

**WHO Evidence Review Group:  
Intermittent Preventive Treatment of malaria in pregnancy (IPTp) with  
Sulfadoxine-Pyrimethamine (SP)**

***WHO Headquarters, Geneva, 9-11 July 2012***

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## Meeting Report

### 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 transmission of *Plasmodium falciparum*, which includes the use of insecticide treated nets (ITNs), the administration during pregnancy of at least 2 doses of intermittent preventive treatment (IPTp) with sulfadoxine-pyrimethamine (SP) after quickening and effective case management of malaria<sup>1</sup>.

Preliminary data from recent observational studies have suggested reduced effectiveness of SP for IPTp in Malawi, the first country where IPTp-SP was implemented in 1993<sup>2</sup>. In addition, there is growing concern over the decreasing effectiveness of the 2-dose regimen of SP for IPTp in other countries with a high level of resistance to SP, especially in Eastern and Southern Africa, regions that also carry the highest incidence of HIV in the world<sup>3</sup>. Even in the absence of resistance to SP, HIV positive women require more doses of SP to achieve effective protection against malaria in pregnancy than women who are HIV negative<sup>4</sup>.

In order to review the WHO policy on IPTp with SP, the Global Malaria Programme (GMP), as part of its new policy making process, convened an Evidence Review Group (ERG) to review evidence from published literature and unpublished studies on the current efficacy and effectiveness of IPTp with SP<sup>5</sup>. The aim of the ERG was to formulate recommendations to the Malaria Policy Advisory Committee (MPAC) for an interim policy statement on IPTp with SP for dissemination to national health authorities of malaria endemic countries where IPTp is implemented.

### Objectives

The specific objectives of the meeting of the Evidence Review Group were to:

- Review new evidence emerging from published literature (since the last WHO recommendations on IPTp with SP were made in 2007<sup>6</sup>) as well as unpublished studies completed more recently.
- Develop draft responses to key questions identified by the WHO secretariat and the MPAC on IPTp with SP.
- Formulate recommendations for an interim policy statement on IPTp with SP for dissemination to Ministries of Health (MoH) of countries where IPTp is implemented.

- Identify the critical gaps in knowledge and priority research agenda that need to be addressed in relation to IPTp with SP.

### **Evidence reviewed**

A series of published articles<sup>2,7-13</sup> describing studies which had evaluated the efficacy and effectiveness of IPTp with SP and patterns of SP drug resistance in Malawi, Mozambique and Tanzania were provided as meeting pre-reads. A recent overview paper on the coverage of IPTp and ITNs among pregnant women in 47 African countries was also included<sup>13</sup>.

An additional background paper for the ERG meeting reviewed studies published since 2007 on IPTp-SP efficacy and effectiveness in relation to the current WHO recommendations on IPTp with SP (González *et al*, unpublished<sup>\*</sup>).

Two unpublished studies were considered, one of which the ERG reviewed in detail. This was a meta-analysis of 7 trials which had compared 3 or more doses of IPTp-SP with the standard 2-dose regimen in preventing low birth weight (LBW) (Kayentao *et al*, unpublished<sup>†</sup>).

In addition, preliminary results of ongoing IPTp-SP effectiveness monitoring studies conducted in HIV negative pregnant women from Burkina Faso, Kenya, Malawi, Mali, Uganda and Zambia were presented and reviewed by the ERG.

The list of pre-reads for the meeting and of the principal studies reviewed is shown in Annex 1.

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<sup>\*</sup> González *et al*. Review on IPTp-SP efficacy, effectiveness and its effects on maternal and infant's health. Unpublished.

<sup>†</sup> Kayentao *et al*. Effect on low birth weight of monthly dosing versus the standard two- dose regimen of IPT with SP for the control of malaria in pregnancy in sub-Saharan Africa: a systematic review and meta-analysis of 5969 pregnancies in seven randomized trials. Unpublished

**Draft Interim Policy Statement on IPTp with SP  
(for dissemination to MoH of countries where IPTp is implemented)**

The ERG proposed the following Interim Policy Statement on intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP) for consideration by the Malaria Policy Advisory Committee (MPAC):

- IPTp with SP remains effective in preventing the adverse consequences of malaria on maternal and fetal outcomes in areas where a high proportion of *Plasmodium falciparum* parasites carry quintuple mutations associated with *in vivo* therapeutic failure to SP<sup>‡</sup>; therefore, IPTp with SP should still be administered to women in such areas.
- In areas of stable (moderate-to-high) malaria transmission, IPTp with SP is recommended for all pregnant women **at each scheduled antenatal care visit**. In particular:
  - The first IPTp-SP dose should be administered as early as possible during the 2<sup>nd</sup> trimester<sup>§</sup> of gestation
  - Each SP dose should be given at least 1 month apart from the other and up to the time of delivery
  - The last dose of IPTp with SP can be administered late (after 36 weeks) in the 3<sup>rd</sup> trimester of gestation without safety concerns
  - IPTp should be administered as directly observed therapy (DOT)
  - SP can be given on an empty stomach
  - Folic acid at a daily dose equal or above 5 mg should not be given concomitantly with SP as this counteracts its efficacy as an antimalarial
  - SP is contraindicated in women receiving cotrimoxazole prophylaxis
- Currently, there is no established threshold level of malaria transmission below which IPTp-SP is no longer cost-effective and should therefore be suspended\*\*.
- There is insufficient evidence to support a general recommendation for the use of IPTp-SP outside Africa.
- Monitoring of IPTp-SP effectiveness is essential and should continue. Research is ongoing to define the best methodology, and this will be shared when available.

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<sup>‡</sup> The findings of an observational study in Tanzanian women in an area where the parasite dhps resistance mutation of codon 581 was present showed increased placental parasite density and inflammatory changes in women reporting IPTp with SP use. This needs further investigation although it is important to note that this specific dhps resistance mutation is not common.

<sup>§</sup> IPTp administration should be avoided during the 1<sup>st</sup> trimester of gestation but should start as soon as possible in the 2<sup>nd</sup> trimester. The fact a woman has entered the second trimester can be determined by the onset of quickening or by measurement of fundal height by ANC health personnel.

\*\* Cost-effectiveness modelling studies are ongoing to address this question. Risk-benefit of SP administration needs also to be taken into account when considering recommendations on IPTp implementation.

## Summary of the discussions and main findings

The review of recent evidence suggests that in sub-Saharan Africa, in spite of the increased prevalence in *Plasmodium falciparum* of molecular markers associated with resistance to SP (based on quintuple mutant *dhps/dhfr* haplotypes prevalence), IPTp-SP remains effective at preventing peripheral parasitemia, maternal anemia, and clinical malaria during pregnancy and is associated with reduced neonatal mortality<sup>14-18</sup>.

An ongoing series of facility-based observational studies evaluating IPTp effectiveness in areas with high prevalence of molecular markers of SP resistance (quintuple mutations) in Kenya, Malawi and Zambia also indicate that IPTp remains safe, and is not associated with worse pregnancy outcomes. The data also suggest a generally beneficial dose dependent effect of SP on maternal and neonatal outcomes when administered on 1, 2 or 3 occasions. The limitations of these facility-based observational studies were acknowledged as women who receive fewer IPTp doses may also receive less antenatal care.

Overall, most studies suggested that IPTp with SP remains effective, or at least it is not associated with any harm, in areas with high prevalence of quintuple mutant *P. falciparum* parasites. The significance of the additional mutation at codon 581, which was particularly prevalent in the Tanzanian study, needs further investigation. This retrospective cross sectional study conducted among 104 women at delivery in an area of Tanzania where the fraction of parasites carrying the resistance allele at *dhps* codon 581 is relatively high (36%) found an increased placental parasite density and inflammatory changes in women who reported taking IPTp with SP<sup>8</sup>. However, these findings have not been confirmed in a larger study conducted in Malawi<sup>12</sup> or in a randomized controlled trial (RCT) comparing IPTp-SP with placebo in Mozambique, where the protective efficacy of IPTp-SP was shown and no association was found between infections with parasites carrying quintuple resistance markers and increased parasite density or malaria-related morbidity in mothers and children<sup>10</sup>. However, the mutation at codon 581 was only detected in low frequencies in samples from these two studies and, furthermore, it cannot be assumed that all parasites carrying the 581 mutation have the same genetic background and biological characteristics.

The number of IPTp doses that need to be administered during pregnancy to achieve the maximal beneficial effects of IPTp was examined in the unpublished meta-analysis by Kayentao *et al.* The meta-analysis, which included 7 controlled trials conducted in 5 sub-Saharan countries from 1994 to 2008, showed that 3 or more doses (median of 4 doses) of IPTp with SP was superior to the standard 2 dose regimen in preventing LBW rates (relative risk reduction of 21% [95% CI 8-32]) both in HIV infected and uninfected pregnant women and in all gravidity groups. Furthermore, women who received a median of 4 doses of IPTp-SP compared to those on the 2-dose regimen also had a lower risk of moderate-severe maternal anemia, maternal malaria at delivery, and placental malaria. The meta-analysis, which included two trials in areas of Burkina Faso and Mali where the efficacy of SP remains high, showed that even in areas of high SP efficacy, 3 doses of SP were more effective than 2 doses. Ongoing observational studies monitoring IPTp effectiveness in Burkina Faso and Mali also show that even in areas with low levels of SP resistance, there is a dose-dependent association with beneficial maternal and fetal outcomes.

The programmatic challenges of implementation of IPTp and achieving high coverage were also raised and discussed briefly. It is estimated that in 2007, 25% of pregnant women received at least 1 dose of IPTp<sup>13</sup>. The importance of providing IPTp under direct observation, as directly observed treatment, was stressed.

It was also suggested that WHO recommendations should state that all possible efforts should be made to avoid SP use as monotherapy for malaria treatment in order to protect its efficacy for IPTp.

The lack of studies on the cost-effectiveness of IPTp-SP in areas with low transmission was noted; cost-effectiveness analysis should be considered to guide health policies for such areas. IPTp-SP has recently been shown to be highly cost-effective for both prevention of maternal malaria and reduction of neonatal mortality in areas with moderate or high malaria transmission<sup>19</sup>. Studies on the cost-effectiveness analysis of 2 dose of IPTp-SP *versus* 3 or more doses are ongoing. The results of modeling cost-effectiveness and risk-benefit analysis could also inform decisions for consideration of suspension of IPTp-SP in areas where the malaria transmission intensity has been reduced to low levels over a sustained period of time.

## Recommendations

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

### 1. What are the key determinants and potential confounders of reduced effectiveness of IPTp with SP emerging from the recent trials?

The ERG identified the following key determinants and potential confounders of IPTp-SP effectiveness:

- Maternal:
  - i. Compliance with antenatal care (including number of ANC visits attended)
  - ii. HIV infection
  - iii. Age
  - iv. Gravidity
- Health system
  - i. Quality of/access to care
  - ii. Directly observed therapy (DOT)
  - iii. SP quality
  - iv. High concomitant dose of folic acid ( $\geq 5$  mg/day)
- Other
  - i. Malaria transmission intensity (high transmission is expected to be associated with a higher effectiveness of IPTp)
  - ii. Number and timing of SP doses in relation to gestational age
  - iii. SP resistance
  - iv. ITN use
  - v. Pharmacokinetic changes in pregnancy

### 2. Which levels of transmission intensity and SP resistance (monitored using molecular markers) are associated with loss of effectiveness of IPTp with SP?

Currently there is insufficient evidence on the level of malaria transmission below which IPTp with SP would no longer be cost-effective and could be suspended.

There is also not enough evidence yet to establish a threshold prevalence of quintuple mutant *dhfr*, *dfps* haplotypes, nor *dhps* 581, *dhps* 540, nor *dhfr* 164 point mutations above which there is a clear loss of IPTp-SP cost-effectiveness.

### 3. Is there evidence of harm with the implementation of IPTp with SP in areas with high level of resistance to SP?

There is currently no consistent evidence of harm associated with administration of IPTp-SP in areas with high levels of resistance to SP. There is good evidence supporting the benefits of IPTp-SP even in areas with a high prevalence of quintuple mutations, which are associated with high levels of therapeutic failures to SP *in vivo*<sup>12,17</sup>. The findings of retrospective observational studies<sup>7,8</sup> in Tanzanian women in an area with a high prevalence of parasites carrying the *dhps* resistant mutation at codon 581 which suggested increased placental parasitemia among those reporting use of SP for IPTp needs further investigation. Of note, this same study<sup>7</sup> found a

generally protective effect against other maternal and infant outcomes among those who reported use of SP, but the findings did not reach statistical significance. A subsequent serial cross sectional analysis in Malawi<sup>12</sup> where the *dhps* 581 mutation was detected in one isolate, indicated that women who received 2 dose IPTp-SP had lower peripheral and placental parasite densities compared to women who received < 2 doses IPTp.

**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?**

Results of an unpublished meta-analysis<sup>††</sup> that compared 3 or more doses of IPTp-SP (median of 4 doses) with the standard 2 dose-regimen in 7 randomized trials demonstrated the benefit of more doses.

In addition, preliminary results of ongoing monitoring studies of IPTp-SP effectiveness suggest that IPTp-SP effectiveness could be improved with the administration of a 3 dose regimen.

Thus, in areas of stable (moderate-to- high) malaria transmission, IPTp with SP is recommended for all pregnant women at each scheduled ANC visit. IPTp-SP should be given as early as possible during the second trimester of gestation, with each dose at least 1 month apart from any other and continuing up to the time of delivery.

**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)?**

There is currently insufficient evidence to support a general recommendation for the use of IPTp-SP outside Africa. Issues requiring additional evidence include: the effectiveness of IPTp-SP in preventing the adverse consequences of *P. vivax* infection during pregnancy; the burden of malaria during pregnancy in different transmission settings; and current data regarding *P. falciparum* resistance to SP outside Africa.

Policy decisions could be based on modelling studies including cost-effectiveness at different levels of transmission.

**6. What are the core elements and methods of a simplified protocol to monitor the effectiveness of SP for IPTp?**

Potential core elements of monitoring studies include:

- Review of ANC (number and timing of IPTp-SP doses) and birth weight data through routine health system records

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<sup>††</sup> Kayentao et al. Effect on low birth weight of monthly dosing versus the standard two- dose regimen of IPT with SP for the control of malaria in pregnancy in sub-Saharan Africa: a systematic review and meta-analysis of 5969 pregnancies in seven randomized trials. Unpublished.

- Use of data on trends of birth weight and neonatal mortality and their association with IPTp-SP coverage (adjusting for other potential confounders routinely collected during ANC visits)
- Specific studies to evaluate IPTp-SP effectiveness controlling for multiple factors (age, gravidity, HIV status, ANC visits, number of SP doses received, etc) such as:
  - i. Cross-sectional studies at delivery units
  - ii. Case-control studies of women delivering LBW babies or with maternal anemia
- Monitoring of prevalence of SP molecular resistance markers, preferably at first ANC (pre-SP administration) although the association of resistance markers with SP effectiveness requires further investigation
- Collection of dried blood spots for analysis of molecular markers of SP resistance
- Assessment of *in vitro* SP efficacy
- Assessment of 42 day *in vivo* SP efficacy in asymptomatic parasitaemic pregnant women

The methods to monitor the effectiveness of IPTp-SP are under study and, based on these findings, will need to be improved and enhanced. Therefore, the ERG suggested establishing a working group to specifically address this question and to develop a simplified protocol template to monitor IPTp-SP effectiveness.

**7. What are the minimum requirements (technical expertise, personnel, laboratory equipment etc) to monitor the effectiveness of SP for IPTp?**

Research is ongoing to define the best methodology of monitoring the effectiveness of IPTp and the minimum requirements to monitor effectiveness of IPTp with SP will be specified once the template monitoring protocol has been developed.

**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)?**

To consider an alternative antimalarial drug for IPTp, data from carefully designed superiority RCTs including efficacy, safety, acceptability/tolerability, feasibility and cost-effectiveness are needed.

In addition, baseline data on *P. falciparum* resistance to the alternative drug, together with information on how commonly this drug is used for other indications (e.g. as first line therapy) are needed to inform where this alternative could be implemented as IPTp policy.

**9. What data are needed to decide if an IPTp policy should be stopped when transmission has been reduced to a certain level?**

Results from modeling studies of cost-effectiveness analyses (including costs, benefits, side effects of SP in the model) together with data from IPTp trials from different levels of malaria endemicity when available, will be needed to determine the level of malaria transmission below which IPTp with SP is no longer cost effective. In areas where transmission has recently been substantially reduced, the likelihood that this low transmission will be sustained should also be considered.



## 10. Based on the review of the evidence available should the current WHO policy recommendations on IPTp be updated?

The ERG advises that an update to the WHO policy on IPTp is needed and recommends that all pregnant women in areas of stable (high or moderate) malaria transmission should receive SP at each scheduled ANC visit. IPTp-SP doses should be administered as early as possible during the 2<sup>nd</sup> trimester<sup>††</sup> of gestation, with each dose given at least 1 month apart from any other and continuing up to the time of delivery.

Please refer to Annex 2 for a detailed description of the suggested changes in the WHO recommendations.

## 11. What core messages should be addressed by a WHO interim position statement on IPTp with SP to the MoH of malaria endemic countries?

- IPTp with SP remains effective in preventing the adverse consequences of malaria on maternal and fetal outcomes in areas where a high proportion of *Plasmodium falciparum* parasites carry a quintuple mutation associated with *in vivo* therapeutic failure to SP<sup>§§</sup>; therefore, IPTp with SP should still be administered to women in such areas.
- In areas of stable (moderate-to-high) malaria transmission, IPTp with SP is recommended for all pregnant women **at each scheduled antenatal care visit**. In addition:
  - i. The first IPTp-SP dose should be administered as early as possible during the 2<sup>nd</sup> trimester<sup>\*\*\*</sup> of gestation
  - ii. Each SP dose should be given at least 1 month apart from the other and up to the time of delivery
  - iii. The last dose of IPTp with SP can be administered late (after 36 weeks) in the 3<sup>rd</sup> trimester of gestation without safety concerns
  - iv. IPTp should be administered as directly observed therapy (DOT)
  - v. SP can be given on an empty stomach
  - vi. Folic acid at a daily dose equal or above 5 mg should not be given concomitantly with SP as this counteracts its efficacy as an antimalarial.
  - vii. SP is contraindicated in women receiving cotrimoxazole prophylaxis
- Currently, there is no established threshold level of malaria transmission below which IPTp-SP is no longer cost-effective and should therefore be suspended<sup>†††</sup>.

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<sup>††</sup> IPTp administration should be avoided during the 1<sup>st</sup> trimester of gestation but should start as soon as possible in the 2<sup>nd</sup> trimester. The fact a woman has entered the second trimester can be determined by the onset of quickening or by measurement of fundal height by ANC health personnel.

<sup>§§</sup> The findings of an observational study in Tanzanian women in an area where the parasite dhps resistance mutation of codon 581 was present showed increased placental parasite density and inflammatory changes in women reporting IPTp with SP use. This needs further investigation although it is important to note that this specific dhps resistance mutation is not common.

<sup>\*\*\*</sup> IPTp administration should be avoided during the 1<sup>st</sup> trimester of gestation but should start as soon as possible in the 2<sup>nd</sup> trimester. The fact a woman has entered the second trimester can be determined by the onset of quickening or by measurement of fundal height by ANC health personnel.

<sup>†††</sup> Cost-effectiveness modelling studies are ongoing to address this question. Risk-benefit of SP administration needs also to be taken into account when considering recommendations on IPTp implementation.

- There is currently insufficient evidence to support a general recommendation for the use of IPTp-SP outside of Africa.
- Monitoring of IPTp-SP effectiveness is essential and should continue. Research is ongoing to define the best methodology, and will be shared when available.

Furthermore, the ERG suggested the following additional recommendations/messages regarding IPTp with SP:

- In order to preserve SP effectiveness for IPTp, increased efforts should be made to avoid SP use as monotherapy for malaria treatment of clinical cases of malaria.
- Preliminary results of observational studies on IPTp effectiveness also show that even in areas with low levels of SP resistance, the efficacy of IPTp-SP is greater when more than 2 doses are administered.

**12. Based on the review of available evidence, including unpublished reports, which key recommendations (if any) could be proposed for a GRADE assessment?**

The following recommendations were proposed for a GRADE assessment:

- Effectiveness of 2-dose IPTp-SP *versus* IPTp-SP at every scheduled ANC visit on birth weight and LBW, placental infection, clinical malaria, maternal anemia and fetal anemia
- Impact of IPTp-SP on neonatal mortality

**13. What are the current knowledge gaps (scientific and operational) for effective implementation of IPTp with SP?**

The following gaps in knowledge and research key areas were identified:

- The safety of IPTp-SP when given 5 times or more during pregnancy
- Interactions between antimalarials and antiretrovirals in HIV infected individuals
- The effect of sustained malaria transmission reduction on IPTp effectiveness
- Relationship between malaria transmission intensity level and IPTp-SP effectiveness (risk-benefit and cost-effectiveness analysis based on modeling data)
- Effectiveness of IPTp-SP against *P. vivax* infection in pregnancy
- The effect of the presence of the *dhps* 581 codon mutation on IPTp effectiveness
- Monitoring protocol for IPTp-SP effectiveness
- Innovative strategies to improve the delivery of IPTp-SP and malaria case management among pregnant women at the primary health center level
- Innovative community strategies that simultaneously do not detract from ANC services to increase IPTp coverage (such as community-based ANC outreach, promotion or distribution of IPTp)
- Methods for using health system information systems for routine monitoring of IPTp-SP implementation and effectiveness
- Operational interventions to improve delivery and use of ITNs to women before they conceive

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

<b>Publications</b>	<b>Country/ies</b>	<b>Study description</b>
Mayor <i>et al</i> , 2012 <sup>9</sup>	Mozambique	Evaluation of the performance of microscopy, placental histology and HRP2-based plasma methods for the diagnosis of malaria in pregnant women and the clinical relevance of undetected infections.
Taylor <i>et al</i> , 2012 <sup>12</sup>	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 9 years.
Taylor <i>et al</i> , 2012 <sup>11</sup>	Malawi	Cross-sectional molecular analysis of samples collected between 1997 and 2006 investigating changes in SP resistant <i>P. falciparum</i> among women at delivery.
Harrington <i>et al</i> , 2011 <sup>7</sup>	Tanzania	Cross-sectional study evaluating the reported use of IPTp and its effects on maternal and fetal outcomes in an area of high SP resistance.
van Eijk <i>et al</i> , 2011 <sup>13</sup>	47 African countries	Analysis of extracted data on malaria control strategies in pregnancy from national policies including an assessment of coverage with ITNs and IPTp.
Menéndez <i>et al</i> , 2011 <sup>10</sup>	Mozambique	Molecular analysis of samples obtained from women at delivery during a RCT of IPTp SP vs placebo, evaluating the impact of IPTp and HIV on molecular markers of SP resistance and its clinical relevance.
Feng <i>et al</i> , 2010 <sup>2</sup>	Malawi	Analysis of longitudinal data from women at delivery collected over 9 years investigating the changes in malaria prevalence and the association between pregnancy outcomes and use of IPTp with SP.
Harrington <i>et al</i> , 2009 <sup>8</sup>	Tanzania	Molecular analysis of resistant parasites obtained from samples of women at delivery and its association with reported use of IPTp.
<b>Manuscript/ presentations</b>	<b>Country/ies</b>	<b>Study description</b>
González <i>et al</i> , unpublished <sup>+++</sup>	Studies from over 11 sub-Saharan countries where IPTp-SP is implemented	Comprehensive literature review of published studies evaluating IPTp-SP efficacy and effectiveness and its effects on maternal and infant's health since 2007, in relation to the current WHO recommendations on IPTp.
Kayentao <i>et al</i> , unpublished <sup>§§§</sup>	Kenya, Zambia, Malawi, Tanzania, Mali, Burkina Faso	Meta-analysis of 7 trials to determine whether regimens containing 3 or more doses of IPTp-SP are more effective than standard 2-dose regimens in preventing LBW.
van Eijk <i>et al</i> , unpublished <sup>****</sup>	47 African countries	Updated analysis of data from national household cluster-sample surveys assessing ITN and IPTp coverage in pregnancy from 2009-2011.
MiP consortium monitoring studies	Kenya, Malawi, Zambia, Uganda, Mali	Series of ongoing observational facility-based studies evaluating the relationship between SP resistance and the effectiveness of IPTp-SP.

RCT: Randomized Controlled Trial; MiP: Malaria in Pregnancy

<sup>+++</sup> González *et al*. Review on IPTp-SP efficacy, effectiveness and its effects on maternal and infant's health. Unpublished.

<sup>§§§</sup> Kayentao *et al*. Effect on low birth weight of monthly dosing versus the standard two- dose regimen of IPT with SP for the control of malaria in pregnancy in sub-Saharan Africa: a systematic review and meta-analysis of 5969 pregnancies in seven randomized trials. Unpublished.

<sup>\*\*\*\*</sup> van Eijk *et al*. Prevention of malaria in pregnancy in sub-Saharan Africa: a synthesis and ecological analysis of national survey data. Unpublished.

**Annex 2****Suggested modifications of current WHO text recommendations on IPTp-SP*****Current WHO recommendations related to ~~combined benefits of IPTp and ITN use~~ Malaria in Pregnancy Prevention and Control***

- *WHO promotes a three-pronged approach for all pregnant women living in stable malaria transmission areas.* The policy for malaria prevention and control during pregnancy in areas of stable transmission should emphasize a package of intermittent preventive treatment (IPTp) and insecticide-treated nets (ITNs) and ensure effective case management of malaria illness and anaemia.
- ITNs should be provided to pregnant women as early in pregnancy as possible. Their use should be encouraged for women throughout pregnancy and during the postpartum period.
- ITNs can be provided through the antenatal clinic or other sources in the private and public sectors.

***Current WHO recommendations related to the number and timing of IPTp doses***

Current scientific evidence suggests that ~~d~~ At least two IPT doses during the second and third trimester IPTp is beneficial to the pregnant woman and her unborn baby 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.~~ In areas of stable transmission, give IPTp-SP, at every scheduled ANC visit, following quickening and at least one month apart. A review of 7 clinical trials conducted in Africa in areas of stable transmission and different levels of SP resistance revealed that 3 or more doses of IPTp-SP yielded better clinical outcomes for the mother and the newborn than the standard two doses of IPTp-SP in all gravidae and HIV groups<sup>††††</sup>

The World Health Organization recommends a schedule of four antenatal clinic visits, with three visits after quickening. The delivery of IPT-SP at each scheduled visit after quickening will assure that a high proportion of women receive at least two doses.

~~In settings with an HIV prevalence among pregnant women greater than 10%, 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.~~

~~IPTp-SP doses should not be given more frequently than monthly.~~

***Current WHO recommendations related to the timing of IPTp-SP doses***

~~All pregnant women in areas of stable malaria transmission should receive at least two doses of IPT after quickening.~~

~~The World Health Organisation recommends a schedule of four antenatal clinic visits, with three visits after quickening. The delivery of IPT-SP at each scheduled visit after quickening will assure that a high proportion of women receive at least two doses.~~

<sup>††††</sup> Kayentao et al. Effect on low birth weight of monthly dosing versus the standard two-dose regimen of IPT with SP for the control of malaria in pregnancy in sub-Saharan Africa: a systematic review and meta-analysis of 5969 pregnancies in seven randomized trials. Unpublished

**Current WHO recommendations related to IPTp and SP resistance**

IPTp with SP remains effective in preventing the adverse consequences of malaria on maternal and fetal outcomes in areas where a high proportion of *Plasmodium falciparum* parasites carry a quintuple mutation associated with in vivo therapeutic failure to SP. The effect of high level of SP resistance on IPTp effectiveness including the significance of the *dhps* 581 codon mutation should be further investigated  
SP-IPTp is threatened by the spread of SP-resistant parasites. Although there must be a relationship between the level of parasite resistance to SP and the benefit provided by SP-IPTp, data on in vivo therapeutic efficacy of SP in young children with symptomatic malaria cannot be extrapolated to protective efficacy of IPTp in pregnant women because of differences in therapeutic efficacy between young children, and pregnant women-related immunity and possibly pharmacokinetics.

~~□ However, in vivo therapeutic efficacy and protective efficacy of SP (and antimalarials in general) used for IPTp need to be determined specifically in pregnant women<sup>17,18</sup>.~~

**Current WHO recommendations related to IPTp and HIV**

Current scientific evidence suggests:

~~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.~~

~~In settings with HIV prevalence among pregnant women greater than 10%, 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.~~

~~Intermittent preventive treatment with sulphadoxine-pyrimethamine (IPTp-SP) should not be given to HIV-infected patients receiving cotrimoxazole (trimethoprim plus sulfamethoxazole) prophylaxis.~~

### Annex 3 List of Participants

#### ERG MEMBERS

Dr Karen BARNES  
University of Cape Town, Cape Town  
SOUTH AFRICA

Dr Brian GREENWOOD (Co-Chair) \*  
Department of Infectious and Tropical Diseases  
London School of Hygiene and Tropical Medicine, London  
UNITED KINGDOM

Dr Davidson H. HAMER  
Center for Global Health and Development, Boston University, Boston, U.S.A.  
Zambia Center for Applied Health Research and Development, Lusaka  
ZAMBIA

Dr Elizabeth JUMA  
Kenya Medical Research Institute, Nairobi  
KENYA

Dr Peter KREMSNER  
Department of Parasitology  
Institute of Tropical Medicine, Tubingen  
GERMANY

Dr Rose Gana Fomban LEKE  
Faculty of Medicine and Biomedical Science, Yaoundé  
CAMEROON

Dr Don P MATHANGA (excused)  
Malaria Alert Centre  
University of Malawi, Blantyre  
MALAWI

Ms Elaine ROMAN  
Maternal and Child Health Integrated Program  
Jhpiego, Baltimore, MD  
U.S.A

Dr Laurence SLUTSKER (Co-Chair)\*  
Centers for Disease Control and Prevention, Atlanta, GA  
U.S.A

\* Also member of the Malaria Policy Advisory Committee



## **REPRESENTATIVES OF RESEARCH INSTITUTIONS/AGENCIES**

Dr Julie GUTMAN  
PMI-supported Project,  
Centers for Disease Control and Prevention, Atlanta  
U.S.A

Dr Kassoum KAYENTAO  
Malaria Research and Training Centre  
Department of Epidemiology of Parasitic Diseases  
Faculty of Medicine, Bamako  
MALI

Professor Feiko ter KUILE  
Liverpool School of Tropical Medicine, Liverpool  
UNITED KINGDOM

Dr Clara MENÉNDEZ  
Barcelona Centre for International Health Research (CRESIB)  
Hospital Clínic, University of Barcelona, Barcelona  
SPAIN

Dr Peter OUMA  
Kenya Medical Research Institute-CDC Project, Kisumu  
KENYA

Dr Stephen ROGERSON  
University of Melbourne  
Department of Medicine (RMH/WH), Melbourne  
AUSTRALIA

## **OBSERVERS**

Jenny HILL  
Liverpool School of Tropical Medicine, Liverpool  
UNITED KINGDOM

Jayne WEBSTER  
London School of Hygiene and Tropical Medicine, London  
UNITED KINGDOM

\* Also member of the Malaria Policy Advisory Committee



**WHO SECRETARIAT**

Dr Andrea BOSMAN, Global Malaria Programme

Dr Raquel GONZÁLEZ (Rapporteur), WHO Consultant

Dr Viviana MANGIATERRA, Research Capacity, Policy and Programme Strengthening

Dr Josephine NAMBOZE, Regional Office for Africa

Dr Robert NEWMAN - Director, Global Malaria Programme

Dr Marian WARSAME, Global Malaria Programme