September 2012. On this basis, WHO recommends that SP should be given for IPTp to all pregnant women at each scheduled antenatal care visit, starting as early as possible during the 2nd trimester of gestation. IPTp-SP is an integral part of WHO’s strategy for prevention and control of malaria in pregnancy, which also includes the use of insecticide-treated nets, prompt diagnostic testing and effective treatment.

The new recommendation is based on the assessment by the Evidence Review Group in July 2012 of more recently available data,†, including a meta-analysis of 7 trials on IPTp-SP, which showed that 3 or more doses of SP for IPTp were associated with a 20% reduction in low birth weight (LBW) compared to 2 doses of SP. The effect was consistent across a wide range of SP resistance levels, and there were no differences in serious adverse events between the two groups‡.

In October 2012, WHO published the new recommendations on IPTp-SP,* and urged national health authorities to disseminate this update widely and ensure its correct application. Based on initial feedback from representatives of national programmes and several implementing partners, the Global Malaria Programme (GMP) and Reproductive Health and Research (RHR) Programme of WHO have also developed a policy briefing paper to offer additional background information, more explanations on operational aspects, a compilation of the scientific evidence, together with a set of frequently asked questions on the new IPTp-SP policy.

* [http://www.who.int/entity/malaria/iptp_sp_updated_policy_recommendation_en_102012.pdf](http://www.who.int/entity/malaria/iptp_sp_updated_policy_recommendation_en_102012.pdf)
Emerging new evidence

The Malaria in Pregnancy Consortium (MIPc) and the US President’s Malaria Initiative (Centers for Disease Control and Prevention (CDC) and USAID) are conducting a series of IPTp-SP effectiveness monitoring studies (known as the IPTp-Mon(itoring) study). These studies involve HIV negative pregnant women from 8 sites in 6 countries (Burkina Faso, Kenya, Malawi, Mali, Uganda and Zimbabwe). This research is evaluating the contribution of SP resistance to IPTp effectiveness, with specific attention to: 1) *in-vivo* clearance of peripheral parasitaemia in pregnant women, 2) impact on maternal and neonatal outcomes, e.g. birth weight, placental infection, clinical malaria, maternal anemia and fetal anemia, and 3) prevalence of molecular markers of SP resistance. A manuscript will be available for WHO to review in June 2013.

In addition, to assess the situation in countries of Central and Western Africa with medium-to-low levels of resistance to SP, a meta-analysis of IPTp effectiveness is being undertaken by MIPc of all published observational studies (1995-2013) reporting LBW as a function of the number of doses received; this will also include DHS data. The study, named IPTp-AMA (aggregate meta-analysis), is being finalised and the manuscript will also be available for WHO to review in June 2013.

Studies on the efficacy and safety of mefloquine for IPTp, in the context of Insecticide-Treated Nets (ITNs), named the MiPPAD study (Malaria in Pregnancy Preventive Alternative Drugs) will be also be completed by June 2013. The MiPPAD study, co-funded by the EDCTP and MIPc, involves two clinical trials: i) a randomized open-label superiority 3-arm trial to compare 2-dose mefloquine (MQ) versus 2-dose SP for IPTp in preventing adverse effects of malaria during pregnancy and to compare the tolerability of 2 different MQ administration regimens (MQ full dose versus 2 doses split over 2 days); and ii) a randomized, double-blind, superiority trial to compare the efficacy of 3- dose MQ as IPTp with that of placebo-IPTp in HIV-infected pregnant women receiving co-trimoxazole (CTX) prophylaxis. The first trial is being conducted in Benin, Gabon, Tanzania and Mozambique, and has enrolled 4750 pregnant women attending antenatal clinics (ANC). The primary endpoint is the proportion of infants born with low birth weight; the study includes infant follow-up for one year. The second trial is being conducted in Kenya, Tanzania and Mozambique, and has recruited 1071 pregnant women. The primary endpoint is the proportion of women at deliver with microscopic or submicroscopic parasitemia; infants are then followed-up for 2 months after delivery. For both studies, manuscripts will be available for WHO to review in June 2013.

In addition to the mefloquine safety data emerging from these two studies, WHO/GMP will seek access to the pregnancy registry on mefloquine of Hoffmann-La Roche (manufacturer of the Lariam brand of mefloquine) as well as to additional relevant safety data from research groups which have conducted trials on mefloquine use/exposures during pregnancy.

Based on the IPTp-Mon(itoring) study, and following the recommendations of the Evidence Review Group convened in 2012, a working group has been established to develop a simplified protocol template to monitor the impact of SP resistance on IPTp-SP effectiveness. The draft protocol will be finalized by May 2013 for review and finalization by the ERG meeting, which is being proposed for July 2013. In addition, a second working group has been established to develop a simplified protocol to monitor the programmatic determinants of IPTp-SP effectiveness. If work progresses well and the draft protocol is ready, it would be possible to also review and finalise this protocol at the ERG meeting in July 2013.
Objectives of the proposed IPTp ERG meeting

The specific objectives of the meeting of the Evidence Review Group will be to:

• Review the evidence regarding the contribution of SP resistance to IPTp effectiveness.
• Finalise the core protocol to monitor the impact of SP resistance on IPTp-SP effectiveness.
• Review evidence on efficacy and safety of mefloquine for IPTp compared to SP (for all women) and to daily co-trimoxazole prophylaxis (for HIV+ pregnant women).
• Develop draft policy recommendations on the contribution of SP resistance to IPTp effectiveness and monitoring methods, as well as on the efficacy and safety of mefloquine for IPTp for consideration by the MPAC in September 2013.

Interactions with the TEG of malaria chemotherapy

The recently published meta-analysis of 7 IPTp trials on 3+ doses of SP versus 2 doses, together with new evidence on the impact of SP resistance on IPTp effectiveness will be assessed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach. The new evidence from the randomized-controlled trials on efficacy and safety of mefloquine for IPTp compared to SP and to daily co-trimoxazole prophylaxis in HIV+ pregnant women will also be assessed using GRADE. Based on these assessments, new recommendations on SP and mefloquine for IPTp will be included in the 3rd edition of the WHO Guidelines for the Treatment of Malaria, that will be released in 2014.