Implementing Malaria in Pregnancy Programs in the Context of World Health Organization Recommendations on Antenatal Care for a Positive Pregnancy Experience

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This technical brief highlights recommendations for the prevention and treatment of malaria in pregnancy (MiP) in the context of the World Health Organization (WHO) *Recommendations on Antenatal Care for a Positive Pregnancy Experience*,[1] published in 2016. While intermittent preventive treatment during pregnancy using sulfadoxine-pyrimethamine (IPTp-SP) recommendations in this brief focus on moderate to high transmission areas in Africa, guidance regarding the use of nets and prompt and effective case management is relevant to all areas with ongoing transmission. Readers should also refer to the key underlying documents, specifically the WHO *Guidelines for the Treatment of Malaria*, third edition,[2] and the WHO *Policy Brief for the Implementation of Intermittent Preventive Treatment of Malaria in Pregnancy Using Sulfadoxine-Pyrimethamine (IPTp-SP)*.[3]

Background

MiP is a major public health problem with substantial risks for mothers and their babies. Each year, MiP is responsible for 20% of stillbirths in sub-Saharan Africa, 11% of all newborn deaths in sub-Saharan Africa, and 10,000 maternal deaths globally.[4,5,6] WHO recommends a package of interventions for controlling malaria and its effects during pregnancy. In areas where malaria is a risk, WHO recommends delivery and use of insecticide-treated nets (ITNs) and effective management of cases by providing

[1] World Health Organization. *WHO recommendations on antenatal care for a positive pregnancy experience*. 2016. Retrieved January 10, 2017, from http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/anc-positive-pregnancy-experience/en/.
[2] World Health Organization. *Guidelines for treatment of malaria*. Third edition. April 2015. Retrieved from http://www.who.int/malaria/publications/atoz/9789241549127/en/.
[3] World Health Organization. *WHO policy brief for the implementation of intermittent preventive treatment of malaria in pregnancy using sulfadoxine-pyrimethamine (IPTp-SP)*. 2013. Retrieved from http://www.who.int/malaria/publications/atoz/iptp-sp-updated-policy-brief-24jan2014.pdf?ua=1.
[4] Lawn J, Blencowe H, Waiswa P, et al. 2016. Stillbirths: rates, risk factors, and acceleration towards 2030. *The Lancet*. 387(10018), 587-603. doi: 10.1016/s0140-6736(15)00837-5.
[5] Desai M, ter Kuile FO, Nosten F, et al. 2007. Epidemiology and burden of malaria in pregnancy. *The Lancet Infectious Diseases*. 7(2), 93-104. doi: 10.1016/S1473-3099(07)70021-X.
[6] Guyatt HL and Snow RW. 2001. The epidemiology and burden of Plasmodium falciparum-related anemia among pregnant women in sub-Saharan Africa. *The American Journal of Tropical Medicine and Hygiene*, 64(1-2 Suppl), 36-44. doi:10.4269/ajtmh.2001.64.36.

prompt quality diagnosis and effective treatment of malaria infections. In areas with moderate to high transmission of *Plasmodium falciparum*, WHO additionally recommends the administration of IPTp-SP that is quality assured.[7] SP is the only drug currently recommended for administration in the context of IPTp, and it is important to note that SP continues to show benefit for both the mother and her baby, even in areas of SP resistance.[8] Further, a recent study by Chico et al. found women who received two or more doses of IPTp-SP were protected not only from adverse outcomes related to malaria, but also from some sexually transmitted infections/reproductive tract infections.[9]

The delivery of high-quality antenatal care (ANC) is essential for successful MiP programming. WHO's *Recommendations on Antenatal Care for a Positive Pregnancy Experience* now promote a minimum of eight contacts between pregnant women and the health system versus the previously recommended four ANC visits. This new WHO ANC model highlights that a woman's contact with her provider should be more than a simple visit. It should be an opportunity for comprehensive, high-quality care, including medical care, support, and the provision of timely and relevant information throughout pregnancy. Depending on the context of the country, the definition of contact may include scheduled ANC visits and information sessions for pregnant women with relevant caretakers at the household, community, and health facility levels. These increased opportunities to support women during their pregnancies are an incentive for countries to deliver comprehensive care, including MiP interventions, to pregnant women.

Considerations for the Implementation of MiP Programming

Timing of IPTp-SP

The new ANC recommendations need to be adapted to each country's context. Complementing the use of an ITN, and prompt and effective case management, the ANC contact schedule for MiP should be **applied flexibly**[10] so that pregnant women always receive IPTp-SP when eligible, starting as early as possible during the second trimester of pregnancy. Table 1 highlights a proposed ANC schedule for countries implementing IPTp, adapted based on the WHO ANC recommended schedule.

It is important to keep in mind that:

- Determining gestational age by clinical examination, especially early in pregnancy, can be challenging. WHO recommends that countries continue to use what is currently practiced for dating—either abdominal palpation or symphysis-fundal height. Doing one ultrasound scan, ideally during the first trimester, where available, is another opportunity to determine early gestational age, among other potential benefits for the pregnancy.
- The period between 13 and 20 weeks is critical for irreversible negative consequences of MiP, when parasite densities are highest,[11,12] and major benefit can be achieved from malaria prevention. For effective MiP programming, contact with a health provider early in the second trimester (between 13 and 16 weeks) is critical to ensuring timely access to the first dose of IPTp-SP for maximal impact.

[7] World Health Organization. *A strategic framework for malaria prevention and control during pregnancy in the African region*. 2004.
[8] Desai M, Gutman J, Taylor SM, et al. 2016. Impact of sulfadoxine-pyrimethamine resistance on effectiveness of intermittent preventive therapy for malaria in pregnancy at clearing infections and preventing low birth weight. *Clinical Infectious Diseases*, 62(3), 323-333. doi:10.1093/cid/civ881.
[9] Chico RM, Chaponda EB, Ariti C, Chandramohan D. Sulfadoxine-pyrimethamine exhibits dose-response protection against adverse birth outcomes related to malaria and sexually transmitted and reproductive tract infections. *Clinical Infectious Diseases*. 64(8):1043-1051. doi: 10.1093/cid/cix026.
[10] http://apps.who.int/iris/bitstream/10665/250796/1/9789241549912-eng.pdf?ua=1; Page 106 notes that "that the frequency and exact timing of some of these ANC practices and interventions—especially related to malaria, tuberculosis and HIV—may need to be adapted, based on the local context, population and health system."
[11] Chico RM, Chaponda EB, Ariti C, Chandramohan D. Sulfadoxine-pyrimethamine exhibits dose-response protection against adverse birth outcomes related to malaria and sexually transmitted and reproductive tract infections. *Clinical Infectious Diseases*. 64(8):1043-1051. doi: 10.1093/cid/cix026.
[12] Brabin BJ. *The risks and severity of malaria in pregnant women*. 1991. World Health Organization.

Table 1: 2016 ANC contact schedule with proposed timelines for implementation of malaria in pregnancy interventions#

ANC Contact Schedule and Proposed Time of IPTp-SP Administration *(To be adapted to country context, also considering disease burden and health needs)*		**MiP-related Interventions and Considerations during ANC Contacts**
Contact 1: Up to 12 weeks		• Register pregnant women, provide ITNs, and counsel on their use. Screen for HIV. • Administer 30 to 60 mg of elemental iron and 400 µg (0.4 mg) of folic acid daily. These supplements should be given as early as possible in pregnancy and continue throughout pregnancy. • **Counsel to return for a visit at 13 to 16 weeks (see contact 1a below) to receive the first dose of IPTp-SP (as directed by national guidelines).*** • Counsel on prompt diagnosis and effective treatment/malaria case management during pregnancy.
Additional contact (1a): *In moderate to high malaria transmission areas in Africa where IPTp-SP is policy,* ***a contact should be made early*** *in the* ***second trimester (13 to 16 weeks) to administer SP as early as possible***.	IPTp-SP dose 1	Remember: • Do not administer IPTp-SP before week 13 of pregnancy. • Administer the first IPTp-SP dose **as early as possible in the second trimester** to fully benefit from the protective capacity in this critical period of pregnancy.† • **Administer the second dose of IPTp-SP one month later**. • Administer the following doses of IPTp-SP starting from the scheduled contact at 20 weeks, **observing at least one-month intervals between SP doses**. • SP can be **safely** administered from the beginning of the second trimester until the time of delivery. • One full dose of IPTp-SP consists of 1,500 mg/75 mg SP (i.e., three tablets of 500 mg/25 mg SP). • Provide IPTp-SP by directly observed treatment. • Pregnant women on co-trimoxazole should not receive IPTp-SP due to an increased risk of adverse events when both drugs are given in parallel. • Continue to administer 30 to 60 mg of elemental iron and 400 mcg (0.4 mg) of folic acid. • Continue counseling as above.
Contact 2: 20 weeks	IPTp-SP dose 2	
Contact 3: 26 weeks	IPTp-SP dose 3	
Contact 4: 30 weeks	IPTp-SP dose 4	
Contact 5: 34 weeks	IPTp-SP dose 5	
Contact 6: 36 weeks	No SP administration if last dose was received at contact 5 in week 34	
Contact 7: 38 weeks	IPTp-SP dose 6 (if no dose was received at contact 6 in week 36)	
Contact 8: 40 weeks		
Pregnant women should receive MiP interventions as appropriate, even when they come at weeks not designated in the contact schedule. Despite the known side effects associated with sulfonamides, SP for IPTp 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 (§,‡). Side effects should be discussed openly and managed in the ANC.		

This schedule is a suggested adaptation of the WHO ANC schedule for countries implementing IPTp; training should highlight that women attending off-schedule should be attended to appropriately, and that it is the interval, rather than the specific weeks, which are most critical

* It is recommended that the first dose of IPTp-SP be given as early as possible in the second trimester of pregnancy to ensure optimal protection from malaria for the mother and her baby. However, pregnant women who come later in pregnancy can and should receive their first dose anytime (as long as it is not in the first trimester), with following doses being given at least one month apart. When malaria-endemic countries are planning their ANC programming, they may wish to add another contact to allow for monthly dosing of IPTp-SP.

† Pregnant women should receive their first dose of IPTp-SP as early as possible at the beginning of the second trimester, defined as 13 weeks gestation (i.e., 12 completed weeks or 13 weeks and zero days).

§ Clerk CA et al. 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;198(8): 1202-11. http://www.ncbi.nlm.nih.gov/pubmed/18752443

‡ Tagbor H et al. Efficacy, safety, and tolerability of amodiaquine plus sulfadoxinepyrimethamine used alone or in combination for malaria treatment in pregnancy: a randomised trial. *Lancet*. 2006;368(9544): 1349-56. http://www.ncbi.nlm.nih.gov/pubmed/17046467

WHO's *Recommendations on Antenatal Care for a Positive Pregnancy Experience and Optimizing Health Worker Roles for Maternal and Newborn Health*[13] promote task shifting of components of ANC, including the provision of IPTp, from staff in health facilities to a broad range of cadres, including auxiliary nurses, nurses, midwives, and doctors. As countries consider the application of the new WHO ANC recommendations and acceleration of MiP programming, delivery approaches at the community level that complement ANC offer promise to achieve increased coverage during the antenatal period, including malaria prevention. Countries could consider piloting and scaling up community approaches that help to increase IPTp uptake and ANC coverage.

Note: While the standard practice in many countries is giving the first dose of IPTp-SP at quickening (mother's first awareness of fetal movement), this practice can leave both the pregnant woman and fetus unprotected for a long period, depending on variations in a woman's perception and timing of quickening.

Frequency of IPTp-SP

Following administration of the first dose of IPTp as early as possible in the second trimester (i.e., 13 to 16 weeks), pregnant women should receive an additional dose of IPTp-SP at each contact with a health care worker trained to deliver IPTp-SP until the time of delivery, ensuring that doses of IPTp-SP are administered at least one month apart. WHO does not recommend a maximum number of doses of IPTp-SP. SP can be safely administered from the beginning of the second trimester until delivery.

Sourcing of quality-assured SP

The availability of quality-assured SP for IPTp is critical to ensure pregnant women have optimal protection from malaria, in addition to using an ITN and accessing effective case management. Countries should procure the drug from manufacturers who produce quality-assured SP (see checklist below) and ensure supporting partners are doing the same.

ITN use

All pregnant women should sleep under an ITN as early as possible in pregnancy, though ideally before becoming pregnant. Providing an ITN at the first contact will help to keep the pregnant woman and her fetus safe from malaria. Additionally, all efforts should be made to ensure women of reproductive age have access to and sleep under an ITN so that they are protected against malaria if they become pregnant.

Key points regarding ITN use include:

- Free delivery of an ITN at the first ANC visit is an incentive to attend antenatal care and provides the pregnant woman with a lifesaving tool for herself and her baby. Sleeping under the ITN will also protect her baby during the first year of life.
- Countries need to plan and budget for continuous ITN distribution to pregnant women at the first ANC contact, in addition to forecasting, procuring, and distributing ITNs for campaigns targeting the whole population.

Effective case management

Pregnant women with signs and symptoms of malaria need immediate access to quality diagnosis and effective treatment. Health care providers must be able to consistently assess all women of reproductive age for pregnancy, and test and treat these women for malaria in accordance with national and WHO guidelines.[14]

As malaria prevalence in a country declines, the clinical manifestations of malaria infection in pregnant women become more severe due to reduced immunity. Having strong public and private health systems in place to rapidly detect and treat MiP becomes increasingly important as malaria transmission levels fall.

[13] World Health Organization. *Optimizing health worker roles for maternal and newborn health*. 2012. http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/978924504843/en.
[14] World Health Organization. *Guidelines for treatment of malaria*. Third edition. April 2015. Retrieved from http://www.who.int/malaria/publications/atoz/9789241549127/en/.

Women living with HIV

Women living with HIV are at increased risk of all adverse consequences of malaria infections due to their compromised immune responses. All pregnant women should be screened for HIV at first ANC contact. Pregnant women living with HIV and taking co-trimoxazole prophylaxis should not receive SP, as concomitant administration of SP and co-trimoxazole could increase adverse drug reactions. When taken daily, co-trimoxazole provides protection against MiP. Despite this, it is especially important that pregnant women living with HIV sleep under an ITN, and seek prompt diagnosis and receive effective treatment if they experience symptoms of malaria.

Iron and folic acid supplementation

Since iron and folic acid requirements increase in pregnancy, WHO recommends supplementation with 30 to 60 mg of elemental iron and 400 mcg (0.4 mg) of folic acid daily for pregnant women to prevent maternal anemia, puerperal sepsis, low birthweight, and preterm birth.[15] These supplements should be given as early as possible in pregnancy and continue throughout pregnancy.

To improve maternal and newborn outcomes, intermittent oral iron and folic acid supplementation with 120 mg of elemental iron and 2,800 mcg (2.8 mg) of folic acid once weekly is recommended for pregnant women who cannot take daily iron supplements due to side effects and for populations in which less than 20% of pregnant women have anemia.

Every effort should be made to ensure that low-dose folic acid (i.e., 0.4 mg, equivalent to 400 mcg) is available and provided as part of routine antenatal care. High doses of 5 mg of folic acid and greater counteract the antimalarial efficacy of SP and should not be given along with SP. In areas where only high-dose folic acid is available, there is presently no scientific consensus on how long high doses of folic acid should be withheld following the dose of SP. Many countries suggest withholding high doses of folic acid (5 mg or more) for two weeks after administration of SP, but this may shorten the duration of efficacy of SP. Countries should advocate for procurement of low-dose folic acid, which does not interfere with the efficacy of SP. In cases where high-dose folic acid is resumed two weeks following SP dosing, the health care provider should strongly advise the pregnant woman to use her ITN, and seek care immediately for proper diagnosis and treatment if signs and symptoms of malaria are present.[16]