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 ! S

MALARIA IN PREGNANCY

Burden and clinical presentation

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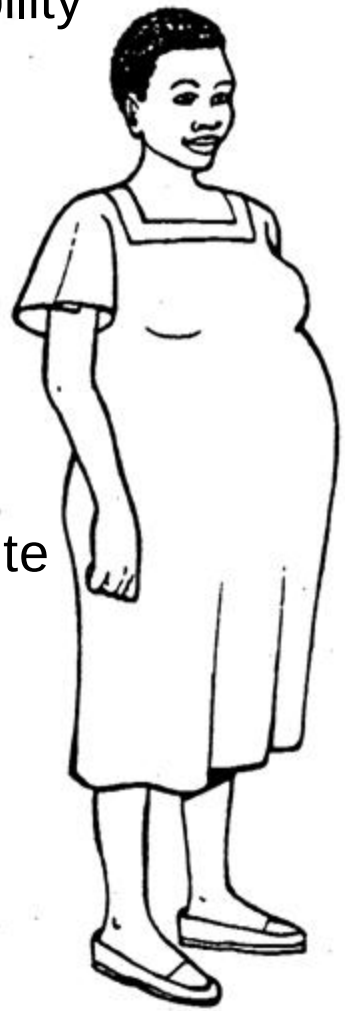
Impact of malaria in pregnancy

Pregnancy
-Increases susceptibility
-More infections
-More severe



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

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

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

Longer term effects
-Neonatal and post neonatal mortality
-Immune modulation (susceptibility)
-Infant anaemia
-Infant growth?
-neuro-cognitive development?

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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

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MALARIA CONTROL IN PREGNANT WOMEN

One of the most common preventable causes of LBW

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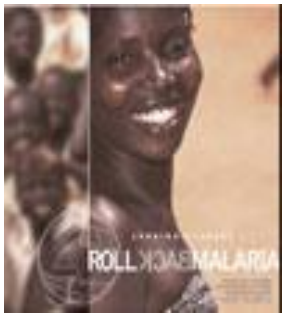
Current recommendations for control of Malaria in Pregnancy

World Health Organization

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 +/-

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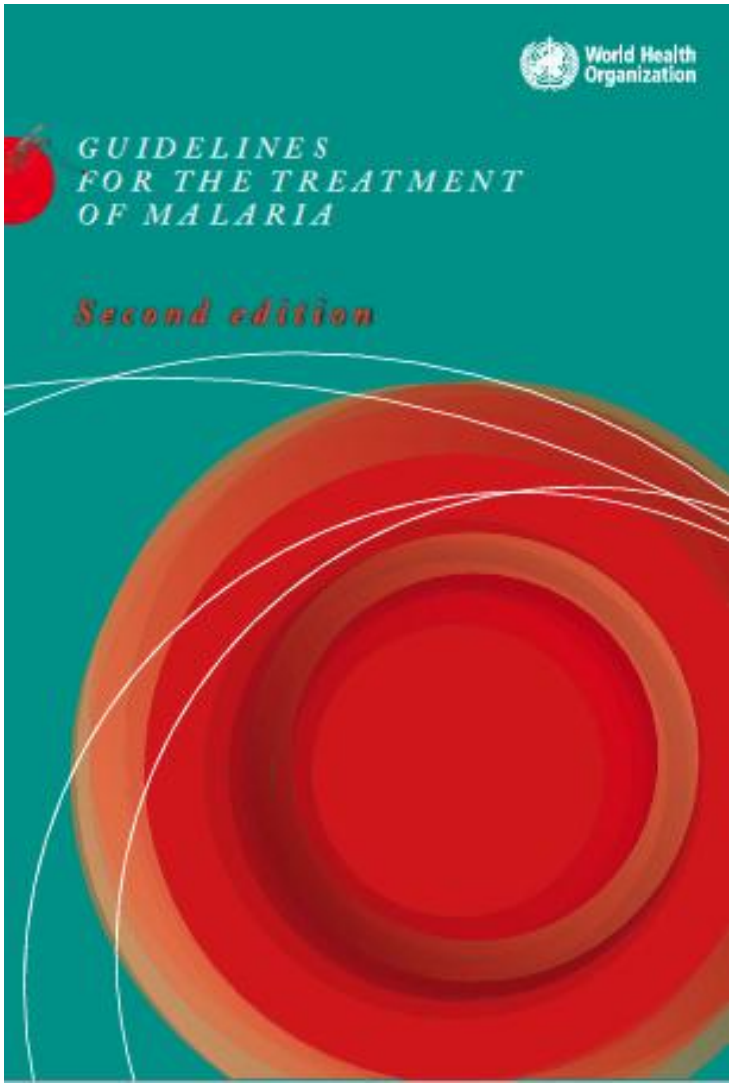
WHO Treatment Guidelines Malaria in Pregnancy 2010

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



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Malaria Control in Pregnancy

PREVENTION

Intermittent Preventive Therapy

IPTp with SP

Concept 1990s

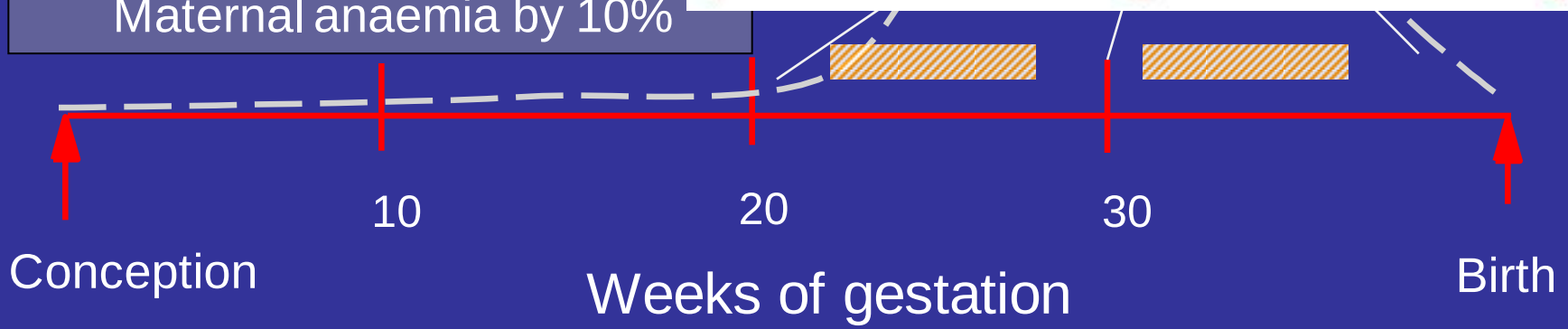
SP

Fetal weight v

Efficacy (meta-analysis)

2-dose IPTp reduces

- Placental malaria by 52%
- LBW by 29%
- Mean birthweight 79g
- Maternal anaemia by 10%



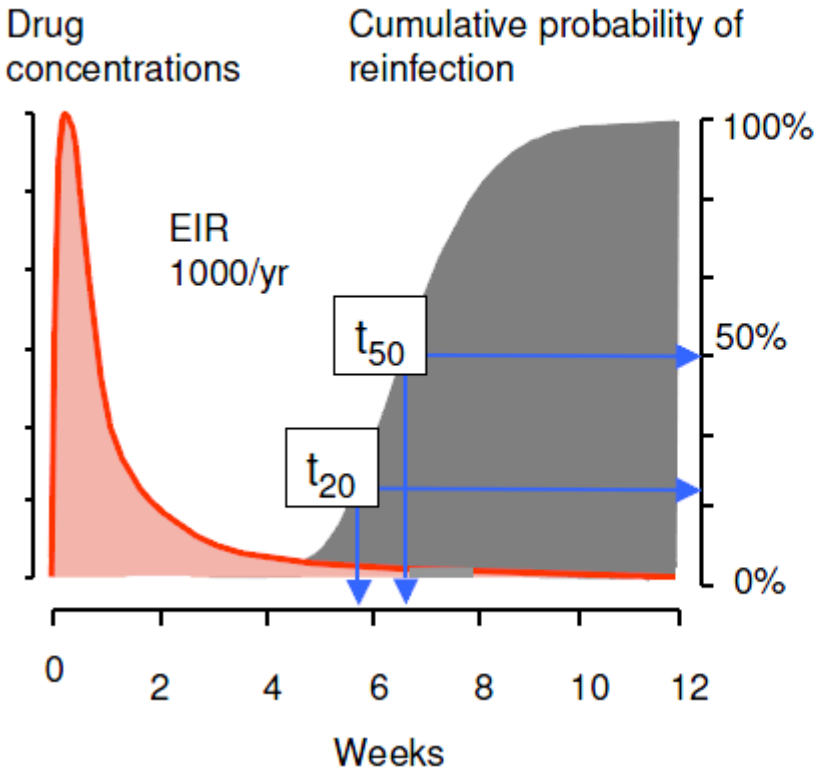
*Systematic review: Ter Kuile FO, van Eijk AM, Filler SJ; Jama 2007

IPTp strategy
Predicated for high transmission areas

Epidemiological features at higher levels of transmission

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

White N. Malaria Journal 2008; 7:9



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IPTp: Are 2 doses of SP enough?

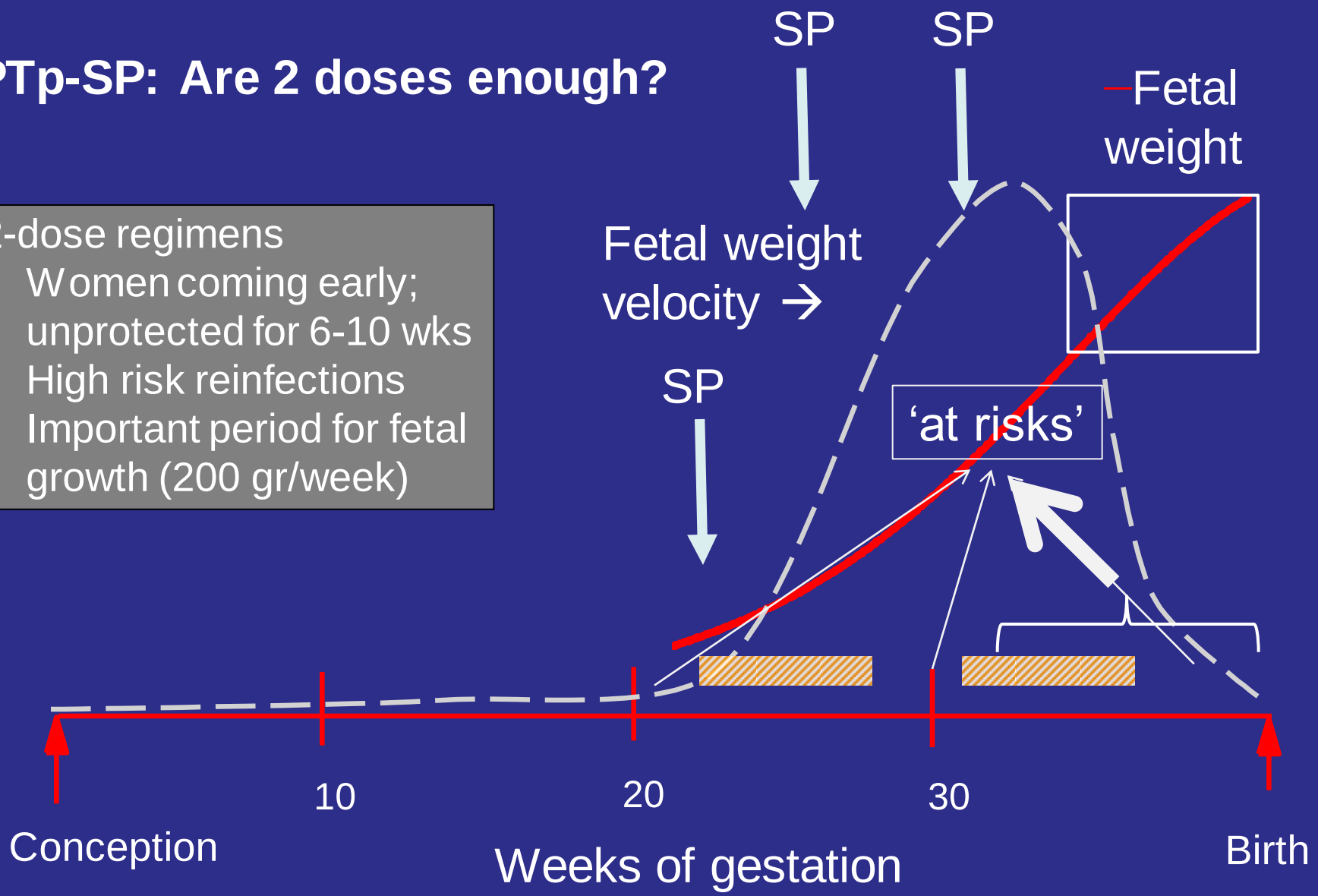
- WHO-AFRO strategic framework
  - HIV-Pos women: 3-doses (if not on CTX)
  - HIV-Neg women: 'at least' 2 doses

- '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)



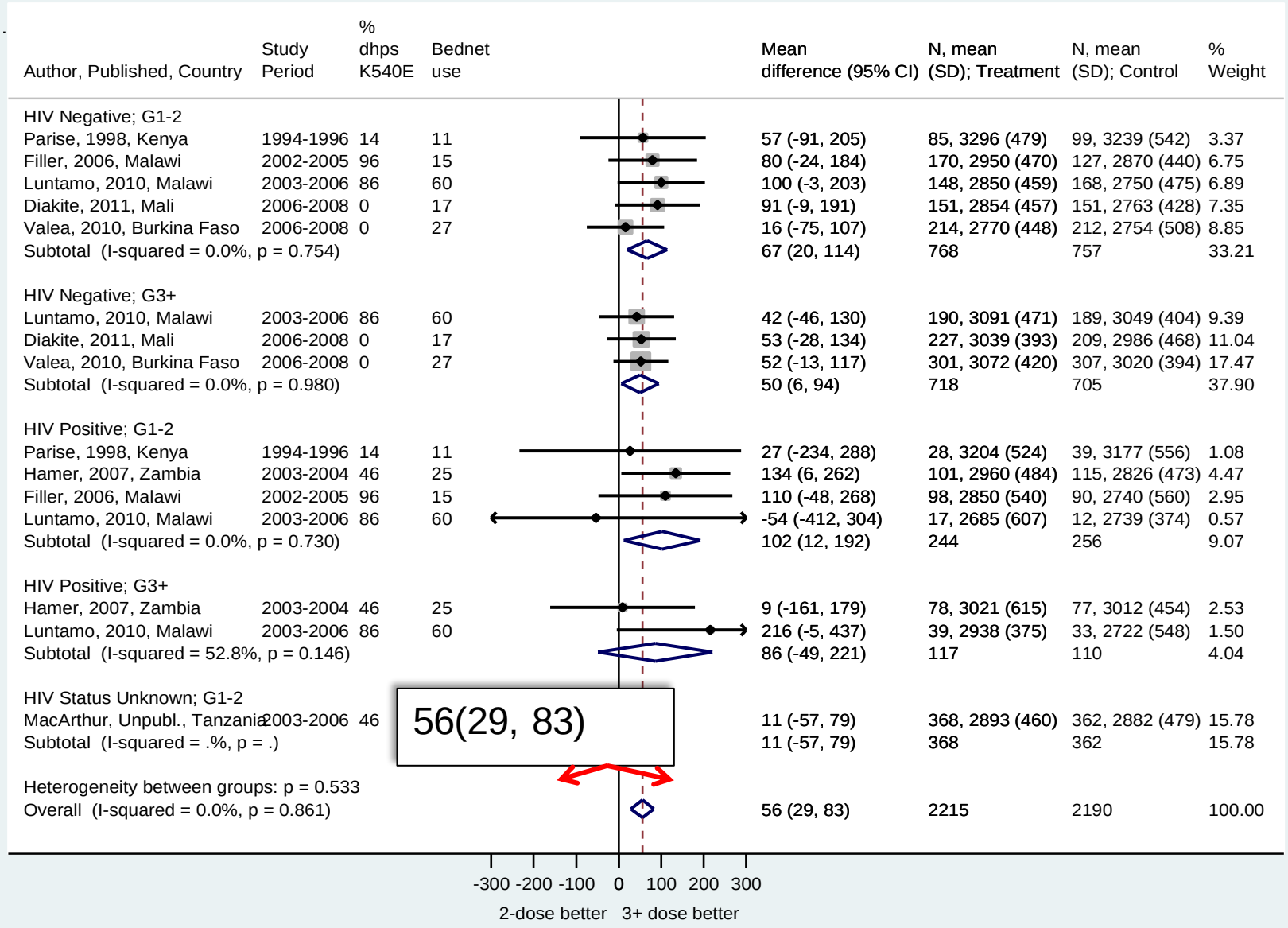
Meta-analysis Kayentao et al 2012

- 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



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Impact of 3+ vs 2-dose IPTp-SP on birth weight (fixed effect models)

	LBW RR (95% CI)	Diff. in Mean Birth-Weight (95% CI)	N Studies	Across studies I^2
All	0.79 (0.68, 0.92)	56 (29, 83)	7	0%
HIV-neg	0.76 (0.62, 0.93)	58 (26, 89)	5	0%
HIV-pos	0.81 (0.58, 1.15)	97 (22, 172)	4	0%
G1-G2	0.80 (0.67, 0.94)	57 (22, 93)	7	0%
G3 +	0.77 (0.54, 1.10)	53 (12, 95)	4	0%

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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

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IPTp-SP: meta-analysis 7 trials
Adding 3rd and 4th dose improves birthweight

Example of added benefit

Placebo: 20% LBW

2-dose: 29% reduction to14.3%

3+dose: 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

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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

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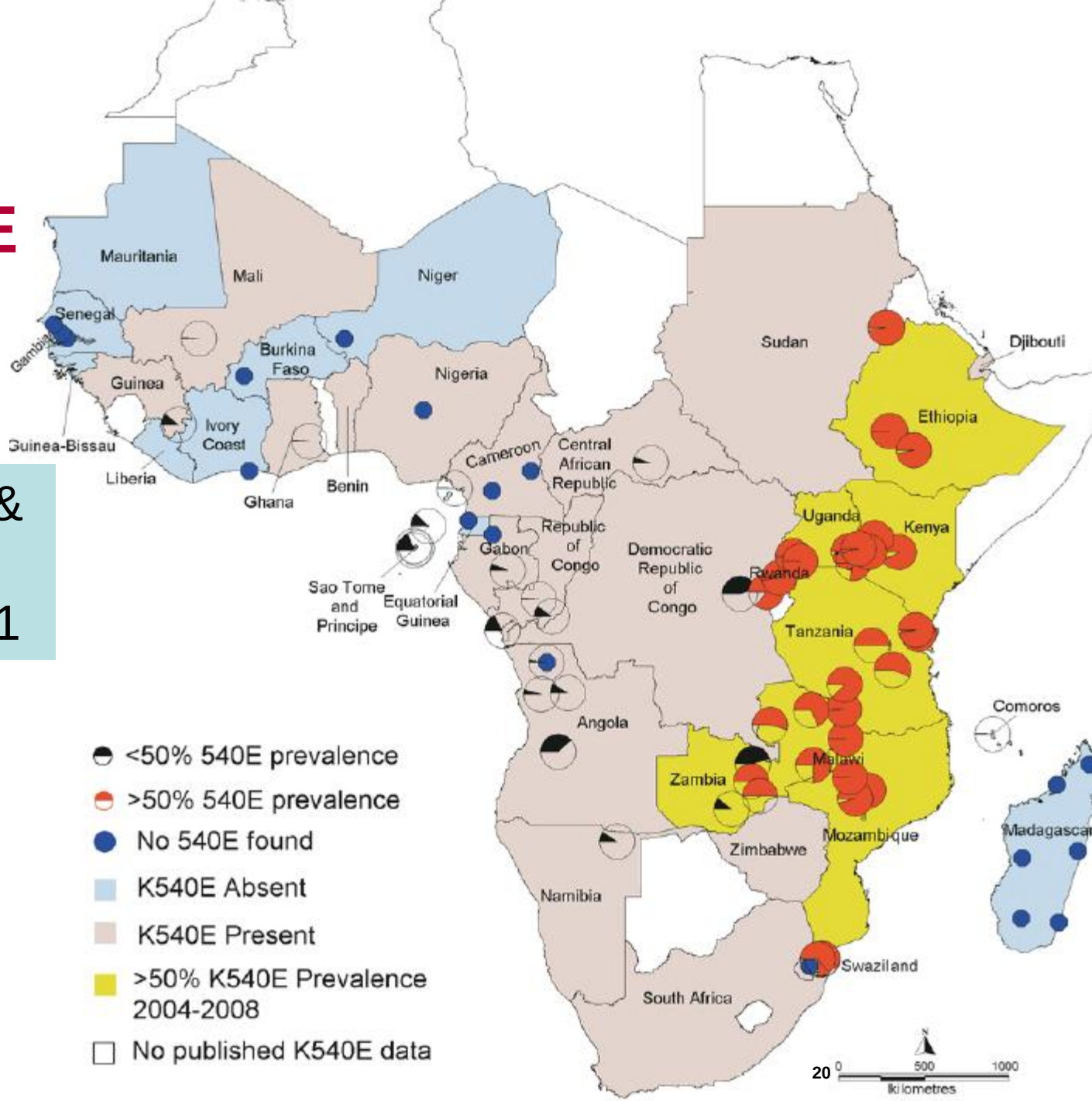
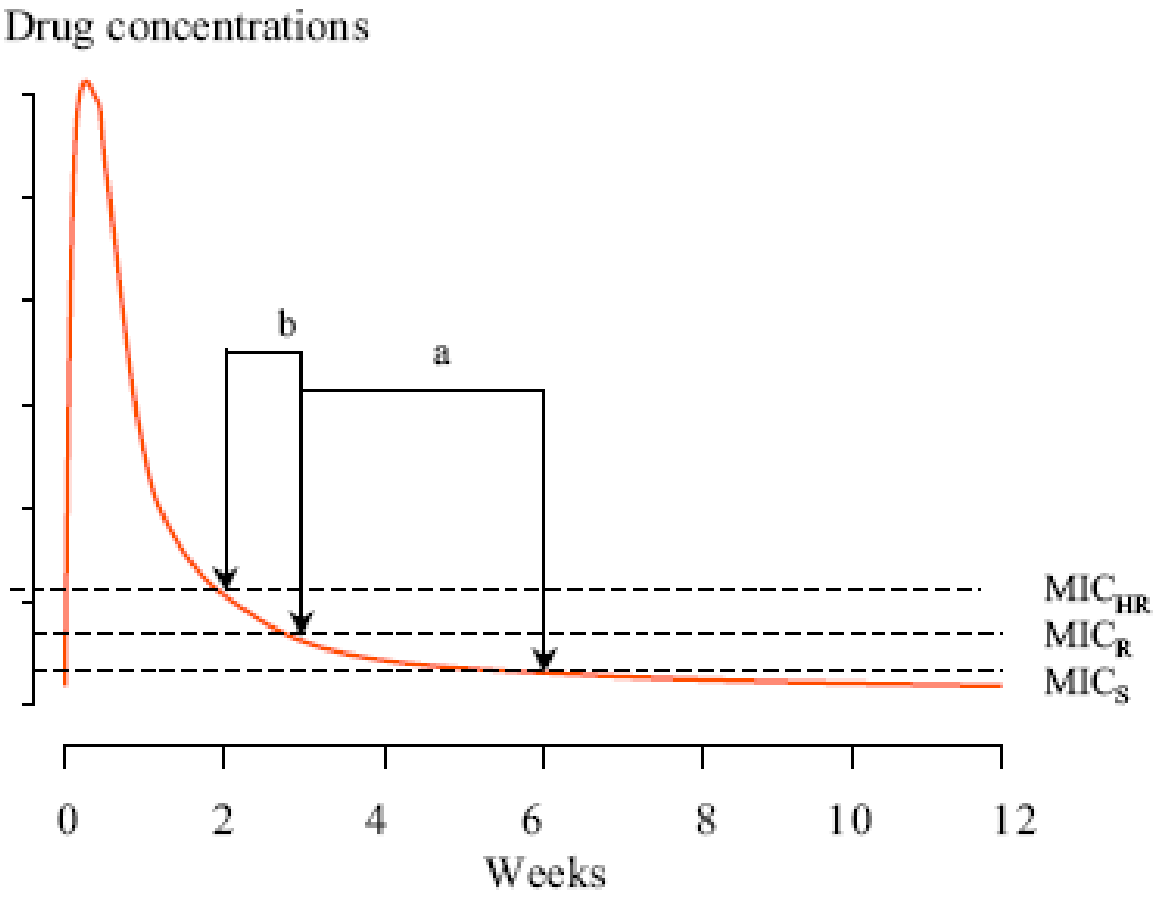
DHPS 540E

Inbarani Naidoo & Cally Roper, Parasitology 2011

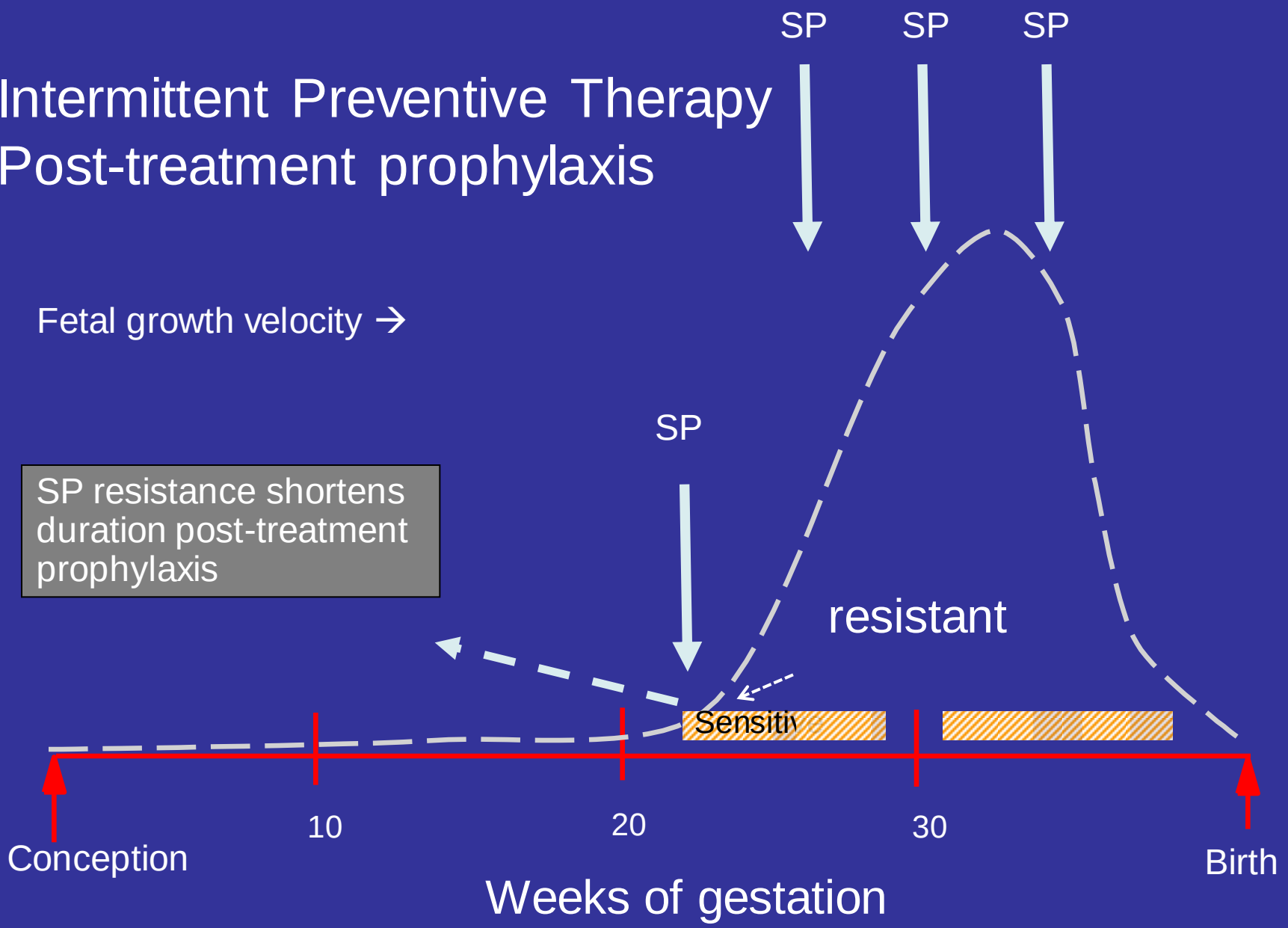


SP resistance shortens duration post-treatment prophylaxis



White N. Malaria Journal 2008; 7:9

Intermittent Preventive Therapy
Post-treatment prophylaxis



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

Feiko O. ter Kuile, MD, PhD
Annemieke M. van Eijk, MD, PhD
Scott J. Filler, MD, DTMH

Effect of Sulfadoxine-Pyrimethamine Resistance on the Efficacy of Intermittent Preventive Therapy for Malaria Control During Pregnancy
A Systematic Review

JAMA, June 20, 2007—Vol 297, No. 23

- 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)

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High grade SP resistance in Tanzania fitness advantage result in higher densities

PNAS

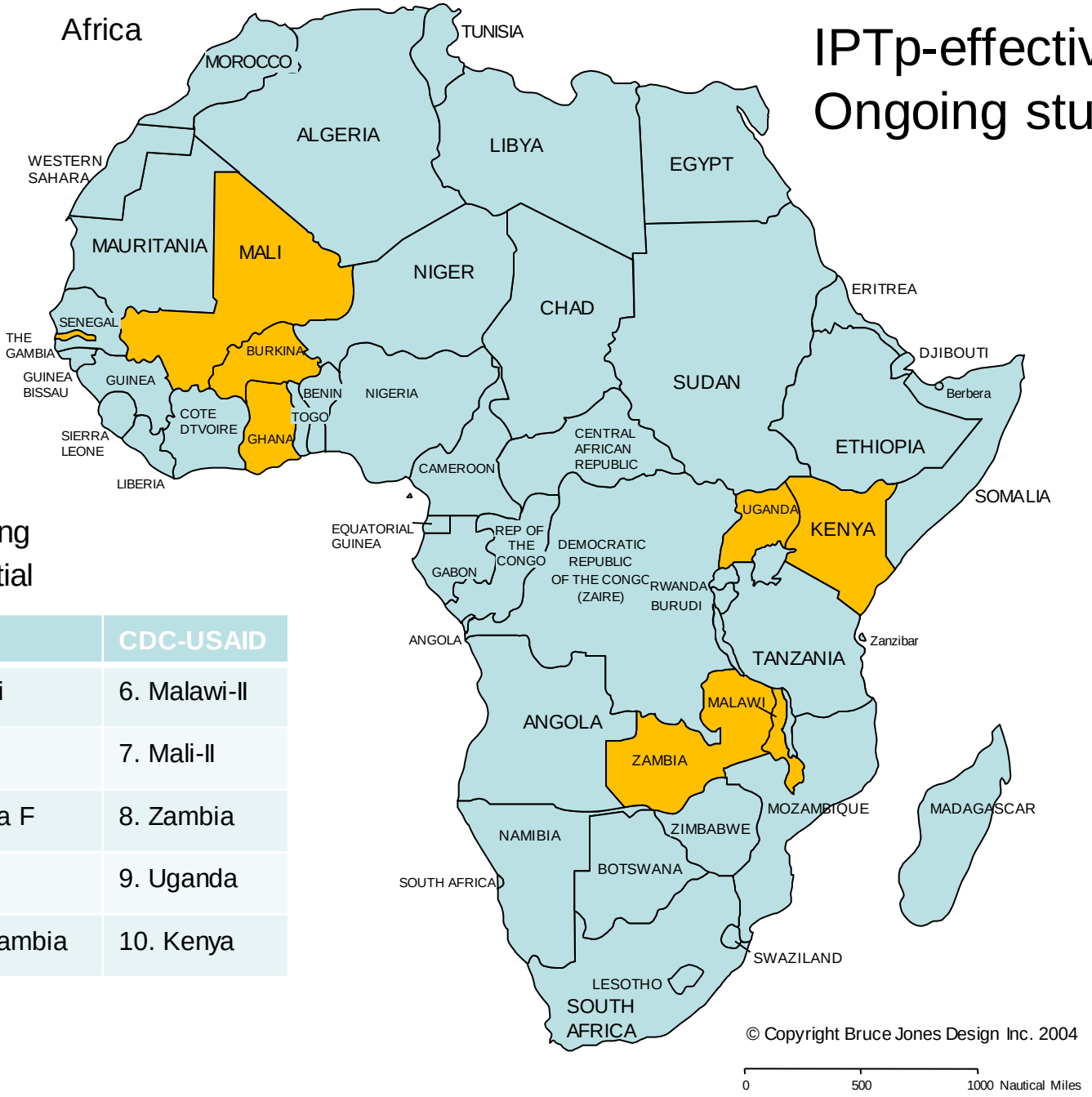
Competitive facilitation of drug-resistant *Plasmodium falciparum* malaria parasites in pregnant women who receive preventive treatment

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



	MIPc	CDC-USAID
MA6	1. Malawi	6. Malawi-II
MA5	2. Mali-I	7. Mali-II
	3. Burkina F	8. Zambia
	4. Ghana	9. Uganda
	5. The Gambia	10. Kenya

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

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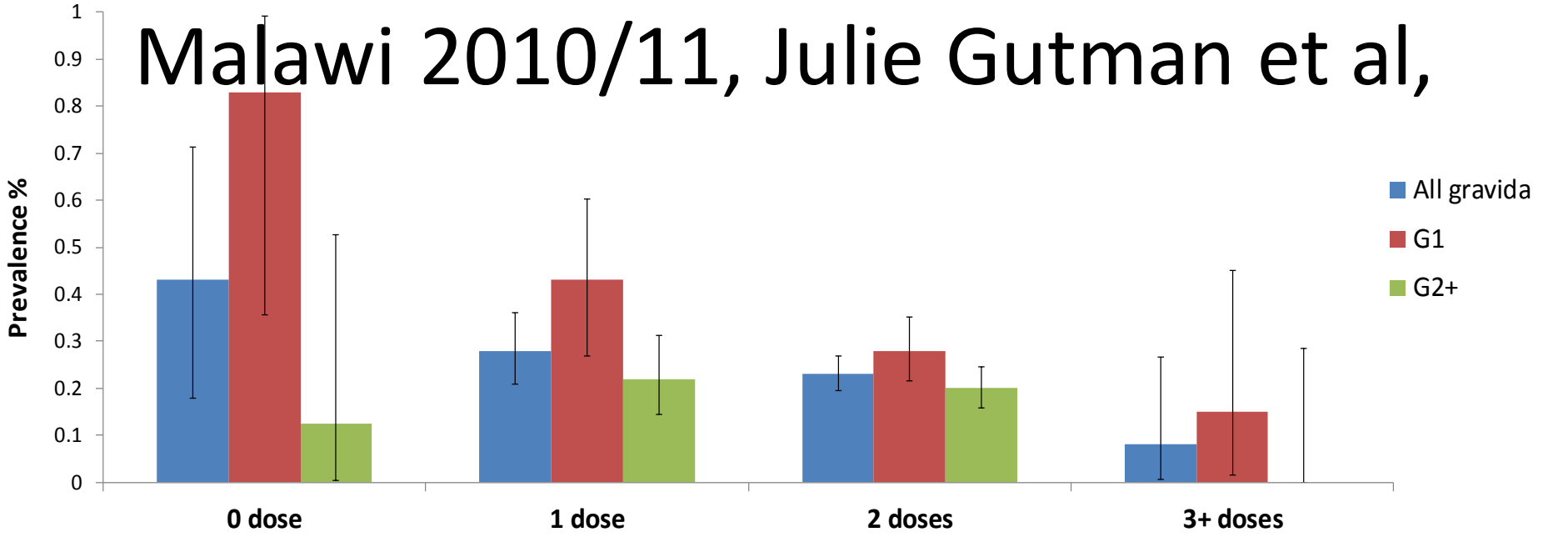
Composite SGA/ LBW/ preterm Malawi 2010/11, Julie Gutman et al,



		PR (95% CI); p-value	PR (95% CI); p-value	PR (95% CI); p-value	type 3 p-value	trend p-value
N	14	141	520	24		
Unadjusted						
All Gravida	ref	0.65 (0.32-1.32); 0.23	0.53 (0.27-1.04); 0.06	0.19 (0.04-0.86); 0.03	0.046	0.008
G1	ref	0.52 (0.31-0.87); 0.01	0.34 (0.22-0.52); <0.0001	0.18 (0.05-0.70); 0.01	0.05	<.0001
G2+	ref	1.77 (0.27-11.5); 1	1.60 (0.25-10.1); 1	-	-	0.40
Adjusted						
All Gravida	ref	0.73 (0.40-1.33); 0.30	0.61 (0.35-1.07); 0.08	0.21 (0.05-0.86); 0.03	0.03	0.02
G1	ref	0.55 (0.35-0.85); 0.008	0.36 (0.25-0.52); <0.0001	0.22 (0.06-0.80); 0.02	0.06	<.0001
G2+	ref	-	-	-	-	-

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 with low SP resistance

- No evidence for harm through competative faciliation 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_{AS} vs AQ_{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

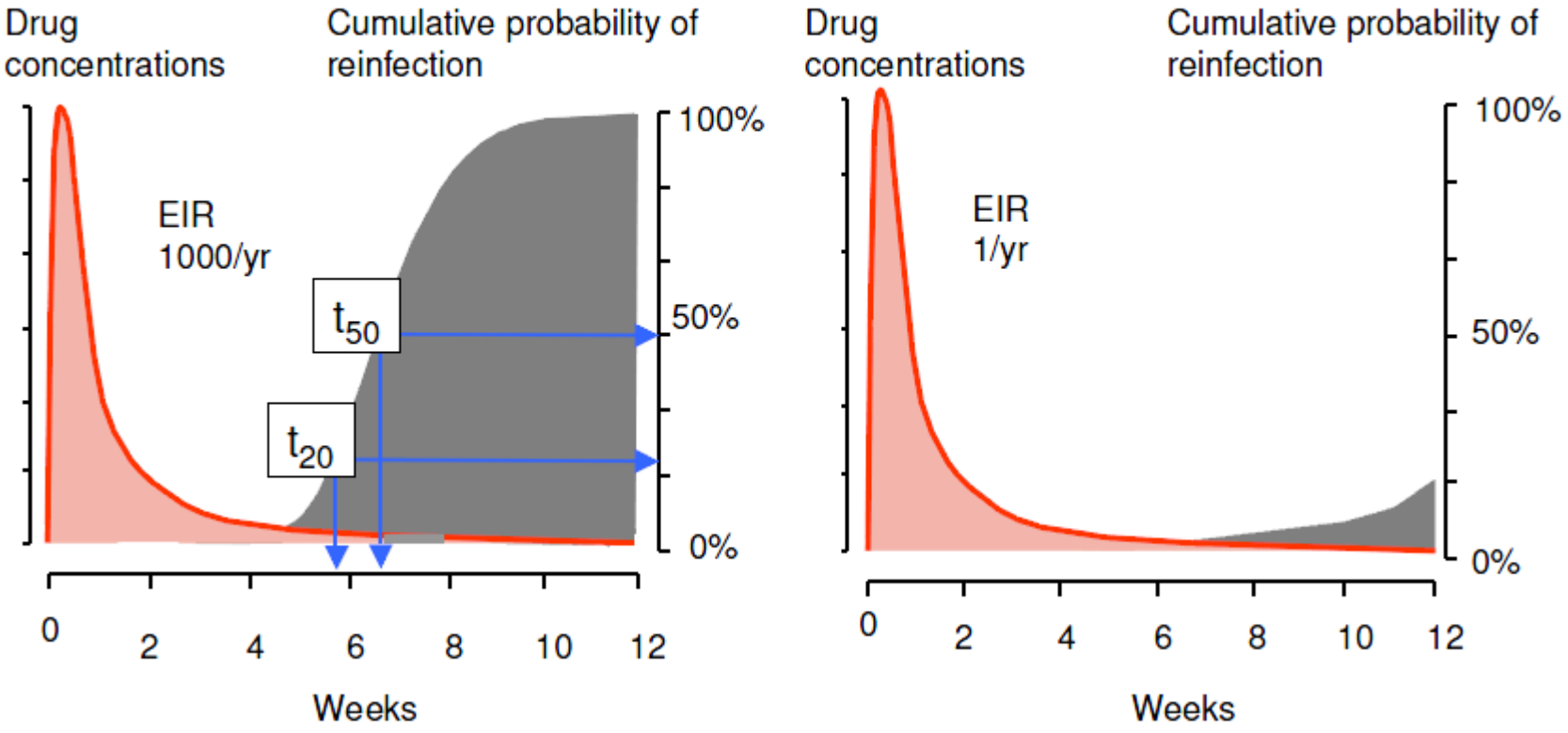
Funding	Drugs	Countries
MIPc	Mefloquine (MQ) mono	Benin, Gabon, Mozmbq, Tanz.
MIPc	MQ + Cotrimoxazole (HIV+)	Kenya, Mozmbq, Tanzania
MIPc	SP + Azithromycin (AZ)	PNG
MIPc / MRC	DHA-Piperaquine	Kenya, Indonesia
NiH	Chloroquine (CQ) mono	Malawi
Pfizer	CQ + AZ	5 countries Africa

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 2nd + 3rd 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

Pro	Con
Drug exposure restricted to those that need it (80:20); primigravidae, peak season, 'hot spots', etc	More complex, expensive Gaps, missing subpatent infections

- Integration with screening for anaemia, HIV and STIs

Intermittent Screening and Treatment ISTp results todate

OPEN ACCESS Freely available online

PLoS one

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Harry Tagbo

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d Kingdom

Ghana: Tagbor et al PlosOne 2010

ISTp was as effective as IPTp with SP in area with low SP resistance and moderate malaria transmission

PLoS ONE | www.plosone.org

December 2010 | Volume 5 | Issue 12 | e14425

Conclusions & Recommendations

- Period major changes, challenges & opportunities

- Challenges MiP Control
  - Low Uptake
  - Increased resistance
  - decreasing transmission

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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

http://www.mip-consortium.org/

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Latest news

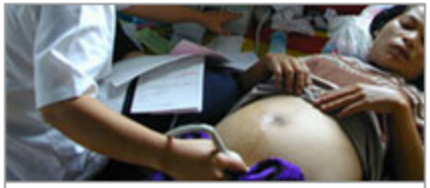
Consortium partners at 3rd annual meeting in Dar es Salaam, Tanzania, June 2010.

Click here to view our latest press releases.

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.



About MiP

Malaria infection during pregnancy is a major cause of severe maternal anaemia and preventable low birth

Projects

The MiP Consortium is involved in a wide range of activities in Africa, Asia and Latin America. Browse our

Partners

The MiP Consortium joins 47 partner institutions across 32 countries globally.

Resource Centre

The MiP Consortium hosts a resource centre managed by the Secretariat at LSTM. The Malaria in Pregnancy Library

Acknowledgements

- Members of MIP Consortium who contributed to discussions

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  - the MiP Consortium which is funded through a grant from the Bill & Melinda Gates Foundation to the Liverpool School of Tropical Medicine and
  - EDCTP

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