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

Unit of Assessment: UoA1 – Clinical Medicine

Title of case study: Evaluating drugs and devising strategies for reducing malaria transmission

1. Summary of the impact

A substantial programme of research carried out by LSHTM has provided evidence for a major shift of strategy and progress in global efforts to eliminate malaria. As a result, WHO now recommends a policy designed to ensure medically-treated individuals are non-infectious to mosquitoes. In addition, drug development partnerships such as the Medicines for Malaria Venture now include transmission interruption in the target product profiles for new medicines. Several countries have made strategic decisions for the prevention of malaria transmission on the basis of the research, and the senior investigators act as advisers to international anti-malaria initiatives.

2. Underpinning research

WHO estimates that in 2010 there were 219m cases of malaria worldwide, resulting in 660,000 deaths, mostly among African children. Reduction in the transmission of malaria is therefore a global health priority, and it has been the focus of a major LSHTM research programme led by Geoffrey Targett (LSHTM from 1970, now Emeritus Professor), Professor Chris Drakeley (LSHTM from 1991, then Research Assistant), Dr Colin Sutherland (LSHTM from 1998, then Post-doctoral Researcher, now Reader) and Dr Teun Bousema (LSHTM from 2008 then Post-doctoral Researcher, now Senior Lecturer).

Working in The Gambia and Kenya (1998–2009), LSHTM researchers were the first to investigate the effect of treating children with standard regimens of drugs on the transmissibility of *P. falciparum* malaria to mosquitoes.[3.1] They found that, compared with other drug regimes, treatment with combinations including artemisinins induced a marked reduction in post-treatment prevalence, density and infectivity of gametocytes (the parasite stage responsible for transmission from human to insect). Parasites carrying genes conferring resistance to antimalarials were shown to have a selective advantage that led to higher rates of transmission from a drug-treated host and increased burdens of infection (oocysts) in mosquitoes,[3.2] but the addition of artesunate overcame this transmission advantage.

In order to evaluate transmission-reducing interventions, LSHTM researchers and leading collaborators from over 20 institutions developed direct membrane feeding assays where blood samples from gametocytaemic individuals were offered to mosquitoes through a membrane feeder.[3.3, 3.4] Overall results from the LSHTM studies indicated that artemisinin-based combination therapies (ACTs) had a marked activity against immature sequestered gametocytes that minimised but did not completely stop transmission.[3.3]

The drug primaquine (PQ) has long been known to have a gametocyticidal effect on infectious gametocytes but its use in high or multiple doses can cause haemolytic episodes in G6PD deficient individuals (G6DP deficiency is a hereditary condition characterised by low levels of the enzyme glucose-6-phosphate dehydrogenase which can cause haemolytic anaemia after exposure to certain medications). Studies of ACT treatment of *P. falciparum* combined with a single dose of PQ, led by LSHTM researchers, found that a single dose of primaquine was effective in reducing the number of gametocytes in both G6DP- deficient and non-deficient populations without significant harmful side effects.[3.4]

To determine where and how such a combination of drugs could best be used, further studies by Drakeley and Bousema investigated who in the population is responsible for transmission of infection to mosquitoes. They found that while individuals who are high-density carriers of gametocytes transmit malaria more often to mosquitoes, even those with sub-microscopic gametocyte carriage (i.e. asymptomatic individuals whose gametocyte levels are detectable only using molecular technology) still account for an important proportion of human to mosquito transmissions.[3.5] In addition, heterogeneity of transmission was found to occur in both low and high

transmission settings. In both settings, there are hotspots where the likelihood of transmission is relatively high compared with adjacent regions.[3.6] Geographical clustering of asymptomatic carriage is a good measure of these infectious reservoirs.

3. References to the research

3.1 Targett, G, Drakeley, C, Jawara, M, von Seidlein, L, Coleman, R, Deen, J, Pinder, M, Doherty, T, Sutherland, C, Walraven, G and Milligan, P (2001) Artesunate reduces, but does not prevent, posttreatment transmission of *Plasmodium falciparum* to *Anopheles gambiae*, *Journal of Infectious Diseases*, 183(8): 1254–1259, doi:10.1086/319689. Citation count: 135

3.2 Hallett, RL, Sutherland, CJ, Alexander, N, Ord, R, Jawara, M, Drakeley, CJ, Pinder, M, Walraven, G, Targett GAT and Alloueche, A (2004) Combination therapy counteracts the enhanced transmission of drug-resistant malaria parasites to mosquitoes, *Antimicrobial Agents and Chemotherapy*, 48(10): 3940–3943, doi:10.1128/AAC.48.10.3940-3943.2004. Citation count: 48

3.3 Sutherland, CJ, Ord, R, Dunyo, S, Jawara, M, Drakeley, CJ, Alexander, N, Coleman, R, Pinder, M, Walraven, G and Targett, GAT (2005) Reduction of malaria transmission to *Anopheles* mosquitoes with a six-dose regimen of Co-Artemether, *PLoS Medicine*, 2(4): e92, doi: 10.1371/journal.pmed.0020092. Citation count: 105

3.4 Shekalaghe, S, Drakeley, C, Gosling, R, Ndaro, A, van Meegeren, M, Enevold, A, Alifrangis, M, Mosha, F, Sauerwein, R and Bousema, T (2007) Primaquine clears submicroscopic *Plasmodium falciparum* gametocytes that persist after treatment with sulphadoxine-pyrimethamine and artesunate, *PLoS One*, 2(10): e1023, doi: 10.1371/journal.pone.0001023. Citation count: 6

3.5 Okell, LC, Bousema, T, Griffin, JT, Ouédraogo, AL, Ghani, AC and Drakeley, CJ (2012) Factors determining the occurrence of submicroscopic malaria infections and their relevance for control, *Nature Communications*, 3: 1237, doi: 10.1038/ncomms2241. Citation count: 14

3.6 Bousema, T, Griffin, JT, Sauerwein, RW, Smith, DL, Churcher, TS, Takken, W, Ghani, A, Drakeley, C and Gosling, R (2012) Hitting hotspots: spatial targeting of malaria for control and elimination, *PLoS Medicine*, 9(1): e1001165, doi:10.1371/journal.pmed.1001165. Citation count: 42

Key grants

- Targett, The Impact of Anti-Malarial Treatment upon the Development and Persistence of *Plasmodium falciparum* Gametocytes in Vivo, Wellcome Trust, 2000–2002, £202,000.
- Sutherland, Evaluating the Effects of Combination Therapy on the Selection of Drug Resistance in *Plasmodium falciparum*, and the Implications for Public Health, Gates Malaria Partnership Project Support, 2001–2005, £376,124.
- Drakeley, Malaria Transmission Consortium, Bill & Melinda Gates Foundation, 2008–2013, £420,000.
- Drakeley and Bousema, Assessment of the Infectious Reservoir of Malaria & Primaquine for Transmission Reduction, Bill & Melinda Gates Foundation, 2012–2015, US$ 3.6m.
- Sutherland and Bousema, Multi-drug Resistance in Malaria Under Combination Therapy: Assessment of Specific Markers and Development of Innovative, Rapid and Simple Diagnostics, EU FP7 MALACTRES Consortium, 2010–2013, €707,904.

4. Details of the impact

In November 2010, Drakeley presented the new findings regarding the effectiveness of single dose PQ-ACT combination in reducing *P. falciparum* gametocyte prevalence for G6PD-deficient and non-deficient populations to the WHO Joint Initiative for Vaccine Research/Global Malaria Programme Scientific Forum. This led directly to the publication of a new WHO guideline: 'Addition of a single dose of primaquine to ACT treatment for uncomplicated *falciparum* malaria as an anti-gametocyte, particularly as a component of pre-elimination or an elimination programme, is therefore recommended'.[5.1] This recommendation marks an important operational change in WHO strategies – essentially, elimination requires a shift in focus from just treating individuals showing malaria symptoms to also treating asymptomatic carriers of the disease – and has put the LSHTM

research at the forefront of activities to identify and attack foci of clinical and asymptomatic infections that perpetuate transmission. These activities include the following.

Development of medicines and vaccines

Among the 30–40 representatives from academia, industry, regulatory and funding agencies who attended a WHO meeting on measures of efficacy of antimalarial interventions against malaria transmission were the Centers for Disease Control and Prevention (CDC), the Gates Foundation, GlaxoSmithKline (GSK) and the Malaria Vaccine Initiative (MVI) of the international non-profit organisation, PATH. LSHTM findings directly contributed to a refocusing of strategies for combating and eliminating malaria.[5.2] The Medicines for Malaria Venture (MMV) – a leading product development partnership in the field of antimalarial drug research and development – changed its definition of the target candidate profile for a single exposure radical cure for the treatment of acute uncomplicated malaria in children and adults to include killing gametocytes to prevent transmission of the parasite to the mosquito. They have since been engaged in a series of tests to determine which marketed and in-development antimalarials will have gametocidal or transmission-blocking capability.[5.3]

How malaria elimination strategies are targeted

LSHTM findings regarding the heterogeneity of transmission and the existence of transmission 'hotspots' have impacted at individual country level where there is new focus on identifying and targeting geographic clusters of asymptomatic carriage. One example of this is Mexico, where the Department of Health used data generated from passive case detection, case investigations and reactive screenings to map cases to identify risk factors for transmission and then target malaria control interventions in the states of Oaxaca and Chiapas.[5.4] These strategies have contributed to an 83% decrease in reported malaria cases between 2000–2010.

Swaziland's National Malaria Control Programme's (SNMCP) also made strategic transition towards malaria pre-elimination using LSHTM methodologies to identify transmission hotspots. All people residing within 1km of an index case were screened for infection, as were groups with increased risk of infection and at ports of entry. Through this process, the government has been able to reduce the disease burden to negligible levels and to save lives: confirmed cases decreased by 42% between January 2011 and June 2012, putting Swaziland on course to become the first mainland sub-Saharan African nation to eliminate malaria by 2015.[5.5]

Since May 2013, as a direct result of their extensive field experience and their application of direct membrane feeding assays to measure the impact of drug interventions, Drakeley and Bousema have been recruited to provide technical, operational and logistic advice to the PATH MVI for protocol development for African field trials of new vaccines. There are 15,000 children currently enrolled in PATH trials. 'Drs Drakeley and Bousema are important members of MVI's technical working groups on malaria transmission blocking vaccines given their involvement in various aspects of malaria control and elimination'.[5.6]

Impact on international malaria elimination programmes

As a direct result of the expertise gained through the research, Drakeley has been called upon to update national malaria programme managers on the use of serological techniques in malaria epidemiology and management at events including the Workshop for Horn of Africa Network for Monitoring Antimalarial Treatment (Egypt 2009).[5.7]

In September 2012, with inclusion of new field data contributed by LSHTM, WHO published an addendum to its 2010 recommendation proposing a new lower dose of primaquine for wider use as part of the control of the spread of drug resistance.[5.8]

Increased public awareness

LSHTM research has been made accessible to the public through interviews with major media organisations such as BBC News Online (January, May 2010) and the BBC World Service's flagship breakfast programme, *Newsday* (September 2012).

5. Sources to corroborate the impact

5.1 WHO (2010) *Guidelines for the Treatment of Malaria,* 2nd edn. Geneva: WHO, http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 27 September 2013) (work of LSHTM researchers on p. xi and Annex 4, 'Antimalarials and malaria transmission).

5.2 Pinder, M, Moorthy, VS, Mendis, K and Brown, GV, on behalf of WHO MALVAC Committee (2010) *MALVAC 2010: Measures of Efficacy of Anti-malarial Interventions Against Malaria Transmission,* MALVAC 2010 meeting report, 15–16 November. Geneva: WHO, http://www.who.int/vaccine_research/MALVAC_2010_meeting_report.pdf (accessed 27 September 2013) (LSHTM staff at meeting included Bousema, Drakeley and Targett – pp.24–5; Bousema and Drakeley study described as 'highly pertinent data' on p. 8 and cited on p. 21 ref. 3).

5.3 Medicines for Malaria Venture (2012), *Annual Report 2012* (Chapter 5: Medicines for malaria elimination/eradication). Geneva: MMV, http://www.mmv.org/sites/default/files/uploads/docs/publications/annual_report_2012/2012MMVAnnualReportChapter5.pdf (accessed 27 September 2013).

5.4 Moonen, B, Cohen, JM, Snow, RW, Slutsker, L, Drakeley, C, Smith, DL, Abeyasinghe, RR, Rodriguez, MH, Maharaj, R, Tanner, M and Targett G **(**2010) Operational strategies to achieve and maintain malaria elimination, *Lancet*, 376(9752): 1592–1603, doi:10.1016/S0140-6736(10)61269-X (see Figures 2 and 3, pp. 1596–1597).

5.5 Roll Back Malaria Partnership (2012) *Focus on Swaziland: Progress and Impact Series*, country reports, no. 5. Geneva: WHO, http://www.rbm.who.int/ProgressImpactSeries/docs/report13-en.pdf (accessed 22 October 2013).

5.6 Director, Clinical Unit, PATH Malaria Vaccine Initiative.

5.7 WHO (2010) *Report on the Workshop on the Use of Serological Techniques in Malaria Epidemiology and Management for HANMAT Countries,* 2–4 June 2009. Alexandria: WHO, http://applications.emro.who.int/docs/who_em_mal_355_e_en.pdf (accessed 27 September 2013) (pp.15–16).

5.8 WHO (2012) *Updated WHO Policy Recommendation: Single Dose Primaquine as a Gametocytocide in Plasmodium falciparum Malaria*. Geneva: WHO, http://www.who.int/malaria/pq_updated_policy_recommendation_en_102012.pdf (accessed 27 September 2013) (cites evidence in meeting report (http://www.who.int/malaria/mpac/sep2012/primaquine_single_dose_pf_erg_meeting_report_aug2012.pdf); meeting attended by Drakeley, p. 18, and his work, p. 17, included in meeting pre-reads).