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

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

Title of case study: The technology of insecticide treated nets for malaria control

1. Summary of the impact

Twenty years of comprehensive research into long-lasting insecticidal nets (LLINs) by LSHTM have contributed substantially to the prevention of around 1m deaths from malaria between 2008 and 2013. The research made a direct impact on guidelines and strategies issued by WHO as well as driving new technologies for insecticide-treated nets (ITNs), with downstream commercial benefits. Without the evolution of LLIN technology driven by LSHTM research, the large-scale roll-out of the new generation of nets (described in more detail in the other LSHTM impact case study on this body of research) would not have been possible.

2. Underpinning research

Insecticide-treated nets (ITNs) have played an important part in recent reductions in malaria incidence and deaths. This case study describes LSHTM research into the technical characteristics required to make nets as effective as possible. Lead researchers were Dr Jo Lines, Reader in Malaria Control and Vector Biology, at LSHTM since 1984 (seconded to WHO 2008–2011); Mark Rowland, Professor of Medical Entomology, at LSHTM since 2000; and Chris Curtis, Professor of Medical Entomology, at LSHTM from 1976 until his death in 2008. As so many LSHTM researchers made a contribution to research in this field, work contributing to introducing and distributing ITNs is described in a separate case study.

By 1993, LSHTM was already established as a leading player in developing LLINs and work in this area continued throughout the research assessment period.

LSHTM made numerous contributions to methods currently used for product development testing, epidemiological research and standardisation and quality control of ITNs and LLINs. One major contribution was the development and modernisation of **experimental hut methods**. Experimental huts were first used to evaluate insecticide treatments in the 1960s, but LSHTM work introduced more rigorous and innovative methods including Latin Square designs and the genotyping of wild mosquitoes after capture to measure the impact of insecticide resistance,[3.1] carried out in 1999.

In 2001–2004, LSHTM researchers undertook a multicentre study that compared various methods of washing LLINs and testing their performance in three contrasting settings.[3.2] Other studies investigated various non-pyrethroid insecticides, and found some to be promising alternative insecticides for bed nets.

During 1994–1996, when LSHTM was developing the first home treatment kits for bed nets (enabling users to re-treat nets with insecticide during washing) WHO stated that ITNs were considered safe, but did not provide supporting evidence. In 1999, LSHTM employed two external consultant toxicologists to carry out and publish a formal **risk assessment**, together with Lines;[3.3] the findings confirmed that the benefits of using ITNs in reducing morbidity and mortality from malaria were considerable and that the risk-benefit ratio was very favourable.

In 2007/2008, Rowland's group carried out further experimental hut research in West Africa, in response to the discovery that **insecticide resistance genes in mosquito vectors** were spreading rapidly. This research was the first to provide clear and conclusive evidence that resistance does reduce the effectiveness of ITNs.[3.4]

In 1993–1997, Curtis had studied methods of responding to or **preventing the emergence of pyrethroid resistance** in *Anopheles* vectors. He concluded that there was no easy solution to the problem of resistance management,[3.5] but that deploying mixtures of dissimilar insecticides was among the most promising strategies. Investigation of various non-pyrethroid insecticides found some to be promising alternatives for bed nets.[3.1]

Recognising the grave threat that resistance presented to the future of pyrethroid LLIN and the long lead time required to develop new safe and effective alternatives, LSHTM joined in strategic partnership with WHOPES and pesticide and textile industry from 2002 to identify and test new active ingredients. Thus when WHO called in 2008 for the **development of products containing new active ingredients, insecticide mixtures and combinations**, studies evaluating several new products were already well advanced, including one formulation using a synergist which has since been marketed (as Permanet 3.0) and another more effective and soon-to-be launched product using the insecticide chlorfenapyr, which is new in public health but has a long history of use in agriculture.[3.6]

3. References to the research

3.1 Kolaczinski, JH, Fanello, C, Hervé, JP, Conway, DJ, Carnevale, P and Curtis, CF (2000) Experimental and molecular genetic analysis of the impact of pyrethroid and non-pyrethroid insecticide impregnated bednets for mosquito control in an area of pyrethroid resistance, *Bulletin of Entomological Research*, 90(2): 125–132, doi: 10.1017/S0007485300000237. Citation count: 70

3.2 Graham, K, Kayedi, MH, Maxwell, C, Kaur, H, Rehman, H, Malima, R, Curtis, CF, Lines, JD and Rowland, MW (2005) Multi-country field trials comparing wash-resistance of PermaNet™ and conventional insecticide-treated nets against anopheline and culicine mosquitoes, *Medical and Veterinary Entomology*, 19(1): 72–83, doi: 10.1111/j.0269-283X.2005.00543.x. Citation count: 55

3.3 Barlow, SM, Sullivan, FM and Lines, J (2001) Risk assessment of the use of deltamethrin on bednets for the prevention of malaria, *Food and Chemical Toxicology*, 39(5): 407–422, doi: 10.1016/S0278-6915(00)00152-6. Citation count: 44

3.4 N'Guessan, R, Corbel, V, Akogbéto, M and Rowland, M (2007) Reduced efficacy of insecticide-treated nets and indoor residual spraying for malaria control in pyrethroid resistance area, Benin, *Emerging Infectious Diseases*, 13(2): 199-206, doi: 10.3201/eid1302.060631. Citation count: 159

3.5 Curtis, CF, Miller, JE, Hodjati, MH, Kolaczinski, JH and Kasumba, I (1998) Can anything be done to maintain the effectiveness of pyrethroid-impregnated bednets against malaria vectors?, *Philosophical Transactions of the Royal Society of London, Series B, Biological Sciences*, 353(1376):1769–1775, doi: 10.1098/rstb.1998.0329. Citation count: 50

3.6 N'Guessan, R, Boko, P, Odjo, A, Akogbeto, M, Yates, A and Rowland, M (2007) Chlorfenapyr: a pyrrole insecticide for the control of pyrethroid or DDT resistant *Anopheles gambiae* (Diptera: Culicidae) mosquitoes, *Acta Tropica*, 102(1): 69-78, doi: 10.1016/j.actatropica.2007.03.003. Citation count: 13.

Key grants

3.1 Curtis, Sustainability of Malaria Control with Impregnated Bednets, MRC, 1998–2004, £1,272,640.
3.3 Lines, Malaria Knowledge Programme, DFID, 1998–2003, £2.5m.
3.4 Rowland, Gates Malaria Partnership Vector Control Research Project, Bill & Melinda Gates Foundation, 2001–2006, £600,000.
3.5 Curtis, Application of Genetics and Etiology of Mosquitoes, MRC, 1993–1998, £450,795.
3.6 Rowland, IVCC Field Site Studies, Bill & Melinda Gates Foundation, 2007–2010, £513,349.

4. Details of the impact

Two decades of research at LSHTM have made a vital contribution to successful efforts to reduce the number of deaths from malaria. Using WHO methods of estimation, it can be estimated that approximately 1m malaria-related deaths were prevented by LLINs between 2008 and 2013, mostly among African children.[5.1, 5.2] Although it is clearly impossible to quantify the contribution of LSHTM research to this development with precision, the leading role LSHTM has played in this field gives an indication of its key role in achieving this impact.

LSHTM research involving experimental huts has made a direct impact on the WHO Pesticide Evaluation Scheme (WHOPES) whose authority in terms of the standardisation and quality control of ITNs is accepted by industry and donors. The **experimental hut methods** and methods of ITN field evaluation developed by LSHTM are described in WHO's *Guidelines for Laboratory and Field Testing of Long-lasting Insecticidal Nets* (2013).[5.3, 5.4] On account of his research expertise, Rowland played a leading role in drafting these guidelines[5.4] and most of the techniques are now too standardised for this second version to cite their origins. LSHTM's influence is still visible however, in the guidelines' use of Curtis' diagram of an experimental hut (p.17) and LSHTM's washing, field testing and quality control methodologies.

Much of WHOPES's work on ITNs prior to producing these guidelines involved evaluating a large number of datasets from field research in Africa, most of them produced by LSHTM and/or the French IRD (Institut de recherche pour le développement). Overall, LSHTM contributed to the data portfolio of 9 out of 11 LLIN products evaluated by WHOPES.[5.3] The key role of the WHOPES process is that it provides donors with a guarantee of product quality and reliability; without this guarantee, the very rapid scaling-up of LLIN procurement in the 2007–2010 period (>140m nets procured in 2010) would not have been possible. The importance of this guarantee is illustrated by the fact that the Global Fund will not allow its funds to be used to buy nets not recommended by WHOPES.

The **risk assessment** carried out by Lines and collaborators[3.3] highlighted the fact that WHO was still lacking a formal and documented position on the safety of ITNs. The LSHTM work prompted WHO to publish a general review of safety aspects and then to employ the same team of toxicologists who had worked with Lines to develop an extended generic set of risk assessment methods (revised edition 2012), using the same approach and format as in the published paper. This document (which also cites the original 2001 paper) gives manufacturers of ITNs a protocol to follow with regard to toxicology and safety.[5.5]

WHO's *Global Plan for Insecticide Resistance Management in Malaria Vectors* (GPIRM), published in 2012,[5.6] represents a radical shift in technical strategies for malaria **vector control**, and its implications will take many years to implement. The plan quotes very little actual data, but in arguing that **resistance** can reduce effectiveness of vector control, it relies heavily on 3.4, and reproduces a figure from that article.

WHO's technical recommendations for **insecticide resistance management strategies**, which form the technical basis of the GPIRM implementation plan, were agreed by a group of experts convened by WHO in 2010, including Lines and Rowland. The meeting report[5.7] quotes 3.4 as a basic source. The meeting concluded that the use of mixtures of dissimilar insecticides was one of the most promising possible methods of resistance management, as had been shown to be the case by LSHTM research, and that manufacturers should be encouraged to develop such products. This recommendation was then included in the GPIRM plan[5.7] and several manufacturers have since started developing such 'mixture' products, for example Japan-based Sumitomo Chemical[5.8] and Swiss-headquartered Vestergaard Frandsen, makers of Permanet 3.0.[5.9] In 2010, German chemical giant BASF announced an agreement with LSHTM and the Innovative Vector Control Consortium to develop a new generation of malaria prevention products based on the BASF insecticide chlorfenapyr, including a new LLIN;[5.10] this decision drew on formative work by Rowland's group since 2003. Although these products are not yet in public health use, they have entered the WHOPES evaluation process and this manufacturers' investment represents a substantial commercial impact in itself, and clearly indicates that manufacturers expect these to gain significant market share in the next generation of vector control products.

5. Sources to corroborate the impact

5.1 WHO (2012) *World Malaria Report 2012.* Geneva: WHO, http://www.who.int/malaria/publications/world_malaria_report_2012/en/ (accessed 11 November 2013) (see pp. 59–61).

5.2 Roll Back Malaria Partnership (2011) *A Decade of Partnership and Results,* Progress & Impact Series, no. 7*,* September. Geneva: WHO, http://www.rbm.who.int/ProgressImpactSeries/docs/report8-en.pdf (accessed 11 November 2013) (pp. 18, 68–69); Roll Back Malaria (2010) *World Malaria Day 2010: Africa Update,* Progress & Impact Series, no. 2, April. Geneva: WHO http://www.rbm.who.int/ProgressImpactSeries/docs/wmd2010report-en.pdf (accessed 11 November 2013) (p. 38).

5.3 See paragraphs 2 and 3 of letter from Coordinator of the Vector Control Unit at the Global Malaria Programme, WHO. Available on request.

5.4 WHO (2013) *Guidelines for Laboratory and Field-testing of Long-lasting Insecticidal Nets*. Geneva: WHO, http://apps.who.int/iris/bitstream/10665/80270/1/9789241505277_eng.pdf (accessed 11 November 2013).

5.5 WHO (2012) *A Generic Risk Assessment Model for Insecticide-treated Nets: Revised Edition*. Geneva: WHO, http://apps.who.int/iris/bitstream/10665/44862/1/9789241503419_eng.pdf (accessed 12 November 2013) (the second paragraph, p. 2, of the *Background* section of this document refers to work led by Lines – Barlow et al. 2001, *Food Chem Toxicol*, 39: 407–422 – as the first 'detailed risk assessment' of a pyrethroid on nets).

5.6 WHO (2012) *Global Plan for Insecticide Resistance Management in Malaria Vectors (GPIRM)*. Geneva: WHO, http://www.who.int/malaria/vector_control/ivm/gpirm/en/index.html (accessed 12 November 2013).

5.7 WHO (2011) *The Technical Basis for Coordinated Action Against Insecticide Resistance: Preserving the Effectiveness of Modern Malaria Vector Control,* meeting report, 4–6 May 2010,. Geneva: WHO, http://www.who.int/malaria/publications/atoz/9789241501095/en/index.html (accessed 12 November 2013) (IM6 is the implementation plan, less technical and IM7 the technical foundation).

5.8 Sumitomo Chemical (2010) Sumitomo Chemical launches 'Olyset® Plus', press release, http://www.olyset.net/resourcecenter/news/20120711_1/ (accessed 12 November 2013).

5.9 Vestergaard (2013) *Permanet® 3.0: First Insecticide-Synergist Combination Net. Technical Basis for Deployment in Areas with Pyrethroid-Resistant Malaria Vectors*. Lausanne: Vestergaard Frandsen S.A., http://www.vestergaard.com/images/pdf/PN3-TechEng_latest.pdf (accessed 14 November 2013).

5.10 BASF (2010) News release: next-generation malaria control, press release, 21 April, http://www.agro.basf.com/agr/AP-Internet/en/content/news_room/news/next-generation-malaria-control (accessed 12 November 2013).