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

Unit of Assessment: UoA2 – Public Health, Health Services & Primary Care

Title of case study: Reducing the overdiagnosis of malaria and improving case management of fever in East and West Africa

1. Summary of the impact

Malaria in Africa, traditionally diagnosed from fever symptoms, has been massively overdiagnosed, and other causes of fever missed. This research demonstrated the magnitude of overdiagnosis, undertook trials of rapid diagnostic tests, identified alternative bacterial diagnoses, completed economic appraisals and studied prescriber behaviour. The research underpinned a major change in policy by WHO (2010), substantial investments by the Global Fund to fight HIV, TB and Malaria (GFATM), and changed clinical practice, to direct antimalarials to malaria patients only. In one country alone, 516,576 courses of inappropriate artemisinin-based combination therapy (ACT) were averted, worth in excess of $1m.

2. Underpinning research

Malaria has been routinely diagnosed from fever symptoms alone in Africa, producing massive overdiagnosis and treatment, and inappropriate treatment for other causes of fever. Until 2010, it was WHO policy to treat all children with fever in sub-Saharan Africa as malaria, unless there was an obvious alternative cause, leading to both unnecessary expenditure on antimalarials and health consequences for children with other causes of fever.

The scale of the problem of overdiagnosis of malaria was demonstrated by a widely cited study in 2004 of over 17,000 patients in 13 Tanzanian hospitals led by Hugh Reyburn (Senior Lecturer, LSHTM since 2001) and Professor Chris Whitty (LSHTM since 2001, then Senior Lecturer).[3.1] This showed that only 46% of the 2,062 people treated for severe malaria had *Plasmodium falciparum* parasites. Among patients aged ≥ 5 years in medium transmission areas, only 31.1% treated for malaria had malaria. Of the patients with severe febrile illness incorrectly treated for malaria, 66% were given no antibiotics and 7.6% died. This paper alerted the public health community to a major preventable problem.

Reyburn and Whitty followed this with collaborative studies in East (2004) and West (2009, 2010) Africa showing that overdiagnosis of malaria in febrile patients was even greater in outpatient settings, where malaria is the commonest diagnosis and fever the commonest presenting syndrome. To address this they undertook trials of the effect of providing rapid diagnostic tests (RDTs) for malaria in outpatients in East Africa[3.2] and outpatients and peripheral clinics in West Africa (several settings).[3.3] In outpatients in both settings, RDTs were sensitive and specific under operational conditions, but clinicians ignored negative test results and prescribed antimalarial drugs in about half the cases. Where microscopic diagnosis of malaria was present, RDTs had no significant impact.

Economic analyses of the cost effectiveness and cost benefit of introducing RDTs in a variety of epidemiological settings, including modelling the reality that clinicians often ignore test results,[3.4] showed that except at the extremes of epidemiological malaria transmission, introducing RDTs is cost effective, but that this is very sensitive to assumptions on changes in prescriber behaviour. These analyses were done by PhD student Yoel Lubell, supervised by Professor Anne Mills (LSHTM since 1979), Whitty and Reyburn.

To understand clinician behaviour and its drivers, Clare Chandler (then Research Fellow, LSHTM since 2008) undertook a series of anthropological studies (2008–2013) on clinicians' diagnostic behaviour with respect to fever in East and West Africa.[3.5] These showed that prescriber behaviour was influenced by multiple factors, including peer opinion, and provided the formative research behind behavioural interventions. A barrier to clinicians reducing overprescribing of antimalarials is lack of alternative diagnoses. There is also a need to ensure overtreatment with antibiotics does not substitute for overprescribing antimalarials. Reyburn and Whitty therefore undertook clinical

and microbiological studies of febrile children and adults who tested negative for malaria. These demonstrated a significant burden of bacterial diseases in severe cases, but much lower in outpatient cases, providing the data for guidelines on what to do when patients were malaria-negative.[3.6]

3. References to the research

3.1 Reyburn, HR, Mbatia, R, Drakeley, C, Carneiro, I, Mwakasungula, E, Mwerine, O, Saganda, K, Shao, J, Kitua, A, Olomi, R, Greenwood, BM and Whitty, CJM (2004) Overdiagnosis of malaria in patients with severe febrile illness in Tanzania: a prospective study, *BMJ*, 329(7476): 1212–1215, doi: 10.1136/bmj.38251.658229.55. Citation count: 243.

3.2 Reyburn, H, Mbakilwa, H, Mwangi, R, Mwerinde, M, Olomi, R, Drakeley, C, and Whitty, CJM (2007) Rapid diagnostic tests compared with malaria microscopy for guiding outpatient treatment of febrile illness in Tanzania: randomised trial, *BMJ*, 334(7590): 403–406A, doi: 10.1136/bmj.39073.496829.AE. Citation count: 172.

3.3 Ansah, EK, Narh-Bana, S, Epokor, M, Akanpigbiam, S, Quartey, AA, Gyapong, J and Whitty, CJM (2010) Rapid testing for malaria in settings where microscopy is available and peripheral clinics where only presumptive treatment is available: a randomised controlled trial in Ghana, *BMJ*, 340(c930), doi: 10.1136/bmj.c930. Citation count: 36.

3.4 Lubell, Y, Reyburn, H, Mbakilwa, H, Mwangi, R, Chonya, S, Whitty, CJM and Mills, A (2008) The impact of response to the results of diagnostic tests for malaria: cost-benefit analysis, *BMJ*, 336(7637): 202–205, doi: 10.1136/bmj.39395.696065.47. Citation count: 66.

3.5 Chandler, CIR, Jones, C, Boniface, G, Juma, K, Reyburn, H and Whitty, CJM (2008) Guidelines and mindlines: why do clinical staff over-diagnose malaria in Tanzania? A qualitative study, *Malaria Journal*, 7(53), doi: 10.1186/1475-2875-7-53. Citation count: 58.

3.6 Nadjm, B, Amos, B, Mtove, G, Ostermann, J, Chonya, S, Wangai, H, Kimera, J, Msuya, W, Mtei, F, Dekker, D, Malahiyo, R, Olomi, R, Crump, JA, Whitty, CJM and Reyburn, H (2010) WHO guidelines for antimicrobial treatment in children admitted to hospital in an area of intense *Plasmodium falciparum* transmission: prospective study, *BMJ*, 340(c1350), doi: 10.1136/bmj.c1350. Citation count: 43.

Key grants

Greenwood (LSHTM PI), The Effects of the Level of *Plasmodium falciparum* Transmission on the Pattern of Malaria in north-eastern Tanzania, MRC, 2000–2002, £1.36m. (funded 2004 Reyburn and Whitty study)
Reyburn and Bygbjorg, Improving the Quality, Effectiveness and Access to Basic Treatment for Severe Febrile Illness and Chronic Anaemia Caused by Malaria and Other Common Infections, European Commision EU SANTE, 2004/078-607, 1/4/2005–6/4/2009, £403,934.
Mills, Methods for Economic Evaluation of New Malaria Control Technologies and Delivery Strategies, MRC Studentship, 2004–2008, £17,240 (plus stipend).
Ansah, supervised by Whitty. An Individually Randomised Trial of Rapid Diagnostic Tests in Rural Ghana, Gates Malaria Partnership Re-entry (postdoctoral) grant, Bill & Melinda Gates Foundation, 1/12/2006–30/11/2008, $149,219.

4. Details of the impact

To address the problem of overdiagnosis of malaria and convince practitioners, national and international policy-makers and aid donors of the value of change required a multidisciplinary approach of coordinated research, which LSHTM helped to provide as summarised above. The impacts have been in terms of policy change at international and national levels, changes in clinical practice and cost savings. Health benefits should emerge, though are difficult to quantify at this point.

LSHTM staff were involved in the technical discussions at national, regional, international and donor levels to explain their research findings and set the research in context. At national level,

Reyburn was a member of the Tanzanian malaria diagnostic working group which met between 2007 and 2010.[5.1] At international level, Reyburn (and eight other LSHTM malaria researchers) also participated in the Technical Consultation on Parasitological Confirmation of Malaria Diagnosis (6–8 October 2009, Geneva), which was convened by WHO.[5.2] To influence the main funder of supplies for malaria diagnosis and treatment, the GFATM, LSHTM provided the background briefing for the Global Fund decisions and co-chairmanship of a key consultation (31 May–1 June 2010) on the economics and financing of universal access to parasitological confirmation of malaria.[5.3]

In 2010 WHO changed its policy from one of treating all fevers in Africa as malaria, to one where only parasite-test positive cases were treated, recommending RDTs as a good way to do this.[5.4] The related *BMJ* editorial by Dr Rob Newman, Director of WHO's Global Malaria Programme, explaining this policy change[5.5] cited three studies in support of it, two of which[3.1, 3.3] were from LSHTM research and the third was influenced by LSHTM research.

With this change in policy, the Global Fund is financing RDT roll-out in Africa (including with significant UK government funds). Many countries have rapidly changed policy – for example, in Tanzania, roll-out of RDTs nationwide was completed by end 2011[5.6] (see also 5.1 who is the person giving the presentation in 5.6).

LSHTM researchers have also engaged with other funders beyond the GFATM. For example, their advice is acknowledged in a recent National Audit Office report in the UK which concentrated heavily on the potential waste of resources if antimalarial drugs financed by UK aid go to children without malaria.[5.7] The report acknowledged progress in introducing testing for malaria but argued this should go further, recommending on p. 12: 'Specify milestones and targets to reduce unnecessary treatment by focusing drug consumption on positively tested cases, in public and private sectors,' reflecting the key message of LSHTM research.

Other LSHTM malaria experts have helped to spread the findings of the research by Reyburn and Whitty through their engagement activities with relevant stakeholders. For example, Schellenberg (Professor of Malaria and International Health, since 2005) included the role of RDTs in reports authored for the UK All Party Parliamentary Group on Malaria in 2011, 2012 and 2013.[5.8] School staff have also worked with the media to raise awareness and understanding of the importance of RDTs, for example Schellenberg's interview with the BBC World Service's *Focus on Africa* programme (September 2011), where he stated that testing is 'revolutionising malaria control'. This interview attracted 10m listeners in Africa.[5.9]

The impact of the WHO policy change and subsequent national programme changes has already been considerable. A study in Senegal (which cited LSHTM work) found that the change to pre-treatment parasitological confirmation reduced ACT prescriptions from 72.9% of malaria-like febrile illness to 31.5%, reaching close equivalence to confirmed malaria (29.9% of 584,873 suspect fever cases). An estimated 516,576 courses of inappropriate ACT prescription were averted, worth in excess of $1m.[5.10]

5. Sources to corroborate the impact

5.1 Deputy Manager of the National Malaria Control Programme, Tanzania.

5.2 WHO (2010) *Parasitological Confirmation of Malaria Diagnosis: Report of a WHO Technical Consultation Geneva, 6–8 October 2009*. Geneva: WHO, http://whqlibdoc.who.int/publications/2010/9789241599412_eng.pdf (accessed 15 November 2013) (Reyburn is acknowledged for his help in preparing the proceedings; eight LSHTM staff are acknowledged for their contributions discussed at the meeting).

5.3 The Global Fund & WHO (2010) *Consultation on the Economics and Financing of Universal Access to Parasitological Confirmation of Malaria, May 31–June 1 2010: Meeting Report*. Geneva: The Global Fund, http://www.theglobalfund.org/documents/amfm/AMFm_EconFinanceDiagnostics_Report_en/

(accessed 15 November 2013) (includes presentations from LSHTM staff; names co-chairs, p. 16; WHO pre-read includes LSHTM authorship:
Schellenberg, D, Reyburn, H, Yeung, S, Bosman, A, Snow, R, Lansang, MA, Gelband, H, Newman, R, Jamison, D and Adeyi, O, (2010) *Consultation on the Economics and Financing of Universal Access to Parasitological Confirmation of Malaria, Pre-read*, draft, Appendix 2, Geneva: The Global Fund, http://www.theglobalfund.org/documents/amfm/AMFm_EconFinancePreread_Appendix02_en/, accessed 15 November 2013).

5.4 WHO (2010) *Guidelines for the Treatment of Malaria*, 2nd edn. Geneva: WHO, http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 15 November 2013).

5.5 Newman, RD (2010) Malaria control beyond 2010', *BMJ*, 340(c2714), doi: 10.1136/bmj.c2714.

5.6 Mandike, R (2011) Recent developments and achievements in malaria control in Tanzania (mainland), presentation given at the DPG-Health Meeting, 4 May. Tanzania: DPG (Development Partners Group), http://www.tzdpg.or.tz/fileadmin/documents/dpg_internal/dpg_working_groups_clusters/cluster_2/health/DPGH_Meeting_Documents_2011/National_Malaria_Control_Program-Tanzania_Mainland.pdf (accessed 15 November 2013).

5.7 National Audit Office (2013) *Malaria*, HC534. London: The Stationery Office, http://www.nao.org.uk/wp-content/uploads/2013/07/10181-001-Malaria-Book.pdf (accessed 15 November 2013).

5.8 All-Parliamentary Group on Malaria and Neglected Tropical Diseases (2011) *The Control of Malaria 2005–15: Progress and Priorities Towards Eradication, the Sixth Report of the All-party Parliamentary Group on Malaria and Neglected Tropical Diseases*. London: House of Commons, http://healthmarketinnovations.org/sites/default/files/The%20Control%20of%20Malaria%202005-2015%202010.pdf (accessed 15 November 2013) (pp. 16–19).

All-Parliamentary Group on Malaria and Neglected Tropical Diseases (2012) *Targeting Zero: Sustaining Success in Malaria Control: All-parliamentary Group on Malaria and Neglected Tropical Diseases Report 2010–2011*. London: House of Commons, http://malaria.lshtm.ac.uk/sites/default/files/uploads/docs/APPMG_7th_Annual_Report_11th_July_2011.pdf (accessed 15 November 2013)(pp. 6–7).

All-Parliamentary Group on Malaria and Neglected Tropical Diseases (2013) *Malaria: Consolidating the Gains: Report for the All-parliamentary Group on Malaria and Neglected Tropical Diseases 2011–2012*. London: House of Commons, http://redballoonhosting.com/appmg/wp-content/uploads/2013/04/APPMG-Malaria-Report-Consolidating-the-Gains.pdf (accessed 15 November 2013) (p. 2).

5.9 Malaria No More (2011) Listen to Professor David Schellenberg on BBC World Service, news briefing, 21 September, http://malarianomore.org.uk/news/listen-to-professor-david-schellenberg-on-bbc-world-service (accessed 15 November 2013).

5.10 Thiam, S, Thior, M, Faye, B, Ndiop, M, Diouf, ML, Diouf, MB, Diallo, I, Fall, FB, Ndiaye, JL, Albertini, A, Lee, E, Jorgensen, P, Gaye, O and Bell, D (2011) Major reduction in anti-malarial drug consumption in Senegal after nationwide introduction of malaria rapid diagnostic tests, *PLoS ONE*, 6(4): e18419, doi:10.1371/journal.pone.0018419.