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

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EDCTP

BILL & MELINDA GATES foundation

World Health Organization

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

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

11 April 2013

mip malaria in pregnancy consortium

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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

Kayentao et al, Jama, 2013

594 JAMA, February 13, 2013—Vol 309, No. 6

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.

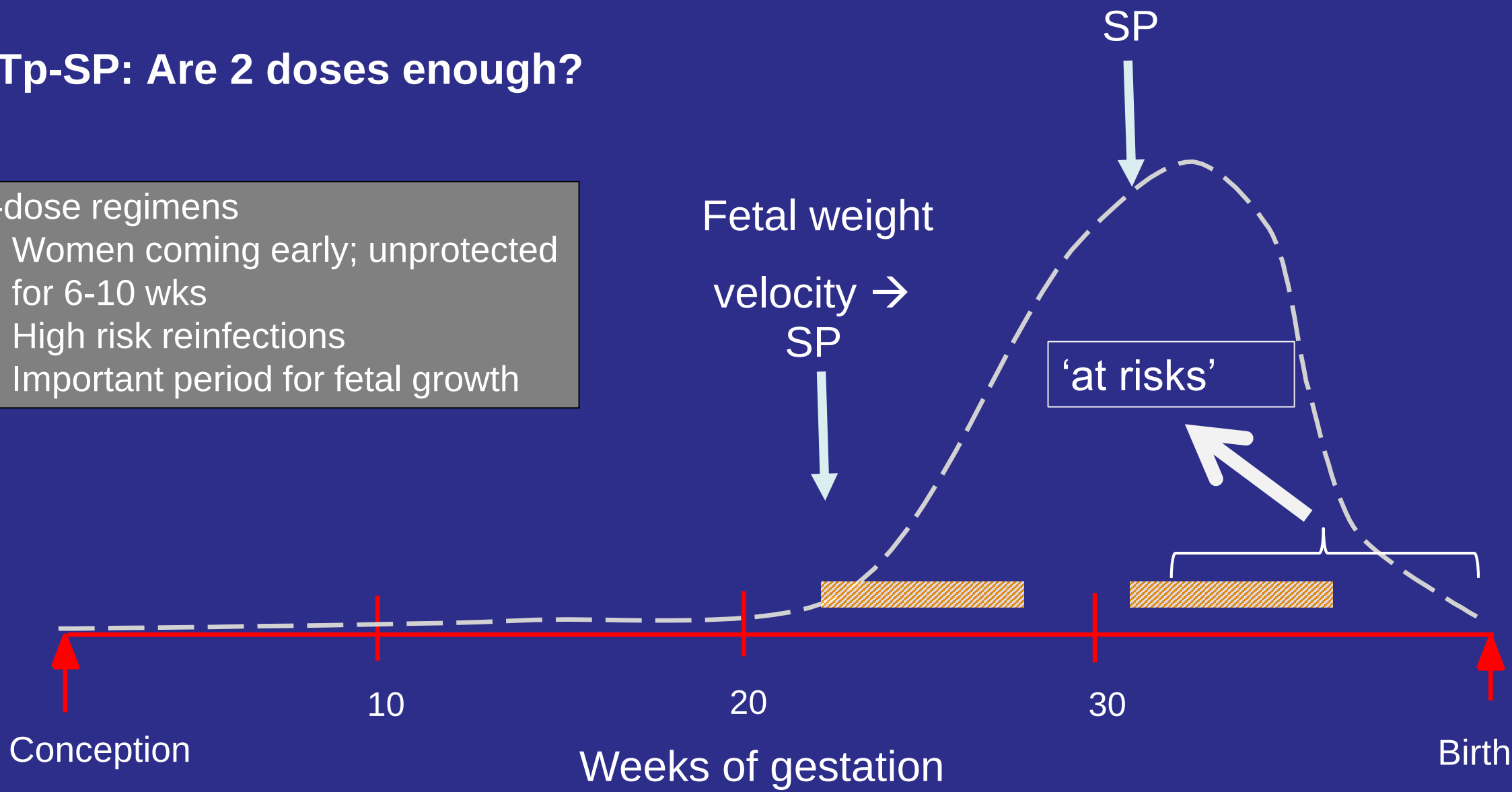
Objective To perform a systematic review and meta-analysis of trials to determine whether regimens containing 3 or more doses of sulfadoxine-pyrimethamine for intermittent preventive therapy during pregnancy are associated with a higher birth weight or lower risk of low birth weight (LBW) (<2500 g) than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



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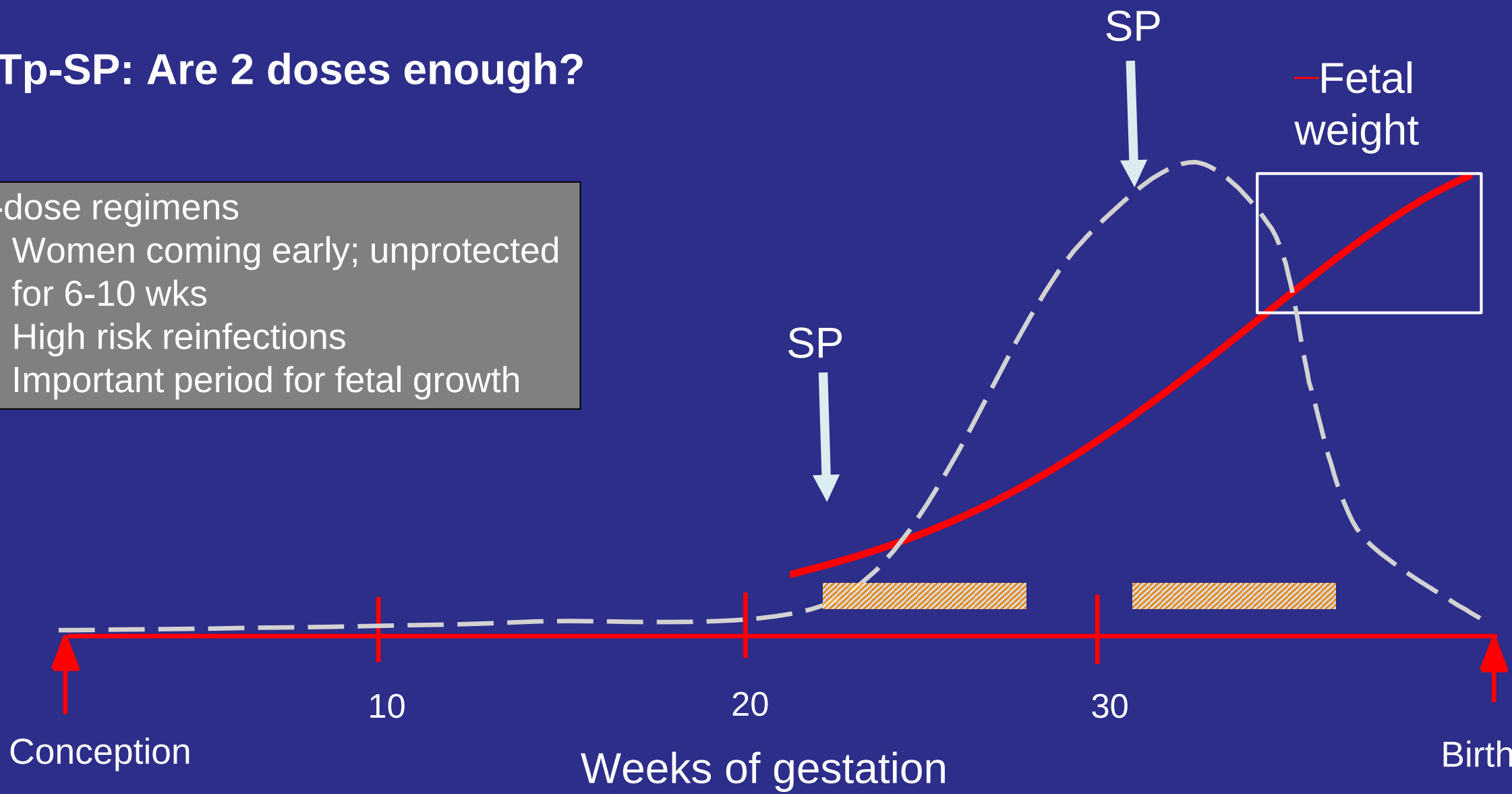

Rationale 3+ doses IPTp-SP

- Protect women from early 2nd 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?

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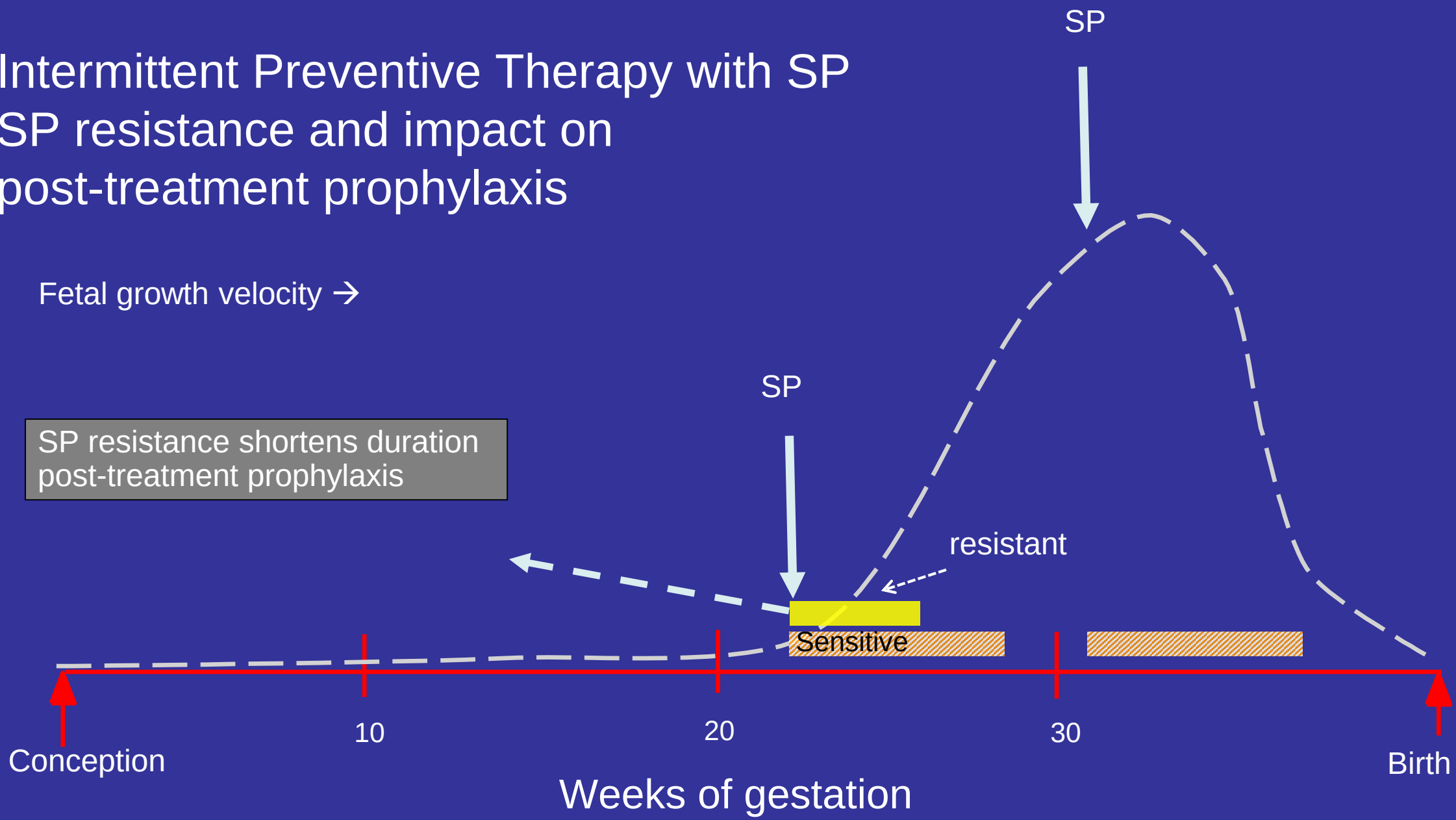
Intermittent Preventive Therapy with SP
SP resistance and impact on post-treatment prophylaxis



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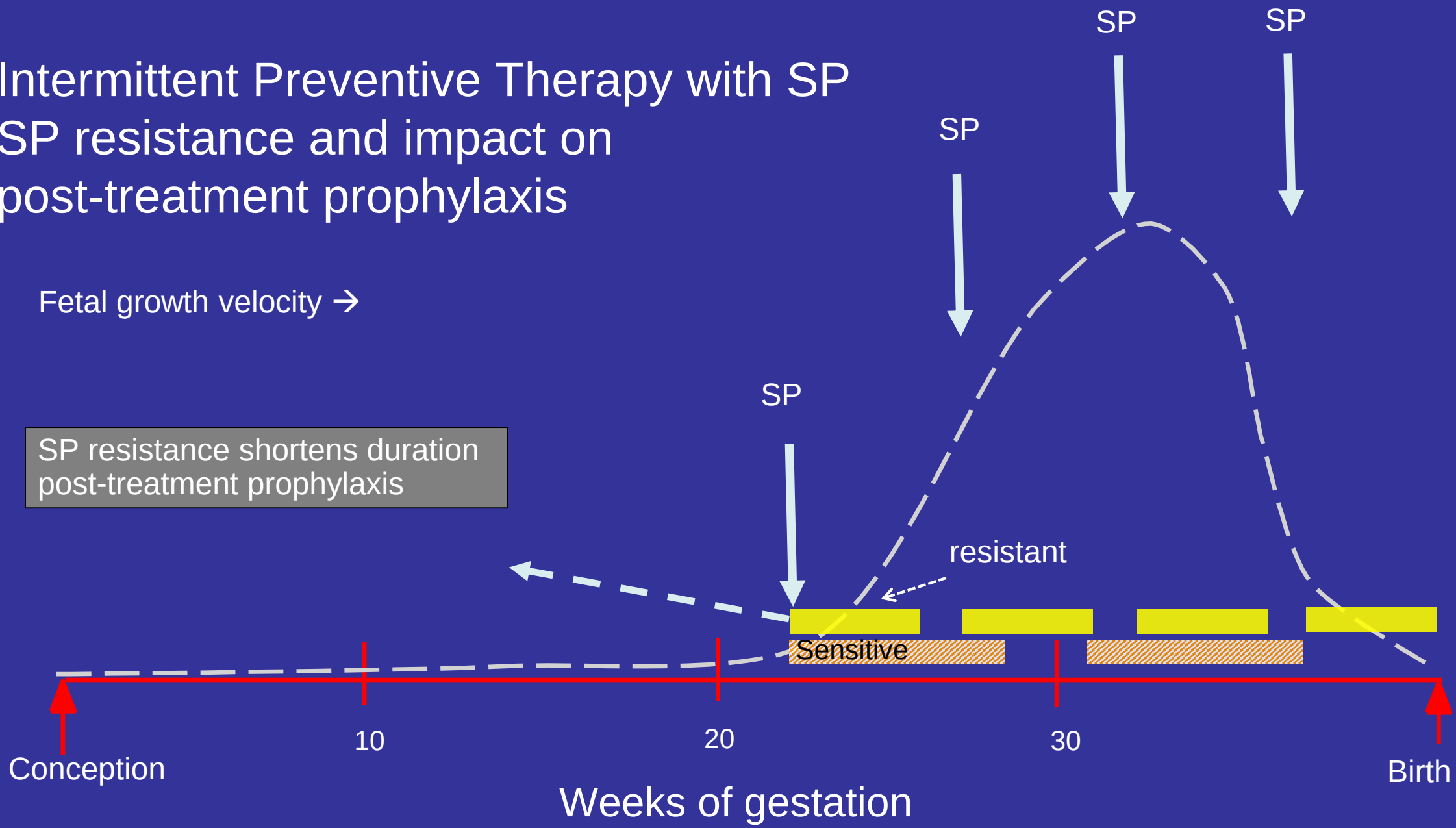

3+ strategies: Ghana, Zambia, Malawi, Kenya

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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

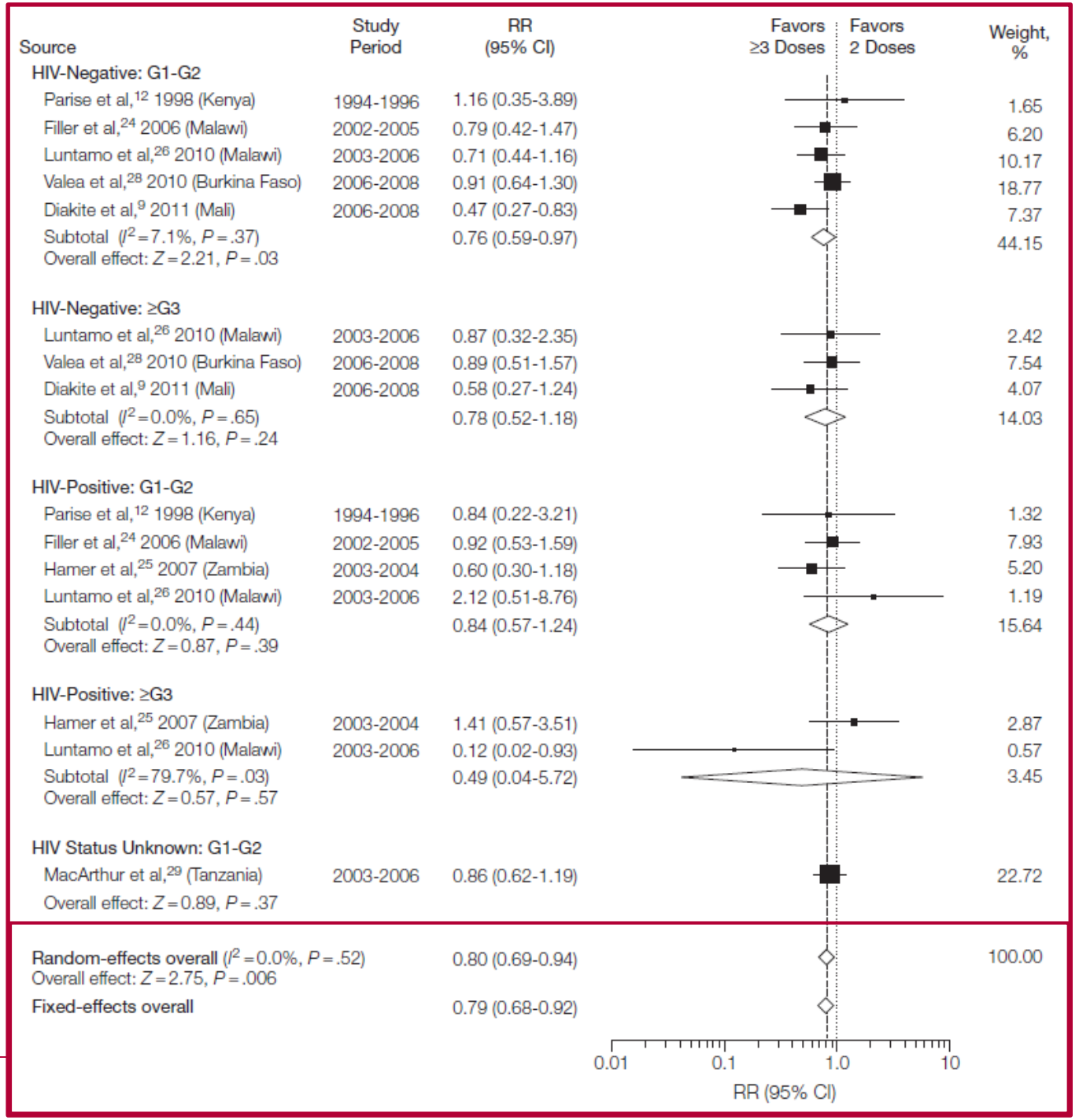
Results: 7 trials, 6,281 pregnancies

	Year publish	Country	Year of study	HIV status	Gravidity	# Subjects
Parise et al.	1998	Kenya	94-96	(+) & (-)	1 & 2	1341
Filler et al.	2006	Malawi	02-05	(+) & (-)	1 & 2	698
Hamer et al.	2007	Zambia	03-04	(+)	All	456
Luntamo et al.	2010	Malawi	03-06	(+) & (-)	All	877
Valea et al.	2010	Burkina F.	06-08	(-)	All	1,296
Maiga et al.	2011	Mali	06-08	(-)	All	814
MacArthur et al.	Unpub	Tanzania	03-06	Unk	1&2	799

Results
Risk of Low birth Weight

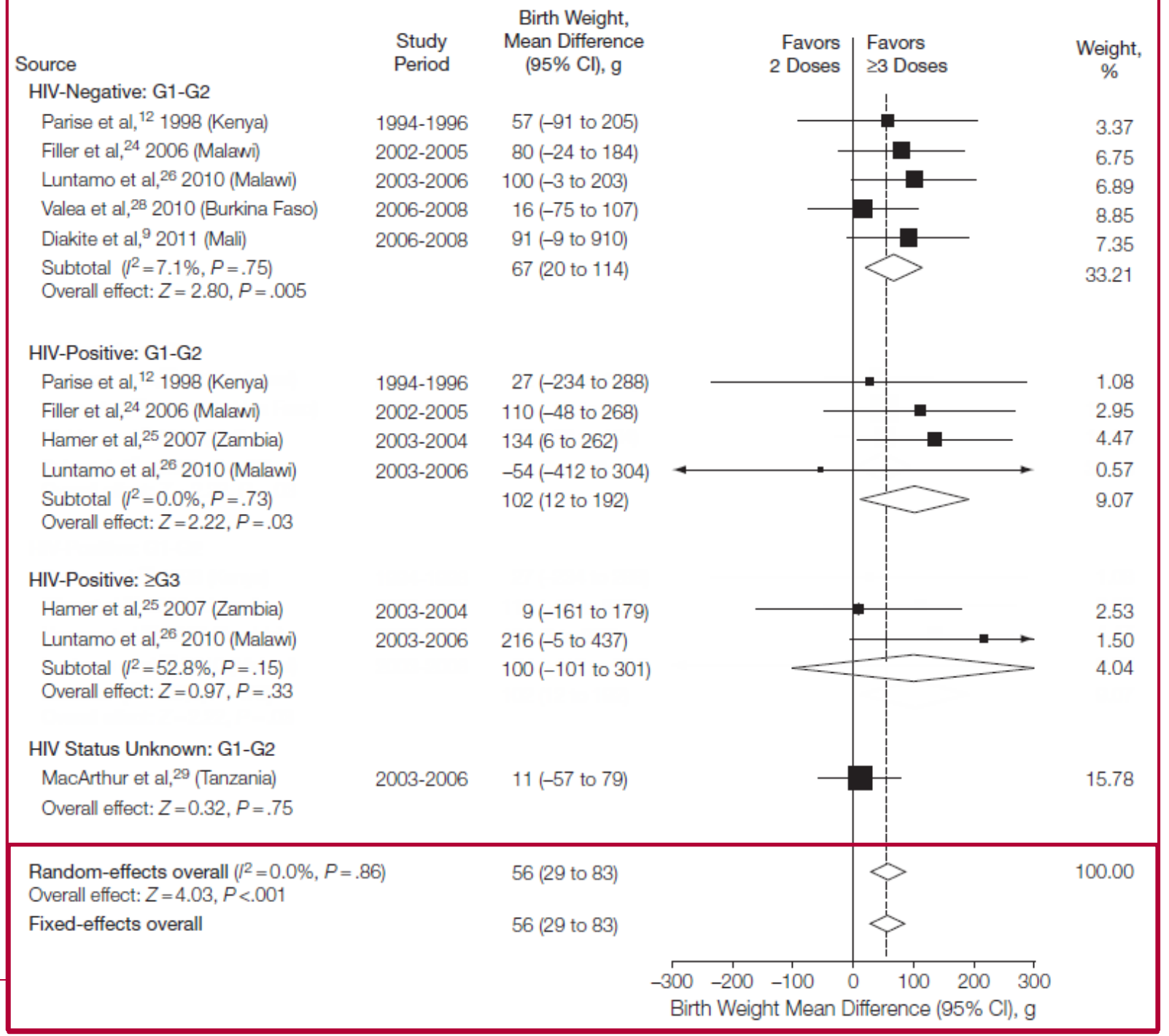
- 3+ doses more effective
  - Reduced by an extra 20%
  - 95 CI: 6-31
  - P=0.006

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

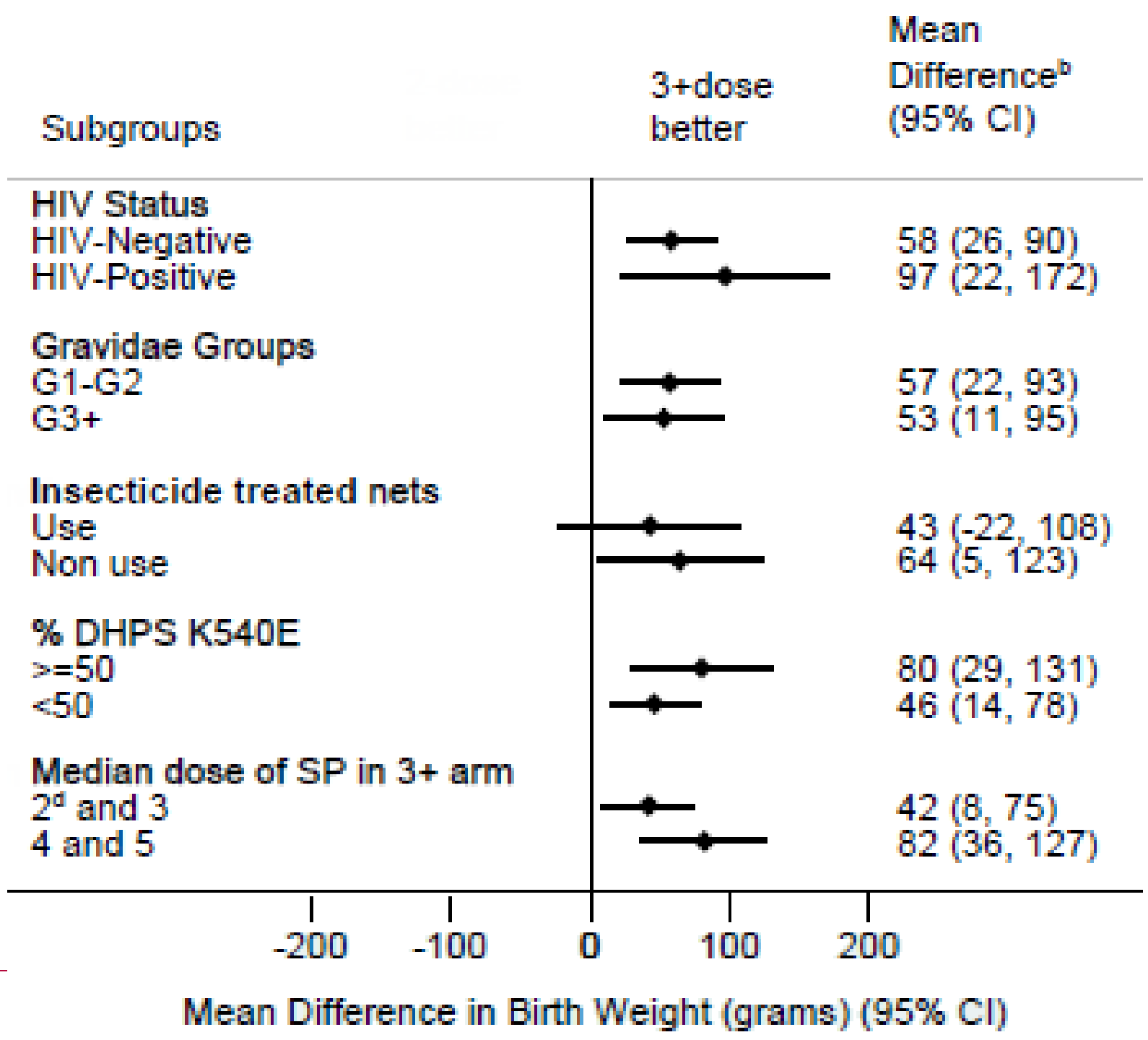


Results
Mean birth Weight

- 3+ doses more effective
  - Increased by an extra 56 grm
  - 95 CI: 29-83
  - P<0.001
- Consistent finding
  - Low Heterogeneity: I^2 = 0%



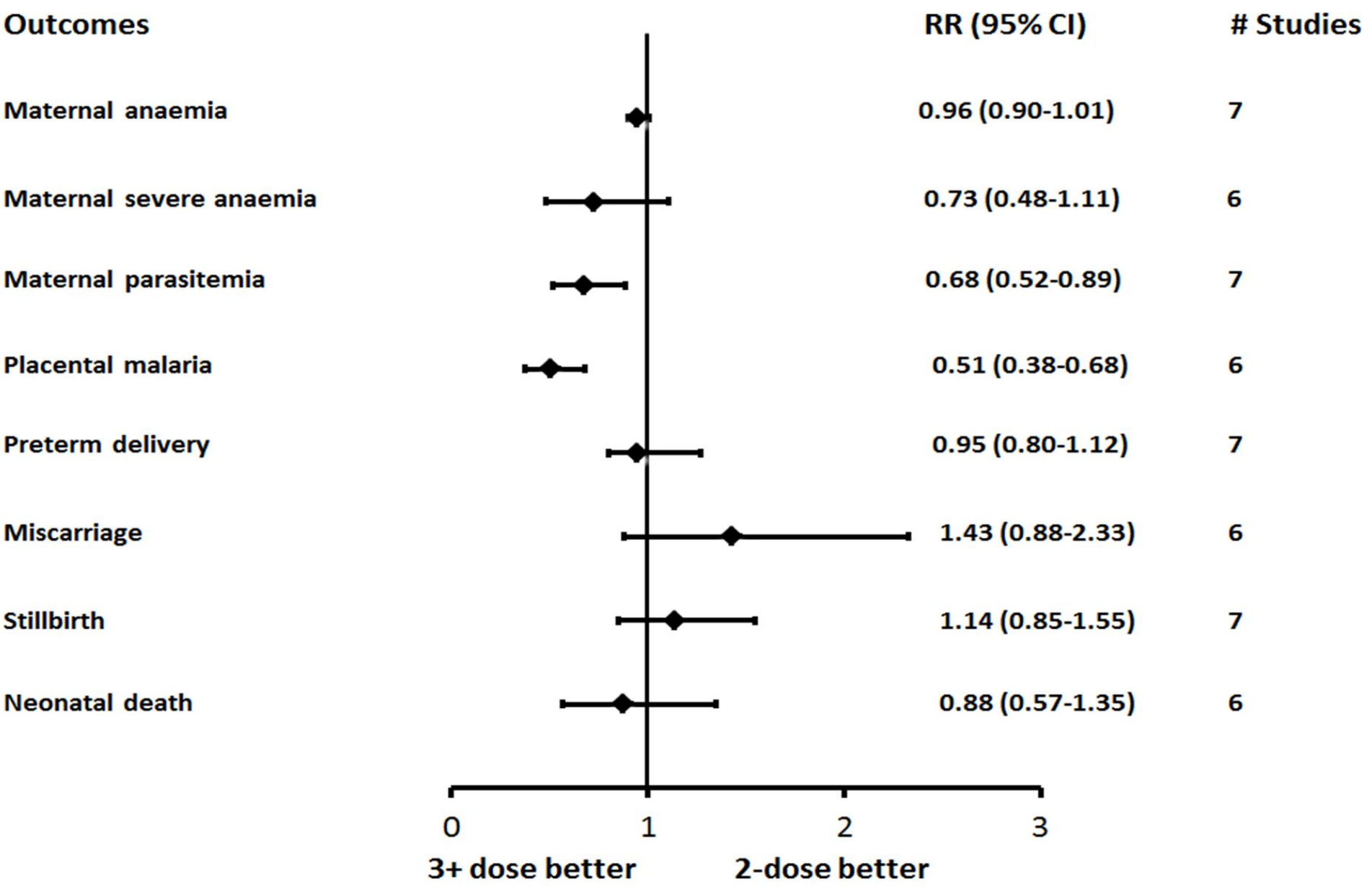
Benefit on birth weight consistent across range of subgroups and sites



Safety Data

- Miscrriage, 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



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

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N ENGL J MED 374;10 NEJM.ORG MARCH 10, 2016

ORIGINAL ARTICLE

Dihydroartemisinin–Piperaquine for the Prevention of Malaria in Pregnancy

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Dihydroartemisinin-Piperaquine (DP) for IPTp: 3 vs monthly dosing Kakuru, NEJM 2016, Uganda

Table 2. Efficacy Outcomes.*

Outcome	Sulfadoxine–Pyrimethamine†	Three-Dose Dihydroartemisinin–Piperaquine			Monthly Dihydroartemisinin–Piperaquine		
			Relative Risk (95% CI)	P Value		Relative Risk (95% CI)	P Value
Preterm delivery‡	8/99 (8.1)	11/89 (12.4)	1.53 (0.64–3.63)	0.33	5/98 (5.1)	0.63 (0.21–1.86)	0.40
Congenital anomaly‡	2/98 (2.0)	4/89 (4.5)	2.20 (0.41–11.7)	0.43	0/96	0 (0–1.62)	0.50
Low birth weight‡	14/99 (14.1)	14/89 (15.7)	1.11 (0.56–2.20)	0.76	8/98 (8.2)	0.58 (0.25–1.31)	0.18
Symptomatic malaria during pregnancy — no. of events (incidence per person-year at risk)	41 (0.95)	12 (0.31)	0.33 (0.17–0.64)¶	0.001	0	0 (0–0.05)¶	<0.001
Detection of malaria parasites by LAMP during pregnancy — no. of events/total no. (%)‖	206/509 (40.5)	74/445 (16.6)	0.41 (0.30–0.54)	<0.001	26/496 (5.2)	0.13 (0.08–0.21)	<0.001
Anemia during pregnancy — no. of events/total no. (%)‖**	94/269 (34.9)	72/237 (30.4)	0.87 (0.61–1.23)	0.43	61/258 (23.6)	0.66 (0.44–0.98)	0.04

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 2nd 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 !

PMI President's Malaria Initiative
Fighting Malaria and Saving Lives

Investigators

Kayentao K, Garner P, Anne van Eijk A, Naidoo I, Roper C, Mulokozi A, MacArthur J., Luntamo M, Ashorn P, Doumbo O, ter Kuile F