

WHO Evidence Review Group on Intermittent Preventive Treatment of malaria in pregnancy (IPTp) 9-11 July 2013, Geneva, WHO



World Health
Organization

**GLOBAL MALARIA
PROGRAMME**

Objectives of the IPTp Evidence Review Group

1. To review the evidence regarding the contribution of **SP resistance** to IPTp effectiveness.
2. To review the analysis on the impact of significant **reduction in transmission** on IPTp effectiveness.
3. To review evidence on **efficacy and safety of mefloquine** for IPTp compared to SP (for HIV negative pregnant women) and the benefit of IPTp-MQ added to daily co-trimoxazole prophylaxis (for HIV+ pregnant women).
4. (To finalise a core protocol to monitor the impact of SP resistance on IPTp-SP effectiveness.)

Develop draft policy recommendations for consideration by the MPAC in September 2013.

Evidence reviewed

On IPTp-SP:

- Nine published articles on IPTp-SP effectiveness, SP drug resistance and safety in Tanzania, Mozambique and Malawi;
- Eight unpublished manuscripts and one abstract, on IPTp-SP safety & acceptability and effectiveness/transmission relations;

On IPTp-MQ:

- Published articles from two randomized controlled trials RCTs conducted in Benin, and unpublished study reports on two multi-centre trials (MiPPAD trials) completed in five sub-Saharan countries (Benin, Gabon, Mozambique, Tanzania, Kenya).
- Unpublished PK study and economic analysis.
- A literature review of published studies on the safety of MQ in pregnant women when used for treatment or prevention (IPTp and chemoprophylaxis).

The new IPTp SP policy recommendation _

- Since the updated IPTp policy was released in October 2012, many countries in sub-Saharan Africa have reviewed or plan to update their country policies and start programme implementation. The WHO Evidence Review Group (ERG) for IPTp recognizes the **progress made in rolling out the new policy and the commitment from countries** to ensure that all pregnant women receive optimal care throughout pregnancy, including access to IPTp-SP
- The new proposed recommendations should be considered by countries with specific patterns of SP resistance, or persistent reduction in malaria transmission and by those considering mefloquine as an alternative medicine for IPTp.

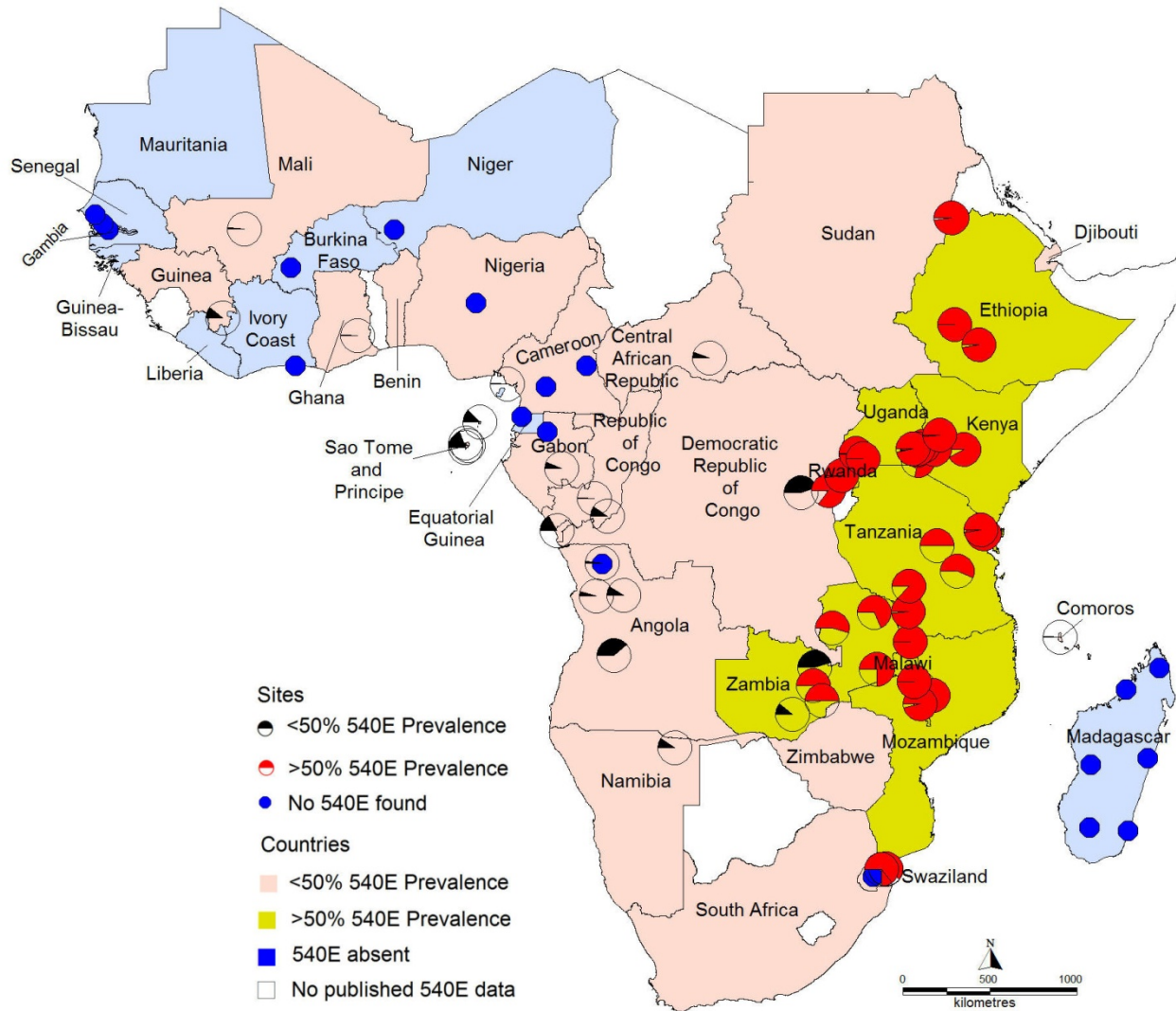
Recommendation 1:_

Consider discontinuing IPTp-SP when the population prevalence of Plasmodium falciparum (Pf) dhps mutation K540E is greater than 95%, AND the prevalence of mutation A581G is greater than 10%, as it is likely to be ineffective. In areas where IPTp-SP is discontinued because of resistance, ensure access of pregnant women to long-lasting insecticide treated nets and prompt diagnosis and effective treatment.

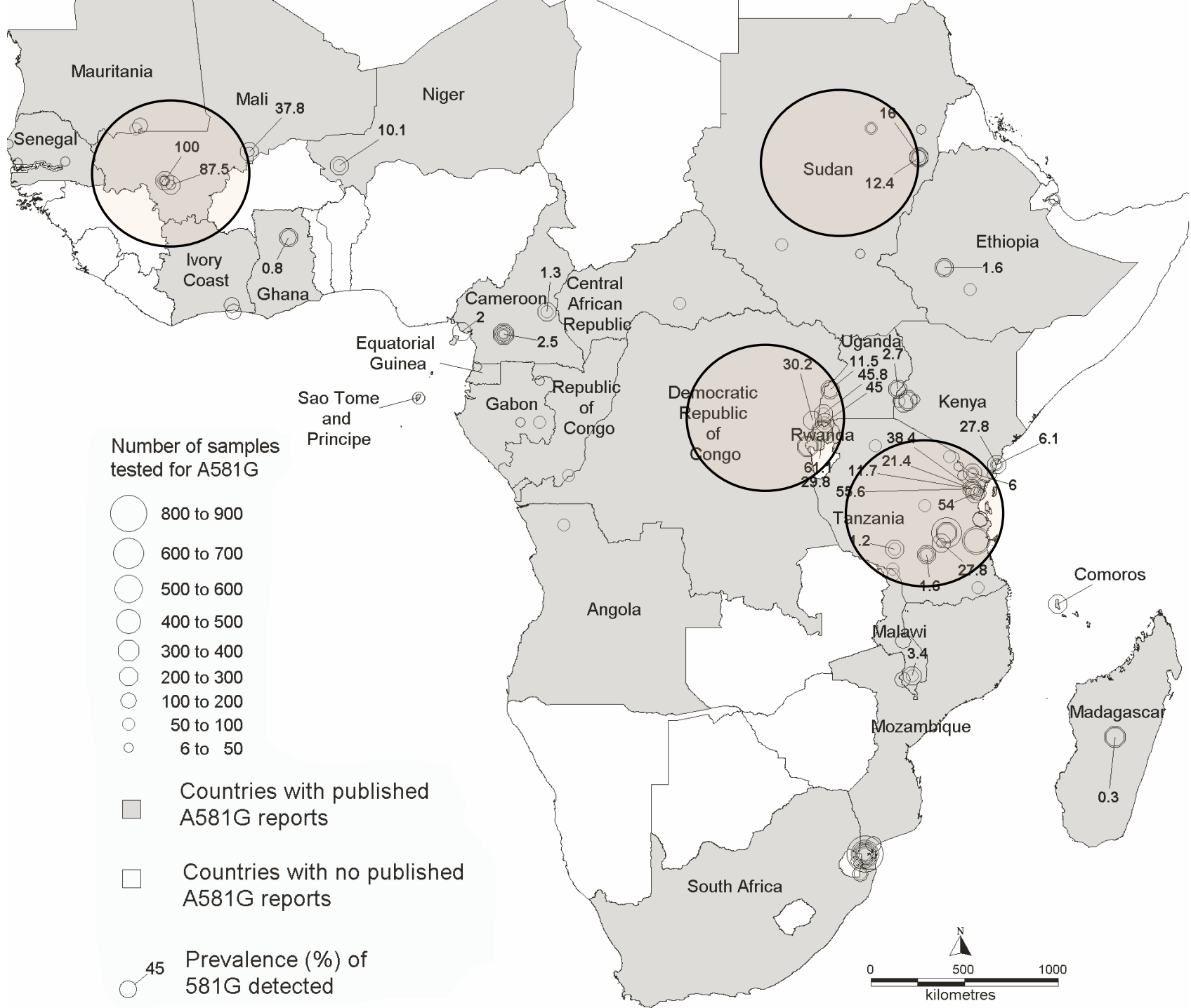
Key Findings:

- Evidence suggests IPTp-SP remains effective in areas of moderate SP Ω
- Marked regional differences in prevalence of *Pf* genotypes
- Continued monitoring SP Ω markers needed, especially in East and Southern Africa , along with maternal and neonatal outcomes.
- Monitoring SP Ω should focus on *Pfdhps* A581G and K540E mutations; in W Africa prevalence of *Pfdhps* A437G should also be monitored
- Two independent studies in areas with a high prevalence of *Pfdhps* A581G and K540E mutations → loss of effectiveness of IPTp-SP; one shows an association of sextuple mutant with LBW.

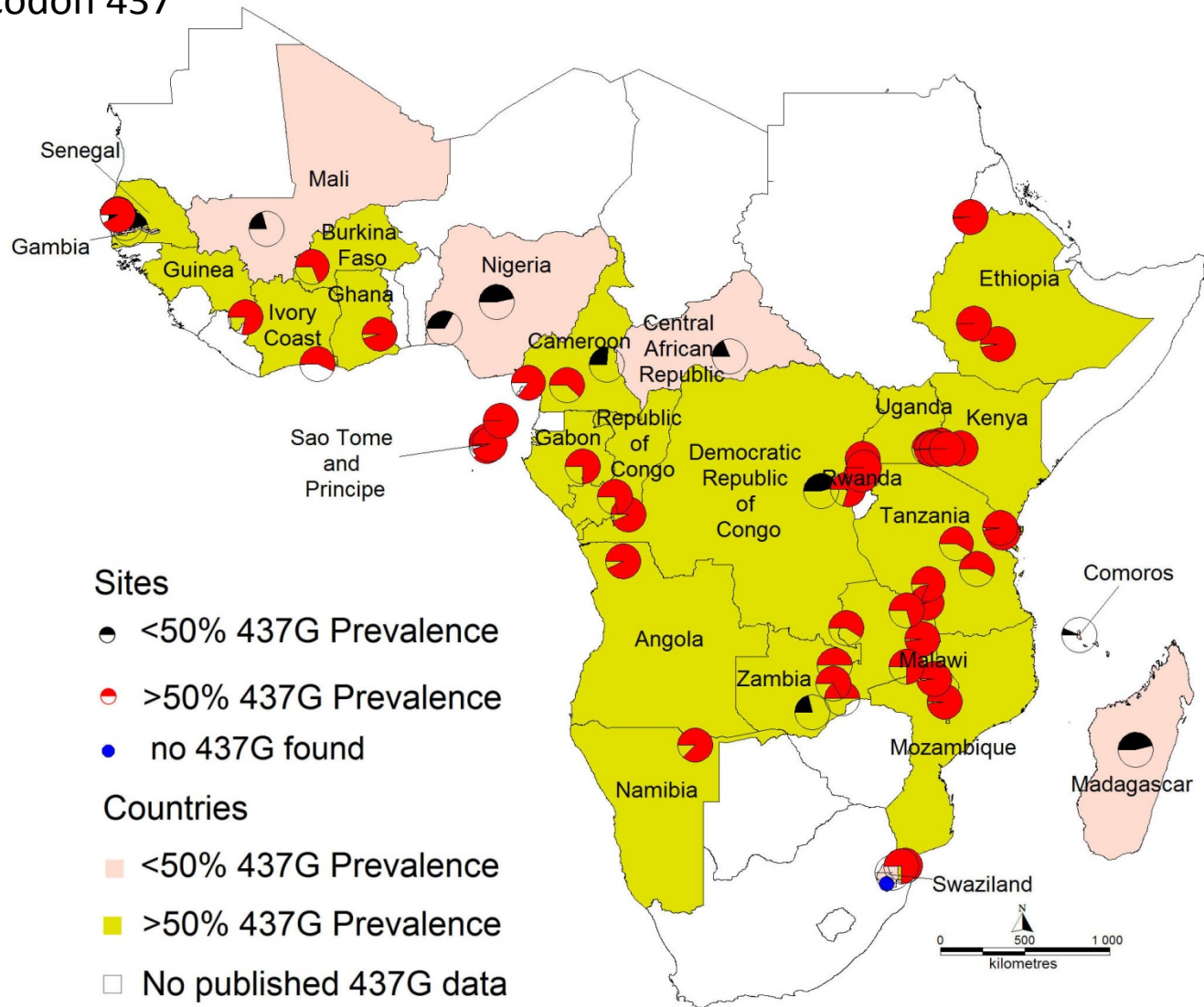
dhps codon 540



Cally Roper, LSHTM; Inbarani Naidoo, *MRC South Africa & LSHTM*; Reginald Kavishe, *KCMC Moshi, Tanzania*; Lucy Okell, *Imperial College London*; Jennifer Flegg, *Oxford University & WWARN*



dhps codon 437



Cally Roper, LSHTM; Inbarani Naidoo, *MRC South Africa & LSHTM*; Reginald Kavishe, *KCMC Moshi, Tanzania*; Lucy Okell, *Imperial College London*; Jennifer Flegg, *Oxford University & WWARN*



IPTp in areas of high SP resistance
Experiences from Tanzania

Plasmodium falciparum mutant haplotype infection
during pregnancy associated with reduced
birthweight, Tanzania

Daniel T.R. Minja, Christentze Schmiegelow, Bruno Mmbando,
Stéphanie Boström, Mayke Oesterholt, Pamela Magistrado, Caroline
Pehrson, Davis John, Ali Salanti, Adrian J.F. Luty,¹ Martha Lemnge,
Thor Theander, John Lusingu, and Michael Alifrangis

EID (in press)



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Results

Determinants of birthweight for these newborns

Stepwise multiple linear regression adjusting for covariates

Variable	Univariate analysis			Multivariate analysis†		
	Coefficient	95% CI	p-value	Coefficient	95% CI	p-value
MUAC at study inclusion, cm	49	1 to 97	0.047	15	-28 to 59	0.47
Gestational age						
At study inclusion, wk	-20	-63 to 22	0.340			
At delivery, wk	90	-23 to 204	0.120	90	1 to 179	0.048
Sex of newborn, F	-106	-432 to 221	0.520			
Maternal age, y	37	10 to 64	0.009	2	-30 to 35	0.890
Gravidity (>2 pregnancies)	477	166 to 788	0.004	434	152 to 716	0.004
Maternal weight at study inclusion, kg	9	-12 to 30	0.370			
Maternal weight gain, kg						
From study inclusion to ANV3	38	-47 to 124	0.372			
From ANV3-ANV4	-22	-72 to 28	0.370			
Infecting haplotype, sextuple	-326	-621 to -31	0.031	-359	-601 to -117	0.005
Parasite density, per 1,000 IE/ μ L	0.09	-3 to 3	0.95			
No. of infections‡	-308	-649 to 34	0.08	-143	-426 to 140	0.31
No. of IPTp doses before delivery	-303	-614 to 8	0.06	-231	-498 to 35	0.087
Maternal HIV status positive	230	-308, to 769	0.390			
Place of delivery						
Hospital	-86	-381 to 209	0.56			
Other than hospital	-12	-696 to 671	0.971			

Birthweight of sextuple mutant haplotype infections reduced by a mean of 359g (95% CI -601 to - 117)



Recommendation 2:_

Consider discontinuing IPTp-SP when malaria transmission has been very low (falciparum malaria population prevalence in children under 15 years of age is below 5%) for at least 3 years.

Key Findings:

- Systematic review evaluated the use of parasite prevalence in children (as detected in population surveys) as a proxy measure of malaria transmission to investigate effect of the level of transmission on IPTp-SP to prevent LBW.
- The preliminary results suggest that IPTp-SP may no longer protect against LBW when the *falciparum* malaria prevalence in children below 15 years is below 7-8%.
- Effective malaria control activities (including effective vector control and prompt diagnosis and effective treatment of malaria) must be sustained to maintain low transmission intensity in areas where IPTp-SP is discontinued.
- Surveillance systems to monitor malaria transmission intensity will need to be reinforced and maintained if IPTp-SP is discontinued.

Assessing effect modification of *P. falciparum* transmission on association between IPTp-SP and low birthweight: evidence from national cross-sectional datasets

Thom Eisele, Josh Yukich, David Larsen and Feiko ter Kuile

WHO Evidence Review Group on Intermittent Preventive Treatment of Malaria in Pregnancy

Geneva

9-11 July, 2013

Background: work to date

Malaria prevention in pregnancy, birthweight, and neonatal mortality: a meta-analysis of 32 national cross-sectional datasets in Africa

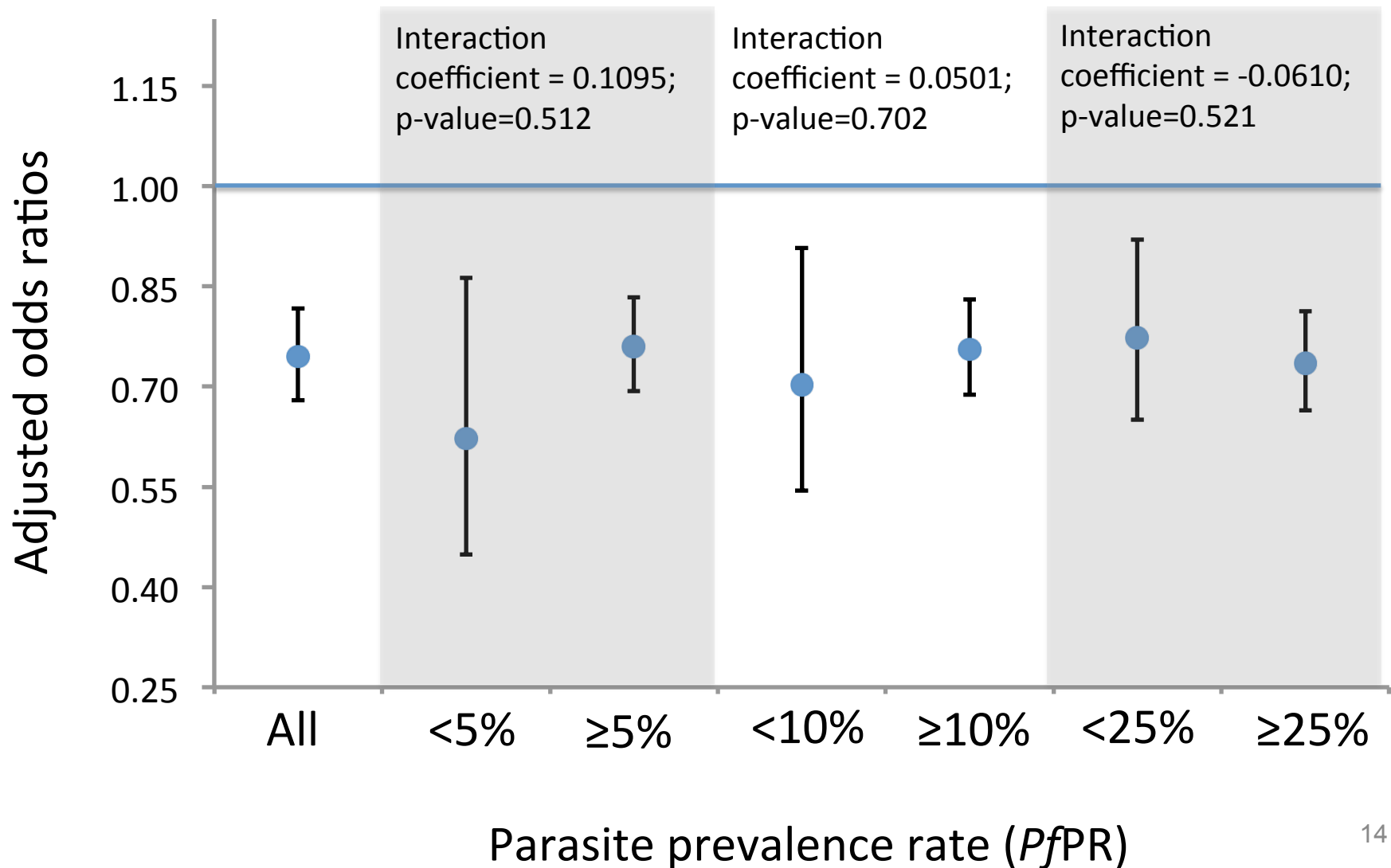


Thomas P Eisele, David A Larsen, Philip A Anglewicz, Joseph Keating, Josh Yukich, Adam Bennett, Paul Hutchinson, Richard W Steketee

- Recent assessment of malaria prevention in pregnancy (ITNs and IPTp) with LBW and neonatal mortality
- **Modified** cross-sectional study design to assess association of **exposure to malaria prevention in pregnancy** of IPTp and ITNs on **birth outcomes** in Africa
- **Limit potential confounding bias through exact matching** on confounding factors associated with both exposure to malaria prevention in pregnancy and birth outcomes
- Nationally-representative surveys in sub-Saharan Africa after the year 2000
 - Surveys must have contained **birth history** and **net roster**
 - Surveys publicly available in 2011
- 26 survey datasets identified that measured **LBW** (2003-2010 across 20 countries)- all DHS
 - **114,047 live births after matching**
- **Used MAP data PfPR2-10**

Preliminary results

Adjusted odds ratios of IPTp on LBW, by *Pf*PR: 1st 2 parities



Conclusions

- Data not ideal to assess the effect modification of *PfPR* on the relationship between IPTp-SP and LBW
 - Cross-sectional
 - **Misclassification** of *PfPR* at small area units (PSU) as estimated from MAP only in 2007 (**Huge** uncertainty of micro-area MAP estimates)
- No clear statistical evidence that the effectiveness of 2 doses of IPTp-SP for reducing LBW is significantly diminished at *PfPR* below 5%
 - However, there is a non-significant ($p=0.267$) trend towards **decreasing effectiveness as *PfPR* decreases** (among all parities) from meta-regression of sub-national adjusted odds ratios for LBW between 0-10% *PfPR*
 - Meta-analysis of sub-national adjusted odds ratios also shows non-significant effect (AOR: 0.90) for <5% *PfPR*, but a significant effect (AOR: 0.75) for 5-15% *PfPR*.

Malaria transmission intensity and the protective effect of intermittent preventive therapy (IPT) using sulphadoxine-pyrimethamine (SP)

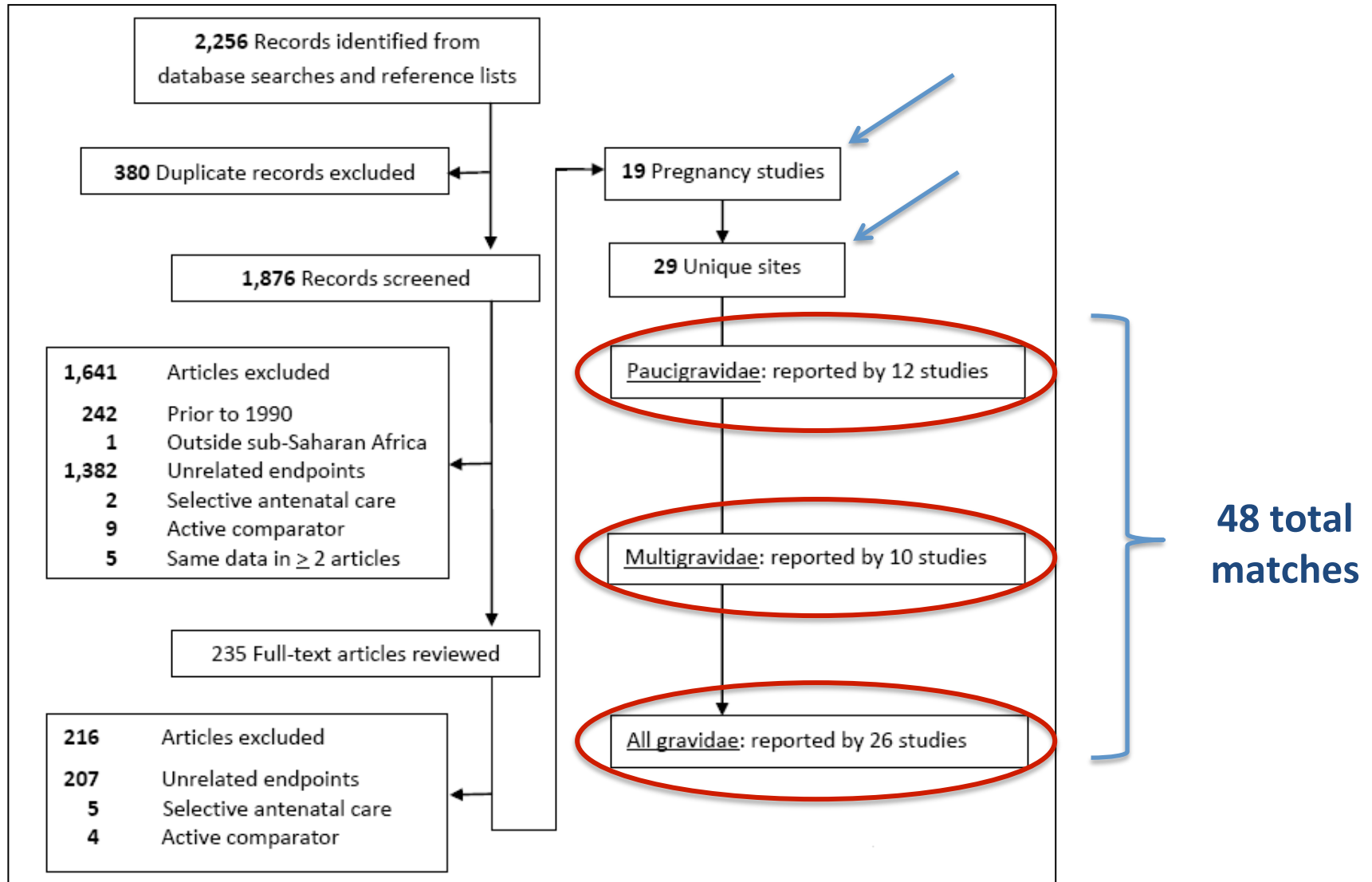
**World Health Organization
Meeting of the Evidence Review Group
Intermittent Preventive Treatment (IPT) in Pregnancy
9-11 July 2013
Geneva**

Matthew Chico
Department of Disease Control
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London School of Hygiene & Tropical Medicine

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Methods



Methods

Selecting the best match using prevalence data available

Malaria Atlas Project 2010 Data

- 12 countries from systematic review
- 11,549 point prevalence estimates comprised of data from:

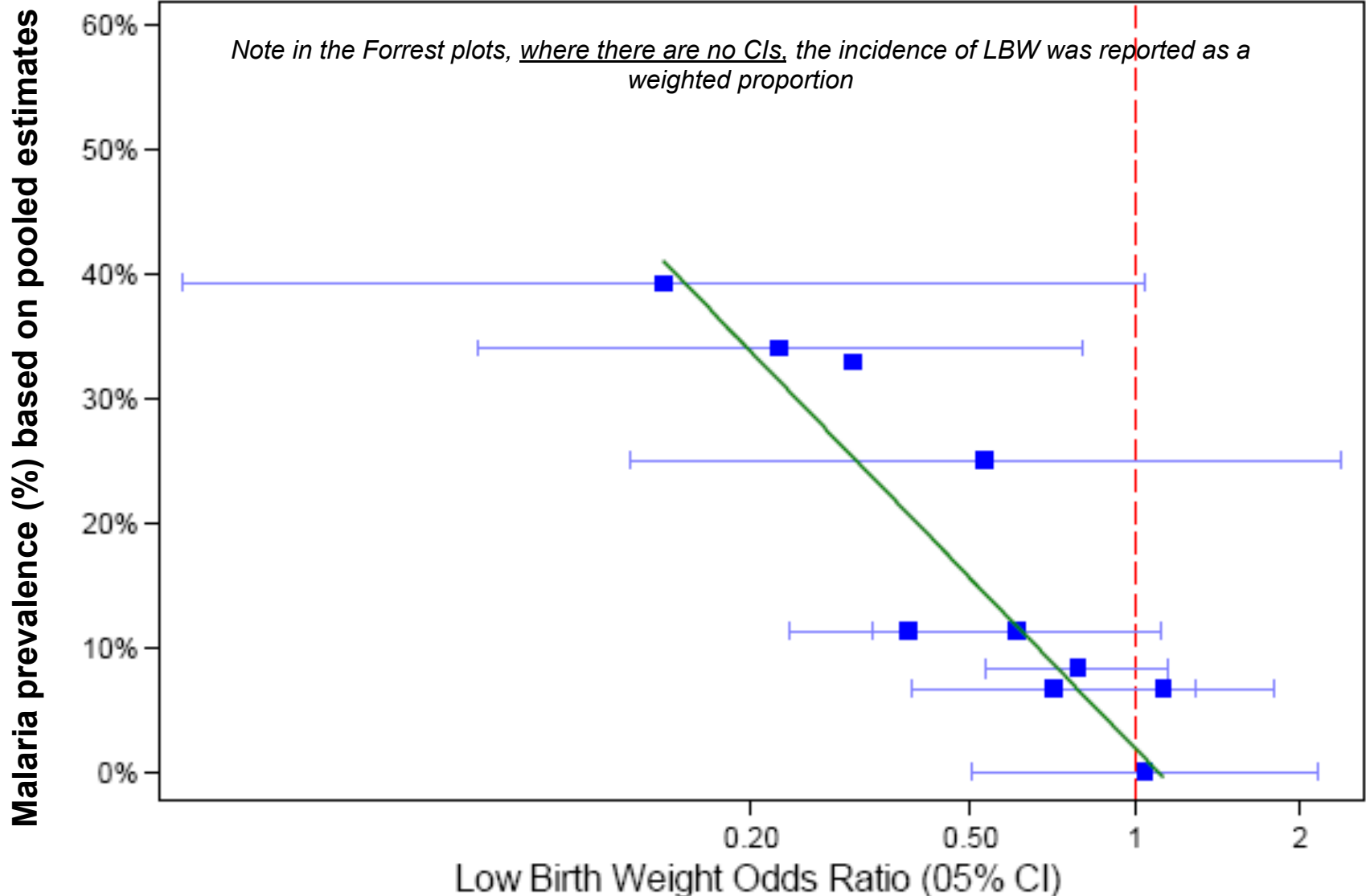
Pre-1990	>4,500 point estimates
1990-1999	1,500 point estimates
2000-2005	2,000 point estimates
2006-2010	>3,600 point estimates

- Aimed to find the best matches within the MAP data set
- Assumed paediatric data could be stratified to gravidae groups

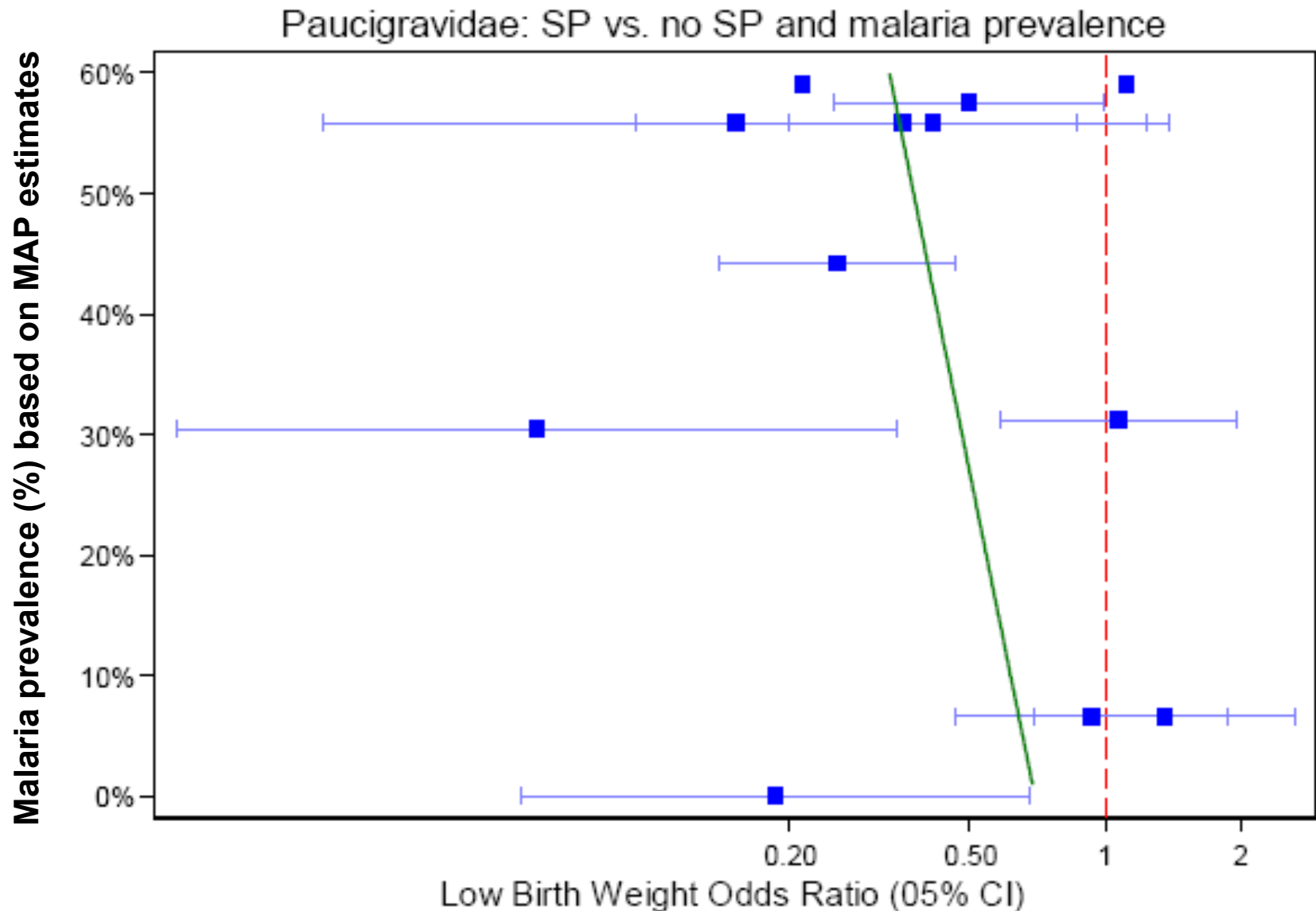
Term	Age	Proxy
Infancy	First year	Primigravidae
Childhood	1-4	Segundigravidae
School-aged	5-15	Multigravidae

The relationship between **pooled estimates** of parasite prevalence in children and the impact of SP-IPTp on LBW in multigravidae

Multigravidae: SP vs. no SP and malaria prevalence



The relationship between **pooled estimates** of parasite prevalence in children and the impact of SP-IPTp on LBW in paucigravidae



Conclusions

- Paucity of data on prevalence at first antenatal visit
- Proxy measure of malaria transmission intensity needed
- Modelling prevalence of malaria in children paired with pregnancy data shows a linear relationship between the intensity of transmission in children and the protective effect of SP-IPTp among multigravidae
- Protection against LBW may no longer be conferred when the prevalence of paediatric parasitaemia is below 7-8%

Recommendation 3:_

Mefloquine, at a dose of 15 mg/kg, is not recommended for IPTp because of its low tolerability, with vomiting and dizziness reported in up to 30% of pregnant women studied.

Key Findings:

- Two doses of IPTp-MQ
 - decreased maternal clinical malaria, parasitaemia, and anemia at delivery, when compared to two doses of IPTp-SP in HIV-negative women resident in Benin, Gabon, Tanzania or Mozambique,
 - did not reduce the incidence of LBW. The ERG noted that the comparator, 2 doses of SP-IPTp, is no longer policy.
- In HIV-infected women taking cotrimoxazole prophylaxis
 - , three doses of IPTp-MQ
 - reduced maternal parasitaemia at deliver
 - reduced overall outpatient visits and hospital admissions.
 - no difference was found between groups in the risk of LBW, or maternal anaemia and peripheral parasitemia at delivery.



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Malaria in Pregnancy Preventive Alternative Drugs (MiPPAD) (NCT 00811421)

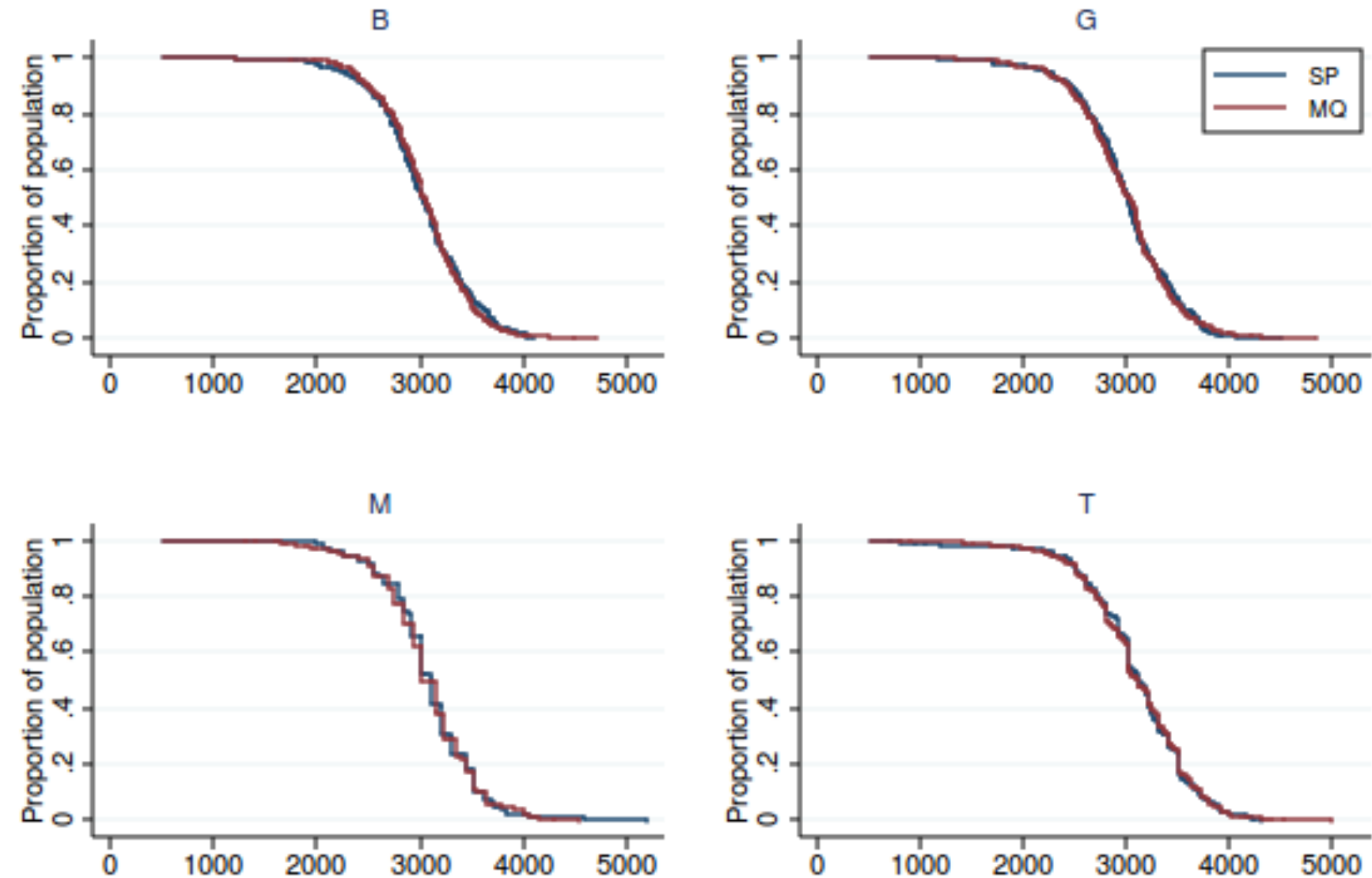
Clara Menéndez & Esperança Sevene

On behalf of the MiPPAD Study Group

WHO Expert Review Group Meeting on IPTp

Geneva, 9th July 2013

Weight by country and treatment



Birth Weight modified according to the days between birth and weight

Efficacy results 2/3

Endpoint	SP		MQ		RR	95% CI	p-value
	n/N	%	n/N	%			
Maternal parasitemia at delivery (O.M.)	63/1372	4.6	88/2737	3.2	0.70	(0.51 , 0.96)	0.0261
Placental infection (Histology or smear)	70/1281	5.6	120/2568	4.7	0.84	(0.63 , 1.10)	0.2053
Placental infection (smear only)	51/1264	4	85/2534	3.4	0.83	(0.60 , 1.17)	0.2871
Maternal anemia at delivery (Hb<11 g/dl)	609/1380	44.1	1110/2743	40.5	0.92	(0.85 , 0.99)	0.0255
Severe maternal anemia at delivery (Hb <7g/dl)	15/1380	1.1	15/2743	0.5	0.50	(0.25 , 1.02)	0.0583
Maternal Hb at delivery mean (SD)[n]	10.97 (1.56) [1380]		11.12 (1.50) [2743]		0.15 ¹	(0.05 , 0.25)	0.0028
Cord blood parasitemia	4/1337	0.3	6/2663	0.2	0.74	(0.21 , 2.62)	0.6441
Cord blood anemia	170/1334	12.7	354/2672	13.2	1.04	(0.88 , 1.22)	0.6877
Maternal parasitemia one month after delivery	21/1149	1.8	42/2280	1.8	1.01	(0.60 , 1.69)	0.9758

ITT cohort ¹Arithmetic difference

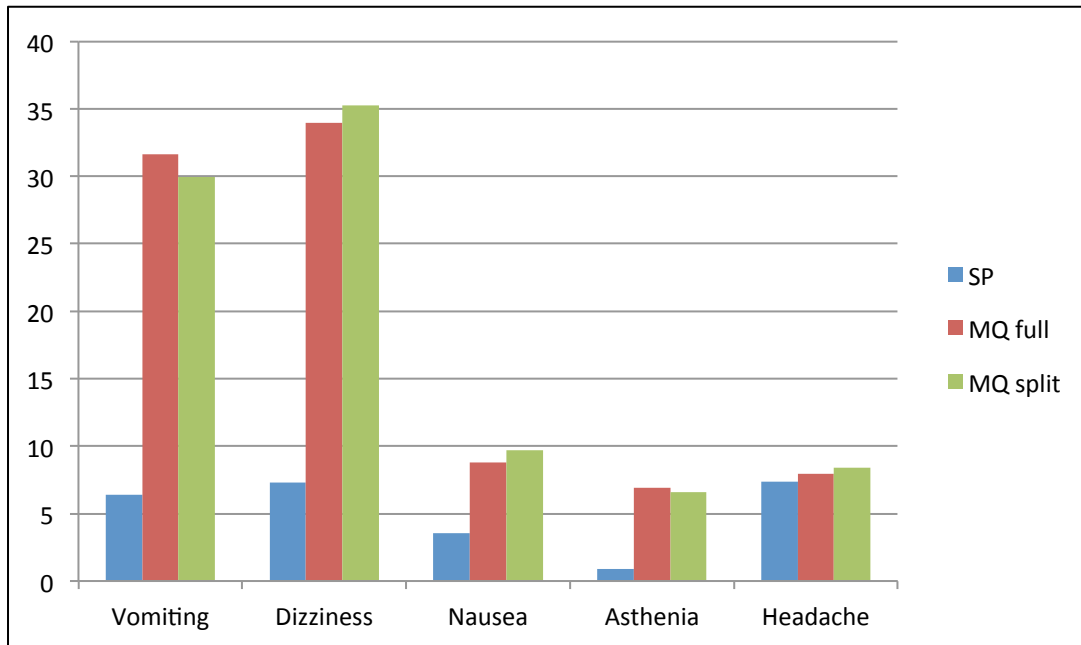
Efficacy results 3/3

Endpoint	SP	MQ	RR	95% CI	p-value
Incidence of clinical malaria	96/1576 0.174 ¹	130/3164 0.118 ¹	0.68	(0.52 , 0.88)	0.0035
Incidence of outpatients visits	850/1576 1.521 ¹	1475/3164 1.326 ¹	0.87	(0.80 , 0.95)	0.0012
Hospital Admissions	106/1576 0.190 ¹	185/3164 0.166 ¹	0.88	(0.69 , 1.11)	0.2832

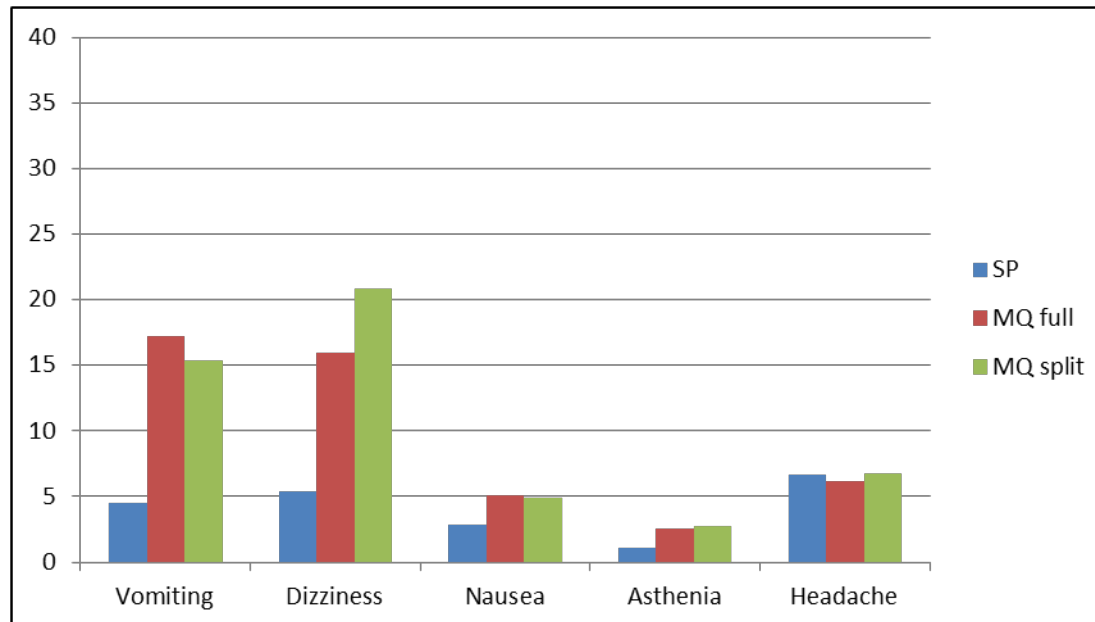
ITT cohort ¹ Episodes person/year

Definition of clinical malaria episode: *P. falciparum* parasitemia of any density plus any signs and/or symptoms suggestive of malaria: fever in the past 24 hours and/or axillary temperature ($T^a \geq 37.5$ °C), and/or pallor and/or arthromyalgias and/or headache and/or history of convulsions.

AEs related to medication after Dose 1



AEs related to medication after Dose 2



Conclusions

- MQ has a better prophylactic efficacy than SP
- MQ is a safe drug in terms of adverse pregnancy outcomes
- MQ has worse tolerability than SP as IPTp
- Splitting the MQ dose does not seem to confer benefits in terms of tolerability



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MiPPAD Trial 2:

Mefloquine as Intermittent Preventive Treatment for malaria in Pregnancy in HIV-infected women receiving cotrimoxazole prophylaxis: a multicenter randomized double-blind placebo-controlled trial

**John Aponte & Esperança Sevene
on behalf of the Mippad study group**

*WHO Expert Review Group Meeting on IPTp
Geneva, 9th July 2013*

Efficacy results 1/3

Primary endpoint	Placebo		MQ		RR	95% CI	p-value
Maternal parasitemia at delivery (by O.M. or submicroscopic)	33/489	6.7%	17/482	3.5%	0.53	(0.30; 0.93)	0.0279
Kenya	20/213	9.4%	14/205	6.8%	0.73	(0.38;1.40)	0.3417
Mozambique	13/257	5.1%	3/257	1.2%	0.23	(0.07;0.80)	0.0209
Tanzania	0/19	0%	0/20	0%	-	-	-

ITT cohort

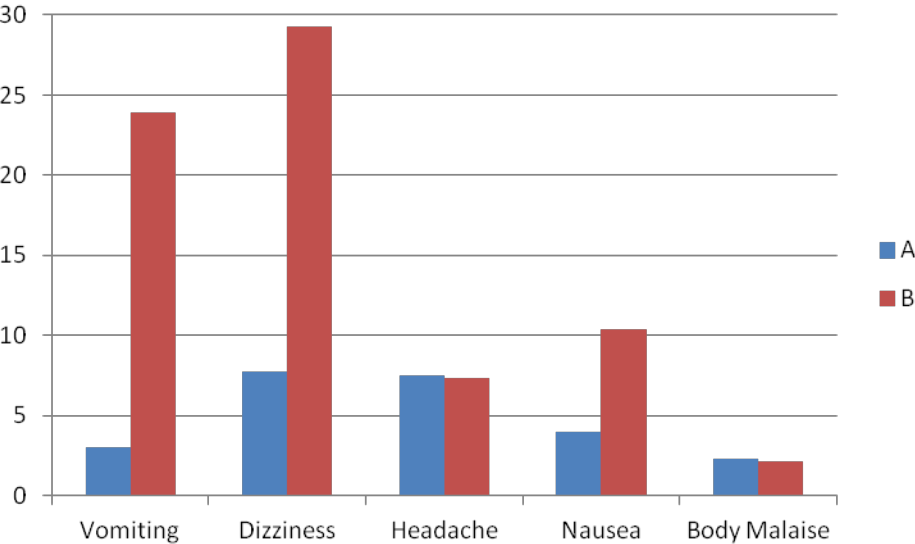
Efficacy results 3/3

Endpoint	Placebo (n=536)		Mefloquine (n=532)		RR	95% CI	p-value
Incidence of clinical malaria	16	0.085 ¹	7	0.038 ¹	0.45	(0.19; 1.10)	0.0785
Incidence of outpatients visits	400	2.108¹	331	1.809¹	0.85	(0.73; 0.98)	0.0277
Hospital Admissions	67	0.353¹	35	0.191¹	0.55	(0.36; 0.82)	0.0037

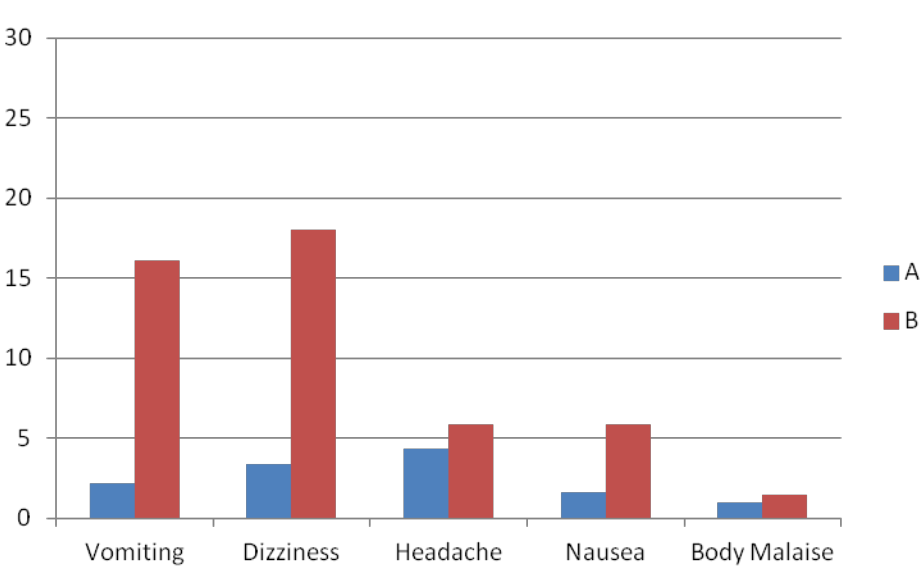
ITT cohort ¹ Episodes person/year

Definition of clinical malaria episode: *P. falciparum* parasitemia of any density plus any signs and/or symptoms suggestive of malaria: fever during the past 24 hours and/or axillary temperature ($T^a \geq 37.5$ °C), and/or pallor and/or arthromyalgias and/or headache and/or history of convulsions

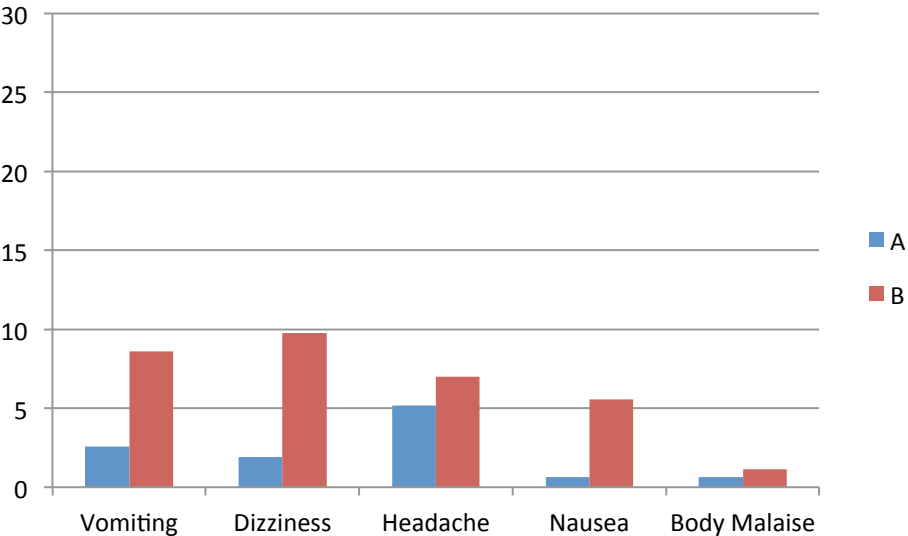
AEs related to medication after Dose 1



AEs related to medication after Dose 2



AEs related to medication after Dose 3



A: Placebo
B: Mefloquine

Recommendation 3 (continued):

Mefloquine, at a dose of 15 mg/kg, is not recommended for IPTp because of its low tolerability, with vomiting and dizziness in up to 30% of PW studied.

Key Findings (continued):

- 15 mg/kg dose of MQ associated with high rates of vomiting (24-30%) and dizziness (~18 - 30%). Therefore MQ is not recommended for IPTp at this dose due to its poor tolerability.
 - Splitting the 15 mg/kg dose over two consecutive days did not improve tolerability.
- MQ does not appear to be associated with an increase in adverse pregnancy outcomes (stillbirths, miscarriages or congenital malformations) when used for prophylaxis, treatment or IPTp.
- Noted difficult to screen women in most antenatal clinic settings for conditions such as a history of epilepsy or psychiatric problems, conditions which predispose to the rare but sometimes severe neuropsychiatric side effects of MQ.
- Continued pharmacovigilance on MQ when used for prophylaxis or treatment of malaria in pregnancy is required, including surveillance for neurological adverse events.

Development of monitoring protocols on IPTp

Work on two specific monitoring protocols was not completed at the time of the ERG at this meeting :

1. Based on the IPTp-Mon(itoring) study, and following the recommendations of the Evidence Review Group convened in 2012, a working group has been established to develop a simplified protocol template to monitor the impact of SP resistance on IPTp-SP effectiveness.

2. A second working group has been established to develop a simplified protocol to monitor the programmatic determinants of IPTp-SP effectiveness.

Points for discussion

- SP resistance
 - Molecular resistance surveillance as a basis for program action
 - Other options?
 - Program effectiveness monitoring (protocol)
 - RCT SP vs placebo
- Mefloquine
 - Further research priorities?
 - Is there a use scenario(s)?
- Transmission reduction and stopping IPTp
 - Evidence convincing ?
 - Guidance to countries