Value of additional chemotherapy for malaria in pregnancy

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In *The Lancet Global Health*, Silke Fernandes and colleagues[1] provide an important and timely assessment of the cost-effectiveness of increasing the doses of intermittent preventive treatment for malaria during pregnancy (IPTp) from two doses to three or more doses, as currently recommended by the WHO.

This analysis provides compelling evidence that the incremental reduction in low birthweight noted in women who receive additional doses of sulfadoxine pyrimethamine (SP) during pregnancy[2] will be highly cost-effective when included as part of standard antenatal care in most areas of sustained malaria transmission in Africa.

The demonstration that monthly IPTp-SP is cost-effective is important to both researchers and policymakers, and this result has clear implications for improving the health of both expectant mothers and their infants in this region. An estimated 32 million pregnancies occurred in such areas in 2010,[3] which would have the potential to lead to an estimated 0·7 million low birthweight deliveries attributable to malaria if these women were not protected from infection.[4]

However, some key questions remain concerning how best to provide protection from malaria during pregnancy. Perhaps the most pressing is why, despite IPTp-SP having demonstrable cost-effectiveness with the previously recommended two doses[5] and antenatal care coverage now being high across much of Africa, the proportion of women receiving even two courses of IPTp in many areas remains low.[6]

As the authors suggest, one contributing factor to this low uptake might be the emergence of resistance to SP, particularly in eastern Africa. SP is no longer efficacious for case management in such settings, and perception of SP as an ineffective drug might be undermining IPTp-SP. This factor has prompted researchers to look at alternatives to IPTp-SP such as the use of more efficacious or longer-lasting artemisinin combination therapies (ACTs), either on the basis of positive diagnosis from a rapid diagnostic test (RDT) at an antenatal care visit, or as an alternative presumptive therapy.[7]

It is reassuring that SP remains effective against low birthweight, the main determinant of cost-effectiveness in this analysis, in all but the most highly resistant areas (those with super-resistance conferred by six sequential resistance mutations).[2] Although in these areas the efficacy of SP is now substantially inhibited,[8,9] this constitutes a small proportion of east Africa. However, parasites with the preceding quintuple mutation are widespread throughout the region,[10] highlighting the need to continually monitor the progress of resistance and its effect on IPTp-SP.

Estimates used in this analysis suggest that additional doses of SP have the same proportional effect on all-cause low birthweight in both moderate and low-resistance settings.[7] This measure, however, depends on the proportion of all-cause low birthweight that is attributable to malaria. As a result, differences in SP effectiveness could feasibly be disguised if there is a higher proportion of malaria-attributable low birthweight in areas where SP is less effective. Similar arguments can be made about the potential limitations of using the impact of SP on all-cause low birthweight to compare effectiveness between higher and lower transmission settings.

The very fact that providing a greater number of doses of IPTp-SP is incrementally effective, even in settings where the parasite is sensitive,[2] also highlights the potential benefit of interventions using more effective drugs. This finding means there is either scope to improve clearance of existing infections or, if the gain from more IPTp-SP courses is due to longer prophylaxis, a longer-acting drug might achieve similar benefits with fewer administrations.

Data were also insufficient for Fernandes and colleagues[1] to extend their analysis to areas of low or unstable transmission, a situation that will hopefully become more common as malaria control progresses across Africa. In such situations, symptomatic disease during pregnancy is likely to cause an increased proportion of the overall burden,[11] and understanding how malaria-attributable risk of low birthweight and immunity to both placental infection and symptomatic disease change as transmission falls will become an increasingly important issue.

Any alternative strategy to IPTp-SP is likely to have its own challenges: concerns remain about providing ACTs during pregnancy to uninfected women; testing using RDTs is likely to be more costly, might miss some infections, and means that uninfected women

do not benefit from prophylaxis; and switching to case management of symptomatic women leaves many asymptomatic women unprotected from prolonged placental infection. The analysis by Fernandes and colleagues[1] is a clear benchmark by which to judge these various merits and limitations and thus is an important step towards ensuring a much higher proportion of women receive adequate care for malaria in pregnancy.

Patrick G T Walker, Matt Cairns
MRC Centre for Outbreak Analysis & Modelling, Department of Infectious Disease Epidemiology, Imperial College London, London, UK (MGTW); and MRC Tropical Epidemiology Group, London School of Hygiene & Tropical Medicine, London, UK (MC)
patrick.walker@imperial.ac.uk

PGTW and MC are supported by fellowships jointly funded by the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement. We declare no competing interests.

1 Fernandes S, Sicuri E, Kayentao K, 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. *Lancet Glob Health* 2015; **3:** 143–56.

2 Kayentao K, Garner P, van Eijk AM, et al. 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. *JAMA* 2013; **309:** 594–604.

3 Dellicour S, Tatem AJ, Guerra CA, Snow RW, ter Kuile FO. Quantifying the number of pregnancies at risk of malaria in 2007: a demographic study. *PLoS Med* 2010; **7:** e1000221.

4 Walker PGT, ter Kuile FO, Garske T, Menendez C, Ghani AC. Estimated risk of placental infection and burden of low birthweight attributable to *Plasmodium falciparum* malaria in Africa in 2010: a modelling study. *Lancet Glob Health* 2014; **2:** e460–67.

5 Sicuri E, Bardají A, Sigauque B, et al. Costs associated with low birth weight in a rural area of Southern Mozambique. *PloS one* 2011; **6:** e28744.

6 Van Eijk AM, Hill J, Larsen DA, et al. Coverage of intermittent preventive treatment and insecticide-treated nets for the control of malaria during pregnancy in sub-Saharan Africa: a synthesis and meta-analysis of national survey data, 2009–11. *Lancet Infect Dis* 2013; **13:** 1029–42.

7 Steketee RW. Malaria prevention during pregnancy—is there a next step forward? *PLoS Med* 2014; **11:** e1001734.

8 Harrington WE, Mutabingwa TK, Kabyemela E, Fried M, Duffy PE. Intermittent treatment to prevent pregnancy malaria does not confer benefit in an area of widespread drug resistance. *Clin Infect Dis* 2011; **53:** 224–30.

9 Gutman J, Kalilani L, Taylor S, et al. *Plasmodium falciparum* dihydropteroate synthetase-A581G mutation reduces effectiveness of sulfadoxine-pyrimethamine preventive therapy in Malawian pregnant women. *J Infect Dis* 2015; published online Jan 6. http://dx.doi.org/10.1093/infdis/jiu836.

10 Flegg JA, Patil AP, Venkatesan M, et al. Spatiotemporal mathematical modelling of mutations of the dhps gene in African *Plasmodium falciparum*. *Malaria J* 2013; **12:** 249.

11 Desai M, ter Kuile FO, Nosten F, et al. Epidemiology and burden of malaria in pregnancy. *Lancet Infect Dis* 2007; **7:** 93–104.