Malaria Policy Advisory Committee Meeting

16–18 September 2015, Geneva, Switzerland
Background document for Session 4

Malaria in pregnancy

WHO Evidence Review Group meeting report
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Summary

Malaria in pregnancy (MiP) is a major, preventable cause of maternal morbidity and poor birth outcomes. To prevent the adverse outcomes of MiP, WHO recommends the use of insecticide-treated mosquito nets (ITNs), and effective case management of malaria and anaemia in pregnant women. In areas of moderate to high malaria transmission of sub-Saharan Africa, WHO also recommends intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP). In recent years, an alternative preventive strategy – consisting of intermittent screening and treatment in pregnancy (ISTp) using rapid diagnostic tests (RDTs) during antenatal care (ANC) visits – has been evaluated in several countries. Moreover, multiple studies have assessed the safety of using artemisinin-based combination therapies (ACTs) in the first trimester of pregnancy. Based on this new evidence, WHO convened a group of experts to develop recommendations on the efficacy and cost-effectiveness of (ISTp) compared to IPTp-SP for prevention of MiP, and on the safety of ACTs in early pregnancy.

The following conclusions and draft recommendations were proposed by the WHO evidence review group (ERG) for consideration by the WHO Malaria Policy Advisory Committee (MPAC).

1. IPTp-SP remains highly cost-effective in preventing the adverse consequences of malaria on maternal and fetal outcomes, and should thus be aggressively scaled up in line with the current WHO recommendations. IPTp-SP also remains effective in areas where quintuple-mutant haplotypes of Plasmodium falciparum to SP are highly prevalent.
2. An association between sextuple mutant haplotypes of *P. falciparum* and decreased low birth weight (LBW) has been reported in limited areas in the United Republic of Tanzania with very high SP resistance, in the context of observational studies using retrospective information about the assignment of SP. However, this has not been observed in other sub-Saharan countries in the context of randomized controlled trials with SP, and requires further investigation. In the limited geographical areas with very high SP resistance, it would be useful to evaluate, in pilot studies, the benefits and cost-effectiveness of adding, at the first ANC visit, a single RDT screening and treatment to the continued provision of IPTp-SP.
3. There is currently no evidence of a threshold level of malaria transmission below which IPTp-SP is no longer cost-effective. Therefore, in areas where IPTp-SP is implemented and transmission is reduced to low levels as a result of successful control strategies, WHO recommends continued implementation until the area has been targeted for malaria elimination by the national programme.
4. Recent studies have shown that IST with RDTs and ACTs of pregnant women at ANC resulted in a higher proportion of maternal infections and clinical malaria during

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pregnancy and lower mean birth weight compared with IPTp-SP. Further, being less cost-effective than IPTp-SP, ISTp with the currently available RDTs should not be recommended as an alternative to IPTp-SP.

6. Recent studies have shown that IPTp with dihydroartemisinin-piperaquine (DHA-PPQ) did not reduce LBW compared to IPTp-SP, but was more efficacious in reducing maternal malaria parasitaemia and anaemia at delivery, incidence of malaria infection and clinical malaria during pregnancy, stillbirths and early infant mortality (i.e. within 6–8 weeks). More research is needed to evaluate the impact of DHA-PPQ for IPTp on LBW, safety of repeated doses and adherence to the required 3-day regimen.
7. New evidence from 1025 pregnancies with confirmed artemisinin exposure in the first trimester indicates that artemisinins do not increase the risk of miscarriage, stillbirths or major congenital malformations compared to women with malaria treated with non-artemisinin regimens. Moreover, comparison of carefully documented and prospectively collected safety data on women exposed only to artemisinin-based treatment with data collected on women exposed only to quinine in the first trimester of pregnancy showed that artemisinin was associated with a significantly reduced rate of miscarriage compared to quinine. Therefore, the WHO recommendations for the treatment of clinical uncomplicated malaria episodes in women in the first trimester of pregnancy should be updated as follows: "Treat pregnant women with uncomplicated P. falciparum malaria with either the first-line ACT for 3 days or quinine and clindamycin for 7 days." Artemether-lumefantrine (AL) should be the preferred ACT, because most of the available data derive from AL exposure.
8. Although the evidence regarding the safety of ACTs in early pregnancy has been strengthened by the recent review, there is the need for continued monitoring of drug safety, birth outcomes and neonatal mortality. Moreover, there is also a need to monitor potential drug–drug interactions in HIV-infected pregnant women who are taking antiretroviral therapies and receive antimalarial medicines, as well as the risk of mother-to-child transmission.

Abbreviations

ACT	artemisinin-based combination therapy	ISTp	intermittent screening and treatment in pregnancy
AE	adverse event	ITN	insecticide-treated mosquito net
AL	artemether-lumefantrine	LBW	low birth weight
ANC	antenatal care	LLN	long-lasting insecticide-treated net
aPR	adjusted prevalence ratio	LMP	last menstrual period
AQAS	amodiaquine-artesunate	MiP	malaria in pregnancy
AS	artesunate	MQ	mefloquine
CEA	cost-effectiveness analysis	OR	odds ratio
CI	confidence interval	pc	post conception
DALY	disability adjusted life year	PCR	polymerase chain reaction
DHA	dihydroartemisinin	pLDH	parasite lactate dehydrogenase
dhfr	dihydrofolate reductase	POR	pooled odd ratio
dhps	dihydropteroate synthase	PPQ	piperaquine
ECG	electrocardiogram	PRR	pooled risk ratio
ERG	evidence review group	RCT	randomized controlled trial
HIV	human immunodeficiency virus	RD	risk difference
HR	hazard ratio	RDT	rapid diagnostic test
HRP2	histidine rich protein-2	RR	relative risk
ICER	incremental cost-effectiveness ratio	SP	sulfadoxine-pyrimethamine
IPTp	intermittent preventive treatment in pregnancy	WHO	World Health Organization

1 Background

Malaria in pregnancy (MiP) contributes significantly to maternal and neonatal mortality (1). Intermittent preventive treatment in pregnancy (IPTp) is a highly cost-effective preventive malaria intervention that significantly improves the health of mothers and their newborns in areas of moderate to high malaria transmission (2-6).

In October 2012, on the advice of the Malaria Policy Advisory Committee (MPAC) and the work of a dedicated evidence review group (ERG), WHO updated the policy for IPTp with sulfadoxine-pyrimethamine (SP) (7). The new policy recommends that women living in areas of moderate to high malaria transmission should receive IPTp-SP as early as possible in the second trimester, and at each scheduled antenatal care (ANC) visit thereafter, with SP doses given at least 1 month apart.

Since the updated IPTp policy was released, several countries throughout sub-Saharan Africa have updated their country policies to align with the new recommendations, but IPTp implementation still remains low. In 2013, the coverage of IPTp with two doses of SP was 43% (among 31 reporting countries) – well below national and international targets – and only 17% of all pregnant women received three or more doses of IPTp (among nine reporting countries) (8). It is of particular concern that, according to some preliminary estimates for 2014, coverage may be declining in some countries.

In 2013, the MPAC concluded that there was insufficient data to determine at what level of SP resistance IPTp-SP should be discontinued in the absence of an established and effective alternative, and to define the level of *Plasmodium falciparum* transmission at which IPTp-SP may cease to be cost-effective from a public health perspective (9).

Since then, several studies have been completed on the efficacy, safety, feasibility, acceptability and cost-effectiveness of alternative interventions to prevent the consequences of MiP, including intermittent screening and treatment in pregnancy (ISTp). This intervention uses rapid diagnostic tests (RDTs) for screening of pregnant women, and treatment of RDT-positive women with an effective combination therapy. The impact of ISTp has been studied with SP, amodiaquine-artesunate (AQAS), dihydroartemisinin-piperaquine (DHA-PPQ) and artemether-lumefantrine (AL). In addition:

- meta-analyses have been completed to evaluate:
    - the impact of antifolate resistance and level of malaria transmission on the effectiveness of IPTp-SP;
    - the efficacy of IPTp-SP compared to ISTp-AL and ISTp-DHA-PPQ in areas with different levels of SP resistance and transmission intensity; and
- studies evaluating the efficacy and safety of DHA-PPQ for IPTp have recently been completed.

During recent years, a growing body of evidence has accumulated on the clinical safety of the artemisinin derivatives in the first trimester of pregnancy, and of the efficacy of different artemisinin-based combination therapies (ACTs) in treatment of uncomplicated MiP. A series of prospective cohort studies of pregnant women have been completed to assess pregnancy outcomes of women with malaria exposed to different artemisinin derivatives or to quinine during the first trimester of pregnancy, compared to pregnant women not exposed to either malaria or antimalarial treatment.

2 Rationale, objectives and process

2.1 Rationale

To review these studies and to update WHO recommendations with the most efficacious and cost-effective interventions for the prevention of the adverse maternal and infant consequences of MiP, the WHO Global Malaria Programme (GMP) convened an ERG with a specific focus on the efficacy of ISTp compared with IPTp, and the safety of artemisinin derivatives in early pregnancy.

2.2 Objectives

The specific objectives of the meeting in relation to potential alternatives to IPTp-SP were as follows:

1. Review all available published and unpublished reports on the efficacy and safety of ISTp compared to IPTp for prevention of the adverse consequences of MiP.
2. Review all available reports on the acceptability of ISTp under trial conditions.
3. Review results of cost-effectiveness analyses (CEA) of ISTp.
4. Review the recent evidence on the effect of submicroscopic infections on maternal and infant outcomes.
5. Review available published and unpublished reports on the impact of SP resistance on the effectiveness of IPTp-SP.
6. Review results of recently completed clinical trials evaluating the efficacy and safety of DHA-PPQ for IPTp.
7. Based on the evidence reviewed, consider whether either ISTp or IPTp-DHA-PPQ could be recommended as a potential alternative to IPTp-SP in some areas with high SP resistance and/or very low transmission.

The specific objectives of the meeting in relation to the safety of ACTs in early pregnancy were as follows:

1. Review the evidence of embryotoxicity of artemisinin derivatives from animal studies.
2. Review available published and unpublished reports on exposures to artemisinin derivatives in the first trimester of pregnancy.
3. Review results of recent clinical trials evaluating the efficacy and safety of different ACTs for malaria treatment in the second and third trimester of pregnancy.
4. Based on the evidence reviewed, consider whether the current WHO recommendations on use of ACTs in pregnancy could be updated.

2.3 Process

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

1. ISTp compared to IPTp-SP in west and east Africa.
2. Acceptability of ISTp under trial conditions.
3. Cost-effectiveness of ISTp.
4. Effects of submicroscopic infections on maternal and infant outcomes.
5. Impact of SP resistance and malaria transmission on IPTp-SP effectiveness.
6. Evaluation of DHA-PPQ for IPTp.
7. Embryotoxicity of artemisinin derivatives in animal studies.
8. Safety of artemisinin exposure in the first trimester of pregnancy.

9. Efficacy and safety of ACTs for malaria treatment in the second and third trimester of pregnancy.
10. General considerations on use of antimalarial medicines in pregnancy.
11. Report of increased mother-to-child transmission of HIV following IPTp with mefloquine (MQ).

Preference was given to studies that were published or accepted for publication in peer-reviewed journals. For a few studies, the manuscript in pre-publication status was accepted. The full list of pre-reads is at Annex 1. Participants came from four different groups: presenters of the evidence, independent reviewers, observers and WHO Secretariat (the list of participants is at Annex 2). The participation of observers complied with WHO rules of observership.[1] All declarations of interest of the reviewers were assessed by the WHO Secretariat, and none were found to have any conflict of interest that could preclude their participation in assessment of the evidence presented. All participants contributed to the sessions in plenary and working groups, but only the independent reviewers and WHO Secretariat attended a final closed session to elaborate the recommendations of the meeting.

The key conclusions emerging from the topics are presented in boxes at the end of the respective sections of the report. The general conclusions and recommendations of the meeting, reviewed and agreed among the independent reviewers, are presented in the summary, and as the last section of the report (Section 4).

3 Evidence reviewed

3.1 Studies on ISTp compared with IPTp-SP in west and east Africa

The results of four randomized controlled trials (RCTs) evaluating ISTp among HIV-negative pregnant women from areas with low SP resistance in west Africa and from areas with high SP resistance in east and southern Africa were presented. The results of a pooled analysis of the two trials in east Africa were also presented and discussed.

3.1.1 RCT in Ghana

The first study was designed as a three-arm **open-label non-inferiority** RCT comparing ISTp with AQAS; ISTp with SP; and standard two-dose IPTp-SP (10). The trial was conducted in 2007–2008 and included **3333 pregnant women** from **Ghana** of **unknown HIV status**. The primary endpoint was the prevalence of severe maternal anaemia (defined by a haemoglobin level <8 g/dL) at the third trimester of pregnancy. All women received a long-lasting insecticide-treated net (LLN). Women on the ISTp groups were screened for malaria infection with an RDT based on parasite lactate dehydrogenase (pLDH). Those found to be positive received either SP or AQAS; only the first dose of the treatment was directly observed. At 36–40 weeks of gestation, the prevalence of asymptomatic parasitaemia was 12.1% in study women overall, and was similar in all treatment groups. The risk of third-trimester severe anaemia or low birth weight (LBW) did not differ significantly between the three treatment groups regardless of gravidity.

ISTp with AQAS or SP was not inferior to two-dose SP-IPTp in reducing the risk of LBW (risk difference, RD=–1.17 [95% CI: –4.39–1.02] for IST-SP versus SP-IPTp and RD=0.78 [95% CI: –2.11–3.68] for IST-AQAS versus SP-IPTp) **and third-trimester severe maternal anaemia** (RD=0.29 [95% CI: –0.69–1.30] for IST-SP versus SP-IPTp and RD=–0.36 [95% CI: –1.12–0.44] for IST-AQAS versus SP-IPTp). The frequency of reported general weakness as an adverse event (AE)

1. See http://www.who.int/malaria/mpac/rulesofobservership/en/

was significantly higher in the ISTp-AQAS than in the other treatment groups. No information on placental infection prevalence was available. The results of this first study suggest that ISTp could be a promising strategy for malaria prevention in pregnancy in some areas but need to be confirmed in larger multicentre trials.

3.1.2 RCT in Gambia, Mali, Burkina Faso and Ghana

A subsequent **multicentre,** open, individually randomized, **non-inferiority RCT** was conducted in **four west African countries** with a low prevalence of resistance to SP (Gambia, Mali, Burkina Faso and Ghana) to evaluate the efficacy and safety of **ISTp with AL compared with IPTp-SP** (11). The trial was conducted in 2010–2012 and included 5354 HIV-negative pregnant women. Participants in the IPTp-SP group received SP on two or three occasions, whereas women in the ISTp group were screened two or three times with a histidine rich protein-2 (HRP2)/pLDH combination (Pf/Pan) RDT and, if positive for malaria, treated with AL. All women received an LLN.

ISTp-AL was non-inferior to IPTp-SP in preventing LBW, anaemia and placental malaria, the primary trial endpoints. No significant differences were found between groups in the prevalence of LBW (15.1% and 15.6% in the IPTp-SP and ISTp-AL groups, respectively; odds ratio, OR=1.03 [95% CI: 0.88–1.22]) and in the mean haemoglobin concentration at the last ANC clinic visit (10.97 g/dL and 10.94 g/dL in the IPTp-SP and ISTp-AL groups, respectively; mean difference: –0.03 g/dL [95% CI: –0.13–0.06]). Active malaria infection of the placenta was found in 24.5% and in 24.2% of women in the IPTp-SP and ISTp-AL groups, respectively (OR=0.95 [95% CI: 0.81–1.12]).

More women in the ISTp-AL than in the IPTp-SP group presented with malaria parasitaemia and clinical malaria between routine ANC visits (310 versus 182 episodes, rate difference: 49.4 per 1000 pregnancies [95% CI: 30.5–68.3]). Unscheduled visits were also more frequent among women in the ISTp-AL group (1204 visits) than in those in the IPTp-SP group (988 visits) (*P*=0.001). These findings suggest that, in the absence of an effective alternative drug to SP for IPTp, ISTp-AL could be considered a potential alternative to IPTp in areas where SP resistance is high or malaria transmission very low.

3.1.3 RCT in Malawi

The third study evaluating ISTp was conducted **in an area of high SP resistance from Malawi** between 2011 and 2013 (12). The study was designed as an open-label two-arm individually randomized superiority trial and included 1873 HIV-negative women (1155 primi+ secundigravidae [paucigravidae], 718 multigravidae). Participants were randomized to receive either IPTp-SP or ISTp-DHA-PPQ at each ANC visit (three or four visits were scheduled in the second and third trimester, 4–6 weeks apart). All women received an LLN, and all treatment doses in both arms were supervised. The prevalence of adverse birth outcome (defined by a composite of LBW, preterm birth and small for gestational age) was similar in both arms: ISTp-DHA-PPQ=29.9%, IPTp-SP=28.8%, RD=1.08% (95% CI: –3.25–5.41); relative risk (RR)=1.04 (0.90–1.20), *P*=0.625;paucigravidae: RR=1.10 [0.92–1.31], *P*=0.282; multigravidae RR=0.92 [0.71–1.20], *P*=0.543.

The prevalence of malaria at delivery was higher in the ISTp-DHA-PPQ arm (48.7% versus 40.8%): RD=7.85 (3.07–12.63); RR=1.19 (1.07–1.33), *P*=0.007 (paucigravidae: RR=1.16 [1.04–1.31], *P*=0.011; multigravidae: RR=1.29 [1.02–1.63], *P*=0.037). **Fetal loss was more common with ISTp-DHA-PPQ** (2.6% versus 1.3%; RR=2.06 [1.01–4.21], *P*=0.046) and highest among non-DHA-PPQ-recipients (3.1%) in the ISTp-DHA-PPQ arm. Consequently, **ISTp was not superior to IPTp-SP in this area with high SP resistance**, and it was associated with higher fetal loss and more malaria at delivery.

3.1.4 RCT in Kenya

The fourth study was an **open-label three-arm randomized superiority trial** conducted in an area of **western Kenya** with high malaria transmission and high levels of SP resistance (4). Between August 2012 and June 2014, 1546 HIV-negative pregnant women of 16–32 weeks gestation were randomized to receive **ISTp-DHA-PPQ, IPTp-DHA-PPQ or IPTp-SP** three to four times during pregnancy at least 1 month apart. The primary outcome was malaria infection at delivery (composite of peripheral or placental parasitaemia detected by placental histology, microscopy or RDT). The results of the comparison between IPTp-SP versus ISTp-DHA-PPQ are presented here. The comparison with IPTp-SP is presented later in this document.

The **prevalence of malaria infection at delivery was not lower in the ISTp-DHA-PPQ** than the IPTp-SP arm (12.6% versus 10.2%, RR=1.23 [0.86–1.77], *P*=0.26). There were **no significant differences in adverse birth outcomes** (composite of small for gestational age, LBW or preterm birth) between study arms (ISTp-DHA-PPQ versus IPTp-SP: 13.5% versus 10.0%, RR=1.35 [0.93–1.96], *P*=0.12), fetal loss (2.4% versus 3.8%, RR=0.65 [0.31–1.36], *P*=0.25), and infant mortality by 6–8 weeks (1.3% versus 2.9%, RR=0.46 [0.18–1.20], *P*=0.11). **The incidence of malaria infection and clinical malaria were significantly higher in the ISTp-DHA-PPQ arm** (malaria infection incidence: 232 versus 192 per 100 person years, IRR=1.21 [1.03–1.41], *P*=0.02; clinical malaria: 53 versus 38 per 100 person years, RR=1.41 [1.00–1.98], *P*=0.05 [*P*=0.04 in paucigravidae]). These findings indicate that **at the current levels of RDT sensitivity, ISTp is not a suitable alternative to IPTp-SP in the context of high SP resistance and malaria transmission**.

3.1.5 Individual participant data meta-analysis of the above RCTs in Malawi and Kenya

A single-stage individual participant-level meta-analysis was conducted using data of the aforementioned trials to compare the effect of ISTp-DHA-PPQ and IPTp-SP on birth outcome and the antenatal incidence and delivery prevalence of *P. falciparum* among all women with singleton births (13). Overall, 2866 women (paucigravidae=1697, multigravidae=1169) were included in the modified intention to treat (mITT) population (Kenya=1022, Malawi=1844). Compared with IPTp-SP, **ISTp-DHA-PPQ was associated with higher incidence of malaria parasitaemia during pregnancy** (47.4% versus 41.6%, IRR=1.14 [95% CI: 1.05–1.24], *P*=0.002) **and higher prevalence at delivery** (47.0% versus 39.1%, RR=1.20 [1.10–1.31], *P*<0.001) overall. **There were no differences in fetal loss** (2.6% versus 2.1%, RR=1.20 [0.73–1.97], *P*=0.46), **or early infant mortality by 6–8 weeks of age** (1.5% versus 1.7%, RR=0.88 [0.48–1.59], *P*=0.66). Results of this meta-analysis support the findings of the previously described single RCT, and indicate that in areas with near fixation of the quintuple dihydrofolate reductase (*dhfr*) and dihydropteroate synthase (*dhps*) mutant and low prevalence of the sextuple mutation, **ISTp-DHA-PPQ was inferior to IPTp-SP and may have resulted in more adverse birth outcomes**. The low sensitivity of currently available RDTs probably contributed to the poor performance of ISTp. These findings may not be generalizable to areas of higher parasite resistance.

Finally, modelling studies considering SP resistance across Africa, malaria transmission, accuracy of RDTs and SP effectiveness data in pregnancy have concluded that IPTp-SP is likely to remain superior to ISTp in areas where SP remains effective (14).

Key conclusions

- ISTp (either with SP or AL as treatment) was not inferior to IPTp-SP in preventing third trimester maternal anaemia, LBW and placental malaria in studies conducted in areas of low SP resistance in west Africa.
- The incidence of outpatient visits and malaria episodes during pregnancy was higher in the ISTp group compared to IPTp-SP.
- The results from the trials conducted in west Africa suggest that **IPTp-SP should be continued where SP resistance is low.**
- ISTp-DHA-PPQ was not superior to IPTp-SP in areas of high malaria transmission and high SP resistance of east and southern Africa and was associated with more malaria during pregnancy and at delivery in all gravidae and lower mean birth weight in paucigravidae.
- **IPTp-SP retains some of its effectiveness in areas of high SP resistance and should be continued in these areas.**

3.2 Acceptability of ISTp under trial conditions

The acceptability of ISTp both by providers (ANC health workers) and users (pregnant women) has been evaluated in three sub-Saharan countries within the RCT context.

In **Ghana**, overall, both ISTp and IPTp appeared equally acceptable to pregnant women as strategies for the control of MiP (*15*). The women were more concerned about quality of services received – in particular, the polite and patient attitude of health staff, and positive health implications for themselves and their babies – than about the nature of the intervention (15).

In **Malawi**, the user and provider acceptability study of ISTp-DHA-PPQ identified six areas of concern for health workers: blood tests, drugs, resources and stock, adherence to DHA-PPQ, communication and workload (16). For pregnant women the main issues identified were blood tests, drugs and reasons for repeat visits. Overall, both providers and users considered ISTp to be an acceptable alternative to IPTp.

Finally, in **Kenya**, ISTp-DHA-PPQ and IPTp-DHA-PPQ in the context of the study were generally acceptable among both users and providers, and were seen as potentially valuable alternatives to IPTp-SP (17). Among the several challenges identified, the most important was adherence to DHA-PPQ for the full course (3 days) among asymptomatic women in the routine setting.

Key conclusions

- Overall, **ISTp** (either with AQAS or DHA-PPQ) was considered to be an **acceptable alternative to IPTp-SP, both by providers and users in trial conditions**.
- Quality of care of ANC services as well as adherence to a 3-day course of treatment were concerns perceived by pregnant women and health workers, respectively.
- Further research would be needed to confirm these findings in larger studies, other settings and non-trial conditions.

3.3 Cost-effectiveness of ISTp

Based on the results of the aforementioned non-inferiority multicentre RCT evaluating ISTp with AL in HIV-negative women from four sub-Saharan countries in west Africa (Section 3.1.2), a CEA of ISTp was undertaken (11, 18).

Simulations were performed considering hypothetical cohorts of 1000 pregnant women receiving either ISTp-AL or IPTp-SP. Disability adjusted life years (DALYs) were calculated for LBW, severe or moderate anaemia, and clinical malaria. Cost estimates were obtained from data collected in observational studies, health facility costing studies and public procurement databases. The main outcome measure was the incremental cost per DALY averted.

The CEA found that delivering ISTp-AL to 1000 pregnant women averted –27.83 DALYs at an incremental cost of US$ 4929.00 (producing an incremental cost-effectiveness ratio [ICER] of US$ –177.10/DALY averted) and that **IPTp-SP averted more DALYs than ISTp-AL**.

In the probabilistic sensitivity analysis, the ICER was US$ –175.12/DALY averted. The CEA model presents the threshold below which the efficacy of IPTp-SP would have to fall for ISTp-AL to become a cost-effective option for the prevention of MiP at different levels of willingness to pay and insecticide-treated mosquito net (ITN) contribution (18). **Cost-effectiveness of ISTp-AL increased as the efficacy of IPTp-SP decreased**, though the level of IPTp-SP efficacy loss is sensitive to assumptions about the contribution of ITNs to malaria control, and the willingness-to-pay threshold used.

Taking these elements into consideration, the results indicate that at the current SP efficacy levels in the trial settings **it would not be cost-effective to switch from IPTp-SP to ISTp-AL.**

Areas of further research include the CEA of ISTp in areas of east Africa where SP resistance prevalence is high, and effects of malaria transmission on cost-effectiveness of the intervention.

Key conclusions

- **ISTp** (with AL) was found to be **more expensive and less effective** for prevention of MiP than IPTp-SP.
- **At the current levels of efficacy of IPTp-SP, it would not be cost-effective to switch from IPTp-SP to ISTp-AL.**

3.4 Effects of submicroscopic infections on maternal and infant outcomes

A longitudinal cohort study including 1037 pregnant women from Benin evaluated the effect of submicroscopic *P. falciparum* infections on maternal and infant outcomes (19). The study was conducted between 2008 and 2011, and enrolled pregnant women who were followed up monthly until delivery. At inclusion, polymerase chain reaction (PCR) and microscopy detected malaria parasites from peripheral blood in 40% and 16% of women, respectively. The proportion of infections declined markedly after two doses of IPTp-SP but rebounded to 34% (by PCR) at delivery. **Submicroscopic infections** during pregnancy **were associated with lower mean haemoglobin** irrespective of gravidity, and with increased **anaemia** risk in primigravidae (OR: 2.23; 95% CI: 0.98–5.07). Prospectively, submicroscopic infections at inclusion were associated with significantly increased risks of LBW in primigravidae (OR: 6.09; 95% CI: 1.16–31.95) **and premature births** in multigravidae (OR: 2.25; 95% CI: 1.13–4.46). In this study, parasitaemia occurred frequently during pregnancy, but routine microscopic and HRP2-detecting **RDTs failed to detect most episodes**.

Another longitudinal study conducted in Burkina Faso and Uganda analysed the correlation of PCR, microscopy and Pf/Pan combination RDTs performed on peripheral blood compared with results of malaria infection by placental histology (20). A total of 990 women were followed up to delivery between 2010 and 2012. Preliminary results indicate that **PCR had the higher detection rate** on peripheral blood than the other diagnostics. Using PCR as standard, all diagnostics typically had a higher sensitivity and lower specificity on samples from women experiencing fever symptoms, compared to those from women not experiencing fever symptoms. The variables of age, gravidity, presence of fever symptoms, prior treatment for malaria or IPTp and month of visit were all significant explanatory variables for predicting sensitivity, specificity, positive predictive value and negative predictive value, but the significance of each variable differed for the different statistics, diagnostics and country. **Country was a significant factor influencing the sensitivity and specificity of the different diagnostic tests** (sensitivity was always higher in Uganda than in Burkina Faso). **The prevalence of adverse birth outcomes** (including LBW, preterm delivery, stillbirths and miscarriage) **did not differ by parasite detection method used (RDT, microscopy or PCR) or by placental histology). However, maternal haemoglobin change between enrolment and delivery was influenced by the sensitivity of the parasite detection method used, gravidity and country.**

The sensitivity of the RDTs to detect malaria parasites in peripheral blood was also evaluated in pregnant women in the context of the ISTp RCT conducted in west Africa (11, 21). In Ghana, the sensitivity of the RDT declined progressively over the course of pregnancy from 89% (95% CI: 85–92%) at enrolment to 49% (95% CI: 31–66%) at delivery. Screening at first enrolment with an RDT detected 53% of all infections diagnosed during pregnancy. Seventy-five RDT negative infections were detected by PCR or microscopy in 540 women; these infections were not associated with maternal anaemia, placental malaria or LBW.

The sensitivity of RDTs in the pooled individual participant data meta-analysis of the two ISTp RCTs in Kenya and Malawi also showed that the highest prevalence of malaria was at enrolment, when 40.1% of women were infected, as measured by PCR (13). The sensitivity of RDTs during the enrolment visit was 64.8% (95% CI: 60.8–68.7%) compared to PCR and highest in paucigravidae women (74.8% [95% CI: 70.6–79.2%]) compared to multigravidae women (43.5% [95% CI: 36.4–50.7%]). At subsequent visits, the proportion of parasitaemic women decreased to 18.8% (95% CI: 17.5–20.1%), and the sensitivity of RDT to 33.8% (95% CI: 30.1–37.5%); 35.2% (95% CI: 30.4–39.9%) in paucigravidae women and 31.8% (95% CI: 26.1–37.5%) in multigravidae women.

Key conclusions

- **Submiscroscopic infections**, especially early in pregnancy, have been associated **with maternal anaemia, LBW and prematurity.**
- The effects of submicroscopic infections on adverse pregnancy outcomes need to be confirmed in large longitudinal studies and in different settings.
- **Malaria infection prevalence is highest at the antenatal booking visit** and declines thereafter. **The sensitivity of RDTs is also highest at the initial visit, in particular in primigravidae.** Thus, the use of RDTs to screen asymptomatic pregnant women for malaria infection is likely to be most beneficial at the first antenatal visit.

3.5 Impact of SP resistance and malaria transmission on IPTp-SP effectiveness

The **effectiveness of IPTp-SP is threatened by drug resistance** of the malaria parasites. SP resistance is due to the presence of mutant alleles in the *P. falciparum* genes encoding *dhfr* and *dhps*. The **triple *Pfdhfr* mutation N51I, C59R and S108N in combination with double *Pfdhps* mutant A437G and K540E – forming quintuple-mutant** haplotypes – has been associated with risk for treatment failure in malaria-infected children and non-pregnant adults who receive SP treatment (22). Moreover, quintuple mutants with an additional *dhps* mutation, **A581G**, have been associated with an even higher risk of SP failure (22, 23).

An initial report of the clinical impact of this A581G mutation was a retrospective cross-sectional study conducted between 2002 and 2005 among 104 delivering women in an area of the **United Republic of Tanzania**, where the fraction of parasites carrying the resistance allele at *dhps* codon 581 is relatively high (24). The study found an increased placental parasite density and inflammatory changes in women who reported taking IPTp-SP, but no effects on the prevalence of LBW was observed (24, 25).

A further study conducted in **Mozambique** during the same period (2003–2006) assessed the impact of IPTp and maternal HIV infection on the prevalence of molecular markers of SP resistance (26). *P. falciparum* isolates collected at delivery from women participating in a randomized, placebo-controlled trial of IPTp-SP were analysed. It was found that the prevalence of infections with parasites carrying quintuple resistance markers was 24% in the SP group and 12% in the placebo group. IPTp-SP increased the prevalence of molecular markers of resistance in the placenta (*P*=0.031), but not in peripheral blood and in HIV-infected women. However, **no association was found between infections with parasites carrying quintuple resistance markers and increased parasite density or malaria-related morbidity in mothers and children, nor on birth weight reduction.**

These findings are in accordance with those from a serial, cross-sectional analysis of the relationship between IPTp-SP use, SP-resistant *P. falciparum* and MiP morbidity during a period of 9 years at a single site in **Malawi** (1997–2006), which showed that, despite increasing SP resistance, MiP morbidity was not exacerbated (27). This study suggested that although IPTp-SP may contribute to the selection of quintuple mutant resistant parasites, **the use of IPTp-SP was not associated with increased parasite densities, greater placental inflammation or adverse delivery outcomes.**

A further cohort study conducted between 2008 and 2010 in the **United Republic of Tanzania** among 924 pregnant women analysed the effect of infecting parasite haplotypes on an infant's birthweight (22). Women received two doses of IPTp-SP. Quadruple-mutated or less-mutated haplotypes were mainly observed early during pregnancy, whereas quintuple-mutated and also 581G were encountered throughout pregnancy. Compared with infections with the less-mutated haplotypes, **infections with the sextuple haplotype mutation were associated with lower (–359 g) birthweights, although there was no association between SP use and lower birthweight.**

The effects of the presence of the sextuple mutant on IPTp-SP effectiveness have also been analysed in 1809 delivering women from **Malawi** between 2009 and 2011 (23). A total of 202 specimens were genotyped at codon 581 of *dhps*, 17 (8.4%) of whom harboured the sextuple mutant. **The presence of the 581G mutation was associated with higher risks of patent infection in peripheral blood** (adjusted prevalence ratio [aPR]: 2.76; 95% CI: 1.82–4.18) and placental blood (aPR: 3.28; 95% CI: 1.88–5.78) and higher parasite densities. Recent **SP use was not associated with increased parasite densities or placental pathology overall or with these outcomes among women with parasites carrying *dhps* A581G.**

A recent analysis of the geographical distribution of *P. falciparum* parasites carrying sextuple mutations indicates that the high prevalence (>30%) is maintained in the original areas where first identified in the United Republic of Tanzania, Kenya and Rwanda (28). Furthermore, detectable prevalence of sextuple mutants of below 10% seems to be increasingly detected in surrounding areas.

A systematic review and meta-analysis evaluated the impact of SP resistance on IPTp effectiveness (ter Kuile et al., unpublished). In vivo studies conducted between 2009 and 2011 on the efficacy of IPTp-SP in parasitaemic asymptomatic pregnant women from Burkina Faso, Kenya, Malawi, Mali and Zambia found that SP treatment failure and risk of reinfection were more frequent in areas with increasing resistance levels in parasite population (29). The meta-analysis using aggregated data from observational studies and trials conducted between 1997 and 2013 found that **IPTp effectiveness decreases with increasing SP resistance, but that even in areas with above 90% presence of quintuple mutations, IPTp-SP is associated with lower risk of LBW.** However, in areas of very high SP resistance (e.g. presence of >10% sextuple mutations) there was no more evidence that SP was associated with a lower risk of LBW or that the effectiveness of SP may be compromised in these limited areas.

Overall, results of these studies indicate the need for continued monitoring of SP resistance markers and further research into their impact on IPTp-SP effectiveness.

Very limited evidence was presented to the ERG on the possible impact of low transmission on the effectiveness of IPTP-SP. Recent modelling work (Walker et al, unpublished) estimated that at very low prevalence of malaria in primigravidae (e.g. ~5%), the number of cases of LBW prevented with IPTp-SP ranged from 1 to 7 per 1000 deliveries, at SP efficacies of 25% and 100%, respectively. The focus of the model on primigravidae was based on data derived from other studies, which estimated that primigravidae may have 20% additional risk of LBW due to malaria if not protected by IPTp or other preventive interventions. This work supports the current WHO position that it is not possible, based on current evidence, to establish a threshold level of malaria transmission below which IPTp-SP is no longer cost-effective.

Key conclusions

- **IPTp-SP remains effective** in preventing the adverse consequences of malaria on maternal and infant outcomes, including in areas where quintuple-mutant haplotypes *P. falciparum* mutations to SP are highly prevalent.
- The **association between *dhfr* 581G mutation and decreased LBW** in women receiving IPTp-SP compared to non-recipients of SP reported in limited areas from the United Republic of Tanzania has not been observed in other sub-Saharan countries and its potential impact on IPTp-SP effectiveness **requires further investigation**.
- **Further research on the impact of other SP resistance markers on IPTp-effectiveness should be done** in sub-Saharan countries where IPTp-SP is used.
- There is currently **no evidence of a threshold level of malaria transmission below which IPTp-SP is no longer cost-effective.**

3.6 Evaluation of DHA-PPQ for IPTp

Two studies have recently evaluated DHA-PPQ for IPTp in HIV-negative women. The results (unpublished) were presented and discussed at the meeting.

3.6.1 RCT comparing ISTp-DHA-PPQ, IPTp-DHA-PPQ and IPTp-SP in Kenya

This is the same study as the one reported for ISTp (see Section 3.1). The study was an **open-label three-arm RCT** conducted between 2012 and 2014 among **HIV-negative** pregnant women in an area of Kenya with high malaria transmission and SP resistance. The trial enrolled **1546** pregnant women of 16–32 weeks gestation who were randomized to receive either **ISTp-DHA-PPQ**, **IPTp-DHA-PPQ** or **IPTp-SP** three to four times during pregnancy at least 1 month apart. The primary outcome was malaria infection at delivery (composite of peripheral or placental parasitaemia detected by placental histology, microscopy or RDT). All participants received an LLN on enrolment.

The **prevalence of malaria infection at delivery was lower in the IPTp-DHA-PPQ than in the IPTp-SP arm**: 3.3% versus 10.2%; RR=0.32 (95% CI: 0.18–0.56); *P*<0.0001. There were no significant differences in adverse infant morbidity (composite of small for gestational age, LBW or preterm birth) between study arms; however, the mean birth weight was 87 g higher (95% CI: 24–150; *P*=0.01) in the IPTp-SP than in the IPTp-DHA-PPQ arm. **Stillbirths** (RR=0.25 [0.08–0.74]; *P*=0.01) **and infant mortality** by 6–8 weeks (RR=0.31 [0.10–0.94]; *P*=0.04) were **lower in the IPTp-DHA-PPQ arm** than in the IPTp-SP arm. The authors concluded that **DHA-PPQ is a potentially promising drug for IPTp.**

3.6.2 RCT comparing IPTp-DHA-PPQ with IPTp-SP in Uganda

This was a double-blind, three-arm RCT that compared three-dose **IPTp-SP** (starting at 20 weeks) with three-dose **IPTp-DHA-PPQ** (starting at 20 weeks) or **monthly DHA-PPQ** (starting as early as 16 weeks) in HIV-negative pregnant women from Uganda. Placebos of SP and DHA-PPQ were used, such that every 4 weeks women received the same number of tablets with the same appearance. The primary outcome was the prevalence of placental malaria based on the presence of any malaria parasites or pigment detected by histopathology. Electrocardiograms (ECGs) were performed to assess QTc intervals in 42 women just before their first daily dose of study drugs and 3–4 hours after their third daily dose of study drugs when they reached 28 weeks gestational age. A total of **300 HIV-negative women** were enrolled, 37% of whom were primigravidae, and 87% reported owning an LLN. At enrolment, 57% of women had malaria parasites detected by microscopy. The incidence of **symptomatic malaria was significantly higher in the SP arm** (41 episodes) compared to the three-dose IPTp-DHA-PPQ (12 episodes, *P*=0.001) or monthly DHA-PPQ (0 episodes, *P*<0.001) arms.

Maternal anaemia during pregnancy was significantly higher in the SP arm (34.9%) compared to the monthly DHA-PPQ arm (23.6%, *P*=0.04) but not to the three-dose DP arm (30.4%, *P*=0.43). The prevalence of any **placental malaria** by histopathology was significantly **higher in the SP arm** (50.0%) than in the three-dose IPTp-DHA-PPQ (34.1%, *P*=0.03) or monthly DHA-PPQ (27.1%, *P*=0.001) arms. There were no differences in individual birth outcomes between the treatment arms, but the risk of any adverse birth outcome was significantly lower in the monthly DHA-PPQ arm (9.2%) than in the three-dose DHA-PPQ arm (21.3%, *P*=0.02) and of borderline significance compared to the SP arm (18.6%, *P*=0.05). There were no significant differences in the incidence of any AEs apart from dysphagia, which was significantly higher in the monthly DHA-PPQ arm than in the three-dose DHA-PPQ arm (0.26 versus 0.04 episodes person year, *P*=0.02). Among 42 women who underwent ECG measurements at 28 weeks gestational age, all pre- and post-dosing QTc intervals were within normal limits (<450 msec) with no differences in the change in QTc intervals between study arms. Given the promising study results, **DHA-PPQ DP could be considered an alternative to SP** in areas with widespread antifolate resistance.

Key conclusions

- Recent studies evaluating **DHA-PPQ for IPTp** have found that the drug was **more efficacious than SP in reducing maternal malaria infection and anaemia at** delivery, **incidence of malaria** during pregnancy, **stillbirths** and infant mortality within 6–8 weeks.
- These **promising results** would need to be confirmed in a larger RCT involving women in areas with similar malaria transmission and SP resistance, and in areas with different malaria transmission and SP resistance levels.
- In addition, the **safety** of administering repeated doses **of DHA-PPQ** (with specific attention to QTc prolongation) requires **further investigation**, as well as adherence to the required 3-day regimen for each DHA-PPQ treatment dose and the safety of DHA-PPQ co-administration with antiretroviral therapy in HIV-infected women.

3.7 Embryotoxicity of artemisinin derivatives in animal studies

Extensive new information about the embryotoxicity of artemisinins has been gathered since the last WHO assessment of artemisinin safety in 2006. The embryotoxic effects, which include embryolethality, malformations and decreased fetal weight, have been further characterized (30-34). Moreover, the embryotoxic effects previously seen primarily with artesunate have now been observed with other artemisinin derivatives (including artemether, arteether, DHA, artemisone and artelinic acid), indicating a general class effect on multiple species of animals, namely rats, rabbits and monkeys (35-39).

A study conducted in pregnant monkeys also found significant embryotoxic effects after 12 days of treatment, when treatment was started on day 20 post conception (pc) (39). The **induction of embryolethality** by artesunate has thus been reported so far **in three species (rat, rabbit and monkey).**

Embryotoxic effects are dose and time dependent. The most sensitive embryonic period is when the primitive erythroblasts, derived from the visceral yolk sac, are predominant in the circulation (40, 41). In rats, this has been established as between **days 10 and 14 pc**, which corresponds developmentally in humans to weeks **4–10 pc (or 6–12 post last menstrual period [LMP]) in human pregnancy**.

The explanation for the apparently lesser sensitivity to artemisinins in human pregnancy has not been determined and needs further investigation. Other gaps in knowledge in animal studies include the mechanisms of embryotoxicity and of erythropoiesis.

Key conclusions

- **Embryo deaths and malformations induced by artemisinin** derivatives have been reported in **rats, rabbits and monkeys**. The effects are dose and time dependent.
- By extrapolation of animal toxicity findings it is possible to estimate in humans a putative sensitive embryonic period between the start of week 4 to the end of week 10 pc, or from the start of week 6 to the end of week 12 post LMP.

3.8 Safety of artemisinin exposure in the first trimester of pregnancy

Data on the safety of artemisinin exposure in the first trimester of pregnancy in the Myanmar–Thai border and sub-Saharan Africa has been gathered and analysed to determine the risk for the development of the fetus.

3.8.1 Retrospective analysis of ANC records of the Shoklo Malaria Research Unit, Thailand

From 1986 to 2010, a total of 773 women were treated for malaria in the first trimester of pregnancy, **64** of them with artemisinin derivatives (42). Single-course treatments were with chloroquine (354), quinine (355) or artesunate (64). Intentional treatment with artemisinins was predominantly monotherapy (21 of 30 women) whereas inadvertent treatment (34 women) was with an ACT in all cases. Among the 34 women inadvertently given an ACT, eight (24%) miscarried. The **risk of miscarriage was similar for women treated with chloroquine** (92 [26%] of 354), **quinine** (95 [27%]) of 355), **or artesunate** (20 [31%] of 64; *P*=0.71) in the first trimester of pregnancy. **Drug exposures between 6 and 12 weeks of gestation** (putative embryonic period of sensitivity) were investigated further: **miscarriage proportions were 40%** (10 of 25) **for women treated with artesunate compared with 26%** (51 of 193; *P*=0.162) **for quinine and 30%** (64 of 215; *P*=0.360) **for chloroquine** (42). Exposure to antimalarial therapies was not randomized, and women with perceived worse prognosis were more like to be given artesunate. Allowing for a plus or minus 14-day error on estimation of gestational age and so broadening the exposure window to between 4 weeks and less than 14 weeks, the miscarriage proportions were 34% (17 of 50) for women who received artesunate compared with 26% (83 of 323; *P*=0.232) for quinine and 26% (87 of 329; *P*=0.307) for chloroquine. No significant excess of congenital malformations was reported in women contributing to this analysis. Malaria episodes in the first trimester of pregnancy were associated with increased risk of miscarriage. Preliminary results of a further analysis of the ANC records from the Shoklo Malaria Research Unit, including **171 exposures to artesunate** in the first trimester of pregnancy between 1994 and 2013, also indicate that there may be no increased risk of miscarriage or congenital abnormalities associated with artemisinin exposure compared with quinine exposure.

3.8.2 Prospective observational studies in sub-Saharan Africa

Data from six prospective cohort studies conducted in Burkino Faso, Kenya, Mozambique, Rwanda, United Republic of Tanzania and Zambia between 2004 and 2013 have been pooled and analysed (43). The number of pregnancies included in the analysis depended on the outcome: 5520 for miscarriage (restricted to women enrolled before 28 weeks gestation and including loss to follow-up until last visit date), 6909 for stillbirths and 6583 for congenital malformations (restricted to live-births and stillbirths). Of the 5520 pregnancies included in the miscarriage analysis, **526 (9.5%) had a confirmed ACT exposure in the first trimester** and 384 (7.0%) of these were in the putative embryo-sensitive period. Another 106 (1.9%) were exposed to quinine anytime in the first trimester and 55 (1.0%) in the putative embryo-sensitive period for artemisinins. The unexposed comparison group included 4888 (88.6%) pregnancies with no indication of malaria or antimalarial treatment in the first 18 weeks of pregnancy.

Pregnancies with a confirmed **ACT exposure in the first trimester were at a significantly lower risk of miscarriage compared to those with a confirmed quinine exposure** (adjusted hazard ratio [HR] 0.40 [0.20–0.82], *P*=0.012). The sensitivity analysis assessing **the effect of ACT exposures in the artemisinin putative embryo-sensitive period showed similar risk of miscarriage among artemisinin and quinine exposed pregnancies** (adjusted HR 0.80 [0.43–1.51], *P*=0.514). There was **no difference in the risk of stillbirth for pregnancies exposed to ACT in the first trimester compared to those unexposed to antimalarial or exposed to quinine in the same period** (adjusted HRs: 0.71 [0.38–1.32] and 0.81 [0.22–2.95], respectively). **The risk of**

stillbirth for exposures restricted to the putative embryo-sensitive period was slightly higher than in the overall first trimester. In this 6–12 weeks gestation period, the effect estimates suggest pregnancies exposed to artemisinin were at higher risk of stillbirth than the quinine exposed comparison, but event numbers were few and this was not statistically significant (adjusted HR: 1.69 [0.62–4.63]).

3.8.3 Aggregated meta-analysis Africa and Myanmar–Thai border

An aggregated meta-analysis that combined the pooled effect estimates from the African analysis with the effect estimates from the Myanmar–Thai border showed a similar lower risk of miscarriage for pregnancies exposed to an artemisinin derivative at any time in the first trimester compared to those exposed to quinine in the same period (summary adjusted HR=0.45 [0.27, 0.75], I^2=0%) and no difference for exposures restricted to the putative embryo-sensitive period (HR=0.93 [0.55, 1.55], I^2=39%) (43). A total of 604 (526 + 78) pregnancies with confirmed artemisinin exposure in the first trimester of pregnancy contributed to this aggregated meta-analysis. Overall, there were 0.67% (155/23 198) cases of major congenital malformation. The prevalence of major congenital malformations was similar among first-trimester artemisinin and quinine exposures (artemisinins=0.58% [3/519]; quinine=0.72% [3/416], prevalence difference=0.002 [–0.015–0.019], I^2=0%, P=0.846).

Overall, these findings suggest that artemisinin-based treatment used for malaria treatment in the first trimester are associated with a lower risk of miscarriage than quinine treatment. However, the analysis has some limitations because it cannot account for potential confounding by indication, given that the data on malaria diagnosis, parasitaemia or severity of symptoms were not available across all African sites and there was limited power to assess congenital malformations (43). Adherence to malaria treatment (7 days oral quinine versus 3 days oral ACT, for uncomplicated malaria) may also be influencing the observed results. Nevertheless, results obtained in Africa and in Thailand (where these data were available and where most treatments were supervised) were consistent. Finally, these studies were not designed to assess fetal cardiovascular effects.

The **artemisinin exposures from the African analysis were predominantly AL** (95% [532/560], and the remaining 40 were AQAS, all from Burkina Faso), whereas artemisinin exposures from the Myanmar–Thai border included a wide range of treatments (MQ-AS, AL, artesunate plus clindamycin, artesunate monotherapy and DHA).

3.8.4 WHO pilot pregnancy registry project

The WHO pilot pregnancy registry project conducted in Ghana, Kenya, Uganda and United Republic of Tanzania has so far captured information on 24 pregnancies exposed to artemisinin derivatives in the first trimester of pregnancy. Thirteen of these pregnancies had confirmed exposures during 6–12 weeks post LMP (the estimated embryo-sensitive period). The preliminary results of the registry indicate that no adverse effects were observed in those pregnancies exposed to artemisinin.

3.8.5 Post-ERG meeting updated analyses

ERG recommended to the groups working on artemisinin exposures in the first trimester of pregnancy that they perform additional analyses presenting the number of pregnancies with known birth outcomes and confirm drug exposure by each study and antimalarial. The analysis has been performed and included in Annex 2.

Key conclusions

- Updated evidence on the safety of artemisinin indicates that **ACT exposure in the first trimester of pregnancy does not increase the risk of miscarriage, stillbirths or major congenital malformations compared to quinine.**
- Women treated with an artemisinin at any time during the first trimester of pregnancy were at similar or lower risk of miscarriages than those treated with oral quinine.
- Based on the available updated evidence, the first-line treatment of uncomplicated malaria in the first trimester of pregnancy could be revised to include ACTs as a therapeutic option.
- Most of the data of artemisinin exposure in the first trimester of pregnancy are from AL exposure; consequently, more safety data are needed with other ACTs.
- There is a need for **continued monitoring and pharmacovigilance of drug exposure in early pregnancy, including more information on congenital malformations.**

3.9 Efficacy and safety of ACTs for malaria treatment in the second and third trimester of pregnancy

A recent study and new meta-analysis on the efficacy and safety of ACTs for treatment of uncomplicated malaria in the second and third trimester of pregnancy were presented at the meeting.

3.9.1 RCT in Africa

A multicentre non-inferiority open-label RCT evaluating the efficacy and safety of four ACTs for the treatment of uncomplicated malaria in the second and third trimester of pregnancy was conducted between 2010 and 2013 in Burkina Faso, Ghana, Malawi and Zambia. The trial included **3428 HIV-negative pregnant women** with detectable falciparum parasitaemia (any density and regardless of symptoms) **treated with either AL, AQAS, mefloquine-artesunate (MQAS) or DHA-PPQ**. The primary endpoints of the study were the PCR-adjusted cure rates at day 63 and for safety outcomes. The PCR-adjusted cure rates were 94.8% for AL, 98.5% for AQAS, 99.2% for DHA-PPQ and 96.8% for MQAS. There was no significant difference between AQAS, DHA-PPQ and MQAS.

The cure rate for AL was significantly lower, although the difference was within the 5% non-inferiority margin. The unadjusted cure rates were significantly lower for AL (52.5%) than for AQAS (82.3%), DHA-PPQ (86.9%) and MQAS (73.8%). No significant difference in serious AEs or birth outcomes was found between treatment arms. **Drug-related AEs** such as asthenia, poor appetite, dizziness, nausea, and vomiting **were significantly more frequent in the MQAS (50.6%) and** AQAS **(48.5%) than in the DHA-PPQ (20.6%) and AL (11.5%) arms (*P*<0.001).** AL had the best tolerability profile and acceptable cure rates, but the shortest post-treatment prophylaxis. Based on efficacy and safety, DHA-PPQ seems the most suitable treatment for uncomplicated malaria and for ensuring long post-treatment prophylaxis.

3.9.2 Meta-analysis of the safety of artemisinin derivatives for treatment of MiP

A systematic review and meta-analysis has evaluated the risk of adverse pregnancy outcomes associated with use of artemisinins during the second and third trimester of pregnancy compared to use of other or no antimalarial therapies (44). The meta-analysis was performed using data of 23 studies (14 cohort studies and 9 RCTs) to generate pooled odds ratios (POR) for

miscarriage, stillbirth, any fetal loss, and congenital anomalies using Mantel-Haenszel fixed effects model using a 0.5 continuity correction for zero cells.

Second-trimester artemisinin exposures were not associated with an increased risk of miscarriage compared to community controls (POR=1.13 [95% CI: 0.77–1.66], I^2=86.7%, 3 studies). Second or third-trimester artemisinin exposure was associated with **similar odds of congenital anomalies** (POR=1.00 [95% CI: 0.27–3.75], I^2=0%, 3 studies) **and lower odds for stillbirth** compared to quinine (POR=0.49 [95% CI: 0.24–0.97], I^2=0%, 3 studies). These findings suggest that use of artemisinins in the second and third trimester does not increase the risk of miscarriage, stillbirth or congenital anomalies compared to quinine.

3.9.3 Meta-analysis of the efficacy and tolerability of ACTs versus oral quinine in the treatment of clinical malaria in the second and third trimester of pregnancy in Africa

A meta-analysis of RCT data to compare the efficacy, safety and tolerability of ACTs versus quinine and other non-ACT antimalarial medicines in the second and third trimester was recently performed (45). Of 372 screened studies, six trials involving 807 pregnancies were included. The median PCR-adjusted failure rate by days 28 to 63 in the non-ACT group was 6 (range 0–37) per 100 women, and lower (not significant) in the ACT group overall (pooled risk ratio [PRR] 0.41 [95% CI: 0.16–1.05], I^2=38%, 6 studies). Subgroup analysis showed effect modification by comparator drug; ACTs were significantly more effective when compared to oral quinine (PRR 0.20 [95% CI: 0.08–0.49], I^2=0%, 4 studies), but not when compared to other non-ACTs (PRR 1.17 [95% CI: 0.35–3.92], I^2=0%, 2 studies). The median birth weight in the non-ACT group was 2887 g (range 2785–3012 g) and on average 75 g higher in the ACT group (95% CI: 3–148, I^2=6%, 6 studies). There were no differences in the risk of fetal death (PRR 1.04, 0.49–2.20, I^2=0%, 6 studies) and congenital abnormalities (PRR 1.38 [0.31–6.08], I^2=0%, 6 studies). ACTs were better tolerated than quinine and associated with less tinnitus (PRR 0.19 [0.03–1.11], I^2=97%, 4 studies), dizziness (PRR 0.64 [95% CI: 0.44–0.93], I^2=46%, 3 studies) and vomiting (PRR 0.33 [95% CI: 0.15–0.73], I^2=65%, 3 studies). Study limitations included limited number of trials, and high heterogeneity of included trials with regards to ACTs used, outcomes measured and differences in malaria endemicity. These results suggest that ACTs are more efficacious, better tolerated and easier to administer than oral quinine for the case management of malaria in the second and third trimester of pregnancy.

Key conclusions

- Data on **ACT use for treatment of clinical uncomplicated malaria** in the second and third trimester of pregnancy indicate that they are **safe in terms of pregnancy outcomes and efficacious** to clear *Plasmodium* parasites (especially DHA-PPQ).
- ACTs can thus be considered a safe and efficacious option for treatment of clinical uncomplicated malaria in women in the second and third trimester of pregnancy.

3.10 General considerations on use of antimalarial medicines in pregnancy

3.10.1 Regulatory processes for recommendation of medicines for use in pregnancy

The European regulatory guidelines for labelling of medicines use in pregnancy were presented. The European Medicines Agency has adopted benchmarking procedures to estimate the embryotoxic risk of drugs in pregnancy. Threshold are used that depend on the number of pregnancies exposed to the medicinal product with known safe pregnancy outcomes. Thus, if no

increase in the global incidence of major malformations has been observed among at least **300 first-trimester prospectively collected drug-exposed pregnancies with known pregnancy outcomes (births or fetopathological examinations),** then the drug would not be responsible for a 10-fold or more increase in the overall incidence of malformations. Similarly, if no increase in the global incidence of major malformations has been observed among at least **1000** first-trimester-exposed prospectively collected pregnancies with known pregnancy outcomes (births or fetopathological examinations), then the drug would not be responsible for a twofold or more increase in the overall incidence of malformations.

3.10.2 WHO experience

In 2012, WHO recommended the use of efavirenz as first-line treatment of HIV infection in pregnancy despite pre-clinical data showing embryotoxicity, based on comprehensive reviews of safety data on pregnant women and programmatic superiority to standard of care (46). A similar approach could be followed to support an updated WHO recommendation of ACT use in the first trimester of pregnancy.

3.11 Report of increased mother-to-child transmission of HIV following IPTp-MQ

The efficacy and safety of MQ have recently been evaluated in two multicentre RCTs for IPTp in five sub-Saharan countries conducted between 2009 and 2013 (47, 48). Results of the trial in HIV-negative women concluded that despite MQ having a better antimalarial prophylactic effect, its tolerability was worse than that of SP, which limited its potential for IPTp in HIV-negative women. The trial in HIV-positive women was designed as a **double-blind placebo-controlled trial that enrolled 1071** participants from Kenya, Mozambique and United Republic of Tanzania (47).

IPTp-MQ was associated with significant reduction in maternal parasitaemia (RR=0.47 [95% CI: 0.27–0.82], *P*=0.008), and placental infection (RR=0.52 [95% CI: 0.29–0.90], *P*=0.021), and reduced incidence of non-obstetric hospital admissions (RR=0.59 [95% CI: 0.37; 0.95], *P*=0.031). There were no differences in the prevalence of adverse pregnancy outcomes between groups. However, drug tolerability was poorer in the MQ group than in the control group (29.6% referred dizziness and 23.9% vomiting after the first IPTp-MQ administration) and HIV viral load at delivery was higher in the MQ group than in the control group (*P*=0.048). The frequency of perinatal **mother-to-child transmission of HIV was increased in women who received MQ** (RR=1.95 [95% CI: 1.14–3.33], *P*=0.015) in an exploratory analysis. This finding needs further studies on the possible mechanisms underlying the twofold increased risk of mother-to-child transmission of HIV associated to three-dose IPTp-MQ. It is also important to understand the **implications of co-administration of antimalarials and antiretroviral therapies** before recommending new antimalarial drugs in HIV-infected individuals.

Key conclusions

- More **studies in HIV-infected pregnant women** are needed, including evaluation of **mother to child transmission and drug interactions** between antimalarial medicines and antiretroviral therapies.

4 General conclusions and recommendations

4.1 Malaria prevention in pregnancy

IPTp-SP remains effective and highly cost-effective in preventing the adverse consequences of malaria on maternal and fetal outcomes, including in areas where quintuple-mutant haplotypes of *P. falciparum* to SP (namely, the triple *Pfdhfr* mutation N51I, C59R and S108N in combination with double *Pfdhps* mutant A437G and K540E) are highly prevalent. IPTp-SP should thus be aggressively scaled up in line with the current WHO recommendations.

In areas of very high SP resistance (defined by high prevalence of *P. falciparum* sextuple SP mutations, including A581G *Pfdhps*), IPTp-SP should be continued as recommended. The association between sextuple parasite mutations and decreased LBW reported in limited areas from the United Republic of Tanzania has not been observed in other sub-Saharan countries where the *Pfdhps* A581G is present, and its potential impact on IPTp-SP effectiveness requires further investigation. In these limited areas, additional measures to prevent malaria in pregnant women could be considered, such as screening and treatment at the first ANC visit, given the higher sensitivity of RDTs in the first ANC visit. The benefits and cost-effectiveness of adding single screening and treatment at the first ANC visit to IPTp-SP should be evaluated in pilot studies.

In areas where IPTp-SP is implemented and transmission has been reduced to very low levels as a result of successful control strategies, IPTp-SP should be continued. There is currently no evidence of a threshold level of malaria transmission below which IPTp-SP is no longer cost-effective and should be discontinued. WHO recommends the continuous implementation of IPTp-SP until countries have reached very low transmission and are targeted for elimination by the national malaria programme.

Recent studies have evaluated ISTp at ANC as an alternative to IPTp-SP. In this strategy, women are screened for malaria with an RDT at each ANC visit and only women who test positive are treated. This strategy resulted in a higher proportion of maternal infections and clinical malaria during pregnancy compared to IPTp-SP, although it was non-inferior in terms of the proportion of LBW infants. In addition, ISTp was found to be less cost-effective than IPTp-SP. Thus, the evidence reviewed does not support a recommendation for IST as an alternative to IPTp-SP.

Recent studies of IPTp-DHA-PPQ found that DHA-PPQ was not associated with improved birth weight compared to IPTp-SP. However, it was more efficacious than SP in reducing maternal and placental malaria infection and anaemia at delivery, incidence of malaria infection and clinical episodes during pregnancy, stillbirths and infant mortality within 6–8 weeks. To confirm the potential of DHA-PPQ for IPTp, larger RCTs are needed with prevalence of LBW as the primary outcomes. In addition, the safety of administering repeated doses of DHA-PPQ (with specific attention to QTc prolongation) requires further investigation as well as adherence to the required 3-day regimen for each DHA-PPQ treatment dose.

4.2 Malaria treatment in pregnancy

The recommended use of quinine plus clindamycin for treatment of uncomplicated malaria episodes in the first trimester of pregnancy was based on safety risk assessment of ACT exposure in early pregnancy, largely based on pre-clinical observations. A more complete risk–benefit assessment that takes into account recent safety data on ACT exposure in the first trimester of pregnancy together with the ease of use and acceptability of administration of ACTs (compared with a 7-day course of quinine plus clindamycin given three times daily) justify the inclusion of ACTs as a potential treatment option.

New evidence from 1025 pregnancies with confirmed artemisinin exposure in the first trimester indicates that artemisinin does not increase the risk of miscarriage, stillbirths or major congenital malformations. Most of the available data reviewed derive from AL exposure (544 pregnant women with confirmed exposure in the first trimester). The comparison of carefully documented safety data on 604 women exposed to only ACTs compared to 595 exposed to only quinine in the first trimester of pregnancy showed that ACT exposure was associated with a significantly reduced rate of miscarriage compared to quinine. Therefore, if available, AL should be considered as the preferred ACT treatment option in the first trimester.

The WHO recommendations for first trimester pregnancy treatment of clinical uncomplicated malaria episodes should be updated as follows: **"Treat pregnant women with uncomplicated *P. falciparum* malaria with either the first-line ACT for three days or quinine and clindamycin for seven days."** AL should be the preferred ACT to be administered. Importantly, AS-SP should not be administered in the first trimester of pregnancy and quinine should always be administered with clindamycin and never alone.

Although the evidence regarding the safety of ACTs in early pregnancy has been strengthened by the review of the recent data, there is the need for continued monitoring of drug safety, birth outcomes and neonatal mortality. In the light of the evidence from an RCT suggesting a possible increased risk of mother-to to-child transmission of HIV associated with IPTp-MQ, more studies in HIV-infected pregnant women are needed, including evaluation of mother-to-child transmission and interactions between antimalarial medicines and antiretroviral therapies.

The WHO recommendation of efavirenz (EFZ) as first-line treatment of HIV infection in pregnancy despite pre-clinical data showing congenital malformations was based on comprehensive reviews of safety data on pregnant women and programmatic advantages compared to standard of care. The assessment was summarized in a WHO publication laying out the rationale for public health use, and then included in the WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. A similar approach could be used by WHO to support the new recommendation of ACT use in the first trimester of pregnancy.

Annex 1 Meeting pre-reads

Publication	Country and study years	Study description and main conclusions
Alifrangis et al. (49)	Uganda, United Republic of Tanzania and Ethiopia 2004–08	Molecular study on the evolutionary origin of the A581G mutation by characterizing microsatellite diversity flanking *Pfdhps* triple-mutant alleles and comparing it with double-mutant alleles from the same areas.
Almond et al. Unpublished (7)	Malawi 2011	Provider and user acceptability study of intermittent screening and treatment in pregnancy (ISTp) with dihydroartemisinin-piperaquine (DHA-PPQ) in Malawi. Although obstacles to the successful implementation of ISTp-DHA-PPQ were acknowledged by health workers and pregnant women, overall both groups consider ISTp an acceptable alternative to intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP).
Awine et al. Unpublished (50)	Ghana 2011–13	Follow-up study on the risk of malaria in infants born to women managed in pregnancy with ISTp for malaria or IPTp-SP (randomized controlled trial, RCT). No differences on infants' malaria incidence were found between groups.
Burger et al. Unpublished (45)	Malawi, United Republic of Tanzania, Uganda and Thailand 1995–2009	Meta-analysis of the efficacy and safety of artemisinin-based combination therapies (ACTs) versus quinine for uncomplicated malaria in the second and third trimester of pregnancy. Results suggest that 3-day ACT regimens are more effective and better tolerated than 7 days of oral quinine.
Cottrell et al. (19)	Benin 2008–11	Cohort study of 1037 pregnant women that evaluated the impact of submicroscopic infections on pregnancy outcomes. Submicroscopic infections were associated with lower mean haemoglobin, increased risk of low birth weight (LBW) in primigravidae and premature births in multigravidae.
D'Allesandro et al. Unpublished (51)	Burkina Faso, Ghana, Malawi and Zambia 2010–13	Open-label, non-inferiority, multicentre RCT evaluating four ACTs for the treatment of uncomplicated malaria in the second and third trimester of pregnancy. A total of 3428 pregnant women were treated with either artemether-lumefantrine (AL), amodiaquine-artesunate (AQAS), mefloquine-artesunate (MQAS) or DHA-PPQ. AL had the best tolerability profile and acceptable cure rates, but the shortest post-treatment prophylaxis. DHA-PPQ seemed to be the most suitable treatment.
Dellicour et al. Unpublished (43)	Zambia, United Republic of Tanzania, Rwanda, Kenya, Mozambique, Burkina Faso and Thailand 1986–2014	Meta-analysis on the safety of artemisinin exposure in the first trimester of pregnancy, on pregnancy outcomes. A total of 7127 pregnancies from six sub-Saharan African countries and 21 659 from Thailand contributed to the analyses. Compared to oral quinine no increased risk of miscarriage or stillbirth was observed following artemisinin treatment for uncomplicated malaria in the first trimester of pregnancy.

Publication	Country and study years	Study description and main conclusions
Desai et al. Unpublished	Kenya 2012–14	Open-label three-arm superiority RCT evaluating the efficacy and safety of ISTp-DHA-PPQ, compared with IPTp-SP and IPTp-DHA-PPQ. A total of 1546 HIV-negative women were enrolled. ISTp-DHA-PPQ was not superior to the IPTp-SP strategy, and was associated with a higher incidence of malaria infection and clinical malaria during pregnancy than IPTp-SP. IPTp-DHA-PPQ reduced the risk of anaemia and malaria infection at deliver, the incidence of clinical malaria during pregnancy, and the risk of stillbirths and early infant mortality.
European Medicines Agency (EMeA)	2009	Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling.
Fernandes et al. Unpublished (18)	Gambia, Mali, Burkina Faso and Ghana 2010–12	Study on the incremental cost and cost-effectiveness of ISTp with AL compared to IPTp-SP (RCT). Results indicate that currently switching from IPTp-SP to ISTp-AL will not be cost-effective.
González et al. (47)	Kenya, Mozambique and United Republic of Tanzania 2010–13	Double-blind, placebo-controlled RCT evaluating the efficacy and safety of IPTp with mefloquine (MQ) in 1071 HIV-infected women on daily contrimoxazole (CTX) prophylaxis. IPTp-MQ + CTX was more efficacious than CTX alone for prevention of maternal parasitaemia and anaemia at delivery. The incidence of hospital admissions in pregnancy was also reduced in MQ recipients. However, MQ was poorly tolerated and found to be associated with an increased risk of mother-to-child transmission of HIV in an exploratory analysis.
González et al. Unpublished (40)	2015	Review on artemisinin derivatives embryotoxicity in animal studies. Embryotoxic effects have been reported in rats, monkeys and rabbits. Effects are dose and time dependent. The estimated period of sensitivity in humans is from the start of week 4 to the end of week 10 post conception.
Gutman et al. (23)	Malawi 2009–11	Observational study of delivering women that evaluated IPTp-SP effectiveness and the effect of sextuple mutations (quintuple + A581G) on parasitological and pregnancy outcomes. The results suggest that IPTp-SP failed to inhibit parasite growth but did not exacerbate pathology among women infected with sextuple-mutant parasites.
Gutman et al. Unpublished (13)	Malawi and Kenya 2011–14	Individual pooled analysis of RCT data from Malawi and Kenya comparing ISTp-DHA-PPQ with IPTp-SP. ISTp-DHA-PPQ was associated with higher risk of malaria parasitaemia during pregnancy.
Gutman et al. Unpublished (52)	2015	Systematic review and meta-analysis of the efficacy and safety of repeated doses of DHA-PPQ for treatment and prevention of malaria in children and adults. The limited data on repeat DHA-PPQ exposures suggest that repeat 3-day courses of the drug given at monthly intervals may be safe and effective and a good option for IPTp.
Harrington et al. (24)	United Republic of Tanzania 2002–05	Molecular analysis of placental blood samples from 87 delivering women that found an increase of mean parasite density of placental parasitaemia in samples from women reporting IPTp use.

Publication	Country and study years	Study description and main conclusions
Hill et al. Unpublished (17)	Kenya 2013–14	User and provider acceptability study of ISTp-DHA-PPQ and IPTp-DHA-PPQ. Within a trial context, both strategies were generally acceptable among both users and providers. The most important challenge identified was concerns with adherence to DHA-PPQ in the routine setting, requiring further studies.
Hopkins et al. Unpublished (20)	Burkina Faso and Uganda 2010–12	Cohort study of pregnant women enrolled at the antenatal care (ANC) clinic to evaluate rapid diagnostic tests (RDTs) performance for screening of malaria in pregnancy (MiP) and its association with placental infection and birth outcomes.
Kakuru et al. Unpublished (53)	Uganda 2014–15	Double-blind, three-arm RCT comparing the efficacy and safety of three-dose IPTp-DHA-PPQ, with three-dose IPTp-SP and monthly DHA-PPQ in 300 HIV-negative women. The prevalence of any placental malaria by histopathology was significantly higher in the SP arm (50.0%) compared to the three-dose DHA-PPQ (34.1%, *P*=0.03) or monthly DHA-PPQ (27.1%, *P*=0.001) arms. Compared to three-dose SP, three-dose DHA-PPQ and monthly DHA-PPQ were equally safe and well tolerated and significantly reduced the incidence of symptomatic malaria and prevalence of parasitaemia during pregnancy.
Kovacs et al. Unpublished (44)	2015	Systematic review and meta-analysis of the risk of adverse pregnancy outcomes associated with use of artemisinins during the second and third trimester of pregnancy compared to use of other or no antimalarial therapies. Data suggest that use of artemisinins in the second and third trimester does not increase the risk of miscarriage, stillbirth or congenital anomalies compared to quinine.
Lagarde et al. (54)	Ghana 2009	Study on the potential barriers of ISTp implementation by ANC providers. Findings suggest that resistance to policy change would be low and would disappear if maternal and infant health outcomes were improved by the new strategy.
Madanitsa et al. Unpublished (12)	Malawi 2011–13	Open-label two-arm RCT comparing ISTp-DHA-PPQ and IPTp-SP. The prevalence of adverse birth outcome was similar in both arms. The prevalence of malaria at delivery was higher in the ISTp-DHA-PPQ arm (48.7% versus 40.8%): RD=7.85 (3.07–12.63); RR=1.19 (1.07–1.33), *P*=0.007 (paucigravidae: RR=1.16 [1.04–1.31], *P*=0.011; multigravidae: RR=1.29 [1.02–1.63], *P*=0.037). Fetal loss was more common with ISTp-DHA-PPQ (2.6% versus 1.3%; RR=2.06 [1.01–4.21], *P*=0.046) and highest among non-DHA-PPQ-recipients (3.1%) in the ISTp-DHA-PPQ arm.
McGready et al. (42)	Thailand 1986–2010	Analysis of antenatal records of women in the first trimester of pregnancy attending Shoklo Malaria Research Unit ANC clinics. Data indicate that a single episode of *falciparum* or *vivax* malaria in the first trimester of pregnancy can cause miscarriage. The risk of miscarriage was similar for women treated with chloroquine (92 [26%] of 354), quinine (95 [27%] of 355), or artesunate (20 [31%] of 64; *P*=0.71).
Menendez et al. (26)	Mozambique 2003–05	Molecular analysis of samples from peripheral and placental blood of 1030 delivering women participating in an RCT of IPTp-SP versus placebo. It showed an increase in resistance markers prevalence in the IPTp-SP group in the placenta and in HIV-infected women. This effect did not translate into severe infections or adverse clinical outcomes.

Publication	Country and study years	Study description and main conclusions
Minja et al. (22)	United Republic of Tanzania 2008–10	Cohort study of 924 pregnant women analysing the effect of infecting parasite haplotypes on birthweight. Compared with infections with the less-mutated haplotypes, infections with the sextuple haplotype mutation were associated with lower (359 g) birthweights.
Pell et al. (55)	Ghana 2010	Study on the attitudes and behaviours of pregnant women related to ISTp and IPTp under trial conditions. Despite the discomfort of the finger-prick required to perform ISTp, trial participants generally expressed more positive sentiments towards IST-AL than IPTp-SP. Nonetheless, questions remain about adherence to a multiple-dose antimalarial regimen during pregnancy.
Medicines for Malaria Venture (MMV)	2013	Confidential report of the MMV–Pregnancy Strategic Advisory Board, London, 4 Nov. 2013.
Tagbor et al. (10)	Ghana 2007–08	Non-inferiority, open-label RCT comparing ISTp-SP, ISTp-AQ-AS and IPTp-SP in 3333 women. ISTp was not inferior to IPTp-SP in preventing severe maternal anaemia at the third trimester of pregnancy and LBW. No information on placental infection was available. The results suggested that IST could be an alternative strategy to IPTp-SP in some areas and concluded that further investigations were required to confirm the study results in other settings.
Tagbor et al. Unpublished (11)	Gambia, Mali, Burkina Faso and Ghana 2010–12	Non-inferiority, open-label multicentre RCT comparing ISTp-AL with IPTp-SP in 5354 HIV-negative pregnant women from four west African countries with low prevalence of SP resistance. IST was found to be not inferior to IPTp-SP in preventing maternal anaemia, LBW and placental infection. However, the incidence of malaria episodes during pregnancy was increased in the IST group compared with the IPTp one.
Taylor et al. (56)	Malawi 1997–2005 & 2010, Democratic Republic of the Congo 2007 and United Republic of Tanzania 2002–05	Analysis of SP mutants haplotypes and emerging lineage of *P. falciparum* parasites in samples obtained from pregnant women from three sub-Saharan countries. Findings support a model of local origination of the triple-mutant SGEG *dhps* haplotypes, rather than geographical diffusion.
Taylor et al. (27)	Malawi 1997–2006	Molecular analysis of samples from delivering women over 9 years. SP resistance increased, together with the proportion of women receiving IPTp-SP, but its use was not associated with poor birth outcomes or exacerbation of placental pathology.
Smith et al. (15)	Ghana 2009	User acceptability study of ISTp compared with IPTp. Both strategies appeared equally acceptable to pregnant women for the control of MiP.
Smith Paintain et al. (57)	Ghana 2009	Provider acceptability study of ISTp at the ANC clinics level. Findings suggest preference for prevention over cure, and increased workload, may be barriers to IST implementation.

Publication	Country and study years	Study description and main conclusions
Walker et al. Unpublished (14)	2015	Modelling study on the African areas of need for more effective intervention than IPTp-SP, given the development of SP resistance and on the relative possible effectiveness of ISTp.
Williams et al. Unpublished (58)	Gambia, Mali, Burkina Faso and Ghana 2010–12	Description of non-falciparum malaria infections among pregnant women participating in the multicentre RCT comparing ISTp with IPTp-SP conducted in west Africa (*11*).
Williams et al. Unpublished (21)	Ghana 2010–12	Description of the performance of RDT used in the RCT comparing IST and IPTp conducted in Ghana (*11*). The sensitivity of the RDT used was high at enrolment but declined during the course of pregnancy. RDT negative malaria infections were uncommon during pregnancy and not associated with adverse birth outcomes, but the number of women with these infections was small.
Yore et al. Unpublished (59)	Ghana, Kenya, United Republic of Tanzania and Uganda	Preliminary results of the WHO pilot pregnancy registry project.

Annex 2 Additional information on artemisinin exposure in early pregnancy, performed after the evidence review group (ERG) meeting

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Table A2.1 Number of documented confirmed first-trimester exposures to artemisinins

Author	Country	Publication year	Number of confirmed first-trimester exposures	AL	AS[a]	MAS	AS-SP	Art (IV/IM)	AQAS	DHA-PPQ
McGready (42)	Myanmar–Thai border	Updated and not yet published	301	14	188	89		5[b]		5
Deen (60)	Gambia	2001	77				77			
Adam (61)	Sudan	2009	62	3			11	48		
Manyando (62)	Zambia	2010	156	156						
Rulisa (63)	Rwanda	2012	96	96						
Mosha (64**)**	United Republic of Tanzania	2014	168	168						
Poespoprodjo (65)	Indonesia	2014	18					10		13
Dellicour (66, 67)	Kenya	Not yet published	85	85						
Sevene (67)	Mozambique	Not yet published	21	21						
Tinto (67)	Burkina Faso	Not yet published	41	1					40	
Total			**1025**	**544**	**188**	**89**	**88**	**58**	**40**	**18**

AL, artemether-lumefantrine; AQAS, amodiaquine-artesunate; AS, artesunate; AS-SP, artesunate-sulfadoxine-pyrimethamine; Art, artesunate; DHA-PPQ, dihydroartemisinin-piperaquine; IM, intramuscular; IV, intravenous; MAS, mefloquine-artesunate.

a AS for 7 days either as monotherapy n=147; or as a non-fixed combination including AS + Clindamycin n=36; AS + Doxycycline n=3; AS + atovaquone-proguanil n=2.

b Includes one women treated with artemether IM for 6 days

Level of risk excluded for miscarriages and stillbirths

A recent meta-analysis of seven prospective cohort studies found no increase in the risk of pregnancy loss (miscarriage or stillbirth) associated with artemisinin exposures early in pregnancy. The risk of miscarriage was lower in pregnancies exposed to artemisinin in the first trimester compared to quinine, with a hazard ratio of 0.45 (95% confidence interval [CI]: 0.27–0.75). For stillbirth, the corresponding hazard ratio was 0.81 (95% CI: 0.22–2.95) and thus suggests a similar risk in pregnancies exposed to artemisinin and quinine in the first trimester, although the upper limit of the 95% CI cannot rule out increases in risk that are <2.95-fold (Table A2.2). Smaller numbers were available for exposures occurring during the putative embryo-sensitive period for artemisinin compounds (4–10 inclusive weeks post conception corresponding to 6–12 weeks post last menstrual period, LMP). The upper limit of the 95% CI of the hazard ratio rules out a 1.55-fold or greater increase in risk of miscarriage and a 4.63-fold or greater increase in risk of stillbirth.

Table A2.2 Hazard ratio and 95% CI for the risk of miscarriage and stillbirth associated with artemisinin exposures compared to quinine exposures in early pregnancy

	Artemisinin compound # events/ # total	Quinine # events/ # total	Adjusted HR (95% CI)	*P*-value
Miscarriage				
First trimester (2–14 weeks post LMP)	27/ 604	85/ 595	0.45 (0.27–0.75)	0.002
Embryo-sensitive period (6–12 weeks post LMP)	22/ 406	49/ 333	0.93 (0.55–1.55)	0.773
Stillbirth				
First trimester (2–14 weeks post LMP)	11/ 560	5/ 107	0.81 (0.22–2.95)	0.745
Embryo-sensitive period (6–12 weeks post LMP)	9/ 383	3/ 57	1.69 (0.62–4.63)	0.309

CI, confidence interval; HR, hazard ratio; LMP, last menstrual period
Hazard ratios account for pregnancy-week under observation through left-truncation and treat exposure as time-dependent variable. Estimates were derived through random effect aggregate data meta-analysis.

Level of risk detectable for major malformations

For all artemisinin compounds combined, sufficient numbers of first-trimester exposures (n=1025) have been monitored to detect at least a 2.1-fold increase in risk of overall major congenital malformations (see Table A2.3 for assumptions). No such increases have been detected to date. For AL, sufficient numbers of first-trimester exposures (n=544) have been monitored to detect at least a 2.6-fold increase in risk of overall major congenital malformations. There are insufficient data to make similar comparisons for other specific artemisinin combinations or compounds or specific subgroups of defects.

For exposures occurring during the putative embryo-sensitive period for artemisinin compounds, it is estimated that 615 out of 1025 documented first-trimester exposures occurred between 6–12 weeks post LMP (about 60% of the first-trimester exposures based on the prospective studies included in the meta-analysis). This number is sufficient to detect at least a 2.5-fold increase in risk of overall major congenital malformation. For AL, sufficient numbers of exposures (n=326) in the putative embryo-sensitive period have been monitored to detect at least a 3.1-fold increase in risk of overall major congenital malformations.

Table A2.3 Minimum level of increase in relative risks for congenital malformations that can be ruled out, according to the number of confirmed exposed pregnancies for each artemisinin treatment type (power 80% and one-sided α=0.05). The exposed to unexposed ratios are based on the number observed from published studies and unpublished studies included in the meta-analysis: for first trimester the ratio is 1:25 and for embryo-sensitive period it is 1:44. These sample size calculations are based on a one-sided approach because pregnancy exposure registries are designed to detect safety signals rather than to examine potential protective effects. Based on the formula for cohort design described in Strom's Pharmacoepidemiology (68): N=1/[p(1-R)]2x [Z 1-α√((1+1/k)U(1-U))+Z1-β√(pR(1-Rp)+(P(1-P))/k)]2 where p is the incidence of disease in unexposed; R is the minimum relative risk to detect; k is the ratio of unexposed controls to exposed; and U=(Kp+pR)/(k+1).

	Any artemisinin compound	AL	ASa	MAS	AS-SP	Art (IV/IM)	AQAS	DHA-PPQ
First-trimester exposures	1025	544	188	89	88	63	40	18
Major malformations (*P*=0.7%)[b]	2.1	2.6	4.0	5.9	5.9	7.1	9.5	15.5
Specific birth defect (*P*=0.1%)	4.6	6.4	12.5	21.5	22.0	28.0	41.0	80.0
Exposures in embryo-sensitive period[c]	615	326	112	53	52	37	24	10
Major malformations (*P*=0.7%)	2.5	3.1	5.1	7.6	7.7	9.5	12.5	25.0
Specific birth defect (*P*=0.1%)	5.9	8.4	17.2	30.0	31.0	41.0	56.0	120.0

AL, artemether-lumefantrine; AQAS, amodiaquine-artesunate; AS, artesunate; AS-SP, artesunate-sulfadoxine-pyrimethamine; Art, artesunate; DHA-PPQ, dihydroartemisinin-piperaquine; IM, intramuscular; IV, intravenous; MAS, mefloquine-artesunate

[a] Treatment categories are not mutually exclusive as some cases were exposed to multiple class of artemisinin treatment.

[b] Based on major malformations detectable at birth by systematic surface examination observed across studies to date.

[c] Estimated at 60% of all first-trimester exposures based on studies included in the meta-analysis.

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