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

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

Title of case study: Intermittent preventive treatment for malaria control

1. Summary of the impact

LSHTM researchers carried out the initial trials of intermittent preventive treatment in infants (IPTi), a strategy to improve malaria control in very young children. LSHTM staff were active in setting up and running a dedicated research consortium which developed and executed a research agenda to provide data to inform policy. School staff presented evidence to a series of WHO policy-making meetings which in 2009 recommended that IPTi should be included as part of routine malaria control. This policy, which has been adopted in one country and discussed by eight others, has the potential to benefit hundreds of millions of lives.

2. Underpinning research

Malaria remains one of the world's major killers. At the start of the millennium it was responsible for a million deaths a year, most of the victims being children in sub-Saharan Africa. In the late 1990s and early 2000s a new strategy, intermittent preventive treatment (IPT), was evaluated. IPT involves the administration of a treatment dose of an antimalarial drug at pre-specified times, irrespective of the presence of malaria parasites.

Randomised, controlled trials (RCTs) of IPTi were led by LSHTM's Professor Daniel Chandramohan in Ghana[3.1] and northern Tanzania.[3.2] Both provided evidence of a beneficial effect of IPTi, the Tanzanian study also providing insights into the drug characteristics (for example, long half-life) required for efficacy of IPTi. This study was undertaken under the auspices of the IPTi Consortium, a research collaboration with partners across Europe, the USA and Africa, set up in 2003 by David Schellenberg at LSHTM. In addition to evaluating the safety and efficacy of IPTi with a number of antimalarial drugs across a range of malaria transmission settings,[3.2] the Consortium generated operational experience of IPTi implementation[3.3] through a large-scale pilot implementation study led by Professor David Schellenberg. Additional in-depth studies led by LSHTM staff included evaluations of the effect of the routine use of IPTi on the spread of drug resistance,[3.4] the cost effectiveness and acceptability[3.5] of IPTi and an assessment – through a systematic review and modelling exercise – of the potential impact of IPTi in a range of settings. A pooled analysis with major contributions from LSHTM staff showed that IPTi reduces clinical malaria by 30% and anaemia by 21% in the first year of life.[3.6] LSHTM staff presented evidence to a series of policy-making meetings at WHO which recommended in 2009 the inclusion of IPTi as part of the global malaria control recommendations.

Key academics involved in the underpinning research are D. Schellenberg (role pre 2004 LSHTM/Ifakara Health Institute, 2003–2007; Senior Lecturer, LSHTM 2004-5 and Professor of Malaria and International Health, LSHTM, 2005-present); D. Chandramohan (Professor of Public Health, 2009–present, LSHTM since 1992, then Research Fellow); and B. Greenwood (LSHTM Professor of Clinical Tropical Medicine 1996–present). Other involved LSHTM staff include Dr I. Carneiro, who examined the potential health impacts of IPTi in different settings and led the development of a web tool (http://ipti.lshtm.ac.uk/) to support decision-making at country level (2004–2007, Lecturer); Dr L. Conteh, who showed that IPTi costs only USD 1.36–4.03 per malaria episode averted (2010, Senior Lecturer); Drs C. Roper and R. Pearce, who confirmed the modest impact of IPTi on drug resistance (2004–2009, Senior Lecturer and Research Fellow); Dr R. Pool, who confirmed the acceptability of IPTi (2004–2008, Senior Lecturer); and Dr J. Schellenberg, who led the development of a strategy for operationalisation of IPTi in Tanzania (2004–2008 Senior Lecturer then Reader).

3. References to the research

3.1. Chandramohan, D, Owusu-Agyei, S, Carneiro, I, Awine, T, Amponsa-Achiano, K, Mensah, N, Jaffar, S, Baiden, R, Hodgson, A, Binka, F and Greenwood B (2005) Cluster randomised trial of intermittent preventive treatment for malaria in infants in area of high, seasonal transmission in

Ghana, *BMJ*, 331(7519): 727–733, doi: 10.1136/bmj.331.7519.727. Citation count: 105

3.2. Gosling, RD, Gesase, S, Mosha, JF, Carneiro, I, Hashim, R, Lemnge, M, Mosha, FW, Greenwood, B and Chandramohan, D (2009) Protective efficacy and safety of three anti-malarial regimens for intermittent preventive treatment for malaria in infants: a randomised, double-blind, placebo-controlled trial, *Lancet*, (374): 9700: 1521–1532, doi: 10.1016/S0140-6736(09)60997-1. Citation count:39

3.3. Manzi, F, Schellenberg, J, Hamis, Y, Mushi, AK, Shirima, K, Mwita, A, Simba, A, Rusibamayila, N, Kitambi, M, Tanner, M, Alonso, P, Mshinda, H and Schellenberg, D (2008) Intermittent preventive treatment for malaria and anaemia control in Tanzanian infants: the development and implementation of a public health strategy, *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 103(1): 79–86, doi:10.1016/j.trstmh.2008.08.014. Citation count: 12

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3.5. Pool, R**,** Mushi, A**,** Armstrong Schellenberg J**,** Mrisho, M**,** Alonso, P**,** Montgomery, C, Tanner, M, Mshinda, H and Schellenberg, D (2008) The acceptability of intermittent preventive treatment of malaria in infants (IPTi) delivered through the expanded programme of immunization in southern Tanzania', *Malaria Journal*, 7(213), doi: 10.1186/1475-2875-7-213. Citation count: 22

3.6. Aponte, JJ, Schellenberg, D, Egan, A, Breckenridge, A, Carneiro, I, Critchley, J, Danquah, I, Dodoo, A, Kobbe, R, Lell, B, May, J, Premji, Z, Sanz, S, Sevene, E, Soulaymani-Becheikh, R, Winstanley, P, Adjei, S, Anemana, S, Chandramohan, D, Issifou, S, Mockenhaupt, F, Owusu-Agyei, S, Greenwood, B, Grobusch, MP, Kremsner, PG, Macete, E, Mshinda, H, Newman, RD, Slutsker, L, Tanner, M, Alonso, P and Menendez, C (2009) Efficacy and safety of intermittent preventive treatment with sulfadoxine-pyrimethamine for malaria in African infants: a pooled analysis of six randomised, placebo-controlled trials, *Lancet*, 374(9700): 1533–1542, doi: 10.1016/S0140-6736(09)61258-7. Citation count: 93

Key grants

Chandramohan, the second study of IPTi, EPI-Linked Intermittent Preventive Treatment for Malaria in Infants, DFID, 1998–2003, £330,000.
Schellenberg D joined LSHTM in 2003 and led the development of the $28 million IPTi Consortium proposal. Funding was approved by the Bill and Melinda Gates Foundation, 2004-2009. This included funds for the following projects, led by LSHTM PIs:
1 Chandramohan, Options of Drugs for Intermittent Preventive Treatment for Malaria in Infants, 2003–2008, $1.8m.
2 Schellenberg D, Community Effectiveness of Intermittent Treatment (IPT) Delivered through the Expanded Program of Immunisation for Malaria and Anemia Control in Tanzanian Infants, 2004–2009, $6.8m.
3 Chandramohan, Gosling, Roper and Schellenberg D, The Measurement of Antimalarial Drug Resistance Across the Trials in the Intermittent Preventive Treatment in Infants (IPTi) Consortium, 2007–2008, $750,356.
4 Carneiro, Intermittent Preventive Treatment for African Children: Where and How Should IPT be applied?, 2004–2007, $561,217.

4. Details of the impact

Few strategies exist to control malaria, despite the fact that, every year, it kills at least 600,000 people, predominantly very young children in Africa. The trials and analyses of IPTi led by LSHTM staff made key contributions to the WHO decision to recommend IPTi as policy.

The IPTi Consortium, developed by Prof. D Schellenberg at LSHTM in 2003, brought together some of the leading centres of malaria research in Africa, Europe and the USA, plus two UN agencies, to complete the evaluation of IPTi. The Consortium generated key evidence to move beyond the proof of concept towards a strategy for deployment as part of routine immunisation programmes. At the time, the Consortium model was a novel approach to generate all the critical information for policy consideration. Under the Consortium, staff from all LSHTM faculties generated information on issues surrounding the choice of drug for IPTi, the relationship between IPTi and the development of drug resistance, and the cost effectiveness, acceptability, mortality impact and community effectiveness of IPTi.

School staff presented evidence to WHO technical expert groups in 2006 and 2007, but the WHO policy-making process became politicised and the US Institute of Medicine (IOM) undertook its own review of the evidence. Prof. D Schellenberg participated in the IOM committee meeting in January 2008,[5.1] giving a two-hour presentation on the acceptability, cost effectiveness and applicability of IPTi, plus an assessment of the impact of IPTi on drug resistance. This was based primarily on data from the pilot implementation study he led in southern Tanzania.

LSHTM staff presented to all three WHO technical review meetings, including the key session in April 2009 which recommended IPTi as policy.[5.2] At this meeting, the Consortium presented robust information on the efficacy and safety of IPTi in different epidemiological settings and excluded the possibility of adverse interactions between IPTi and the serological response to EPI vaccinations. Prof. D Schellenberg presented information on the safety of IPTi, its health impacts, effect on drug resistance and the feasibility of large-scale deployment based on experience in the southern Tanzania study.

In September 2009 another WHO expert committee was convened to consider the relationship between IPTi and drug resistance.[5.3] Dr Roper presented her analyses of the molecular markers of resistance to *sulfadoxine-pyrimethamine* and their relationship to IPTi efficacy in the Consortium's studies. Prof D Schellenberg presented the evaluation of the impact of IPTi on the spread of resistant parasites in the pilot implementation study in southern Tanzania. This led to a key resistance-based criterion for countries to consider prior to implementation.

The final step in the policy process was the endorsement in October 2009[5.4] of the Strategic Advisory Group of Experts (SAGE) for the WHO Expanded Programme on Immunisation. Prof. D Schellenberg once more presented information (on efficacy, coverage, effectiveness, acceptability, cost effectiveness, implementation lessons and impact on EPI time use) from the southern Tanzania project.

WHO recommended IPTi as a malaria control tool for implementation in areas of moderate to high transmission in March 2010.[5.5] This recommendation was based on the findings of seven studies, including those carried out by LSHTM staff, showing the benefits of IPTi in reducing malaria, anaemia and hospital admissions. Joint WHO/UNICEF implementation guidelines[5.6] were released in September 2011. These draw heavily on the LSHTM-led southern Tanzanian pilot implementation study. At the time of writing, IPTi has been adopted by the national malaria control programme of Burkina Faso.[5.7] In 2012 a further eight nations met to discuss implementation.[5.8] Unpublished estimates suggest that up to a million malaria episodes could be prevented annually if IPTi were rolled out in the countries where studies have been conducted.

LSHTM's work on IPTi produced a number of additional benefits. Firstly, the Consortium model of malaria research has been adopted by others, including the Artemisinin-based Combination Treatment (ACT) Consortium funded in 2007 and led by Prof. D Schellenberg since 2009. Secondly, the review and modelling-based exercise to understand the age-pattern of malaria disease and death in different transmission settings, led by Dr Ilona Carneiro, continues to inform discussions in WHO, regulators and within industry, about the possible deployment and dose scheduling of new tools to control malaria. For example, this work has been presented and discussed at several meetings during the reporting period of WHO's Joint Technical Expert Group on malaria vaccines in pivotal phase 3 evaluation.[5.9] Finally, the complexities of the policy-making

process provided a learning opportunity, as captured by the LSHTM's Dr Cruz,[5.10] helping groups (including the ACT Consortium) to engage better with policy-makers.

5. Sources to corroborate the impact

5.1 Committee on the Perspectives on the Role of Intermittent Preventive Treatment for Malaria in Infants (2008) *Assessment of the Role of Intermittent Preventive Treatment for Malaria in Infants: Letter Report*. Washington, DC: National Academies Press, http://books.nap.edu/openbook.php?record_id=12180 (accessed 16 October 2013). Note references to work of IPTi Consortium Appendix B, p. 69 and David Schellenberg's presentation on 9 January 2008, 2.30–4:30 p.m., *Acceptability, Cost Effectiveness, Drug Resistance, Applicability of IPTi-SP, Effectiveness study of IPTi-SP*, http://www.iom.edu/Activities/Nutrition/PrevMalariaTreatment/2008-JAN-09.aspx.

5.2 WHO (2009) *Report of the Technical Consultation on Intermittent Preventive Treatment in Infants (IPTi), Technical Expert Group on Chemotherapy,* 23 –24 April. Geneva: WHO, http://www.who.int/malaria/publications/atoz/tegconsultiptiapr2009report.pdf (accessed 16 October 2013) (note references 3, 6, 9–13, 15 and list of participants/observers).

5.3 WHO (2009) *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,* 10–11 September. Geneva: WHO, http://www.who.int/malaria/publications/atoz/who_sp_ipti_resistance_march_2010.pdf (accessed 16 October 2013) (note p. 6, list of participants).

5.4 WHO (2009) Reports from other immunization-related advisory committees: Malaria: co-administration of intermittent preventive treatment of infants (IPTi) for malaria at time of immunization, *WHO Weekly Epidemiological Record,* 50(84): 529–530, http://www.who.int/wer/2009/wer8450.pdf (accessed 16 October 2013).

5.5 WHO (2010) *WHO Policy Recommendation on Intermittent Preventive Treatment During Infancy with Sulfadoxine-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 16 October 2013) (note footnote 2 referencing the 2009 TEG meeting).

5.6 WHO Global Malaria Programme (GMP), WHO Department of Immunization, Vaccines & Biologicals (IBV) and UNICEF (2011) *Intermittent Preventive Treatment for Infants Using Sulfadoxine-pyrimethamine (SP-IPTi) for Malaria Control in Africa: Implementation Field Guide*. Geneva: WHO, http://whqlibdoc.who.int/hq/2011/WHO_IVB_11.07_eng.pdf (accessed 16 October 2013) (see footnotes on p. 9, contents of Chapters 4–6, e.g. Figure 6 on p. 32 and Figure 8 on p. 35, and key references on p. 47).

5.7 WHO (2012) *World Malaria Report 2012*. Geneva: WHO, http://www.who.int/malaria/publications/world_malaria_report_2012/wmr2012_no_profiles.pdf (accessed 16 October 2013) (see section 5.2.2, p. 32).

5.8. WHO (2011) *World Malaria Report 2011*. Geneva: WHO, http://apps.who.int/iris/bitstream/10665/44792/2/9789241564403_eng_full.pdf (accessed 16 October 2013) (see section 5.1.2, p. 36).

5.9. WHO-UNAIDS HIV Vaccine Initiative, WHO.

5.10. Cruz, VO and Walt, G (2013) Brokering the boundary between science and advocacy: the case of intermittent preventive treatment among infants, *Health Policy and Planning*, 28(6): 616–625, doi: 10.1093/heapol/czs101.