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

World Health Organization

WHO policy brief for the implementation of intermittent preventive treatment of malaria in pregnancy using sulfadoxine-pyrimethamine (IPTp-SP)

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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 seven trials evaluating IPTp-SP was undertaken. It showed that three or more doses of IPTp-SP were associated with higher mean birth weight and fewer low birth weight (LBW) births than two 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.

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 transmission[1] 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 500 mg/25 mg SP) giving the total required dosage of 1500 mg/75 mg 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 0.4 mg daily; this dose may be safely used in conjunction with SP. Folic acid at a daily dose equal or above 5 mg 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

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 the 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.
- In some countries of sub-Saharan Africa, transmission of malaria has been reduced substantially due to the successful implementation of malaria control efforts. At present there is insufficient evidence on the level of malaria transmission below which the risks and cost for IPTp-SP exceed its benefits and when it should be stopped. Because of natural fluctuations in the incidence of malaria from year to year, the low cost of IPTp-SP and the challenges of reintroducing IPTp after a potential withdrawal, countries should be cautious in discontinuing IPTp-SP until more information is obtained that would allow the formulation of more specific guidelines.

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.

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[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

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. 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 5 mg or above) have been shown to counteract the efficacy of SP as an antimalarial, and thus only the low dose (i.e. 0.4 mg 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.

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 programme conditions *(10)*.

[3] http://www.who.int/medicines/publications/pharmacopoeia/overview/en/index.html

Relevant ongoing research

- Monitoring IPTp-SP effectiveness and the safety of multiple doses is essential and should continue. Research is ongoing 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. There are currently insufficient data to define the point at which IPTp-SP should be withdrawn. The risks and benefits of SP administration also need to be taken into account when considering recommendations on IPTp-SP implementation in low transmission[4] settings.
- One observational study in Tanzanian women in an area with high levels of quintuple mutation, and where the sextuple 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)*. Another study, also undertaken in Tanzania, monitored a cohort of 924 pregnant women receiving IPTp-SP in an area with declining malaria transmission. It was reported that pregnant women infected with malaria and carrying the sextuple haplotype mutation gave birth to children with lower (359 g) birth weights *(12)*. These findings have not been confirmed in other studies and need further investigation *(13, 14)*.
- 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 ongoing.
- Other relevant ongoing research includes the evaluation of alternative strategies (e.g., Intermittent screening and treatment) and alternative medicines (e.g. azithromycin-chloroquine, dihydroartemisinin-piperaquine) for potential future use for intermittent preventive treatment in pregnancy. Mefloquine, at a dose of 15 mg/kg as single or split dose, is not recommended for IPTp due to its low tolerability, with vomiting and dizziness reported in up to 30% of the pregnant women studied *(15)*.[5]

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[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

[5] Recommendation of the Malaria Policy Advisory Committee (MPAC) in September 2013, following the outcome of a review of multicentre studies by the Evidence Review Group (ERG) on Intermittent Preventive Treatment of malaria in pregnancy (IPTp).

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 four 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, 16)*. 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 thirteenth 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 three doses," "three or more doses," or "at least three 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 30-60 mg of elemental iron[6] plus 0.4 mg of folic acid, daily *(17)*. Every effort should be made to ensure that low dose folic acid (0.4 mg or 400 micrograms) 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 120 mg elemental iron daily (given in two separate doses, i.e., 60 mg in the morning and 60 mg in the evening) and 0.4 mg folic acid supplementation until her haemoglobin concentration rises to normal *(18)*. She can then switch to the standard antenatal dose to prevent recurrence of anaemia, i.e. 30-60 mg of elemental iron plus 0.4 mg of folic acid, daily.

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

  Folic acid at a dose of 5 mg 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.

[6] Note: 60 mg of elemental iron equals 300 mg of ferrous sulfate heptahydrate, 180 mg of ferrous fumarate or 500 mg 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 5 mg 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 5 mg 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 *(19)*.

  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 quintuple mutations, IPTp-SP remains effective in preventing the adverse consequences of malaria on maternal and fetal outcomes *(7)*. Two studies undertaken in pregnant women receiving IPTp-SP in Tanzania showed increased placental parasite density, placental signs of inflammation and lower birth weights (359 g) in areas with sextuple mutations *(11, 12)*. These findings have not been confirmed on other studies and need further investigation *(13, 14)* – (see section 5. Relevant ongoing research).

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