Effectiveness of 2 versus 3+ dose of IPTp with SP to prevent malaria in pregnancy: n

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WHO Policy Brief for the Implementation of Intermittent Preventive Preventive Treatment of Malaria in Pregnancy using Sulfadoxine-Pyrimethamine (IPTp-SP)

11 April 2013
WHO’s Updated IPTp-SP Policy Apr 2013

• Start as early as possible in 2nd trimester
• **At each scheduled ANC visit until delivery**, at least one month apart
• Last dose can be administered up to delivery without safety concerns
  
  – Ideally as DOT
  – Can be given either on an empty stomach or with food.
  – Not be administered to women receiving co-trimoxazole
  – Avoid Folic acid > 5mg daily
Intermittent Preventive Therapy for Malaria During Pregnancy Using 2 vs 3 or More Doses of Sulfadoxine-Pyrimethamine and Risk of Low Birth Weight in Africa: Systematic Review and Meta-analysis

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Importance Intermittent preventive therapy with sulfadoxine-pyrimethamine to control malaria during pregnancy is used in 37 countries in sub-Saharan Africa, and 31 of those countries use the standard 2-dose regimen. However, 2 doses may not provide protection during the last 4 to 10 weeks of pregnancy, a pivotal period for fetal weight gain.

Objective To perform a systematic review and meta-analysis of trials to determine whether regimens containing 3 or more doses of sulfadoxine-pyrimethamine for intermittent preventive therapy during pregnancy are associated with a higher birth weight or lower risk of low birth weight (LBW) (<2500 g) than standard 2-dose regimens.

Data Sources and Study Selection ISI Web of Knowledge, EMBASE, SCOPUS, PubMed, LILACS, the Malaria in Pregnancy Library, Cochrane CENTRAL, and trial registries from their inception to December 2012, without language restriction. Eligible studies included randomized and quasi-randomized trials of intermittent preventive therapy during pregnancy with sulfadoxine-pyrimethamine monotherapy.

Data Extraction Data were independently abstracted by 2 investigators. Relative risk...
IPTp-SP: Are 2 doses enough?

2-dose regimens
- Women coming early; unprotected for 6-10 wks
- High risk reinfections
- Important period for fetal growth

Fetal weight velocity → SP

'at risks'

Conception 10 20 30 Birth
Weeks of gestation
IPTp-SP: Are 2 doses enough?

2-dose regimens
• Women coming early; unprotected for 6-10 wks
• High risk reinfections
• Important period for fetal growth

Weeks of gestation

Conception 10 20 30 Birth

SP

Fetal weight
Rationale 3+ doses IPTp-SP

• Protect women from early 2\textsuperscript{nd} trimester
• Protect women during last 4-10 weeks
• May improve the coverage of 2-dose IPTp
• Already recommended for HIV+ women (not on cotrimoxazole)
• Used for HIV-neg women in several countries
• Can compensate for moderate SP resistance
• But what evidence of efficacy and safety?
Rationale 3+ doses IPTp-SP

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Intermittent Preventive Therapy with SP SP resistance and impact on post-treatment prophylaxis

Fetal growth velocity →

SP resistance shortens duration post-treatment prophylaxis

Weeks of gestation

SP

Sensitive

resistant

Conception

10

20

30

Birth
Intermittent Preventive Therapy with SP
SP resistance and impact on post-treatment prophylaxis

Fetal growth velocity →

SP resistance shortens duration post-treatment prophylaxis

3+ strategies: Ghana, Zambia, Malawi, Kenya
Rationale 3+ doses IPTp-SP

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Methods

- **Search strategies: All relevant studies**
  - CIDG, CENTRAL, MEDLINE, EMBASE, LILACS
  - Cochrane Central Register of Controlled Trial
  - Database: Malaria in Pregnancy Library
  - Individual researchers and organizations
  - Reference lists

- **Inclusion criteria**
  - Type of studies: RCT
  - Type of participants: Pregnant women
  - Type of interventions: 3-or monthly versus 2-dose IPT

- **Data extraction**

- **Risk of Bias → Quality of studies**

- **Data synthesis Stata**
  - Measure of the effect: RR and Mean diff (95%CI)
  - Heterogeneity I-square
  - Sub group by gravidity and HIV status
  - Sensitivity analysis
Results: 7 trials, 6,281 pregnancies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year Publish</th>
<th>Country</th>
<th>Year of Study</th>
<th>HIV Status</th>
<th>Gravidity</th>
<th># Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parise et al.</td>
<td>1998</td>
<td>Kenya</td>
<td>94-96</td>
<td>(+) &amp; (-)</td>
<td>1 &amp; 2</td>
<td>1341</td>
</tr>
<tr>
<td>Filler et al.</td>
<td>2006</td>
<td>Malawi</td>
<td>02-05</td>
<td>(+) &amp; (-)</td>
<td>1 &amp; 2</td>
<td>698</td>
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<tr>
<td>Hamer et al.</td>
<td>2007</td>
<td>Zambia</td>
<td>03-04</td>
<td>(+)</td>
<td>All</td>
<td>456</td>
</tr>
<tr>
<td>Luntamo et al.</td>
<td>2010</td>
<td>Malawi</td>
<td>03-06</td>
<td>(+) &amp; (-)</td>
<td>All</td>
<td>877</td>
</tr>
<tr>
<td>Valea et al.</td>
<td>2010</td>
<td>Burkina F.</td>
<td>06-08</td>
<td>(-)</td>
<td>All</td>
<td>1,296</td>
</tr>
<tr>
<td>Maiga et al.</td>
<td>2011</td>
<td>Mali</td>
<td>06-08</td>
<td>(-)</td>
<td>All</td>
<td>814</td>
</tr>
<tr>
<td>MacArthur et al.</td>
<td>Unpub</td>
<td>Tanzania</td>
<td>03-06</td>
<td>Unk</td>
<td>1&amp;2</td>
<td>799</td>
</tr>
</tbody>
</table>
Results
Risk of Low birth Weight

- 3+ doses more effective
  - Reduced by an extra 20%
  - 95 CI: 6-31
  - P=0.006

- Consistent finding
  - Low Heterogeneity: $I^2 = 0\%$
## Results

### Mean birth Weight

- **3+ doses more effective**
  - Increased by an extra 56 grm
  - 95 CI: 29-83
  - P<0.001

- **Consistent finding**
  - Low Heterogeneity: $I^2 = 0\%$

### Table: Mean birth Weight by Dose Group

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Period</th>
<th>Birth Weight, Mean Difference (95% CI), g</th>
<th>Favors 2 Doses</th>
<th>Favors &gt;3 Doses</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-Negative: G1-G2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parise et al., 1999 (Kenya)</td>
<td>1994-1996</td>
<td>57 (-91 to 205)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filler et al., 2006 (Malawi)</td>
<td>2002-2005</td>
<td>60 (-24 to 184)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luntamo et al., 2010 (Malawi)</td>
<td>2003-2006</td>
<td>100 (-3 to 203)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valea et al., 2010 (Burkina Faso)</td>
<td>2006-2008</td>
<td>16 (-75 to 107)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diakite et al., 2011 (Mali)</td>
<td>2006-2008</td>
<td>91 (-9 to 910)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal ($I^2 = 7.1%, P = .75$)</td>
<td></td>
<td>57 (20 to 114)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall effect: Z = 2.90, P = .005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| HIV-Positive: G1-G2 | | | | | |
| Parise et al., 1999 (Kenya) | 1994-1996 | 27 (-234 to 288) | | | |
| Filler et al., 2006 (Malawi) | 2002-2005 | 110 (-48 to 268) | | | |
| Hamor et al., 2007 (Zambia) | 2003-2004 | 134 (6 to 262) | | | |
| Luntamo et al., 2010 (Malawi) | 2003-2006 | -54 (-412 to 304) | | | |
| Subtotal ($I^2 = 0.0\%, P = .73$) | | 102 (12 to 192) | | | |
| Overall effect: Z = 2.22, P = .03 |

| HIV-Positive: ≥G3 | | | | | |
| Hamor et al., 2007 (Zambia) | 2003-2004 | 9 (-161 to 170) | | | |
| Luntamo et al., 2010 (Malawi) | 2003-2006 | 216 (-5 to 437) | | | |
| Subtotal ($I^2 = 52.8\%, P = .15$) | | 100 (-101 to 301) | | | |
| Overall effect: Z = 0.97, P = .33 |

| HIV Status Unknown: G1-G2 | | | | | |
| MacArthur et al., 2009 (Tanzania) | 2003-2006 | 11 (-57 to 79) | | | |
| Overall effect: Z = 0.32, P = .75 |

Random-effects overall ($I^2 = 9.0\%, P = .86$)

- Overall effect: Z = 4.03, P<.001
- Fixed-effects overall: Z = 5.62, P<.001
Benefit on birth weight consistent across range of subgroups and sites
Safety Data

• Miscarriage, stillbirth, congenital malformations similar in both arms
• Severe skin reactions
  – 1 case reported (IPTp Monthly) in one study over the 6 studies with 2744 participants in the 3-dose regimen (before the second dose)
Secondary outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>RR (95% CI)</th>
<th># Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal anaemia</td>
<td>0.96 (0.90-1.01)</td>
<td>7</td>
</tr>
<tr>
<td>Maternal severe anaemia</td>
<td>0.73 (0.48-1.11)</td>
<td>6</td>
</tr>
<tr>
<td>Maternal parasitemia</td>
<td>0.68 (0.52-0.89)</td>
<td>7</td>
</tr>
<tr>
<td>Placental malaria</td>
<td>0.51 (0.38-0.68)</td>
<td>6</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>0.95 (0.80-1.12)</td>
<td>7</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>1.43 (0.88-2.33)</td>
<td>6</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>1.14 (0.85-1.55)</td>
<td>7</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>0.88 (0.57-1.35)</td>
<td>6</td>
</tr>
</tbody>
</table>
Summary

- 7 trials, 6281 pregnancies
- 3+ doses associated with
  - 56 g higher birth weight (95% CI, 29-83 g), $I^2=0\%$
  - 20% less LBW: RR 0.80 (0.69-0.94), $I^2=0\%$
  - 49% less placental malaria: RR 0.51 (0.38-0.68), $I^2=0\%$
  - 40% less severe mat. anaemia: RR 0.60 (0.36-0.99), $I^2=20\%$ (G1/G2)
- Benefit consistent across studies
- No differences in rates of serious adverse events
Dihydroartemisinin-Piperaquine (DP) for IPTp: 3 vs monthly dosing

Dihydroartemisinin–Piperaquine for the Prevention of Malaria in Pregnancy

Abel Kakuru, M.D., Prasanna Jagannathan, M.D., Mary K. Muhindo, M.D.,
Paul Natureeba, M.D., Patricia Awori, M.D., Miriam Nakalembe, M.D.,
Bishop Opira, B.Pharm., Peter Olwoch, B.S., John Ategeka, B.S.,
Patience Nayebare, B.S., Tamara D. Clark, M.H.S., Margaret E. Feeney, M.D.,
Edwin D. Charlebois, Ph.D., Gabrielle Rizzuto, M.D., Ph.D.,
Atis Muehlenbachs, M.D., Ph.D., Diane V. Havlir, M.D.,
Moses R. Kamya, M.Med., Ph.D., and Grant Dorsey, M.D., Ph.D.
### Table 2. Efficacy Outcomes.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sulfadoxine–Pyrimethamine†</th>
<th>Three-Dose Dihydroartemisinin–Piperaquine</th>
<th>Monthly Dihydroartemisinin–Piperaquine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative Risk (95% CI)</td>
<td>P Value</td>
<td>Relative Risk (95% CI)</td>
</tr>
<tr>
<td>Preterm delivery‡</td>
<td>1.53 (0.64–3.63)</td>
<td>0.33</td>
<td>5.98 (1.51)</td>
</tr>
<tr>
<td>Congenital anomaly‡</td>
<td>2.20 (0.41–11.7)</td>
<td>0.43</td>
<td>0/96</td>
</tr>
<tr>
<td>Low birth weight‡</td>
<td>1.11 (0.56–2.20)</td>
<td>0.76</td>
<td>8/98 (8.2)</td>
</tr>
<tr>
<td>Symptomatic malaria during pregnancy — no. of events (incidence per person-year at risk)</td>
<td>0.33 (0.17–0.64)†</td>
<td>0.001</td>
<td>0</td>
</tr>
<tr>
<td>Detection of malaria parasites by LAMP during pregnancy — no. of events/total no. (%)‡</td>
<td>0.41 (0.30–0.54)</td>
<td>&lt;0.001</td>
<td>26/496 (5.2)</td>
</tr>
<tr>
<td>Anemia during pregnancy — no. of events/total no. (%)**</td>
<td>0.87 (0.61–1.23)</td>
<td>0.43</td>
<td>61/258 (23.6)</td>
</tr>
</tbody>
</table>

* Table adapted from Kakuru, NEJM 2016, Uganda.
Conclusion

- 3+ courses of SP better than 2 courses of SP
- Monthly dosing of DP is better than 3 courses of DP
- Significantly reduces
  - The risk of placental malaria and LBW, severe maternal anaemia among HIV negative pregnant women
- Starting early in 2\textsuperscript{nd} trimester is likely beneficial
- Countries should switch to the ‘at each scheduled visit’ WHO regimen
- Highly Cost-effectiveness way to reduce LBW
- Counteracts reduced effectiveness due to partial resistance
- Uptake: Could it enhance ANC repeat visits? (aligned with FANC)
Thank you!

Investigators
