**Resistance: A problem without an easy solution.**

**Janet Hemingway**

[Janet.hemingway@lstmed.ac.uk](mailto:Janet.hemingway@lstmed.ac.uk)

Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, L3 5QA, UK

Keywords:

Resistance Management, Malaria, Pyrethroid, Mosquito, Anopheles

Abstract

Insecticide resistance can no longer be ignored if we are to retain our ability to control many insect borne diseases. We need new public health insecticides, but these must be embedded in real resistance management strategies. Calls for Integrated Vector Management will continue to fail unless the evidence for the use of different interventions is dramatically improved. The donor community will also need to be prepared for the increased cost of effective long-term vector control. This will not happen without advocacy based on solid economic evaluation, which needs to happen before the opportunity to manage resistance becomes impossible.

*Background:*

The problem of resistance to antibiotics, drugs and, to a lesser extent, insecticides has become more evident in the last five years. Antibiotic resistance was extensively highlighted by Dame Sally Davies, the UKs Chief Medical Advisor. This triggered a UK Government commissioned review on antimicrobial resistance by the economist Lord O’Neill in 2015 (1), and multiple high level international funding initiatives to try and re-start the antibiotic development pipeline.

Artemesinin Combination Therapies (ACTs) were introduced for malaria treatment to prevent or retard the selection of resistance by simultaneously administering two drug components with different modes of action. Despite this proactive resistance management policy, drug resistance issues came to the fore with the detection of ACT resistance in *P. falciparum* in South East Asia, triggering an international effort to stop this resistance spreading and reaching Africa (2). The issues of rapidly spreading high level pyrethroid insecticide resistance, particularly in the African Anopheles malaria vectors and the global arbovirus vector *Aedes aegypti* pre-date ACT resistance, but have received less attention and significantly less funding (3). There are several reasons for this, not least the difficulties of demonstrating a causal link between insecticide resistance and increased human disease transmission before catastrophic failure of the insecticide has occurred.

Major reductions in disease transmission require multiple different interventions, especially in the high transmission areas where conditions are optimal, or when epidemics are triggered. Concerted efforts to reduce malaria in Africa in the last two decades have benefitted from better diagnosis, new combination drug therapy and massive scaling up of pyrethroid Long Lasting Insecticide Treated Nets (LLINs) and pyrethroid-based Indoor Residual Spraying (IRS). The timing and scale of the changes allowed accurate estimates of the relative contributions of the different interventions. For the first time we have a measure of the direct impact that insect control using LLINs and IRS have on our ability to reduce human mortality from malaria. Many were surprised that these two interventions account for 81% of the gains in transmission reduction over this period (4).

This benefit is also apparent for other insect borne diseases. For example, increasing IRS coverage from 60 to 80%, is predicted to have a much greater impact on reducing the time taken to eliminate Visceral leishmaniasis (VL) than halving the time taken to start treatment from 40 – 20 days, although the greatest benefit comes from combining the two interventions (5). If vector control interventions were to fail the goal of eradicating malaria and VL would be unattainable and millions more children would die each year.

*The evidence base for resistance causing control failure*

Four recent international workshops have concluded that our ability to sustain and further reduce child mortality due to malaria will be compromised unless resistance is addressed. The impact that pyrethroid resistance is already having on the efficacy of IRS and malaria prevalence in several countries was highlighted. This includes a resurgence of malaria in South Africa, co-inciding with the re-emergence of pyrethroid resistant *Anopheles funestus* (6) and the introduction of the new long-lasting formulation of the organophosphate insecticide pirimiphos methyl in Ghana to replace pyrethroids, triggering a major drop in malaria prevalence. This IRS formulation has subsequently been rolled out in multiple countries where pyrethroid resistance is at similar high frequencies to Ghana, with beneficial results. A WHO led multi-country study on the impact of resistance also confirmed that pyrethroid-based IRS was failing in Sudan, after the pyrethroid was replaced with bendiocarb [7].

While resistance is increasing in frequency across Africa, the underlying cause of resistance and the level of resistance conferred can differ. If high quality resistance surveillance is in place the response options can increase. For example, on Bioko Island, Equatorial Guinea, pyrethroid IRS could control insects with the common ‘kdr’- type pyrethroid resistance, conferred by a sodium channel mutation in the insects’ nervous system, but failed when a second more intense metabolic pyrethroid resistance mechanism was selected in 2015, and bendiocarb IRS had to be introduced (8). However, despite WHO recommending increased resistance surveillance (9), the global data remain weak (10).

A bigger question until very recently was the impact of pyrethroid resistance on LLIN effectiveness. The early waves of kdr resistance, that were first selected in African *Anopheles,* generated less than 10-fold resistance, and had little or no impact on LLINs [11], creating complacency. The metabolic mechanisms that were subsequently selected have led to anecdotal reports that nets may be failing, with increasing numbers of live blood fed female mosquitoes being collected inside treated nets [12]. The results of a recent trial in Tanzania comparing LLINs with pyrethroids and PBO + pyrethroids demonstrated that the PBO nets in area of moderate pyrethroid resistance reduced parasitaemia significantly compared to the pyrethroid only nets (13).

Responses to the insecticide resistance issue to date can broadly be classified as a reactive response to the problem, rather than proactive resistance management. The latter requires action to avoid resistance being selected, rather than a belated response to resistance having been selected. So how do we manage this resistance problem?

*Breaking the Resistance Cycle.*

Heavy reliance on any single intervention will lead to the selection of resistance. This is true for insecticides and drugs. Resistance management requires strategies to be put in place that reduce the selection pressure for resistance. In crops, this would involve using crop rotations, including refugia to retain a pool of susceptible pests and maintain beneficial predators, using mixtures or rotations of insecticides and tolerating a certain level of crop damage. The options for public health are currently more limited. The international community has adopted the use of malaria combination drug therapy, to slow the selection of resistance, but the pyrethroid insecticides have been left exposed to intense selection. For decades there have been calls for Integrated Vector Management (IVM), but these calls do not sit on solid foundations. Unless the basic issues of proper evaluation of different interventions at scale, generation of a robust evidence base for single or layered use of interventions, and the economic case for the operational implementation of IVM are tackled, IVM will remain a paper excercise.

Resistance management should not be limited to the use of new insecticides. To sustain LLIN and IRS use we certainly need new public health insecticides, but if these continue to be used sequentially until they fail, we have generated an unsustainable commitment to maintaining a pipeline of new insecticides.

*Restarting the Public Health Insecticide Product Development Pipeline*

Today even the most basic resistance management strategy of using a rotation, mosaic or combination of insecticides with different mode of action is not straight forward. This strategy to be most effective requires the use of insecticides to which significant levels of resistance have not yet been selected. Before we can even start to implement this basic strategy a larger range of new public health insecticides needs to be made available and the economic case for more expensive vector control needs to be better articulated so that it is understood, accepted and funded by the donor community.

The over-reliance on pyrethroids, a class of insecticides first brought to market in the 1970s, is a direct result of market failure. Insecticides used in public health have traditionally been compounds repurposed from agriculture. The switch from broad spectrum contact insecticides to narrow spectrum stomach poisons for the control of crop pests in the late 1990s effectively stopped the pipeline for new public health insecticides. This was recognised in 2005, with the formation of the Innovative Vector Control Consortium (IVCC), which rapidly evolved into a product development partnership between industry and academia [14]. IVCC was established with an initial US$50M investment from the Bill and Melinda Gates Foundation to allow us to engage industry and re-establish the pipeline to produce three new Public Health Insecticides, improve IRS formulations and generate new diagnostics and IT systems to monitor insecticide concentrations at the point of use and integrate entomology data with operational prevention and treatment and transmission data. This has been one of the most successful PDPs supported by the Foundation and others over the last two decades, generating new non-pyrethroid and pyrethroid IRS formulations that last 9 – 12 months [15], and engaging with all the major agrochemical companies involved in insecticide research and development to generate a robust pipeline of potential new insecticide classes. This gives us certainty that catastrophic failure of vector control will not happen with the next few years, but is not a cause for complacency.

With new insecticides in development, attention has now shifted to timely and cost-effective evaluation of new products and reducing the market cost of the new insecticide formulations to control programmes. The latter is being tackled through two large UNITAID funded programmes, aimed at giving more price and volume certainty for the companies to bring down the unit price [16].

*A new model for operational evaluation of vector control interventions*

While efforts to define new non-chemical interventions that work progresses, we need a means of increasing the speed at which new chemically based products are deployed if they are to be the base of resistance management for the foreseeable future. In contrast to the relatively rapid uptake of new IRS formulations, non-pyrethroid based LLINs or ‘second generation’ combination nets, with a pyrethroid plus a second insecticide or synergist, have had a much harder route to market. There is a circular problem that for the last decade has prevented proper evaluation of any new generation net. The major donors, such as the Global Fund, will not procure nets that do not have a WHO recommendation that they are substantively better than the pyrethroid only nets, to justify the price differential. To generate the data to demonstrate this impact, large randomised control trials over several years are needed, as the efficacy of treated nets is likely to decline gradually as nets start to develop holes and the protection of the net as a physical barrier declines. These are beyond the financial resources of the manufacturers and the capacity of most disease endemic countries to design and run the trials. Unless we can break this cycle, and generate the data needed to assess whether the new generations of nets represent a more effective and sustainable way of preventing malaria, then innovation in this area will cease and eventual major failure of the pyrethroid treated LLINs will be catastrophic.

For vector control interventions where there is no large-scale evidence of effectiveness at reducing disease transmission, standalone randomised control trials (RCTs) are required. For interventions that we already know are as effective as current interventions and can predict will be better, there is the opportunity for donors, ministries of health and scientists to collaboratively evaluate these products in RCTs embedded within operational activities. The trial of PBO nets from two different manufacturers currently underway in Uganda as part of the routine countrywide net distribution provides a workable model of how this might be done.

*Stemming the failure of vector biology:*

There is general agreement with the principle of reducing selection pressure on new insecticides by combining them with other robust, cost effective, operationally viable vector control activities. The problem is not the theory, but in having properly evaluated interventions that can be recommended for use and deployed cost-effectively in a variety of transmission settings. This is particularly important, as internationally financial support for malaria control is already well below that needed for interventions that work, reducing coverage still further by diverting resources to alternative interventions, that may or may not work, is ethically unacceptable.

The alternative interventions cited numerous times over the last 20 years include larvicides, sugar baits, larvivorous fish, odour baited traps, environmental management, repellents, house screening and more recently house vents/eave tubes. The proponents of specific interventions usually highlight several small-scale studies to support their use. Sadly, the vector control literature is awash with poorly designed intervention ‘trials’ that are riddled with bias, lack robust controls and have insufficient statistical power.

To bring the same degree of rigor to assessing the evidence base for vector control interventions as we would apply to drugs or vaccines, in 2004 the Cochrane infectious disease group commissioned a series of Systematic reviews. The review on larval source management (LSM) in 2013, which assessed all published and unpublished data from 1900 – 2012, located only 13 studies of sufficient quality to include in the assessment. They concluded that LSM is another policy option, alongside LLINs and IRS in limited situations where sufficient breeding sites can be targeted. However, they point out that further research is still needed to evaluate LSM feasibility in rural Africa (17). Reviews on LLINs (2004) and IRS (2010) supported the use of these interventions (18,19). The review on electronic buzzer devices, sold direct to the public as mosquito repellents, concluded they do not work and should not be used to reduce mosquito bites or malaria infection rates (20).

The review on larvivorous fish (2013) concluded that there were no reliable studies demonstrating an impact on malaria infection rates in nearby communities and all the studies that reported reductions in mosquito numbers had a high risk of bias. The evidence for use of fish was insufficient to recommend their use (21). The review on larvicides, which will include Bti, was commissioned in 2017, and the protocol for the study search is published (22).

Other potential interventions, such as entomopathogenic fungi, are not yet at the point where the evidence can be sensibly evaluated. The fatal flaw in this intervention, that has yet to be overcome despite the efforts of several groups, is the inability of the spore formulation to survive for any significant periods at tropical storage temperatures, severely limiting its shelf life.

A few interventions, such as odor-baited traps and house eave tubes are entering large scale trials, most with significant funding from the Bill and Melinda Gates Foundation. These trials take several years and will need to be completed before they generate the evidence that may allow them to be recommended for wide-scale operational use.

All of the different elements will need to be progressed if the management of resistance is to become a reality. The alternative is that the new insecticides under development will be over used operationally, rapidly fail, and our ability to control or eliminate several major diseases will decline dramatically.

1. J. O’Neill Securing new drugs for future generations. The pipeline of antibiotics. <https://amr-review.org>
2. malERA refresh panel. malEra: an updated research agenda for insecticide and drug resistance in malaria elimination and eradication. PLOS Medicine <https://doi.org/101371/journal.pmed.1002450>
3. J.Hemingway, H. Ranson, A. Magill, J. Kolaczinski, C. Fornadel, J. Gimnig et al. Averting a malaria disaster: will insecticide resistance derail malaria control? Lancet 2016 https://doi.org/10.1016/S0140-6736(15)00417-1
4. S. Bhatt, D. J. Weiss, E. Cameron, D. Bisanzio, B. Mappin, U. Dalrymple, K. E. Battle, C. L. Moyes, A. Henry, P. A. Eckhoff, E. A. Wenger, O. Brie, M. A. Penny, T. A. Smith, A. Bennett, J. Yukich, T. P. Eisele, J. T. Griffin, C. A. Fergus, M. Lynch, F. Lindgren, J. M. Cohen1, C. L. J. Murray, D. L. Smith, S. I.Hay, R. E. Cibulskis, P.W. Gething. The effect of malaria control on Plasmodium falciparum in Africa between 2000 and 2015. Nature **526;** 206 – 211 (2015) doi:10.1038/nature15535
5. [E. A. Le Rutte](http://pubmedcentralcanada.ca/pmcc/solr?term=author:(Epke%20A.%20Le%20Rutte)),. [L. A.C. Chapman](http://pubmedcentralcanada.ca/pmcc/solr?term=author:(Lloyd%20A.C.%20Chapman)),.[L. E. Coffeng](http://pubmedcentralcanada.ca/pmcc/solr?term=author:(Luc%20E.%20Coffeng)),. [S. Jervis](http://pubmedcentralcanada.ca/pmcc/solr?term=author:(Sarah%20Jervis)),. [E. C. Hasker](http://pubmedcentralcanada.ca/pmcc/solr?term=author:(Epco%20C.%20Hasker)),. [S. Dwivedi](http://pubmedcentralcanada.ca/pmcc/solr?term=author:(Shweta%20Dwivedi)),. [M. Karthick](http://pubmedcentralcanada.ca/pmcc/solr?term=author:(Morchan%20Karthick)),. [A. Das](http://pubmedcentralcanada.ca/pmcc/solr?term=author:(Aritra%20Das)),. [T. Mahapatra](http://pubmedcentralcanada.ca/pmcc/solr?term=author:(Tanmay%20Mahapatra)),. [I. Chaudhuri](http://pubmedcentralcanada.ca/pmcc/solr?term=author:(Indrajit%20Chaudhuri)),. [M. C. Boelaert](http://pubmedcentralcanada.ca/pmcc/solr?term=author:(Marleen%20C.%20Boelaert)), [G. F. Medley](http://pubmedcentralcanada.ca/pmcc/solr?term=author:(Graham%20F.%20Medley)), [S. Srikantiah](http://pubmedcentralcanada.ca/pmcc/solr?term=author:(Sridhar%20Srikantiah)), [T. D. Hollingsworth](http://pubmedcentralcanada.ca/pmcc/solr?term=author:(T.%20Deirdre%20Hollingsworth)), [S. J. de Vlas](http://pubmedcentralcanada.ca/pmcc/solr?term=author:(Sake%20J.%20de%20Vlas)). Elimination of visceral leishmaniasis in the Indian subcontinent: a comparison of predictions from three transmission models. Epidemics. **18:** 67–80. (2017), doi:  [10.1016/j.epidem.2017.01.002](http://dx.doi.org/10.1016%2Fj.epidem.2017.01.002)
6. K., Hargreaves, L.L., Koekemoer, B.D., Brooke, R.H., Hunt, J., Mthembu, M.Coetzee. Anopheles funestus resistant to pyrethroid insecticides in South Africa. Med Vet Entomol 14: 181–189 (2000).
7. I.Kleinschmidt, A. P. Mnzava, H. Toto Kafy, C. Mbogo, A. I. Bashir, J. Bigoga, A. Adechoubou, K. Raghavendra, T. Bellamy Knox, E. M Malik, Z. J. Nkun, N. Bayoh, E. Ochomo, E. Fondjo, C. Kouambeng, H. P. Awono-Ambene, J. Etang, M. Akogbeto, R. Bhatt, D. K Swain, T. Kinyari, K. Njagi, L. Muthami, K. Subramaniam, J. Bradley, P. West, A. Massougbodji, M. Okê-Sopoh, A. Hounto, K. Elmardi, N. Valecha, L. Kamau, E. Mathenge, M. J. Donnelly. Design of a study to determine the impact of insecticide resistance on malaria vector control: a multi-country investigation. Malaria Journal (2015) **14**:282. <https://doi.org/10.1186/s12936-015-0782-4>
8. J. Vontas, L. Grigoraki, J. Morgan, D. Tsakireli, G. Fuseini, L. Segura, J. Niemczura de Carvalho, R. Nguema, D. Weetman, M. A. Slotman, and J.Hemingway. Rapid selection of a pyrethroid metabolic enzyme CYP9K1 by operational malaria control activities. PNAS . 2018. <https://doi.org/10.1073/pnas.1719663115>
9. World Health Organisation 2012. Global Plan for Insecticide Resistance Management in Malaria Vectors. ISBN 9789241564472
10. P. A. Hancock, A. Wiebe, K. A. Gleave, S. Bhatt, E. Cameron, A. Trett, D.Weetman, D. L. Smith, J. Hemingway, M. Coleman, P. W. Gething, and C. L. Moyes. Associated patterns of insecticide resistance in field populations of malaria vectors across Africa. PNAS May 21, 2018. 201801826; published ahead of print May 21, 2018. <https://doi.org/10.1073/pnas.1801826115>
11. F. Chandre, F. Darriet, S. Duchon, L. Finot, S. Manguin, P. Carnevale, P. Guillet. Modifications of pyrethroid effects associated with *kdr* mutation in *Anopheles gambiae.* Med. Vet. Ent. **14;** 81- 88 DOI: 10.1046/j.1365-2915.2000.00212.x (2000)
12. Trape, J-F, Tall, A, Diagne, N et al. Malaria morbidity and pyrethroid resistance after the introduction of insecticide-treated bednets and artemisinin-based combination therapies: a longitudinal study. *Lancet Infect Dis*. 2011; **11**: 925–932
13. [N. Protopopoff](javascript:void(0);), [J. F Mosha](javascript:void(0);), [E. Lukole](javascript:void(0);), [J. D Charlwood](javascript:void(0);), [A.Wright](javascript:void(0);), [C. D Mwalimu](javascript:void(0);), [A. Manjurano](javascript:void(0);), [F. W Mosha](javascript:void(0);), [W. Kisinza](javascript:void(0);), [I. Kleinschmidt](javascript:void(0);), [M.Rowland](javascript:void(0);), 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. DOI: <https://doi.org/10.1016/S0140-6736(18)30427-6>
14. J. Hemingway, B.J. [Beaty](https://www.ncbi.nlm.nih.gov/pubmed/?term=Beaty%20BJ%5BAuthor%5D&cauthor=true&cauthor_uid=16713358) , M. Rowland, T.W. [Scott](https://www.ncbi.nlm.nih.gov/pubmed/?term=Scott%20TW%5BAuthor%5D&cauthor=true&cauthor_uid=16713358) , B.L. [Sharp](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sharp%20BL%5BAuthor%5D&cauthor=true&cauthor_uid=16713358) . The Innovative Vector Control Consortium: improved control of mosquito-borne diseases. [Trends Parasitol.](https://www.ncbi.nlm.nih.gov/pubmed/16713358) **22**: 308-12. DOI:[10.1016/j.pt.2006.05.003](https://doi.org/10.1016/j.pt.2006.05.003)
15. M. Rowland,\* E-mail: [mark.rowland@lshtm.ac.uk](mailto:mark.rowland@lshtm.ac.uk) P. Boko, A. Odjo, A. Asidi, M. Akogbeto, R. N’Guessan. 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 <https://doi.org/10.1371/journal.pone.0069516> (2013).
16. UNITAID. Investing in new insecticides to combat malaria. <https://unitaid.eu/project/new-insecticides-combat-malaria/>
17. Tusting. LS et al. Mosquito larval source management for controlling malaria. Cochrane systematic review (2013). DOI. 10.1002/14651858.CD008923.pub2.
18. Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database of Systematic Reviews 2004, Issue 2. Art. No.: CD000363. DOI: 10.1002/14651858.CD000363.pub2
19. Pluess B, et al. Indoor residual spraying for preventing malaria. Cochrane Database of Systematic Reviews 2010, Issue 4. Art. No.: CD006657. DOI: 10.1002/14651858.CD006657.pub2

# Enayati et al. Electronic mosquito repellents for preventing mosquito bites and malaria infection. Cochrane systematic review (2007). DOI. 10.1002/14651858.CD005434.pub2

1. Walsh, DP et al. Larvivorous fish for preventing malaria transmission. Cochrane database of systematic reviews 2013. DOI. 10.1002/14561858.CD008090
2. Choi L **&** Wilson A. Larviciding to control malaria [Cochrane Infectious Diseases Group](http://onlinelibrary.wiley.com/o/cochrane/clabout/articles/INFECTN/frame.html) 2017. DOI: 10.1002/14651858.CD012736

**Affiliation** London School of Hygiene & Tropical Medicine, London, United Kingdom

⨯