Institution:
UNIVERSITY OF LIVERPOOL and LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Unit of Assessment:
UOA1 - Clinical Medicine

Title of case study: The Epidemiology and Control of Malaria in Pregnancy

1. Summary of the impact

Malaria in pregnancy causes the deaths of 200,000 newborns and 10,000 mothers annually. The Liverpool School of Tropical Medicine is the coordinating centre of the global Malaria in Pregnancy Consortium. LSTM-led research from 2007 has contributed to the World Health Organisation's (WHO) estimates of the global burden of malaria in pregnancy, showing that 125M pregnancies are at risk, more than double previous estimates. The Consortium has also contributed to a better understanding of the low uptake of existing interventions by pregnant women, and identification of the best prevention strategies. Consequently, WHO updated its policy recommendations in 2007on intermittent-preventive-treatment for prevention of malaria in pregnancy, adopted in 37 sub-Saharan countries, and in 2012, already adopted in 9 countries.

2. Underpinning research

The Liverpool School of Tropical Medicine (LSTM) is the coordinating centre of the Malaria in Pregnancy Consortium (MiPc), established in 2007 and comprises 41 partner institutions in 29 countries. Professor Feiko Ter Kuile, LSTM Professor of Tropical Epidemiology (2003-present), is the CEO and Jenny Hill (1995-present) is Project Manager; both lead research activities. Additional LSTM researchers include: Stephanie Dellicour (2007-present), RA in pharmacovigilance; Dr Annemieke van Eijk (2009-present), Senior Clinical RA; and Dr Kassoum Kayentao (2010-present), LSTM PhD student based at the Malaria Research Training Centre, Mali.

Burden: Malaria is an important health and development challenge in Africa, where pregnant women and young children are most at risk. Until 2010, comprehensive and contemporary estimates of the number of pregnancies at risk of malaria and its consequent impact on maternal and newborn health were not available. Malaria in pregnancy contributes to a vicious cycle of ill-health in Africa, causing babies to be born with low birthweight (LBW), which increases the risk of newborn and infant deaths. Dellicour and ter Kuile, in collaboration with the University of Oxford, derived global estimates of the annual number of women who became pregnant in areas with malaria transmission [1], showing that 125m pregnancies are at risk, more than double previous World Health Organisation (WHO) estimates.

Increasing access: Hill and ter Kuile conducted field studies in Mali and Kenya and together with Van Eijk, compiled data on the progress of coverage of intermittent preventative therapy in pregnancy (IPTp) and insecticide treated nets (ITNs), the two interventions recommended by WHO for the prevention of malaria in pregnancy in sub-Saharan Africa. In two sequential meta-analyses in 2011 and 2013 [2,3], they showed that although uptake has improved it remains far below the goals set by Roll Back Malaria (RBM). Hill [4] identified key interacting barriers to access, delivery, and use of IPTp and ITNs and showed that these were relatively consistent across countries. Some could be resolved in the short term by simplification and standardisation of country IPTp policies and improved guidance to health providers, but others are entrenched within weak healthcare systems and require medium- to long-term strategies to improve antenatal care access and service provision.

Policy: The 2002 WHO recommendation of 2 doses of sulphadoxine-pyrimethamine (SP) as ITPp has been adopted in 37 African countries. High level resistance threatens its efficacy in some areas, and lack of data on the impact of SP resistance on the effectiveness of IPTp became a major concern for policy makers. In 2007, ter Kuile was requested by WHO to conduct a meta-analysis to address this question [5]. Findings showed that even though SP failed to achieve radical cure in at least 40% of children with acute malaria, it still performed very well as preventive therapy in semi-immune pregnant women and was associated with marked reductions in the risk of LBW, leading to a WHO recommendation to continue with IPTp-SP.

Professor ter Kuile's subsequent meta-analysis of seven randomised controlled trials of IPTp compared the standard 2-dose regimen of IPTp-SP against regimens providing SP 3 times or

monthly. It provided definitive evidence that 3 or more doses of SP is far more effective compared to 2-doses, reducing the risk of severe maternal anaemia in the mother by an additional 40% and the risk of LBW by an additional 20%, and was also well tolerated and safe [6].

3. References to the research

1. **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. (2010). PLoS Med 7: e1000221. Citations: 76. Impact Factor: 15.617

2. **van Eijk AM, Hill J**, Alegana VA, Kirui V, Gething PW, **ter Kuile FO**, Snow RW.. Coverage of malaria protection in pregnant women in sub-Saharan Africa: a synthesis and analysis of national survey data. (2011) Lancet Infect Dis 11: 190-207. Citations: 32. Impact Factor: 19.966.

3. **van Eijk AM**, **Hill J**, Larsen DA, Webster J, Steketee R, Eisele TP, **ter Kuile FO.**. 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. (2013) Lancet Infect Dis 13:1029-42. Citations: 0. Impact Factor: 19.966.

4. **Hill J**, **Hoyt J**, **van Eijk AM**, **D'Mello-Guyett L**, **Ter Kuile FO**, Steketee R, **Smith H,** Webster J. Factors Affecting the Delivery, Access, and Use of Interventions to Prevent Malaria in Pregnancy in Sub-Saharan Africa: A Systematic Review and Meta-Analysis. (2013). PLoS Med 0(7): e1001488. Citations: 0. Impact Factor: 15.253.

5. **ter Kuile FO**, **van Eijk AM**, Filler SJ. Effect of Sulfadoxine-Pyrimethamine Resistance on the Efficacy of Intermittent Preventive Therapy for Malaria Control During Pregnancy: A Systematic Review. (2007). JAMA. 297(23):2603-2616. Citations: 133. Impact Factor: 25.547.

6. **Kayentao K**, **Garner P**, **van Eijk AM**, Naidoo I, Roper C, Mulokozi A, MacArthur JR, Luntamo M, Ashorn P, Doumbo OK, **ter Kuile FO.** 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. (2013). JAMA 309: 594-604. Citations: 7. Impact Factor: 29.978.

Key Research Grants

2011–2015. **DFID/MRC/Wellcome Trust**. Intermittent screening and treatment or IPT for control of malaria in pregnancy in Indonesia, £2.1m, **Feiko ter Kuile** (PI)

2010–2015. **CDC Atlanta USA**. Prevention of Malaria cooperative agreement with the Malaria Branch, Centers for Disease Control and, £1.67m. **Feiko ter Kuile** (PI)

2009–2013. **European Developing Countries Clinical Trials Partnership (EDCTP)**. Optimisation of the existing dose and regimen of IPT with sulfadoxine-pyrimethamine for the prevention of MiP in the context of high coverage of insecticide treated nets and highly seasonal malaria transmission, £2.9m, **Feiko ter Kuile** (PI)

2007–2014. **Bill & Melinda Gates Foundation**. Malaria in Pregnancy Consortium, a global network of 41 research institutions £15m, **Feiko ter Kuile** (PI)

4. Details of the impact

Approximately 125 million women in malaria-endemic countries become pregnant every year, over 32 million of whom live in areas with intense transmission of *Plasmodium falciparum* [1]. This is estimated to result in 900,000 preventable LBW births each year and the deaths of 200,000 newborns and 10,000 mothers. Since 2007, LSTM research has contributed significantly to the formulation and maintenance of international and national policies specifically designed to reduce

this risk. Thus, policy makers, mothers and their newborns will have benefited from this research as 37 African countries benefited from continued use of IPTp (2007-present), and 9 recently updated their policy to more frequent doses (2012/13), which will have greater impact on LBW. [7]

LSTM's research to better define the global burden of MiP has revised WHO's global and region specific estimates of the potential burden of MiP [8, page 34] and they are the new default estimates in policy documents [9, page 1 ref 1].

The lack of data on the impact of SP resistance on the effectiveness of IPTp was a major concern for policy makers in 2007. The findings of the meta-analysis [5] were presented by ter Kuile at WHO's African Regional Office (AFRO), Harare in 2005 [10] and at the Technical Expert Group on MiP in Geneva, July 2007 [11]. As a direct result, WHO-AFRO issued a statement in 2005 on the continued use of SP for IPT during pregnancy [10], and in 2007 WHO-Geneva recommended the continued use of IPTp-SP in pregnant women, influencing on-going policy in Africa [11], where IPTp remains the only drug-based prevention regimen today [12]. It is also cited in a 2013 WHO policy brief for implementers and programme managers in Africa, stating "*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*" [13]. The impact of LSTM's research is the formulation of policy guidelines that, since 2008, have increased the chances of a healthy pregnancy. A recent review using retrospective birth cohort data from national cross-sectional datasets in 25 African countries from 2000-10 estimated that IPTp-SP has reduced neonatal mortality by 18% and LBW by 20% under routine programme conditions [14].

Increasing SP resistance in parts of Africa led to pressure from malaria-endemic countries on WHO to provide guidance. LSTM's meta-analysis [6] has been crucial in helping WHO update its policy recommendation on IPTp in 2012 [13]. Ter Kuile presented the findings at WHO's Evidence Review Group (ERG) for MiP in July 2012 who, in turn, presented their recommendations to the Malaria Policy Advisory Committee of the WHO in September 2012 [15]. This led WHO to update its IPTp policy, subsequently communicated to African Member States of the WHO [12]. Several countries in East, West and Central Africa have now ratified the updated policy and a few have begun implementation.

One challenge to implementing MiP policies effectively has been lack of integration between malaria control and maternal and neonatal health programmes at global and country levels. Field studies and reviews of the barriers to implementation have been presented by Hill at key meetings where the maternal health and malaria communities have come together, many of them NGOs seeking guidance to improve practices in endemic countries [16,17]. Findings contributed to the policy brief by WHO on the updated IPTp policy in terms of appropriate messaging to simplify the guidance specifically on the timing, frequency, and safety of taking SP on an empty stomach [13]. Hill is a member of the core group of the RBM Partnership on MiP, comprised of donors and technical agencies that support countries to implement MiP policies, and her research helps develop consensus strategies to scale-up MiP interventions [18]. One output is the WHO/RBM consensus statement calling for renewed commitment to fighting MiP, using the 3-pronged approach including the updated IPTp policy based on LSTM's evidence [9]. The target audience includes national-level policy-makers, malaria control and maternal and neonatal health programme managers, and other health-care providers. The statement was developed and co-signed by 19 leading global organisations including WHO, DFID, USAID, UNICEF, BMGF, it was co-sponsored by UNDP, World Bank, WHO and UNFPA [9]. Hill has been invited by WHO to co-lead the development of a standardized tool to evaluate effectiveness of MiP programme [15].

5. Sources to corroborate the impact

Each source listed below provides evidence for the corresponding numbered claim made in section 4 (details of the impact).

7. Contact: Programme Leader of the Global Malaria Programme at the WHO, confirming health impacts as 37 African countries benefited from continued use of IPTp (2007-present), and 9 recently updated their policy to more frequent doses (post-2012), impacting on LBW. [12]

8. WHO Global Malaria Programme, 2012. World Malaria Report 2012 http://www.who.int/malaria/publications/world_malaria_report_2012/wmr2012_no_profiles.pdf. (page 34, better defines the global burden of malaria in pregnancy) (in Spanish)

9. WHO consensus statement, 2013 http://www.rbm.who.int/docs/2013/MIP-consensus-statement-en.pdf

10. AFRO recommendations on the use of SP for Intermittent Preventive Treatment during Pregnancy (IPT) in areas of moderate to high resistance to SP in the African Region 2005. http://www.who.int/malaria/publications/atoz/who_sp_statement/en/

11. WHO Technical Expert Group meeting on IPTp 2007 (meeting report). http://whqlibdoc.who.int/publications/2008/9789241596640_eng.pdf

12. WHO Malaria Policy Advisory Committee Secretariat, 2012. Conclusions and Recommendations of September 2012 meeting. Malar J 11: 424. http://www.malariajournal.com/content/11/1/424

13. World Health Organization, 2013. WHO policy brief for the implementation of IPTp using sulfadoxine-pyrimethamine (IPTp-SP) April 2013. http://www.who.int/malaria/publications/atoz/Policy_brief_IPTp-SP_implementation_11april2013.pdf.pdf

14. Contact: Co-Chair of the RBM Working Group on MiP confirming IPTp with SP, resulted in reductions in neonatal mortality (by 18%) and LBW (by 20%) under routine malaria control programme conditions.

15. Malaria Policy Advisory Committee Meeting 11-13 September 2013, WHO Evidence Review Group on (IPT) of malaria in pregnancy: Draft Recommendations on Intermittent Preventive Treatment in Pregnancy (IPTp). http://www.who.int/malaria/mpac/mpac_sep13_erg_ipt_malaria_pregnancy_report.pdf

16. Maternal Health Task Force, 2012. Malaria in Pregnancy: Bringing the maternal Health and malaria communities together (MiP2012). Meeting report 26-28 June 2012 Turkey. http://maternalhealthtaskforce.org/images/MiP_Meeting_Report_Final_10-4-12.pdf (Results were disseminated at a meeting convened in June 2012.)

17. Hill J, 2013. Improving quality of Care. Malaria in pregnancy: What it takes to deliver quality health services as a component of comprehensive MNCH. Jenny Hill. Available at: https://meeting.tfigroup.com/tfi/frontend/reg/titem.csp?pageID=277724&eventID=743&popup=1&eventID=743 (Results were presented at the global MNH conference in Arusha)

18. Annual Meeting Minutes of the RBM MIP Working Group. Commitment to strengthening, accelerating and supporting MIP programming, 13-14 May, 2013 http://www.rollbackmalaria.org/mechanisms/mpwg.html