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Meeting report of the WHO Evidence Review Group on Malaria in Pregnancy

12–14 July 2017, Geneva, Switzerland

Summary

Malaria in pregnancy adversely affects maternal and infant health outcomes. The effects of *Plasmodium falciparum* infection and disease in sub-Saharan Africa have been well documented. However, the incidence and impact of *P. vivax* infection in pregnant women mainly outside Africa is less well known. Recently, different malaria control strategies among pregnant women – such as intermittent preventive treatment in pregnancy (IPTp), intermittent screening and treatment in pregnancy, and single screening and treatment – have been evaluated in Asia and the Pacific, in areas with both vivax and falciparum transmission.

WHO convened a group of experts to develop draft recommendations based on the review of recent evidence derived from malaria in pregnancy studies conducted in Africa, the Americas and Asia. Other studies reviewed also included evaluations on antimalarial drug pharmacokinetics in pregnant women, impact of maternal use of azithromycin added to IPTp-sulfadoxine-pyrimethamine on birth outcomes and sexually transmitted infections and reproductive tract infections, and the interactions between HIV infection and malaria in pregnancy.

The following conclusions and recommendations were proposed by the WHO Evidence Review Group for consideration by the WHO malaria Policy Advisory Committee.

Proposed conclusions and recommendations

1. Recent information indicates that although the overall incidence of *Plasmodium vivax* infection in pregnancy is low, it is associated with maternal anaemia, fetal loss, small for gestational age and preterm births, particularly in symptomatic pregnant women. Overall, the evidence reviewed does not support a change in the current recommendations on prevention, early diagnosis and treatment of clinical malaria followed by chloroquine prophylaxis to prevent parasitaemia following relapses.

2. Further research is needed on the effects of *P. falciparum* and *P. vivax* coinfection in pregnancy.

3. Evidence of pharmacokinetic (PK) and pharmacodynamics evaluations indicate that PK effects of pregnancy vary substantially among the different studies and antimalarial medicines. Given the inconsistency of the findings it is not entirely

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clear whether dosage adjustment is required during pregnancy. Importantly, the clinical relevance of PK changes needs to be established before any dosage modification in pregnant women is suggested.

4. A cluster-randomized controlled trial compared monthly intermittent preventive treatment in pregnancy (IPTp) with dihydroartemisinin-piperaquine (DHA-PPQ) with intermittent screening and treatment (IST) and single screening and treatment (SST) conducted in two sites in Indonesia. Preliminary results indicate that IPTp halved the risk of malaria during pregnancy and at delivery compared with SST, but only on the higher transmission site in Papua Indonesia. Study findings were not consistent across sites and study outcomes, and there was no consistent positive impact on birth outcomes. IST did not result in the detection of significantly more malaria infections than the existing SST strategy. Based on the current level of evidence, IPTp-DHA-PPQ is not currently recommended for malaria prevention in pregnant women.

5. The provision of SP through IPTp does not cure sexually transmitted infections (STIs) and reproductive tract infections (RTIs). Also, the impact of adding azithromycin to IPTp with sulfadoxine-pyrimethamine (SP) on STIs or RTIs and adverse birth outcomes requires further research, since current evidence of improved outcomes is limited. Additionally, the risk of increases in antimicrobial resistance associated with azithromycin use also requires further assessment.

6. Studies evaluating the additional benefit of azithromycin added to IPTp-SP for preventing adverse birth outcomes in Malawi and Papua New Guinea have yielded contradictory results. Low birth weight and preterm birth rates were reduced in two studies but not in one of the largest studies. Since study designs differed across sites, further research is needed to evaluate the impact of adding azithromycin to IPTp-SP on adverse birth outcomes.

7. HIV-infected pregnant women are particularly vulnerable to malaria. Co-trimoxazole (CTX) prophylaxis provides only partial protection against malaria during pregnancy. Research is needed to evaluate new strategies, including alternative medicines for IPTp to be safely administered concomitantly with CTX prophylaxis.

Abbreviations

A	artemether
ACT	artemisinin-based combination therapy
AE	adverse event
AL	artemether lumefantrine
ANC	antenatal care
AQ	amodiaquine
ART	antiretroviral therapy
ARV	antiretroviral drug
AS	artesunate
AZ	azithromycin
CEA	cost–effectiveness analysis
CQ	chloroquine
CI	confidence interval
CTX	co-trimoxazole
DALY	disability-adjusted life year
DHA	dihydroartemisinin
DHA-PPQ	dihydroartemisinin-piperaquine
EFV	efavirenz
ERG	Evidence Review Group
Hb	haemoglobin
HIV	human immunodeficiency virus
HR	hazard ratio
IPT	intermittent preventive treatment
IPTp	intermittent preventive treatment in pregnancy
IRS	indoor residual spraying
IRR	incidence rate ratio
IST	intermittent screening and treatment in pregnancy
ITN	insecticide-treated mosquito net
L	lumefantrine
LAMP	loop mediated isothermal DNA amplification
LBW	low birth weight
LLIN	long-lasting insecticidal mosquito net
msec	millisecond
MTCT	mother-to-child transmission
MQ	mefloquine
OR	odds ratio
PCD	passive case detection
PCR	polymerase chain reaction
PD	pharmacodynamics
PK	pharmacokinetics
PPQ	piperaquine
py	person-years
RCT	randomized controlled trial
RDT	rapid diagnostic test
RR	relative risk
RTI	reproductive tract infection
SAE	serious adverse event
SGA	small for gestational age
SMRU	Shoklo malaria Research Unit
SP	sulfadoxine-pyrimethamine
SST	single screening and treatment
SSTp	single screening and treatment in pregnancy
STI	sexually transmitted infection
WHO	World Health Organization

1. Introduction

1.1. Background

Recent mapping estimates of the number of pregnancies at risk of malaria indicate that the number of pregnancies in areas outside Africa with low malaria transmission or with *Plasmodium vivax* exceed the number of pregnancies occurring in areas with stable *P. falciparum* malaria, yet there is limited information on the burden of malaria in pregnancy (malaria in pregnancy) in these endemic areas *(1)*. In these regions outside Africa, with the exception of Papua New Guinea and Papua Indonesia, the incidence of falciparum malaria in pregnant women is lower but infections are more likely to cause symptomatic and severe disease in the mothers, as well as preterm births and fetal loss *(2)*.

P. vivax is common in the Americas and Asia. Unlike *P. falciparum, P. vivax* does not cytoadhere to placental structures; nonetheless, vivax malaria during pregnancy is also associated with maternal anaemia and low birth weight (LBW) *(2)*. malaria prevention guidelines in pregnancy do not include endemic regions outside Africa, except Papua New Guinea where intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP) is recommended. In these regions, control of malaria in pregnancy relies mainly on case management, although some countries recommend chloroquine (CQ) chemoprophylaxis, passive case detection (PCD), strategies for single screening and treatment (SST) and insecticide-treated mosquito nets (ITNs) *(3)*.

WHO convened a group of experts to develop recommendations based on new evidence derived from recent pregnancy studies conducted in Africa, the Americas and Asia. The studies reviewed also included evaluations on the pharmacokinetics (PK) of antimalarial medicines in pregnant women, the impact of maternal use of azithromycin (AZ) plus IPTp-SP on birth outcomes and sexually transmitted infections (STIs) and reproductive tract infections (RTIs), and the interactions between HIV infection and malaria in pregnancy.

1.2. Objectives

1. To review the burden of vivax malaria in pregnant women, including impact on maternal and birth outcomes.

2. To review the efficacy and safety of medicines to treat uncomplicated falciparum and vivax malaria in pregnancy in Asia and Latin America.

3. To review the efficacy and safety of intermittent screening and treatment in pregnancy (IST) and intermittent preventive treatment (IPT) of malaria in pregnancy in Asia.

4. To review the effects of SP and AZ protection against adverse birth outcomes related to STIs and RTIs.

5. To review the PK of dihydroartemisinin (DHA), piperaquine (PPQ), artesunate (AS), artemether (A), lumefantrine (L), amodiaquine (AQ) and mefloquine (MQ) during pregnancy, and implications for dose adjustments.

6. To review key challenges and knowledge gaps for malaria in pregnancy in HIV-infected women including:

    - the efficacy and effectiveness of co-trimoxazole (CTX) prophylaxis for prevention of malaria and its adverse consequences;
    - the efficacy and effectiveness of IPTp; and
    - the PK of antimalarial medicines in these women, including their interactions with antiretroviral medicines (ARVs).

1.3. Process

Data were presented as pre-reads and oral presentations for each of the following topics:

- burden of *P. vivax* in pregnancy;
- treatment of falciparum and vivax malaria in pregnancy;
- prevention of falciparum and vivax malaria in pregnancy;
- SP and AZ against STIs and RTIs; and
- HIV and malaria in pregnancy.

2. Evidence reviewed

2.1. Burden of *P. vivax* in pregnancy

2.1.1. Prevalence and clinical impact of P. vivax *infection in pregnant women: findings from a prospective multicentre project*

The results of a multicentre prospective facility-based study (the Pregvax study) to determine the burden and clinical impact of *P. vivax* in pregnant women from Brazil (BR), Colombia (CO), Guatemala (GT), India (IN) and Papua New Guinea (PNG) were presented and reviewed *(4)*.

Between 2008 and 2011, a total of 9388 women were enrolled at antenatal care (ANC) clinics of study sites; of these, 53% (4957) were followed until delivery. Prevalence of *P. vivax* mono-infection in maternal blood at delivery was 0.4% (20/4461) by microscopy (BR 0.1%, CO 0.5%, GT 0.1%, IN 0.2% and PNG 1.2%) and 7% (104/1488) by polymerase chain reaction (PCR). *P. falciparum* mono-infection was found in 0.5% (22/4463) of the women by microscopy (BR 0%, CO 0.5%, GT 0%, IN 0% and PNG 2%) and 2% by PCR (24/1191; performed in a subsample).

P. vivax infection was observed in 0.4% (14/3725) of placentas examined by microscopy and in 3.7% (19/508) by PCR. *P. vivax* in newborn blood was detected in 0.02% (1/4302) of samples examined by microscopy, and it was found in 0.05% (2/4040) of cord blood examined by microscopy, and 2.6% (13/497) by PCR. Only 0.5% of the study participants took CQ chemoprophylaxis during pregnancy.

Clinical *P. vivax* infection was associated with increased risk of maternal anaemia (odds ratio [OR] 5.48, 95% confidence interval [CI]: 1.83±16.41, p=0.009). Submicroscopic vivax infection (defined as an infection with a PCR positive for *P. vivax* and negative for *P. falciparum*, and a concomitant blood film negative by microscopy) was not associated with increased risk of moderate to severe anaemia (haemoglobin [Hb] <8 g/dL) (OR 1.16, 95% CI: 0.52–2.59, p=0.717), or LBW (<2500 g) (OR 0.52, 95% CI: 0.23–1.16, p=0.110) in the adjusted multivariate analysis. No impact of *P. vivax* infection was observed on other fetal or neonatal outcomes (e.g. prematurity or stillbirth). The impact of *P. vivax* and *P. falciparum* malaria on maternal anaemia and LBW is presented in Table 1.

TABLE 1.
Impact of *P. vivax* and *P. falciparum* malaria on maternal anaemia and LBW

	P. vivax						*P. falciparum*					
	Maternal anaemia *			Low birth weight			Maternal anaemia *			Low birth weight		
	Adjusted OR †	(95% CI)	p-value	Adjusted OR †	(95% CI)	p-value	Adjusted OR †	(95% CI)	p-value	Adjusted OR †	(95% CI)	p-value
At enrolment												
Non-infected	1		**0.009**	1		0.350	1		**0.001**	1		0.092
Asymptomatic malaria infection	0.96	(0.37-2.44)		0.92	(0.21-4.14)		4.01	(1.59-10.11)		2.03	(1.07-3.85)	
Clinical malaria	5.48	(1.83-16.41)		2.29	(0.74-7.04)		5.57	(1.22-25.34)		1.39	(0.16-12.03)	
At delivery												
Non-infected	1		0.754	1		0.298	1		0.122	1		**0.004**
Asymptomatic malaria infection	0.66	(0.22-1.96)		1.01	(0.22-4.63)		8.19	(1.08-62.38)		4.52	(1.63-12.49)	
Clinical malaria	1.05	(0.07-15.58)		9.39	(0.56-158.25)		1.29	(0.23-7.18)		4.29	(0.70-26-24)	
Non-infected	1		0.384	1		0.895	1		**<0.001**	1		**0.001**
Microscopic infection	0.62	(0.22-1.81)		0.90	(0.20-4.10)		4.07	(1.93-8.58)		4.28	(1.75-10.44)	
Non-infected	1		0.717	1		0.110	1		0.402	1		0.359
Sub-microscopic infection ‡	1.16	(0.52-2.59)		0.52	(0.23-1.16)		2.93	(0.24-36.23.16)		1.97	(0.46-8.46)	

* Maternal anaemia: Hb<11 g/dL
† Adjusted Odds Ratio (OR) for site and previous malaria episodes
‡ Neste case-control study

CI, confidence interval; LBW, low birth weight; OR, odds ratio
Source: Bardají et al. 2017 *(4).*

The incidence rate during pregnancy of *P. vivax* infection detected by microscopy was not associated with parity (incidence rate ratio [IRR] for multigravidae women with four or more pregnancies 1.14, 95% CI: 0.70±1.87, p=0.619). In contrast, the incidence rate of *P. falciparum* infection detected by microscopy decreased with parity (compared to primigravida, IRR for multigravidae 0.39, 95% CI: 0.25±0.62, p<0.001).

Studies on the humoral and cellular responses to *P. vivax* infection during pregnancy within the frame of the Pregvax study showed that naturally acquired binding-inhibitory antibodies to *P. vivax* Duffy binding protein in pregnant women were associated with higher birth weight *(5)*. Also, the virulence (VIR) antigens were shown to induce the natural acquisition of antibody and T cell memory responses that may be important in immunity to *P. vivax* during pregnancy in diverse geographical settings *(6)*.

With regard to the genotyping studies of *P. vivax* and *P. falciparum* isolates from pregnant women, *P. vivax* population diversity was higher in all sites than their sympatric *P. falciparum* populations *(7)*. *P. vivax* was associated with placental infection. However, placental inflammation was not observed in *P. vivax* mono-infections, suggesting other

causes of poor delivery outcomes associated with vivax infection *(8)*. Furthermore, *P. vivax* peripheral isolates from pregnant women did not exhibit a prominent adhesion to placental chondroitin sulfate A (CSA). Finally, in studies conducted in Brazil, rosetting was found to be a frequent cytoadhesive phenotype in peripheral blood *P. vivax* infections associated with anaemia *(9)*.

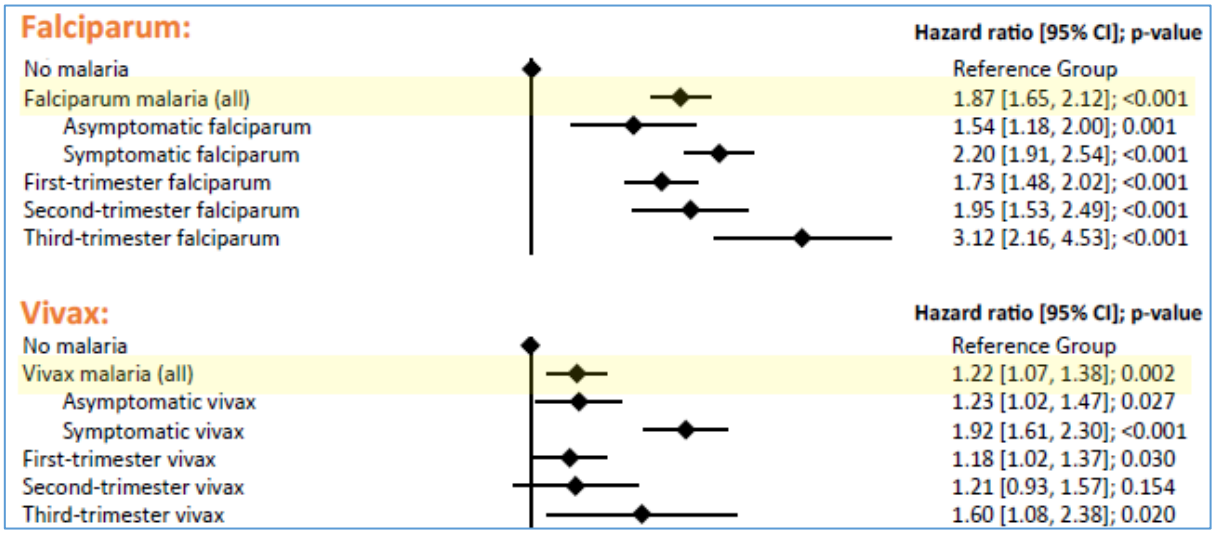
Costs associated with malaria in pregnancy in areas where *P. vivax* predominates constitute a substantial economic burden *(10)*. For instance, for a clinical malaria episode in pregnancy in Brazil, patients' costs reached up to 3.4% of the local average annual per capita income, while in Colombia, median inpatient costs represented 18% of the monthly minimum salary in the country. In Bikaner district, India, the economic costs of one hospital admission was over 12 times higher than the monthly average per capita income of the district. Therefore, a reduction of the burden of malaria in pregnancy is likely to have a significant economic benefit to households and might help to improve economic growth in endemic areas.

2.1.2. Association between vivax and falciparum malaria in pregnancy and adverse pregnancy outcomes in an area of low transmission

Two analyses of prospective observational data routinely collected at ANC clinics from the Shoklo malaria Research Unit (SMRU), in the Thai–Myanmar border area between 1986 and 2015 were presented and reviewed *(11, 12)*.

The effect of falciparum and vivax malaria in pregnancy on antepartum (death in utero) and intrapartum (death during labour) stillbirth and neonatal mortality was analysed in 61 836 women *(11)*. *Stillbirth* was defined as a baby born dead from 28 weeks' gestation, *malaria* as the presence of asexual parasites in the peripheral blood, and *symptomatic malaria* as parasitaemia plus a temperature ≥37.5 °C or a history of fever in the past 48 hours. A total of 9350 women (15%) had malaria in pregnancy detected by microscopy, and 526 (0.8%) had stillbirths (49% [260/526] antepartum, 34% [178/526] intrapartum and 17% [88/526] uncertain). In a subset of 9090 liveborn singletons followed from birth there were 153 (1.7%) neonatal deaths. Fig. 1 shows the observed association between falciparum and vivax malaria in pregnancy and fetal loss (miscarriage or stillbirth) in the study. Associations between malaria and fetal loss in the first and second trimester were driven by miscarriages, while associations in the third trimester were due to stillbirths.

FIG. 1.
Association between malaria in pregnancy and fetal loss (miscarriage or stillbirth)



CI, confidence interval
Source: Moore et al., 2017 *(11)*

The hazard of antepartum stillbirth increased 2.24-fold (95% CI: 1.47–3.41) following falciparum malaria, with 42% mediated through small for gestational age (SGA) status and anaemia. This was driven by symptomatic falciparum malaria (hazard ratio [HR] 2.99 [1.83–4.89]) rather than asymptomatic falciparum malaria infections (HR 1.35 [0.61–2.96]).

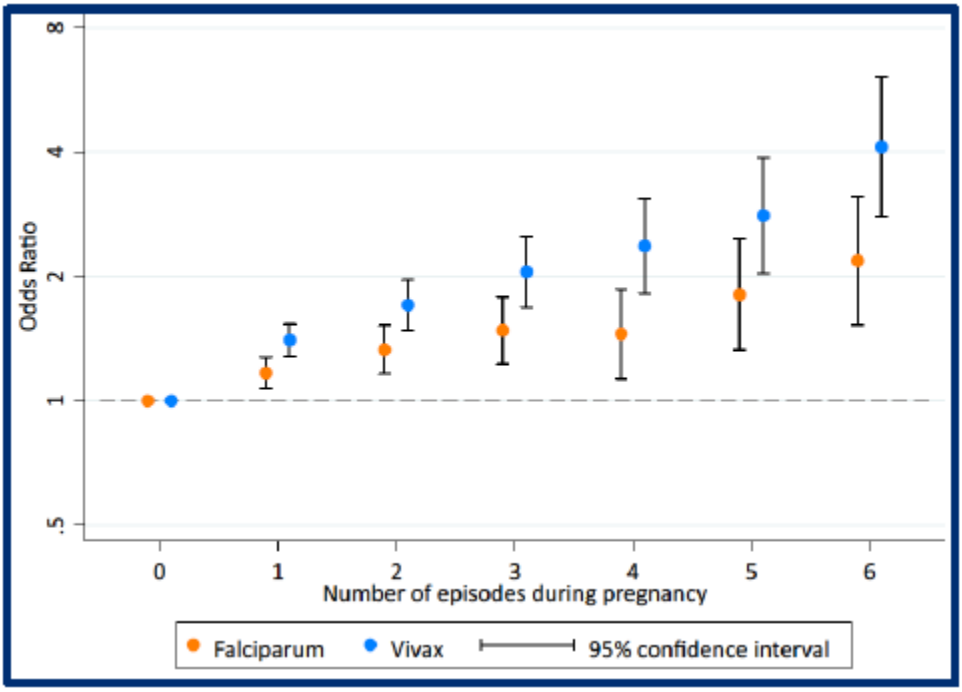
The hazard of antepartum stillbirth increased 2.21-fold (1.12–4.33) following symptomatic vivax malaria (24% mediated through SGA status and anaemia). Similar to falciparum malaria, asymptomatic vivax malaria infection was not associated with stillbirth (HR 0.54 [0.20–1.45]). The association between malaria and miscarriage was greater after a recurrence, whether the recurrence was due to a novel infection, recrudescence or relapse in the case of vivax infection. The hazard of miscarriage increased 3.24-fold following falciparum recurrence (2.24–4.68, p<0.0001), and 2.44-fold (1.01–5.88, p=0.0473) following recurrent symptomatic vivax malaria *(13)*.

There was no association between falciparum or vivax malaria in pregnancy and intrapartum stillbirth (falciparum HR 1.03 [0.58–1.83]; vivax HR 1.18 [0.66–2.11]). Overall, falciparum and vivax malaria in pregnancy increased the hazard of neonatal death 2.55-fold (1.54–4.22) and 1.98-fold (1.10–3.57), respectively (40% and 50%, respectively, mediated through SGA status and preterm birth).

The second analysis on the effects of the total number of malaria episodes in pregnancy on SGA and of the effects of malaria in pregnancy on SGA by the gestational age at malaria detection and treatment included 50 060 pregnant women enrolled at the SMRU ANC clinics between 1985 and 2015 *(12)*. A total of 8221 (16%) of them had malaria during their pregnancy. The analysis used WHO definitions of very preterm birth (≥28 and <32 weeks) and late preterm birth (≥32 and <37 weeks) and international SGA standards (INTERGROWTH-21st). Of the 50 060 neonates, 10 005 (21%) were SGA, 540 (1%) were very preterm and 4331 (9%) were late preterm. The rates of falciparum and vivax malaria were highest at 6 and 5 weeks' gestation, respectively.

The odds of SGA increased linearly by 1.13-fold (95% CI: 1.09–1.17) and 1.27-fold (95% CI: 1.21–1.33) per episode of falciparum and vivax malaria, respectively. Falciparum malaria at any gestation period after 12–16 weeks, and vivax malaria after 20–24 weeks, were associated with SGA (falciparum OR range: 1.15–1.63 [p range: <0.001–0.094] and vivax OR range: 1.12–1.54 [p range: <0.001–0.138]). The association between the number of malaria episodes and SGA is shown in Fig. 2.

FIG. 2.
Association between the number of malaria episodes and SGA



SGA, small for gestational age
Source: Moore et al., 2017 *(12)*

Falciparum malaria at any gestation period after 24–28 weeks was associated with either very or late preterm birth (OR range: 1.44–2.53; p range: <0.001–0.001). Vivax malaria at 24–28 weeks was associated with very preterm birth (OR 1.79 [1.11–2.90]), and vivax malaria at 28–32 weeks was associated with late preterm birth (OR 1.23 [1.01–1.50]). Many of these associations held for asymptomatic malaria (defined as clinically asymptomatic infections detected by microscopy).

Finally, we reviewed the results of a systematic review and meta-analysis on the association between malaria in pregnancy and stillbirth including 59 studies conducted in areas of different malaria endemicity (Moore et al., in press). The association between falciparum malaria and stillbirth was almost 2-fold greater in areas of low-to-intermediate endemicity than in areas of high endemicity, but few studies (18%) from areas of low transmission contributed to this analysis. Vivax malaria detected and treated at delivery, but not during pregnancy, was also associated with stillbirth. However, only seven studies of vivax malaria were included, resulting in wide confidence intervals. Additionally, no information about mixed infections (falciparum and vivax) was available.

Key conclusions on burden of *P. vivax* in pregnancy

- The incidence of *P. vivax* infection in pregnancy was low (<2%) across different endemic settings in a multicentre health facility-based prospective cohort study conducted between 2008 and 2011 in Brazil, Colombia, Guatemala, India and Papua New Guinea. Additionally:
  - *P. vivax* malaria was associated with anaemia in symptomatic women;
  - most *P. vivax* infections were of low density and were undetected with routine microscopy; and
  - *P. vivax* was associated with placental infection; however, placental inflammation was not observed in *P. vivax* mono-infections, suggesting other causes of poor delivery outcomes associated with vivax infection.
- Analyses of data routinely collected at ANC clinics between 1986 and 2015 in the Thai–Myanmar border area indicate that both treated falciparum and vivax malaria were associated with fetal loss, SGA and preterm birth. In these analyses, the associations between malaria in pregnancy and miscarriage and SGA were stronger following recurrence, whether that recurrence was due to a novel infection, treatment failure or relapse in the case of vivax malaria.

2.2. Treatment of falciparum and vivax malaria in pregnancy

2.2.1. Efficacy and safety of artesunate plus sulphadoxine-pyrimethamine (AS-SP) and artesunate plus mefloquine (AS-MQ) to treat uncomplicated falciparum malaria in pregnancy in India

The results of an open-label clinical trial evaluating the efficacy and safety of AS-SP and AS-MQ for treatment of falciparum malaria in pregnant women in India were presented and reviewed (Anvikar et al., unpublished).

Between 2010 and 2013, a total of 7064 pregnant women were screened for participation in the trial, which was conducted in the states of Jharkhand and Odisha (India). Of these women, 248 (3.5%) with uncomplicated *P. falciparum* mono-infection were enrolled in the trial, of whom 123 received AS-MQ and 125 received AS-SP. The prevalence of malaria was low in the study sites and this compromised the recruitment rate (it was not possible to reach the target sample size of 300).

A total of 239 women (121 in the AS-SP arm and 118 in the AS-MQ arm) completed the day 63 follow-up (per protocol). Among these women, the adequate clinical and parasite response was 100% in the AS-SP group and 99.2% (95% CI: 95.4–99.97) in the AS-MQ group.

There were five serious adverse events (SAEs) among pregnant women (four in AS-SP and one in AS-MQ) and 13 fetal or neonatal SAEs (seven in AS-SP and six in AS-MQ), but none of them were considered related to the study medicines. A higher proportion of women in the AS-MQ arm reported vomiting within 7 days post-treatment than in the AS-SP arm (12.2% versus 1.6%, p=0.001). The prevalence of LBW was found to be higher in the AS-SP group

than in the AS-MQ group (28.3% versus 16.8%, p=0.037). Placental biopsy sample was available for 181 women (73%), and none of the biopsies showed evidence of active placental malaria.

Both treatments were efficacious and safe, but AS-MQ appeared to be less well tolerated than AS-SP.

2.2.2 Safety, tolerability and pharmacokinetic (PK) properties of co-administered azithromycin and piperaquine in pregnant women from PNG

A recently published study evaluated the safety, tolerability and PK properties of co-administered AZ and PPQ in 30 pregnant women from Papua New Guinea attending their first ANC visit (median gestational age of 26) *(14)*. Participants were given three daily doses of 1 g AZ plus 960 mg PPQ tetraphosphate, with detailed monitoring and blood sampling over 42 days.

The treatment was found to be well tolerated. The median (interquartile range) increase in the rate-corrected electrocardiographic QT interval 4 hours post-dose (12 [6–26] $msec^{0.5}$) was similar to that found in previous studies in pregnancy with DHA-PPQ or SP-PPQ. Electrocardiographic changes were assessed at multiple intervals (4, 12 and 24 hours) after the first dose of PPQ, but not at the predicted maximum concentration (about 52 hours).

Six women with asymptomatic malaria cleared their parasitaemias within 72 hours. Two aparasitaemic women developed late uncomplicated *P. falciparum* infections on days 42 and 83; these infections were treated with a 3-day course of artemether-lumefantrine (AL). The remaining pregnant women were uninfected throughout the study.

Compared with previous studies among pregnant women, the area under the concentration-time curve ($AUC_{0-\infty}$) for PPQ (38 818 [24 354–52 299] µg h l^{-1}) was similar to published values, but there was a 52% increase in relative bioavailability with each subsequent dose.

The $AUC_{0-\infty}$ for AZ (46 799 [43 526–49 462] µg h l^{-1}) was at least as high as that reported for higher dose regimens, suggesting saturable absorption or concentration-dependent tissue uptake and clearance from the central compartment (or both).

2.2.3. K/PD analysis of dihydroartemisinin, piperaquine, artesunate, artemether, lumefantrine, amodiaquine and mefloquine during pregnancy and possible implications for dose adjustments

A comprehensive literature review on the pharmacokinetics (PK) and pharmacodynamics (PD) properties of different antimalarial medicines used in pregnancy was presented and reviewed at the meeting. The main findings are summarized in the tables below.

TABLE 2.
Summary of PK properties of artemisinin derivatives found in studies conducted among pregnant women

Antimalarial	Study patients	Country	Pregnancy effects
Artesunate	Pregnant women (n=24)	Thailand	Decreased exposure to DHA compared to historical controls.
	Pregnant and postpartum women (n=20/15)	Thailand	23% decreased exposure to DHA compared with postpartum women.
	Pregnant, postpartum and non-pregnant women (n=26/26/25)	DRC	42% decreased exposure to DHA compared with non-pregnant women.
	Pregnant and non-pregnant women (n=24/24)	Burkina Faso	No difference in exposure to DHA compared non-pregnant women.
	Contradictory results; no difference and decreased exposure reported in pregnant women.		
Artemether	Pregnant and non-pregnant women (n=30/30)	Uganda	No difference in exposure to DHA compared non-pregnant women.
	Pregnant and non-pregnant women (n=33/22)	Tanzania	No difference in exposure to DHA compared non-pregnant women.
	Pregnant women (n=21)	Uganda	Decreased exposure to DHA compared to historical controls.
	Pregnant women (n=13)	Thailand	Decreased exposure to DHA compared to historical controls.
	Contradictory results; no difference and decreased exposure reported in pregnant women.		
DHA	Pregnant and non-pregnant women (n=32/33)	PNG	No difference in exposure to DHA compared to non-pregnant women.
	Pregnant and non-pregnant women (n=24/24)	Thailand	38% decreased exposure to DHA compared to non-pregnant women.
	Pregnant and non-pregnant women (n=31/30)	Uganda	47% decreased exposure to DHA compared to non-pregnant women.
	Contradictory results; no difference and decreased exposure reported in pregnant women.		

DHA, dihydroartemisinin; DRC, Democratic Republic of the Congo; PK, pharmacokinetics; PNG, Papua New Guinea; Tanzania, United Republic of Tanzania
Source: Tarning et al., unpublished
Studies showing an effect of pregnancy on antimalarial medicines PK properties are highlighted in red.

Overall, PK studies of artemisinin derivatives in pregnant women showed contradictory results. However, most studies showed a lower drug exposure to artemisinins in pregnant women than in non-pregnant women.

TABLE 3.
Summary of PK properties of 4-amino-quinolones derivatives and quinolone methanols in studies conducted among pregnant women

Antimalarial	Study patients	Country	Pregnancy effects
Chloroquine	Pregnant and non-pregnant women (n=30/30)	PNG	34% decreased exposure to chloroquine compared to non-pregnant women.
	Pregnant and non-pregnant women (n=12/15)	Thailand	No difference in exposure to chloroquine compared to non-pregnant women.
	Pregnant women (n=49)	Tanzania	Decreased exposure to chloroquine compared to historical controls.
	Contradictory results; no difference and decreased exposure reported in pregnant women.		
Amodiaquine	Pregnant and postpartum women (n=24/18)	Thailand	No difference in exposure to amodiaquine and desethylamodiaquine compared to postpartum women.
	No difference in exposure reported in pregnant women.		
Piperaquine	Pregnant and non-pregnant women (n=32/33)	PNG	42% decreased exposure to piperaquine compared to non-pregnant women.
	Pregnant and non-pregnant women (n=24/24)	Thailand	No difference in exposure to piperaquine compared to non-pregnant women.
	Pregnant and non-pregnant women (n=12/12)	Sudan	No difference in exposure to piperaquine compared to non-pregnant women.
	Pregnant and non-pregnant women (n=31/30)	Uganda	40% decreased exposure to piperaquine compared to non-pregnant women.
	Contradictory results; no difference and decreased exposure reported in pregnant women.		
Mefloquine	Pregnant and non-pregnant women (n=24/24)	Burkina Faso	No difference in exposure to MQ compared to non-pregnant women.
	Pregnant and non-pregnant women (n=9/8)	Burkina Faso	No difference in exposure to MQ compared to non-pregnant women.
	Pregnant women (n=20)	Thailand	Decreased exposure to MQ compared to historical controls.

Antimalarial	Study patients	Country	Pregnancy effects
	Contradictory results; no difference and decreased exposure reported in pregnant women.		
Quinine	Pregnant women (n=22)	Uganda	Decreased exposure to quinine women compared to historical controls.
	Pregnant and non-pregnant women (n=8/8)	Sudan	No difference in exposure to quinine compared to non-pregnant women.
	Pregnant and non-pregnant women (n=9/8)	Sudan	No difference in exposure to quinine compared to non-pregnant women.
	Contradictory results; no difference and decreased exposure reported in pregnant women.		
Lumefantrine	Pregnant and non-pregnant women (n=30/30)	Uganda	No difference in exposure to L compared to non-pregnant women.
	Pregnant and non-pregnant women (n=33/22)	Tanzania	34% decreased exposure to L compared to non-pregnant women.
	Pregnant and non-pregnant women (n=26/17)	Uganda	No difference in exposure to L compared to non-pregnant women.
	Pregnant women (n=13)	Thailand	Decreased exposure to L compared to historical controls.
	Pregnant and non-pregnant women (n=116/17)	Uganda	No difference in exposure to L compared to non-pregnant women.
	Pregnant women (n=103)	Thailand	Decreased exposure to L compared to historical controls.
	Contradictory results; no difference and decreased exposure reported in pregnant women.		

L, lumefantrine; MQ, mefloquine; PK, pharmacokinetics; PNG, Papua New Guinea; Tanzania, United Republic of Tanzania

Source: Tarning et al., unpublished

Studies showing an effect of pregnancy on antimalarial medicines PK properties are highlighted in red.

The efficacy of the standard six-dose AL regimen given over 3 days for treatment of falciparum malaria was shown to be unacceptably low (82%) in one small study in pregnant women in a low malaria intensity transmission setting in the Thai–Myanmar border area *(15)*. This high treatment failure rate may have been due to the low concentrations of A and of L. Decreased AL concentrations were also seen in high malaria transmission areas in Uganda and the United Republic of Tanzania, but without significant increases in treatment failure rates, possibly as a result of partial immunity or lower levels of antimalarial resistance (or both). A recent study on a small sample of pregnant women (n=48)

conducted in the Democratic Republic of the Congo prolonged treatment by adding a twice daily 80/480 mg AL dose on days 4 and 5 to the standard AL dosage regimen. This prolonged treatment ensured that pregnant women safely achieved antimalarial drug exposure equivalent to that of non-pregnant women given the standard six-dose AL regimen given over 3 days (Onyamboko et al., unpublished). No differences were observed in the therapeutic efficacy of AL between the 3-day standard regimen and the 5-day experimental treatment, which again may reflect higher levels of partial immunity or lower levels of antimalarial resistance in the African study site.

Regarding DHA-PPQ (DHA-PPQ), although there is no evidence of higher DHA-PPQ treatment failure rates in pregnancy, lower terminal drug concentrations may shorten the post-treatment prophylactic period of PPQ in pregnant women. Pharmacometrics modelling (i.e. science that quantifies drug, disease and trial information to aid efficient drug development or regulatory decisions *(16)*) is ongoing to determine the optimal DHA-PPQ dosage regimens for prospective testing in pregnant women.

Overall, the clinical significance of the PK changes of antimalarial medicines in pregnancy needs to be established before taking decisions on dose adjustments.

Key conclusions on treatment of falciparum and vivax malaria in pregnancy

- The prevalence of falciparum mono-infection among Indian pregnant women from Jharkhand and Odisha states was low (<3.5%).
- A recent study in India has shown that both AS-SP and AS-MQ are efficacious and safe for the treatment of falciparum malaria in pregnant women, but AS-MQ was less well tolerated than AS-SP, with a higher frequency of vomiting.
- A small study in Papua New Guinea has shown the combination of AZ-PPQ to be safe and well tolerated among pregnant women.
- The systematic review of antimalarial drug PK properties in studies among pregnant women found:
  - generally lower drug exposure to artemisinins, L, PPQ and SP in pregnant women compared with non-pregnant women;
  - contradictory results reported for CQ and pyrimethamine in pregnant women compared with non-pregnant women;
  - no difference in drug exposure to AQ, MQ and quinine in pregnant women compared to postpartum women; and
  - that the clinical impact of the reported PK changes and dose optimization need to be established.

2.3. Prevention of falciparum and vivax malaria in pregnancy

2.3.1. RCT on the efficacy and safety of intermittent screening and treatment (IST) with AS-SP versus passive case detection in India.

Between 2012 and 2015, a two-arm, cluster-randomized controlled trial (RCT) comparing the effectiveness of IST with the current policy of PCD for malaria during ANC visits was conducted in four districts of Jharkhand, India (Kuepfer et al., unpublished). A total of 3300 pregnant women in 46 clusters were enrolled in the IST arm, and 3568 women in 41 clusters in the PCD arm. Women in the IST group were screened with a rapid diagnostic test (RDT) for malaria at each ANC visit, and those in the PCD arm were screened only if they had a symptom or sign suggestive of malaria. Women in either arm who had a positive RDT for malaria were treated with AS-SP.

The proportion of women in whom RDT positive malaria was detected at least once during an ANC visit was significantly higher in the IST arm (4.8%) (157/3300) than in the PCD arm (0.6%) (22/3568) ($p<0.001$). However, there was no difference in the risk of placental malaria (active or past) between the IST and PCD arms (6.0% versus 4.5%, $p=0.29$). Most cases of placenta malaria were not detected by RDT (88.5%; 77/87). There was no significant difference in any of the secondary endpoints (birth weight, gestational age, vital status at birth and maternal anaemia) between the two groups. However, there were 30 maternal deaths (14 in the IST arm and 16 in the PCD arm; four of these deaths were attributable to malaria [2 in each arm]), representing an exceptionally high maternal mortality ratio of 437/100 000 live births for the study area.

Overall, IST detected a significantly higher number of women with malaria in pregnancy compared with PCD, indicating that malaria in pregnancy is mostly asymptomatic, even in this very low transmission setting. However, this intervention did not reduce the risk of placental malaria or adverse birth outcomes compared to PCD.

2.3.2. Evaluation of implementation of IST for control of malaria in pregnancy in Jharkhand, India

A study to evaluate implementation of IST in health facilities from Jharkhand (India) along with the previously presented RCT was conducted between 2013 and 2014 (Webster et al., unpublished). The study methods included two cross-sectional household surveys conducted before and after implementation of the intervention, in-depth interviews with health workers delivering the intervention and focus group discussions with pregnant women eligible to receive the intervention.

A total of 1087 questionnaires were completed – 553 before and 534 after the implementation of IST. In-depth interviews were conducted with 29 health providers, and 13 focus group discussions were conducted with currently and recently pregnant women. The proportion of pregnant women who received an RDT for malaria at ANC at least once during their current or recent pregnancy increased from 19.2% (95% CI: 14.9–24.3) before implementation to 42.5% (95% CI: 36.6–48.7) after implementation ($p<0.0001$), and the proportion of women who had more than one RDT during their current or recent pregnancy also increased ($p<0.0001$). Health workers were positive about IST, mainly due to their perception that many pregnant women with malaria were asymptomatic. Health workers perceived pregnant women to have reservations about IST due to dislike of frequent blood taking, but the pregnant women themselves were more positive.

The study concluded that the proportion of pregnant women tested for malaria at least once during their pregnancy increased with implementation of IST. However, if IST is implemented, efforts would need to be made to further increase the proportion of women tested because, overall, less than half of women were reached.

2.3. Intermittent preventive treatment (IPT) or intermittent screening and treatment (IST) with dihydroartemisinin-piperaquine for malaria in pregnancy: an open label cluster-randomized controlled trial in Indonesia

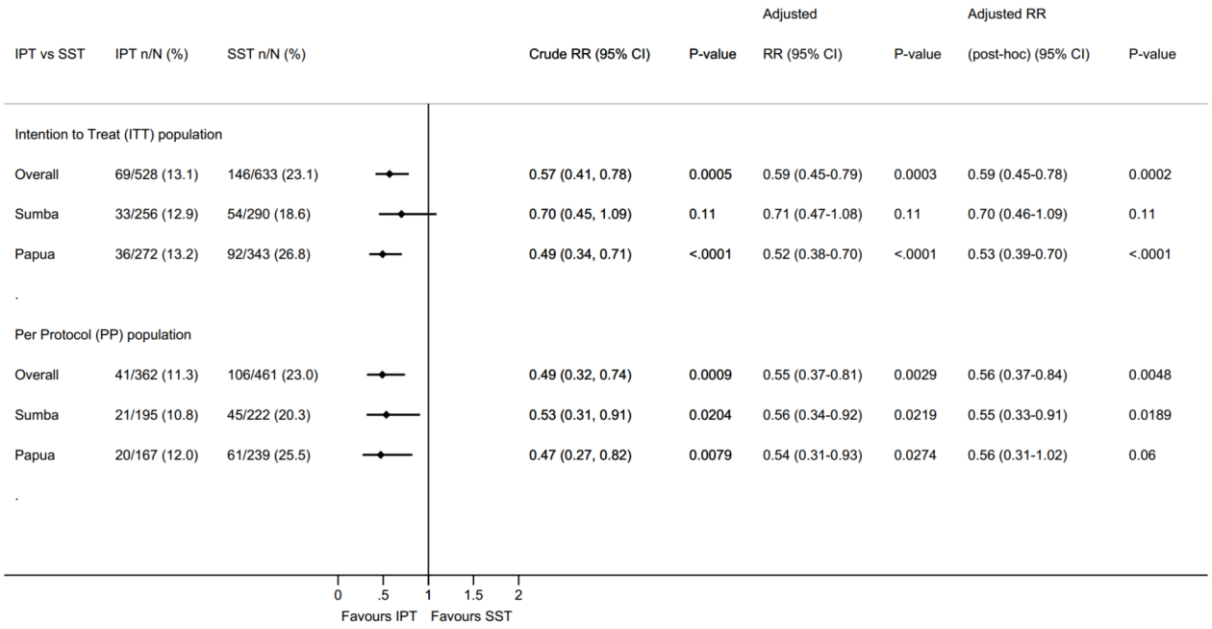
The preliminary results of a recently completed open-label three-arm cluster-RCT in Indonesia comparing the safety and efficacy of monthly IPT with DHA-PPQ, monthly IST with DHA-PPQ, and SST with DHA-PPQ was presented and reviewed (Ahmed et al., unpublished, STOPmalaria in pregnancy project). The trial was carried out in two sites in Indonesia with low (Sumba) and moderate year-round transmission (Papua), and enrolled a total of 2279 pregnant women (Sumba=989; Papua=1290) between 2013 and 2016. Patent *Plasmodium* infection was defined as microscopy or RDT positive and PCR-confirmed loop mediated isothermal DNA amplification (LAMP) positive (where PCR-confirmed LAMP is a LAMP positive sample that was subsequently confirmed as positive by quantitative PCR or nested PCR). Subpatent infection was defined as PCR-confirmed LAMP positive, but microscopy or RDT negative.

At baseline, about 15% of the women were infected with malaria parasites; the level was similar in the SST and IPT arms (18.3% and 17.8%), but was significantly lower in the IST arm (10.4%). Most of these infections were subpatent and below the level of detection by RDT. Ultimately, 1874 (82.1%) women contributed to the primary endpoint at delivery (IST=83.5%, IPT=77.5% and SST=85.1%). Retention was significantly lower in the IPT arm than in the IST arm (relative risk [RR] 0.83, 95% CI: 0.73–0.95, p=0.0032) or SST arm (RR 0.77, 95% CI: 0.66–0.90, p=0.0002), because of a higher withdrawal of consent in two of the seven IPT clusters in Papua, a situation that did not occur in Sumba.

IPT versus SST comparison

At delivery, the prevalence of malaria infection was lower in the IPT than SST arm: 69/528 (13%) versus 146/633 (23%) (RR 0.57, 95% CI: 0.41–0.78, p=0.0005) (Fig. 3). IPT prevented 92% of patent infections in the peripheral blood (RR 0.08, 95% CI: 0.01–0.61, p=0.0147) and 38% of the subpatent infections (RR 0.62, 95% CI: 0.41–0.93, p=0.0192). The protective effect was seen in all gravidae, and was not modified by ITN use, season or socioeconomic status.

FIG. 3.
Malaria at delivery (primary endpoint) in the IPT and SST groups



CI, confidence interval; IPT, intermittent preventive treatment; RR, relative risk; SST, single screening and treatment

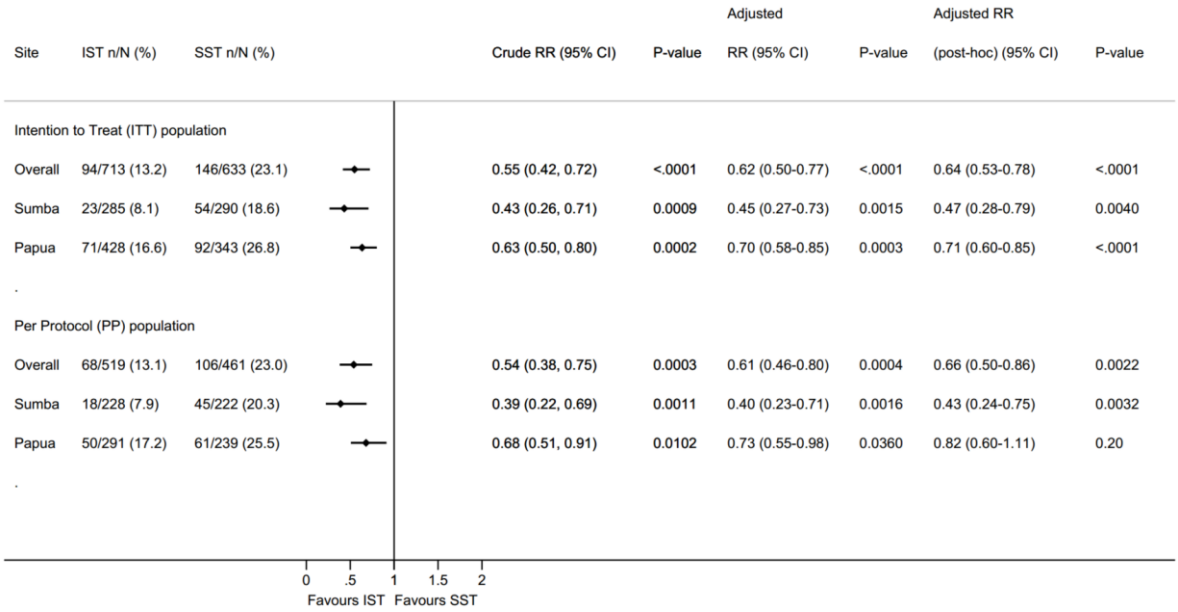
IPT was also associated with lower incidence rates of malaria infection during pregnancy (47.9 versus 91.4 events/100 person-years (py), incidence rate ratio (IRR) 0.56, 95% CI: 0.36–0.88, p=0.0125), but only in Papua Indonesia (higher transmission intensity) (IRR 0.22, 95% CI: 0.14–0.36, p=<0.0001), not in Sumba (low transmission intensity) (IRR 1.14, 95% CI: 0.73–1.77, p=0.57). IPT was also more effective than SST at reducing placental malaria detected by histology (RR 0.47, 95% CI: 0.23–0.95, p=0.0363), but again only in Papua (RR 0.32, 95% CI: 0.18–0.55, p<0.0001), not in Sumba (RR 1.31, 95% CI: 0.50–3.44, p=0.58). In Papua, IPTp-DHA-PPQ reduced the risk of maternal Hb <9 g/dL (RR 0.64, 95% CI: 0.44–0.92, p=0.0157), but not in Sumba (RR 0.91, 95% CI: 0.68–1.23, p=0.55).

The beneficial impact of IPTp with DHA-PPQ on maternal parasites at delivery – and placental malaria – did not translate into benefits for the newborn at birth. Relative to SST, there were no differences in adverse pregnancy outcomes (composite of fetal loss, SGA, LBW or preterm birth, or neonatal death) overall (IPT: RR 1.16, 95% CI: 0.88–1.54, p=0.29). The risk was higher in Sumba (RR 1.44, 95% CI: 1.15–1.81, p=0.0016), but not in Papua (RR 0.88, 95% CI: 0.59–1.30, p=0.52).

IST versus SST comparison

Compared with SST, IST was associated with a lower prevalence of malaria infection at delivery (any measure: 94/713 [13%] versus 146/633 [23%]; RR 0.55, 95% CI: 0.42–0.72, p<0.0001) (Fig. 4), in both sites, but not for placental malaria detected by histology (RR 0.98, 95% CI: 0.57–1.68, p=0.94), and IST was also not associated with a lower incidence of malaria infection during pregnancy (IRR 0.92, 95% CI: 0.64–1.33, p=0.67). There were also no differences in adverse pregnancy outcomes (composite of fetal loss, SGA, LBW or preterm birth, or neonatal death) (RR 1.00, 95% CI: 0.75–1.33, p=0.99).

FIG. 4.
Malaria at delivery (primary endpoint) in the IST and SST groups



CI, confidence interval; IST, intermittent screening and treatment in pregnancy; RR, relative risk; SST, single screening and treatment

IPT versus IST comparison

Overall, only five infections were detected by RDT during 2886 visits in the IST arm, compared to 18 in 2392 visits in the SST arm (all 18 in Papua). Compared with IST, IPT was more effective at reducing the incidence of malaria infection (IRR 0.61, 95% CI: 0.39–0.95, p=0.0303), but only in Papua (IRR 0.33, 95% CI: 0.22–0.49, p<0.0001), not in Sumba (IRR 0.96, 95% CI: 0.62–1.49, p=0.85). IPT was also more effective than IST at reducing placental malaria detected by histology (RR 0.48, 95% CI: 0.25–0.92, p<0.0261), but again only in Papua (RR 0.34, 95% CI: 0.20–0.58, p<0.0001), not in Sumba (RR 1.25, 95% CI: 0.49–3.17, p=0.65). IPT was not associated with less adverse pregnancy outcomes compared with IST (RR 1.16, 95% CI: 0.82–1.65, p=0.39).

Summary of effectiveness of IPT

Compared with SST, IPTp-DHA-PPQ was associated with substantial reductions in multiple malaria infection incidence and prevalence measures during pregnancy and at delivery, but this effect was only observed in the higher transmission intensity study site (where the incidence of malaria infections detected by microscopy during pregnancy was 46/100 py) and not in the lower transmission site (6/100 py). This reduction in malaria in the higher transmission sites was not associated with a lower risk of adverse pregnancy outcomes. Regarding IST, at the current levels of RDT sensitivity, monthly screening with RDTs did not result in the detection of more malaria infections than the existing SST strategy.

The study has several limitations and some of the results (e.g. differences between sites and the observed increased risk of LBW associated with IPT in Sumba) are difficult to interpret. The possibility that DHA-PPQ reduced intrauterine growth in Sumba was explored in two analyses of the per-protocol population. Importantly, there was no evidence of a dose–response effect of DHA-PPQ on either mean birth weights or mean birth weight-for-

age Z-scores, in analyses that included women receiving between two and six doses of the drug. Therefore, it remains unexplained why, in Sumba, compared with SST, exposure to IPTp-DHA-PPQ reduced birth weights, probably owing to intrauterine growth restriction.

The cardiac safety of monthly doses of DHA-PPQ was evaluated in 33 pregnant women from Papua Indonesia (ter Kuile et al., unpublished). Statistically significant increases of the QT interval corrected using the Fridericia method (QTcF) following the final dose of each course were observed (mean 20 msec range –20 to 71). The mean increases in QTcF following DHA-PPQ declined with subsequent doses, suggesting an absence of cumulative effects of DHA-PPQ on QTcF. There were no cardiac events and no QTcF values above 500 msec.

2.3.4. Evaluation of the implementation of single screening and treatment (SST) for the malaria in pregnancy in Eastern Indonesia

The Asia-Pacific region has no standardized and widely recognized strategy for prevention of malaria in pregnancy, and the most common strategy currently in practice for malaria in pregnancyis passive case detection (PCD). However, in 2010–2011, in malaria endemic areas of Indonesia, SST on first visit to ANC followed by PCD at all subsequent visits was introduced, together with provision of a long-lasting insecticidal mosquito net (LLIN).

The preliminary results of a study evaluating the implementation of SST for prevention of malaria in pregnancy in two islands of eastern Indonesia, as per the national guidelines, were presented (Webster et al., unpublished). This study was conducted within the frame of the STOPmalaria in pregnancy project 2013 (in Mimika, Papua) and 2014 (in Sumba). Mixed methods were used, including cross-sectional surveys at hospitals, health centres and health posts in the two study sites. Observations and exit interviews of the ANC visit were conducted to assess compliance with SST guidelines.

A total of 865 ANC visits in Mimika and 895 in West Sumba were included in the study across seven and 10 health facilities, respectively. The study was conducted in hospitals, health centres and health posts. Adherence to malaria screening at first ANC visits among pregnant women varied by level of health facility. In Mimika, among pregnant women attending health centres for their first visit, adherence to screening was high at 94.8% (95% CI: 81.1–98.7), whereas among those attending hospitals it was lower at 60.0% (95% CI: 32.6–82.3) and it was lowest among those attending health posts at 3.8% (95% CI: 1.6–8.8). In West Sumba, corresponding estimates for adherence to screening at first ANC visit for pregnant women attending health centres, hospitals and health posts were 60.0% (95% CI: 32.6–82.3), 0.0% and 9.8% (95% CI: 4.4–20.5), respectively. Most screening conducted at first ANC visit in both sites was by microscopy. In Mimika, 1.1% (2/185) of first ANC visits were screened by RDT, and in West Sumba 1.2% (2/161).

Screening for malaria at first ANC visit in health centres was highly feasible in Mimika, and feasible in West Sumba. The success of the strategy at this level of health facility was due to screening by microscopy. However, in the health posts of both Mimika and West Sumba, where the strategy relies on the use of RDTs, the findings suggest that screening at first ANC visit is not feasible.

2.3.5. *Cost–effectiveness of intermittent preventive treatment (IPT) or intermittent screening and treatment (IST) with DHA-PPQ versus single screening and treatment (SST) for malaria in pregnancy: analysis from a superiority trial in Indonesia*

The preliminary results of the cost–effectiveness analysis (CEA) of the cluster-randomized trial evaluating IPTp, IST and SST in two sites in Indonesia were presented and reviewed (Paintain et al., unpublished). Disability-adjusted life years (DALYs) were calculated using disability weights from the 2015, 2010 and 2004 global burden of disease studies, local life expectancies, no age weighting, and 3% discounting for each trial arm and four outcomes (fetal loss or infant death by 6–8 weeks, LBW, maternal anaemia and malaria infection during pregnancy).

In addition to the costs of the intervention, the provider costs of the consequences of malaria in pregnancymalaria in pregnancy were also calculated per event for each of the four trial outcomes. Step-down costing was used to estimate the unit cost per outpatient consultation, per adult inpatient day and per paediatric inpatient day. The incremental cost–effectiveness ratio (ICER) was calculated for a hypothetical cohort of 1000 women by dividing the incremental cost of the intervention by the incremental DALYs averted.

Provider costs were considerably higher in the Papua health facilities than in the Sumba health facilities, due to a greater number of personnel and therefore higher salary commitments:

- the cost of delivering the current strategy of SST-DHA-PPQ per pregnant woman is US$ 1.64 in Sumba and US$ 2.06 in Papua;
- the cost of delivering IPTp-DHA-PPQ per pregnant woman is US$ 11.54 in Sumba and US$ 10.70 in Papua; and
- the cost of delivering IST-DHA-PPQ per pregnant woman is US$ 7.01 in Sumba and US$ 8.82 in Papua.

Different results for the CEA were found by site:

- in Sumba, the current strategy of SST in pregnancy (SSTp) with DHA-PPQ incurred lower costs (for intervention delivery and cost of consequences) and resulted in fewer DALYs compared with IPTp with DHA-PPQ or IST with DHA-PPQ; and
- in the higher malaria transmission setting of Papua, IPTp-DHA-PPQ and IST-DHA-PPQ were both incrementally more cost effective than the current strategy of SSTp-DHA-PPQ; although IPTp-DHA-PPQ and IST-DHA-PPQ incurred higher incremental costs than SSTp-DHA-PPQ, they resulted in incrementally fewer DALYs.

2.3.6. *Health provider acceptability of intermittent preventive treatment (IPT) or intermittent screening and treatment (IST) versus current policy (single screening and treatment (SST) with DHA-PPQ) in Indonesia*

Within the frame of the STOPmalaria in pregnancy project, health provider acceptance of the current (SSTp) strategy was assessed compared with IPTp and IST in Indonesia (Hoyt et al., unpublished). Between 2015 and 2016, qualitative data were collected through individual in-depth interviews with 121 health providers working in the provision of ANC (midwives, doctors, laboratory staff, pharmacists and heads of drug stores), heads of health

facilities and District Health Office staff. Staff involved in the clinical trial in south-west Sumba and Mimika districts were also interviewed. Health providers were receptive to screening pregnant women at every ANC visit because it provided an increased frequency to detect asymptomatic infections, thereby providing more comprehensive care for mother and baby than the current policy of screening at first ANC visit only. A primary concern was the accuracy and availability of RDTs used for screening; the RDTs were considered less accurate than microscopy. Providers expressed serious reservations about giving antimalarial medicines presumptively as IPTp, because of concerns of causing potential harm to mother and baby, and of contributing to drug resistance.

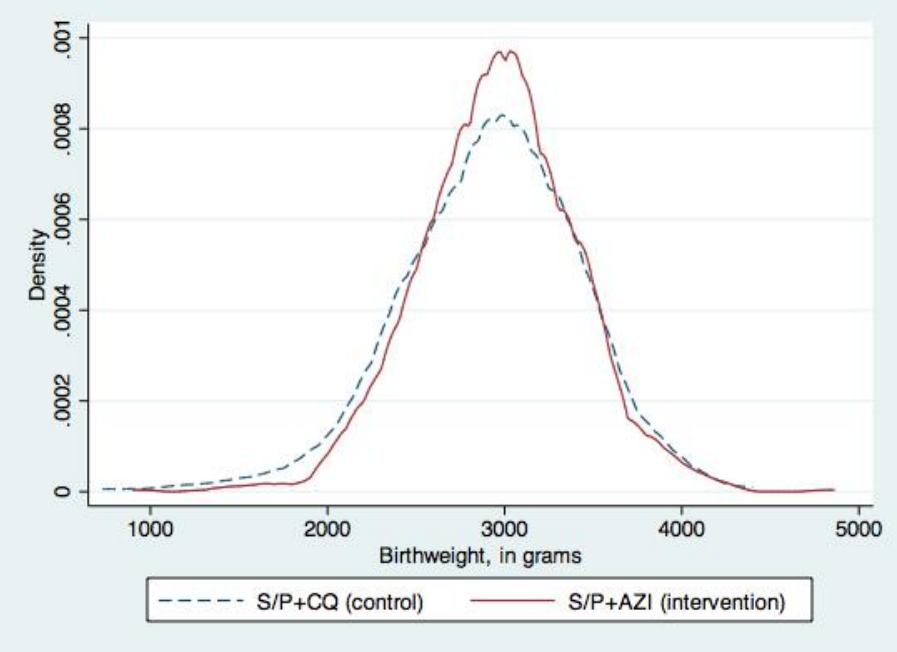
Within the trial context, screening women at every ANC visit (IST) was thus considered an acceptable strategy among health providers owing to an existing culture of screening women at ANC and providing treatment based on positive test results. In contrast, adoption of IPTp would require a considerable shift in health provider attitudes.

2.3.7 IPTp of three courses of SP plus AZ twice daily for 2 days compared to an initial course of SP plus CQ (3 days) followed by placebo for the prevention of LBW: a randomised controlled trial in Papua New Guinea

An RCT conducted between 2009 and 2013 in Papua New Guinea compared IPTp-SP plus AZ (1 g twice daily for 2 days) (SP-AZ) three times from the second trimester (intervention) against SP-CQ (450–600 mg daily for 3 days) given once, followed by SP-CQ placebo (control) *(17)*. Participants were blinded to assignments.

Of the 2793 women randomized, 2021 (72.4%) were included in the primary outcome analysis of LBW (SP-CQ: 1008; SP-AZ: 1013). Overall, the prevalence of LBW was 15.1% (305/2021). SP-AZ reduced LBW (RR 0.74, 95% CI: 0.60–0.91, p=0.005; absolute risk reduction 4.5%, 95% CI: 1.4–7.6), and preterm delivery (RR 0.62, 95% CI: 0.43–0.89, p=0.010); it also increased mean birthweight (41.9 g, 95% CI: 0.2–83.6, p=0.049), as shown in Fig. 5.

FIG. 5.
Distribution of birth weights by treatment arm



AZI, azithromycin; CQ, chloroquine; S/P, sulfadoxine-pyrimethamine

Additionally, SP-AZ reduced maternal parasitaemia (RR 0.57, 95% CI: 0.35–0.95, p=0.029) and active placental malaria (RR 0.68, 95% CI: 0.47–0.98, p=0.037), and reduced carriage of *Neisseria gonorrhoeae* (RR 0.66, 95% CI: 0.44–0.99, p=0.041) at second visit. A reduction in preterm birth in the intervention arm was noted (RR 0.62, 95% CI: 0.43–0.89, p=0.010; absolute risk reduction 4.0%, 95% CI: 1.0–7.0). There were no treatment-related SAEs, and the number of SAEs (intervention 13.1% [181/1378], control 12.7% [174/1374], p=0.712) and adverse events (AEs) (intervention 10.5% [144/1378], control 10.8% [149/1374], p=0.737) was similar. A major limitation of the study was the high loss to follow-up for birthweight.

Compared to a single dose of SP-CQ, three-dose IPTp with SP-AZ was thus efficacious and safe in reducing LBW, possibly acting through multiple mechanisms, including the effect on malaria and on STIs. However, caution is required when interpreting these results because the trial compared three-dose IPTp-SP-AZ with a single dose of SP-CQ, and therefore it is not possible to attribute the benefits observed specifically to AZ or to increased number of SP doses.

The study also assessed the effect on maternal nasopharyngeal carriage and antibiotic susceptibility of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus* at delivery among a subsample of 854 women *(18)*. Nasopharyngeal carriage at delivery was significantly reduced among women who had received SP-AZ for *S. pneumoniae* (SP-AZ, 7.2% [30/418] versus SP-CQ, 19.3% [84/436], p<0.001) and *H. influenzae* (2.9% [12/418] versus 6.0% [26/436], p=0.028), but not for *S. aureus*.

Key conclusions on prevention of falciparum and vivax malaria in pregnancy

- IST did not reduce the risk of placental malaria or adverse birth outcomes compared with PCD in a trial conducted in India. In this trial, most cases of placenta malaria were not detected by RDT.
- The proportion of pregnant women tested for malaria at least once during their pregnancy increased with implementation of IST (compared with PCD) in India.
- Preliminary results of a cluster randomized trial comparing monthly IPTp-DHA-PPQ with IST and SST conducted in two sites in Indonesia indicate that IPTp halved the risk of malaria during pregnancy and at delivery compared with SST, but only in the higher transmission site, and study findings on IPTp were not consistent across sites. IST did not result in the detection of more malaria infections than the existing SST strategy. Based on the current level of evidence, which is inconclusive, additional evaluation and research is needed to determine the potential of IPTp-DHA-PPQ as a malaria control strategy in areas of high transmission in Asia. Further research on IST using highly sensitive RDTs is also required.
- Three doses of IPTp with SP-AZ compared with a single dose of SP-CQ reduced the prevalence of LBW and preterm birth in a trial in Papua New Guinea. Because this effect could at least partly be explained by more frequent SP-dosing in the AP-AZ arm, the impact of adding AZ to IPTp-SP on adverse birth outcomes requires further research.
- IPTp with SP-AZ reduced nasopharyngeal carriage at delivery of S. pneumoniae and *H. influenzae*, but not of *S. aureus*.

2.4 SP and AZ against sexually transmitted and reproductive tract infections

2.4.1 Impact of SP and AZ against sexually transmitted and reproductive tract infections

Curable sexually transmitted and reproductive tract infections (STIs and RTIs include infections by *Treponema pallidum, Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis* and bacterial vaginosis, and have been associated with increased risk of adverse birth outcomes such as stillbirths, preterm, intrauterine growth restriction (IUGR) and LBW *(19)*. AZ-based therapies have been suggested as potential candidates to replace SP for IPTp, since they may offer important public health benefits by also reducing the burden of curable STIs and RTIs in pregnancy *(19)*.

A systematic review and meta-analysis of malaria and STI and RTI prevalence estimates in sub-Saharan Africa indicates that such infections impose a considerable burden on pregnant women attending ANC facilities *(20)*. In a cohort study conducted among Zambian pregnant women between 2013 and 2014, 38.7% (95% CI: 35.7–41.6) were coinfected with malaria parasites and at least one STI or RTI *(21)*. Importantly, HIV-infected women had a higher risk of being coinfected than HIV-uninfected women (OR 3.59, 95% CI: 1.73–7.48, p<0.001) *(21)*.

A prospective observational cohort study conducted between 2013 and 2014 in Zambia analysed the incidence of malaria infection and curable STIs and RTIs, maternal exposure to IPTp-SP during the antenatal period (0–1 doses versus ≥2 doses and, separately, 2 doses versus ≥3 doses), and the resulting incidence of stillbirth, LBW, preterm delivery and IUGR *(22)*. In this study, the presence of curable STIs or RTIs by *T. pallidum*, *N. gonorrhoeae*, *C. trachomatis*, *T. vaginalis* and bacterial vaginosis was diagnosed at study enrolment only.

No significant differences in baseline prevalence of infection across IPTp-SP exposure groups were found. However, among women given two doses compared to no or one dose, the odds of any adverse birth outcome were reduced by 45% (OR 0.55, 95% CI: 0.36–0.86) and 13% further with at least three doses (OR 0.43, 95% CI: 0.27–0.68). Two or more doses compared to no or one dose reduced preterm delivery by 58% (OR 0.42, 95% CI: 0.27–0.67) and 21% further with at least three doses (OR 0.21, 95% CI: 0.13–0.35).

Women with malaria at enrolment who received at least two doses versus no or one dose had 76% lower odds of any adverse birth outcome (OR 0.24, 95% CI: 0.09–0.66), whereas women who had *N. gonorrhoeae* or *C. trachomatis* (or both) at enrolment and were provided with at least two doses versus no or one dose had 92% lower odds of any adverse birth outcome (OR 0.08, 95% CI: 0.01–0.64). Women with neither a malaria infection nor an STI or RTI who received at least two doses had 73% fewer adverse birth outcomes (OR 0.27, 95% CI: 0.11–0.68).

The study was limited by its observational methodology, the effect of unmeasured potential confounders, and the lack of information on whether women were treated for STIs or RTIs. Importantly, available evidence on the pathogens responsible for STIs and RTIs suggests that it is unlikely that intermittent administration of multiple doses of SP given 1 month apart might cure any of these infections.

2.4.2. Efficacy and safety of azithromycin-chloroquine versus sulfadoxine-pyrimethamine for intermittent preventive treatment of P. falciparum *malaria infection in pregnant women in Africa*

A multicentre open-label RCT evaluated the efficacy, tolerability and safety of a fixed-dose combination of AZCQ (250 mg AZ/155 mg CQ base) for IPTp compared with IPTp-SP between 2010 and 2013 in Benin, Kenya, Malawi, Uganda and the United Republic of Tanzania *(23)*.

Pregnant women received three IPTp courses with AZCQ (each course: 1000/620 mg AZCQ QD for 3 days) or SP (each course: 1500/75 mg SP QD for 1 day) at 4- to 8-week intervals during the second and third trimester. Study participants were followed up until day 28 post-delivery (time window: day 28–42). The primary endpoint was the proportion of participants with suboptimal pregnancy outcomes – a composite endpoint comprising liveborn neonates with LBW (<2500 g), premature birth (<37 weeks), stillbirth (>28 weeks), abortion (≤28 weeks), lost to follow-up before observation of pregnancy outcome or missing birth weight. The study was terminated early after recruitment of 2891 of the planned 5044 participants, due to futility observed in a pre-specified 35% interim analysis of the primary endpoint of suboptimal pregnancy outcome.

In the final intent-to-treat dataset, 378/1445 (26.2%) participants in the AZCQ and 342/1445 (23.7%) in the SP group had suboptimal pregnancy outcomes, with an estimated RR of 1.11 (95% CI: 0.97–1.25, p=0.12). There was no significant difference in the incidence

of LBW between treatment groups (57/1138 [5.0%] in the AZCQ group, 68/1188 [5.7%] in the SP group, RR 0.87, 95% CI: 0.62–1.23, p=0.44). IPTp-AZCQ was less well tolerated in mothers than IPTp-SP. Occurrences of congenital anomalies, deaths and SAE were similar in both groups. The limitation of the open-label design may have influenced the reported low tolerability of the AZCQ combination treatment.

2.4.3. Impact of intermittent AZ in addition to IPTp with SP in Malawi

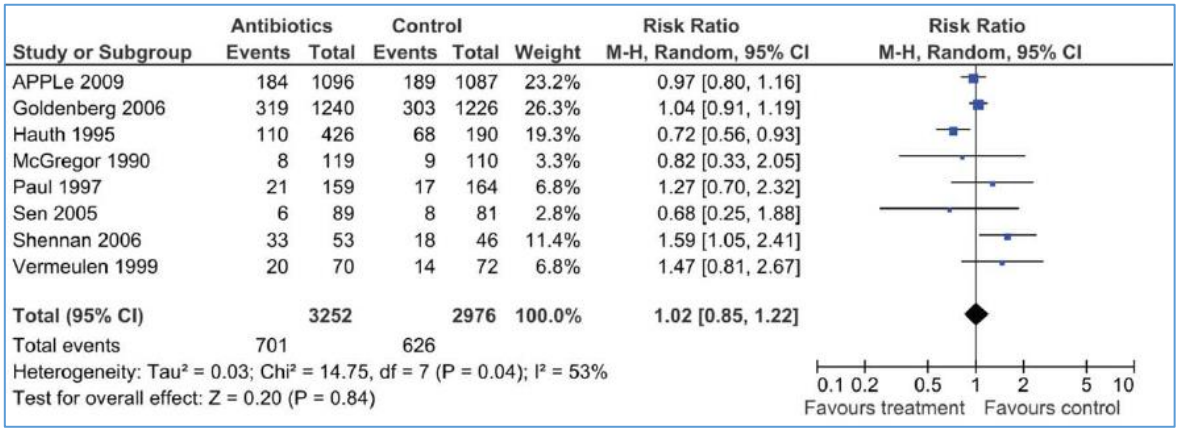
Results from the APPLe placebo-controlled trial conducted in southern Malawi between 2004 and 2005 were presented and reviewed *(24)*. The study evaluated the impact of routine prophylaxis with AZ as directly observed, single-dose therapy at two gestational windows on the incidence of preterm birth.

A total of 2297 pregnant women attending three rural and one periurban health centres were randomized to either 1 g AZ or placebo given at both 16–24 and 28–32 weeks gestational windows. Additionally, all women received two-dose IPTp-SP, as per the national guidelines. Women and their infants were followed up until 6 weeks post-delivery. The primary outcome was incidence of preterm delivery, defined as less than 37 weeks. Secondary outcomes were mean gestational age at delivery, perinatal mortality, birthweight, maternal malaria and anaemia.

There were no significant differences in study outcome between the azithromycin group (n=1096) and the placebo group (n=1087) with regard to preterm birth (16.8% versus 17.4%), OR 0.96 (95% CI: 0.76–1.21); mean gestational age at delivery (38.5 weeks versus 38.4 weeks), mean difference 0.16 (95% CI: 20.08–0.40); mean birthweight (3.03 kg versus 2.99 kg), mean difference in birthweight (0.04 kg, 95% CI: –0.005–0.08); perinatal deaths (95% CI: 4.3% versus 5.0%), OR 0.85 (95% CI: 0.53–1.38); or maternal malarial parasitaemia (11.5% versus 10.1%), OR 1.11 (95% CI: 0.84–1.49) and anaemia (44.1% versus 41.3%) at 28–32 weeks, OR 1.07 (95% CI: 0.88–1.30).

Of note, meta-analysis of seven additional studies of routine antibiotic prophylaxis in pregnancy (>6200 pregnancies) shows no effect on preterm birth (RR 1.02, 95% CI: 0.86–1.22), as shown in Fig. 6 *(24)*.

FIG. 6.
Meta-analysis of trials of routine antibiotic prophylaxis in pregnancy that report preterm birth as outcome



Source: van den Broek et al., 2009 (24)

These findings are in contrast with those of a single-centre, randomized, partially placebo-controlled trial conducted in another region from Malawi *(25)*. A total of 1320 pregnant women were enrolled and received either two-dose IPTp-SP (controls), monthly SP, or monthly SP and two doses of 1 g AZ (AZ-SP).

The incidence of preterm delivery was 17.9% in controls, 15.4% in the monthly SP group (p=0.32), and 11.8% in AZ-SP group (RR 0.66, p=0.01). Moreover, compared with controls, those in AZ-SP group had an RR of 0.61 (95% CI: 0.40–0.93, p=0.02) for LBW. Incidence of SAEs was low and similar in all groups.

Infant follow-up also revealed beneficial effects of AZ-SP. Babies in the AZ-SP group were on average 140 g (95% CI: 70–200 g) heavier at birth and 0.6 cm (0.2–0.9 cm) longer at 4 weeks of age than control group babies *(26)*. Additionally, they had an RR of 0.60 (0.44–0.81) for stunting and 0.48 (0.29–0.79) for underweight at 4 weeks of age compared with controls *(26)*. The analysis of the 5-year follow-up of children born to women who participated in the trial indicates that incidence of stunting and severe stunting was also reduced among children aged under 5 years born to women in the AZ-SP group (Hallamaa et al., unpublished).

2.4.4. Perspective from WHO reproductive health programme

Current WHO recommendations and guidelines for the treatment of STIs (including *T. pallidum*, *N. gonorrhoeae* and *C. trachomatis*) were presented and reviewed.

Syphilis screening is recommended at least once for all women during pregnancy (dual RDTs for HIV/syphilis are now available).

With regard to the potential use of maternal AZ for preventing adverse birth outcomes, the risk of contributing to the development of AZ resistance needs to be taken into account. Besides, it was pointed out that additional laboratory capacity at country level is needed to monitor the possible emergence of antimicrobial resistance to *N. gonorrhoeae*.

Key conclusions on SP and AZ against STIs and RTIs

- Evidence from an observational study conducted in Zambia suggests that, as noted previously in other studies and WHO recommendations, IPTp-SP provides dose-related protection against adverse birth outcomes related to malaria, provided at least three doses of SP are received. This dose–response protection extended to women coinfected with malaria and curable STIs or RTIs. The mechanisms by which sulfadoxine may protect against non-malaria causes of adverse birth outcomes requires more investigation. It is unlikely that multiple doses of SP given 1 month apart provides a cure for any of the major causes of STI or RTIs.
- IPTp-AZCQ was not superior to IPTp-SP in an open-label, multicentre RCT conducted in five sub-Saharan countries.
- Two trials conducted in Malawi evaluating AZ in addition to IPTp-SP in preventing preterm birth yielded conflicting results. The differences may be due to differences in the study population and frequency of SP-dosing in the study intervention. The risk of contributing to the development of AZ resistance needs to be taken into account when considering IPTp-AZCQ.

2.5. HIV and malaria in pregnancy

HIV-infected pregnant women in Africa are especially vulnerable to malaria infection. Paradoxically, these women have been described as the least protected against malaria due to fear of potential drug interactions between IPTp-SP and co-trimoxazole (CTX) prophylaxis and between some antimalarial and ARVs *(27)*.

It has been estimated that about one million pregnancies per year are complicated by the coinfection of malaria and HIV in sub-Saharan Africa *(28)*. Recently, in a randomized placebo-controlled trial, the addition of IPT with an efficacious antimalarial drug (mefloquine) to CTX prophylaxis in HIV-infected pregnant women improved malaria prevention, as evidenced by reductions in peripheral parasitaemia and placental infection, as well as improvement in overall maternal health through decreased hospital admissions *(29)*. However, MQ prophylaxis was not well tolerated, and it was associated with both an increased maternal HIV viral load at delivery and risk of mother-to-child transmission (MTCT) of HIV.

There is thus a need to evaluate antimalarial medicines that can be safely administered to HIV-infected pregnant women on antiretroviral therapy (ART) and CTX prophylaxis.

2.5.1. Effects of HIV infection on malaria in pregnancy: review of the literature

A review of the evidence of HIV and malaria interactions in pregnancy was presented and reviewed (González et al., unpublished).

Malaria and HIV coinfection in pregnant women leads to poorer health for the women and their babies, as well as to higher maternal mortality. This is particularly true in sub-Saharan Africa, which harbours the highest burden of both diseases. Malaria and HIV coinfection during pregnancy leads to a higher risk of poor birth outcomes in infants, including LBW and infant morbidity. Furthermore, treatment of malaria in HIV-infected pregnant women is complicated by HIV-induced immunosuppression and potential interaction with some antiretroviral (ARV) medicines and other medication given concomitantly. Tables 4 and 5 summarize the main evidence on the effects of HIV and malaria coinfection in pregnant women.

TABLE 4.
Main effects of HIV and malaria coinfection in pregnant women

Effect of HIV on malaria	• ↑ Risk of infection • ↑ Parasite density • ↓ Antibodies against placental-type parasites • Loss of parity-dependent malaria immunity
Effect of malaria on HIV	• ↑ HIV viral load • ↑ Production of IL-6, IFN-γ, TNF-α cytokines • Possible ↑ of MTCT of HIV (conflicting results, see Table 5)
Effect of dual infection	• ↑ Severity of illness • ↑ Maternal mortality • ↑ Adverse birth outcomes (LBW, FGR) • ↑ Neonatal mortality

FGR, fetal growth restriction; HIV, human immunodeficiency virus; IFN, interferon; IL, interleukin; LBW, low birth weight; MTCT, mother-to-child transmission; TFN, tumour necrosis factor

Source: adapted from Hochman et al., 2009 (30)

TABLE 5.
Summary of studies reporting on the association between MTCT of HIV and malaria

Reference	Countries & years	Main results
Brahmbhatt et al., 2003	Uganda 1994–1999	Placental malaria associated with MTCT (RR 2.85, 95% CI: 1.53–5.32)
Inion et al., 2003	Kenya 1996–1999	No association was found between placental malaria and either maternal virus load
Ayisi et al., 2004	Kenya 1996–2000	Low-density placental malaria (<10 000 parasites/µL) was associated with reduced MTCT (absolute risk reduction 0.4). In women dually infected with malaria and HIV, high-density placental malaria (>10 000 parasites/µL) was associated with increased risk of MTCT (aRR 2.0), compared to low-density malaria.
Brahmbhatt et al., 2008	Uganda 1994–2000	Placental malaria associated with MTCT adjusted for maternal HIV viral load (RR 7.9, 95% CI: 1.4–58.5)
Naniche et al., 2008	Mozambique 2003–2006	Placental malaria was associated with a decrease in MTCT (aOR 0.23, 95% CI: 0.06–0.89, p=0.034)
Msamanga et al., 2009	Malawi, Tanzania, Zambia 2001–2003	Placental malaria was not associated with the infant HIV-1 infection status at birth (p=0.67)
Bulterys et al., 2011	Rwanda 1989–1994	Placental malaria associated with MTCT (aOR 6.3, 95% CI: 1.4–29.1), especially among primigravidae

Reference	Countries & years	Main results
Ezeama et al., 2014	Tanzania 2004–2008	HIV MTCT risk increased by 29% (95% CI: 4–58%) per malaria in pregnancy episode.
González et al., 2014	Kenya, Mozambique, Tanzania 2010–2013	Clinical malaria associated with MTCT in adjusted multivariate analysis (RR 4.76, 95% CI: 2.01–11.24)

aOR, adjusted odds ratio; aRR, adjusted relative risk; CI, confidence interval; HIV, human immunodeficiency virus; malaria in pregnancy, malaria in pregnancy; MTCT, mother-to-child transmission; RR, relative risk; Tanzania, United Republic of Tanzania

Prevention of malaria in HIV-infected women remains a challenge since IPTp-SP cannot be co-administered with CTX prophylaxis. Alternative medicines to SP for IPTp have been evaluated in two trials that are summarized in Table 6.

TABLE 6.
Summary of trials evaluating alternative medicines for IPTp among HIV-infected women

Reference	Study design	Countries, years and sample size	Main results
González et al., 2014 *(29)*	Double-blinded, multicentre, placebo superiority trial comparing three-dose IPTp-MQ with placebo in women on CTX prophylaxis	Kenya, Tanzania and Mozambique 2010–2013 N=1071	IPTp-MQ reduced the risk of maternal parasitaemia at delivery, placental infection and hospital admissions in pregnancy. No differences were observed on adverse birth outcomes between groups. However, MQ was associated with transient vomiting, dizziness and an increased MTCT of HIV.
Natureeba et al., 2017 *(31)*	Double-blinded, single-centre, placebo-controlled trial comparing monthly IPTp-DHA-PPQ with placebo in women on CTX prophylaxis	Uganda 2014–2015 N=200	No differences were found between arms on placental malaria, secondary outcomes and frequency of AEs. The frequency of MTCT of HIV was not reported.

AE, adverse event; CTX, co-trimoxazole; DHA-PPQ, dihydroartemisinin-piperaquine; HIV, human immunodeficiency virus; IPTp, intermittent preventive treatment in pregnancy; MTCT, mother-to-child transmission; MQ, mefloquine

Most knowledge on drug interactions comes from in vitro studies or from studies conducted among healthy non-pregnant adults; the clinical relevance of the findings still needs to be assessed. Research is also limited since pregnant women, who constitute one of the most vulnerable populations to malaria and HIV, are generally systematically excluded from clinical trials.

2.5.2. *An assessment of mefloquine, co-trimoxazole and antiretroviral medicines interaction among HIV-infected pregnant women in Kenya*

In the context of the double-blinded placebo-controlled trial evaluating MQ for IPTp *(29)* in combination with CTX prophylaxis, a substudy was conducted in women from Kenya to determine the PK properties of MQ and its effect on the blood levels of CTX *(32)*.

CTX prophylaxis did not influence MQ half-life, observed clearance, and the area under the curve. Although trimethoprim steady-state levels were not significantly different between arms, sulfamethoxazole levels decreased significantly, by 53%, after MQ administration relative to the placebo group, and returned to pre-dose levels after 28 days *(32)*.

A recent analysis of ART concentrations in maternal and cord plasma samples of pregnant Kenyan women participating in the aforementioned IPTp-MQ trial found that women taking nevirapine who received MQ had reduced nevirapine concentrations compared with women who received placebo [Haaland et al., unpublished]. However, the clinical significance of this remains uncertain.

2.5.3. *Intermittent preventive treatment with DHA-PPQ for the prevention of malaria among HIV-infected pregnant women in Uganda*

A double-blinded, randomized, placebo-controlled trial recently published compared daily CTX prophylaxis plus monthly DHA-PPQ with daily CTX prophylaxis plus monthly placebo in HIV-infected pregnant women between 2014 and 2015 in an area of Uganda where indoor residual spraying (IRS) for malaria control had been implemented *(31)*.

A total of 200 pregnant women were enrolled between gestation weeks 12 and 28, and given an LLIN. All women were on ART. The primary outcome was detection of active or past placental malarial infection by histopathologic analysis. Secondary outcomes included incidence of malaria, parasite prevalence and adverse birth outcomes. Those enrolled were followed through delivery, and the primary outcome was assessed in 194 women. In this small study, there was no statistically significant difference in the risk of placental malarial infection between the daily CTX prophylaxis plus monthly DHA-PPQ arm, and the daily CTX prophylaxis plus monthly placebo arm (6.1% versus 3.1%; RR 1.96, 95% CI: 0.50–7.61, p=0.50). Similarly, there were no differences in secondary outcomes. The low prevalence of placental malaria in both arms may reflect the remarkable drop in malaria transmission observed following the introduction of IRS in the study district around the time study enrolment began. Vomiting occurred in less than 0.2% of women after administration of study medicines, with no differences between study arms.

In addition, a PK study was conducted within the frame of the RCT among HIV-infected, uninfected pregnant and non-pregnant women *(33)*. The study found that exposure to DHA and PPQ were lower among pregnant women, particularly in those on efavirenz (EFV)-based ART *(33)*. Additional data on pharmacodynamics and on the clinical impact of this PK study are needed to fully interpret the results. Cardiac monitoring did not suggest that PPQ-associated QTc prolongations were worse in HIV-infected women receiving CTX and EFV-based ARTs than in HIV-uninfected women receiving DHA-PPQ; also, they were not associated with pregnancy status, or the number of previous IPTp courses taken *(33)*.

2.5.4. Perspective from WHO HIV programme

Consolidated ARV 2016 guidelines for HIV-infected individuals living in malaria endemic areas were reviewed. The recommendation on the use of CTX prophylaxis in women and adolescents living with HIV is primarily for prophylaxis against *Pneumocystis* pneumonia, serious bacterial infection and toxoplasmosis. This is relevant to all contexts including malaria endemic settings. The need to avoid simultaneous IPT-SP use is retained in current guidelines, based on a systematic review showing that CTX prophylaxis is not inferior to IPTp with respect to mortality, LBW, placental malaria, maternal deaths and SAEs *(34)*. However, there are limited data on adherence to CTX prophylaxis, and there is a need for further evaluation of its effectiveness in preventing malaria.

Currently, more than 88% of 144 low- and middle-income countries use option B+ (lifelong ARV therapy, ART). Consequently, a high proportion of HIV-infected pregnant women receive ARVsmedicines. Adherence to lifelong treatment is a major objective of national and international efforts to reduce HIV burden and transmission.

First-line antiretroviral treatment is likely to be replaced in the short to medium term by dolutegravir-based ART. Dolutegravir is an integrase inhibitor that has a better profile in terms of drug–drug interactions, which are currently of particular concern with EFV-based ARVs.

Recent reports indicate that EFV-based ART significantly reduce exposure to both DHA-PPQAL and DHA-PPQ. Pharmacometric modelling is ongoing to determine the optimal AL and DHA-PPQ dosage regimens for pregnant women. Given their potential increased risk of treatment failure, full adherence and closer monitoring of their malaria treatment response is essential. However, available evidence does not support a specific dose adjustment in HIV-infected pregnant women.

Key conclusions on HIV and malaria in pregnancy

- HIV-infected pregnant women are particularly vulnerable to malaria and should be targeted in malaria in pregnancy control programmes with specific strategies and tools.
- Recent reports indicate a possible reduction in nevirapine exposure associated to MQ (which was associated with an increased risk of MTCT of HIV) and of DHA-PPQ in women receiving efavirenz (EFV).
- Results of a small RCT conducted in Uganda evaluating monthly DHA-PPQ in HIV-infected women on CTX prophylaxis did not find differences between study arms in placental malaria and birth outcomes. However, maternal and infant HIV-related parameters were not assessed.
- Use of CTX prophylaxis during pregnancy in HIV-infected women is recommended by the WHO HIV programme to prevent Pneumocystis pneumonia, serious bacterial infection, toxoplasmosis and malaria. In malaria endemic areas, CTX prophylaxis is recommended regardless of immunosuppression levels for malaria prevention.
- A large RCT found that an efficacious antimalarial as IPTp added to daily CTX prophylaxis is beneficial for optimal malaria control in HIV-infected pregnant women.
- There is a need to further study drug interactions between CTX, antimalarial and ARV medicines for use in pregnancy to find the best strategy to adequately control malaria during pregnancy in HIV-infected women.

Annex 1. List of meeting pre-reads

Publication	Countries	Description
Ahmed et al., unpublished	Indonesia, Papua Indonesia	Open-label three-arm cluster-randomized trial of SST, IPT and IST in pregnant women
Ahmed et al., 2015 *(35)*	Indonesia	Diagnostic study to compare the performance of four different RDTs in predominately asymptomatic pregnant women under field condition
Anvikar et al., unpublished	India	A Phase II/III randomized open-label two-arm clinical trial of the efficacy and safety of AS-SP and AS-MQ to treat uncomplicated falciparum malaria in pregnancy
Bardají et al., 2017 *(4)*	Brazil, Colombia, Guatemala, India, Papua New Guinea	Multicentre facility-based prospective study to determine the burden and clinical impact of *P. vivax* infection in pregnant women
Bôtto-Menezes et al., 2016 *(10)*	Brazil	Evaluation of the costs associated with malaria treatment among pregnant and postpartum women in a low endemic area of Brazil where *P. vivax* infection predominates
Chico et al., 2011 *(36)*	NA	Comprehensive review on the safety, tolerability and efficacy data of AZ and CQ, alone or in combination, when used to prevent or treat malaria and several curable STIs and RTIs
Chico et al., 2012 *(20)*	NA	Systematic review and meta-analysis of malaria and STI/RTI prevalence estimates among pregnant women attending antenatal care facilities in sub-Saharan Africa
Chico et al., 2013 *(19)*	NA	Systematic review on AZ and curable STIs
Chico et al., 2017 *(22)*	Zambia	Cohort study among pregnant women who received IPTp-SP that relates the incidence of malaria infection and curable STIs and RTIs
Ding et al., unpublished	NA	Pooled PK analysis to investigate the impact of pregnancy on the PK properties of PPQ to optimize the antimalarial dosing regimen
González et al., unpublished	Benin, Gabon, Kenya, Mozambique, Tanzania, Thailand	Cochrane review on the efficacy and safety of mefloquine for preventing malaria in pregnancy
González et al., 2016 *(27)*	NA	Essay on the challenges and way forward of malaria prevention in HIV-infected pregnant women
González et al., unpublished	NA	Literature review on HIV and malaria interactions in pregnancy
Green et al., 2016 *(32)*	Kenya	Study on the PK interactions of MQ, sulfamethoxazole and trimethoprim in pregnant, HIV-infected women

Hill et al., unpublished	Indonesia	Qualitative study on health providers' acceptability and perceptions on the feasibility of implementing the SST strategy in the context of the national programme in Indonesia
Hoyt et al., unpublished	Indonesia	Qualitative study on health provider acceptability of the current SST strategy compared to two potential alternative strategies – IPTp and IST – in the context of a cluster-randomized clinical trial
Kloprogge et al., unpublished	NA	Individual patient data meta-analysis of the PK and PD properties of lumefantrine and the PK properties of its metabolite, desbutyl-lumefantrine
Kuepfer et al., unpublished	India	Cluster-RCT comparing IST and PCD
Luntamo et al., 2010 *(25)*	Malawi	Single-centre RCT comparing two-dose IPTp-SP (controls), monthly SP or monthly SP and two doses of AZ (AZ-SP) on preterm rates (LAIS trial)
Luntamo et al., 2012 *(37)*	Malawi	PCR malaria analysis of samples collected at delivery of women participating in the LAIS trial (Luntamo et al., 2010)
Luntamo et al., 2013 *(26)*	Malawi	Single-centre RCT evaluating the effect of antenatal monthly SP, alone or with AZ, on fetal and neonatal growth (follow-up data of Luntamo et al., 2010)
Marin-Menendez et al., 2013 *(9)*	Brazil	Description of clinically relevant cytoadhesive phenotypes of *P. vivax* isolates
Mayor et al., 2012 *(8)*	PNG	Histopathologic examination of placental biopsies from pregnant women combined with quantitative PCR
Menegon et al., 2016 *(7)*	Brazil, Colombia, India, Papua New Guinea	Characterization of the genetic structure of *P. vivax* populations obtained from pregnant women from different malaria endemic settings
Moore et al., 2016 *(14)*	Papua New Guinea	Study on the safety, tolerability and pharmacokinetics of co-administered AZ and PPQ for treating malaria in pregnant women
Moore et al., 2016 *(13)*	Thailand	Analysis of data collected at ANC clinics between 1994 and 2013 on the safety of artemisinins in first trimester of pregnancy
Moore et al., 2017 *(11)*	Thailand	Analysis of data collected at ANC clinics between 1986 and 2015 on the effects of falciparum and vivax malaria in pregnancy on antepartum and intrapartum stillbirth and neonatal mortality

Moore et al., 2017 *(12)*	Thailand	Analysis of data collected at ANC clinics between 1986 and 2015 on the effects of the total number of malaria episodes in pregnancy on SGA and the effects of malaria in pregnancy on SGA and preterm birth, by the gestational age at malaria detection and treatment
Natureeba et al., 2017 *(31)*	Uganda	Double-blinded, single-centre, placebo-controlled trial comparing monthly IPTp-DHA-PPQ with placebo in HIV-infected women on ART and CTX prophylaxis
Paintain et al., unpublished	Indonesia	Cost–effectiveness analysis of IPTp or IST with DHA-PPQ versus SST for the control of malaria in pregnancy
Requena et al., 2014 *(38)*	Papua New Guinea, Spain	Study of the combined impact of high malaria exposure and pregnancy in B cell subpopulations, where peripheral blood mononuclear cells from pregnant and non-pregnant individuals from a malaria non-endemic country (Spain) and from a high malaria endemic country (Papua New Guinea) were analysed
Requena et al., 2017 *(5)*	Brazil, Colombia, Guatemala, India, Papua New Guinea	Analysis of IgG responses to *P. vivax* and *P. falciparum* antigens, and cellular immune responses to two *P. vivax* antigens, in a subset of 1056 pregnant women
ter Kuile et al., unpublished	Papua Indonesia	Cardiac safety study of monthly IPTp with DHA-PPQ in 33 pregnant women
Unger et al., 2015 *(17)*	Papua New Guinea	RCT that compared IPTp-SP plus AZ monthly from second trimester (intervention) against SP-CQ given once, followed by SP-CQ placebo (control)
van den Broek et al., 2009 *(25)*	Malawi	Placebo RCT that evaluated the impact of routine prophylaxis with AZ as directly observed, single-dose therapy at two gestational windows on the incidence of preterm birth
Webster et al., unpublished	Indonesia	Evaluation of the implementation of SST for the control of malaria in pregnancy
Webster et al., unpublished	India	Evaluation of the implementation of IST for control of malaria in pregnancy

ANC, antenatal care; ART, antiretroviral therapy; AS, artesunate; AZ, azithromycin; CQ, chloroquine; CTX, co-trimoxazole; DHA-PPQ, dihydroartemisinin-piperaquine; HIV, human immunodeficiency virus; IgG, immunoglobulin G; IPT, intermittent preventive treatment; IPTp, intermittent preventive treatment in pregnancy; IST, intermittent screening and treatment in pregnancy; malaria in pregnancy, malaria in pregnancy; MQ, mefloquine; NA, not applicable; PCD, passive case detection; PCR, polymerase chain reaction; PD, pharmacodynamics; PK, pharmacokinetics; PPQ, piperaquine; RCT, randomized controlled trial; RDT, rapid diagnostic test; RTI, reproductive tract infection; SGA, small for gestational age; SP, sulfadoxine-pyrimethamine; SST, single screening and treatment; STI, sexually transmitted infection

Annex 2. Questions addressed and proposed responses to the Evidence Review Group panel

Q1 – What are the consequences of vivax malaria in pregnancy (malaria in pregnancy) in terms of birth outcomes and morbidity for the pregnant women?

With regard to maternal morbidity, the evidence reviewed indicates that vivax malaria in pregnancy increases the risk of maternal anaemia.

Additionally, analyses of data from the Thai–Myanmar border area indicate that vivax malaria is associated with fetal loss, small for gestational age (SGA) babies, preterm birth and neonatal mortality. Fetal loss was particularly relevant in pregnant women suffering malaria symptomatic episodes and SGA in those with recurrent infections.

Q2 – What are the consequences of falciparum and vivax coinfections in pregnancy in terms of birth outcomes and morbidity for the pregnant women?

No studies have yet been carried out to evaluate the consequences of falciparum and vivax coinfections on birth outcomes and maternal morbidity.

Q3 – Is there evidence from clinical trials or pharmacokinetics/pharmacodynamics (PK/PD) studies of specific PK changes in pregnancy of any of the following antimalarials: dihydroartemisinin (DHA), piperaquine (PPQ), artesunate (AS), artemether (AM), lumefantrine (L), amodiaquine (AQ) and mefloquine (MQ)? Is there evidence that these changes are affecting therapeutic efficacy or safety of antimalarial medicines for the treatment of uncomplicated falciparum malaria, so to require specific dose adjustments during pregnancy?

The PK effects of pregnancy vary substantially between the different studies and antimalarial medicines. Some prospective studies have shown a significantly decreased exposure to AS, DHA, L, PPQ and sulfadoxine during pregnancy, but these findings have not been consistent for all studies reported.

The limited prospective data available do not suggest pregnancy associated pharmacokinetic changes for AQ, AM, quinine and MQ. The findings on the effect of pregnancy on pyrimethamine exposure have been inconsistent, with decreased, unchanged and increased exposure reported.

Given the inconsistency of the above findings it is not entirely clear whether dosage adjustment is required during pregnancy.

Q4 – Is intermittent screening and treatment (IST) or intermittent preventive treatment (IPT) with dihydroartemisinin-piperaquine (DHA-PPQ) more effective in the prevention of the consequences of malaria in pregnancy compared to single screening and treatment (SST)?

The preliminary results of a randomized controlled trial (RCT) conducted in Indonesia comparing the three strategies do not allow conclusions to be drawn on which is the most

effective strategy, because the findings were not consistent across sites and study outcomes.

IST was superior to SST for the prevention of malaria at delivery, but did not improve birth outcomes, and the ability to interpret this comparison meaningfully was undermined by the very low (4/713) number of women in the IST arm that received DHA-PPQ. Therefore, based on the results from this study it is not possible to confirm or reject the potential efficacy of IST as a strategy.

Intermittent preventive treatment in pregnancy (IPTp) was superior to SST on the primary outcome, namely the prevention of malaria at delivery. Overall, IPTp reduced the risk of parasites at delivery by 41%. This effect was driven by the site in Papua (47% reduction), and was not significantly observed in Sumba (30% reduction). In Papua only, IPTp also reduced the risk of maternal haemoglobin (Hb) of below 9 (by 31%) and placental malaria (by 58%). Antenatal clinical malaria was rare in all arms; therefore, no strategy significantly prevented clinical malaria in mothers. However, these benefits on maternal parasites at delivery – and placental malaria – did not translate into benefits for the newborn.

Q5 – Is IST with AS plus sulfadoxine-pyrimethamine (SP) more effective in the prevention of the consequences of malaria in pregnancy than passive case detection (PCD)?

Results from a cluster-RCT conducted in India comparing IST-AS-SP with PCD found no difference in the risk of placental malaria (active or past) between study arms (6.0% versus 4.5%, p=0.29). In addition, prevalence was similar in the different arms in terms of adverse birth outcomes including preterm birth, stillbirth, low birth weight (LBW) and perinatal death. Therefore, in this setting, IST with AS-SP was not found to be more effective than PCD.

Q6 – Is IST with DHA-PPQ or with AS-SP feasible and cost effective in the context of the studies implemented in India and Indonesia?

In Indonesia, the acceptability of IST to providers was high owing to the existing clinical practices of screening women for malaria. However, the feasibility of IST in Indonesia is undermined by inconsistent supplies of rapid diagnostic tests (RDTs).

With regard to the cost–effectiveness analyses of IST-DHA-PPQ, IPTp-DHA-PPQ and SSTp-DHA-PPQ conducted within the frame of the RCT in Indonesia, different results were found by site. In Sumba, IPTp-DHA-PPQ and IST-DHA-PPQ resulted in higher costs and a greater number of disability-adjusted life years (DALYs) (for intervention delivery and cost of consequences) compared with the current strategy of SSTp-DHA-PPQ. In contrast, in the higher malaria transmission setting of Papua, IPTp-DHA-PPQ and IST-DHA-PPQ were both incrementally more cost effective than the current strategy of SSTp-DHA-PPQ; although IPTp-DHA-PPQ and IST-DHA-PPQ incurred higher incremental costs than SSTp-DHA-PPQ, they resulted in fewer DALYs.

Q7 – What is the impact of intermittent treatment for malaria in pregnancy with SP and azithromycin (AZ) on adverse birth outcomes?

Compared with IPTp with SP plus chloroquine (SP-CQ+) monthly placebo, IPTp-SP-AZ reduced the prevalence of LBW and preterm delivery in a trial in Papua New Guinea. The risk of placental malaria and maternal parasitaemia was also reduced.

Q8 – What is the additive impact of AZ when added to IPTp with SP on adverse birth outcomes?

Two trials conducted in Malawi evaluating AZ in addition to IPTp-SP in preventing preterm birth yielded opposite results. The difference can be explained by differences in prevalence of malaria and frequency of SP dosing in the study intervention.

Q9 – What is the additive impact of IPTp with SP and AZ on sexually transmitted diseases (STIs) and reproductive tract infections (RTIs)?

The trial comparing IPTp-SP-CQ plus monthly placebo with IPTp-SP-AZ conducted in Papua New Guinea found a reduced carriage of gonorrhoea (OR 0.66, 95% CI: 0.44–0.99, p=0.041) at the second antenatal care visit in the AZ arm.

The potential of IPTp-SP for reducing the burden and consequences of STIs and RTIs as suggested in a recent observational study is contrary to current knowledge that multiple doses of SP given 1 month apart do not cure STIs and RTIs caused by *Treponema pallidum, Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis* and bacterial vaginosis mentioned in the study. More research is needed to determine whether sulfadoxine has an inhibitory effect on or other clinically important pathogens, or whether sulfadoxine reduces maternal inflammatory responses that might otherwise contribute to preterm delivery in the presence of maternal infection.

More research would be thus needed to establish the additive effect of AZ to IPTp-SP plus AZ on STIs and RTIs. The minimum dose of AZ to prevent the syphilis-related adverse pregnancy outcomes is 2 g. The impact of AZ on bacterial antibiotic resistance also requires further evaluation.

Q10 – Among pregnant women with malaria and HIV coinfections, what is the efficacy and effectiveness of co-trimoxazole (CTX) prophylaxis for prevention of malaria and its adverse consequences compared to the efficacy and effectiveness of IPTp using alternative medicines (MQ or DHA-PPQ)

Studies have evaluated the effect of adding MQ or DHA-PPQ as IPTp in HIV-infected women receiving CTX prophylaxis.

The multicentre placebo-controlled trial evaluating IPTp-MQ in HIV-infected women on CTX prophylaxis from Kenya, Mozambique and Tanzania (n=1071) showed three-dose IPTp-MQ reduced the risk of maternal parasitaemia at delivery, placental infection and hospital admissions in pregnancy. No differences were observed on adverse birth outcomes between groups. However, MQ was associated with vomiting, dizziness and an increased risk of mother-to-child transmission (MTCT) of HIV.

A recent placebo-controlled trial conducted in Uganda evaluated monthly IPTp-DHA-PPQ among 200 HIV-infected pregnant women receiving antiretroviral therapy (ART) and CTX prophylaxis in a setting where indoor residual spraying was practised. The study reported no significant differences between arms in pregnancy outcomes. The frequency of MTCT of HIV has not been reported.

Further research is needed on optimal malaria prevention in HIV-infected pregnant women.

Q11 – Is there evidence from clinical trials or PK/PD studies of specific changes in HIV-infected pregnant women affecting the therapeutic efficacy or safety of medicines for the treatment of uncomplicated falciparum malaria, so to require specific dose adjustments during pregnancy?

Recent reports indicate that efavirenz-based ART significantly reduces exposure to both DHA-PPQ and AL. Pharmacometric modelling is ongoing to determine the optimal AL and DHA-PPQ dosage regimens for pregnant women. Given their potential increased risk of treatment failure, full adherence and closer monitoring of their malaria treatment response is essential. However, current evidence does not support a specific dose adjustment in HIV-infected pregnant women.

Annex 3. List of participants

ERG Panel Members

Dr Karen BARNES
University of Cape Town
South Africa

Dr Marta BOFFITO
Chelsea and Westminster Hospital
London
United Kingdom

Dr Michel COT
Institute for Research for Development
Marseille
France

Dr Rose LEKE (Co-Chairperson)
Immunology and Parasitology
Faculty of Medicine and Biomedical Sciences of the University of Yaounde
Yaounde
Cameroon

Dr David MABEY
London School of Hygiene & Tropical Medicine
London
United Kingdom

Dr Larry SLUTSKER (Co-Chairperson)
PATH
Seattle
USA

Dr Steve TAYLOR
Division of Infectious Diseases & International Health
Duke University Medical Center
Durham
USA

ERG Participants

Dr Rukhsana AHMED
Liverpool School of Tropical Medicine, UK
Based at Eijkman Institute for Molecular Biology
Jakarta
Indonesia

Dr Azucena BARDAJI
ISGlobal
Barcelona Institute for Global Health
Hospital Clínic – Universitat de Barcelona
Barcelona
Spain

Dr Daniel CHANDRAMOHAN
London School of Hygiene & Tropical Medicine
London
United Kingdom

Dr Matthew CHICO
Faculty of Infectious & Tropical Diseases
London School of Hygiene & Tropical Medicine
London
United Kingdom

Dr Meghna DESAI
Centers for Disease and Prevention
Atlanta
USA

Dr Raquel GONZALEZ (Rapporteur)
ISGlobal
Barcelona Institute for Global Health
Hospital Clínic – Universitat de Barcelona
Barcelona
Spain

Dr Jenny HILL
Liverpool School of Tropical Medicine
Liverpool
United Kingdom

Dr Abel KAKURU
Infectious Diseases Research Collaboration
Tororo District Hospital
Tororo
Uganda

Dr Clara MENENDEZ
ISGlobal
Barcelona Institute for Global Health
Hospital Clínic – Universitat de Barcelona
Barcelona
Spain

Dr Kerryn MOORE
Burnet Institute
University of Melbourne
Melbourne
Australia

Dr Kamija PHIRI
College of Medicine
University of Malawi
Blantyre
Malawi

Dr Stephen ROGERSON
University of Melbourne
Melbourne
Australia

Dr Joel TARNING
Mahidol Oxford Tropical Medicine Research Unit (MORU)
Mahidol University, Faculty of Tropical Medicine
Bangkok
Thailand

Dr Feiko ter KUILE
Liverpool School of Tropical Medicine/
Kenya Medical Research Institute
Kisumu
Kenya

Dr Jayne WEBSTER
London School of Hygiene and Tropical Medicine
London
United Kingdom

Observers

Dr Stephan DUPARC
Medicines for Malaria Venture
Geneva

WHO Secretariat

Dr Pedro ALONSO
Director
Global Malaria Programme

Dr Per Allan Ilmari ASHORN
Research and Development
Maternal, Newborn and Adolescent Health

Dr Andrea BOSMAN
Coordinator,
Prevention, Diagnostics and Treatment
Global Malaria Programme

Dr Shaffiq Mustafa ESSAJEE
Medical Officer
PMTCT & Maternal Child Health
HIV Department

Dr Peter OLUMESE
Medical Officer,
Prevention, Diagnostics and Treatment
Global Malaria Programme

Ms Silvia SCHWARTE
Technical Officer,
Prevention, Diagnostics and Treatment
Global Malaria Programme

Dr Melanie TAYLOR
Medical Officer
HRX Human Reproduction
Reproductive Health and
ResearchSwitzerland

Dr Iveth GONZALEZ
Foundation for Innovative New Diagnostics
Geneva
Switzerland

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