Institution: Liverpool School of Tropical Medicine (LSTM)

Unit of Assessment: UOA1

Title of case study: Treatment and control of malaria in pregnancy: Improved policy guidelines and practice

Period when the underpinning research was undertaken: 2007 – 2019

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Feiko ter Kuile	Professor of Tropical Epidemiology	2003 –
Jenny Hill	Senior Programme Manager and Public Health Epidemiologist	1995 –
Annemieke van Ejik	Senior Clinical RA	2009 –
Rukhsana Ahmed	PDRA Clinical Epidemiologist	2011 – 2019
Stephanie Dellicour	RA in Pharmacovigilance	2007 – 2017

Period when the claimed impact occurred: 2013 – 2020

Is this case study continued from a case study submitted in 2014? Y/**N NO**

1. Summary of the impact (indicative maximum 100 words)

Malaria in pregnancy is a leading cause of adverse pregnancy outcomes. Research led by LSTM contributed directly to improved World Health Organisation (WHO) and endemic country policies and practices for the treatment and prevention of malaria in pregnancy in different transmission and drug resistance strata in sub-Saharan Africa and Asia-Pacific. Specifically, ministries of health in 36 African nations are now implementing a more effective malaria prevention strategy improving the outcome of approximately 32,000,000 pregnancies at risk annually and thereby the lives of mothers and their infants. Furthermore, following our studies on the safety of artemisinin-based combination therapy, regulatory authorities and WHO pre-qualification have updated drug labels for use in pregnancy.

2. Underpinning research (indicative maximum 500 words)

Between 2007 and 2017, ter Kuile (Head) and Hill (Project Manager) led the MiP (Malaria in Pregnancy) Consortium, a global network of 40 research institutions, that aimed to evaluate new strategies for the control of malaria in pregnancy to inform policy and improve the lives of mothers and their infants.

WHO recommends intermittent preventive treatment (IPTp) with sulphadoxine-pyrimethamine (SP) for the prevention of malaria in pregnancy in Africa. IPTp comprises a treatment dose of an antimalarial given presumptively at each scheduled antenatal care (ANC) visit, alongside case management and use of insecticide-treated nets in malaria-endemic countries. These strategies have come under threat due to increasing drug resistance and suboptimal coverage of these interventions.

Treatment (global)

Since 2006, WHO has recommended 3-day regimens with artemisinin-based combination therapies (ACTs) as first-line treatment for uncomplicated malaria in the 2nd and 3rd trimesters of pregnancy. Due to lack of safety data, ACTs are not recommended for 1st trimester treatment unless no other suitable antimalarials are available. Treatment recommended in the first trimester involves 7-day quinine regimens, which are badly tolerated and associated with poor adherence and therefore high rates of treatment failure. In a systematic review of health provider practices and access to case management of malaria during pregnancy (2014), Hill found widespread substandard practices for the case-management of pregnant women with the

continued use of obsolete antimalarials in the 2nd and 3rd trimester that are no longer recommended by WHO and use of ACTs in the 1st trimester [1]. This led Dellicour and ter Kuile to undertake the largest individual participant data meta-analysis on the safety of artemisinin antimalarials in the 1st trimester involving 717 well-documented artemisinin and 947 quinine exposures from Asia and Africa. This showed that, contrary to data from animal models, artemisinin exposure in early pregnancy does not increase the risk of pregnancy loss or congenital anomalies compared to quinine and can be more effective at reducing pregnancy loss [2] as low adherence to the 7-day quinine regime results in a 4-fold higher risk of treatment failure.

Prevention (Africa)

Until 2012, IPTp with SP comprised at least two doses given in the 2nd and 3rd trimester. ter Kuile's 2013 meta-analysis of IPTp trials showed that three or more doses of SP was well tolerated and safe and far more effective than the 2-dose regimen resulting in 49% (95% CI 32-62) and 20% (6-31) greater reductions in placental malaria and low birth weight, respectively [3]. However, the IPTp strategy is under threat due to increasing resistance to SP. ter Kuile and US Center for Disease Control colleagues showed that the efficacy of SP to clear existing malaria infections or prevent new ones is severely compromised in areas with high SP resistance. In a 2019 meta-analysis involving approximately 100,000 births, van Eijk and ter Kuile showed that alternative strategies are urgently needed in areas where over 37% of parasites carry the highly resistant sextuple-mutant Pfdhps-A581G-containing genotype [4].

In two trials of potential alternatives to IPTp-SP coordinated by ter Kuile (between 2011 and 2016), intermittent screening and treatment strategies (where only women testing positive for malaria are treated) was found not to be a suitable alternative at current levels of rapid diagnostic test (RDT) sensitivity [5,6]. By contrast, IPTp with the antimalarial dihydroartemisinin-piperaquine resulted in a decrease of 68% (44-82) in malaria infections during pregnancy, and a 59% (1-83) reduction in spontaneous miscarriage or stillbirth compared to IPTp-SP. This was the first of eight IPTp trials with dihydroartemisinin-piperaquine which is now considered the most promising alternative to replace SP for IPTp in high SP resistance areas [5]. By November 2020, three trials had been completed (the first of which was led by LSTM), and a further 5 are ongoing (the largest of which is led by LSTM). Results are expected in Q4 2021.

Prevention (Asia)

In the first trial of its kind in Asia, Ahmed and ter Kuile showed that malaria infection decreased by 41% (17-58) with monthly IPTp with dihydroartemisinin-piperaquine and is a promising alternative to the current policy of screening pregnant women for malaria at their first antenatal care visit in areas of moderate-to-high transmission in the Asia-Pacific region [6].

3. References to the research (indicative maximum of six references)

1. **Hill J**, D'Mello-Guyett L, Hoyt J, **van Eijk AM**, **ter Kuile FO**, Webster J. Women's access and provider practices for the case management of malaria during pregnancy: a systematic review and meta-analysis. PLoS Med. 2014. DOI: 10.1371/journal.pmed.1001688
2. **Dellicour S**, Sevene E, McGready R, Tinto H, Mosha D, Manyando C, Rulisa S, Desai M, Ouma P, Oneko M, Vala A, Rupérez M, Macete E, Menéndez C, Nakanabo-Diallo S, Kazienga A, Valéa I, Calip G, Augusto O, Genton B, Njunju EM, Moore KA, d'Alessandro U, Nosten F, **ter Kuile F**, Stergachis A. First-trimester artemisinin derivatives and quinine treatments and the risk of adverse pregnancy outcomes in Africa and Asia: A meta-analysis of observational studies. PLoS Med. 2017. DOI: 10.1371/journal.pmed.1002290
3. 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. JAMA. 2013. DOI: 10.1001/jama.2012.216231

4. **van Eijk AM**, Larsen DA, Kayentao K, Koshy G, Slaughter DEC, Roper C, Okell LC, Desai M, Gutman J, Khairallah C, Rogerson SJ, Hopkins Sibley C, Meshnick SR, Taylor SM, **ter Kuile FO**. Effect of Plasmodium falciparum sulfadoxine-pyrimethamine resistance on the effectiveness of intermittent preventive therapy for malaria in pregnancy in Africa: a systematic review and meta-analysis. Lancet Infect Dis. 2019. DOI: 10.1016/S1473-3099(18)30732-1
5. Desai M, Gutman J, L'lanziva A, Otieno K, Juma E, Kariuki S, Ouma P, Were V, Laserson K, Katana A, Williamson J, **ter Kuile FO**. Intermittent screening and treatment or intermittent preventive treatment with dihydroartemisinin-piperaquine versus intermittent preventive treatment with sulfadoxine-pyrimethamine for the control of malaria during pregnancy in western Kenya: an open-label, three-group, randomised controlled superiority trial. Lancet. 2015. DOI: 10.1016/S0140-6736(15)00310-4
6. **Ahmed R**, Poespoprodjo JR, Syafruddin D, Khairallah C, Pace C, Lukito T, Maratina SS, Asih PBS, Santana-Morales MA, Adams ER, Unwin VT, Williams CT, Chen T, Smedley J, Wang D, Faragher B, Price RN, **ter Kuile FO**. Efficacy and safety of intermittent preventive treatment and intermittent screening and treatment versus single screening and treatment with dihydroartemisinin-piperaquine for the control of malaria in pregnancy in Indonesia: a cluster-randomised, open-label, superiority trial. Lancet Infect Dis. 2019. DOI: https://doi.org/10.1016/S1473-3099(19)30156-2

4. Details of the impact (indicative maximum 750 words)

Prof ter Kuile and Dr Hill applied a systematic approach to ensure the translation of research into policy by working with WHO to convene four consecutive Evidence Review Group meetings on malaria in pregnancy (between 2012 and 2017), which reviewed results from research led by LSTM and other partners and made recommendations both to WHO's Malaria Policy Advisory Committee (MPAC) [1] and regulators (see below). Dissemination and technical support activities targeting policymakers and practitioners were undertaken to support policy uptake in endemic countries, improving pregnancy outcomes of millions of women in malaria-endemic countries.

Update to drug labels of ACTs for treatment of malaria in pregnancy

The safety studies in 1st trimester pregnancy described above resulted in label changes by the United States Food and Drug Administration (FDA, August 2019), the Coordination Group for Mutual Recognition and Decentralised Procedures at the European Medicines Agency (September 2020), and the WHO pre-qualification team (March 2018) for the use of the ACT artemisinin-lumefantrine in pregnancy [2-4]. The label change requested by the FDA was to lift the restriction on the use of Coartem® in pregnancy, including in the 1st trimester, based on the results of the 2017 meta-analysis. These label changes affect the use of these drugs in pregnancy by clinical practitioners and enable national malaria programmes to improve the quality of case management in the 1st trimester by shifting to the more effective 3-day ACT regimens from the current 7-day quinine regimen, which is poorly tolerated and badly adhered to, leading to adverse pregnancy outcomes.

The results were also reviewed by WHO's MPAC in 2015 (6) which recommended a change from quinine to artemisinin combination therapies (ACTs) as a first-line therapeutic option for uncomplicated malaria in the 1st trimester, which was subsequently endorsed by WHO's Technical Expert Group on Malaria Chemotherapy in December 2017 [1]. As a result of the label changes by the Stringent Regulatory Authorities (SRAs), WHO is proceeding and has requested our group to update the meta-analysis with any new data in preparation for the development of an update to the WHO treatment guidelines in 2021. Independent of WHO, Indonesia was the first country (September 2019) to change its national policy for treatment of malaria in 1st trimester to the ACT, dihydroartemisinin-piperaquine [7], which was already the first line therapy for treatment in all population groups, including in the 2nd and 3rd trimester.

WHO's updated policy on prevention of malaria in pregnancy in sub-Saharan Africa

IPTp with SP: Increasing resistance to SP in parts of Africa led malaria-endemic countries to place pressure on WHO to provide further guidance on whether to continue using IPTp with SP.

The LSTM-led studies on the continued effectiveness of IPTp-SP on reducing low birth weight, even in areas with relatively high SP resistance (likely due to the non-malarial effects of SP), led WHO in September 2013 to recommend continued implementation of IPTp-SP in all endemic areas until alternative drugs become available [5].

IPTp with DP: Our research showing the efficacy of dihydroartemisinin-piperaquine, for use in areas with very high SP resistance, and related studies of its acceptability and feasibility presented to WHO's MPAC in 2015 [6], led WHO to recommend further studies with IPTp-DP to provide definitive evidence for consideration of IPTp-DP for policy in 2021 [8].

Implementation of revised guidelines on prevention of malaria in pregnancy in Africa

Results from our key meta-analysis comparing 3-or-more doses vs the standard 2-dose regimen of IPTp with SP led WHO to revise its guidelines in 2012, and updated in 2014, from 2 doses to monthly doses of SP [9]. The IMPPACT project (between 2016 and 2019), led by Hill, supported the uptake of evidence from the MiP Consortium in African country-level policies and guidelines. In collaboration with the Roll Back Malaria (RBM) Partnership, and the West Africa Health Organisation (WAHO), the MiP Consortium results were disseminated to 21 African countries [10a]. The WAHO meeting in 2017 involving National Malaria Control Programme Managers, M&E Officers, and Reproductive Health Managers from the 15 Economic Community of West African States (ECOWAS) member States, WHO, UNICEF, RBM, research organisations and the private sector, took place in the context of the preparation of country Global Fund applications between 2018 and 2020 [10b]. Countries reached a regional consensus on the implementation of malaria control activities, including the monthly IPTp-SP policy, articulated in the ECOWAS Regional Strategic Plan for Malaria Control and Elimination. WHO's 2019 World Malaria Report reported that the updated policy had been adopted in 36 endemic countries in Africa [11]. As a result, annually, 32,000,000 pregnancies in Africa continue to benefit from this life-saving strategy for pregnant women annually.

National prevention policy uptake in Asia-Pacific

Results from the prevention trial with dihydroartemisinin-piperaquine (DP) and nested acceptability, feasibility and cost effectiveness studies in Indonesia were discussed with more than 110 ministries of health representatives from 18 countries in the Asia/Pacific region at a dissemination meeting in collaboration with WHO-WPRO and WHO-SEARO regional offices in 2017 [10c]. In 2019, as a direct result of these studies, the Indonesian Ministry of Health requested support from Hill and ter Kuile to evaluate the pilot implementation of IPTp-DP in Papua-Indonesia, and an LSTM-led study funded by the Medical Research Council (MRC) is ongoing.

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. Statement letter from the office of the Director of the Global Malaria Programme at the WHO, confirming WHO ERG and TEG meeting recommendations.
2. WHO prequalification medicines: MA122 - Artemether/Lumefantrine - 80mg/480mg - Tablet - Cipla Ltd - India. Part 4 - WHO-PQ recommended summary of product characteristics* March 2018 https://extranet.who.int/prequal/sites/default/files/MA122part4v1.pdf
3. FDA HIGHLIGHTS OF PRESCRIBING INFORMATION. COARTEM® (artemether and lumefantrine) tablets, for oral use. Initial U.S. Approval: 2009/Revised 8/2019 https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022268s021lbl.pdf
4. EMA approved and regulated prescribing and patient information for licensed medicines: Riamet 20 mg/120 mg Tablets. https://www.medicines.org.uk/emc/product/1628#CONTRAINDICATIONS
5. 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

6. WHO Malaria Policy Advisory Committee (2016). "Malaria Policy Advisory Committee to the WHO: conclusions and recommendations of the eighth biannual meeting (September 2015)." Malar J 15(1): 117. http://www.ncbi.nlm.nih.gov/pubmed/26911803
7. Minister of Health, Republic of Indonesia. National Guidelines for Medical Services Malaria Management, documenting policy for treatment with DP of malaria in all trimesters of pregnancy. No. HK.01.07/Menkes / 556/2019. (Page 27)
8. World Health Organization. Intermittent screening and treatment in pregnancy and the safety of ACTs in the first trimester, November 2015, recommendations (WHO/HTM/GMP/2015.9). 2015. http://www.who.int/malaria/publications/atoz/istp-and-act-in-pregnancy.pdf?ua=1
9. WHO policy brief for the implementation of intermittent preventive treatment of malaria in pregnancy using sulfadoxine-pyrimethamine (IPTp-SP). WHO/HTM/GMP/2014.4. April 2013 (Revised January 2014). https://www.who.int/malaria/publications/atoz/iptp-sp-updated-policy-brief-24jan2014.pdf?ua=1
10. (a) IMPPACT regional meeting report, Nairobi 2016 Research on the treatment and prevention of malaria in pregnancy in sub-Saharan Africa: East Africa Regional Meeting, 11-12 July 2016 - Fairview Hotel - Nairobi, Kenya. https://www.mip-consortium.org/sites/mip/files/upload/FinalMeetingReportPDF.pdf (b) IMPPACT regional meeting report, Togo 2017. Malaria in Pregnancy Consortium session on malaria in pregnancy (MiP) at the ECOWAS National Control Malaria Managers' Review Meeting organized by the West Africa Health Organization (WAHO), 4-7th April 2017 in Lomé, Togo. https://www.mip-consortium.org/sites/mip/files/upload/West%20Africa%20Research%20Meeting%20Report%20v4_Publisher_0.pdf (c) APMEN Vivax Working Group Meeting report 9-11 October 2017, Bali. http://apmen.org/apmen/Working%20Groups/Vivax%20Working%20Group/APMEN%20MIP%20report%20%20Day%202%20VxWG%20meeting.pdf
11. World Malaria Report 2019 p.50 https://www.who.int/publications/i/item/9789241565721"