MALARIA PROTECTION IN PREGNANCY: *A lifesaving intervention for preventing*

Introduction

The devastating consequences of *Plasmodium falciparum* malaria in pregnancy (MiP) are well documented; these include higher rates of maternal anemia and low birth weight (LBW) babies in areas of stable malaria transmission. In areas of unstable *P. falciparum* malaria transmission, pregnant women are at increased risk of severe malaria, death and still birth of the fetus. Approximately 11% of neonatal deaths in malaria endemic African countries are due to low birth weight resulting from *P. falciparum* infections in pregnancy.[1] However, until recently, there was limited documented evidence of the protective effect of malaria prevention in pregnancy on neonatal mortality. A recent meta-analysis of national survey datasets by Eisele *et al*, 2012 showed exposure to intermittent preventive treatment during pregnancy (IPTp) with sulfadoxine pyrimethamine (SP) and insecticide treated bed nets (ITNs) to be associated with reductions of both neonatal mortality and LBW under routine program conditions. Menéndez *et al*, 2010 also showed the protective role of IPTp-SP in reducing neonatal mortality under trial conditions. Further, Sicuri *et al*,[2] in the context of the Menéndez trial showed IPTp to be highly cost effective in the context of routine antenatal care (ANC) services. These studies highlight the critical importance of continuing IPTp as well as ITN use among pregnant women to prevent the adverse consequences of malaria in pregnancy.[3,4] This paper synthesizes the information and key findings from these articles and implications for MiP programs.

Background

In 2000, countries across sub-Saharan Africa signed the Abuja Declaration pledging to fight MiP; specifically, committing to give pregnant women access to IPTp-SP and ITNs as well as effective case management. By 2007, all 39 African countries with stable malaria transmission had adopted the World Health Organization (WHO) three-pronged approach: IPTp-SP during the 2nd and 3rd trimester, sleeping under an ITN, and prompt case management among pregnant women with symptoms of malaria.[5] Malaria in pregnancy is a maternal and newborn health issue, impacting both the mother and her newborn. In the best circumstances, countries have forged partnerships between Reproductive Health (RH) programs and Malaria Control (MC) programs to manage comprehensive implementation of MiP on a platform of focused ANC (where IPTp-SP and ITNs are accessed) and ensure technical oversight. In countries like Malawi, Zambia and Senegal, this has contributed to higher population coverage of IPTp-SP uptake and to an extent increased ITN use among pregnant women. Where these partnerships were and are not in place, national level policy documents between RH and MC are often not harmonized, adequate resources are not in place and implementation can be uncoordinated and sometimes duplicative.

In October 2012, the WHO Malaria Policy Advisory Committee (MPAC) reviewed guidance based on the most recent evidence of the efficacy and effectiveness of IPTp-SP in light of growing SP resistance in children and also potential SP resistance in pregnant women receiving IPTp-SP. **Based on the review the MPAC determined that frequent dosing of IPTp-SP is effective in reducing the consequences of MIP.** The new WHO guidance recommends:

In areas of moderate-to-high malaria transmission, IPTp with SP is recommended for all pregnant women at each scheduled ANC visit. WHO recommends a schedule of four ANC visits.

- The first IPTp-SP dose should be administered as early as possible during the 2nd trimester of gestation
- Each SP dose should be given at least 1 month apart
- The last dose of IPTp-SP can be administered up to the time of delivery, without safety concerns[6]

Malaria in Pregnancy: Preventing Neonatal Mortality and Low Birth Weight

Using a retrospective birth cohort from 32 national cross-sectional datasets in 25 African countries from 2000-2010, Eisele *et al* assessed the effectiveness of malaria prevention in pregnancy (IPTp or ITNs) under routine program conditions. Neonates born to women in their first or second pregnancies who self-reported taking at least two doses of IPTp-SP and/or had an ITN in their household continuously at least six months prior to giving birth was significantly associated with decreased risk of neonatal mortality (18%; $p<0.006$) and reduced odds of low birth weight (21%; $p<0.001$) when compared with newborn babies of mothers with no protection. The protective effect on both outcomes (neonatal mortality and low birth weight) held true for women of all parities.

In a randomized, placebo controlled trial of IPTp-SP in 1030 pregnant Mozambican women, Menéndez *et al* found use of IPTp was associated with a 61.3% reduction in neonatal mortality. Among the 997 live born babies (500 born to women in the placebo group and 497 to women in the IPTp-SP group) there were 25 neonatal deaths; 18 were born to women in the placebo group and 7 to women who received IPTp. Eighty percent of neonatal deaths occurred in the first week of life. In the context this same trial, Sicuri *et al* found IPTp-SP was highly cost effective for both prevention of maternal malaria and reduction of neonatal mortality, with an incremental cost-effectiveness ratio of US$1.02 per disability-adjusted life year averted.

Malaria in pregnancy is a significant contributor to neonatal mortality. IPTp-SP and ITNs continue to have an important and significant effect on reducing neonatal mortality and low birth weight and need to be recognized as interventions to reduce newborn mortality. Eisele's *et al* meta-analysis in programmatic settings is consistent with expectations but has not been previously demonstrated because all single studies were underpowered to examine this effect. It clarifies across the chain that MiP leads to multiple effects including placental infection and consequent nutrient transfer disruption and LBW; maternal anemia and newborn anemia and their effect on LBW as well, which contributes to neonatal mortality. Among other studies that have investigated this, Menéndez *et al* showed a substantial impact for MIP on neonatal survival, although other similar studies have not. Since IPTp-SP is a highly cost effective intervention, as shown by Sicuri *et al,* and combined with its effect on neonatal mortality and low birth weight – **prioritizing it as a key intervention for pregnant women (combined with ITN use and effective case management) should remain a priority across stable malaria transmission countries.** The WHO's recent policy update, confirms the critical importance of increasing the frequency of IPT-SP, in addition to ITN use among pregnant women and effective case management.

Considerations for Maternal & Newborn Health Programs and Malaria Programs

- IPTp-SP and ITNs continue to have an important and significant effect on reducing neonatal mortality and LBW and need to be recognized as interventions to reduce newborn mortality.
  - 3.3 million neonatal deaths occur every year;
  - ~120,000 of those neonatal deaths (11%) are likely related to malaria infection during pregnancy.[7]
- IPTp and ITNs reduce neonatal mortality even in programmatic settings, where use may be less than optimal and where SP resistance may exist.
- Not only is IPTp-SP lifesaving and straight forward to implement, it is also highly cost effective for both prevention of maternal malaria and reduction of neonatal mortality.
  - IPTp-SP as a key intervention for pregnant women, combined with ITN use and effective case management, should remain a priority across stable malaria transmission countries.
- These data indicate that Ministries of Health should aim for full coverage and scale up of these life-saving interventions.
  - Efforts should be made to provide ITNs to women as early in pregnancy as possible and to provide IPTp at every ANC visit, beginning in the 2nd trimester.
- Strengthening comprehensive ANC services including access to and demand for these services is critical to improve MiP outcomes.
  - Although the majority of women attend ANC at least once during pregnancy and often twice, IPTp-SP uptake as well as ITN coverage among pregnant women is alarmingly low across most countries. This is a major missed opportunity, at present.
- The new WHO guidance on IPTp-SP dosing and timing promotes frequent dosing of IPTp-SP to reduce the consequences of MiP.
  - This is in the context of a comprehensive approach, delivered through routine ANC services, including ITN use among pregnant women and effective case management.

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[1] Guyatt HL, Snow RW. Malaria in pregnancy as an indirect cause of infant mortality in sub-Saharan Africa. *Trans R. Soc Trop Med Hyg* 2001; 95: 569-76.
[2] Elisa Sicuri, Asucena Bardaji, Tacita Nhampossa, Maria Maixenchs, Ariel Nhacolo, Delino Nhalungo, Pedro L. Alonso, Clara Menéndez. Cost-Effectiveness of Intermittent Preventive Treatment of Malaria in Pregnancy in Southern Mozambique. *PLoS ONE;* Oct. 2010; Volume 5, Issue 10
[3] Clara Menéndez, Azucena Bardaji, Betuel Sigauque, Sergi Sanz, John J. Aponte, Samuel Mabunda, Pedro L. Alonso. Malaria Prevention with IPTp during Pregnancy Reduces Neonatal Mortality. *PLoS ONE*; Feb 2010; Vol. 5, Issue 2.
[4] Thomas P Eisele, David A Larsen, Philip A Anglewicz, Joseph Keating, Josh Yukich, Adam Bennett, Paul Hutchinson, Richard W Steketee. Malaria prevention in pregnancy, birthweight, and neonatal mortality; a meta-analysis of 32 national cross-sectional datasets in Africa. *The Lancet*. Published online Sept 18, 2012.
[5] Anna Maria van Ejik, Jenny Hill, Victor A Alegana, Viola Kirui, Peter W Gething, Feiko O ter Kuile, Robert W Snow. Coverage of malaria protection in pregnant women in sub-Saharan Africa: as synthesis and analysis of national survey data. *The Lancet*. Vol. 11. March 2011.
[6] WHO. http://www.who.int/malaria/iptp_sp_updated_policy_recommendation_en_102012.pdf October 2012
[7] Guyatt HL, Snow RW. Malaria in pregnancy as an indirect cause of infant mortality in sub-Saharan Africa. *Trans R. Soc Trop Med Hyg* 2001; 95: 569-76.