Institution: Edge Hill University		
Unit of Assessment: A5 Biological Sciences		
Title of case study: Informing policies, strategies and action on mosquito vector control and surveillance		
Period when the underpinning research was undertaken: 2014 - 2019		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Dr Clare Strode	**Role(s) (e.g. job title):** Reader in Vector Biology	**Period(s) employed by submitting HEI:** January 2013-present
Period when the claimed impact occurred: 2014-2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Mosquitoes are vectors of devastating diseases such as malaria and dengue with 3.5 billion people at risk. Malaria kills over 600,000 people a year, mostly children under 5 years old, and dengue risk is increasing. Disease prevention via insecticide control of mosquitoes is threatened by insecticide resistance. This case study reports how the work of Dr. Strode has: informed the continued use of insecticide-treated bed nets (ITNs) for malaria prevention; underpinned the World Health Organisation's (WHO) policies and strategies relating to mosquito management; led to the establishment of a UK-wide surveillance network for *Aedes* invasive mosquitoes; prompted the UK governments to update risk assessment and preparedness for mosquito borne diseases; acted as a basis for public engagement in Colombia to raise awareness of mosquito surveillance and control. The research has been described by Public Health England as making a vital contribution to UK preparedness and response to vector borne disease.

2. Underpinning research

Mosquito borne diseases (MBD) exert a significant global health burden for both mortality and morbidity. The malaria burden is greatest in Africa whilst arboviruses e.g. dengue, Zika and chikungunya are significant causes of morbidity. In the absence of vaccines for malaria and dengue mosquito, control via chemical insecticides is the primary method of disease prevention. Insecticide resistance in mosquito vectors is an increasing global problem which threatens disease prevention. Furthermore, two invasive dengue vector species have colonised new countries, thereby increasing the public health threat. The research of Strode spans both of these key problems to include screening mosquito populations against insecticides used in public health to determine their susceptibility, unravelling the genetic mechanisms underpinning resistance and surveillance of invasive mosquito vectors.

Insecticide resistance in mosquito vectors

Mosquito control via insecticide-treated bed nets (ITNs) and indoor residual house spraying are the core interventions for malaria set by the World Health Organisations (WHO). Arbovirus prevention incorporates aerial spraying of insecticides and larviciding of breeding sites. Insecticide resistance in mosquitoes threatens MBD control, therefore understanding its mechanisms and impact is vital for tracing resistance and developing new tools to circumvent it.

As part of the President's Malaria Initiative an extensive country wide investigation was performed in Zambia into the extent and genetic mechanisms underpinning insecticide resistance in malaria vectors [1]. The study revealed heterogeneity in insecticide resistance in different malaria vectors from seven provinces to insecticides used for malaria prevention. In the target-site of the insecticide, the study also identified mutations and elevated gene expression of two key enzymes among the mosquitoes that have since been used as key markers for tracking resistance across Southern African countries. The study findings provide evidence to support informed decision-making for National Malaria Control Programmes (NMCP) to develop a resistance management plans at a province rather than country-wide level.

Additionally, a multi-country study of *Ae. aegypti* (dengue vector) populations revealed gene signatures associated with resistance common to Guiana and Guadalupe, despite different historical use of insecticides [2]. More distinct gene patterns were found in the more geographically isolated New Caledonia populations where resistance was lower compared with the other two countries. Identifying common signatures across different populations is necessary for understanding resistance development and tracking its spread, and it also offers the possibility to target these with innovative vector control tools.

Impact on malaria prevention

To address the question of resistance to ITN's reducing their efficacy, Strode undertook a meta-analysis of ITN trials against insecticide susceptible and resistant malaria vectors from Africa under a strict criteria; this was funded by the Roll Back Malaria via the Vector Control Working Group [3]. The study determined that, whilst a modifying effect was observed with mosquito mortality, ITNs still remain effective against resistant malaria vectors. The study was also critical of the heterogeneity in how ITN field trials are conducted and reported. It called for a more cohesive approach to address this problem to allow trials to be executed in a consistent manner in order to be comparable.

Invasive Aedes Mosquitoes (AIMs)

Aedes aegypti and *Ae. albopictus* (arbovirus vectors) have invaded new territories leaving 50% of the world's population at risk. Originating in Asia, *Ae. albopictus* has recently established in several European countries e.g. France, Spain and Italy. Climate change scenarios puts the UK at risk from *Ae. Albopictus,* which has evolved to overwinter in cooler climates. Both species are on the European Centre of Disease Control's invasive species list for surveillance and control.

The startling discovery of *Ae. aegypti* in Merseyside UK [4] and the even more worrying repeated introductions of *Ae. albopictus* [5] brought into sharp focus the need for a co-ordinated plan for tackling AIMs. The global trade of used tyres harbouring undetected eggs of *Ae. aegypti* has led to new invasions in a country previously free of these vectors, bringing with them a public health risk. With no method available to screen this high risk route, Strode developed a low cost accessible method to screen used tyres for AIM eggs as an early warning system of the introduction of AIMs; thereby facilitating rapid elimination through preventing adult establishment [6]. The method involves using inexpensive, and easily available, adhesive tapes that proved effective in removing eggs from tyres; it allows for species identification and proved non-toxic to the eggs allowing mosquitoes to be reared for further analysis if required (e.g. insecticide resistance screening).

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

1. Thomsen, E.K., **Strode, C** *, Hemmings, K., Hughes, A.J., Chanda, E., Musapa, M., Kamuliwo, M., Phiri, F.N., Muzia, L., Chanda, J. and Kandyata, A. *Underpinning sustainable vector control through informed insecticide resistance management.* PLoS One, 2014. **9**(6): p. e99822.*joint first author https://doi.org/10.1371/journal.pone.0099822
2. Dusfour, I., Zorrilla, P., Guidez, A., Issaly, J., Girod, R., Guillaumot, L., Robello, C. and **Strode, C.** *Deltamethrin Resistance Mechanisms in Aedes aegypti Populations from Three French Overseas Territories Worldwide.* PLoS Negl Trop Dis, 2015. **9**(11): p. e0004226. https://doi.org/10.1371/journal.pntd.0004226
3. **Strode, C**., Donegan, S., Garner, P., Enayati, A.A. and Hemingway, J. *The impact of pyrethroid resistance on the efficacy of insecticide-treated bed nets against African anopheline mosquitoes: systematic review and meta-analysis.* PLoS Med, 2014. **11**(3): p. e1001619. https://doi.org/10.1371/journal.pmed.1001619
4. Dallimore, T., Hunter, T., Medlock, J.M., Vaux, A.G., Harbach, R.E. and **Strode, C.** *Discovery of a single male Aedes aegypti (L.) in Merseyside, England.* Parasites & Vectors, 2017. **10**(1). doi: 10.1186/s13071-017-2251-0
5. Vaux, A.G.C., Dallimore, T., Cull, B., Schaffner, F., **Strode, C**., Pflüger, V., Murchie, A.K., Rea, I., Newham, Z., McGinley, L. and Catton, M. *The challenge of invasive mosquito vectors in the U.K. during 2016-2018: a summary of the surveillance and control of Aedes albopictus.* Med Vet Entomol, 2019. doi: 10.1111/mve.12396

6. Dallimore, T., Goodson, D., Batke, S. and **Strode, C.** *A potential global surveillance tool for effective, low-cost sampling of invasive Aedes mosquito eggs from tyres using adhesive tape.* Parasites & Vectors, 2020. **13**(1): p. 91. https://doi.org/10.1186/s13071-020-3939-0

The articles above were all published in open access peer reviewed journals allowing for the immediate access on publication. Article 3 currently has 126 citations, placing it in the top 5% of articles in its field. (Scopus).

4. Details of the impact

The research has acted as evidence to inform international mosquito management strategies of the WHO and other leading non-profit organisations. It has contributed to stronger surveillance activities in the UK and informed national contingency planning. The research has formed the basis of a public engagement and education campaign in Colombia to strengthen understanding amongst the local population of the mosquito threat and risk of insecticide resistance.

Informing the continued use of ITNs to prevent malaria

Since 2004, 2 billion ITNs have been deployed for malaria prevention contributing to global efforts that saved more than 7 million lives and prevented more than 1 billion malaria cases. Concerns that resistance could reverse such impressive gains have been explored in several field trials of ITNs which were tested for efficacy against resistant populations but without a consensus emerging. Given that ITNs averted 68% of malaria deaths (2000-2015), concerns that resistance would significantly affect malaria prevention at an operational level and would render ITNs ineffective in controlling resistant mosquitoes were allayed by Strode's research [3]. The findings of this highly cited study, which showed that ITNs remain more effective than an untreated bed net against resistant African malaria vectors, were utilised in key WHO policy documents. The WHO Global Malaria Programme's global report on resistance in malaria vectors [7], with evidence from 79 countries, is designed to guide national malaria control programmes' operational planning and responses to address insecticide resistance and maintain the effectiveness of malaria vector control using current intervention tools. This is important since, whilst new innovative vector control tools are being developed, ITNs and IRS remain the core tools for malaria prevention. In the report, Strode's research [3] was presented as evidence for continued ITN efficacy *'A 2014 review found that, even in the presence of pyrethroid resistance, treated nets perform better than untreated nets in terms of protection against blood-feeding, and that ITNs can induce significant mosquito mortality*' [7]. Additionally [1] was used as part of the evidence in the report to demonstrate the extensiveness and heterogeneity of insecticide resistance at a country level. Similarly, the 2019 'Guidelines for malaria vector control' [8, page 21] stated that the recommendation for continued use of ITNs was substantiated by the same study [3].

The Malaria Consortium (one of the world's leading non-profit organisations specialising in comprehensive malaria control in Africa and Asia) cited the Strode study [3] in an advocacy brief as evidence to advocated for the continued procurement of ITNs despite concerns over resistance [9]. *'Despite growing resistance of mosquitoes to the insecticide used in ITNs, the net itself still provides a physical barrier offering the user protection. Furthermore, a recent analysis found that ITNs remain at least somewhat effective even when resistance has developed and remain more effective in malaria control than untreated nets. It is, therefore, advisable for ITNs to be continued to be used, despite growing insecticide resistance' [9].*

Purchasing of ITNs relies significantly on donors so it is vital that there is confidence in the continued efficacy of ITNs based on scientific evidence. GiveWell is a not-for-profit charity evaluation group which directs donor funding to the best giving opportunities for saving or improving lives. GiveWell endorsed the 'Against Malaria Foundation' as a priority programme and used the Strode study [3] as part of their research in assessing the appropriateness of ITNs in the face of resistance [10].

Enhancing the understanding of mosquito surveillance and control in Colombia
A ‘British Council Institutional links Newton Fund’ forged a new collaboration between EHU and Universidad de Antioquia investigating insecticide resistance in *Ae. aegypti* populations. The project was carried out in the context of the 2016 WHO declared Zika global health emergency which affected Colombia. Extensive surveillance and collections of *Ae. aegypti* was performed in 10 dengue and Zika endemic cities with insecticide resistance monitoring. Part of the project consisted of a programme of knowledge exchange between the research team led by Strode and local health authorities (LHAs) and public health divisions.

A gap often exists between the academic and the operational such that the problem of insecticide resistance and its importance in disease prevention does not reach the local level. To address this gap, local health officers (LHO) in each of the cities were provided with training on mosquito surveillance and the importance of resistance monitoring. LHA’s were also provided with the results of resistance to insecticides screening used in public health campaigns for disease prevention. This enables them to make informed choices regarding the rationale for use of insecticides within their area. As explained by the local project partner at Universidad de Antioquia ‘*when results from the study of the local reproduction patterns and resistance to insecticides were available the findings were reported back to the establishments via the public health officers. An increased awareness and renewed interest in mosquito borne diseases was a clear outcome of the successful relation with the local community authorities’* [16].

Aedes aegypti is a day-biting mosquito which has superbly adapted to living in, and close to, homes in human-made containers making it challenging to control. As part of the educational campaign, doo- to-door visits were made to householders by the research team as they collected samples. During these visits householders were provided with practical advice on simple, cost-free water management practices to reduce breeding sites and interrupt the mosquito’s life cycle (e.g covering water storage containers, removal of disused containers, cleaning water vessels once a week). *‘Such activities enable the people most at risk from arboviral diseases to be proactive in their own protection’* [16].

Improving AIM surveillance and preparedness in the UK
The UK’s ability to remain free of mosquito borne viruses, such as dengue, is contingent on maintaining the absence of the key vectors *Ae. aegypti* and *Ae. albopictus*. The global trade in used tyres is one route that has allowed these mosquitoes to colonise new countries, hence the development of a new tool to monitor eggs transported in tyres [6]. In 2014 Strode partnered with Public Health England (PHE) to establish a large UK-wide surveillance network of 57 sites (seaports, airports, truck stops and distribution centres) for AIMs [11]. The Head of Medical Entomology at PHE states that the partnership has been critical in establishing stronger surveillance ‘*Dr Strode and her team have helped develop the surveillance network…. over recent years, our groups have developed the UK’s surveillance work for invasive mosquitoes, particularly focussing on seaports, airports, and vehicular transport sites such as truck stops and distribution centres’* [11].

Stage two of the work involved the delivery of training for Environmental Health and Port Health Officers across the country. *‘Engagement activities such as these are crucial to providing the training and support to those undertaking surveillance work at their sites’* [11]. On the recommendation of attendees, an annual newsletter was produced by EHU and PHE [12] and circulated to all UK PHOs and EHOs in June 2020. It detailed the previous year’s surveillance results and explained the management of a variety of scenarios if an AIM is found. The research undertaken by Strode further underpinned these emergency planning activities with the development of a rapid PCR test for the identification of these samples [11]. This collaboration has been ‘*vital to UK preparedness and response to vector borne disease’* [11].

Over recent years Strode undertook sites visits to Liverpool Docks, Liverpool John Lennon Airport, Manchester airport, Glasson and Heysham Docks at the request of PHOs to offer expertise on strategic use of traps. The network, training course and site visits helps PHOs deliver their obligation to monitor the introduction of disease vectors at points of entry as mandated by the International Health Regulations (Annex 5). *'Our collaboration has resulted in Mersey Port Health Authority being able to target the most likely route of introduction by invasive Aedes mosquitoes through the ports and docks, and the subsequent deployment of a suitable, robust, surveillance strategy'* [13]. In addition, these front-line efforts led to raised awareness of the threat and, as an example, Lancashire county council chose to prioritise surveillance at Heysham and Glasson Docks as an essential service by during the COVID-19 pandemic, allowing further resources to be dedicated to the ongoing programme [14]. In 2020 PHOs from Lancashire implemented Strode's method [6] of taping used tyres as part of their surveillance activities. This is the first time such a technique has been used in the field as part of a surveillance programme.

Surveillance activities discovered repeated introductions of *Ae. albopictus* into Kent, UK (2016-2019), an alarming discovery which amplified the importance of the network. EHU performed rapid molecular diagnostic species identification of *Ae. albopictus* eggs from traps which was vital in permitting a speedy response from PHE and Local Health Authorities for eliminating the mosquito populations [11]. Given the lessons of *Ae. albopictus* establishment in other countries, it is imperative that the UK does not let this species establish as control thereafter is a significant challenge.

Finally, the research team's partnership with Public Health England led to the co-production of an article detailing the discovery of *Ae. aegypti* [4]. This article prompted action by the UK government with discussions between the Civil Contingencies Secretariat Cabinet Office and representatives from government agencies; PHE, The Department of Health and Social Care, The Department for Environment, Food and Rural Affairs, the Ministry of Defence and The Chartered Institute of Environmental Health [11]. The outcome was the publication of the '*National Contingency Plan for Invasive Mosquitoes: Detection of Incursions'* [15]. The plan is important since it is the first time the UK has developed a national plan to deal with the threat of invasive mosquito species, further it lays out the roles and responsibilities in the event of such an incident at national level. '*In the National Contingency Plan the roles and responsibilities of key partners are set out, with clear delineations of requirements at each defined Response Level. Surveillance and control are integral to this, and our collaboration with Edge Hill University ensures these objectives are met'* [11].

5. Sources to corroborate the impact

7. WHO - Global report on insecticide resistance in malaria vectors: 2010–2016 (PDF) https://www.who.int/malaria/publications/atoz/9789241514057/en/
8. WHO - Guidelines for malaria vector control (PDF) https://www.who.int/malaria/publications/atoz/9789241550499/en/
9. Malaria Consortium Malaria prevention through insecticide treated nets (PDF) https://www.malariaconsortium.org/resources/publications/802/malaria-prevention-through-insecticide-treated-nets
10. https://www.givewell.org/international/technical/programs/insecticide-treated-nets
11. Factual statement from Medical Entomology group at Public Health England.
12. AIM surveillance newsletter 2020 EHU and PHE
13. Factual statement from Merseyside Port Health Authority
14. Factual statement from Lancaster City Council
15. National contingency plan for invasive mosquitoes (PDF) https://www.gov.uk/government/publications/national-contingency-plan-for-invasive-mosquitoes
16. Factual statement from Universidad de Antioquia