

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

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1. Background

Malaria infection during pregnancy is a major public health problem, with substantial risks for the mother, her fetus and the newborn. In areas with moderate to high transmission of *Plasmodium falciparum*, the World Health Organization (WHO) recommends a package of interventions for controlling malaria and its effects during pregnancy, which includes the promotion and use of insecticide-treated nets (ITNs), the administration during pregnancy of intermittent preventive treatment with sulfadoxine-pyrimethamine (IPTp-SP), and appropriate case management through prompt and effective treatment of malaria in pregnant women (1).

During the last few years, WHO has observed a slowing of efforts to scale-up IPTp-SP in a number of countries in Africa. Although there may be several reasons for this, an important factor is confusion among health workers about sulfadoxine-pyrimethamine administration for intermittent preventive treatment in pregnancy.

At a recent WHO evidence review (2), a meta-analysis of 7 trials evaluating IPTp-SP was undertaken. It showed that 3 or more doses of IPTp-SP were associated with higher mean birth weight and fewer low birth weight (LBW) births than 2 doses of IPTp-SP. The estimated relative risk reduction for LBW was 20% (95% CI 6-31). This effect was consistent across a wide range of SP resistance levels. The 3+ dose group also was found to have less placental malaria. There were no differences in serious adverse events between the two groups (3).

Based on this evidence review, in October 2012, WHO updated the recommendations on IPTp-SP as outlined below, and urges national health authorities to disseminate this

update widely and ensure its correct application. IPTp-SP is an integral part of WHO's three-pronged approach to the prevention and treatment of malaria in pregnancy, which also includes the use of insecticide-treated nets and prompt and effective case management.

2. New WHO recommendations for IPTp-SP

All possible efforts should be made to increase access to IPTp-SP in all areas with moderate to high malaria transmission¹ in Africa, as part of antenatal care services. WHO recommends a schedule of at least four antenatal care visits during pregnancy.

- Starting as early as possible in the **second** trimester, IPTp-SP is recommended for all pregnant women at **each** scheduled antenatal care (ANC) visit until the time of delivery, provided that the doses are given at least **one month apart**. SP should not be given during the first trimester of pregnancy; however, the last dose of IPTp-SP can be administered up to the time of delivery without safety concerns (4).
 - IPTp-SP should ideally be administered as directly observed therapy (**DOT**) of three tablets sulfadoxine/pyrimethamine (each tablet containing 500mg/25mg SP) giving the total required dosage of 1500mg/75mg SP.
 - SP can be given either on an empty stomach or with food.
 - SP should not be administered to women receiving co-trimoxazole prophylaxis due to a higher risk of adverse events.
 - WHO recommends the administration of folic acid at a dose of 0.4mg daily; this dose may be safely used in conjunction with SP. Folic acid at a daily dose equal or above 5mg should not be given together with SP as this counteracts its efficacy as an antimalarial.
- In some countries of sub-Saharan Africa, transmission of malaria has been reduced substantially due to the successful implementation of malaria control efforts. In the absence of data to help determine when to stop IPTp-SP, WHO recommends that countries continue to provide IPTp-SP until data to guide this decision making is available.
- There is currently insufficient evidence to support a general recommendation for the use of IPTp-SP outside Africa.

¹ "Moderate transmission" areas are meso-endemic areas in which the prevalence rate of malaria is 11–50% during most time of the year among children from 2 to 9 years old. In these areas, the maximum prevalence of malaria infection occurs in childhood and adolescence, though it may not be unusual to acquire the first infection as an adult.

"High transmission" areas are hyperendemic and holo-endemic areas in which the prevalence rate of malaria is over 50% during most time of the year among children from 2 to 9 years old. In these areas, practically all individuals have acquired their first infection by late infancy or early childhood.

Source: Parasitological confirmation of malaria diagnosis – Report of a WHO technical consultation, Geneva, 6-8 October 2009. Geneva, World Health Organization, 2010.

http://whqlibdoc.who.int/publications/2010/9789241599412_eng.pdf

3. Considerations for implementing the new IPTp-SP recommendations

For more information, please refer to Annex 2: Frequently Asked Questions.

Administration and scale up

- Every effort should be made to integrate IPTp-SP with initiatives for promoting focused antenatal care (FANC)² services. WHO recommends a schedule of at least four antenatal care visits. IPTp-SP should be delivered at each scheduled ANC visit (except during first trimester and with doses given at least one month apart), and compliance with antenatal care should be encouraged as much as possible.
- WHO recommends that SP be given at each scheduled ANC visit except during the first trimester. SP can be given every month until the time of delivery, with doses given at least one month apart. This will ensure that a high proportion of women receive at least three doses of SP during pregnancy.
- SP should be made available at antenatal care clinics, so that pregnant women have immediate access to IPTp-SP during routine care. SP should ideally be given as directly observed treatment (DOT), since this ensures that pregnant women take the full dose.
- If a woman presents to an antenatal care clinic with symptoms of malaria, these symptoms should be investigated before the administration of IPTp-SP. If the woman tests positive for malaria – by either microscopy or rapid diagnostic test (RDT) – she should be treated following national case management guidelines. If she is negative, she should receive IPTp-SP.

Management of side effects

- Despite the known side effects associated with sulfonamides, SP for intermittent preventive treatment in pregnancy is generally very well tolerated. Mild and transient side effects including nausea, vomiting, weakness and dizziness have been reported by some women, particularly with the first dose of SP. Studies have demonstrated that side effects tend to decrease with the administration of further doses. (5, 6) Side effects should be discussed openly and managed in the ANC.

Quality, efficacy and resistance

- Only SP of proven quality (i.e., in line with international standards such as the International Pharmacopoeia [Ph. Int.]³), should be used.
- In order to preserve SP efficacy for IPTp-SP, all possible efforts should be made to avoid SP use as monotherapy for the treatment of clinical cases of malaria.

² Focused Antenatal Care (FANC) is defined as the minimum package of evidence-based services to all pregnant women during ANC to promote health, detect existing diseases, prevent and detect complications of pregnancy and encourage birth preparedness.

Source: Antenatal Care Randomized Trial: Manual for the Implementation of the New Model. Geneva, World Health Organization, 2002.

http://whqlibdoc.who.int/hq/2001/WHO_RHR_01.30.pdf

³ <http://www.who.int/medicines/publications/pharmacopoeia/overview/en/index.html>

Reserving available SP stocks for use as intermittent preventive treatment in pregnancy at antenatal care clinics limits the risk of stock outs due to non-recommended use as monotherapy for clinical cases. Reserving SP for dispensing from the pharmacy and giving SP to take at home can both inhibit the use of IPTp-SP by pregnant women.

- In several countries in Africa, some *P. falciparum* parasites carry quintuple mutations linked to SP resistance – which are associated with *in vivo* therapeutic failure to SP. However, recent evidence suggests that IPTp-SP remains effective in preventing the adverse consequences of malaria on maternal and fetal outcomes in areas where a high proportion of *P. falciparum* parasites carry these quintuple mutations. Therefore, IPTp-SP should still be administered to women in such areas (7).

Co-administration of other medication

- High doses of folic acid (i.e. daily dose equal to 5mg or above) have been shown to counteract the efficacy of SP as an antimalarial, and thus only the low dose (i.e. 0.4mg daily) should be co-administered with SP.
- SP should not be administered concurrently with co-trimoxazole prophylaxis due to their redundant mechanisms of action and synergistic worsening of adverse drug reactions. Therefore, HIV-infected pregnant women who are already receiving co-trimoxazole prophylaxis should not receive IPTp-SP (4).

Insecticide-treated nets

- Insecticide-treated nets should be provided to pregnant women as early in pregnancy as possible. Women should be encouraged to use ITNs throughout the entire pregnancy, as well as during the postpartum period when the risk of malaria is also increased. IPTp-SP is not a replacement for ITN use; both interventions provide important benefits.

4. Expected benefits

- IPTp-SP prevents the adverse consequences of malaria on maternal and fetal outcomes, such as placental infection, clinical malaria, maternal anaemia, fetal anaemia, low birth weight and neonatal mortality (8).
- IPTp-SP has recently been shown to be highly cost-effective for both prevention of maternal malaria and reduction of neonatal mortality in areas with moderate or high malaria transmission (9).
- Despite the spread of SP resistance, IPTp-SP continues to provide significant benefit, resulting in protection against both neonatal mortality (protective efficacy 18%) and low birth weight (21% reduction in LBW) under routine program conditions (10).

5. Relevant on-going research

- Monitoring IPTp-SP effectiveness and the safety of multiple doses is essential and should continue. Research is on-going to define the best methodology for such monitoring.
- Cost-effectiveness modelling studies are on-going to evaluate the level of malaria transmission below which IPTp-SP is no longer cost-effective. The risks and benefits of SP administration also need to be taken into account when considering recommendations on IPTp-SP implementation in low transmission⁴ settings.
- One observational study in Tanzanian women in an area with high levels of quintuple mutation, and where the parasite *dhps* resistance mutation of codon 581 was also present, showed increased placental parasite density and placental signs of inflammation in women reporting use of IPTp-SP shortly before delivery (11). These findings have not been confirmed in other studies and need further investigation. (12, 13)
- Monitoring the programmatic effectiveness of IPTp-SP delivery within ANC is essential to ensure the protection of pregnant women against the adverse outcomes of malaria in pregnancy. WHO is working with partners to develop a tool for monitoring the programmatic effectiveness of this intervention.
- Operational research to understand the barriers for low IPTp-SP uptake is on-going.
- Other relevant on-going research includes areas such as alternative strategies (e.g., Intermittent Screening and Treatment) and alternative medicines (e.g., azithromycin, dihydroartemisinin-piperaquine and mefloquine) for potential future use for intermittent preventive treatment in pregnancy.

⁴ “Low transmission” areas are hypo-endemic areas in which the prevalence rate of malaria is 10% or less during most of the year among children aged 2–9 years. Malaria infection and disease may occur at a similarly low frequency at any age, as little immunity develops and people may go through life without being infected.

Source: Parasitological confirmation of malaria diagnosis – Report of a WHO technical consultation, Geneva, 6-8 October 2009. Geneva, World Health Organization, 2010.

http://whqlibdoc.who.int/publications/2010/9789241599412_eng.pdf

Annex 1: Frequently Asked Questions

The purpose of this document is to provide guidance to both national policy makers and health care providers on the implementation of the WHO recommendations for intermittent preventive treatment of malaria in pregnancy using sulfadoxine-pyrimethamine (IPTp-SP). It answers frequently asked questions about the safety and efficacy of IPTp-SP, as well as questions about translating the new WHO Policy Recommendation issued in October 2012 into clinical practice.

Administration of SP

- **How many antenatal clinic visits does WHO recommend?**

WHO recommends a schedule of at least four antenatal care visits during pregnancy. The WHO AFRO Regional Office has prepared a new Focused Antenatal Care (FANC) Training Manual which outlines 4 ANC visits during the second and third trimesters. In addition, a booking visit in the first trimester may be scheduled to promote early entry into care. It is recommended that IPTp-SP be administered at all scheduled ANC visits, starting at the beginning of the second trimester. ITNs should be distributed as early as possible in the first trimester.

- **Why should IPTp-SP be avoided in the first trimester of pregnancy?**

There is limited evidence of potential teratogenicity when SP is used in the first trimester (4, 14). Thus, and until more safety data becomes available, this medicine should not be used during the first trimester. During these early weeks of pregnancy, a woman should protect herself against malaria by using an insecticide-treated net.

- **When is the earliest point in time when IPTp-SP can be safely administered in pregnancy?**

IPTp-SP can be administered safely at the beginning of the second trimester, starting at the beginning of the 13th week.

- **How can the beginning of second trimester be determined?**

The second trimester begins at 13 weeks. In the absence of gestational dating by ultrasound, the beginning of the second trimester can be determined by measuring fundal height which may serve as a proxy for gestational age. The fundal height corresponds to the distance between the symphysis pubis and the top of the uterus, in centimetres. At the beginning of the second trimester around 13 weeks of gestational age, the fundal height is around 13 cm. However, there is some variation in the fetal growth, and it is not unusual that some women present a fundal height that is slightly smaller or larger than expected. In addition, quickening (i.e. the first detection by the woman of fetal movement) is used in many countries to determine if a woman is in her second trimester. However, it is not a marker of the beginning of the second trimester. While some pregnant women experience quickening as early as 16 weeks, others may not do so until 20 weeks of gestation.

- **How many doses of IPTp-SP does the new policy recommend?**

The new policy recommends that SP should be given at each scheduled ANC visit except during the first trimester, and it can be repeated every month with the doses given at least one month apart until the time of delivery. The previous WHO policy recommendation proposed that IPTp-SP be delivered at each ANC visit in order to ensure that pregnant women received at least two doses of SP. However, this resulted in many countries adopting a policy that recommended the administration of SP only twice during pregnancy. The new WHO policy recommendation calls for the administration of IPTp-SP at each ANC visit, starting as early as possible during the second trimester. This recommendation reflects the need to increase in the number of SP doses. This decision was based on the most recent evidence that among pregnant women in sub-Saharan Africa, intermittent preventive

treatment in pregnancy with 3+ doses of SP was associated with a higher birth weight and lower risk of LBW than compared to the standard two-dose regimens. (3) The new policy does not refer to a specific number of doses, as experience has shown that once the policy states a specific number of doses, even if qualified (e.g. "minimum of 3 doses," "3 or more doses," or "at least 3 doses"), this becomes a programmatic target for many countries. The new policy, calling only for administration of IPTp-SP at each ANC visit except during the first trimester and with the doses given at least one month apart until the time of delivery, is not restrictive and the implementation can be modified should the number of recommended ANC visits increase in the future.

- **What is the maximum number of doses of IPTp-SP that can be administered during pregnancy?**

The new policy does not recommend a maximum number of doses of IPTp-SP, as previously noted. SP can be safely administered from the beginning of the second trimester until delivery, provided that doses are given one month apart.

- **How late in pregnancy can the last dose of SP be administered?**

The last dose of SP can be administered up to the time of delivery without safety concerns. Previously there was concern that the administration of SP late in pregnancy could result in kernicterus. However, review of the evidence suggests that there is no clinical association between SP use and kernicterus, despite the extensive use of SP and related compounds to prevent maternal malaria and treat congenital toxoplasmosis in near-term pregnant women and newborns.

Iron and folic acid supplementation

- **What daily dose of iron and folic acid supplementation does WHO recommend during pregnancy?**

Folic acid requirements are increased in pregnancy because of the rapidly dividing cells in the fetus and elevated urinary losses. WHO recommends iron and folic acid supplementation in pregnant women at a dose of 30-60mg of elemental iron⁵ plus 0.4mg of folic acid, daily (15). Every effort should be made to ensure that low dose folic acid (0.4mg or 400µg) is available and provided as part of routine antenatal care.

- **What daily dose of iron and folic acid supplementation does WHO recommend for treating anaemia in pregnancy?**

If a woman is diagnosed with anaemia in a clinical setting, WHO recommends treatment with 120mg elemental iron daily (given in two separate doses, i.e., 60mg in the morning and 60mg in the evening⁴) and 0.4mg folic acid supplementation until her haemoglobin concentration rises to normal (16). She can then switch to the standard antenatal dose to prevent recurrence of anaemia, i.e. 30-60mg of elemental iron plus 0.4mg of folic acid, daily.

- **What are the clinical indications for higher dose folic acid (at doses of 5mg or above) during pregnancy?**

Folic acid at a dose of 5mg is recommended for prevention of neural tube defects among women who have previously delivered a child with a neural tube defect. Folic acid supplementation after the first month of pregnancy will not prevent neural tube defects, as the neural tube closes by day 28 of pregnancy.

⁵ Note: 60mg of elemental iron equals 300mg of ferrous sulfate heptahydrate, 180mg of ferrous fumarate or 500mg of ferrous gluconate.

- **How long should SP be withheld if a pregnant woman is receiving 5mg of folic acid?**

Folic acid at a daily dose equal or above to 5mg should not be given together with SP as this counteracts the antimalarial efficacy of SP. There is presently no scientific consensus on how long SP should be withheld. However, expert opinion states that withholding SP for two weeks after administration of 5mg or more of folic acid, as is the practice in many countries, is likely to be too short an interval between treatments. Strong advice should be given by the health care provider to the pregnant women to use her ITN and to immediately come back in case of malaria symptoms for proper diagnosis and treatment.

Efficacy and resistance

- **Why is SP still effective for intermittent preventive treatment in pregnancy but should not be used as monotherapy for the treatment of confirmed clinical cases of malaria?**

Treatment efficacy is determined by testing how well the medicine works to cure malaria in young children, who have very little immunity to malaria. Evidence shows that SP prevents consequences of malaria in pregnant women, who have already had a number of malaria infections and thus a certain level of immunity (7). It is thought that SP primarily works through a prophylactic effect.

For the treatment of uncomplicated malaria, WHO recommends different medicines during the first, second and third trimester; for details on the different treatment options please refer to the WHO Guidelines for the Treatment of Malaria (17).

The use of SP monotherapy should be restricted to pregnant women for IPTp-SP only; this will also prevent IPTp-SP stock-outs in facilities, which are often due to misuse of SP for treatment of uncomplicated malaria.

- **Why should IPTp-SP be continued in areas with high resistance to SP?**

Recent evidence demonstrates that SP is associated with higher mean birth weight and fewer low birth weight births across a wide range of SP resistance levels (3). Even in areas where a high proportion of *P. falciparum* parasites carry these quintuple mutations, IPTp-SP remains effective in preventing the adverse consequences of malaria on maternal and fetal outcomes (7).

Transmission intensity and deployment of IPTp-SP

- **How does WHO define low, moderate and high malaria transmission?**

“Low transmission” areas are hypo-endemic areas in which the prevalence rate of malaria is 10% or less during most of the year among children aged 2–9 years. Malaria infection and disease may occur at a similarly low frequency at any age, as little immunity develops and people may go through life without being infected.

“Moderate transmission” areas are meso-endemic areas in which the prevalence rate of malaria is 11–50% during most time of the year among children from 2 to 9 years old. In these areas, the maximum prevalence of malaria infection occurs in childhood and adolescence, though it may not be unusual to acquire the first infection as an adult.

“High transmission” areas are hyper-endemic and holo-endemic areas in which the prevalence rate of malaria is over 50% during most time of the year among children from 2 to 9 years old. In these areas, practically all individuals have acquired their first infection by late infancy or early childhood.

- **Even if transmission has been reduced substantially, should administration of IPTp-SP continue?**

Yes. In some countries of sub-Saharan Africa, transmission of malaria has been reduced substantially due to the successful implementation of malaria control efforts. To maintain this impact, control interventions should be sustained. In addition, it is important to maintain IPTp-SP delivery systems for possible changes to new, more effective antimalarials which might replace SP for intermittent preventive treatment in pregnancy in the future. For these two reasons, IPTp-SP should be continued in these countries for the present. There is currently insufficient evidence on the level of malaria transmission below which the risks and cost for IPTp-SP exceed its benefits and when the intervention should be stopped. On-going research is in advanced stages to determine if there is a transmission threshold below which IPTp-SP should be suspended, as well as trials to evaluate alternative medicines to SP for intermittent preventive treatment in pregnancy.

Monitoring

- **How should the implementation of the new IPTp-SP policy recommendations be monitored?**

WHO recommends monitoring the implementation of the new IPTp-SP policy via routine monitoring systems and household surveys. Each dose of IPTp-SP given should be recorded in order that the proportion of the pregnant women receiving each dose (i.e., IPTp-1, IPTp-2, IPTp-3 and IPTp-4) can be monitored. Health providers should be encouraged to administer and record SP doses given at each scheduled antenatal visit. ANC registers and the Health Management Information System (HMIS) forms will need to be adapted to now also record the third and fourth doses of SP for IPTp-SP. Demographic Health Surveys (DHS) reports and certain national survey instruments will also need to be updated to monitor the implementation of the new recommendations.

Cost

- **What are the costs associated with adopting the new policy recommendations?**

SP is an inexpensive medicine, and there are minimal costs to the health service associated with increasing the actual number of recommended doses. In addition, most countries already have a delivery system for IPTp-SP in place, which is often integrated into a comprehensive Focused Antenatal Care (FANC) package. New infrastructure does not need to be adopted. Countries, however, may require investments associated with reviewing national guidelines to ensure harmonization and disseminating updated training packages and Information, Education and Communication (IEC) materials or job aids, as well as adapting tools to capture new indicators.

Annex 2: Annotated Bibliography

1. WHO (2004). *A strategic framework for malaria prevention and control during pregnancy in the African region*. Brazzaville, World Health Organization, Regional Office for Africa, 2004 (AFR/MAL/04/01).

http://whqlibdoc.who.int/afro/2004/AFR_MAL_04.01.pdf

2. WHO Evidence Review Group: Intermittent Preventive Treatment of malaria in pregnancy (IPTp) with Sulfadoxine-Pyrimethamine (SP). WHO Headquarters, Geneva, 9-11 July 2012. Meeting report. Geneva, World Health Organization, 2012.

http://www.who.int/malaria/mpac/sep2012/iptp_sp_erg_meeting_report_july2012.pdf

3. Kayentao K. et al. (2013). Intermittent preventive therapy for malaria during pregnancy using 2 vs 3 or more doses of sulfadoxine-pyrimethamine and risk of low birth weight in Africa: systematic review and meta-analysis. *Journal of the American Medical Association*. 2013 Feb 13;309(6):594-604. doi: 10.1001/jama.2012.216231.

<http://www.ncbi.nlm.nih.gov/pubmed/23403684>

This article presents the results from a meta-analysis on 7 trials, including 6281 pregnancies. It showed that 3 or more doses of SP for IPTp was associated with higher mean birth weight (MD=55g, 95% CI 29-83, $I^2=0\%$) and fewer low birth weight (LBW) births (RR=0.80, 95% CI 0.69-0.94, $I^2=0\%$), corresponding to a relative risk reduction of 20% (95% CI 6-31) for LBW and an absolute risk reduction of 33 per 1000 births (95% CI 10-52). The effect was consistent across a wide range of SP resistance levels (0% to 96% dihydropteroate-synthetase K540E mutations). The 3+dose group also had less placental malaria (RR=0.51; 95% CI, 0.38-0.68; $I^2=0\%$, in 6 trials). In primi+secundigravidae, the risk of moderate-severe maternal anaemia was lower in the 3+dose group (RR=0.60; 95% CI, 0.36-0.99; $I^2=20\%$; in 6 trials). There were no differences in serious adverse events (3).

4. Peters PJ et al. (2007). Safety and toxicity of sulfadoxine-pyrimethamine: implications for malaria prevention in pregnancy using intermittent preventive treatment. *Drug Safety*. 2007;30(6):481-501.

<http://www.ncbi.nlm.nih.gov/pubmed/?term=peters+malaria+pregnancy+drug+safety+2007>

This paper is a review on the safety and toxicity of SP and highlights that no clinical association between SP use and kernicterus has been reported despite its extensive use to treat maternal malaria and congenital toxoplasmosis in near-term pregnant women and newborns. It concludes that SP has a favourable safety profile delivered as IPTp. In addition, this article highlights that SP should not be administered concurrently with co-trimoxazole because of the potential for worsening adverse drug reactions.

5. Clerk CA et al. (2008). A randomized, controlled trial of intermittent preventive treatment with sulfadoxine-pyrimethamine, amodiaquine, or the combination in pregnant women in Ghana. *Journal of Infectious Diseases*. 2008 Oct 15;198(8): 1202-11. doi: 10.1086/591944.

[http://www.ncbi.nlm.nih.gov/pubmed/?term=Clerk+CA%2C+Bruce+J%2C+Affipunguh+PK%2C+Mensah+N%2C+Hodgson+A%2C+et+al.+\(2008\)+A+randomized%2C+controlled+trial+of+intermittent+preventive+treatment+with](http://www.ncbi.nlm.nih.gov/pubmed/?term=Clerk+CA%2C+Bruce+J%2C+Affipunguh+PK%2C+Mensah+N%2C+Hodgson+A%2C+et+al.+(2008)+A+randomized%2C+controlled+trial+of+intermittent+preventive+treatment+with)

The study, performed in Ghana from June 2004 through February 2007, examined efficacy, safety, and tolerance of amodiaquine (AQ) or the combination of AQ and SP (SPAQ) as possible alternative treatments. Women were individually randomized to receive IPTp with SP (n=1328), AQ (n= 986), or SPAQ (n=1328). Delivery outcomes and the incidence of adverse events were investigated for all women. Women who received AQ or SPAQ were more likely to report adverse events than were those who received SP. The effects of IPTp with AQ or SPAQ on maternal anemia and LBW were comparable to the effects of IPTp with SP; however, IPTp regimens that contain AQ are unlikely to be useful as an alternative to IPTp with SP in Ghana, because of a high frequency of associated adverse events.

6. Tagbor H et al. (2006) Efficacy, safety, and tolerability of amodiaquine plus sulfadoxine-pyrimethamine used alone or in combination for malaria treatment in pregnancy: a randomised trial. *Lancet*. 2006 Oct 14;368(9544): 1349-56.

<http://www.ncbi.nlm.nih.gov/pubmed/17046467>

The study aimed to assess the safety and efficacy of amodiaquine alone or in combination with sulfadoxine-pyrimethamine as alternative regimens. 900 pregnant women with a gestational age of 16 weeks or more who had a positive test result and *P. falciparum* asexual stage parasitaemia were enrolled and randomly assigned chloroquine, sulfadoxine-pyrimethamine, amodiaquine, or amodiaquine plus sulfadoxine-pyrimethamine. The primary outcome was parasitological failure by day 28 of treatment; additionally, reports of adverse effects were solicited and monitored during follow-up visits. Analysis was by intention to treat. No serious liver toxic effects or white-blood-cell dyscrasias were noted. Minor side-effects were reported more often on day 3 by women receiving amodiaquine (86%) or amodiaquine plus sulfadoxine-pyrimethamine (90%) than those receiving sulfadoxine-pyrimethamine (48%) or no antimalarial drugs (34%; $p < 0.0001$ for every comparison).

7. ter Kuile FO, van Eijk AM, Filler SJ (2007). Effect of sulfadoxine-pyrimethamine resistance on the efficacy of intermittent preventive therapy for malaria control during pregnancy: a systematic review. *Journal of the American Medical Association*. 2007 Jun 20;297(23):2603-16.

<http://www.ncbi.nlm.nih.gov/pubmed/?term=ter+kuile+Effect+of+sulfadoxine-pyrimethamine+resistance+on+the+efficacy+of+intermittent+preventive+therapy+for+malaria+control+during+pregnancy>

The focus of this study was to determine the effect of increasing resistance to sulfadoxine-pyrimethamine on the efficacy of IPT during pregnancy in Africa. Multiple databases and the trial register and bibliographic database of the Malaria in Pregnancy Library were searched for relevant studies published between 1966 and December 2006. The analysis concluded that in areas in which 1 of 4 treatments with sulfadoxine-pyrimethamine fail in children by day 14, the 2-dose IPT with sulfadoxine-pyrimethamine regimen continues to provide substantial benefit to HIV-negative semi-immune pregnant women. However, more frequent dosing is required in HIV-positive women not using co-trimoxazole prophylaxis for opportunistic infections.

8. Menéndez et al. (2010). Malaria Prevention with IPTp during pregnancy reduces neonatal mortality. *Public Library of Science PLoS ONE*. 2010 Feb 26;5(2):e9438. doi: 10.1371/journal.pone.0009438.

<http://www.ncbi.nlm.nih.gov/pubmed/20195472>

Randomized placebo-controlled trial (RCT) evaluating the efficacy of 2-dose IPTp-SP that followed up 997 newborns until 12 months of age in Mozambique. It was found that IPTp reduced neonatal mortality by 61% (95%CI 7.4 – 83.4%).

9. Sicuri E. et al. (2010). Cost-effectiveness of intermittent preventive treatment of malaria in pregnancy in southern Mozambique. *Public Library of Science PLoS ONE*. 2010 Oct 15;5(10):e13407. doi: 10.1371/journal.pone.0013407.

<http://www.ncbi.nlm.nih.gov/pubmed/?term=sicuri+cost-effectiveness+intermittent+pregnancy+mozambique>

Article presenting the results of a cost-effectiveness analysis of IPTp delivered through the antenatal clinic and in the context of insecticide-treated nets in Mozambique. IPTp-SP was found to be highly cost-effective for both prevention of maternal clinical malaria and reduction of neonatal mortality. The intervention remained cost-effective even with a significant increase in drug and other intervention costs.

10. Eisele TP. et al. (2012). Malaria prevention in pregnancy, birth weight, and neonatal mortality: a meta-analysis of 32 national cross-sectional datasets in Africa. *The Lancet Infectious Diseases*. 2012 Dec;12(12):942-49.

[http://dx.doi.org/10.1016/S1473-3099\(12\)70222-0](http://dx.doi.org/10.1016/S1473-3099(12)70222-0)

Recently published meta-analysis of 32 national cross-sectional datasets assessing the effectiveness of IPTp or ITNs at preventing LBW and neonatal mortality under routine programme conditions in malaria endemic African countries. The results show that the use of IPTp or ITNs decrease the risk of neonatal mortality (protective efficacy of 18%, 95%CI 4-30) and of low birth weight (protective efficacy of 21%, 95%CI 14-27) in women in their first or second pregnancy.

11. Harrington WE et al. (2009). Competitive facilitation of drug-resistant *Plasmodium falciparum* malaria parasites in pregnant women who receive preventive treatment. *Proceedings of the National Academy of Sciences*. 2009 Jun 2; 106(22):9027-32. doi: 10.1073/pnas.0901415106. Epub 2009 May 18.

<http://www.ncbi.nlm.nih.gov/pubmed?term=harrington%20competitive%20pregnant%20receive>

Molecular analysis of placental blood samples from 87 women found an increase of mean parasite density of placental parasitemia in samples from women reporting IPTp use in Tanzania. IPTp use was associated with increased prevalence of resistance allele at DHPS codon 581, the significance of which needs further investigation.

12. Taylor SM, et al. (2012). Antenatal receipt of sulfadoxine-pyrimethamine does not exacerbate pregnancy-associated malaria despite the expansion of drug-resistant *Plasmodium falciparum*: Clinical outcomes from the QuERPAM Study. *Clinical Infectious Diseases*. 2012 Jul;55(1):42-50. doi: 10.1093/cid/cis301. Epub 2012 Mar 22.

<http://www.ncbi.nlm.nih.gov/pubmed/22441649>

Molecular analysis of placental and peripheral blood samples from delivering women over 8 years in Malawi. 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.

13. Menendez C, et al. (2011). HIV and placental infection modulate the appearance of drug-resistant *Plasmodium falciparum* in pregnant women who receive intermittent preventive treatment. *Clinical Infectious Diseases*. 2011 Jan 1; 52(1):41-8. doi: 10.1093/cid/ciq049.

<http://www.ncbi.nlm.nih.gov/pubmed?term=menendez%20hiv%20placental%20infection%20resistant%20intermittent>

Molecular analysis of samples from peripheral and placental blood of delivering women participating in a RCT of IPTp-SP vs placebo. The study showed an increase of 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.

14. Hernández-Díaz et al. (2000). Folic acid antagonists during pregnancy and the risk of birth defects. *New England Journal of Medicine*. 2000 Nov 30;343(22):1608-14

<http://www.ncbi.nlm.nih.gov/pubmed/11096168>

The study examined the associations between maternal use of folic acid antagonists in the first trimester and congenital malformations. It compared data on exposure to folic acid antagonists that act as dihydrofolate reductase inhibitors and to certain antiepileptic drugs for 3870 infants with cardiovascular defects, 1962 infants with oral clefts, and 1100 infants with urinary tract defects with data for 8387 control infants with malformations the risk of which is not reduced after vitamin supplementation. Mothers were interviewed within six months after delivery about their medication use. Folic acid antagonists may increase the risk not only of neural-tube defects, but also of cardiovascular defects, oral clefts, and urinary tract defects. The folic acid component of multivitamins may reduce the risks of these defects.

15. WHO (2012). Guideline: *Daily iron and folic acid supplementation in pregnant women*. Geneva, World Health Organization, 2012.

http://www.who.int/nutrition/publications/micronutrients/guidelines/daily_ifa_supp_pregnant_women/en/index.html

16. WHO/UNICEF/UNU (2001). *Iron deficiency anaemia. Assessment, prevention, and control: A guide for programme managers*. Geneva, World Health Organization, 2001 (WHO/NHD/01.3).

http://www.who.int/nutrition/publications/micronutrients/anaemia_iron_deficiency/WHO_NHD_01.3/en/index.html

17. WHO (2010). *Guidelines for the Treatment of Malaria, Second Edition*. Geneva, World Health Organization, 2010.

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