Institution: London School of Hygiene & Tropical Medicine (LSHTM)

Unit of Assessment: UoA1 – Clinical Medicine

Title of case study: Elucidation of the global dispersal of antimalarial drug resistance and strategies to combat future emergence and spread

1. Summary of the impact

Multidisciplinary research at LSHTM has increased understanding of how antimalarial drug resistance emerges and spreads, resulting in impacts on national, regional and international policy-makers and donors, and especially benefiting malaria patients and communities in Southeast Asia. The research influenced (1) WHO recommendations on using sulphadoxine-pyrimethamine for intermittent preventive treatment in Africa and (2) policy responses to the threat of artemisinin resistance including the WHO 'Global Plan for Artemisinin Resistance Containment' (2011) and the Thai-Cambodia Artemisinin Resistance Containment programme (2009–2011). These efforts were associated with decreased malaria cases, and reduction in availability of artemisinin monotherapies in Cambodia.

2. Underpinning research

Drug resistance has been a major problem in treating malaria, and in the recent past failing drugs have led to substantial increases in malaria mortality across the developing world. Understanding how drug resistance develops and spreads, and preventing this, is essential to protect current drugs and prevent future increased burdens of malaria.

DNA analysis at LSHTM traced the geographical dispersal of drug resistance mutations in *Plasmodium falciparum* malaria in Africa, Asia and South America and found that resistance mutations arise infrequently but can spread over thousands of miles.

Research into the evolutionary origins of drug resistance mutations in African *P. falciparum* malaria was led by Cally Roper (Senior Lecturer, LSHTM since 1996, then Research Fellow). Roper developed a novel genetic approach by which drug resistance mutations with a common ancestral origin could be identified through DNA matches in their flanking sequence. She applied this in population surveys in South and East Africa in partnership with colleagues from the Tanzanian National Institute of Medical Research and the South African Medical Research Council, showing that point mutations in the *dhfr* gene (conferring pyrimethamine resistance) and the *dhps* gene (conferring sulphadoxine resistance) in Tanzania and South Africa were derived from the same few ancestral lineages. This contradicted the widely accepted view that such mutations arise repeatedly at the individual patient level. The findings[3.1] resulted in a major shift in understanding how drug resistance evolves in African malaria parasite populations.

Roper extended the analysis to compare African and Southeast Asian parasites in collaboration with research groups in Thailand and the USA. The unexpected results showed that the highly pyrimethamine resistant mutants found in Africa were derived from an Asian ancestor and highlighted the significance of international migration in the dispersal of drug resistant malaria and its importation to Africa.[3.2]

The spatial analysis of *dhfr* and *dhps* resistance lineages was expanded to include surveys in 20 African countries. Maps of the pattern of dispersal of resistance lineages of *dhps* across Africa upheld the earlier findings, that there was infrequent emergence of new resistance mutations and a large-scale pattern of regional dispersal.[3.3] A literature search enabled all the published data on *dhfr* and *dhps* mutations in Africa to be geo-referenced (http://www.drugresistancemaps.org/), providing the framework for a technical report commissioned by the WHO Global Malaria Programme and maps indicating where the prevalence of *dhps* resistance mutations precludes the use of sulfadoxine-pyrimethamine (SP) for intermittent preventive treatment in infants.[3.4]

Concurrently, research undertaken by Shunmay Yeung (research degree student LSHTM 2000–2006, Senior Lecturer LSHTM 2008–) explored determinants of antimalarial drug use and the

policies and practices required to decrease the risk of drug resistance emerging and spreading. A bio-economic model of antimalarial drug resistance developed with Wirichada Pongtavronipinyo (Mahidol-Oxford Tropical Medicine Research Unit (MORU), Bangkok) predicted that changing first-line drug from monotherapy to artemisinin combination therapy (ACT) would be cost effective from a societal perspective.[3.5] Community treatment-seeking behaviour and antimalarial drug use were studied in Cambodia, the first country to introduce ACTs as a first-line drug. These studies demonstrated worryingly widespread use of artemisinin monotherapies and the effectiveness of village volunteers in improving diagnosis and treatment.[3.6]

3. References to the research

3.1 Roper, C, Pearce, R, Bredenkamp, B, Gumede, J, Drakeley, C, Mosha, F, Chandramohan, D and Sharp, B (2003) Antifolate antimalarial resistance in southeast Africa: a population-based analysis, *Lancet*, 361(9364): 1174–1181, doi: 10.1016/S0140-6736(03)12951-0. Citation count: 171.

3.2 Roper, C, Pearce, R, Nair, S, Sharp, B, Nosten, F and Anderson, T (2004) Intercontinental spread of pyrimethamine-resistant malaria, *Science*, 305(5687): 1124, doi: 10.1126/science.1098876. Citation count: 189.

3.3 Pearce, RJ, Pota, H, Evehe, MSB, Ba, EH, Mombo-Ngoma, G, Malisa, AL, Ord, R, Inojosa, W, Matondo, A, Diallo, DA, Mbacham, W, van den Broek, IV, Swarthout, TD, Getachew, A, Dejene, S, Grobusch, MP, Njie, F, Dunyo, S, Kweku, M, Owusu-Agyei, S, Chandramohan, D, Bonnet, M, Guthmann, JP, Clarke, S, Barnes, KI, Streat, E, Katokele, ST, Uusiku, P, Agboghoroma, CO, Elegba, OY, Cisse, B, A-Elbasit, IE, Giha, HA, Kachur, SP, Lynch, C, Rwakimari, JB, Chanda, P, Hawela, M, Sharp, B, Naidoo, I and Roper, C (2009) Multiple origins and regional dispersal of resistant *dhps* in African *Plasmodium falciparum* malaria, *PLoS Medicine*, 6(4): article e1000055, doi: 10.1371/journal.pmed.1000055. Citation count: 58.

3.4 Naidoo, I and Roper, C (2011) Drug resistance maps to guide intermittent preventive treatment of malaria in African infants, *Parasitology*, 138(12): 1469–1479, doi: 10.1017/S0031182011000746. Citation count: 11.

3.5 Yeung, S, Pongtavornpinyo, W, Hastings, IM, Mills, AJ and White, NJ (2004) Antimalarial drug resistance, artemisinin-based combination therapy, and the contribution of modelling to elucidating policy choices, *American Journal of Tropical Medicine and Hygiene*, 71(Suppl. 2): 179–186, http://www.ajtmh.org/content/71/2_suppl/179.abstract (accessed 15 November 2013). Citation count: 70.

3.6 Yeung, S, Van Damme, W, Socheat, D, White, NJ and Mills, A (2008) Access to artemisinin combination therapy for malaria in remote areas of Cambodia, *Malaria Journal*, 7(96), doi: 10.1186/1475-2875-7-96. Citation count: 40.

Key grants

Roper, Population Genetic Analysis of Drug Resistance in Plasmodium falciparum, Wellcome Trust Advanced Training Fellowship, 2000–2005, £400,000.
Yeung, work funded through Wellcome Trust award to Mahidol Oxford Tropical Medicine Research Unit, Bangkok.

4. Details of the impact

The new knowledge produced on the origins and spread of antimalarial drug resistance has informed treatment policy in sub-Saharan Africa, and the national and global response to reports of decreased sensitivity to artemisinins on the Thai-Cambodia border. There has been a reduction in the availability of artemisinin monotherapies, one of the main drivers of drug resistance, and in malaria morbidity and mortality on the Thai-Cambodia border, but the main beneficiaries of successful containment of artemisinin resistance will be future populations in malaria-endemic countries.

Treatment policy in sub-Saharan Africa

Given her expertise, Roper was asked to serve in 2009 on the WHO Expert Committee on Monitoring SP Resistance in the context of intermittent preventive therapy in infants (IPTi), which produced recommendations which informed WHO policy recommendation on the use of SP for IPTi produced in 2010. [5.1] [5.2] Her evidence that resistance alleles are shared amongst *P.falciparum* populations regionally underpins the use of *dhps* mutation data from a single codon as proxy for high level resistance in the recommendations. The Global Malaria Programme Coordinator of Drug Resistance and Containment confirms her 'maps have been a useful guide'.[5.3]

Response to resistance on Thai-Cambodia border

DNA evidence of the previous spread of resistance from Asia and the impact this had on child morbidity and mortality in sub-Saharan Africa underpinned the urgent response by the malaria community to the threat posed by the emergence of artemisinin resistance on the Thai-Cambodia border. The case was made by Nick White – Chairman of the WHO Global Malaria Programme Technical Expert Group on the case management of malaria – at early high-level discussions that fed into strategic thinking on how to manage artemisinin resistance.[5.4] The prevention of spread through 'containment' is central to WHO's 2011 Global Plan for Artemisinin Resistance Containment (GPARC)[5.5] in which Roper and Yeung are named contributors.

LSHTM staff played a significant role in formulating the response to artemisinin resistance, drawing on their technical understanding of the determinants of the development of drug resistance gained through literature reviews and modeling,[3.5] and knowledge of the local context gained from field studies.[3.6] In January 2008, Yeung served as temporary advisor at a WHO meeting that was rapidly convened to review available evidence and discuss the immediate priorities for response to the evidence of artemisinin tolerance.[5.6] On behalf of WHO, Yeung drafted the grant proposal to the Bill & Melinda Gates Foundation (BMGF) in 2008 that resulted in the funding of the Artemisinin Resistance Confirmation, Characterisation and Containment consortium (ARC3c), which she subsequently led as Programme Coordinator. The consortium was a two-year programme coordinated by WHO and MORU and involving the Ministries of Health of Cambodia and Thailand, Institut Pasteur-Cambodia and the US Armed Forces Research Institute of Medical Science (AFRIMS). As coordinator, Yeung helped to convene a meeting in Bangkok in February 2008 which issued a consensus statement recognising the potential catastrophic consequences of failing to contain the emerging tolerance and/or resistance and recommending efforts to eliminate malaria in the region.[5.7, 5.8]

Yeung focused on the 'containment' aspect of ARC3c, and played an important role in drafting the key strategy documents and grant proposals that resulted in funding and implementing the Artemisinin Resistance Containment programme in 2009.[5.8, 5.9] Formal and informal meetings and briefings were held throughout, with a wide range of stakeholders including Ministry of Health officials, donors, NGO partners, researchers, public and private health care providers. This process of proactive engagement contributed to the successful development and implementation of the strategy. Yeung also directly facilitated the switching of first-line drug in the epicenter of drug resistance in Cambodia from a co-blistered ACT to a single tablet fixed-dose combination, and also the introduction of a ban on the sale of oral artemisinin monotherapies in 2009.

There has been a marked decline in the availability of oral artemisinin monotherapies from around 40% of private outlets in 2007 to less than 5% in 2011 according to the ACTWatch survey. There has also been a large reduction in incidence of both uncomplicated and severe malaria nationwide but most marked in the 'containment' zone.[5.10] However there is evidence that the efficacy of ACTs is continuing to decline. A similar containment programme has been implemented in Mynamar, and at a global level, and these combined efforts have resulted in high levels of awareness of the risk of artemisinin resistance and the need for urgent action to prevent emergence and spread.[5.5]

5. Sources to corroborate the impact

5.1 WHO (2010) *Defining and Validating a Measure of Parasite Resistance to Sulfadoxine-pyrimethamine (Sp) that would be Indicative of the Protective Efficacy of Sp for Intermittent*

Preventive Treatment in Infancy (SP-IPTi), report of the technical consultation, Geneva 10–11 September 2009. Geneva: WHO, http://www.who.int/malaria/publications/atoz/who_sp_ipti_resistance_march_2010.pdf (accessed 15 November 2013) (Roper listed as member on p. 6).

5.2 WHO (2010), *WHO Policy Recommendation on Intermittent Preventive Treatment During Infancy with Sulphadoxine-pyrimethamine (SP-IPTi) for* Plasmodium Falciparum *Malaria control in Africa*. Geneva: WHO http://www.who.int/malaria/news/WHO_policy_recommendation_IPTi_032010.pdf (accessed 15 November 2013).

5.3 Coordinator, Drug Resistance and Containment, Global Malaria Programme, WHO.

5.4 White, NJ (2010) Artemisinin resistance-the clock is ticking, *Lancet*, 376(9758): 2051–2052, doi: 10.1016/S0140-6736(10)61963-0 (Roper et al. Science paper is reference 5).

5.5 WHO (2011) *Global Plan for Artemisinin Resistance Containment (GPARC)*. Geneva: WHO, http://www.who.int/malaria/publications/atoz/9789241500838/en/index.html (accessed 15 November 2013) (Roper's contribution acknowledged p. 2, Yeung's p. 3).

5.6 WHO (2008) *Global Malaria Control and Elimination: Report of a Meeting on Containment of Artemisinin Tolerance, 19 January 2008, Geneva, Switzerland*. Geneva: WHO, http://whqlibdoc.who.int/publications/2008/9789241596817_eng.pdf (accessed 15 November 2013) (p. 29, Yeung listed as rapporteur and temporary advisor).

5.7 WHO (2008) *Proceedings of the First Meeting of the Artemisinin Resistance, Confirmation, Characterization and Containment (ARC3) Project. 9 February 2008, Bangkok*. Geneva: WHO, Published by WHO, restricted distribution (available on request) (Yeung's contribution in Acknowledgements on p. 1)

5.8 WHO-Mekong Malaria Programme (2009) *Strategic Plan to Strengthen Malaria Control and Elimination in the Greater Mekong Subregion: 2010–2014*, working document. Thailand, Nonthaburi: WHO, http://whothailand.healthrepository.org/bitstream/123456789/696/1/Strategic%20Plan%20to%20Strengthen%20Malaria%20Control%20and%20Elimination%20in%20the%20Greater%20Mekong%20Subregion%20%2020102014.pdf (accessed 15 November 2013) (on p. 22, the meeting of the ARC3 consortium, organised by Shunmay Yeung, is cited in a description of the process of strategy development; consensus statement on artemisinin resistance printed on p. 16).

5.9 WHO Regional Office for the Western Pacific (2008) Minutes of an informal consultation on resource mobilization for the containment of artemisinin tolerant malaria on the Cambodia-Thailand border, RS/2008/GE/28(CAM), meeting held at Phnom Penh, Cambodia, 17–18 June. Manila: WHO Regional Office for the Western Pacific (copy available on request) (Yeung gave a presentation, and is listed as the Coordinator of the ARC3 project in the list of stakeholders and representatives on p. 26)

5.10 Cambodia National Malaria Center (2013) *Cambodia Malaria Bulletin,* June, http://www.cnm.gov.kh/index.php?action=ID80 (accessed 15 November 2013) (this is the Ministry of Health website with graphs/tables of numbers showing the decline in burden).