Malaria in pregnancy (MIP)

RBM MIP WG meeting
Geneva, 18-20 September 2017

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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 recommendations on IPTp-SP
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** 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
**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.

<table>
<thead>
<tr>
<th>Intervention area</th>
<th>Project</th>
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<tbody>
<tr>
<td><strong>Workstream 1: IPTp-SP</strong></td>
<td>UNITAID-funded project: <strong>TIPTOP</strong> (Transforming IPTp for Optimal Pregnancy)</td>
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<td>Project countries: DRC, Madagascar, Mozambique, and Nigeria</td>
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<td>Malaria enabler grant duration: 5 years</td>
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<td><strong>Workstream 2: RAS</strong></td>
<td>UNITAID-funded project: <strong>CARAMAL</strong> (previously named RAS)</td>
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<td>(Pre-referral treatment of severe malaria with quality-assured rectal artesunate)</td>
<td>Lead grantee: CHAI. Partners: Swiss TPH, UNICEF. Enablers: MMV, WHO.</td>
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<tr>
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<td>Project countries: DRC, Nigeria, and Uganda</td>
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<td>Malaria enabler grant duration: 3 years</td>
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New WHO ANC guidelines – increased number of opportunities to receive IPTp-SP

ANC Contact Schedule and Proposed Time of IPTp-SP Administration
(To be adapted to country context, also considering disease burden and health needs)

<table>
<thead>
<tr>
<th>Contact</th>
<th>IPTp-SP dose</th>
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<tbody>
<tr>
<td>1: Up to 12 weeks</td>
<td></td>
</tr>
<tr>
<td>2: 20 weeks</td>
<td>IPTp-SP dose 2</td>
</tr>
<tr>
<td>3: 26 weeks</td>
<td>IPTp-SP dose 3</td>
</tr>
<tr>
<td>4: 30 weeks</td>
<td>IPTp-SP dose 4</td>
</tr>
<tr>
<td>5: 34 weeks</td>
<td>IPTp-SP dose 5</td>
</tr>
<tr>
<td>6: 36 weeks</td>
<td>No SP administration if last dose was received at contact 5 in week 34</td>
</tr>
<tr>
<td>7: 38 weeks</td>
<td>IPTp-SP dose 6 (if no dose was received at contact 6 in week 36)</td>
</tr>
<tr>
<td>8: 40 weeks</td>
<td></td>
</tr>
</tbody>
</table>

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.

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."

Remember:
- Do not administer IPTp-SP before week 13 of pregnancy.
- 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.
- Administer the second dose of IPTp-SP one month later.
- Administer the following doses of IPTp-SP starting from the scheduled contact at 20 weeks, observing at least one-month intervals between SP doses.
- SP can be safely administered from the beginning of the second trimester until the time of delivery.
- One full dose of IPTp-SP consists of 1,500 mg/75 mg SP (i.e., three tablets of 500 mg/25 mg SP).
- Provide IPTp-SP by directly observed treatment.
- 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.
- Continue to administer 30 to 60 mg of elemental iron and 400 mcg (0.4 mg) of folic acid.
- Continue counseling as above.
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), artemesunate (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 its adverse consequences;
  2. efficacy/effectiveness of IPTp; and
  3. pharmacokinetics of antimalarials in these women including their interactions with anti-retroviral medications
**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
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 does 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