# Malaria in pregnancy (MIP)

**RBM MIP WG meeting**

**Geneva, 18-20 September 2017**

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Global **Malaria** Programme

World Health Organization

# Outline

- WHO/UNITAID Enabler Grant and TIPTOP project
- IPTp-SP: New WHO Antenatal Care (ANC) guidelines and interagency briefing
- ACT use in 1st trimester – Technical Expert Group (TEG) meeting December 2017
- MIP Evidence Review Group (ERG) meeting July 2017

# Malaria in pregnancy (MIP)

- MIP: major public health problem, with substantial risks for mother, fetus and newborn

- WHO-recommends **three-pronged intervention package**:
  - promotion and use of insecticide-treated nets **(ITNs)**,
  - appropriate **case management** through prompt and effective treatment of malaria in pregnant women.
  - administration of intermittent preventive treatment with sulfadoxine-pyrimethamine **(IPTp-SP)** in medium to high transmission areas

- WHO evidence review (meta-analysis of 7 trials)
  - 3+ doses of IPTp-SP associated with higher mean birth and fewer low birth weight (LBW) births than 2 doses
  - estimated relative risk reduction for LBW was 20% (95% CI 6-31), consistent across a wide range of SP resistance levels.
  - 3+ dose group found to have less placental malaria
  - no differences in serious adverse events between the 2 groups

➡ October 2012, WHO updates its recommen-dations on IPTp-SP

WHO Global Malaria Programme
WHO Department of Reproductive Health and Research
WHO Department of Maternal, Newborn, Child and Adolescent Health

World Health Organization

**WHO policy brief for the implementation of intermittent preventive treatment of malaria in pregnancy using sulfadoxine-pyrimethamine (IPTp-SP)**

**April 2013**
**(revised January 2014)**

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**Background**

Malaria infection during pregnancy is a major public health problem, with substantial risks for the mother, her fetus and the newborn. In areas with moderate to high transmission of *Plasmodium falciparum*, the World Health Organization (WHO) recommends a package of interventions for controlling malaria and its effects during pregnancy, which includes the promotion and use of insecticide-treated nets (ITNs), the administration during pregnancy of intermittent preventive treatment with sulfadoxine-pyrimethamine (IPTp-SP), and appropriate case management through prompt and effective treatment of malaria in pregnant women *(1)*.

During the last few years, WHO has observed a slowing of efforts to scale-up IPTp-SP in a number of countries in Africa. Although there may be several reasons for this, an important factor is confusion among health workers about sulfadoxine-pyrimethamine administration for intermittent preventive treatment in pregnancy.

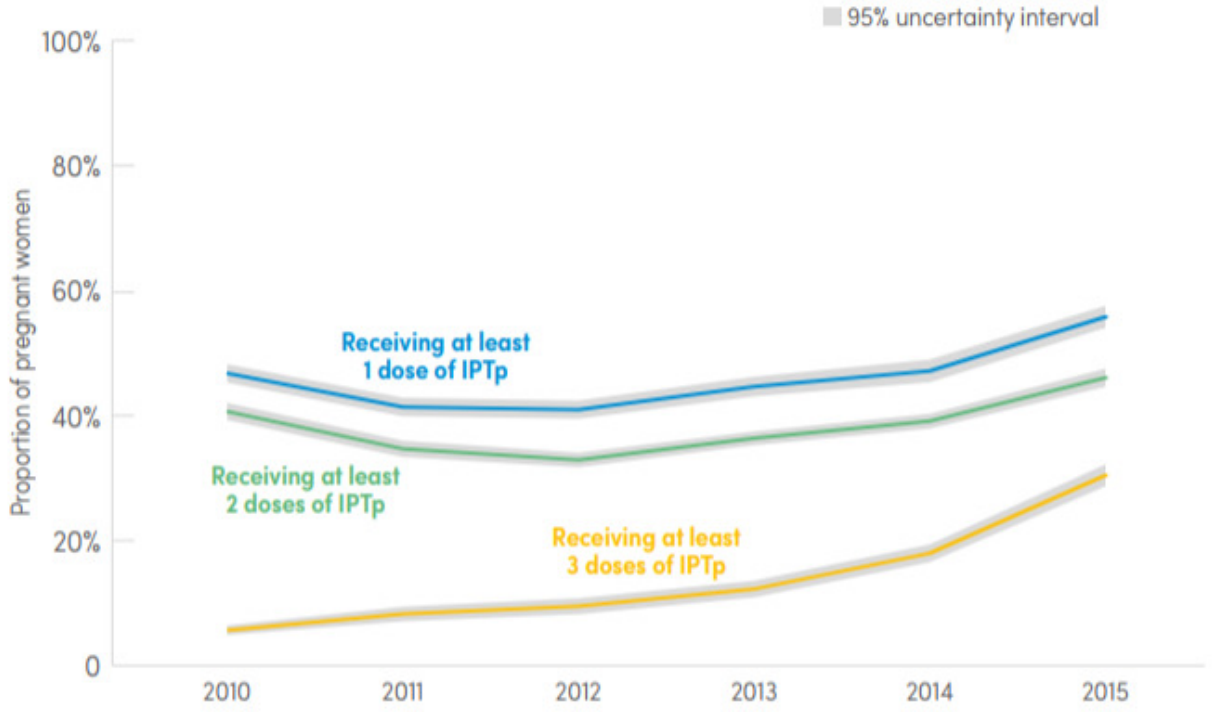
At a recent WHO evidence review *(2)*, a meta-analysis of seven trials evaluating IPTp-SP was undertaken. It showed that three or more doses of IPTp-SP were associated with higher mean birth weight and fewer low birth weight (LBW) births than two doses of IPTp-SP. The estimated relative risk reduction for LBW was 20% (95% CI 6-31). This effect was consistent across a wide range of SP resistance levels. The 3+ dose group also was found to have less placental malaria. There were no differences in serious adverse events between the two groups *(3)*.

Based on this evidence review, in October 2012, WHO updated the recommendations on IPTp-SP as outlined below, and urges national health authorities to disseminate this update widely and ensure its correct application. IPTp-SP is an integral part of WHO's three-pronged approach to the prevention and treatment of malaria in pregnancy, which also includes the use of insecticide-treated nets and prompt and effective case management.

WHO/HTM/GMP/2014.4

# World Malaria Report 2016

**Figure 3.7 Proportion of pregnant women receiving IPTp, by dose, sub-Saharan Africa, 2010–2015.** Source: National malaria control programme reports and United Nations population estimates




IPTp, intermittent preventive treatment in pregnancy

It is estimated that, in 2015, among 20 countries that reported,
**31%** of eligible pregnant women (UI: 29–32%) received three or more doses of IPTp
in 36 African countries that have adopted the policy –
a large increase from the 18% receiving three or more doses in 2014 and 6% in 2010.

# WHO/UNITAID Enabler Grant – Structure

**WHO-UNITAID Enabler Grant** covers three disease areas:

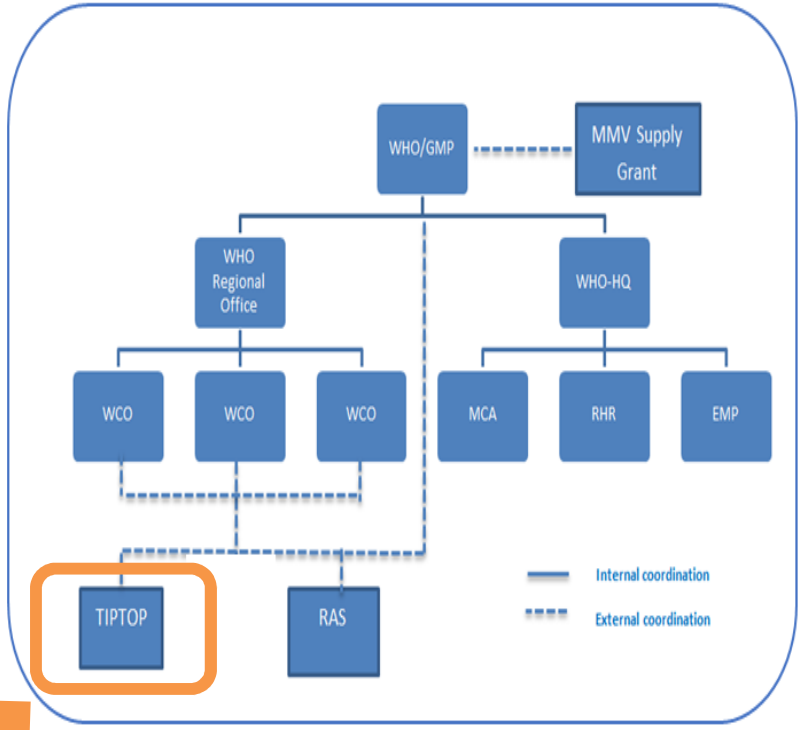
- HIV (grant signed May 2017)
- TB (grant documents under preparation)
- **Malaria** (pending approval - grant documents currently under review by the UNITAID Board)

The **malaria enabler component,** led by WHO/GMP, is designed to…

… support two projects, i.e. TIPTOP and RAS, plus the MMV Supply Grant

… leverage the three levels of the organization, i.e. WHO headquarters (HQ), regional (RO) and country offices (CO)

… liaise with different departments in-house, i.e. MCA, RHR, EMP



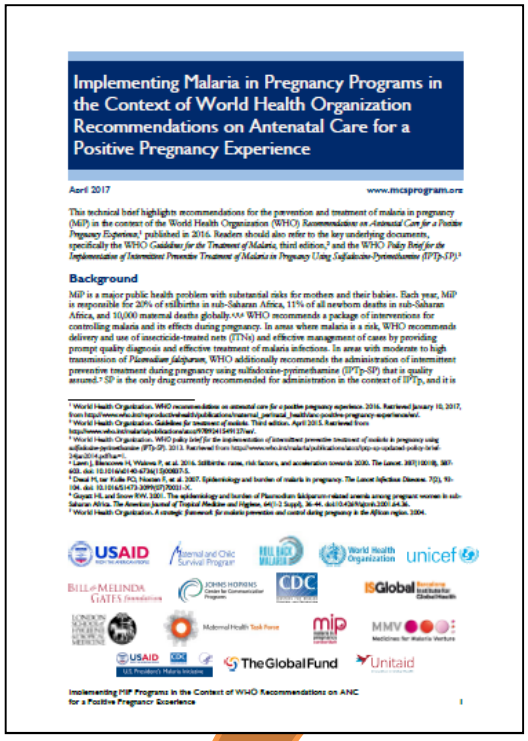
# Malaria Enabler Grant – Workstreams

## GMP's strategic approach and vision

Creation of a policy environment that favours the adoption, deployment and correct use of specific quality-assured antimalarial formulations for malaria prevention and treatment for the most vulnerable groups through community-based delivery approaches.

| Intervention area | Project |
|---|---|
| Workstream 1: IPTp-SP (Intermittent Preventive Treatment in pregnancy with sulfadoxine-pyrimethamine) | UNITAID-funded project: **TIPTOP** (Transforming IPTp for Optimal Pregnancy)<br>Lead grantee: Jhpiego. Partner: ISGlobal. Enablers: MMV, WHO.<br>Project countries: DRC, Madagascar, Mozambique, and Nigeria<br>Malaria enabler grant duration: 5 years |
| Workstream 2: RAS (Pre-referral treatment of severe malaria with quality-assured rectal artesunate) | UNITAID-funded project: **CARAMAL** (previously named RAS)<br>Lead grantee: CHAI. Partners: Swiss TPH, UNICEF. Enablers: MMV, WHO.<br>Project countries: DRC, Nigeria, and Uganda<br>Malaria enabler grant duration: 3 years |

# New WHO ANC guidelines – increased number of opportunities to receive IPTp-SP



Implementing Malaria in Pregnancy Programs in the Context of World Health Organization Recommendations on Antenatal Care for a Positive Pregnancy Experience

April 2017 www.mcsprogram.org

This technical brief highlights recommendations for the prevention and treatment of malaria in pregnancy (MiP) in the context of the World Health Organization (WHO) *Recommendations on Antenatal Care for a Positive Pregnancy Experience*,[1] published in 2016. Readers should also refer to the key underlying documents, specifically the WHO *Guidelines for the Treatment of Malaria*, third edition,[2] and the WHO *Policy Brief for the Implementation of Intermittent Preventive Treatment of Malaria in Pregnancy Using Sulfadoxine-Pyrimethamine (IPTp-SP)*.[3]

**Background**

MiP is a major public health problem with substantial risks for mothers and their babies. Each year, MiP is responsible for 20% of stillbirths in sub-Saharan Africa, 11% of all newborn deaths in sub-Saharan Africa, and 10,000 maternal deaths globally.[4,5,6] WHO recommends a package of interventions for controlling malaria and its effects during pregnancy. In areas where malaria is a risk, WHO recommends delivery and use of insecticide-treated nets (ITNs) and effective management of cases by providing prompt quality diagnosis and effective treatment of malaria infections. In areas with moderate to high transmission of *Plasmodium falciparum*, WHO additionally recommends the administration of intermittent preventive treatment during pregnancy using sulfadoxine-pyrimethamine (IPTp-SP) that is quality assured.[7] SP is the only drug currently recommended for administration in the context of IPTp, and it is

[1] World Health Organization. WHO recommendations on antenatal care for a positive pregnancy experience. 2016. Retrieved January 10, 2017, from http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/anc-positive-pregnancy-experience/en/.
[2] World Health Organization. Guidelines for treatment of malaria. Third edition. April 2015. Retrieved from http://www.who.int/malaria/publications/atoz/9789241549127/en/.
[3] World Health Organization. WHO policy brief for the implementation of intermittent preventive treatment of malaria in pregnancy using sulfadoxine-pyrimethamine (IPTp-SP). 2013. Retrieved from http://www.who.int/malaria/publications/atoz/iptp-sp-updated-policy-brief-24jan2014-pdf?ua=1.
[4] Lawn J, Blencowe H, Waiswa P, et al. 2016. Stillbirths: rates, risk factors, and acceleration towards 2030. The Lancet. 387(10018), 587-603. doi: 10.1016/s0140-6736(15)00837-5.
[5] Desai M, ter Kuile FO, Nosten F, et al. 2007. Epidemiology and burden of malaria in pregnancy. The Lancet Infectious Diseases. 7(2), 93-104. doi: 10.1016/S1473-3099(07)70021-X.
[6] Guyatt HL and Snow RW. 2001. The epidemiology and burden of Plasmodium falciparum-related anemia among pregnant women in sub-Saharan Africa. The American Journal of Tropical Medicine and Hygiene. 64(1-2 Suppl), 36-44. doi: 0.4269/ajtmh.2001.64.36.
[7] World Health Organization. A strategic framework for malaria prevention and control during pregnancy in the African region. 2004.

USAID | Maternal and Child Survival Program | Roll Back Malaria | World Health Organization | unicef | Bill & Melinda Gates Foundation | Johns Hopkins Center for Communication Programs | CDC | ISGlobal | London School of Hygiene & Tropical Medicine | Liverpool School of Tropical Medicine | Maternal Health Task Force | mip | MMV | USAID | CDC | U.S. President's Malaria Initiative | The Global Fund | Unitaid

Implementing MiP Programs in the Context of WHO Recommendations on ANC for a Positive Pregnancy Experience 1

| ANC Contact Schedule and Proposed Time of IPTp-SP Administration *(To be adapted to country context, also considering disease burden and health needs)* | | MiP-related Interventions and Considerations during ANC Contacts |
|---|---|---|
| Contact 1: Up to 12 weeks | | • Register pregnant women, provide ITNs, and counsel on their use. Screen for HIV.<br>• Administer 30 to 60 mg of elemental iron and 400 µg (0.4 mg) of folic acid.<br>• **Counsel to return for a visit at 13 to 16 weeks (see contact 1a below) to receive the first dose of IPTp-SP (as directed by national guidelines).***<br>• Counsel on prompt diagnosis and effective treatment/malaria case management during pregnancy. |
| Additional contact (1a): *In moderate to high malaria transmission areas in Africa where IPTp-SP is policy, a contact should be made early in the second trimester (13 to 16 weeks) to administer SP as early as possible.* | IPTp-SP dose 1 | Remember:<br>• Do not administer IPTp-SP before week 13 of pregnancy.<br>• Administer the first IPTp-SP dose **as early as possible in the second trimester** to fully benefit from the protective capacity in this critical period of pregnancy.†<br>• **Administer the second dose of IPTp-SP one month later.**<br>• Administer the following doses of IPTp-SP starting from the scheduled contact at 20 weeks, **observing at least one-month intervals between SP doses.**<br>• SP can be **safely** administered from the beginning of the second trimester until the time of delivery.<br>• One full dose of IPTp-SP consists of 1,500 mg/75 mg SP (i.e., three tablets of 500 mg/25 mg SP).<br>• Provide IPTp-SP by directly observed treatment.<br>• Pregnant women on co-trimoxazole should not receive IPTp-SP due to an increased risk of adverse events when both drugs are given in parallel.<br>• Continue to administer 30 to 60 mg of elemental iron and 400 mcg (0.4 mg) of folic acid.<br>• Continue counseling as above. |
| Contact 2: 20 weeks | IPTp-SP dose 2 | |
| Contact 3: 26 weeks | IPTp-SP dose 3 | |
| Contact 4: 30 weeks | IPTp-SP dose 4 | |
| Contact 5: 34 weeks | IPTp-SP dose 5 | |
| Contact 6: 36 weeks | No SP administration if last dose was received at contact 5 in week 34 | |
| Contact 7: 38 weeks | IPTp-SP dose 6 (if no dose was received at contact 6 in week 36) | |
| Contact 8: 40 weeks | | |

Pregnant women should receive MiP interventions as appropriate, even when they come at weeks not designated in the contact schedule.

Despite the known side effects associated with sulfonamides, SP for intermittent preventive treatment in pregnancy is generally very well tolerated. Mild and transient side effects including nausea, vomiting, weakness and dizziness have been reported by some women, particularly with the first dose of SP. Studies have demonstrated that side effects tend to decrease with the administration of further doses (§,‡). Side effects should be discussed openly and managed in the ANC.

# Malaria in pregnancy (MIP) Evidence Review Group (ERG) meeting, Geneva, July 2017

**Meeting objectives – To review:**

- **Burden of vivax** malaria in PW, including impact on birth outcomes;
- **Efficacy and safety** of medicines to treat uncomplicated Pf and Pv MIP in **Asia and South America**;
- **Efficacy and safety** of intermittent screening and treatment **(IST)** and intermittent preventive treatment **(IPT)** of MIP in **Asia**;
- Effects of sulfadoxine-pyrimethamine **(SP)** and azithromycin **(AZ)** protection against adverse birth outcomes related to sexually transmitted and reproductive tract infections
- **Pharmacokinetics** of dihydroartemisinin (DHA), piperaquine (PPQ), artesunate (AS), artemether (A), lumefantrine (L), amodiaquine (AQ) and mefloquine (MQ) during pregnancy and implications for dose adjustments
- **Key challenges and knowledge gaps for MIP in HIV-infected women** including:
  (1) the efficacy/effectiveness of co-trimoxazole (CTX) prophylaxis for prevention of malaria and it adverse consequences;
  (2) efficacy/ effectiveness of IPTp; and
  (3) pharmacokinetics of antimalarials in these women including their interactions with anti-retroviral medications

# **MIP ERG** – Findings pending MPAC review (I)

## Burden of *P. vivax* malaria in pregnancy

- low incidence
- associated with maternal anaemia, foetal loss, small for gestational age and preterm births, particularly in symptomatic PW

➡ Evidence does not support change in current recommendations on prevention and case management

## Pf and Pv co-infection in pregnancy

➡ Further research is needed

## Pharmacokinetic (PK) effects of pregnancy

- vary substantially among different studies and medicines

➡ Inconsistencies: not clear whether dosage adjustment is required; clinical impact of PK changes needs to be established

# MIP ERG – Findings pending MPAC review (II)

## IPTp with DHA-PPQ

- IPTp with DHA-PPQ: Halved risk of malaria during pregnancy and at delivery compared with SST, but study findings were not consistent across sites and study outcomes, and there was no consistent positive impact on birth outcomes
- IST did not result in the detection of significantly more malaria infections than the existing SST strategy

➡ Current evidence inconclusive, more research is required

## SP and azithromycin (AZ) against sexually transmitted and reproductive tract infections

- Impact of adding azithromycin to IPTp-SP on STI/RTIs and adverse birth outcomes requires further research
- Repeated SP doses as given through IPTp do~~es~~ not cure STI/RTI
- Risk of antimicrobial resistance increase associated with AZ use in this context requires further assessment

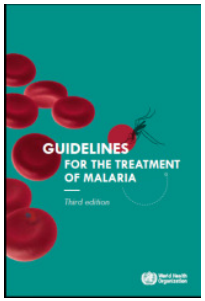
## HIV and malaria in pregnancy

- Co-trimoxazole prophylaxis (CTXp) provides only partial protection against MIP

➡ Research needed to evaluate new strategies, including alternative medicines for IPTp to be safely administered concomitantly with CTXp

# WHO Guidelines for the Treatment of Malaria

## Current recommendations to treat Pf malaria (MTG, 3rd ed 2015)




- **1st trimester:** 7 days of quinine + clindamycin
  Only use an ACT if quinine not available or adherence to 7 day treatment not guaranteed
- **2nd and 3rd trimesters:** ACT effective in the region
- Primaquine is **contraindicated** in pregnancy both for transmission reduction (anti-gametocyte) in falciparum infections and anti-relapse treatment in vivax or ovale infections

## Update plans

- Recent data available on exposure to **ACTs in the 1st trimester** of pregnancy: Stephanie Dellicour et al: First-trimester artemisinin derivatives and quinine treatments and the risk of adverse pregnancy outcomes in Africa and Asia: A meta-analysis of observational studies. (PLOS Medicine | https://doi.org/10.1371/journal.pmed.1002290 May 2, 2017)
- The **GRADE** and evidence table on malaria in pregnancy in the MTG is presently been updated by the Cochrane Infectious Disease Group.
- The WHO malaria chemotherapy **Technical Expert Group** is scheduled to meet in December 2017, to review the updated evidence and formulate revised recommendations on the use of artemisinin derivatives in the 1st trimester of pregnancy.

# Thank you very much for your attention