Feiko ter Kuile, LSTM
Overview Malaria in Pregnancy and control

Istanbul 26 June 2012
Overview

• Brief overview malaria in pregnancy
• Overview MiP Control
  – IPTp: concept and evidence for impact
  – Not on uptake (see Next presentations)
• Regimen considerations: impact of frequency of dosing
• Alternative regimens and strategies on the horizon

• Take away messages and potential program implications
• Surprising findings!
MALARIA IN PREGNANCY

Burden and clinical presentation
Impact of malaria in pregnancy

**Pregnancy**
- Increases susceptibility
- More infections
- More severe

**Mother**
- Asymptomatic to acute clinical illness / death
- Severe anaemia

**Foetus**
- Miscarriage
- Stillbirth
- Low birth weight (2x) IUGR / Preterm

**Effects depend on**
- Malaria endemicity
- Maternal age
- Gravidity
- HIV status

**Longer term effects**
- Neonatal and post neonatal mortality
- Immune modulation (susceptibility)
- Infant anaemia
- Infant growth?
- Neuro-cognitive development?
Africa: Infection risk & impact LBW
32m pregnancies at risk

• 1980s-90s: Guyatt et al 2004
  – Prevalence: 25%
  – Responsible for 19% of LBW (570,000), and 100,000 infant deaths per year
• 2000+: Meta-analysis 97 studies (work-in-progress)
  – Prevalence: 14%
  – Responsible for approximately 300,000 LBW /yr
• Declining trend over time: halved compared to 1990s
• Minimum estimates (based on prevalence!)
• Insufficient data for low/unstable malaria transmission
MALARIA CONTROL IN PREGNANT WOMEN

One of the most common preventable causes of LBW
Current recommendations for control of Malaria in Pregnancy

WHO AFRO

’Strategic framework for malaria prevention and control during pregnancy’

1. Case management
2. Insecticide treated nets (ITNs)
3. Intermittent preventive treatment (IPTp)
4. Cotrimoxazole in HIV+ women

Other WHO Regions

1. Case management
2. Passive case detection
3. ITNs +/-
WHO Treatment Guidelines Malaria in Pregnancy 2010

2nd & 3rd trimester
- ACTs (3 days)
- Quinine [+ clindamycin (7d)]
- [Artesunate + clindamycin (7d)]

1st trimester
- Quinine [+ clindamycin (7d)]
- Artemisinins not recommended unless
  - in severe disease
  - no other drugs available
    - Rescue therapy; e.g. Quinine failures
Malaria Control in Pregnancy
PREVENTION

Intermittent Preventive Therapy
IPTp with SP

Concept 1990s

Fetal weight velocity

Efficacy (meta-analysis)

2-dose IPTp reduces
- Placental malaria by 52%
- LBW by 29%
- Mean birthweight 79g
- Maternal anaemia by 10%

*Systematic review: Ter Kuile FO, van Eijk AM, Filler SJ; Jama 2007
IPTp strategy
Predicated for high transmission areas

Epidemiological features at higher levels of transmission

• Most infections asymptomatic
• High % infected at 1\textsuperscript{st} visit = treatment effect
• High % re-infected = prevention
• Most consequences in G1/2

White N. Malaria Journal 2008; 7:9
IPTp: Are 2 doses of SP enough?

• WHO-AFRO strategic framework
  – HIV-Pos women: 3-doses (if not on CTX)
  – HIV-Neg women: ‘at least’ 2 doses

• ‘At least 1 month between doses’

• 2-dose regimen used in 89% of IPTp countries
  – 3+dose: Ghana, Zambia, Zimbabwe, [Cameroon], [Kenya], [Malawi]

• 2-doses associated with 29% reduction in LBW, but ‘only’ a 52% reduction in placental malaria
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 (200 gr/week)

Fetal weight velocity →

‘at risks’

Fetal weight

- Conception
- 10
- 20
- 30

Weeks of gestation

Birth
Meta-analysis Kayentao et al 2012

- All trials comparing 2-dose vs 3 or ‘monthly’ IPTp-SP

- 7 trials conducted between 1995-2011
  - 4 trials completed /published since 2010

- 5969 women
- ‘3+ dose’ = Median 4 doses
Impact of 3+ versus 2-dose on MBW; 7 trials

<table>
<thead>
<tr>
<th>Author, Published, Country</th>
<th>Study Period</th>
<th>% dhrs K540E</th>
<th>Bednet use</th>
<th>Mean difference (95% CI)</th>
<th>N, mean (SD); Treatment</th>
<th>N, mean (SD); Control</th>
<th>% Weight</th>
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<td>2002-2005</td>
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<td>MacArthur, Unpubl., Tanzania 2003-2006</td>
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<td>11 (-57, 79)</td>
<td>368</td>
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<td>Heterogeneity between groups: p = 0.533</td>
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<td>56 (29, 83)</td>
<td>2215</td>
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<td>Overall</td>
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<td>56 (29, 83)</td>
<td>2215</td>
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</table>
Impact of 3+ vs 2-dose IPTp-SP on birth weight (fixed effect models)

<table>
<thead>
<tr>
<th></th>
<th>LBW RR (95% CI)</th>
<th>Diff. in Mean Birth-Weight (95% CI)</th>
<th>N Studies</th>
<th>Across studies I²</th>
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<tbody>
<tr>
<td>All</td>
<td>0.79 (0.68, 0.92)</td>
<td>56 (29, 83)</td>
<td>7</td>
<td>0%</td>
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<tr>
<td>HIV-neg</td>
<td>0.76 (0.62, 0.93)</td>
<td>58 (26, 89)</td>
<td>5</td>
<td>0%</td>
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<tr>
<td>HIV-pos</td>
<td>0.81 (0.58, 1.15)</td>
<td>97 (22, 172)</td>
<td>4</td>
<td>0%</td>
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<td>G1-G2</td>
<td>0.80 (0.67, 0.94)</td>
<td>57 (22, 93)</td>
<td>7</td>
<td>0%</td>
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<tr>
<td>G3 +</td>
<td>0.77 (0.54, 1.10)</td>
<td>53 (12, 95)</td>
<td>4</td>
<td>0%</td>
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</tbody>
</table>
IPTp-SP: meta-analysis 7 trials
Adding 3rd and 4th dose improves birthweight

• No evidence for heterogeneity
  – across trials ($I^2=0\%$)
  – across subgroups ($I^2=0\%$)

• Benefit of extra dose evident in
  – all gravidae groups,
  – HIV-negative and HIV-positive women,
  – Net users and non-users
  – Low and high resistance areas
    • 0 to 96% DHPS 540 mutation
IPTp-SP: meta-analysis 7 trials
Adding 3\textsuperscript{rd} and 4\textsuperscript{th} dose improves birthweight

Example of added benefit
Placebo: 20\% LBW
\textbf{2-dose}: 29\% reduction to 14.3\%
\textbf{3+dose}: \underline{extra} 21\% reduction to 11.3\%

Conclusion
More complete coverage during 2nd+3rd trimester provides better improvements in birthweight than the standard 2-dose regimen of IPTp-SP
3+dose IPTp
Policy implications?

• 2-dose policy used in 32/37 (86%) countries
• More frequent dosing should be considered
  – Areas low to high resistance where DHPS-581 mutation is rare
    (most of Africa today)
• Operationally easier to implement as part of FANC?
• May reduces ‘missed opportunities’
• Increases coverage of at least 2 doses
• Important lesson for next generation drugs
IPTp

IMPACT SP RESISTANCE
DHPS 540E

Inbarani Naidoo & Cally Roper, Parasitology 2011
SP resistance shortens duration post-treatment prophylaxis

White N. Malaria Journal 2008; 7:9
Intermittent Preventive Therapy
Post-treatment prophylaxis

Fetal growth velocity →

SP resistance shortens duration post-treatment prophylaxis

SP

Weeks of gestation

Conception  10  20  30  Birth

Sensitive  resistant
Impact of SP Resistance on IPTp efficacy
WHO TEG IPTp meeting July 2007

- IPTp-SP remains highly effective even in areas with 25% failure by D14 in children (40% by day 28)
- No data from high SP resistance areas (yet)
- 3+ doses SP may ‘buy time’, but alternative antimalarials soon required
- Reserve SP for IPT(p)
High grade SP resistance in Tanzania fitness advantage result in higher densities

Competitive facilitation of drug-resistant *Plasmodium falciparum* malaria parasites in pregnant women who receive preventive treatment

W. E. Harrington\(^{a,b}\), T. K. Mutabingwa\(^{a,c}\), A. Muehlenbachs\(^{a,d}\), B. Sorensen\(^{a}\), M. C. Bolla\(^{a}\), M. Fried\(^{a,b}\), and P. E. Duffy\(^{a,b,1}\)

\(^{a}\)Seattle Biomedical Research Institute, 307 Westlake Avenue N, Seattle, WA 98109; \(^{b}\)University of Washington, Department of Global Health, Harborview Medical Center, 325 9th Avenue, Box 359931, Seattle, WA 98104; \(^{c}\)National Institute of Medical Research, P.O. Box 9653, Dar es Salaam, Tanzania; and \(^{d}\)University of Washington, Department of Pathology, Box 357470, Seattle, WA 98195-7470

- Quintuple mutations saturated (>95%): [DHFR (3x) and DHPS (2x)]
- Additional DHPS 581 mutation associated with less parasite diversity, higher parasite densities, more placental inflammation
- High grade resistant parasites have a fitness advantage resulting in MORE malaria; taking IPTp with SP potentially harmful
IPTp-effectiveness
Ongoing studies

<table>
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<tr>
<th>MIPc</th>
<th>CDC-USAID</th>
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<tr>
<td>MA6</td>
<td>1. Malawi</td>
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<td>6. Malawi-II</td>
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<tr>
<td>MA5</td>
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<td></td>
<td>3. Burkina F</td>
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<td></td>
<td>8. Zambia</td>
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<tr>
<td></td>
<td>4. Ghana</td>
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<td></td>
<td>9. Uganda</td>
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<td></td>
<td>5. The Gambia</td>
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<td></td>
<td>10. Kenya</td>
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IPTp-SP effectiveness Malawi 2010

• DHFR/DHPS quintuple combined haplotype: 90+%

• 42-day In-vivo follow-up (not PCR corrected)
  – G1+2: 49% failure
  – G3+: 25% failure
  – Compared to 5% in 2000

• Delivery: effect of IPTp-SP
  – No impact on placental malaria
  – Significant impact on growth retardation in primigravidae
Composite SGA/ LBW/ preterm
Malawi 2010/11, Julie Gutman et al,

<table>
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<th></th>
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<th>1 dose</th>
<th>2 doses</th>
<th>3+ doses</th>
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<td>141</td>
<td>520</td>
<td>24</td>
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<td>All Gravida</td>
<td>ref</td>
<td>0.65 (0.32-1.32); 0.23</td>
<td>0.53 (0.27-1.04); 0.06</td>
<td>0.19 (0.04-0.86); 0.03</td>
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<td>G1</td>
<td>ref</td>
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<td>0.34 (0.22-0.52); &lt;0.0001</td>
<td>0.18 (0.05-0.70); 0.01</td>
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<td>1.77 (0.27-11.5); 1</td>
<td>1.60 (0.25-10.1); 1</td>
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<td>All Gravida</td>
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<td>0.73 (0.40-1.33); 0.30</td>
<td>0.61 (0.35-1.07); 0.08</td>
<td>0.21 (0.05-0.86); 0.03</td>
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<td>0.02</td>
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<td>G1</td>
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<td>0.55 90.35-0.85); 0.008</td>
<td>0.36 (0.25-0.52); &lt;0.0001</td>
<td>0.22 (0.06-0.80); 0.02</td>
<td>0.06</td>
<td>&lt;.0001</td>
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<td>G2+</td>
<td>ref</td>
<td>-</td>
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</table>
SP resistance and IPTp effectiveness

Preliminary conclusions

• Evidence for decreasing efficacy over time with increasing SP resistance, but,…
  – continued benefit in primigravidae in areas where quintuple dhfr/dhps haplotype is saturated (90%+),
  – albeit less than in areas with low SP resistance

• No evidence for harm through competitive facilitation in areas where quintuple dhfr/dhps haplotype is saturated, but additional mutations in dhps 581 or dphs 164 are absent or rare

• Difficult to monitor: methodology important
ALTERNATIVES TO SP
IPTp potential alternative drugs
Long-acting drugs needed

• Initially treatment effect considered important
• IPTi (infants) 2 trials: short vs long-acting drugs
  – Odhiambo et al, PlosOne 2010 (CD vs SP\textsubscript{AS} vs AQ\textsubscript{AS})
  – Gosling et al, Lancet, 2009 (CD, SP, MQ)
• Long acting drugs much more effective than CD
• Conclusions
  – Effect not sustained beyond window of pharmacological protection (no lasting ‘vaccine’ effect)
  – Short-acting drugs provide little (if any) benefit
  – Drugs with protracted suppressive activity needed for prophylaxis
Alternative antimalarials for IPTp
Ongoing trials

<table>
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<td>MIPc</td>
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<td>MIPc</td>
<td>SP + Azithromycin (AZ)</td>
<td>PNG</td>
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<td>NiH</td>
<td>Chloroquine (CQ) mono</td>
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<td>Pfizer</td>
<td>CQ + AZ</td>
<td>5 countries Africa</td>
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More expensive, more complex split dose multi-day regimens, less well tolerated and less available than SP
CHALLENGE OF DECLINING TRANSMISSION
Malaria transmission declining
Role IPTp in low transmission areas?

White N. Malaria Journal 2008; 7:9
Intermittent Screening and Treatment ‘ISTp’: Concept

- Scheduled screening by RDTs as part of focused ANC
  - E.g. 3 or 4 times in 2\textsuperscript{nd} + 3\textsuperscript{rd} trimester
  - Among women protected by ITNs
- Treat RDT positive women with a long acting ACT
  - 1. Early detection & treatment of asymptomatic malaria
  - 2. Prophylactic effect

<table>
<thead>
<tr>
<th>Pro</th>
<th>Con</th>
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<tbody>
<tr>
<td>Drug exposure restricted to those that need it (80:20); primigravidae, peak season, ‘hot spots’, etc</td>
<td>More complex, expensive Gaps, missing subpatent infections</td>
</tr>
</tbody>
</table>

- Integration with screening for anaemia, HIV and STIs
Intermittent Screening and Treatment (ISTp) results to date

Ghana: Tagbor et al PLOS One 2010

ISTp was as effective as IPTp with SP in an area with low SP resistance and moderate malaria transmission.
Conclusions & Recommendations

• Period major changes, challenges & opportunities

• Challenges MiP Control
  – Low Uptake
  – Increased resistance
  – Decreasing transmission
Key ‘Take away’ messages

1. 3+ doses more effective than 2-dose regimens
   – In all gravidae, net users and non-users, HIV+ and HIV-
   – in low to high grade SP resistance areas (excluding dhps-540)
   – IPTp-SP likely to have long shelf life in western-Africa
   – Simpler regimen → FANC - positive impact on uptake?

2. Continued effectiveness IPTp-SP despite resistance
   – Remain vigilant: potentially harmful if DHPS-581 common?

3. Trial results next IPTp drugs & IST available 2013-14
Application to programs

1. IPTp-SP is likely to remain key component MiP control for several years, especially in W-Africa

2. WHO 9-11 July review impact SP-resistance:
   – Some re-assurance about impact of SP-resistance in east and southern Africa
   – However monitoring Mol. markers SP resistance required

3. Moving away from 2 doses allows for better alignment with FANC
   – Could simplification of guidelines increase uptake?

4. Likely to see more variation in MiP control strategies
   – Move away from one-size-fits all;
   – Multiple strategies per region and country
Malaria in Pregnancy Consortium

Welcome to the website of the Malaria in Pregnancy (MiP) Consortium. The MiP Consortium is a global research initiative of 47 research institutions, led by the Liverpool School of Tropical Medicine, undertaking a five year programme of research (2007-2012) to evaluate new and improved existing interventions for the prevention and treatment of malaria in pregnancy, which places up to 50 million women at risk every year.

Ten major projects direct research in four key areas of malaria in pregnancy: burden assessment, prevention, treatment and how best to scale up existing strategies and interventions. Expert institutions from all over the world are involved in conducting this research and sharing information to provide the evidence needed to improve the control of malaria in pregnancy. The MiP Consortium is supported by the Bill & Melinda Gates Foundation, the European and Developing Countries Clinical Trials Partnership (EDCTP) and the European Union. The Secretariat is based at the Liverpool School of Tropical Medicine.
Acknowledgements

• Members of MIP Consortium who contributed to discussions

• This work was partly funded by
  – the MiP Consortium which is funded through a grant from the Bill & Melinda Gates Foundation to the Liverpool School of Tropical Medicine and
  – EDCTP