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

Unit of Assessment: 2

Title of case study: Methods for malaria control: evaluation of vector control products to improve personal and community protection from malaria

Period when the underpinning research was undertaken: 2000-2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed:
Mark Rowland	Reader; Professor	1/1/00-present
Immo Kleinschmidt	Reader; Professor	26/2/07-present
Natasha Protopopoff	Assistant Professor	1/1/11-present
Raphael N'Guessan	Research Fellow; Assistant Professor	1/10/07-present
Corine Ngufor	Research Fellow; Assistant Professor	20/5/11-present
Jo Lines	Reader; Professor	1/10/82-present (WHO secondment 2009-2012)
& associated research teams		

Period when the claimed impact occurred: 2013-2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact (indicative maximum 100 words)

Research by LSHTM and partners helped protect people from malaria through extensive and innovative testing of ways of controlling mosquitoes in homes and communities. Their methodology to test the effectiveness of long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) led to rigorous criteria for WHO to use to evaluate and validate vector control products. As a result, over 20 new products were approved, accelerating the market for LLINs. Since 2014, 1.3 billion safe and effective nets have been distributed by malaria programmes to those in need. LSHTM staff expertise and research also underpinned the implementation of crucial insecticide resistance monitoring on a global scale.

2. Underpinning research (indicative maximum 500 words)

In 2019, there were approximately 229 million cases of malaria and 209,000 deaths. The World Health Organization (WHO) African Region carries a disproportionately high share of the global malaria burden, accounting for approximately 94% of the world's cases and deaths. Controlling mosquitoes, as the vector which spreads the disease, is key to preventing malaria, and relies on 2 main strategies: long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS). LLINs are mosquito nets treated with insecticides at the point of manufacture which remain effective for up to 3 years. The net provides a physical barrier against mosquitoes and the insecticide repels and kills susceptible mosquito vectors that come into contact with the net. Various manufacturers have developed LLIN brands involving different insecticide combinations and different technologies.

Trials before 2000 demonstrated the efficacy of standard LLINs treated with pyrethroid insecticide in reducing mortality, and provided evidence on cost-effectiveness and implementation strategies. However, technical developments such as improved durability after washing LLINs, and standardised performance testing, were required to enable approval, production and rollout of quality-controlled nets across the range of eco-epidemiological conditions in malaria endemic countries. In addition, researchers needed to develop and test new insecticides for nets and wall spraying because mosquitoes have become resistant to current insecticides.

Assessing performance of nets

From 2001 to 2004, researchers at LSHTM led by Rowland and Lines carried out a landmark study in Iran, Pakistan and Tanzania testing different methods of washing LLINs to compare their performance. This showed that the prototype LLIN, PermaNet, varied in wash durability depending on formulation and quality control of production, but that the subsequent version 2.0 readily withstood multiple washes (3.1).

From 2002 to 2007 Rowland led further important research in 'experimental huts' (rooms of standard size and shape simulating a human dwelling) to determine the effects of insecticide by monitoring unimpeded mosquito activity. This enabled controlled testing and evaluation, mimicking the field performance of LLINs on mosquitoes and malaria control. The methodology was used to test new LLIN and IRS products in household and community randomised intervention trials. The experimental hut trials became the gold standard in LLIN and IRS research, with outputs from these studies forming the basis for predicting the likely effectiveness of certain products or methods to control malaria mosquito vectors in a community.

Addressing the problem of resistance

Research in 2007 in Benin produced the first conclusive evidence that more mosquitoes were surviving insecticides, and that insecticide resistance reduced entomological effectiveness and personal protection for people using insecticide-treated nets (3.2, 3.3). At this time, LSHTM entered into strategic partnership with WHO and manufacturers to develop new methods of field evaluation, new insecticides and wash-resistant formulations for nets to address the threat of mosquitoes resistant to pyrethroids, the main class of insecticide used. The growing network of African laboratories and field sites of experimental huts formed the Pan-African Malaria Vector Research Consortium (PAMVERC), of which LSHTM was a member. In partnership with the Innovative Vector Control Consortium, established in 2005 through an initial grant to the Liverpool School of Tropical Medicine, Rowland identified novel insecticides sourced from the agrochemical industry, such as piperonyl butoxide (PBO), and chlorfenapyr. These were evaluated at PAMVERC sites by teams led by LSHTM staff in Tanzania (Protopopoff), Cote d'Ivoire (N'Guessan) and Benin (Ngufor, N'Guessan).

Key research findings included the following:

- In Benin, a repurposed and reformulated organophosphate insecticide (brand name Actellic) was found to last 6 to 12 months on interior walls instead of decaying within 3 months, demonstrating IRS was a viable approach to mosquito control in Africa (3.4).
- A 3-year cluster randomised trial of more than 15,000 children in Tanzania demonstrated that a LLIN treated with piperonyl butoxide (PBO LLIN) reduced the prevalence of malaria by 44% and 33% in the first and second year respectively, compared to a standard pyrethroid only LLIN, by killing mosquitoes that carried pyrethroid-resistance genes. This study also investigated the value of combining LLINs and IRS. A single spray of Actellic reduced malaria prevalence by 48% for an entire year, but showed no additional effect over the PBO LLIN used alone (3.5).

A further multi-country study led at LSHTM in 2016 and 2017 by Kleinschmidt, in collaboration with WHO, showed that standard LLINs remained partially protective against malaria transmitted by resistant mosquitoes. It concluded that despite resistance, people in malaria zones should still use standard LLINs to reduce risk of infection (3.6).

3. References to the research (indicative maximum of six references)

3.1 Graham K, Kayedi MH, Maxwell C, **Kaur H,** Rehman H, Malima R, Curtis CF, **Lines J**, **Rowland M.** 2005. Multi-country field trials comparing wash-resistance of Perma-Net and conventional insecticide-treated nets against anopheline and culicine mosquitoes. *Medical and Veterinary Epidemiology.* 19(1):12-83. doi:10.1111/j.0269-283X.2005.00543.x

3.2 Asidi A, **N'Guessan R**, Akogbeto M, **Curtis C**, **Rowland M.** 2012. Loss of household protection from use of insecticide-treated nets against pyrethroid-resistant mosquitoes, Benin. *Emerging Infectious Diseases.* 18(7):1101-1106. doi:10.3201/eid1807.120218

3.3 N'Guessan R, Corbel V, Akogbeto M, **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

3.4 Rowland M, Boko P, Odjo A, **Asidi A**, Akogbeto M and **N'Guessan R.** 2013. A new long-lasting indoor residual formulation of the organophosphate insecticide pirimiphos methyl for prolonged control of pyrethroid-resistant mosquitoes: an experimental hut trial in Benin. *PLoS One* 8: e69516. doi:10.1371/journal.pone.0069516.

3.5 Protopopoff N, Mosha JF, Lukole E, Charlwood JD, Wright AW, Mwalimu CD, Manjurano A, Mosha FW, Kisiinza W, **Kleinschmidt I, Rowland M.** 2018. Effectiveness of a long-lasting piperonyl butoxide-treated insecticidal net and indoor residual spray interventions, separately and together, against malaria transmitted by pyrethroid-resistant mosquitoes: a cluster, randomised controlled, two-by-two factorial design trial. *The Lancet.* Vol 391, 10130, p1577-1588. doi:10.1016/S0140-6736(18)30427-6

3.6 Kleinschmidt I, Bradley J, Knox TB, Mnzava AP, Kafy HT, Mbogo C et al. 2018. Implications of insecticide resistance for malaria vector control with long-lasting insecticidal nets: a WHO-coordinated, prospective, international, observational cohort study. *Lancet Infectious Diseases.* 18(6): 640-649. doi:10.1016/S1473-3099(18)30172-5

We believe this body of research meets the 'at least 2*' definition given its reach, significance and rigour.

4. Details of the impact (indicative maximum 750 words)

This long-term programme of research by LSHTM and overseas partners into LLINs and IRS contributed substantially to the approximately 800 million malaria cases and 300,000 malaria-related deaths which have been prevented since 2013 according to the World Malaria Report 2020 (5.1). LSHTM evaluated LLINs for licensing for malaria control, providing epidemiological evidence via community trials of effectiveness for both controlling malaria and combatting insecticide resistance. This led to WHO prequalification of new vector control products and their widespread procurement and distribution.

Approval and distribution of standard LLINs for malaria protection

WHO's Pesticide Evaluation Scheme (WHOPES) evaluates LLINs and recommends whether a product meets the criteria for WHO prequalification. Rowland served as a working group expert to this group, advising on safety and efficacy of nets (5.2). WHO transitioned WHOPES to a prequalification team for vector control (PQT-VC) from 2015 to 2017. The methods of LLIN field evaluation, co-developed by LSHTM and WHO, were included in the 2013 WHO Guidelines for Laboratory and Field Testing of LLINs (5.3), and in 2017 influenced WHO advice on trial design for vector control products (5.4).

Pyrethroid-only LLINs are recommended by the WHO as a core intervention in all malaria-endemic areas. Between 2017 and 2020, 20 brands of LLIN entered the global market, of which 15 were standard pyrethroid LLINs (5.2). Each of these was evaluated by LSHTM at PAMVERC trial sites in experimental huts (all 15 brands) or in household 3-year cluster randomised trials (6 brands) before the WHO approved them.

Influenced by LSHTM's pre-2014 research and subsequent testing of new products, over 2 billion LLINs were distributed in sub-Saharan Africa (as recorded by the Alliance for Malaria Prevention (AMP)) from 2004 to 2020. A total of 65% (1.3 billion) were distributed in the current reporting period of 2014 to 2020, an average of 162 million per year (5.5). 86% of nets were distributed to sub-Saharan Africa; the World Malaria Report 2020 estimates that in 2019, 68% of households in this region had at least one LLIN, and 46% of all those at risk of malaria in Africa were protected by a LLIN (5.1).

Key market stakeholders UNICEF, the President's Malaria Initiative (PMI), and the Global Fund all invested in and scaled-up their LLIN distribution programmes. For example, UNICEF procurement grew from 29 million LLINs in 2013, to 47.4 million LLINs for 30 countries in 2019. The PMI bought more than 100 million nets in the financial year 2018-19 for the 19 PMI-supported countries (5.6).

Indoor residual spraying
In 2014, the WHO Malaria Policy Advisory Committee Meeting reviewed the evidence – including studies from LSHTM – on combining indoor residual spraying and LLINs. This evidence supported the Operational Manual for Indoor Residual Spraying (IRS) for Malaria Transmission Control and Elimination, published by WHO in 2015 (5.7).

5 new classes of IRS were prequalified by WHO and entered the market following LSHTM evaluation at PAMVERC sites, and LSHTM evidence has been used to determine the optimal strategy depending on insecticide resistance in different settings (5.2). For example, PMI switched IRS strategy in many countries from a formulation requiring bi-annual application to a different, LSHTM-evaluated IRS (Actellic) after it was shown to be effective after only one application per year and to have long residual activity, saving on costs and logistics (5.8).

New tools to fight insecticide resistance
WHO convened a meeting of the Evidence Review Group on PBO-pyrethroid LLINs in October 2017 to review evidence from the LSHTM-led Tanzania trial that PBO-pyrethroid LLINs reduced malaria by 44% compared to the standard pyrethroid LLIN, which was facing increasing mosquito resistance. This led to the WHO making an interim policy recommendation in favour of the PBO-pyrethroid LLIN as a new product class to control malaria in all areas of pyrethroid resistance, which is the majority of endemic Africa (5.9).

The market changed dramatically following this decision. 5 brands of PBO-pyrethroid LLINs were subsequently prequalified by WHO (joining the 15 standard pyrethroid LLIN prequalified products) following LSHTM evaluation (5.4). From less than 1% of international procurements in 2017, PBO-pyrethroid LLINs rose year on year to 21% (43 million) of nets purchased in 2020 (5.4).

Surveillance of insecticide resistance
WHO's Global Plan for Insecticide Resistance Management in Malaria Vectors (GPIRM), was published in 2012 as a call to action and implemented over subsequent years. Rowland, Lines and Kleinschmidt were all credited for their roles in developing the plan, which represented a radical shift in WHO policy to include resistance surveillance (5.10). Monitoring resistance is crucial to inform malaria control methods for particular settings and to keep the threat of resistance at bay.

The GPIRM spawned the development in 2017 of the WHO 'Framework for a national plan for monitoring and management of insecticide resistance in malaria vectors', to ensure adherence to its recommendations. By the end of 2019, the World Malaria Report 2020 stated that 82 countries reported data on insecticide resistance to the WHO. 2019 reporting was disrupted by COVID-19, but in 2018 alone, 45 countries completed insecticide resistance monitoring and management plans in line with the GPIRM's 5-pillar strategy, and 36 countries had plans under development (5.1).

5. Sources to corroborate the impact (indicative maximum of 10 references)

5.1 World Health Organization. World Malaria Report 2020: 20 years of global progress and challenges. Geneva; 2020. Licence: CC BY-NC-SA 3.0 IGO

5.2 WHO Pesticides Evaluation Scheme listing approved vector control products, by year. Accessed at: https://www.who.int/whopes/resources/by_year/en/

- Current REF period: **2018:** Vectron T500 (IRS), Fusion Fludora (IRS), Veeralin LN (PBO-LLIN) **2017:** Sumishield (IRS), Interceptor G2 LN (LLIN), Dawaplus 3.0 LN (PBO-LLIN), Dawaplus 4.0 LN (PBO-LLIN), Chlorfenapyr 240 SC,). **2015:** MiraNet LN (LLIN), Panda Net 2.0 LN (LLIN), Yahe LN (LLIN), SafeNet LN (LLIN). **2014:** Icon maxx (LLIN), Netprotect (LLIN), Pirimiphos-methyl 300 (Actellic) (IRS), Deltamethrin 62.5 SC-PE (IRS), Duranet LN, Netprotect LN, Yahe LN. **2013**: Olyset plus, Interceptor LN.
- Previous REF period: 2011: lifenet® LN, magnetTM® LN, royal sentry® LN, yahe® LN. 2010: Olyset® LN, Dawaplus® 2.0 LN, Tianjin Yorkool® LN. 2009, 2008: Permanet 2.0, Permanet

3.0, Permanet 2.5, Lambda-cyhalothrin LN. 2007: Netprotect®, Duranet®, Dawaplus®, Icon® MAXX.

- Rowland listed as working group expert: 15 standard pyrethroid LLINs, 5 PBO-pyrethroid LLINs, 2 Insecticide-mixture LLIN and 5 new chemical classes of IRS have WHO prequalification recommendation.

World Health Organization. List of WHO Prequalified Vector Control Products. January 2020. Accessed at: https://www.who.int/pq-vector-control/prequalified-lists/PrequalifiedProducts27January2020.pdf?ua=1

5.3 World Health Organization/ Department of Control of Neglected Tropical Diseases. Guidelines for laboratory and field testing of long-lasting insecticidal nets. October 2013.

- Methods of field evaluation co-developed by LSHTM
- Rowland listed as contributor

5.4 World Health Organization. 2017. Design of epidemiological trials for vector control products, report of a WHO Expert Advisory Group. Geneva, Switzerland.

5.5 Alliance for Malaria Prevention. Net Mapping Project. Current ITN Global Delivery Quarterly Report. 2020. Accessed at: https://allianceformalariaprevention.com/working-groups/net-mapping/

5.6 The Global Fund. Long-lasting Insecticidal Nets Supplier & Partner Consultative Meeting. 26 September 2019. Singapore. Accessed at: https://www.theglobalfund.org/media/8834/psm_2019-09-llin-supplier-and-partner-consultative-meeting-singapore_presentation_en.pdf?u=637319004880400000

- Includes details of key stakeholder procurement and distribution of LLINs to demonstrate market acceleration

UNICEF Supply Division. Long-lasting Insecticidal Nets: Supply Update. March 2020.

5.7 World Health Organization. Review of current evidence on combining indoor residual spraying and long-lasting insecticidal nets. 2014.

- Supported by LSHTM research references 5, 6, 7, 10, 11, 13
- Fed into 'Indoor Residual Spraying: An operational manual for indoor residual spraying (IRS) for malaria transmission control and elimination.' Second Edition. World Health Organization, 2015.

5.8 Oxborough RM. 2016. Trends in US President's Malaria Initiative-funded indoor residual spray coverage and insecticide choice in sub-Saharan Africa (2008–2015): urgent need for affordable, long-lasting insecticides. *Malaria Journal.* 15:146. doi:10.1186/s12936-016-1201-1

5.9 World Health Organization/ Global Malaria Programme. Outcomes from Evidence Review Group on Deployment of Pyrethroid-PBO Nets. Malaria Policy Advisory Group Meeting. Geneva, Switzerland. 17 October 2017.

- Details of Tanzania trial and interim recommendations on PBO-pyrethroid LLINs

5.10 World Health Organization Global Malaria Programme. Global plan for insecticide resistance management in malaria vectors. May 2012.
LSHTM research used and Rowland and Lines credited as contributors (pg 5). Research referenced pg 33 & 59