Introducing Intermittent Preventive Treatment of Malaria during Pregnancy for Ethiopia: Evidence brief

Who is this Evidence brief for?

Policymakers, their support staff, and other stakeholders with an interest in the problem addressed by this Evidence brief.

Why was this Evidence brief prepared?

To inform policy makers by summarizing the best available evidence about the problem and its solution.

What is evidence brief?

This Evidence briefs brings together global and local evidence to inform policy makers about health policies and programs.

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Key Findings

Malaria in pregnancy (MiP) is a major, preventable cause of maternal morbidity and adverse 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 anemia 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 Ethiopia IPTp-SP is not in use so far but based on the fact of current malaria transmission intensity as well as proven effectiveness, safety, cost effectiveness and easily applicability to our current system it worth to be introduced in our country by complementing with available interventions.

Preface

The purpose of this report

The purpose of this evidence brief is to summarize the best available evidence regarding IPTp-SP intervention and implementation considerations to be introduced in Ethiopia for prevention of malaria in pregnancy. It is not intended to prescribe or proscribe this specific intervention. Rather, its purpose is to allow policymakers and stakeholders to systematically and transparently consider the available evidence about the likely impacts of this intervention with other already available interventions in preventing malaria in pregnancy.

How this report was prepared

This evidence brief brings together global research evidence and local evidence on IPTp-SP to prevent malaria in pregnancy. We searched for relevant evidence describing the problem in Ethiopian context, the impact of this intervention, barriers to implement, and implementation strategies to address these barriers. Different studies like relevant systematic reviews, RCTs, and other relevant and up to date studies were searched.

Limitations of this report

This evidence brief only focuses on this specific intervention and other viable options are not included. The intention of this evidence brief is not to replace available interventions rather to complement with this specific intervention to maximize the prevention of malaria during pregnancy in Ethiopia.

Background

Malaria infection during pregnancy is a significant public health problem with substantial risks for the pregnant woman, her fetus, and the newborn child. Infection with Plasmodium vivax, as with Plasmodium falciparum, leads to chronic anemia and placental malaria infection, reducing the birth weight and increasing the risk of neonatal death. Pregnant women are more likely than non-pregnant women to become infected with malaria and to have severe infection. The effects of malaria during pregnancy include spontaneous abortion, preterm delivery, low birth weight, stillbirth, congenital infection, and maternal death (1-2).

The symptoms and complications of malaria in pregnancy vary according to malaria transmission intensity in the given geographical area, and the individual's level of acquired immunity. In high-transmission settings, where levels of acquired immunity tend to be high, plasmodium falciparum infection is usually asymptomatic in pregnancy. Yet, parasites may be present in the placenta and contribute to maternal anemia even in the absence of documented peripheral parasitaemia. Both maternal anemia and placental parasitaemia can lead to low birth weight, which is a significant contributor to infant mortality. In high-transmission settings, the adverse effects of plasmodium falciparum infection during pregnancy are most pronounced for women in their first pregnancy (3).

In low-transmission settings, where women of reproductive age have relatively little acquired immunity to malaria, malaria in pregnancy is associated with anemia and increased risk of severe malaria. In such settings, all pregnant women, regardless of the number of times they have been pregnant, are highly vulnerable to malaria (4).

Malaria in pregnancy is a major public health problem each year. It is responsible for 20% of stillbirths and 11% of all newborn deaths in Sub-Saharan Africa, and 10,000 maternal deaths globally. According to Ethiopian Federal Ministry of Health, Health Management Information System (HMIS) report between June 2016 and July 2017 about 1,530,739 confirmed malaria illnesses including 1,059,847 P. falciparum and 470,892 P. vivax malaria illnesses were reported. In addition, there were 225,009 clinical malaria cases and 356 deaths were reported during the period (5).

Malaria is a significant challenge to social and economic development in Ethiopia. In endemic areas, malaria has affected the population during main harvesting seasons, affecting productive capacity at a time when there is the greatest need for agricultural work. The disease has also been associated with loss of earnings, low school attendance, and high treatment cost, and when it happened to pregnant women its consequence even worse (6).

World Health Organization (WHO) recommends a package of interventions for controlling malaria and its effects during pregnancy. These include 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 (1-3).

Despite its effectiveness in many African countries IPTp-SP is not implemented so far in Ethiopia. The Ethiopian Ministry of health (MOH) does not support the use of IPTp with sulfadoxine-pyrimethamine. The main reasons were; (i) relatively low intensity of malaria transmission in most areas of Ethiopia, and (ii) the anticipated minimal expected benefits compared with the relatively high costs of implementation. However, in many Sub-Saharan African countries it remains effective even in low transmission areas (6-7)

In Ethiopia currently the other two interventions recommended by WHO are in use for malaria in pregnancy but as many studies suggested these three interventions complement each other and when implemented together effectiveness increases. Therefore, this evidence brief is prepared to inform policy makers and others influential bodies to consider the implementation of this intervention in our country.

Description of Intermittent preventive treatment in pregnancy with SulfadoxinePyrimethamine (IPTp-SP)

Intermittent preventive treatment of malaria in pregnancy is a full therapeutic course of anti-malarial medicine given to pregnant women at routine antenatal care visits, regardless of whether the recipient is infected with malaria. It reduces maternal malaria episodes, maternal and fetal anemia, placental parasitaemia, low birth weight, and neonatal mortality.

World Health Organization recommends all possible efforts should be made to increase access to IPTp-SP in all areas with moderate to high malaria transmission in Africa, as part of antenatal care services.

Basic issues on administration of IPTp-SP:

- It 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.
- It can be given either on an empty stomach or with food.
- Administration of folic acid at a dose of 0.4 mg daily; this dose may be safely used in conjunction with SP
- SP should not be administered concurrently with cotrimoxazole prophylaxis due to their redundant mechanisms of action and synergistic worsening of adverse drug reactions. Therefore, HIV-infected pregnant women who are already receiving cotrimoxazole prophylaxis should not receive IPTp-SP

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. Sulfadoxine/pyrimethamine 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 (1-4).

Effectiveness

According to a meta-analysis study of 32 national cross-sectional datasets in Africa, 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).IPTp-SP still effective for intermittent preventive treatment in pregnancy but should not be used as mono therapy for the treatment of confirmed clinical cases of 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. It is thought that SP primarily works through a prophylactic effect (8-9).

Safety

Although few drugs in pregnancy can be considered completely safe, sulfadoxine pyrimethamine when delivered as IPTp has a favorable safety profile. Sulfadoxine/pyrimethamine use in IPTp programs in Africa, with 2-4 treatment doses over 6 months, has been well tolerated in multiple IPTp trials. However, sulfadoxine/pyrimethamine should not be administered concurrently with cotrimoxazole given their redundant mechanisms of action and synergistic worsening of adverse drug reactions. Therefore, HIV-infected pregnant women in malaria endemic areas who are already receiving cotrimoxazole prophylaxis should not also receive IPTp-SP.

Folic acid supplementation is recommended for all pregnant women to reduce the rate of congenital anomalies but high doses of folic acid (5 mg/day) may interfere with the anti malarial efficacy of sulfadoxine/pyrimethamine. However, the recommended standard dose of folic acid supplementation (0.4 mg/day) does not affect anti malarial efficacy and may provide the optimal balance to prevent neural tube defects and maintain the effectiveness of IPTp-SP (10).

Applicability

Among the approximately 840 million persons at risk of malaria in endemic countries in sub-Saharan Africa, an estimated 35 million pregnant women could benefit from IPTp each year. As of 2016, 36 African countries have adopted a policy of providing 3 or more doses of IPTp-SP to pregnant women (11).

Complementing the use of an ITN, and prompt and effective case management, the ANC contact schedule for Malaria in Pregnancy could be applied flexibly so that pregnant women always receive IPTp-SP when eligible, starting as early as possible during the second trimester of pregnancy (12).

Expected benefits

IPTp-SP prevents the adverse consequences of malaria on maternal and fetal outcomes, such as placental infection, clinical malaria, maternal anemia, fetal anemia, low birth weight and neonatal mortality. 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 (13-14).

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 (15).

Economic Consideration

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. Studies conducted in Mozambique suggested that this intervention is highly cost-effective when compliance with ITNs use is high. It is a very cheap prevention when provided through the ANC. Net intervention costs for 1000 pregnant women were 13.17 US$, Thus, IPTp-SP is likely to be a cost saving intervention in a context of very limited economic resources for health care (16).

When provided as part of the existing antenatal care package, IPTp-SP more than three doses in combination with insecticide-treated bed nets provides highly cost-effective protection from malaria for pregnant women in most of sub-Saharan Africa (16-17).

Implementation Consideration

Intermittent preventive treatment in pregnancy with SP is an inexpensive medicine, and there are minimal costs to the health service associated with increasing the actual number of recommended doses. It is easily integrated with already established comprehensive Focused Antenatal Care (FANC) package in our country. The only investments required may be associated with reviewing national guidelines to ensure harmonization and disseminating

updated training packages and Information, Education and Communication (IEC) materials or job aids (18-19).

To achieve ambitious national malaria elimination plan main target groups like pregnant women and newborn should get special attention so that FMOH should exhaustively use available evidences globally and nationally on this issue. In addition to above mentioned facts to consider IPTp-SP intervention for prevention of malaria during pregnancy; the following enablers, possible barriers, and their implementation considerations are listed below.

Enablers

- Having already established antenatal care at all levels of the health facilities and the increasing trend ANC coverage from time to time which could help to integrate IPTp-SP easily.
- Availability of Health extension program with more than 40,000 Health extension workers to facilitate static and outreach services
- Commitment from government and ambitious malaria elimination program in place at national level
- Commitment from international and local donors and stakeholders towards malaria elimination program
- Best experience available in many Sub-Saharan African countries which may only need to customize in our context
- Introducing this intervention does not require huge investment and it can be easily integrated with available systems and programs

Barriers

The barriers and implementation considerations are summarized in Table 1.

Table 1: Barriers and implementation strategies

Barriers	Descriptions	Implementation strategies
Administration by DOT	SP is recommended to be administered only by direct observation (DOT) of health professionals	By using outreach sessions of HEWs and primary health care professionals it can be administered without compromising DOT
Associated side effects	SP have some minor side effects such as nausea, vomiting, weakness and dizziness	It is rare and minor but when it happens, it should be discussed openly and managed accordingly.
It needs budget allocation	As it is new intervention it may incur some cost to introduce in our health system	Considering the additional benefits associated with this intervention and many enabling situations in place it worth to take initiative and allocate budget
Absence of IPTp-SP treatment guideline	Absence of national IPTp-SP treatment guideline could lead health care professional's misuse of SP for treatment of uncomplicated malaria.	There should be IPTp-SP treatment guideline in place to use for preventive treatment rather than for treatment of uncomplicated malaria.
Uncertainty of health professionals to SP administration	Health professionals might not familiar with SP administration could affect the medication adherence	Simplified IPTp messages and health worker training should be provided to improve adherence towards SP

References

1. WHO (2013). WHO Evidence Review Group on Intermittent Preventive Treatment (IPT) of malaria in pregnancy. WHO Headquarters, Geneva, 9-11 July 2013. Draft Recommendations on Intermittent Preventive Treatment in Pregnancy (IPTp). http://www.who.int/malaria/mpac/mpac_sep13_erg_ipt_malaria_pregnancy_report.pdf
2. 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
3. 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
4. WHO Evidence Review Group meeting report: Malaria in Pregnancy, WHO Headquarters, Geneva, 13–16 July 2015
5. Roll Back Malaria, Working Group Meeting: Implementing Malaria in Pregnancy Programs in the Context of World Health Organization Recommendations on Antenatal Care for a Positive Pregnancy Experience, January, 2018. www.rollbackmalaria.com/organizational-structure/working-groups/mipwg/
6. Ethiopia malaria operational plan, 2019, Minstry of Health, Addis Ababa, Ethiopia
7. National strategic plan for malaria prevention control and elimination in Ethiopia 2011 – 2015 August 2010 Addis Ababa, Ethiopia
8. 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
9. 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/17536875
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
11. 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/18752443

12. Tagbor H et al. (2006) Efficacy, safety, and tolerability of amodiaquine plus sulfadoxinepyrimethamine used alone or in combination for malaria treatment in pregnancy: a randomised trial. Lancet. 2006 Oct 14; 368(9544): 1349-56.
13. 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
14. Minja et al. (2013). Plasmodium falciparum Mutant Haplotype Infection during Pregnancy Associated with Reduced Birthweight, Tanzania. Emerging Infectious Diseases. 2013; 19(9). doi: 10.3201/eid1909.130133. http://www.ncbi.nlm.nih.gov/pubmed/23969132
15. 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. Clin Infect Dis 2017; 64: 1043–51.
16. 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/20976217
17. Fernandes S, Sicuri E, Kayentao K, van Eijk AM, Hill J, Webster J et al. Cost-effectiveness of two versus three or more doses of intermittent preventive treatment for malaria during pregnancy in sub-Saharan Africa: a modelling study of meta-analysis and cost data. The Lancet. Global health. 2015; 3(3):e143-153.
18. 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
19. Desai M, Phillips-Howard PA, Odhiambo FO, Katana A, Ouma P, Hamel MJ et al. An analysis of pregnancy-related mortality in the KEMRI/CDC health and demographic surveillance system in western Kenya. PLoS One. 2013;8(7):e68733

Annexes

Annex 1. How this evidence brief was prepared

The problem that the evidence brief addresses was clarified iteratively through discussion among the authors, review of relevant documents and research. Research describing the problem was identified by reviewing government documents, routinely collected data, searching Pub Med and Google Scholar, through contact with key informants, and by reviewing the reference lists of relevant documents that were retrieved.

Strategies used to identify potential options to address the problem included considering interventions described in systematic reviews and other relevant documents, considering ways in which other jurisdictions have addressed the problem, consulting key informants and brainstorming.

We searched electronic databases of systematic reviews, including the Cochrane Library (CENTRAL, Cochrane Database of Systematic Reviews), Health Systems Evidence and supplemented these searches by checking the reference lists of relevant policy documents and with focused searches using PubMed, Google Scholar, and personal contacts to identify systematic reviews for specific topics. The final selection of reviews for inclusion was based on a consensus of the authors.

Potential barriers to implement this intervention were identified by brainstorming using a detailed checklist of potential barriers (SURE guide for identifying and addressing barriers) to implement health policies. Implementation strategies that address identified barriers were identified by brainstorming and reviewing relevant documents.

Annex 2. How WHO define malaria transmission intensity

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.

Acronyms

ANC	Ante Natal Care
DALY	Disability Adjusted Life Years
DOT	Direct Observation Therapy
EPHI	Ethiopian Public Health Institute
FMOH	Federal Ministry of Health
FANC	Focused Ante Natal Care
IEC	Information, Education and Communication
ICER	Incremental Cost Effectiveness Ratio
IPTp	Intermittent Preventive Treatment in Pregnancy
ITN	Insecticide Treated Nets
HEW	Health Extension Worker
HIV	Human Immuno Virus
HMIS	Health Management Information System
MIP	Malaria in Pregnancy
PF	Plasmodium Falciparum
PV	Plasmodium Vivax
SP	Sulphadoxine Pyremethamine
WHO	World Health Organization