

WHO Evidence Review Group on Intermittent Preventive Treatment (IPT) of malaria in pregnancy

WHO Headquarters, Geneva, 9-11 July 2013

Draft Recommendations on Intermittent Preventive Treatment in Pregnancy (IPTp)

The recommendations outlined below build on the WHO IPTp Policy (October 2012), and should be considered by countries with specific patterns of SP resistance, or a persistent reduction in malaria transmission and by those considering mefloquine as an alternative medicine for IPTp.

The ERG proposed the following recommendations for consideration by the MPAC:

Recommendation 1:

Consider discontinuing IPTp-SP when the population prevalence of Plasmodium falciparum (Pf) dhps mutation K540E is greater than 95%, AND the prevalence of mutation A581G is greater than 10%, as it is likely to be ineffective. In areas where IPTp-SP is discontinued because of resistance, ensure access of pregnant women to long-lasting insecticide treated nets and prompt diagnosis and effective treatment.

Key Background Points:

- The evidence reviewed indicated that IPTp-SP continues to be effective in areas of moderate SP resistance.
 - Marked regional differences in the prevalence of *P. falciparum* genotypes responsible for SP resistance have been documented, indicating that continued monitoring of resistance markers is needed, especially in East and Southern Africa where antifolate resistance in *P. falciparum* is highest. Monitoring of SP resistance should focus on the *P. falciparum dhps* A581G and K540E mutations; in West Africa the prevalence of *P. falciparum dhps* A437G should also be monitored, as its increasing prevalence has been associated with progressive reduction in IPTp-SP effectiveness.
 - Of note, two independent studies in areas with a high prevalence of *P. falciparum* strains carrying *dhps* A581G and K540E mutations have demonstrated loss of effectiveness of IPTp-SP, and shown an increased risk of LBW associated with IPTp-SP. These studies highlight the importance of continued monitoring of resistance along with maternal and neonatal outcomes.
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Recommendation 2:

Consider discontinuing IPTp-SP when malaria transmission has been very low (falciparum malaria population prevalence in children under 15 years of age is below 5%) for at least 3 years.

Key Background Points:

- A systematic review evaluated the use of parasite prevalence in children (as detected in population surveys) as a proxy measure of malaria transmission, in order to investigate the effect of the level of transmission on the ability of IPTp-SP to prevent LBW¹. The preliminary results suggest that IPTp-SP may no longer protect against LBW when the *falciparum* malaria prevalence in children below 15 years is below 7-8%.
- Effective malaria control activities (including effective vector control and prompt diagnosis and effective treatment of malaria) must be sustained to maintain low transmission intensity in areas where IPTp-SP is discontinued.
- Surveillance systems to monitor malaria transmission intensity will need to be reinforced and maintained if IPTp-SP is discontinued.

Recommendation 3:

Mefloquine, at a dose of 15 mg/kg, is not recommended for IPTp because of its low tolerability, with vomiting and dizziness reported in up to 30% of pregnant women studied.

Key Background Points:

- Two doses of IPTp-MQ decreased maternal clinical malaria, parasitaemia, and anemia at delivery, when compared to two doses of IPTp-SP in HIV-negative women resident in Benin, Gabon, Tanzania or Mozambique, but did not reduce the incidence of LBW. The ERG noted that the comparator, 2 doses of SP-IPTp, is no longer policy.
- In HIV-infected women taking cotrimoxazole prophylaxis, three doses of IPTp-MQ reduced maternal parasitaemia at delivery, and the incidence of both overall outpatient visits and hospital admissions compared to three doses of IPTp-placebo, in women resident in Kenya, Tanzania or Mozambique. However, no difference was found between groups in the risk of LBW, maternal anaemia or peripheral parasitaemia at delivery.
- The 15 mg/kg dose of MQ used in the reported controlled trials caused high rates of vomiting (24-30%) and dizziness (~18 - 30%). Therefore mefloquine is not recommended for IPTp at this dose due to its poor tolerability. Splitting the 15 mg/kg dose over two consecutive days did not improve tolerability.
- Based on current evidence, mefloquine is not associated with an increase in adverse pregnancy outcomes (stillbirths, miscarriages or congenital malformations) when used for prophylaxis, treatment or IPTp.
- It may be difficult to screen women in most antenatal clinic settings for conditions such as a history of epilepsy or psychiatric problems, conditions which predispose to the rare but sometimes severe neuropsychiatric side effects of MQ.
- Continued pharmacovigilance is required when mefloquine is used for prophylaxis or treatment of malaria in pregnancy, including surveillance for neurological adverse events.

¹ Chico *et al.* Malaria transmission intensity and the protective effect of intermittent preventive therapy using sulphadoxine-pyrimethamine. Unpublished.

Meeting Report

Background

In October 2012, the World Health Organization (WHO) Malaria Policy Advisory Committee (MPAC) updated the malaria in pregnancy (MIP) policy for intermittent preventive treatment during pregnancy with sulfadoxine-pyrimethamine (IPTp-SP). The updated policy recommends that women who live in moderate to high malaria transmission areas should receive IPTp-SP as early as possible in the second trimester and at every scheduled antenatal (ANC) visit thereafter, provided that these are at least one month apart [1].

Since the updated IPTp policy was released, multiple countries throughout sub-Saharan Africa have reviewed the new policy and plan to update their country policies and start programme implementation. The WHO Evidence Review Group (ERG) for IPTp recognizes the commitment from countries to ensure that all pregnant women receive optimal care throughout pregnancy, including access to IPTp-SP.

As a further step in the policy making process to prevent the adverse consequences of MIP, and to assess possible new drugs for use with IPTp, the WHO Global Malaria Programme (GMP) convened an Evidence Review Group (ERG) on July 9th -11th, 2013 to review the latest evidence on the effectiveness of IPTp-SP in relation to *Plasmodium falciparum* antifolate resistance and decreasing malaria transmission. The ERG also reviewed the results of recently completed multicentre clinical trials that evaluated the efficacy and safety of mefloquine as IPTp (IPTp-MQ).

Objectives

The specific objectives of the consultation were:

1. To review the evidence on the impact of SP resistance on IPTp-SP effectiveness.
2. To review analyses of the impact of a persistent reduction in malaria transmission on IPTp effectiveness.
3. To review evidence on the efficacy and safety of MQ for IPTp, when:
 - compared to SP in HIV negative pregnant women; and
 - the benefit of three doses of IPTp-MQ added to daily co-trimoxazole (CTX) prophylaxis in HIV-infected pregnant women.
4. To finalize the core protocol for monitoring the impact of SP resistance on IPTp-SP effectiveness.

Evidence reviewed

A series of 9 published articles which evaluated IPTp-SP effectiveness and SP drug resistance patterns, as well as safety, in Tanzania, Mozambique and Malawi were selected as meeting pre-reads. A total of eight unpublished manuscripts and one abstract which reported on IPTp-SP effectiveness and safety and acceptability were presented and discussed during the meeting.

Regarding IPT-MQ efficacy and safety, published and unpublished study reports from two randomized controlled trials RCTs conducted in Benin, and two multi-centre trials (MiPPAD² trials) recently completed in five sub-Saharan countries (Benin, Gabon, Mozambique, Tanzania, Kenya) were

² MiPPAD: Malaria in Pregnancy Preventive Alternative Drugs

reviewed. The ERG also reviewed results from a pharmacokinetic study in Gabon and an economic evaluation of IPTp-MQ. In addition, a comprehensive literature review of all published studies on the safety of MQ in pregnant women when used for treatment or prevention (IPTp and chemoprophylaxis) was prepared as a pre-read for the meeting.

Finally, two draft protocols prepared by *ad-hoc* working groups were provided as pre-reads and presented at the meeting. These were:

- A protocol for assessing the programmatic effectiveness of antenatal clinics in delivering intermittent preventive treatment and long lasting insecticide treated nets.
- A protocol for monitoring the impact of SP resistance on IPTp-SP effectiveness.

Lists of the pre-reads for the meeting and of the principal studies reviewed are presented in Tables 1 and 2 in Annex 1.

A Summary of the IPTp -SP discussions

1. SP resistance and IPTp effectiveness

A series of recently completed studies (see tables 1 and 2 of Annex 1) have shown that IPTp-SP is still effective at reducing low birth weight (LBW) in areas of low and moderate SP resistance (including those with >95% prevalence of *dhps* K540E mutation)^{3,4}.

A retrospective cross sectional study conducted in 104 women resident in an area of Tanzania where the prevalence of *P. falciparum* parasites carrying the resistance allele at *dhps* codon 581 was high [2], found an increased density of placental parasitaemia and increased placental inflammation in women who reported IPTp use. These results were not confirmed in a larger study conducted in Malawi where the mutation at codon 581 has also been detected [3]. An independent, second study conducted in Tanzanian women found that babies born to pregnant women infected with *P. falciparum* parasites carrying the sextuple haplotype (triple *Pf dhfr* and triple *Pf dhps*, including the resistance allele at *dhps* codon 581) had a significantly lower mean birth weight (359 g) than those infected with parasites not carrying this mutation [4]. In the latter study IPTp with SP was not associated with an increased risk of LBW.

Recent analysis of *P. falciparum* genotypes of samples collected from Malawian women at delivery showed that the presence of both *dhps* A581G and *dhps* K540E mutations was associated with increased maternal peripheral parasite densities at delivery⁵. However, a study conducted in the same area during the same time period found that IPTp-SP still improved birth outcomes [5].

A meta-analysis that has evaluated the population prevalence of resistance mutations has shown that IPTp-SP effectiveness decreased with increasing population prevalence of the *dhps* A437G mutation in West Africa, and with that of the *dhps* K540E mutation in East and Southern Africa. Therefore,

³ Desai *et al.* Intermittent preventive treatment with sulfadoxine-pyrimethamine for the control of malaria in pregnancy. Unpublished.

⁴ ter Kuile *et al.* Impact of sulphadoxine-pyrimethamine resistance on the effectiveness of intermittent preventive therapy for malaria in pregnancy (IPTp) in Africa: a systematic review and meta-analysis. Unpublished.

⁵ Gutman *et al.* *Plasmodium falciparum dhps*-A581G mutation reduces the effectiveness of sulfadoxine-pyrimethamine intermittent preventive therapy in Malawian pregnant women. Unpublished.

monitoring of SP resistance should include *P. falciparum dhps* A581G, A437G and K540E mutation markers.

Further priority research on SP resistance and IPTp should include the following:

- Genome sequencing of *P. falciparum* parasites carrying the A581G mutation, especially those prevalent in the areas of Tanzania where adverse effects of IPTp-SP in women carrying the A518G mutation have been reported.
- The effect of cotrimoxazole prophylaxis on the prevalence of SP-resistance markers.
- Randomized placebo-controlled trials evaluating IPTp-SP efficacy in regions with high SP resistance, to assess protective efficacy and to inform decisions on the level of SP resistance at which IPTp-SP should be discontinued.

2. *Malaria transmission intensity and IPTp*

A systematic review analysed the use of parasite prevalence in children (detected in population surveys) as a proxy measure of malaria transmission, in order to investigate the effect of the level of transmission on the ability of IPTp-SP to prevent LBW⁶. The preliminary results suggest that IPTp protection against LBW may no longer be conferred when the *falciparum* malaria prevalence in children under 15 years of age is below 7-8%.

The ERG reached consensus that:

- IPTp-SP should be continued in all areas where SP is still effective and where the prevalence of falciparum malaria is $\geq 5\%$ (as measured in population surveys in children under 15 years of age).
- In areas where the prevalence of falciparum malaria in children remains below 5% for at least 3 years, discontinuing IPTp with SP could be considered.
- Effective malaria control activities (including vector control and or prompt diagnosis and effective malaria treatment) must be sustained in order to maintain low transmission intensity in the areas where IPTp is discontinued.
- Surveillance systems to monitor changes in malaria transmission intensity will need to be reinforced and maintained if IPTp-SP is discontinued.

Further research is needed on:

- Risk-benefit and cost-effectiveness analyses to define further the threshold of malaria transmission at which IPTp-SP can be discontinued.
- Development of alternative strategies to prevent, identify and treat malaria in pregnant women in very low transmission areas.
- Development of standardized methods to assess parasite prevalence in pregnant women attending antenatal clinics.

3. *Use of mefloquine (MQ) as IPTp*

A recently completed multicentre RCT in 4749 HIV-negative pregnant in four sub-Saharan countries, found that two doses of IPTp-MQ (15 mg/kg) significantly reduced the incidence of maternal clinical malaria, anaemia and peripheral parasitaemia at delivery when compared to two doses of SP⁷. The study also evaluated also the efficacy and safety of split versus single dose of MQ for IPTp. However,

⁶ Chico *et al.* Malaria transmission intensity and the protective effect of intermittent preventive therapy using sulphadoxine-pyrimethamine. Unpublished.

⁷ Menéndez *et al.* Safety and Efficacy of mefloquine as intermittent preventive treatment for malaria in pregnancy: a multicenter trial in HIV-negative women. Unpublished.

no difference was found in the risk of LBW between the MQ and SP groups. The ERG noted that the comparator, 2 doses of SP-IPTp, which was standard of care when the trials were initiated, is no longer considered effective. The frequency of adverse events (mainly dizziness and vomiting) was significantly higher in the MQ than the SP group and was not reduced substantially when the dose was split over two days. No differences were found in adverse pregnancy outcomes (stillbirths, miscarriages and congenital malformations) between women exposed to MQ and those exposed to SP.

A previous RCT, which had enrolled 1601 women from Benin, found that MQ (15 mg/kg) was more efficacious than SP in preventing placental malaria, clinical malaria and maternal anemia at delivery, but also documented the poor tolerability of MQ [6].

In another double-blind RCT conducted in 1071 HIV-infected women on co-trimoxazole prophylaxis, three doses of IPTp-MQ (15 mg/kg) significantly reduced maternal peripheral parasitemia, the incidence of all-cause outpatient visits and all-cause hospital admissions. The frequency of adverse events was significantly higher in women in the MQ compared to the placebo group. However, no difference was found between groups in the risk of LBW, or maternal anaemia and peripheral parasitaemia at delivery.

Cost-effectiveness analysis of MQ when used for IPTp indicates that in HIV-negative women, the price of MQ per tablet should not be higher than 0.54 US\$ for IPTp-MQ to be a cost-effective strategy to reduce clinical malaria during pregnancy and anaemia at delivery⁸. The current average international price is about 1 US\$ per tablet.

The 15 mg/kg dose of MQ used in the reported controlled trials caused high rates of vomiting (24-30%) and dizziness (~18 - 30%). Therefore mefloquine is not recommended for IPTp at this dose due to its poor tolerability. Splitting the dose over two consecutive days did not reduce the poor tolerability of IPTp-MQ.

It may be difficult to screen women in most antenatal clinic settings for conditions such as a history of epilepsy or psychiatric problems, conditions which predispose to the rare but sometimes severe neuropsychiatric side effects of MQ. A further possible risk is that mefloquine could lower the seizure threshold in women with pre-eclampsia.

Further research on MQ could potentially include:

- Evaluation of different MQ dosage regimens, combined with pharmacokinetic studies, to determine if it is possible to improve the tolerability of MQ in pregnant women whilst retaining its efficacy for intermittent preventive treatment.
- Exploration of the concomitant use of anti-emetics to improve the tolerability of MQ.
- Evaluation of MQ interactions with HIV antiretroviral drugs (ARVs).

⁸ Sicuri *et al.* Economic evaluation of mefloquine as IPTp in the context of ITNs in African pregnant women. Unpublished.

Annex 1. List of the pre-read meeting documentation and principal studies reviewed

Table 1. Published articles reviewed

Publications	Country/ies	Study description
Briand <i>et al</i> , 2009 [6]	Benin	First RCT, open-label, comparing the efficacy and safety of two dose- MQ as IPTp with SP.
Harrington <i>et al</i> , 2009 [2]	Tanzania	Molecular analysis of resistant parasites from samples of women who had delivered and its association with reported IPTp use.
Harrington <i>et al</i> , 2011[10]	Tanzania	Cross-sectional study evaluating the reported use of IPTp and its effects on maternal and fetal outcomes.
Menéndez <i>et al</i> , 2011[11]	Mozambique	Molecular analysis of samples from women in a RCT of IPTp SP vs placebo,evaluating the impact of IPTp and HIV on molecular markers of SP resistance and its clinical relevance.
Taylor <i>et al</i> , 2012[3]	Malawi	Serial cross sectional analysis of the relationship between IPTp-SP, SP resistant <i>P falciparum</i> and pregnancy associated malaria during a period of nine years.
Eisele <i>et al</i> , 2012 [12]	Datasets from 25 African countries	Retrospective data analysis of national cross-sectional datasets assessing the effectiveness of IPTp and ITNs at preventing LBW and neonatal mortality under routine programme conditions.
Harrington <i>et al</i> , 2013 [13]	Tanzania	Cross-sectional study evaluating the reported use of IPTp and its effects on the risk of parasitaemia and severe malaria in the offspring.
Gutman <i>et al</i> , 2013 [5]	Malawi	Cross sectional delivery survey that analysed IPTp-SP effectiveness on maternal and infants outcomes.
Minja <i>et al</i> , 2013 [4]	Tanzania	Prospective cohort study analyzing the effect of infecting <i>P falciparum</i> haplotypes on birthweight.

RCT: Randomised Controlled Trial; ITN: Insecticide treated nets; LBW: Low Birth weight

Table 2. Unpublished Manuscripts reviewed

Manuscripts	Country/ies	Study description
Arinaitwe <i>et al.</i> ⁹	Uganda	Cross-sectional study in women at delivery assessing the association between SP use in pregnancy and the risk of adverse pregnancy outcomes.
Boene <i>et al.</i> ¹⁰	Mozambique	Qualitative analysis through in-depth interviews describing the perceptions and behaviors of pregnant women in relation to malaria and the currently recommended control interventions.
Chico <i>et al.</i> ¹¹	Studies from 12 sub-Saharan countries	Systematic review of published articles that analyzes parasite prevalence in children as a proxy measure to investigate the effect of the level of malaria transmission on the ability of IPTp-SP to prevent LBW.
Denoeud-Ndam <i>et al.</i> ¹²	Benin	RCT open label, evaluating the efficacy and safety of 3 dose of IPTp-MQ in HIV-infected women receiving cotrimoxazole prophylaxis.
Desai <i>et al.</i> ¹³	Burkina Faso, Kenya, Malawi, Mali, Uganda and Zambia	<i>In-vivo</i> efficacy study of IPTp-SP and analysis of IPTp-SP effect on pregnancy outcomes.
Eisele <i>et al.</i> ¹⁴	Datasets from 25 African countries	Retrospective data analysis of national cross-sectional datasets assessing the relationship between IPTp and LBW across malaria parasite prevalence levels.
González R. ¹⁵	Thailand, Nigeria, Sudan, Malawi, Somalia and Benin	Systematic literature review of published articles on safety of MQ used in pregnant women for malaria treatment and prevention.
Gutman <i>et al.</i> ¹⁶	Malawi	Cross-sectional study that analyzes <i>P falciparum</i> genotypes of samples collected from women at delivery and their relation with parasitological and pregnancy outcomes.
Menéndez <i>et al.</i> ¹⁷	Benin, Gabon, Mozambique and Tanzania	Multicenter RCT open-label, comparing the efficacy and safety of 2 dose IPTp-MQ with IPTp-SP in HIV-negative women (MiPPAD trial 1).

⁹ Arinaitwe *et al.* Intermittent preventive therapy with sulfadoxine-pyrimethamine for malaria in pregnancy: a cross-sectional study from Tororo, Uganda. Unpublished.

¹⁰ Boene *et al.* Perceptions of malaria during pregnancy and acceptability of preventive tools among Mozambican pregnant women: implications for effectiveness of malaria control in pregnancy. Unpublished

¹¹ Chico *et al.* Malaria transmission intensity and the protective effect of intermittent preventive therapy using sulphadoxine-pyrimethamine. Unpublished.

¹² Denoeud-Ndam *et al.* Cotrimoxazole prophylaxis versus mefloquine IPT to prevent malaria in HIV-infected pregnant women: two randomized controlled trials. Unpublished.

¹³ Desai *et al.* Intermittent preventive treatment with sulfadoxine-pyrimethamine for the control of malaria in pregnancy. Unpublished.

¹⁴ Eisele *et al.* Assessing the effect modification of *Plasmodium falciparum* transmission on association between IPTp with SP and low birthweight: evidence from national cross-sectional datasets. Unpublished (only abstract available).

¹⁵ González R. Literature review on mefloquine safety in pregnancy. Unpublished.

¹⁶ Gutman *et al.* *Plasmodium falciparum dhps-A581G* mutation reduces the effectiveness of sulfadoxine-pyrimethamine intermittent preventive therapy in Malawian pregnant women. Unpublished.

¹⁷ Menéndez C. on behalf of the MiPPAD study group. Safety and efficacy of mefloquine as intermittent preventive treatment for malaria in pregnancy: a multicenter trial in HIV-negative women. Unpublished.

Table 2. Unpublished Manuscripts reviewed (continued)

Manuscripts	Country/ies	Study description
Menéndez <i>et al.</i> ¹⁸	Kenya, Mozambique and Tanzania	Multicenter RCT double-blind, comparing the efficacy and safety of three dose IPTp-MQ with IPTp-placebo in HIV-infected women receiving cotrimoxazole prophylaxis (MiPPAD trial 2).
Munguambe <i>et al.</i> ¹⁹	Mozambique	Qualitative analysis of the acceptability of alternative drugs to SP for IPTp by pregnant women and healthcare providers.
Naidoo <i>et al.</i> ²⁰	Data from 37 African countries	Literature review and map of the prevalence of Pf <i>dhfr</i> and Pf <i>dhps</i> mutations
Oumar <i>et al.</i> ²¹	Burkina Faso and Mali	<i>In-vivo</i> efficacy study of IPTp-SP.
Radeva-Petrova <i>et al.</i> ²²	Thailand and 13 sub-Saharan countries	Meta-analysis of randomized and quasi-randomized controlled trials assessing the effects of malaria prevention in pregnant women.
Ramharter <i>et al.</i> ²³	Gabon	Rich pharmacokinetic analysis of MQ from women who received two doses of IPTp-MQ (within MiPPAD trial 1).
Sicuri <i>et al.</i> ²⁴	Benin, Gabon, Kenya, Mozambique and Tanzania	Economic evaluation of MQ as IPTp, compared with IPTp-SP (MiPPAD trial 1) and with IPTp-placebo (MiPPAD trial 2).
Taylor S. <i>et al.</i> ²⁵	Tanzania	Design and validation of a second-generation sequencing (SGS) protocol to quantify mutant allele in the <i>P. falciparum</i> genes in mixed isolates from Tanzanian children.
Ter Kuile <i>et al.</i> ²⁶	Studies from 15 African countries	Meta-analysis evaluating the relationship between the population prevalence of resistance mutations in the parasite genes Pf <i>dhfr</i> and Pf <i>dhps</i> , IPTp use and LBW.

¹⁸ Menéndez C. on behalf of the MiPPAD study group. Mefloquine as Intermittent Preventive Treatment for malaria in pregnancy in HIV-infected women receiving cotrimoxazole prophylaxis: a multicenter randomized double blind placebo-controlled trial. Unpublished.

¹⁹ Munguambe *et al.* Perceptions and acceptability of Mefloquine as an alternative to sulphadoxine-pyrimethamine as IPT against malaria during pregnancy in Mozambique. Unpublished.

²⁰ Naidoo *et al.* Mapping “partially-resistant”, “fully-resistant” and “super-resistant” malaria for intermittent preventive treatment with Sulphadoxine-Pyrimethamine. Unpublished.

²¹ Oumar *et al.* Parasite clearance following treatment with sulfadoxine-pyrimethamine for Intermittent Preventive Treatment in Burkina-Faso and Mali: 42-day in-vivo follow-up study.

²² Radeva-Petrova *et al.* Drugs for preventing malaria in pregnant women. Cochrane Database of Systematic Reviews 2013. Unpublished.

²³ Ramharter M. on behalf of the MiPPAD study group. Pharmacokinetics of mefloquine as IPTp in HIV-negative African pregnant women. Unpublished.

²⁴ Sicuri *et al.* Economic evaluation of Mefloquine as IPTp in the context of ITNs in African pregnant women. Unpublished.

²⁵ Taylor *et al.* Pooled deep sequencing of *Plasmodium falciparum* isolates: an efficient and scalable tool to quantify prevailing malaria drug-resistance genotypes. Unpublished.

²⁶ ter Kuile *et al.* Impact of sulphadoxine-pyrimethamine resistance on the effectiveness of Intermittent Preventive Therapy for malaria in pregnancy (IPTp) in Africa: a systematic review and meta-analysis. Unpublished.

**Annex 2: Answers to key questions posed to ERG members
(participants were divided in three working groups addressing the same list questions)**

The ERG addressed the following key questions and made the aforementioned recommendations.

1. *Is mefloquine exposure during pregnancy for chemoprophylaxis, treatment or intermittent preventive treatment (IPTp), associated with an increased risk of teratogenicity, abortion or stillbirth, when compared to pregnant women not exposed to this medicine?*
 - The available evidence reviewed does not show an increased risk of teratogenicity, miscarriages or stillbirths in women exposed to MQ.
 - Limited data are available on first trimester exposure and continued pharmacovigilance of the safety of exposure to MQ during pregnancy is advised.
 - There are few studies on the use of MQ for malaria treatment in African pregnant women.

2. *What are the adverse drug reactions attributed to mefloquine exposure during pregnancy (when used for chemoprophylaxis, treatment or IPT) and what is their frequency, when compared to pregnant women not exposed to this medicine?*
 - The most frequent adverse drug reactions related to MQ use in pregnancy are transient dizziness, vomiting, nausea and weakness.
 - The frequency of adverse drug reactions depends on the MQ dose administered and the indication for use:
 - MQ for treatment of malaria in pregnancy (25 mg/kg):
dizziness (36%) and anorexia (23%) [7]
 - MQ for chemoprophylaxis (250 mg/week):
a limited number of studies have given inconclusive results on the incidence of adverse events frequencies following use of MQ for chemoprophylaxis [8,9]
 - MQ as IPTp (15 mg/kg):
mild and transient vomiting ($\approx 30\%$ in MQ recipients *versus* $\approx 7\%$ in SP recipients⁷) and dizziness ($\approx 30\%$ in MQ recipients *versus* $\approx 7\%$ in SP recipients⁷)
 - The frequency of adverse drug reactions decreases with subsequent doses of MQ (when used for chemoprophylaxis, as well as for IPTp [6,9]).

3. *Which specific mefloquine adverse drug reactions (if any) are considered significant enough (based on severity and frequency) to prevent the use of MQ for IPTp?*
 - Vomiting, nausea and dizziness would limit the use of MQ as IPTp since they may reduce adherence to further MQ doses, and could reduce drug absorption and thus efficacy.

4. *Are there other issues related to mefloquine use and adverse events that should be considered in formulating a recommendation on IPTp and MQ?*
 - Screening for contraindications to use of MQ such as a known history of neuropsychiatric problems or epilepsy is probably not feasible in most ANC settings.
 - Directly observed therapy (DOT) to ensure IPTp compliance is particularly important for poorly tolerated drugs.
 - MQ is associated with rare serious neuropsychiatric adverse events (although not observed in the recently completed multicenter RCT involving more than 3700 recipients of MQ^{7,27}). A further risk could be that mefloquine could lower the seizure threshold in women with pre-eclampsia.

²⁷ Menéndez *et al.* Mefloquine as intermittent preventive treatment for malaria in pregnancy in HIV-infected women receiving cotrimoxazole prophylaxis: a multicenter randomized double blind placebo-controlled trial. Unpublished.

- Cost-benefit analysis of the use of new regimens of MQ as IPTp is needed for areas with very high SP resistance.
5. *To prevent the consequences of malaria in pregnancy in HIV-negative pregnant women what is the efficacy of two doses of IPTp with MQ compared with two or more doses of sulfadoxine-pyrimethamine (SP)?*
- Two doses of IPTp with MQ reduced significantly the incidence of maternal clinical malaria, peripheral parasitaemia and placental malaria at delivery compared with two doses of IPTp-SP in HIV-negative pregnant women in one trial in Benin [6]. The ERG noted that the comparator, 2 doses of SP-IPTp, is no longer considered effective.
 - No significant differences were seen between MQ and SP groups in the rates of LBW and adverse pregnancy outcomes (stillbirths, miscarriages and congenital malformations).
6. *In HIV-negative women, based on the frequency and severity of adverse events, are there data to recommend that MQ (15 mg/kg) be given as a split dose over two days rather than as a single dose?*
- Splitting the MQ dose (15 mg/kg) over two days did not reduce the overall frequency of related adverse events.
 - In addition, if the IPTp drug cannot be administered as a single intake it may also be compromised by challenges in adherence, logistics and costs.
 - Based on the similar tolerability and PK profile of the split *versus* single dose, a split dose of IPTp-MQ dose is also not recommended.
7. *In HIV-negative pregnant women, what is the overall frequency of adverse events when two doses of IPTp with MQ are given as split doses over two days, or as single dose, compared with the frequency of adverse events in women receiving two or more doses of SP for IPTp?*
- Women who received MQ (15 mg/kg) as IPTp split dose over two days had comparable frequencies of adverse events to women who received IPTp-MQ as a full dose in one day ($\approx 30\%$ dizziness and $\approx 30\%$ vomiting)
8. *To prevent the consequences of malaria in pregnancy in HIV-positive pregnant women receiving daily cotrimoxazole prophylaxis, what is the efficacy of adding three doses of IPTp-MQ to CTX, when compared to control group receiving the IPTp-placebo plus CTX?*
- Three doses of IPTp-MQ reduced significantly the incidence of maternal peripheral parasitemia at delivery and placental malaria (only in the Beninese trial²⁸) at delivery, when compared with IPTp-placebo in HIV-infected women receiving CTX.
 - The incidence of all-cause outpatient visits and of all-cause hospital admissions was also significantly reduced in HIV-infected women who received three doses of IPTp-MQ (compared to those receiving placebo).
 - No differences were found between groups in rates of maternal and foetal anaemia, LBW and adverse pregnancy outcomes.
9. *In HIV-positive pregnant women what is the frequency of adverse events of three doses of IPTp-MQ given in addition to daily co-trimoxazole (CTX) prophylaxis compared to the placebo-control group (receiving CTX alone)?*
- The frequency of vomiting ($\approx 24\%$) and dizziness ($\approx 18\%$) was significantly higher in women receiving MQ than in those receiving placebo.

²⁸ Denoed-Ndam *et al.* Cotrimoxazole prophylaxis versus mefloquine IPT to prevent malaria in HIV-infected pregnant women: two randomized controlled trials. Unpublished.

- These frequencies were reduced following subsequent IPTp doses of MQ but still remained higher than in the placebo group.
10. To prevent the consequences of malaria in pregnancy, which patterns and frequency of molecular markers of SP resistance are consistently associated with evidence of no impact of IPTp with SP (given at two or more doses) compared to places with persistent evidence of IPTp-SP impact?
- The presence of both *P. falciparum dhps* A581G and *dhps* K540E mutations has been found to be associated with increased parasite densities in Malawian women at delivery, suggesting reduced IPTp effectiveness²⁹.
 - Available evidence indicates that IPTp-SP effectiveness is compromised if A581G mutation is prevalent at >10% in addition to a prevalence >95% of the K540E mutation.
 - Further studies are needed to establish a *dhps* A581G mutation prevalence threshold between 1% and 10% above which IPTp-SP is no longer effective and should be discontinued.
 - IPTp with SP is still effective in reducing LBW rates in areas of low and moderate SP resistance (even in areas with >95% prevalence of *dhps* K540E)^{30, 31}.
11. In countries/places where malaria transmission has been substantially reduced following successful malaria control, at what level of malaria transmission does IPTp-SP no longer have a significant impact in preventing the consequences of malaria in pregnancy, and should therefore no longer be recommended?
- Limited data suggest that IPTp-SP could be discontinued at a level of sustained *falciparum* malaria prevalence ≤5% in children below 15 years of age.
 - Malaria prevalence in children detected in population surveys remains below 5% for at least 3 years before considering discontinuation of IPTp-SP.
 - Surveillance systems to monitor changes in malaria transmission intensity will need to be reinforced and maintained if IPTp-SP is discontinued.
12. Discuss the protocol for monitoring the programmatic determinants of IPTp effectiveness, and provide specific suggestions for its finalization.

In view of the limited time available and the importance of addressing the above listed questions it was not possible to discuss in detail the protocol for monitoring the programmatic determinants of IPTp effectiveness. The protocol will, therefore, be finalized by inputs via email before proceeding to its field testing in multiple sites.

²⁹ Gutman *et al.* *Plasmodium falciparum dhps*-A581G mutation reduces the effectiveness of sulfadoxine-pyrimethamine intermittent preventive therapy in Malawian pregnant women. Unpublished.

³⁰ Desai *et al.* Intermittent preventive treatment with sulfadoxine-pyrimethamine for the control of malaria in pregnancy. Unpublished.

³¹ ter Kuile *et al.* Impact of sulphadoxine-pyrimethamine resistance on the effectiveness of intermittent preventive therapy for malaria in pregnancy (IPTp) in Africa: a systematic review and meta-analysis. Unpublished.

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