INTERMITTENT PREVENTIVE TREATMENT OF MALARIA
IN PREGNANCY WITH SULPHADOXINE/PYRIMETHAMINE

WHO EVIDENCE REVIEW GROUP
WHO, Geneva,
July 9th – 11th 2012

MPAC MEETING
September 11th - 13th 2012
CURRENT WHO RECOMMENDATIONS ON THE COMBINED USE OF IPTp AND ITNs IN PREGNANCY

Overall recommendation

- The policy for malaria prevention and control during pregnancy in areas of stable transmission includes 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.
Current WHO Recommendations Related to the Number and Timing of IPTP-SP Doses

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

- WHO 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.
CURRENT WHO RECOMMENDATIONS RELATED TO IPTp AND HIV

- 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 should not be given to HIV-infected patients receiving cotrimoxazole (trimethoprim plus sulfamethoxazole) prophylaxis.
**TASK OF THE EVIDENCE REVIEW GROUP**

To review the current WHO recommendations on SP IPTp and to make recommendations on any changes that are needed related to –

a. The number of treatments with SP that should be given,

b. The effectiveness of SP IPTp in areas of high SP resistance,

c. The level of transmission below which SP IPTp is no longer cost effective.

d. To identify the critical gaps in knowledge and a priority research agenda for IPTp with SP.
FORMAT OF THE CONSULTATION

Pre-meeting

- Discussions between WHO secretariat and co-chairs on the scope and format of the meeting and preparation of a set of questions for review by the ERG members.

- Preparation of a background paper summarising the results of SP IPTp studies published since 2007 (Raquel Gonzáles).

- Preparation of a manuscript on meta-analysis of 2 vs 3 or more doses of SP for IPTp (Kayentao et al.).
FORMAT OF THE CONSULTATION

Meeting

July 9th – 11th 2012

- Presentation at the meeting by members of the MIP consortium on programmatic evaluation of 2 vs 3 or more doses of SP IPTp in high SP resistance areas.

- Wide ranging discussions by two working groups on a common set of issues/questions related to SP IPTp.

- Formulation of new policy recommendations by ERG members for consideration by MPAC.
# PARTICIPANTS TO THE IPTp-SP ERG MEETING

**Members**
- Karen Barnes
- Brian Greenwood*
- Davidson Hamer
- Elizabeth Juma
- Peter Kremsner
- Rose Leke
- Don Mathanga***
- Elaine Roman
- Laurence Slutsker*

**Evidence providers**
- Julie Gutman
- Kassoum Kayento
- Feiko ter Kuile
- Clara Menendez
- Peter Ouma
- Stephen Rogerson

**WHO Secretariat**
- Andrea Bosman
- Raquel Gonzalez**
- Vivians Mangiaterra
- Josephine Namboze
- Robert Newman
- Marian Warsame

**Observers**
- Jenny Hill
- Jayne Webster

* Co-chairs  ** Rapporteur  *** Unable to attend
EVIDENCE OF EFFICACY OF MORE FREQUENT DOSES OF SP IPTp IN REDUCING LOW BIRTHWEIGHT

RR = 0.79 (0.68, 0.92)
EVIDENCE OF EFFICACY OF MORE FREQUENT DOSES OF SP IPTp ON BIRTHWEIGHT

<table>
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<tr>
<th>HIV Status</th>
<th>Group</th>
<th>Study Details</th>
<th>% dHps K540E</th>
<th>Bednet Use</th>
<th>Mean Difference (SD)</th>
<th>N. mean (SD) Treatment</th>
<th>N. mean (SD) Control</th>
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<td>37</td>
<td>11 (-57, 79)</td>
<td>366, 2896 (460)</td>
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2 doses better 3+ doses better

56 (29, 83) g
NUMBER OF DOSES OF SP FOR SP IPTp

Conclusions

Three or more doses are more effective than two
EVIDENCE OF THE EFFICACY OF SP IPTp IN AREAS WITH SP RESISTANCE

- Results from a retrospective study in an area of Tanzania with a high level of SP resistance (including a 36% prevalence of 581 dhfr mutation) indicated damage to the placenta in women who received SP.

- Results from a randomised, placebo-controlled trial in an area of Mozambique with a high level of quintuple mutation (not at codon 581) showed protective efficacy of SP IPT and no association between the presence of quintuple mutant parasites and increased parasite densities or malaria-related morbidity in mothers or children.

- Longitudinal studies in Malawi showed a waning over time in the efficacy of SP IPT in the prevention of peripheral and placental parasitaemia and low birth weight in association with a scale up in ITN use and an increasing prevalence in SP resistance markers.

- Observational studies in Kenya, Malawi, and Zambia, where there is significant SP resistance, have shown an increase in birth weight and a reduction in maternal anaemia with increasing number of doses of SP, however, their observational design limits the ability to control for potential confounders.
USE OF SP IPTp IN AREAS OF SP RESISTANCE

Conclusions

- There is some evidence of benefit from SP IPTp in areas of high prevalence of quintuple mutant *P. falciparum* parasites.

- There is no evidence of harm from SP IPTp in areas with a high level of resistance to SP. The findings of increased parasite density and inflammatory changes in women reporting use of IPTp with SP, from an observational study in Tanzanian women need further investigation.
EVIDENCE OF THE EFFECTIVENESS OF SP IPTp AT DIFFERENT LEVELS OF MALARIA TRANSMISSION

- There are insufficient data on which to make a decision as to the level of malaria transmission below which SP IPTp is no longer a cost effective intervention.

- There is insufficient evidence on which to decide on the usefulness of SP IPT outside Africa.
EVIDENCE OF THE EFFECTIVENESS OF SP IPTp AT DIFFERENT LEVELS OF MALARIA TRANSMISSION

Conclusion

There are insufficient data to make a recommendation on the level of malaria transmission below which implementation of SP IPTp is no longer cost effective.
In areas of stable (moderate-to-high) malaria transmission, IPTp with SP is recommended for all pregnant women at each scheduled antenatal care visit.

- The first IPTp-SP dose should be administered as early as possible during the 2nd trimester 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 3rd 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.
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; therefore, IPTp with SP should still be administered to women in such areas.
RECOMMENDATIONS FOR FURTHER RESEARCH

Implementation of SP IPTp

- Innovative community strategies to increase IPTp coverage that do not detract from ANC services.
- Operational interventions to improve delivery and use of ITNs to women before they conceive.

Efficacy

- Effectiveness of IPTp-SP against *P. vivax* infection in pregnancy.
- The effect of the presence of the *dhps* 581 codon mutation on IPTp-SP effectiveness.

Safety

- The safety of IPTp-SP when given 5 times or more during pregnancy.
- Interactions between antimalarials and antiretrovirals in HIV infected individual.

Monitoring

- Monitoring protocol for IPTp-SP effectiveness.
- Methods for using health system information systems for routine monitoring of IPTp-SP implementation and effectiveness.

Epidemiology

- Relationship between malaria transmission intensity level and IPTp-SP effectiveness (risk-benefit and cost-effectiveness analysis based on modeling data).
- The effect of sustained malaria transmission reduction on IPTp effectiveness.
CONCLUSIONS

➢ SP IPTp remains an effective strategy for the prevention of malaria in pregnancy in Africa, even in the majority of areas of moderate to high SP resistance, provided that it is given at least three times during pregnancy.

➢ Currently, there is no established threshold level of malaria transmission below which IPTp-SP is no longer cost-effective.
## Timelines of upcoming MiP studies of potential relevance to ERG and MPAC

### 2013

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° CQ + AZ multicenter trial in Africa will be completed in 2014
§ IST trials in Malawi and India will be completed in 2014