Innovative strategies for vector control

Progress in the global vector control response

edited by:

Constantianus J.M. Koenraadt, Jeroen Spitzen and Willem Takken

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Ecology and control of vector-borne diseases
Volume 6

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Ecology and control of vector-borne diseases

In the past century, many advances were made in the control of vector-borne diseases. Malaria disappeared from the northern hemisphere, diseases such as typhus, *Bartonella* and yellow fever were seriously reduced in prevalence and in many countries effective methods of disease control contributed to a greatly reduced incidence of such diseases. Most of these advances were beneficial to the industrialised world, whereas underdeveloped countries continued to suffer much as before. Indeed, several diseases such as malaria, Rift Valley fever and African sleeping sickness are still highly prevalent in parts of the tropics. 'New' vector-borne diseases such as dengue, chikungunya fever and West Nile fever, have emerged and are invading previously disease-free regions. The discovery of new drugs and vaccines has made great advances and allows for the effective treatment and control of many diseases. In contrast, vector control has lagged behind in development, even though it is realised that effective vector control would allow for an immediate interruption of the transmission of disease, and aid in disease control and eradication. In the last decade new initiatives on vector control have been undertaken, leading to a rapid development of effective and lasting methods of vector control. For example, the Roll Back Malaria control programme of the World Health Organization has led to significant reductions in malaria in many countries. In order to achieve further advances, however, additional tools are required. The development of molecular genetics has provided new insight in vector biology and behaviour, which is being used for developing new strategies of vector control. Advances in geographic information systems allow for precision targeting of interventions. The collective information on new developments in vector ecology and control for vector-borne diseases is scattered over numerous periodicals and electronic databases. This book series intends to bring together this information in sequential volumes arranged around selected themes that are currently of interest.

Willem Takken is the senior editor of the series. Each volume is co-edited by one or more guest editors, which in Volume 6 are Constantianus J.M. Koenraadt and Jeroen Spitzen. The editors of the current volume are well-known experts in the field of ecology, control and management of vector borne diseases.

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Introduction

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1. Where do we stand with the Global Vector Control Response?

Constantianus J.M. Koenraadt[1], Raman Velayudhan[2], Jeroen Spitzen[1] and Willem Takken[1]*
[1]Laboratory of Entomology, Wageningen University & Research, P.O. Box 16, 6700 AA, Wageningen, the Netherlands; [2]Veterinary Public Health, Vector Control and Environment unit (VVE), Department of Control of Neglected Tropical Diseases (UCN/NTD), World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland; sander.koenraadt@wur.nl

In human history, it is only yesterday that pioneering scientists, such as Ronald Ross and Walter Reed, unravelled the role of mosquitoes in the transmission of disease-causing entities, such as malaria parasites and Yellow Fever virus particles. For long, mosquitoes have plagued numerous empires and have played a decisive role in human history (Winegard 2019). Many battles were not won because of superior strength of one of the contesting parties, but rather because of a decline in troops that were seriously weakened by deadly diseases such as malaria. Although the association between swampy, smelly sites and the prevalence of disease has been recorded in many ancient texts (Winegard 2019), only the knowledge on the true transmission mechanism and the role of vectors therein has enabled us to design efficient ways to combat diseases transmitted by mosquitoes and other vector species.

In the early days of vector control, environmental management played a critical role in reducing the impact of vector-borne diseases. This was mostly achieved through elimination or alteration of the aquatic habitats in which vectors developed. In Malaysia and Indonesia, for example, this concept was developed by Malcolm Watson and Nicolaas Swellengrebel and the approach was termed 'species sanitation' (Swellengrebel 1937, Watson 1921). Other famous examples include the elimination of *Aedes aegypti* (1960-1970) and *Anopheles gambiae* from Brazil (1930's), the reduction of malaria in the Zambian copperbelt and the virtual elimination of malaria in the Tennessee Valley (USA) (Carter 2014; Killeen *et al.* 2002).

In addition to environmental management, chemical control made its entry, which initially consisted of larviciding with Paris Green or with the use of oils, and later of massive spraying campaigns with DDT (Fletcher *et al.* 1948, Gachelin *et al.* 2018, Schofield 1992). Later vector control programmes showed an almost exclusive reliance on insecticides applied via Indoor Residual Spraying (IRS) and insecticide treated bed nets. Along with the use of similar classes of insecticides used in agriculture, this reliance has led to the current situation in which insecticide resistance is limiting the effectiveness of interventions. As a result, we currently have only few tools available in the toolbox to tackle vector-borne diseases (Hemingway 2018, Williams *et al.* 2018, Wilson *et al.* 2020).

Although Zika virus already circulated for some years, the enormous impact of the virus became particularly visible in 2015-2016 when thousands of people in Latin America became infected and when the link with microcephaly in new-born babies was established (Barzon *et al.* 2016). *Aedes aegypti* mosquitoes were quickly identified as the main vectors responsible for transmission of the disease, although quite uniquely, Zika virus could also spread sexually. The virus went global, and by 2017, 84 countries and territories reported evidence of mosquito-borne Zika infection (Baud *et al.* 2017). This unprecedented spread and the lack of a proper response to prevent further infections, triggered the World Health Organization to initiate a consultative process on a global vector control response with member states and stakeholders.

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This consultative process eventually resulted in the adoption of a resolution on Global Vector Control Response (GVCR) 2017-2030 (WHO 2017). It outlines roles and responsibilities for both Member States and WHO's secretariat. Member States are particularly urged to strengthen existing national vector control strategies, build adequate human resources, and promote basic research and collaboration in line with the One Health approach. The Secretariat is committed to develop technical guidance and policy advice, promote development of innovative products, tools and technologies, to oversee ethical aspects, e.g. to tackle health inequities, and to monitor the implementation of the strategic approach. The GVCR has defined a series of important targets, such as the reduction of mortality due to vector-borne diseases globally, relative to 2016, by at least 75%, and to reduce case incidence by at least 60%. The aim is to reduce these threats through effective locally adapted and sustainable vector control. The response was eventually adopted by the Seventieth World Health Assembly in May 2017.

Although arboviral diseases, such as Zika and chikungunya, can be spotted frequently in news headlines, numerous other pathogens, such as bacteria, parasites and nematodes are transmitted by a wide diversity of arthropods, including fleas, sand flies, black flies, triatomine bugs, mites, lice and ticks. Overall, 80% of the world's population is at risk of one or more of vector-borne diseases, and of the global burden of infectious diseases, vector-borne infections account for 17%. Yearly, it is estimated that 700,000 deaths are caused by vector-borne diseases, stressing the importance of a concerted effort to mitigate the burden of these infections.

In June 2019, Wageningen University and the World Health Organization organised a conference to critically reflect on the progress in the Global Vector Control Response 2017-2030. Where do we stand? What are the challenges? What are the roles of the various stakeholders? These were all questions and topics that were discussed. The conference brought together not only experts and policy makers in vector-borne disease epidemiology, entomology and public health, but also young professionals from disease-endemic countries who were challenged to make suggestions on how current strategies could further be improved and/or made more sustainable.

This 6th volume of the Ecology and Control of Vector-borne Diseases series reflects the various topics that were addressed during the meeting and pays particular attention to the various pillars of GVCR, such as intersectoral collaboration, scaling up of innovative strategies and social aspects of integrated vector management. The contributions are a reflection of the presentations and discussions held during the conference, which was concluded with an interactive workshop in which practical ideas and suggestions for the advancement of the current strategies of vector-control were evaluated. The output of the workshop has been included as an appendix to the final chapter (Chapter 13).

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Insecticides

Children under an insectide-treated bed net (photograph: Vestergaard-Frandsen)

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2. Insecticides and malaria

Immo Kleinschmidt[1,2*] *and Mark Rowland*[3]
[1]MRC International Statistics and Epidemiology Group, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom; [2]Department of Pathology, School of Health Sciences, University of Witwatersrand, 7 York Road, Parktown, Johannesburg, South Africa; [3]Department of Disease Control, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom; immo.kleinschmidt@lshtm.ac.uk

Abstract

Reductions in the global burden of malaria have been mainly due to the massive scale-up of insecticide-based malaria vector control over the past two decades. Pyrethroid insecticides played a key role in this success due to their unique properties and low cost. The continued efficacy of insecticides as a means of malaria prevention and transmission reduction is under threat due to biological, commercial and financial factors. This chapter charts the evolution of long-lasting insecticidal nets and indoor residual spraying into becoming the two principal malaria vector control classes and the innovation that has led to a new generation of these tools which aim to counter the growing threat of insecticide resistance. At the same time a need for new classes of vector control tools has been recognised to overcome not just the hazard of insecticide resistance but also the problems posed by outdoor vector biting, residual transmission and changes in human behaviour. The main developments in new vector control classes are described, including the role of non-insecticidal vector control. The chapter further outlines the type of evidence of efficacy that needs to be demonstrated for new classes of tools to achieve policy recommendation, and some of the challenges in generating the necessary evidence. For low transmission settings the potential of innovation in the deployment of vector control to accelerate the goal of malaria elimination is discussed. Finally, the chapter highlights the specific need for adapting vector control in conflict and humanitarian emergency situations to prevent the development of new foci of transmission.

Keywords: insecticides, malaria, vector control, new tools, new generation, resistance

The role of insecticides in the changing global burden of malaria

One of the foremost successes in global health since 2000 has been the dramatic decline in the world-wide malaria burden, particularly in sub-Saharan Africa (WHO 2019c). According to WHO World Malaria reports (WHO 2015, 2019c) malaria incidence declined globally from 146 cases per 1000 to 57 per 1000 population at risk between 2000 and 2018. Over the same period annual malaria deaths in all ages have decreased from 839,000 to 405,000. Most of the world's malaria burden is concentrated in Africa: in 2018, 93% of all malaria cases and 94% of all malaria deaths occurred in Sub-Saharan Africa. Children under 5 years remain the group most at risk of malaria accounting for 67% of all malaria deaths worldwide in 2018.

The reductions in malaria cases and malaria deaths coincided with a massive investment in the use of insecticide-based methods of malaria prevention, in particular insecticide-treated mosquito nets (ITNs) and indoor residual spraying (IRS). During the period from 2015 to 2017 alone, 552 million ITNs, mainly long-lasting insecticidal nets (LLINs), were distributed globally (83% of these were distributed in Africa). By 2018, 50% of the population at risk of malaria in Africa were sleeping under an ITN, compared to <2% in 2000. Key to the success of LLINs was the development of insecticide formulations that would withstand up to 3 years of household use and multiple washing cycles without necessity for re-treatment (Hill *et al.* 2006).

The US-funded President's Malaria Initiative (PMI) was started in 2005, initially as a 5-year programme to scale up malaria prevention and treatment interventions in 15 highly endemic countries in sub-Saharan Africa (PMI 2015). PMI funding resulted in IRS coverage increasing substantially from <2% of the at-risk population protected in 2005 to 11% or 78 million people in 2010. Pyrethroids were widely used initially but from 2011 to 2015 they were replaced by other classes of insecticide (Oxborough 2016). Due to its cost and operational challenges, IRS is less widely deployed than LLINs in malaria endemic countries; nevertheless, in 2018, 130 million people in Africa were protected by IRS (WHO 2019c).

A comprehensive modelling study using malaria indicator surveys and other data from the years 2000 to 2015 has shown that 663 million clinical cases of malaria have been averted through malaria control interventions over this period (Bhatt *et al.* 2015). Of these averted cases, 68 and 10% have been attributed to the use of ITNs and IRS, respectively, with the remainder being contributed by the treatment of clinical malaria cases with artemisinin-based combination therapy. With nearly 80% of the reduction in the malaria burden being due to the large-scale implementation of insecticide-based vector control with ITNs and IRS, it is clear that insecticides have played a pivotal role in the global fight against malaria. Foremost among these has been the pyrethroid class of insecticides. Their unique properties of high insect toxicity at low concentrations, rapid knock-down and speed of action, excito-repellency to mosquitoes and safety to humans, made the pyrethroids ideal for use on ITNs (Hill *et al.* 2006). Before the synthetic pyrethroids were developed the main classes of insecticide used in malaria vector control were organochlorines, such as dichlorodiphenyltrichloroethane (DDT), organophosphates, such as malathion, and carbamates, such as bendiocarb (Gilles and Warrell 1993). All of these insecticide classes, including the pyrethroids have neural modes of toxic action. DDT and the pyrethroids disrupt nerve impulses by preventing closure of voltage gated sodium channels in axonal membranes. Organophosphates and carbamates disrupt nerve transmission by inhibiting the enzyme acetylcholinesterase which is responsible for the degradation of acetylcholine at synapses. While most organophosphates and carbamates are too toxic and water soluble to use on nets, their stability and residual activity on household surfaces make them ideal for use as IRS (BCPC 2018). All of these classes function by contact with the tarsus or feet of the mosquito when it alights on the insecticidal wall or net fibres and the insecticide is absorbed through the cuticle.

Why has insecticidal vector control been so effective? In large part this is due to ITNs and IRS killing female mosquitoes that are either just about to, or have just taken a blood meal. If properly implemented at high population coverage, these interventions have a major effect on the average age to which female mosquitoes survive. To transmit malaria, a mosquito has to live long enough to become infected, survive the pathogen latent period, and then survive long enough to give infectious bites. According to malaria transmission models (Mandal *et al.* 2011), reducing the daily survivorship of adult female mosquitoes, has an exponential effect on reducing the reproductive number and hence transmission of malaria (Mandal *et al.* 2011, Smith *et al.* 2012). This is particularly true for anthropophilic vectors like *Anopheles gambiae* and *Anopheles funestus* which enter houses to feed or digest their blood-meals at each gonotrophic cycle. The personal protective effects provided by the barrier of the net and by pyrethroids repelling mosquitoes is also important. Untreated nets provide a mechanical barrier when new and intact, but most nets readily acquire holes and tears through which anthropophilic anophelines easily penetrate. Experimental hut trials have shown that ITNs, on account of the repellency provided by the pyrethroid, are more effective than holed untreated nets (N'Guessan *et al.* 2007b). Personal protection may be more evident against partially zoophilic vectors, such as *Anopheles arabiensis* in Africa and a range of vector species in Asia whose population densities are less likely to be reduced by the killing effect of LLIN or IRS (Kitau *et al.* 2012, Rowland *et al.* 2002). WHO recommends that in endemic countries all those at risk of malaria should be protected by ITNs or IRS (WHO 2019b).

Of special concern are conflict-affected countries. These have some of the highest malaria burdens in Africa and Asia (e.g. Democratic Republic of Congo, South Sudan and Afghanistan) driven by broken health systems and mass movement of vulnerable populations. During the early stages of emergencies, the displaced or refugee populations may subsist outdoors in makeshift shelters unsuited to standard ITN and IRS intervention (WHO 2013) and alternative solutions need to be developed. If the conflict is protracted, the displaced populations may build simple dwellings from mud brick more conducive to ITN and IRS intervention.

Despite the aforementioned major achievements in reducing the global malaria burden, the overall decline in malaria incidence has stalled in recent years (WHO 2019c). Whilst the reasons for this are likely to be multi-factorial, the question for malaria vector control is whether insecticide-based interventions can continue the success of reducing the global malaria burden, and ultimately bring about elimination?

Threats to continued efficacy of insecticide-based vector control

The continued effectiveness of insecticidal vector control is threatened by commercial, biological and financial factors. The principal commercial threat to public health insecticides arises from the mismatch of attributes required in a typical LLIN or IRS insecticide versus those required for agricultural insecticides which constitute over 99% of the pesticide market (Hoppe *et al.* 2016, Sternberg and Thomas 2018, Turner *et al.* 2016). The principal biological factor is evolving insecticide resistance, which has emerged widely in endemic countries (WHO 2018b). Other limitations to the effectiveness of current malaria vector control interventions are mosquito biting that does not occur indoors at night, so-called residual transmission (Killeen 2014), and the high level of resources needed to cover escalating costs of new insecticides (WHO 2019c).

Public health versus agricultural insecticides

Whilst a typical product profile for an agro-insecticide is short residual life, ingestion via the midgut, water solubility and moderate human toxicity, the profile for a public health insecticide is more typically long residual activity, cuticular absorption via the tarsus or feet, wash-resistance and low human toxicity. The dichotomy of these characteristics has historically acted as a disincentive to chemical companies to invest and develop specific public health insecticides for which there had been a relatively small market, compared to agricultural pesticides of which only a few have proven suitable for repurposing to vector control application (N'Guessan *et al.* 2007a, c). As a consequence there had been no new class of insecticide for adult anopheline control, until recently (N'Guessan *et al.* 2016, Ngufor *et al.* 2016), since the pyrethroids were introduced more than 30 years ago. This situation changed fundamentally after the philanthropic intervention by the Bill & Melinda Gates Foundation to fund research and development costs for public health insecticides (Sternberg and Thomas 2018, Turner *et al.* 2016), which has resulted in new insecticide formulations becoming available for public health use in recent years and a promising pipeline of new insecticides in the near future.

Insecticide resistance

A policy of 'universal coverage' of vector control including LLINs to populations at risk of malaria was initiated by the UN Secretary General over a decade ago (WHO 2017a). Pyrethroid resistance in *An. gambiae* and *An. funestus* has since become widespread. According to the World Malaria Report of 2019, of the 81 malaria endemic countries that reported standard insecticide resistance monitoring between 2010 and 2018, resistance was detected in 73 countries to at least one insecticide in at least one malaria vector in at least one monitoring site. Of these 73 countries, 26 detected resistance to all four classes of insecticides. Only eight countries that monitored insecticide resistance did not confirm resistance to any insecticide class. The *WHO Global report on insecticide resistance in malaria vectors, 2010-2016* (WHO 2018b), reported increases in resistance frequency over time i.e. increases in mosquito survival in standard WHO bioassays, for all major vectors. Increases in resistance frequency were observed to all four classes of insecticides but were most marked for pyrethroid resistance.

A WHO coordinated study that monitored resistance frequency at a large number of locations successively over time in five countries over several years found that there was very high variability in these measurements, i.e. they varied over small geographical distances and also between time points at the same location (Anonymous 2018). Nevertheless, there was an increase in resistance frequency with mosquito mortality on average falling steadily over the course of the five-year study, corresponding to an odds ratio of 0.8 per year. The study found that higher net usage was associated with higher resistance frequency due to the increased selection pressure in places where net use was higher.

Has increasing resistance frequency led to a reduction in the effectiveness of insecticide-based interventions, particularly insecticide treated nets? The WHO five country investigation (Kleinschmidt *et al.* 2018) as well as other studies (Lindblade *et al.* 2015, Ochomo *et al.* 2017) showed that people sleeping under nets were always more protected against malaria infection than people who were not sleeping under nets, even in areas of pyrethroid resistance. There was no evidence that the level of protection varied between places with different levels of resistance frequency. Accordingly, WHO recommends that populations living in malaria-endemic areas should continue to use insecticide-treated nets to reduce their risk of infection even in areas of insecticide resistance (WHO 2019b). Nevertheless, users of nets although better protected against malaria than non-users, are still subject to high infection rates indicating that standard insecticide treated nets provide only partial protection against malaria infection (Bradley *et al.* 2017).

While changes in the frequency of phenotypic resistance in response to discriminating concentrations of insecticide is the usual indicator used to designate increases in resistance (WHO 2016), the measure takes little or no account of changes in the strength of resistance that accrue when genes for different pyrethroid resistance mechanisms are selected sequentially over time. For example, an early mechanism of pyrethroid resistance selected to high frequency in West African *An. gambiae* was the L1014 *kdr* mutation of the voltage gated sodium channel (VGSC) gene. This site-insensitivity mechanism, by itself, even at high allelic frequency conferred only limited survival value (25%) to mosquito carriers which attempted to feed through LLIN in household settings (Asidi *et al.* 2005). Contemporary community randomised trials in the same locality produced no evidence that ITNs had become any less effective in areas of high *kdr* compared to trials in areas of pyrethroid susceptibility (Henry *et al.* 2005, Pryce *et al.* 2018). Similarly, pyrethroid-based IRS was still used for malaria control on Bioko Island to good effect despite high frequency of *kdr* in the *An. gambiae* population (Hemingway *et al.* 2013). In mainland

West Africa, selection of *kdr* was followed by selection of P450 mono-oxygenases mechanisms which conferred increasing levels of resistance (Bagi *et al.* 2015, Corbel *et al.* 2007, Ranson and Lissenden 2016, WHO 2016). As resistance intensity increases when mechanisms accumulate over time, the capacity of the pyrethroid to kill the vector or reduce longevity diminishes (Asidi *et al.* 2005, N'Guessan *et al.* 2007b). In response to this, insecticide resistance monitoring now includes measurement of surviving mosquitoes (or their progeny) to multiple insecticide concentrations, i.e. an assessment of resistance intensity (WHO 2016). Currently there are insufficient data over time of the resistance intensity metric to analyse time trends.

During a community randomised trial in northwest Tanzania, where pyrethroid resistance intensity in *An. gambiae* and *An. funestus* was 38- and 34-fold, respectively, compared to susceptible mosquitoes, the prevalence of malaria infection in the reference arm of the trial that received standard pyrethroid LLIN was 55% after one year of use (Protopopoff *et al.* 2018). Independent evidence from experimental hut studies in Tanzania confirmed that pyrethroid LLIN were no longer killing host-seeking pyrethroid-resistant *An. gambiae* and *An. funestus* that entered huts to feed on LLIN users, compared to the earlier period of pyrethroid susceptibility in the same location (Yadav 2015). Experimental hut studies, before and after selection of pyrethroid resistance, demonstrated that standard LLINs confer a modicum of protection through pyrethroid exito-repellency to host-seeking resistant mosquitoes, and provide a mechanical barrier when in good condition (Asidi *et al.* 2012, N'Guessan *et al.* 2007b). Whilst standard pyrethroid LLINs still help prevent malaria in many countries, the standard LLIN is no longer the best protection available as this is provided by the next generation of LLINs (Rowland 2018). Nevertheless, those who only have standard LLINs available should continue to use them as it is always better to sleep under a net in a malaria endemic area.

New generation tools

New generation long lasting insecticidal nets

Entomological efficacy of new nets can be assessed in experimental hut studies in which volunteers sleep under candidate nets under controlled household conditions so that the numbers of mosquitoes killed by the LLIN or succeeding in blood-feeding can be measured precisely. LLIN nets containing the synergist PBO (piperonyl butoxide) will neutralise metabolic forms of pyrethroid resistance conferred by P450 mono-oxygenases (Gleave *et al.* 2018, Rowland 2018, WHO 2017b). In experimental hut studies PBO-pyrethroid LLIN were shown to kill 1.85 times more pyrethroid-resistant mosquitoes and induce 0.60 times less blood feeding than standard pyrethroid-only LLIN (Gleave *et al.* 2018). The first community randomised epidemiological trial of PBO-pyrethroid LLIN being conducted against pyrethroid-resistant *An. gambiae* and *An. funestus* in northwest Tanzania showed that among villages that used PBO-pyrethroid LLIN, malaria infection prevalence was 44% lower compared to villages that used standard pyrethroid LLIN (Protopopoff *et al.* 2018). As a result, WHO recommended the deployment of pyrethroid-PBO nets in areas where the main malaria vectors have 'pyrethroid resistance that is … conferred (at least in part) by a monooxygenase-based resistance mechanism' (WHO 2017b). In 2018-19, procurement of PBO LLIN gathered pace and the Global Fund and President's Malaria Initiative (the major funding agencies for malaria prevention) approved orders for PBO-pyrethroid LLIN from national Malaria Control Programs across Africa. A large study in Uganda in which health sub-districts were randomised to receive either pyrethroid-PBO LLINs or standard pyrethroid LLINs, confirmed the superior protective efficacy of PBO nets against pyrethroid resistant mosquitoes (Staedke *et al.* 2020)

Apart from PBO-pyrethroid LLIN, several other types of dual-active ingredient (AI) or mixture LLINs are under development and evaluation. These incorporate alternative insecticides to complement the companion pyrethroid. The alternatives differ in chemical class and mode of action to pyrethroids. Most have been re-purposed from agricultural insect pest control use and reformulated for binding to polyethylene or polyester nets. Candidate insecticides should express no cross resistance to current mechanisms of resistance and pose no safety risk to LLIN users at the concentration applied (WHO 2018a).

One of these insecticides, pyriproxyfen, is an insect growth regulator developed to prevent mosquito larvae from moulting and adult insects from producing fertile eggs. Following its initial application as a long-lasting larvicide in water storage containers for urban *Aedes* control and in irrigated sites for *Anopheles* control, pyriproxyfen came to greater prominence for its unusual property of auto-dissemination in which insecticide is transferred on the tarsae of adult females to container breeding sites in doses that kill the larvae (Lwetoijera *et al.* 2014, Yapabandara and Curtis 2004). Incorporated into fibres of polyethylene nets, pyriproxyfen sterilises host-seeking females that contact the net by disrupting oocyte maturation from blood meals and of oviposition of fertile eggs and reducing adult longevity (Kawada *et al.* 2014, Ngufor *et al.* 2016). A sterile survivor may continue to bite but makes no contribution to the next generation, and mosquito populations should decrease over time through the mass sterilising action of pyriproxyfen on nets. Two pyriproxyfen-pyrethroid LLIN have been developed: Olyset Duo (Sumitomo Chemicals, Osaka, Japan) which combines pyriproxyfen with permethrin, and Royal Guard (DCT, Greer, USA) which combines pyriproxyfen with alphacypermethrin. Both brands of net show some loss of activity after multiple washes. A cluster randomised trial of Olyset Duo conducted in Burkina Faso using a stepped wedge design demonstrated a 12% reduction in the incidence of clinical malaria and 51% reduction of infective mosquito bites in the intervention arm compared to the permethrin LLIN arm (Tiono *et al.* 2018). Cluster randomised trials of Royal Guard are presently underway in Tanzania and Benin.

The insecticide mixture LLIN, Interceptor G2 (BASF, Ludwigshafen, Germany) combines the pyrethroid alphacypermethin with the pyrrole insecticide chlorfenapyr. While alphacypermethrin is a fast-acting neurotoxin, chlorfenapyr is a slower acting pro-insecticide which, after metabolic activation, disrupts cellular respiratory pathways (oxidative phosphorylation), proton transfer in mitochondria and the conversion of Adenosine Diphosphate (ADP) to Adenosine Triphosphate (ATP) (Black *et al.* 1994). The insecticide is particularly toxic to host-seeking mosquitoes at night when contacting nets during the high metabolic phase of their circadian cycle (Oxborough *et al.* 2015). Owing to its unique mode of action, chlorfenapyr exhibits no cross resistance to mechanisms associated with the insect nervous system, and is safe to use on nets. The formulation of pyrethroid and pyrrole in the mixture LLIN is able to withstand 20 standardised washes and in experimental hut trials kills 76-90% of pyrethroid-resistant mosquitoes and inhibits blood-feeding by up to 60% (N'Guessan *et al.* 2016). Interceptor G2 is presently undergoing cluster randomised trials in Tanzania and Benin to obtain evidence of public health impact of malaria control efficacy that is required by WHO for recommendation of new product classes. Simultaneously, small scale distributions are being piloted in several African countries.

New generation indoor residual spraying

A number of studies have convincingly demonstrated that insecticide resistance causes a substantial and possibly total loss of effectiveness of IRS in protecting populations against malaria (Kafy *et al.* 2017, Kigozi *et al.* 2012, Maharaj *et al.* 2005). In response to this, manufacturers with the support of research donors have developed several new insecticides for IRS, including a new class of insecticides, the neonicotinoids, that has been added to the previously existing four classes of insecticides available for IRS (pyrethroids, organochlorines, carbamates, and organophosphates). Currently at least 23 IRS products are pre-qualified by WHO, plus DDT, which is not pre-qualified but which is recommended if no suitable, affordable alternative is available. With the new products there is a transition to longer-lasting, resistance breaking insecticides. Three new recent products are: Actellic® 300CS (Syngenta International AG, Basel, Switzerland), a long lasting formulation of pirimiphos methyl (Rowland *et al.* 2013); Sumishield® (Sumitomo Chemicals, Osaka, Japan), which is based on the neonicotinoid clothianidin; and Fludora Fusion® (Bayer AG, Leverkusen, Germany) which contains clothianidin and deltamethrin as active ingredients. It should be noted that insecticides with slow-acting compounds are not automatically pre-qualified for IRS use without evidence of public health impact.

A number of, mostly observational, operations research studies have been conducted to assess the impact of IRS using new generation insecticides (http://www.ivcc.com/ngenirs/news-and-media/news/irs-expanding-the-evidence-base). These studies have shown that reductions of between 20 and 40% in malaria cases were achieved after spraying with the new insecticides. One of these studies indicated that IRS with Actellic 300CS, when deployed in combination with standard LLINs, provided additional protection against malaria transmission compared to the use of LLINs alone (Chaccour *et al.* 2018). Previous studies, including randomised trials, have shown contradictory results when comparing the effectiveness of IRS and LLINs in combination against LLINs alone, with some showing enhanced control of malaria for the combination (Hamel *et al.* 2011, Protopopoff *et al.* 2018, West *et al.* 2014), whereas other studies recorded no added benefit over the use of LLINs alone (Corbel *et al.* 2012, Pinder *et al.* 2015, Protopopoff *et al.* 2018). These apparently conflicting results may be due to differences in insecticide resistance to either the insecticide on the net, or the insecticide used for IRS, or due to low power to show an effect. A cluster randomised trial in which IRS with Actellic 300CS, to which there was no resistance, was sprayed in combination with the high coverage of PBO-LLINs, which were effective against pyrethroid resistant mosquitoes, showed no added benefit compared to the use of PBO-LLINs alone (Protopopoff *et al.* 2018). There may therefore be an argument against the additional cost of IRS for enhanced malaria control if the Dual AI LLINs are effective against resistant vectors. However, it may be the case that there have been insufficient trials of dual AI LLIN and different classes of IRS to reach this conclusion. Some combinations may turn out to be additive. It remains a research priority to identify and test combinations which will stop transmission and help drive towards elimination.

The need for new vector control tools and the future role of insecticides

Despite the reports of impact achieved with new generation LLINs and novel IRS insecticides, it is evident that even with such tools deployed at high coverage, malaria burden remains unacceptably high. For example, in the PBO trial in Tanzania the study arm with nets that were effective against pyrethroid resistant mosquitoes – the PBO nets – infection prevalence was still around 30% after two years of intervention. In the Burkina Faso trial, despite the use of resistance breaking nets – the pyriproxifen nets – clinical incidence of malaria was still 1.5 cases per child per year, despite high net usage. New generation IRS has shown high impact, but spraying poses significant operational and logistical challenges to achieve not just high coverage but also high-quality application (Smith Gueye *et al.* 2016). Furthermore, all indoor control methods are ultimately unable to address residual transmission that occurs when people are not indoors and not protected by either IRS or LLINs (Killeen 2014). Residual transmission is likely to be holding back elimination in countries where these methods have been deployed to scale whilst low levels of transmission stubbornly persist, year after year (Loha *et al.* 2019, Zhu *et al.* 2017). There is therefore an urgent need for new, more effective classes of vector control tools, with and without the use of insecticides, as well as innovative strategies of deployment of existing tools (Medzihradsky *et al.* 2018).

A few of the new classes of vector control tools that are currently being evaluated, that are insecticide based and that have high potential for providing effective protection against malaria in future, are briefly described below, but this list is not intended to be exhaustive. These products currently do not have a policy recommendation as they have not yet been shown to provide public health impact in at least two randomised trials, as required by WHO.

- Insecticide treated eaves tubes are inserted into specially drilled holes in the eaves of a house. The tube contains a mesh which can be treated with different insecticides. The idea is that the house with its occupants acts as a lure to mosquitoes who are attracted by human odours and therefore try to enter through the eaves where they are trapped and killed by the insecticide. A recently completed cluster randomised trial in Cote d'Ivoire (Sternberg *et al.* 2018) to evaluate the effectiveness of eaves tubes in controlling malaria used a pyrethroid based eaves tube but clearly there is potential for other insecticides to be used. The trial results had not been published at the time of writing (July 2020).
- Tools for conflict affected countries include insecticide-treated tents and tarpaulins. Pyrethroid treated materials devised specially for early-stage emergencies and natural disasters include pyrethroid treated blankets (Rowland *et al.* 1999) and polyester tarpaulins or tents (Burns *et al.* 2012). Evaluated in household and community randomised trials in emergency settings, these interventions function like ITN and IRS respectively and have shown good protection against clinical malaria. Pyrethroid resistance will render these tools ineffective and new safe insecticides need to be developed and appropriately formulated into emergency materials and stock-piled in readiness. A spin-off from the emergency tarpaulin is the insecticide treated durable wall lining designed for long-lasting domestic use. (Mtove *et al.* 2016).
- Attractive targeted sugar baits (ATSBs) are a method of targeting the sugar-feeding behaviours of vector mosquitoes (Zhu *et al.* 2015). The ATSB station is hung on the outside walls of buildings and has the potential for targeting both outdoor and indoor transmission. A version of the product that is being evaluated in three separate cluster-randomised trials in Mali, Kenya and Zambia respectively, contains a plant-based attractant, sugar as a feeding stimulant and the neonicotinoid dinotefuran as active ingredient. A protective membrane covers the bait station but allows mosquitoes to feed through it. The ATSB has undergone one entomological field trial in Mali which demonstrated high impact on mosquito survival and entomological inoculation rate (Traore *et al.* 2020). Since this tool kills mosquitoes that feed on the baited active ingredient, rather than by contact, it will have the potential to use a wide range of active ingredients, including those initially developed for agricultural insect pests. The ATSB concept enables access to insecticide classes previously unavailable to public health entomology and rotation should thus provide resilience against resistance developing. Its utility in a range of environments with competing natural sources of sugar that are possibly used by vector mosquitoes is not yet clear. The three independent CRT should resolve this.
- Ivermectin is a drug used to treat many types of parasite infestations, including head lice and scabies. In West Africa mass drug administration of Ivermectin has been widely deployed to treat or eliminate river blindness (onchocerciasis), roundworm (strongyloidiasis) and lymphatic filariasis. In this context it has been shown that longevity of *Anopheles* mosquitoes that feed on Ivermectin treated hosts is reduced (Kobylinski *et al.* 2011, Sylla *et al.* 2010). Modelling studies claim that this intervention (generically known as an endectocide) has the potential of eliminating malaria if high coverage can be achieved as it kills or reduces survival of female

mosquitoes that take blood from Ivermectin treated individuals (Slater *et al.* 2014). Cluster randomised trials are planned in the Gambia, Guinea Bissau, Tanzania and Mozambique to evaluate the potential of Ivermectin mass drug administration to reduce malaria transmission.

These new product classes demonstrate the important role that insecticides are likely to continue to play in malaria control and elimination in future.

A number of non-insecticidal tools are also under development. An advantage they have over insecticide-based tools is that they do not select for resistant vector populations. One such new tool is the odour-baited trap, which has shown public health effect in combination with LLINs in a stepped wedge randomised trial in Kenya: There was a 30% reduction in *Plasmodium falciparum* prevalence and a 70% reduction in *An. funestus* density compared to LLINs alone (Homan *et al.* 2016). Integration of this and other non-insecticide tools alongside traditional IRS and dual-AI LLIN in an Integrated Vector Management (WHO 2012) approach should reduce selection pressure for insecticide-resistance in the vector population as well as having a direct impact on outdoor biting mosquitoes.

The path to evidence of public health impact and the need to innovate

Due to the inadequacy of funding that is available for malaria control globally (WHO 2018c), including for vector control, it is important that precise estimates of effectiveness and cost effectiveness of new product classes are generated, so that scarce resources are not wasted on tools that are ineffective or not cost effective. Randomised trials are regarded as the gold standard for assessing evidence of efficacy and for generating unbiased estimates of the effect size of new classes of interventions. It is for these reasons that the WHO Vector Control Advisory Group (VCAG) (https://www.who.int/vector-control/vcag/en/) demands that claims of effectiveness of new classes of tools are backed up by evidence from randomised trials. If randomised trials are not conducted at the time a new class of tool is developed, it is harder to generate the necessary data on effect size later as it may no longer be ethically acceptable to randomise communities to the 'new' method, if some measure of effectiveness, however imprecise, has already been established.

To receive WHO recommendation, a new vector control product class has to show evidence of effectiveness not just in killing mosquitoes, but in reducing malaria cases in human populations. The role of VCAG is to guide developers on the type of evidence they need to generate; to examine evidence upon which claims of public health impact are based; and to advise the WHO Malaria Policy Advisory Committee on whether a new vector control class should receive WHO recommendation (WHO 2017c). According to VCAG guidelines, any new first in class product needs to show actual reduction in cases of disease or infection, in at least two separate, robustly designed and appropriately executed randomised trials that each run over at least two years. In this context new generation long-lasting nets, i.e. nets with new or repurposed chemicals are regarded as new tools that need to demonstrate evidence of epidemiological impact. New tools and product classes currently undergoing evaluation in different stages of evidence generation are listed on the VCAG website.

Once a first-in-class product has received a policy recommendation, further products of the same class, called second-in-class products need to demonstrate the same entomological effect as the first-in-class products, without undergoing epidemiological trials. This is based on non-inferiority assessment of candidate products using a defined set of entomological measures which emanate from experimental hut trials (WHO 2019a). Several commercial brands of PBO-pyrethroid LLIN, all differing in concentration of PBO and pyrethroid compound, are currently the subject of non-inferiority entomological evaluation against the first-in-class that provided the disease control evidence. New IRS insecticides are generally not regarded as new classes and therefore do not require evidence of public-health efficacy as long as they satisfy the criteria for entomological effect.

The time taken to prove a product's worth versus the race to achieve disease impact and saving of lives, has led to frustration at times (Killeen and Ranson 2018). An extreme example is the PBO LLIN. First developed in 2008, it took a further 10 years before its superiority to the standard of care was demonstrated definitively in a community randomised trial (Protopopoff *et al.* 2018). With the benefit of hindsight, it did take too long to prove the class' worth, but this was because systems for establishing that proof were inadequate at the time, and neither public nor private sector organisations were willing to make the financial commitment to fund randomised trials with epidemiological outcomes (Protopopoff and Rowland 2018). The balance has since shifted with new WHO policy and procedures put in place, and with donors more willing to fund trials of new product classes. This should shorten the interval between initial product development, evaluation, policy recommendation and roll-out (Rowland 2018).

Nevertheless, trials take time, effort and money. A case has been made to replace or supplement the evidence generated by community randomised trials with malaria transmission modelling of new malaria vector control interventions (Sherrard-Smith *et al.* 2018). The transmission models make use of entomological surrogates of epidemiological outcomes, such as local vector species, insecticide resistance frequency, vector survival and blood feeding rates derived from experimental hut trials of LLIN and IRS interventions. The aim is to model and predict the epidemiological outcomes of a cluster randomised trial (CRT) of the new generation LLIN from local entomological data gathered during contemporaneous Phase II experimental hut studies held in the vicinity of the CRT. It remains to be seen whether reliable entomological correlates of epidemiological trial outcomes can be generated from hut trial data to predict public health impact. In the meantime, WHO does not accept modelling of disease control impact as an acceptable alternative to observed evidence of epidemiological outcomes from cluster randomised vector control trials.

Vector control in pre-elimination settings

Although the number of countries that have eliminated malaria is slowly increasing, not a single country in mainland sub-Saharan Africa has so far achieved this goal, despite a number having declared elimination as a policy goal. The intractability of malaria elimination in African countries with low but persistent malaria transmission is likely to be multi-factorial, but one of the reasons could be the plasticity in host biting and indoor resting behaviour of vectors such as *An. arabiensis* (Killeen 2014, Zhu *et al.* 2017), and hence using LLINs or IRS, alone or in combination, may not be enough to eliminate malaria (Kenea *et al.* 2019, Loha *et al.* 2019). Supplementary interventions that address residual malaria transmission may be needed in these settings. Innovative ways of deploying existing insecticide-based tools also have a role to play. One such method of deploying existing vector control is reactive focal IRS in response to passively reported index cases, alone or in combination with reactive focal mass drug administration, i.e. treatment with a full dose of anti-malarial drugs to high risk populations without first testing for parasites. Focal reactive strategies aim resources to higher risk populations and are intended to target the parasite reservoir in resurgent outbreaks. These reactive targeted interventions may provide extra transmission reduction if used in addition to existing interventions. A recent trial in Namibia showed that reactive focal mass drug administration and reactive focal IRS each reduced malaria incidence by about 50% when used on their own, and by 75% when used in combination (Hsiang *et al.* 2020, Medzihradsky *et al.* 2018). Adoption of the principles of integrated vector management using insecticidal and non-insecticidal tools (WHO 2012), in addition to those of integrated disease management, including chemoprevention, will be needed to achieve malaria elimination.

Conclusions

While the pyrethroid era of vector control may prove to be past its prime, insecticide interventions will remain at the heart of malaria prevention in years to come. The core interventions may remain ITN and IRS, but the net and spray formulations of the future will contain mixtures of active ingredients and will be deployed not only to maximise control but also to manage the selection for resistance. In light of inadequate funding for malaria control globally (WHO 2018c), the cost-effectiveness of interventions will increasingly be a factor in their deployment at scale. The conventional tools are likely to be supplemented by new classes of insecticide-based as well as non-insecticidal tools: ATSBs, endectocides, spatial repellents and an array of insecticide impregnated materials adapted for use in a variety of settings, including emergencies and disasters, long-lasting domestic applications and outdoor use for the control of residual malaria transmission and for elimination.

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3. Creating long-term resilience against malaria vectors while addressing the immediate need to suppress pathogen transmission

Fredros O. Okumu[1,2,3,4*] *and Marceline F. Finda*[1,2]
[1]Environmental Health & Ecological Sciences, Ifakara Health Institute, P.O. Box 53, Ifakara, Tanzania; [2]School of Public Health, University of the Witwatersrand, 1 Smuts Avenue, Braamfontein 2000, Republic of South Africa; [3]Institute of Biodiversity, Animal Health & Comparative Medicine, University of Glasgow, G12 8QQ Glasgow, United Kingdom; [4]School of Life Science and Bioengineering, Nelson Mandela African Institution of Science & Technology, P.O. Box 447, Arusha, Tanzania; fredros@ihi.or.tz

Abstract

Recent decades of malaria control have been dominated by extensive commoditisation of frontline interventions. Bed nets, insecticides, drugs and diagnostics have been scaled up in endemic countries, preventing millions of malaria cases and deaths. Unfortunately after years of progress, such gains are stagnating or diminishing due to challenges, such as insecticide and drug resistance, sub-optimal user compliance and the high costs for supply and replacements of these commodities. Without any viable vaccines or approaches that effectively tackle the environmental basis of malaria transmission, current commodities, and in particular the insecticide-based interventions, are incapable of preventing reinfections and rebounds, especially in low-income communities. This paper discusses a transitional approach for malaria prevention, involving judicious use of current tools while gradually building long-term resilience to sustain control of important vectors. The idea should be to carefully transition from insecticide-based to non-insecticidal approaches, without losing the gains made so far against malaria. In the short and medium-term, countries may deploy evidence-driven suites of current tools, e.g. insecticide treated nets (ITNs) and indoor residual spraying (IRS), while gradually introducing improved versions, such as nets with multiple chemical ingredients and long-lasting IRS formulations to suppress transmission. Depending on local evidence, these may be supplemented with niche technologies, such as spatial repellents, endectocides, odour-baited traps or mosquitocidal sugar baits to address gaps such as outdoor-biting and pyrethroid resistance. Once this is in place, countries should establish programmes to build long-term resilience to sustain the accrued gains and prevent transmission rebounds. Examples may include: incentivising the private sector to supply high-quality commodities e.g. locally-manufactured mosquito nets, providing subsidies to promote mosquito-free dwellings for low-income families, expanding community engagement in disease control and strengthening health systems to more effectively detect and manage cases. To secure these developments, endemic countries should also establish multi-sectorial initiatives prioritising disease control beyond malaria. Examples may include environmental sanitation to reduce vectors, institutionalised health education and capacity-building on biology and control of disease, appropriate legislation to improve compliance and protect vulnerable sub-populations and long-term domestic financing for malaria control. These programmes should be supported by a strong in-country research culture to constantly identify gaps, monitor progress and seek transformative approaches with potential to accelerate progress. If integrated in the wider public health context, this phased approach could contain ongoing malaria transmission, reduce over-reliance on insecticide-based tools and minimise transmission rebounds even in poor communities.

Keywords: integrated vector control, malaria elimination, insecticides, resilient communities, multi-sectoral approaches

Background

Malaria is among the oldest parasitic diseases known to man and also one of the most researched in modern times. Yet it remains a major cause of death and ill health, with more than 200 million cases and 400,000 deaths annually, most of these in sub-Sahara Africa (WHO 2019). Once its transmission by *Anopheles* mosquitoes was described more than 100 years ago (Ross 1897, 1923), early control efforts mostly focused on addressing the problem at source and minimising human exposure to mosquito bites (Wilson *et al.* 2020). Vector control relied heavily on environmental sanitation, protective housing and management of water ways, though these were often supplemented with biological control and toxic larvicides (Barat 2006, Bruce-Chwatt and Zulueta 1980, Gladwell 2001, Greenwood 2008, Lindsay *et al.* 2002, 2004, Najera 2001, Soper and Wilson 1943). Despite the relatively poor physical infrastructure at that time, major gains were made and several places stayed malaria-free for many years. Unfortunately, these approaches declined after arrival of effective 'seemingly-magical' commodities.

First was the discovery of DDT (Najera 2001, Sadasivaiah *et al.* 2007), which in 1950s became the foundation of the first attempt to eradicate malaria globally (Nájera *et al.* 2011). DDT and other insecticides were mainly sprayed inside dwellings, but were also tested for fabric treatment against insect-borne diseases, e.g. in South East Asia (Harper *et al.* 1947). Widespread use of insecticides was a major disincentive for development of other anti-malaria innovations until insecticide resistance began to slow the progress. For another four decades, even mosquito nets remained rare and were not widely promoted as malaria control intervention.

The second major commodity was insecticide-treated nets (ITNs), which have now dominated malaria vector control since the mid-2000s. Widespread use of nets against malaria was officially adopted into global health policy in 1993 (Jamet 2016, WHO 1993), following early evidence of effectiveness against malaria-related mortality and morbidity in countries such as The Gambia and Tanzania (Alonso *et al.* 1991, 1993, Curtis and Mnzava 2000). Starting 1998, the Roll Back Malaria (RBM) managed an intensive campaign to promote ITNs, which has today delivered more than two billion ITNs mostly in low-income endemic countries (Roll Back Malaria 2020). The current consensus is that most of the gains accrued against malaria since 2000 can be attributed to vector control with ITNs and IRS (Bhatt *et al.* 2015). As a result there is a genuine desire to continue their deployment in endemic countries, but with the understanding that further advancements are necessary to maintain progress. ITNs are still mostly dependent on pyrethroid class of insecticides though there are growing calls for nets containing either synergists or multiple active ingredients. Indeed, some ITN manufacturers already produce nets containing the synergist, piperonyl butoxide (PBO), or other active ingredients, such as pyriproxifen and chlophenapyr in addition to the pyrethroids (WHO 2020b). On the other hand, IRS which also remains pivotal in both high and low-transmission settings can be done using multiple insecticide classes, including carbamates, organophosphates and neonicotinoids (WHO 2020b).

Another common feature of current malaria control approaches is that the supply chains for key commodities are heavily reliant on importations and international financing by organisations, such as the Global Fund for AIDS, Malaria and Tuberculosis and US President's Malaria Initiative. While these commodities make for tangible deliverables that are easy to report upon, e.g. number of nets distributed, they rarely provide the long-term control especially in low-income communities. For example, ITNs have to be replaced every 3-4 years and IRS redone at least every year.

After years of progress, the anti-malaria gains are also stagnating or diminishing due to challenges such as insecticide resistance, sub-optimal user compliance and the high costs necessary to maintain supplies and replacements of these commodities (Haakenstad *et al.* 2019). Yet it is unlikely that current financing mechanisms will be sustained for several years to come. The immediate health benefits of the continued use of ITNs and IRS are evident (Bhatt *et al.* 2015), but this does not guarantee long-term solution to the problem of vector borne disease control. Recent examples from agriculture show that with concerted action, the economic and effective implementation of integrated pest management is feasible and beneficial (Sternberg and Thomas 2018, Thomas *et al.* 2012). However, these will require far greater financial investments than currently available for malaria control (Haakenstad *et al.* 2019). Without a viable vaccine or approaches that effectively tackle the environmental basis of malaria transmission, current commodities mostly provide temporary protection but are incapable of preventing reinfections especially for low-income households. Endemic countries should therefore transition towards a more sustainable approach that prevents disease transmission in the short and medium-term while also ensuring that future generations remain sustainably protected.

This chapter therefore proposes a set of strategies for sustainable malaria vector control, and includes a phased approach that involves judicious use of current insecticide-based interventions while gradually transitioning towards insecticide-free options and structural resilience to sustain the gains over the long-term. There is no expectation that all endemic countries can immediately begin this transition. However, evidence from complex settings such as Sri Lanka, which eliminated both *Plasmodium falciparum* and *Plasmodium vivax* malaria despite having an ongoing war in some parts of the country (Premaratne *et al.* 2019), indicate that most challenges are surmountable given long-term commitment to the mission.

Malaria prevention should be guided by detailed understanding of how the pathogen is transmitted locally

Despite the absence of a viable malaria vaccine, our current understanding of the disease is theoretically adequate to effectively control it to such extents that it is no longer a major public health concern. Fundamentally, it requires radical prevention of contacts between humans and female *Anopheles* mosquitoes or complete cure of infected persons. In both cases, there are proven approaches to achieve the objectives at scale, given an effective public health administration system and sustained financing. Yet in many low-income communities, persistent implementation gaps have compounded the evolutionary processes in mosquito populations and yielded complex epidemiological scenarios where elimination is now elusive.

Following the renewed call for global malaria eradication in 2007 (Roberts and Enserink 2007), Ferguson *et al.*, emphasised that improved understanding of the ecology of malaria vectors will be vital in identifying additional interventions to complement existing efforts (Ferguson *et al.* 2010). Such knowledge would also be vital for adapting current interventions to achieve maximum impact under changing circumstances. To demonstrate this point, Figure 1 shows key behaviours of *Anopheles* mosquitoes in and around households, and how they may interact with current core interventions, i.e. ITNs and IRS. While this is only one aspect of the much more complicated mosquito lifecycle processes, it illustrates how the biology of the vector can influence the success of any interventions used.

The most dominant African malaria vector species, such as *Anopheles gambiae* and *Anopheles funestus* have very strong preferences to bite and blood-feed on humans compared to other animal

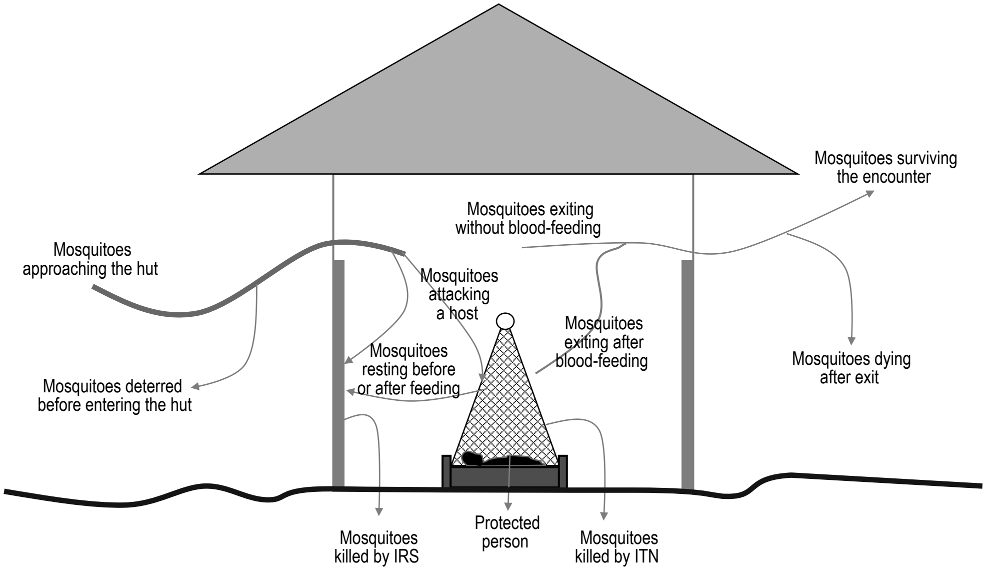

Figure 1. Diagrammatic representation of various effects of mosquito nets (ITNs) and indoor residual spraying (IRS) on mosquitoes that enter or attempt to enter houses. Mosquitoes can be deterred and diverted before they enter houses, killed by the insecticides used on IRS or ITNs inside houses, or irritated so that they exit huts earlier than normal. This exit may occur before or after the mosquitoes have blood-fed, but both fed and unfed mosquitoes may die later after exiting, due to sub-lethal effects of the insecticides. The net and IRS may also reduce mosquitoes' ability to successfully bite and transmit disease (Adapted from Okumu and Moore 2011).

hosts (Killeen 2014, Takken and Verhulst 2013). As a result, they cause higher stability of malaria and greater efficiency of transmission than species elsewhere (Killeen 2014, Kiswewski *et al.* 2004). Yet, these same characteristics can be targeted to effectively crash the vector populations and overall malaria transmission. Where vectors are susceptible to insecticides used on ITNs or for IRS, greater value beyond personal protection can be derived from the mass-killing effect on vector populations. Given the strong dependence of these vectors on humans, even non-insecticidal barriers, such as house screening or untreated nets may heavily impact malaria transmission by simply limiting access to host blood, otherwise essential for reproduction.

Where there are multiple vector species at the same location, ecological studies should focus on each individual species as their contributions to the overall transmission and responses to interventions may be dissimilar. For example, in some sites across east Africa, widespread use of ITNs has significantly reduced populations of the formerly dominant *An. gambiae* (Bayoh *et al.* 2010, Lwetoijera *et al.* 2014). While these sites still have *An. funestus* co-occurring with *Anopheles arabiensis* and several other species, detailed analysis suggests that *An. funestus* is responsible for most infective bites and overall transmission (Kaindoa *et al.* 2017, Lwetoijera *et al.* 2014, McCann *et al.* 2014). In some rural districts in south-eastern Tanzania, *An. funestus* (which bites mostly humans indoors) is implicated in 80-90% of all infective bites, even where its densities are lower than *An. arabiensis* (which readily bites non-human vertebrates outdoors) (Kaindoa *et al.* 2017, Swai *et al.* 2019).

It is therefore important to identify the main drivers of local transmission and deploy appropriate interventions. For best results, evidence on behaviours of adult *Anopheles* should be gathered locally and considered together with other observations such as insecticide resistance profiles as well as knowledge of their aquatic habitats. For example, additional studies on the dominant *An. funestus* in Tanzania have shown that while their aquatic habitats are rare and difficult to find, they have unique characteristics potentially targetable by larval source management to further improve control (Nambunga *et al.* 2020) (Figure 2). In settings where this is the dominant malaria vector, a strategy that combines indoor interventions and source reduction could be highly cost-effective.

Figure 2. Typical larval habitats of Anopheles funestus *mosquitoes in Tanzania: (A) medium-sized ponds that retain water at the center most of the year and have emergent surface vegetation, (B) small spring-fed wells with well-defined perimeters and (C) slow-moving waters at the river side with emergent vegetation (Adapted from Nambunga* et al. *2020).*

Such source reduction strategies may also be desirable in places where significant biting exposure occurs outdoors, such as recently described in Zanzibar (Monroe *et al.* 2020). In fact, as malaria transmission declines in an area, it may become more difficult to find infected persons than it is to find aquatic habitats of *Anopheles* mosquitoes. Elimination efforts should therefore also include detailed mapping and targeting of all plausible habitats, so as to further reduce receptivity and completely disrupt local infections.

Use of insecticide-based interventions should be judicious, temporary and integrated with local practices in agriculture

Since the arrival of DDT, insecticide-based interventions have yielded significant gains in the fight against vector-borne diseases. Current consensus is that approximately 80% of all gains made against malaria between 2000 and 2015 were attributable to ITNs and IRS (Bhatt *et al.* 2015). These interventions now form the basis of malaria control strategies in most endemic countries, and will likely remain so in the near future. Yet, the insecticide resistance treadmill coupled with growing environmental health concerns highlight the need to minimise overdependence on insecticides. To remain effective, the use of insecticides must therefore be carefully done, relying on local evidence of efficacy and safety so as to adapt the implementation strategies going forward.

A recent analysis has documented great details of widespread and increasing strength of pyrethroid resistance across Africa (Hancock *et al.* 2020). While such observations are generally followed by recommendations for more effective insecticides, insecticide rotations or combinations of insecticide classes, the ultimate aim should be to eventually transition from insecticide-based interventions. Greater focus should be put on more sustainable and environmentally friendly approaches that are equally or more effective but are not affected by the evolutionary pressures driving resistance.

While ITNs still rely mostly on pyrethroids, their mosquitocidal effects are greatly attenuated in areas where pyrethroid resistance is widespread. ITNs with multiple actives or synergists may remain effective in specific settings where malaria vectors are susceptible, or for managing emergencies and outbreaks. However, mixed results of their field performance (Gleave *et al.* 2018, Protopopoff *et al.* 2018, Staedke *et al.* 2020, Tiono *et al.* 2018), unknown longevity of the synergists (Skovmand 2018), high costs and drawn-out innovation timelines do not justify continuing singular focus on insecticides. The new net types may also present interim options for transitioning towards non-insecticidal approaches. To more realistically assess overall value, the main indicator for selecting net brands should be the functional survival and durability in field settings rather than simply bio-efficacy (Lorenz *et al.* 2019). Moreover, given that durable nets, if widely used, may remain substantially effective in resistance settings, countries may consider long-lasting non-insecticidal nets at high coverage to fill the vector control gaps.

IRS on the other hand have multiple insecticide options still available for use, though most are repurposed from Agriculture. Therefore, one way to achieve judicious use of insecticides may be the removal of chemical pesticides from mosquito nets, and instead restricting them on high quality IRS (Paaijmans and Huijben 2020), where the non-pyrethroid insecticide classes can be rotated, combined or used in mosaics (WHO 2012). The IRS campaigns should be conducted cautiously and constantly improved to minimise current challenges faced by implementers. Other than insecticide resistance, these challenges generally include the high costs of implementation, the need for large teams of trained personnel, the need to remove people's belongings from houses before spraying, extensive supply chain requirements, e.g. transportation, storage and waste disposal.

The applications should also ensure that important mosquito resting surfaces in different house types are effectively targeted. While IRS practices still rely on evidence from the 1950s and 60s (Davidson 1953, Smith 1962a,b), housing standards in Africa have improved over the years. An analysis by Tusting et al showed that proportions of people living in improved houses (i.e. houses with durable construction materials, e.g. metal roofing and screened openings, sanitation and adequate living space) doubled between 2000 and 2015 (Tusting *et al.* 2019). These improvements can influence mosquito resting behaviours and should therefore be considered to improve IRS (Figures 1 and 3). One study in Tanzania by Msugupakulya *et al.* (2020) showed that as much as two thirds of mosquitoes that enter metal-roofed homes end up resting on surfaces not typically sprayed by insecticides. This study also indicated that IRS would be more impactful in grass-thatched roofs and un-plastered walls, where higher proportions of mosquitoes rest on sprayable surfaces (Msugupakulya *et al.* 2020). Improved understanding of mosquito behaviours inside local households is thus critical to maximise effectiveness of IRS. The selected insecticides should not be pyrethroids or any insecticide class for which there is evidence of cross-resistance with pyrethroids. Actual deployment should begin at the end of the dry season to prevent rising malaria cases in the subsequent wet season.

Figure 3. Examples of common house types in the study villages in rural south-eastern Tanzania: (A) houses with thatched roofs and mud walls, (B) houses with thatched roofs and brick walls, (C) houses with metal roofs and unplastered brick walls and (D) houses with metal roofs and plastered brick walls. Understanding these gaps may help improve the quality and outcomes of IRS operations (Adapted from Msugupakulya et al. *2019).*

Another consideration is to integrate the usage patterns of pesticides in agriculture and public health (Matowo *et al.* 2020). In a recent analysis of critical gaps in the life cycle management of agricultural and public health pesticides, Van den Berg *et al.* showed that low-income countries including malaria-endemic countries had shortcomings in pesticide registration and inadequate measures against pesticide exposures (Van den Berg *et al.* 2020). As opposed to current practice where resistance management in public health is mostly disconnected from what happens in the agriculture programmes, decision makers must consider the reality that insecticides from both arms do end up in the same ecological environments (Nkya *et al.* 2013). While the trend of repurposing agricultural pesticides for public health use continues, there are no direct efforts in most countries to integrate insecticide management practices between the two sectors. Yet, resistance to public health pesticides can build up early due to agricultural exposures (Nkya *et al.* 2013), thereby effectively limiting the overall impact in public health. Moreover, some agricultural pesticide classes, such as neonicotinoids (Kweka *et al.* 2018, Ngwej *et al.* 2019), which are now being repurposed for IRS in Africa, were found to impact pollinators even in very small environmental concentrations (Calvo-Agudo *et al.* 2019). Integrated pest and vector management strategies should therefore be prioritised at both local and international levels (Van den Berg *et al.* 2020).

Matowo *et al.* (2020) observed multiple similarities of chemical actives used in agriculture and malaria vector control in rural Tanzanian communities, which also had poor pesticide management practices and low levels of awareness among farmers and pesticide retailers. Although both retailers and farmers had at least primary-level education and recognised pesticides by their trade names, they lacked essential knowledge on pest control or proper usage and disposal of these pesticides. These factors may enhance selection of resistance in the vector populations and compromise disease control. Matowo *et al.* therefore recommended improving awareness among retailers and farmers on usage and management of pesticides as well as integrating resistance management approaches between agricultural and public health sectors (Matowo *et al.* 2020).

Going forward, all insecticide use should be considered temporary measures for short and medium-term, rather than as the ultimate solution for all-time use. In a 2018 review, Hemingway described insecticide resistance as a problem without any easy solutions, and called for a multipronged approach to pursue not only new insecticides but also non-insecticidal tools (Hemingway 2018). It is therefore important to continue building evidence for such non-insecticidal interventions to aid future decisions for vector control. However, the ultimate idea should be to carefully transition from insecticide-based to non-insecticidal approaches, without losing the gains made so far against malaria. If done judiciously, such practices can lower malaria burden to significant extents, enabling communities to build the necessary resilient ecosystems and eventually wean off the insecticides as primary tools. At that point, pesticides may continue to be in stockpiled only for emergencies and outbreaks.

Control programmes should be supported by multiple sectors beyond health

A common feature of most malaria control or elimination programmes is that they are implemented as vertical programmes, usually under the Ministry of Health or its equivalent. While this approach may enhance focus and delivery in the short-term, it limits access to complementary resources and ideas from other sectors also important for disease control. One manifestation of this disconnect is that typical malaria strategies rarely include proven vector control methods such as housing improvement and environmental management, and instead rely primarily on commodities such as ITNs. For example, while entomologists at the Ministry of Health may consider using larvicides as the main tools against malaria vectors, engineers at the Ministries of Environment or Housing may deploy more permanent environmental sanitation and landscape approaches. Similarly, departments of infrastructural development and civil works may have budgets for health impact assessment and mitigation programmes to reduce risk of mosquito-borne diseases.

Tapping into the expertise and resources in the other sectors will enable acceleration of vector control efforts and generate multiple positive externalities across sectors (WHO 2017). Since the inception of the WHO Global Vector Control Response plan (WHO 2017), an increasing number of countries have set up relevant task forces to champion a more integrated and multi-sectoral approaches. It is likely therefore that there will be greater opportunities to accelerate progress in much more sustainable ways. Historical lessons already suggest that most of the highly impactful mosquito control programmes were managed or at supported from outside the typical ministries of health (Wilson *et al.* 2020). Endemic countries should therefore establish national-level coordinating mechanisms to manage the inter-sectoral malaria control initiatives for the long-term. In addition, effective legislative oversight and enforcements may be required to improve compliance and protect vulnerable populations. Where necessary, staff from local health agencies, working together with community-owned resource persons may be co-opted as the key personnel for initiatives such as larval source management and vector surveillance (Chaki *et al.* 2011). Lastly, the education sector may be relied upon to institutionalise vital public health knowledge on the biology and control of diseases including malaria.

Integrated vector management (IVM) is a concept widely discussed yet poorly implemented by malaria endemic countries. This is partly due to its vague definition at policy level (WHO 2008), and the lack of actionable policies to guide its implementation (Mutero *et al.* 2012). Shortly after publications of the functional genomes of malaria parasites and vectors at the beginning of the century, Utzinger *et al.* (2002) warned that too much attention to genomics should not be allowed to result in a neglect of proven malaria control initiatives, notably the integration of multiple approaches. Yet, IVM practices continued dwindling despite evidence of effectiveness (Utzinger *et al.* 2001). In one study in Uganda, investigating the level of awareness and uptake of integrated approaches for malaria control, it was reported that cooperation between health and other sectors needed substantial strengthening and funding (Mutero *et al.* 2012). Elsewhere in Tanzania, Mlozi *et al.* (2015) investigated inter-sectoral involvement of 12 different sectors (health, agriculture, environment, livestock, fisheries, education, works, irrigation, water resources, land development, forestry, and community development), in malaria control initiatives. They observed that development of the national malaria strategic plans (2007-2013 and 2013-2020) had involved staff from only a small number of sectors, and that there had been no national coordinating framework nor budget for inter-sectoral activities. The participating sectors included only the ministry of health and social welfare, regional administration and local government, some public universities and non-governmental organisations. Moreover, all individuals participating in strategy development were either medical or health professionals, indicating significant deficiencies in the multi-sectorial approaches (Mlozi *et al.* 2015).

Inclusion of the education sector is particularly essential for improving awareness but also maintaining community compliance necessary for effectiveness of interventions. Results of one study in Pakistan showed that organised health education improved knowledge and usage of LLINs among pregnant women for the prevention of malaria (Kumar *et al.* 2020). In the study by Matowo *et al.* (2020), which focused on subsistence farmers in Tanzanian villages with pyrethroid-resistant mosquitoes, it was observed that the farmers, most of whom had no more than elementary education, lacked knowledge on appropriate pesticide use but broadly applied multiple insecticide classes on their farms (Matowo *et al.* 2020). These knowledge gaps could be minimised through basic training programmes affordable to rural and urban households. For best results, the programmes may be institutionalised and delivered at high quality using proven pedagogic skills in public and private schools.

Countries should promote local development and production of effective intervention tools

The demand for cost-effective products and preference for pooled procurement of essential products has led to many small and medium-sized enterprises delivering health solutions at local level to lose competitiveness. This problem is widespread in malaria control where nearly all major interventions are imported by endemic countries.

Although greater than 90% of the current malaria burden, and nine of the ten most affected countries are in Africa (WHO 2019), the WHO-recommended ITNs are manufactured mostly outside Africa (Table 1). Of the 20 ITNs that had been approved by WHO as at May 2020, only four have manufacturers in Africa, two of these being 'cut and pack' operations using imported insecticide-treated fabric (WHO 2020b). The manufacturing gap is even wider for the new generation ITNs, such as those with multiple actives or synergists (WHO 2020b). One reason for this deficiency is that the respective African countries do not have capabilities to manufacture the recommended ITNs at competitive scale, volumes and pricing. Many of the countries already have strong apparel industries serving the export market, but they lack access to technologies for incorporating insecticides into the net fibers. As a result, malaria-endemic countries have to import the intervention products that they need the most.

Lessons from the ongoing coronavirus pandemic in 2020 show that international supply chains can be heavily disrupted (WHO 2020a), putting the health of populations at great risk. In such situations, local production is vital for maintaining access and sustainability. Tanzania has already demonstrated great examples in local manufacturing of ITNs (Masum *et al.* 2010) and biolarvicides (National Development Corporation (NDC) 2020), both of which are crucial for sustaining the gains so far made against malaria. The A to Z Textiles in Arusha, Tanzania is currently the largest ITN producer in Africa, and already had capacity for more than 30 million nets annually by 2010 (Masum *et al.* 2010). Similarly, Tanzania Biotech Products Limited aims to archive production and commercialisation of biological products for control of disease vectors and agricultural pests in Tanzania and beyond (National Development Corporation (NDC) 2020). The neighbouring Rwanda has also recently began producing ITNs locally to reduce procurement costs and guarantee access (Nkurunziza 2020). Many more countries would benefit from incentivised private or public sector programmes that not only provide jobs, but also deliver essential mosquito control products.

Other products to consider for local manufacturing may include materials for mosquito-proofing houses and new vector control tools for complementing ITNs, e.g. eave ribbons used for expanding protection against outdoor-biting and early-biting risk (Mmbando *et al.* 2018). In one survey in rural Tanzania, residents were aware that poor housing was associated with high mosquito-biting risk but raised the concern of competing priorities and lack of financing (Kaindoa *et al.* 2018). Incentivising low-cost designs of mosquito-proofed housing and housing materials could address these gaps. The analysis by Tusting *et al.* (2019) revealed that African housing was already improving significantly, and that proportions of people living in improved housing doubled from 11 to 23% between 2000 and 2015. Most of this growth happened without any incentives, and was instead paid for mostly using household savings or loans. The analysis also revealed significant housing gaps among the lowest income communities, indicating that any incentives

Table 1. Long lasting insecticide treated nets and insecticide treatment kits with WHO prequalification and recommendation for use by malaria endemic countries and procurement by national and international agencies.[1]

	Product	Company/address	Manufacturing facilities	Active ingredients
Long-lasting insecticide nets (LLINs)				
1	Olyset Net	Sumitomo Chemical Co., Ltd, Japan	• Kinh 2A, Phuoc Lap, Tan Phuoc, Tien Giang, Vietnam • A to Z Textile Mills Limited Tanzania; Net Health Limited, Tanzania	permethrin
2	Olyset Plus	Sumitomo Chemical Co., Ltd, Japan	• Kinh 2A, Phuoc Lap, Tan Phuoc, Tien Giang, Vietnam • A to Z Textile Mills Limited Tanzania; Net Health Limited, Tanzania	permethrin; piperonyl butoxide
3	Interceptor	BASF SE, Germany	• Shanghai Gongtai Textile Co Ltd; China Taicang City, Jiangsu Province No.2, Fada Road • SunshineThailand Nonthaburi 11000, Office: 18/2 Moo 7 Rattanatibet Rd., Bangkrasaw, Muang, Thailand	alpha-cypermethrin
4	Interceptor G2	BASF SE, Germany	• Shanghai Gongtai Textile Co Ltd; China Taicang City, Jiangsu Province No.2, Fada Road • SunshineThailand Nonthaburi 11000, Office: 18/2 Moo 7 Rattanatibet Rd., Bangkrasaw, Muang, Thailand	alpha-cypermethrin; chlorfenapyr
5	Royal Sentry	Disease Control Technologies, LLC, USA	• Dean Superior Textile Co., Ltd., China	alpha-cypermethrin
6	Royal Sentry 2.0	Disease Control Technologies, LLC, USA	• Dean Superior Textile Co., Ltd., China	alpha-cypermethrin
7	Royal Guard	Disease Control Technologies, LLC, USA	• Dean Superior Textile Co., Ltd., China	alpha-cypermethrin and pyriproxyfen
8	PermaNet 2.0	Vestergaard S.A, Switzerland	• Vestergaard S.A. Place Saint Francois 1, CH-1003, Lausanne, Switzerland • 10/10 Textile Joint Stock Company Production site n.1: 9/253 Minh Khai street, Hai Ba Trung district, 114034 Hanoi, Vietnam	deltamethrin
9	PermaNet 3.0	Vestergaard S.A., Switzerland	• Vestergaard S.A. Place Saint Francois 1, CH-1003, Lausanne, Switzerland • 10/10 Textile Joint Stock Company Production site n.1: 9/253 Minh Khai street, Hai Ba Trung district, 114034 Hanoi, Vietnam	deltamethrin and piperonyl butoxide
10	Duranet LLIN	Shobikaa Impex Private Limited, India	• Shobikaa Inpex Private Limited SF No.558,559, Athur SIDCO Industrial Estate, Vennaimalai PO Karur-639 006, Tamilnadu, India • Shobikaa Inpex Private Limited SF No.37A/1, b&C,D,E Coimbatore Road, Thannerpandhal, Karur-2, India	alpha-cypermethrin

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Table 1. Continued.

Product	Company/address	Manufacturing facilities	Active ingredients
11 MiraNet	A to Z Textile Mills Ltd, Tanzania	• A to Z Textile Mills Ltd; Plot No.698, Net world Area, Dodoma road, Arusha, Tanzania	alpha-cypermethrin
12 MAGNet	V.K.A. Polymers Pvt Ltd, India	• V.K.A. Polymers Pvt Ltd (UNIT-1) 169/1,170/1,192/3 Balarajapuram, Village,Veerarakkiam, Karur District, Tamil Nadu 639114, India • V.K.A. Polymers Pvt Ltd (UNIT-2 (EOU)) 1/79 Maduari By-pass Road (NH7), Sadiaya Goundan Pudhur, Kakavadi (PO), Kakavadi Village, Karur District 639003, Tamil Nadu, India	alpha-cypermethrin
13 Veeralin LLIN	V.K.A. Polymers Pvt Ltd, India	• V.K.A. Polymers Pvt Ltd (UNIT-1) 169/1, 170/1, 192/3 Balarajapuram • Village,Veerarakkiam, Karur District, Tamil Nadu 639114, India • V.K.A. Polymers Pvt Ltd (UNIT-2 (EOU)) 1/79 Maduari By-pass Road (NH7), Sadiaya Goundan Pudhur, Kakavadi (PO), Kakavadi Village, Karur District 639003, Tamil Nadu, India	alpha-cypermethrin & piperonyl butoxide
14 Yahe LN	Fujian Yamei Industry & Trade Co Ltd, China	• Heranba Industries Ltd 101/102, Kanchanganga, Factory Lane, Borivli (W), Mumbai 400 092 India • Agros Chemicals India Ltd. Jhaver Centre, Rajah Ananmalai Building, IV Floor,19, Marshalls Road, Egmore, Chennai 600 008, India	deltamethrin
15 DawaPlus 2.0 LLIN	Tana Netting FZ LLC, Dubai	• Sheikh Noor-ud-Din & Sons 4km, Kanha Kacha Road, off Ferozepur Road, Lahore, Pakistan • Rosie's garment factory nig. Ltd; 49a Milverton Avenue, P.O. Box 920, Aba Abia state, Nigeria	deltamethrin
16 DawaPlus 3.0	Tana Netting FZ LLC, Dubai	• Sheikh Noor-ud-Din & Sons 4km, Kanha Kacha Road, off Ferozepur Road, Lahore, Pakistan • Rosie's garment factory nig. Ltd 49a Milverton Avenue, P.O. Box 920, Aba Abia state, Nigeria	deltamethrin; pyperonil butoxide
17 SafeNet	Mainpol GmbH, Germany	• Jin Xun Ye (Huizhou) Textile Company Ltd (Main manufacturing facility) No.431 Bo Yuan Road, He Shan Village, Yuan Zhou Town, Bolou County, Huizhou City, Guangdong Province, China • Fujian Changle Xingcheng Synthetic Co. Ltd Baihu Section, Lianggang Road, Zhanggang Town, Changle City, Fujian Province, China	alpha-cypermethrin

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Table 1. Continued.

Product		Company/address	Manufacturing facilities	Active ingredients
18	YorkoolLN	Tianjin Yorkool International Trading Co., Ltd, China	• Tianjin Yorkool International Trading Co., Ltd.North of Yangliuqing Power Station, 104 National Road, Tianjin, China • Gaotang Xingyuan Textile Factory The Wind Road South Middle, Gaotang County Economic Development Zone, Liaocheng City, ShanDong Province, China	deltamethrin
19	Panda Net 2.0 LLIN	LIFE IDEAS Biological Technology Co., Ltd, China	• Life Ideas Biological Technology Co., Ltd, (Building 1#) No.6-4, North Jianda Road, Jiangmen 529000,China • Life Ideas Biological Technology Co., Ltd., Chengxi Industrial District, Hutang Town, Changzhou City, Jiangsu,China	deltamethrin
20	Tsara Boost	NRS Moon netting FZE, Dubai	• Sheikh Noor-ud-Din & Sons 4km, Kanha Kacha Road, off Ferozepur Road, Lahore, Pakistan • Sunpack Hanjiang Road 368#, Changzhou, Jiangsu, China	deltamethrin, piperonyl butoxide
Insecticide treated net (ITN) treatment kits				
1	Fendona 10 SC	BASF SE, Germany	• Tagros, India; Bayer Vapi, India	alpha-cypermethrin
2	Fendona 6 SC	BASF SE, Germany	• Tagros, India; Bayer Vapi, India	alpha-cypermethrin
3	Pendulum 6 SC	Gharda Chemicals Limited, India	• D-1/2, B-1/7, F-1/1, MIDC, Lote Parshuram, Talika-Khed, Distt-Ratnagiri Maharashtra 415722, India	alpha-cypermethrin
4	Pendulum 10 SC	Gharda Chemicals Limited, India	• D-1/2, B-1/7, F-1/1, MIDC, Lote Parshuram, Talika-Khed, Distt-Ratnagiri Maharashtra 415722, India	alpha-cypermethrin
5	ICON CS – ITN Kit	Syngenta Crop Protection AG, Switzerland (Parent; ChemChina)	• Syngenta Seneffe BV Syngenta Seneffe, Rue de Tyberchamps 37, B-7180, Seneffe, Belgium and Syngenta Hellas S.A. 2nd km Kinotiki odos Enofyta.Ag. Thomas 32011 Enofyta Viotias, Greece	lambda-cyhalothrin
6	Vectron 10EW	Mitsui Chemicals Agro, Inc, Japan	• Utsunomiya Chemical Industry Co., Ltd Shinshiro Factory, 11-4 Ihara, Oomi, Shinshiro-shi, Aichi 441-1315, Japan	etofenprox

[1] Source: WHO Vector Control Product Prequalification Program, as at February 2020 (WHO 2020b).

should be targeted to poorest families. Endemic countries could therefore leverage the housing trends to accelerate coverage of improved housing, which would further prevent several vector-borne diseases including malaria (Tusting *et al.* 2017). To complement the incentives programme, a legislative agenda may be added to raise compliance and protect the low-income households from any malpractices.

Countries should consider a phased approach to disrupt ongoing transmission, transition from insecticides and sustain gains for long-term

After several years of progress, the gains made against malaria have begun stagnating or diminishing in some locations, suggesting the need to rejuvenate the efforts and prevent stakeholder fatigue. There are several reasons for the declines, chief among them the rise of insecticide resistance, sub-optimal user compliance and the high costs necessary to maintain supplies and replacements of key commodities. Insecticide resistance is particularly crucial given that current top interventions are insecticide-based (Ranson and Lissenden 2016). This is compounded by changes in the biting and resting behaviours of the main malaria vectors, e.g. increases in proportions of *Anopheles* biting outside dwellings (Sherrard-Smith *et al.* 2019). Current consensus among malaria control experts is that today's core interventions are therefore inadequate for achieving and sustaining malaria elimination (malERA Refresh Consultative Panel on Tools for Malaria Elimination 2017). Without effectively tackling the biological basis of malaria transmission on a sustainable basis, commodities such as ITNs and IRS insecticides will only provide temporary protection but are incapable of preventing rebounds especially for low-income households.

Endemic countries should therefore consider a phased approach, involving judicious use of current insecticide-based interventions while gradually building structural resilience to sustain control in affected communities for the long term. At its core, this strategy should involve transitioning towards insecticide-free approaches. A recent review argued for greater emphasis on durability of mosquito nets over their insecticidal efficacy, but also noted that there are still many settings and circumstances where insecticides may remain impactful (Okumu 2020). The transition towards an insecticide-free world should therefore not be abrupt, as this could potentially cause major transmission rebounds as well as gaps in essential supply chains for vector control.

The phased approach may take different forms depending on settings, but should constitute overlapping initiatives, all considered and planned from the start (Table 2). Countries may rely on the current international goodwill and financing to support immediate needs for transmission control, but they should use domestic resources to build structural resilience for the long-term. To the maximum extents possible, the countries should also consider multi-sectoral backing and possibly a one government approach with budgets secured beyond political cycles.

Short- and medium-term activities

In the short and medium-terms, endemic countries should continue to deploy proven effective interventions, e.g. mosquito nets and IRS based on local evidence. Insecticide-resistance profiling should be done regularly to monitor performance of the tools and to select the most suitable pesticides in specific locations. Depending on such observations, the countries may gradually introduce improved versions such as nets that contain synergists or multiple active ingredients (Gleave *et al.* 2018, Protopopoff *et al.* 2018, Staedke *et al.* 2020, Tiono *et al.* 2018), and long-lasting formulations of IRS with effective insecticides to suppress disease in the affected areas. Where there are gaps related to vector behaviours or physiological resistance, supplementary approaches

Table 2. Examples of activities that could be implemented in a phased approach to disrupt ongoing malaria transmission, transition from insecticides and sustain gains for the long-term. This plan focuses on vector control and assumes that effective case management is maintained.

Phase	Examples of activities for effective vector control (list not conclusive)
Short & medium-term initiatives	• Expand the use of current core interventions, e.g. ITNs, IRS, ensuring high coverage and quality in the deployment. • Generate and use local evidence at sub-national level, e.g. phenotypic resistance data for selecting IRS insecticides. • Pursue and deploy improved versions of the core interventions, e.g. ITNs with synergists or multiple actives, and improved formulations or delivery methods for IRS. • Consider evaluation and deployment of durable but non-insecticidal bed nets (as opposed to pyrethroid-treated nets) alongside effective case management, and where possible IRS. • Identify and deploy additional tools to address gaps in different settings. Examples may include focal larviciding, incremental house improvement practices such as house screening, attractive targeted sugar baits (ATSBs), and eave-based tools, e.g. eave ribbons to protect people indoors and outdoors.
Long-term initiatives	• Engage the private and public sectors to support local production and access to vector control products. • Incentivise and subsidise housing improvements and environmental sanitation (and larval source management). • Institutionalise health education in schools and public places on biology and control of vector-borne diseases. • Initiate and test different mechanisms for long-term domestic financing opportunities for malaria control. • Create research and development (R&D) initiatives to address current research gaps and to develop new approaches for disease control. • Build local capacity for implementers and decision makers. • Strengthen health system components for vector control. • Develop programmes promoting insecticide-free options such as safe housing and environmental sanitation.
Multi-sectorial initiatives (to be deployed in parallel to the other initiatives)	• Identify relevant activities in different government agencies and initiate leverages to support malaria vector control. • Promote approaches for sustainable domestic financing. • Establish appropriate legislation to support disease control efforts: this may include tax rebates for housing materials and vector control supplies, local government by-laws to discourage vector proliferation and protect the vulnerable, and regulations for infrastructure development programmes to assess and mitigate health impacts from disease vectors. • Align agricultural practices, such as pesticide use and irrigation, to address core indicators of vector control. • Integrate malaria control in different aspects of the private sector; including expanded engagement of employers. • Institutionalise general public health education (including but not limited to malaria) in schools and public places. • Support low-income households to address competing financial priorities, so that vector control remains a focus. • Expand investments in basic and applied sciences to pursue potential 'game-changer' approaches against challenges such as insecticide resistance and high costs.

may be deployed to protect specific sub-populations e.g. migrant workers or people outdoors (Sougoufara *et al.* 2020, Williams *et al.* 2018). Examples may include: (1) attractive targeted sugar baits, which kill mostly old mosquitoes and use oral toxicants, but have so far been tested mainly in dry localities with limited competing natural vegetation (Traore *et al.* 2020), (2) mass-drug administration with endectocides, such as ivermectin to kill large populations of dominant malaria vectors biting humans (Burrows *et al.* 2018, Chaccour *et al.* 2018), (3) the use of spatial repellents such as transfluthrin (which is poorly metabolised by metabolic enzymes and can be temporarily used in pyrethroid resistance areas (Horstmann and Sonneck 2016, Swai *et al.* 2019)) or (4) odour-baited mosquito-traps, which are known to be effective in areas with low vector densities and can be cost-effective over long-term (Homan *et al.* 2016, Okumu *et al.* 2010). Generally, such niche tools should be considered temporary and not intended to replace the long-term programmes to build resilience (Table 2).

In places with significant outdoor biting, such as in the islands of Zanzibar where ITNs now prevent only less than 50% of all exposures (Monroe *et al.* 2020), public health authorities may also deploy larval source management to target all *Anopheles* mosquitoes at source regardless of their resistance status, biting behaviours or blood-feeding preferences.

Long-term programmes

Once the countries have initiated programmes to suppress disease in the short term, they should begin building longer-term resilience to sustain the gains accrued from the first onslaught, and to prevent rebounds. The activities in this second phase should overlap with, rather than replace the first phase of interventions, and should be designed to allow transitioning away from the commodity-based approaches and insecticides. While some countries may rely significantly on overseas development assistance to support the first phase of activities, it is important that this second phase of activities is financed as much as possible from domestic sources, and protected from uncertainties associated with external funding.

Examples of activities in this phase may include: incentivising the private and public sectors to supply high-quality vector control products, e.g. locally-manufactured mosquito nets or bio-larvicides, as currently practiced in Tanzania (Masum *et al.* 2010, National Development Corporation (NDC) 2020). At this stage, countries should also begin including longer-time insecticide-free approaches as core interventions. This may include government-subsidised improvements for low-income families to achieve mosquito-free dwellings and environments, strengthening health system components relevant to vector control, and expanding public engagement programmes in vector control.

Both improved housing and environmental management, though expensive, can be particularly effective when deployed after ITNs and/or IRS given that they are agnostic to vector behaviours and resistance and are less affected by user compliance. Their effectiveness against malaria vectors is best evident in African cities and small towns, where the *Anopheles* ecology has been impacted. In one example in south-eastern Tanzania, entomological surveys were done in the fast-growing town of Ifakara, which is located at the centre of historically holoendemic Kilombero valley (Finda *et al.* 2018). The surveys showed that the town and its surroundings areas had experienced 99% reduction in malaria transmission between 2003 and 2015, reaching nearly undetectable intensities (Finda *et al.* 2018). Though the neighbouring villages had also experienced significant reduction, they still experienced moderate to high transmission (Kaindoa *et al.* 2017, Swai *et al.* 2019). In a follow-up epidemiological survey, malaria prevalence was less than 1% in the town area, compared to more than 40% in villages just 20-30 km away (Swai *et al.* unpublished). While bed net use in the town area was similar to the neighbouring villages, housing structures have modestly improved (>50% houses have screened windows and most have metal roofs (Finda *et al.* 2018)). These improved housing practices, *Anopheles*-deficient environments and greater access to case management in Ifakara area have created substantial resilience, allowing the commodity-derived gains to be sustained.

Multi-sectoral initiatives

The two phases outlined above will put vector control programmes onto a path to medium-term sustainability and could lead to multi-generational suppression of malaria and other mosquito-borne diseases. However, given the extensive resources and goodwill necessary to maintain these gains, countries should establish multi-sectorial programmes that prioritise infectious diseases beyond just malaria. The objective should be to leverage and coordinate efforts to deliver a common goal of malaria-free society.

Achieving long-term resilience against disease will require significant increases in domestic financing using proven approaches in both public and private sectors. Despite the heightened talk about malaria elimination, the incremental benefits of active programs may become increasingly marginal once the disease rates go below certain thresholds of public health importance. In such cases, sustained domestic funding may become the only justifiable mechanisms for keeping the malariogenic potential at a minimum. One way to achieve long-term domestic financing targets is through effective engagement of key stakeholders across agencies to generate broad interest and support. In Tanzania, Finda *et al.* assessed opinions of different stakeholders regarding technical and budgetary feasibility of alternative malaria vector control measures, including house improvements and larval source management (Finda *et al.* 2020). While community members strongly approved house improvement as a long-term measure to control malaria, the decision makers and government officials were concerned about feasibility and costs of such initiatives. Separately, Mutero *et al.* investigated factors influencing malaria policy decisions in Kenya, Uganda and Tanzania in the context of multi-sectoral interests (Mutero *et al.* 2014). They focused on whether decision makers typically consider health and environmental impacts, alongside costs of different interventions. The study observed important gaps in engagement of key interest groups and therefore recommended improved engagement of government legislators and other policy makers (Mutero *et al.* 2014). They concluded that such engagement could potentially increase funding from domestic sources, reduce donor dependence, sustain interventions and consolidate gains in malaria (Mutero *et al.* 2014). There are several examples of governments gradually improving investments in health. In Ghana, where malaria elimination is estimated to eventually cost 1 billion USD by 2029, government expenditure on malaria control has been expanding, though this is still below 25% of the total funding (Shretta *et al.* 2020).

To encourage greater investments, endemic country scientists and planners should generate evidence for both epidemiological and economic gains associated with long-term malaria vector control programmes. This should include multi-sectoral initiatives, with long-term perspectives. In one study, Utzinger *et al.* reviewed multiple malaria control programmes incorporating environmental management as the central feature (Utzinger *et al.* 2001). They concluded that over the initial 3-5 years, the costs per disability adjusted life year (DALY) averted were US$ 524-591, but was just US$ 22-92 per DALY averted over the long-term. Evaluations of multi-sectoral initiatives are therefore best done with a long-term perspective. Appropriate legislation will further improve compliance, protect vulnerable people, and guarantee long-term domestic financing for malaria control.

Countries should advance R&D programmes to address evidence gaps, accelerate progress and seek potential game changers

Public health experts have recently consolidated key research questions that must be addressed to achieve malaria elimination in Africa and beyond (malERA Refresh Consultative Panel on Tools for Malaria Elimination 2017, Rabinovich *et al.* 2017). While there is already substantial knowledge available to effectively reduce malaria transmission below the levels where it is considered a major public health concern, the current approaches will be inadequate to achieve elimination. There is also concern about how the available knowledge is being deployed and whether the vectors are being sufficiently targeted.

Given the need for local evidence to address the unique transmission systems in different settings, endemic countries should prioritise R&D platforms to support intervention updates, identify new gaps in control and guide resource allocation for maximum impact. The researchers should also pursue potentially disruptive technologies or highly-impactful approaches that could accelerate control efforts, while retaining robustness against key challenges such as insecticide resistance. These may include the use of genetically modified mosquitoes, e.g. using gene drives to suppress or transform *Anopheles* populations (James *et al.* 2018).

For best results, the programmes should be integrated across multiple research and implementation fields. As outlined in the WHO Global Vector Control response plan, the programmes should also include both basic and applied studies, integrating entomological and epidemiological data in different settings (WHO 2017). While entomological data may be useful for tracking malaria transmission in high and moderate transmission settings, such data become fuzzy at low transmission where key indicators may become too low to detect with standard entomological tools. In such circumstances, entomological surveys may remain relevant only for assessing receptivity (presence/absence of malaria vectors), insecticide resistance and performance of interventions. Parallel assessments of malaria parasite prevalence in humans can therefore help identify sub-populations or villages that remain strongly affected, and guide interventions. Equally important is assessment of human activities in relation to mosquito behavioural responses. Without incorporating such details, some of the current gaps in vector control will not be fully addressed (Finda *et al.* 2019, Monroe *et al.* 2019).

Public health authorities should cultivate effective public engagement practices to support vector control

Considering the increasing difficulties in curbing malaria transmission, significant efforts need to be allocated in engaging the local communities in malaria control efforts in order to create local, site-specific and effective solutions (Baltzell *et al.* 2019). Effective malaria control and elimination can only be achieved when the affected communities are able to define, believe in, and commit to the selected strategies (Baltzell *et al.* 2019, Whittaker and Smith 2015). Community engagement therefore needs to be a legal, ethical, and practical requirement for any new or improved malaria control interventions (Resnik 2017). In addition, the engagement efforts should not be confused with simply raising community education and awareness to malaria and malaria control interventions (Figure 4). Instead, it should be a continuous process, largely driven by local experts and authority, which would ensure active participation of the community (Baltzell *et al.*

Figure 4. Public health authorities should cultivate effective public engagement practices to support vector control. Such engagement should not merely be about raising community awareness about malaria control, but should instead be continuous and driven by locals in ways that ensure active participation of all interested persons.

2019, Thizy *et al.* 2019, Whittaker and Smith 2015). It also needs to be conducted from early on in the planning stages, and needs to be done regularly and frequently.

Given the high levels of disenfranchisement that is common in rural low-income settings that harbour most malaria burden, community involvement in vector control must be done in way that significantly minimise barriers to participation. One study in Malawi investigated factors influencing community participation in a district-wide larval source management project (Gowelo *et al.* 2020). The investigators observed that key concerns of community members included labour-intensiveness, lack of financial incentives and concerns of health risks. To sustain participation, such challenges must be progressively identified and addressed.

Empowering and involving local authorities and experts

Public health authorities need to acknowledge that achieving effective community engagement in malaria control can be a major challenge, especially in settings with reduced transmission or where the residual transmission is concentrated in remote and hard to reach settings. Indeed, declines in malaria transmission may result in lower perception of risk at both personal and community level (Whittaker and Smith 2015). Support and guidance by local leaders and experts may restore a sense of importance, trust, security and familiarity for the programmes within the community (Lavery *et al.* 2010, Quinlan *et al.* 2016, Thizy *et al.* 2019). Empowering local experts in designing and implementing community engagement activities is also critical as these have a deeper understanding of dynamics of the communities and may have better insights into effective and locally-appropriate methods of involving the communities (Quinlan *et al.* 2016). Local experts can be individuals or groups with project relevant skills, and may include local technicians, anthropologists, social workers, communication experts and community health workers whose knowledge would be essential for malaria elimination efforts. Understanding of the social structures and dynamics of the targeted communities is essential for designing engagement interventions specific for different groups within the community.

Early, frequent and sustained engagement

The aim of transitioning towards more sustainable vector control will itself be long-term and costly. For this reason, it is critical to ensure that the community perceptions and attitudes towards the proposed new approaches are well understood at every stage. This will ensure that the new initiatives are responsive to multiple community priorities relevant to malaria elimination, and will minimise backlash or non-compliance during implementation (Lavery *et al.* 2010). Such early engagement will also ensure greater community understanding and ownership for malaria elimination efforts in general (Baltzell *et al.* 2019). Lastly, community engagement efforts should be organised to run for extended duration and should be responsive to any emerging concerns associated with the malaria control interventions and multi-sectoral initiatives. For best results, the community members themselves should be regularly updated on how their contributions are being integrated and acted upon.

Conclusions

This paper proposes important transitional approaches for malaria control, involving judicious use of current insecticide-based interventions while gradually building structural resilience to sustain control in endemic communities. The ultimate goal should be to carefully transition from insecticide-based to non-insecticidal approaches, without losing the gains made so far against malaria. In the short- and medium-terms, affected countries may deploy a selected suite of current tools, e.g. standard ITNs and IRS, while gradually introducing improved versions such as PBO Nets and long-lasting IRS formulations to suppress disease. These may be supplemented with certain new technologies such as repellents and lethal sugar baits to protect specific sub-groups, e.g. migrant workers or people outdoors.

Second, countries may establish programmes to build long-term resilience so as to sustain the accrued gains and prevent transmission rebounds. Examples may include: incentivising the private sector to supply high-quality commodities, e.g. locally-manufactured mosquito nets, subsidised improvements for low-income families to achieve mosquito-free dwellings, expanding public engagement in disease control and strengthening health systems to effectively detect and manage cases. Other initiatives include environmental sanitation to reduce disease vectors, institutionalised health education and capacity-building on biology and control of disease. Once these two phases are running, countries should establish multi-sectorial programmes that prioritise infectious diseases beyond just malaria. These could include appropriate legislation to improve compliance while protecting the vulnerable, and long-term domestic financing for malaria control. The programmes should be supported by a strong research culture to continually identify gaps, monitor progress and seek new opportunities to accelerate progress.

If integrated in the wider public health context, this phased approach could gradually reduce malaria burden, reduce overreliance on commodities notably insecticides, sustain the accrued gains and minimise transmission rebounds even in poor communities. The success of these approaches is highly dependent on effective engagement of the communities in targeted areas, hence substantial efforts should also be allocated to ensuring that the communities are engaged from the planning stages through the different implementation stages of the programmes.

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4. Insecticide-based approaches for dengue vector control

Scott A. Ritchie[1], Gregor J. Devine[2], Gonzalo M. Vazquez-Prokopec[3], Audrey E. Lenhart[4], Pablo Manrique-Saide[5] and Thomas W. Scott[6]*

[1]Australian Institute of Tropical Health & Medicine, James Cook University, 1/14-88 McGregor Road, Smithfield QLD 4878, Australia; [2]Mosquito Control Laboratory, QIMR Berghofer Medical Research Institute, Locked Bag 2000, Royal Brisbane Hospital, Herston, QLD 4006, Australia; [3]Department of Environmental Sciences, Math & Science Centre, Emory University, 400 Dowman Drive, Atlanta, GA 30322, USA; [4]Entomology Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, 1600 Clifton Road, MS G-49, Atlanta, GA 30329, USA; [5]Unidad Colaborativa para Bioensayos Entomologicos, Departamento de Zoologia, Universidad Autonoma de Yucatan, Km. 15.5 Carretera Mérida-Xmatkuil s.n., Merida, Yucatan, C.P. 97315, Mexico; [6]Department of Entomology and Nematology, University of California Davis, 367 Briggs Hall, One Shields Avenue, Davis, CA 95616, USA; twscott@ucdavis.edu; all authors contributed equally to this work

Abstract

Vector control is, and will continue to be, an essential component of dengue prevention programs, but in modern cities with highly mobile human populations and inadequate vector control infrastructure the global burden of dengue is increasing. This is in part, because effective vector control is difficult to achieve and sustain. Despite these challenges, past successes indicate that when it is carefully and thoroughly applied, mosquito control will reduce dengue, particularly when targeting *Aedes aegypti* in urban habitats. Herein we review insecticide-based approaches for dengue vector control. We conclude that to fight dengue it is important to use locally derived and adapted vector control tools and strategies. To achieve this, it is critical to thoroughly understand the local vector and its ecology, including its insecticide susceptibility. Available evidence indicates that most space sprays (both aerial and ground) are relatively ineffective unless they are repeatedly delivered inside homes where *Ae. aegypti* rests. Novel delivery methods have been developed to control *Aedes* vector populations using residual killing agents, including targeted indoor residual spraying, which shows promise for reducing dengue. Adulticiding for dengue prevention is most effective when it is conducted as part of an integrated vector management plan that includes source reduction and larviciding. Successful dengue prevention programs include a combination of tools and strategies (e.g. insecticides in combination with vaccines and non-insecticide-based interventions) that are applied with enhanced intersectorial and interdisciplinary cooperation and strong community engagement.

Keywords: dengue, *Aedes aegypti*, *Aedes albopictus*, insecticide, larvicide, adulticide, vector control

Introduction

Vector control has been a core component of dengue prevention programs since the beginning of the 20th century when Cleland *et al.* (1916, 1918) showed that *Aedes aegypti* could transmit dengue to uninfected human volunteers. The concept of dengue vector control is straightforward: reduce mosquito vector populations and/or their contact with humans in order to reduce or prevent virus transmission (WHO Guidelines 2009a). Well-documented successes demonstrate that when rigorously and thoroughly applied, mosquito control effectively reduces dengue (Achee *et al.* 2015). A combination of exhaustive elimination of larval development sites and the advent of dichlorodiphenyltrichloroethane (DDT) in 1946 led to a hemisphere-wide program from the early

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1940s through the 1960s across Central and South America that dramatically reduced *Ae. aegypti* populations and resulted in impressive reductions in yellow fever and dengue (Camargo 1967, Monath 1994). Singapore during the 1970s and 1980s (Ooi *et al.* 2006) and Cuba during the 1980s and 1990s (Kouri *et al.* 1998) successfully used adult mosquito control and larval source reduction to reduce human dengue virus (DENV) infections and, thus, disease. Recent investigations of indoor residual spraying in Australia (Vazquez-Prokopec *et al.* 2010, 2017b), indoor space spraying in Peru (Stoddard *et al.* 2014), and community mobilisation in Mexico and Nicaragua (Andersson *et al.* 2015) similarly reported reductions in human DENV infections. Regrettably, these achievements are exceptions and they were transient. Dengue re-emerged in Latin America after the *Ae. aegypti* eradication campaign ended; rebounded in Singapore and Cuba after 20 and 16 years of successful control, respectively; continues in Peru, Mexico, and Nicaragua; and is increasingly reported in Africa (Amarasinghe *et al.* 2011).

Ae. aegypti's close association with humans facilitates efficient transmission of arboviruses (Ritchie *et al.* 2014, Scott and Takken 2012). Immature forms (eggs, larvae, and pupae) develop primarily in water held in human-made containers that are in and around human habitation (Morrison *et al.* 2008). Adult females are highly anthropophilic, endophilic, and endophagic (Scott and Takken 2012). They are day biting mosquitoes that rest inside houses where females feed preferentially, frequently, and multiple times during each egg laying cycle, on human blood (Scott and Takken 2012, Scott *et al.* 1993, 2000). Males and females tend not to disperse far; i.e. <100 m (Harrington *et al.* 2005). Thus *Ae. aegypti* is almost exclusively an urban mosquito, and epidemic dengue transmission is typically concentrated in towns and cities. Because females make frequent contact with humans and are infectious for life, virus transmission, and even epidemics, can occur when the density of *Ae. aegypti* populations and human herd immunity are low (Kuno 1995). Vector control for *Ae. aegypti,* therefore, needs to be comprehensive, thorough, and continuous if it is to achieve sustained disease prevention (Scott and Takken 2012). In some regions, *Aedes albopictus* is the primary dengue vector. These are typically in areas that lack *Ae. aegypti*, have warm and wet weather, and lush sylvan vegetation that encourages rapid population growth of the vector (Gratz 2004).

Although the concept of dengue vector control is superficially straightforward, successful broad-scale application has been difficult to achieve and even harder to maintain (Bowman *et al.* 2014, Reiner *et al.* 2016). In most settings, contemporary dengue vector control programs have not prevented epidemics nor have they slowed the rapid geographic expansion of the virus (Messina *et al.* 2014, 2015, 2019) or vectors (Kraemer *et al.* 2015, 2019). Unsuccessful control programs are often attributed to expansion of *Ae. aegypti* populations, growth of urban centres with poor sanitation and inadequate water supply, human travel networks that disperse virus and mosquitoes, inadequate vector control infrastructure, deficiency in resources to mount effective interventions, lack of political will, insecticide resistance, and unsuccessful application of existing tools and strategies (Horstick *et al.* 2010, 2017, Morrison *et al.* 2008, Reiner *et al.* 2016). Despite these challenges, a critical review concluded that dengue vector control can be effective if implementation and coverage (i.e. the proportion of habitats that can be targeted by the available tools and resources) is expedient, comprehensive, and sustained (Achee *et al.* 2015).

We focus on insecticide-based approaches for vector control to limit DENV transmission. Based on the best available information, we recommend how best to apply insecticides under locally specific circumstances to reduce the public health threat of dengue. Although they are central components of successful programs, we do not address vector surveillance or the detection and management of insecticide resistance. The following are recent reviews of these topics: Achee *et al.* (2015), Bowman *et al.* (2014), Moyes *et al.* (2017), and Smith *et al.* (2016).

Locally tailored vector control strategies are important because ecological and epidemiological variation is a fundamental feature of *Ae. aegypti* populations and DENV transmission dynamics (Bisanzio *et al.* 2018, Reiner *et al.* 2016, Wilder-Smith *et al.* 2017). A single intervention tool or strategy should not be expected to be successful everywhere. The recently adopted World Health Organization (WHO) Global Vector Control Response (WHO 2017a) provides a vision for how to reduce the burden and threat of diseases like dengue through the application of effective, locally adapted, and sustainable interventions. This approach goes beyond integrated vector management (IVM), which is defined as a rational decision-making process that supports optimal use of available resources (WHO 2017a). The Global Vector Control Response includes enhanced intersectorial and interdisciplinary cooperation with improved human resource capacity across national and subnational scales. It stresses the need to strengthen general infrastructure and supporting systems, which is consistent with sustainable development and includes the added benefit of improved living conditions. Accomplishing effective and locally adapted vector control also requires broad community and government participation that reorients intervention programs toward proactive, rather than predominantly reactive, approaches.

An inventory of methods that is useful for executing locally adapted control is the chapter on 'vector management and delivery of vector control services' in the 2009 *Dengue Guidelines for Diagnosis, Treatment, Prevention and Control* (WHO 2009a). That document provides a thorough review of the vector control tools and strategies that may reduce dengue. During the past decade, a surge in innovation in vector control, including important contributions against dengue (see https://www.who.int/vector-control/vcag/en/), is adding to the existing *Aedes* control toolbox. The stimulus for improvement was twofold. First, dengue has become one of the most rapidly increasing infectious diseases, both in terms of the number of cases and its geographic range (Global Burden of Disease Study 2013 Collaborators 2015, Stanaway *et al.* 2016). Second, the dramatic rise of viruses other than DENV that are transmitted by *Ae. aegypti* (i.e. chikungunya and Zika viruses) further highlight the urgent need for innovation against diseases caused by the viruses this mosquito transmits. The vector control community is responding with an encouraging, and growing, list of new intervention options and creative designs for assessing their public health impact (Achee *et al.* 2015, Anders *et al.* 2018, Devine *et al.* 2019, Reiner *et al.* 2016, Wilson *et al.* 2015).

Using an understanding of the dengue/vector/human ecosystem to develop effective approaches for vector control

Ae. aegypti is one of the most thoroughly studied mosquitoes. Consequently, there is an increasingly comprehensive understanding of its ecological, evolutionary, and epidemiological diversity. Although other mosquito species, such as *Ae. albopictus*, *Aedes polynesiensis* and some species in the *Aedes scutellaris* complex can play secondary roles in DENV, chikungunya (CHIKV), and Zika virus (ZIKV) transmission in specific geographic areas (MacKenzie *et al.* 2004), *Ae. aegypti* is the primary global DENV vector. Other mosquito species have different ecologies and behaviours that make them less susceptible to urban management. For example, *Ae albopictus* tends to be more exophagic and exophilic than *Ae. aegypti*, and it exploits a wider range of hosts and habitats, especially in peri-urban and rural environments (Lambrechts *et al.* 2010, Richards *et al.* 2006). The greater range of habitats exploited by other species may make them less vulnerable to strategies designed for *Ae. aegypti* management. For example, a previously successful integrated control program in the Caribbean failed when resource constraints forced it to abandon its outdoor adulticiding campaign (which had targeted *Ae. albopictus*) and rely solely on source reduction (Wheeler *et al.* 2009). Due to its central role in virus transmission, recommendations herein will focus on *Ae. aegypti aegypti*; i.e. populations in the recently described pantropical cluster (Brown *et al.* 2011).

In the absence of effective vaccines or prophylactic drugs, control of *Ae. aegypti* remains the mainstay of dengue, chikungunya and Zika virus management programs (Achee *et al.* 2015). Vector control efforts are comprised of two complementary approaches (1) an immediate reactive response to outbreaks with an emphasis on indoor adulticiding to rapidly reduce mosquito population density and to kill virus-infected mosquitoes and (2) proactive approaches that target adults in combination with immatures in aquatic habitats (Achee *et al.* 2015). Specialist teams under the direction of local governments typically lead adulticiding programs, which can be reactive or proactive. Reactive responses can be costly, time-consuming, and challenging to maintain but, if properly timed, can lead to reductions in virus transmission (Cavany *et al.* 2020, Vazquez-Prokopec *et al.* 2010). The control of immature stages is typically proactive, involves a considerable community-led component, and attempts to reduce mosquito population densities, but can also be challenging to maintain.

Given *Ae. aegypti*'s peridomestic habits, key tools for control are those that reduce the survival of adult mosquitoes through contact with insecticides in domestic environments. Fast-acting space sprays can be delivered indoors through ultra-low volume sprays or thermal fogging. Residual insecticides can be delivered on treated surfaces such as walls, curtains, window screens, and water-container covers (Focks *et al.* 1997). The reduction of larval production, through either container removal or applications of insecticides or biological agents, can decrease adult mosquito production (Hoffmann *et al.* 2014), but this has a less direct impact on transmission than targeting adults directly. In order to reduce virus transmission, source reduction or larviciding campaigns must be maintained at very high coverage. This is typically difficult to achieve because immature *Ae. aegypti* exploit water in myriad, cryptic containers that are hard to locate and treat. An exception was the use of copepods in water storage vessels in rural Vietnam, which eliminated *Ae. aegypti* from several communes and was associated with reductions in reported dengue cases (Kay and Nam 2005). To be most effective, larval control should be combined with methods targeting adult mosquitoes (Focks *et al.* 1997). Recent evidence suggests that insecticide-treated curtains, window screens, and covers on water-holding containers can reduce *Ae. aegypti* densities (Horstick *et al.* 2018), indicating that these tools should be considered for controlling adults as part of an integrated approach. The application of residual formulations of insecticides to walls and other surfaces within the home is proven to reduce *Ae. aegypti* infestations and prevent DENV transmission if coverage is high (Cavany *et al.* 2020, Hladish *et al.* 2018, Vazquez-Prokopec 2010, 2017b).

Dengue disease is part of a complex ecosystem involving a virus, mosquito vector, and human host. This triad is required for transmission to occur and each participant in the process exists in its own ecosystem, which relates to the others in complex ways. Vector control programs can perturb these multifaceted interactions in ways that can lead to unanticipated results; i.e. over time, decreased herd immunity can result in transmission even when vector populations are low (Egger *et al.* 2008, Hladish *et al.* 2018, Okamoto *et al.* 2016). Consequently, to successfully control dengue, program managers need to fully understand the system that they want to manipulate. Table 1 breaks down the DENV transmission system into four categories and addresses key questions related to those categories that will aid in developing a locally designed, successful dengue vector control program.

Table 1. Key information for dengue managers to develop a locally derived and adapted vector control program for dengue.

Category Parameter	Why it is important	How to obtain critical information
The virus		
Is dengue endemic?	If endemic, transmission can be continuous and often undetected by public health surveillance. Endemic areas tend to have high herd immunity. If transmission is not endemic, the detection of imported cases, that may spark new outbreaks, is extremely important.	• infectious disease staff • health records • cross-sectional serososurvey, or similar population assessment, to measure herd immunity • relevant literature
Are outbreaks seasonal, with geographic hotspots?	Wet and dry seasons can define times of the year with high and low virus transmission and/or human cases. Are there geographic areas/locations that are consistently prone to high levels of transmission and/or human cases?	• infectious disease staff, maps and geographical information systems (GIS) are very useful • health records • meteorological data • relevant literature
Are there other viruses transmitted by *Aedes* in your area?	Chikungunya, Zika, and Yellow Fever viruses are also transmitted by Aedes, and may require diagnosis and control, perhaps using different strategies. Other viruses, not currently recognised in your area, might be introduced and become established.	• health records • infectious disease staff
What is the predominant DENV serotype?	Outbreaks with different serotypes can increase risk of an epidemic with severe disease.	• infectious disease staff • health records
The vector		
What species is a proven dengue vector in your area?	Are there other *Aedes*, such as *Aedes albopictus*, that can transmit DENV and may require a different control strategy than *Aedes aegypti*?	• virus detection from local mosquitoes • contemporary vector surveillance • laboratory-based vector competence studies • relevant literature
From what larval development sites do most adult *Ae. aegypti* emerge?	A larval control program needs to target productive sites, many of which are cryptic (i.e. pits, tanks, wells, and gutters) and may go undetected and thus untreated.	• vector (container) surveillance; • vector control staff • adult trapping (discrepancies between adults trap catches and larval development sites may imply the existence of cryptic aquatic habitats) • relevant literature
Where do adult vectors rest?	*Ae. aegypti* generally rest inside people's homes, while *Ae. albopictus* are typically found outdoors. This information will determine where adulticides need to be applied.	• indoor/outdoor sampling (using aspirator, sweep nets or traps) • vector control staff • relevant literature

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Table 1. Continued.

Category Parameter	Why it is important	How to obtain critical information
Are local vectors susceptible to insecticides that will be used?	Insecticide resistance is a growing problem that can prevent a control program from being successful. There must be plans in place to monitor for insecticide resistance, prevent or impede resistance, and apply alternative insecticides if resistance is detected.	• bioassays for resistance testing using standard methods (i.e. WHO cylinders, CDC bottle assay) • vector control staff • analysis for genetic markers of resistance • relevant literature
The human host		
What are the local types of domestic housing?	Should some areas be prioritised in control campaigns? Can *Ae. aegypti* readily enter local houses? Are the doors and windows of houses screened?	• historical outbreak records • house survey • vector control staff • adult mosquito sampling indoors (using aspirator, sweep nets or BG sentinel traps)
What are local sources for domestic water?	Do residents of local communities have access to piped water? Do they store water in drums, tanks or jars? Do they have unmanaged containers that accumulate rainwater? Managed and unmanaged water storage containers can be key sites for production of adult *Ae. aegypti*.	• house survey • vector control staff • larval/pupal surveys to confirm development sites • relevant literature
Is insecticide application logistically feasible and acceptable by the community?	Is public willing to let spray team into their yard or house to spray insecticides? Do gated properties and/or dogs prevent entry? What can be done legally to enter a private property? Access to properties for delivery of control tools is critical.	• vector control staff • community engagement • health regulations and legislation for property access • house inventory (number of inaccessible properties) • GIS records (mapping inaccessible properties)
Where do people socialise?	Do people gather and socialise, outdoors or indoors, where they can be bitten by Ae. aegypti? Some cultures have outdoor gathering areas (under houses, summer houses, decks) that are open and exposed to mosquitoes. In other cultures, people tend to socialise indoors behind screens that protect them from mosquitoes.	• vector control staff • interview public – community engagement • house survey
Do people use 'do it yourself' vector control?	Coils, plug-in zappers, repellents, and space sprays are commonly used in some communities. Most have a limited impact, but could potentially be used as part of an emergency consumer-based program.	• vector control staff • interview public – community engagement

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Table 1. Continued.

Category Parameter	Why it is important	How to obtain critical information
Are there non-residential (i.e. commercial/industrial/ educational, religious) meeting places where transmission is occurring?	Houses are not the only potentially important sites for exposure to infective mosquito bites.	• vector and infectious disease staff • health records – have there been outbreaks in industrial areas, schools or health facilities • vector surveys of high-risk areas, such as, tire yards and construction sites
Are there visitors or workers who can import virus?	Human movement can introduce the virus from one area to another. This risk can be pronounced at work sites, travel destinations or during seasonal migrations.	• vector and health staff • health records – have outbreaks been linked to visitors?
The system		
Who is responsible for vector control?	Is vector control carried out by the private sector, local, state (regional) or national government? Responsibilities and the chain of command must be established.	• intersectorial manager planning meetings • established management plans with clear roles and repsonsibilities
Is there a delay in notification of human dengue cases?	This is important for a rapid vector control response to local transmission events. It is especially important for non-endemic areas where control programs target imported cases before the virus can spread throughout the community.	• infectious disease staff, laboratory diagnosis staff, and attending physicians
Is there rapid, effective communication and collaboration between the vector control program and disease diagnostic/ notification systems	Rapid transfer of information between public health staff managing patient diagnosis and vector control staff is critical for management and planning of vector control activities.	• meetings with infectious disease managers (Incident Management Team) • daily updates with public health nurses during outbreaks • situation reports, yearly review and planning meetings prior to the high transmission season
How is dengue diagnosed?	It is critical to understand clinical diagnoses and laboratory test results: PCR, NS1, and serology (IgM or IgG ELISA) to understand the virus transmission risk. Are clinical cases laboratory confirmed?	• infectious disease staff, laboratory diagnosis staff, and attending physicians • established management plans

Immature mosquito control

Ae. aegypti preferentially lays its eggs just above the meniscus of standing water, on the walls of water-holding containers that are inside or in close proximity to human habitation (MacKenzie *et al.* 2004, Morrison *et al.* 2008, Ritchie 2014). Its immature stages are found in a variety of artificial containers closely associated with urban living. Aquatic habitats may contain passively collected rainwater or drainage water (e.g. discarded tires, bottles, pots and pans, crumpled tarpaulins or old machine parts) or may have been deliberately filled (e.g. tanks, drums, water cisterns, buckets or plant pots) for a variety of purposes, such as, cooking, washing, bathing or maintaining domestic animals. *Ae. aegypti* also exploits urban infrastructure for oviposition, being increasingly found in catch basins (Manrique-Saide *et al.* 2013, Ocampo *et al.* 2014) and septic tanks (Burke *et al.* 2010).

We know of no larval management program that seeks to eliminate *Ae. aegypti* from areas where it has become well-established. There is no universally applicable target threshold for any of the adult, pupal or larval indices that might be used to as a proxy to indicate program success in terms of reducing human infections and/or disease (Bowman *et al.* 2014, Brady *et al.* 2015, Cromwell *et al.* 2017). The objective of *Ae. aegypti* immature management has, therefore, become a largely pragmatic one; i.e. to maximise the reduction in vector population density given available resources. Control of the immature stages of dengue vectors is generally conducted through the targeting or destruction of larval habitats using biological, chemical, environmental, or mechanical methods. The highly local, frequently underresourced, and often reactive nature of many dengue control efforts often means that individual components of programs, including larval control, have not been rigorously evaluated (Achee *et al.* 2015, Bowman *et al.* 2014). Site-specific identification, however, of the most important and more productive larval development sites (i.e. key containers) can guide targeted immature control (WHO 2011a).

Larvicides, pupicides, and persistence

A limited subset of larvicides and pupicides are approved by the WHO and are widely used to treat *Ae. aegypti* larval habitats. When used following locally approved label instructions and with the acceptance of the community, these can be safely applied to water that is used for drinking. Approved insecticides include *S*-methoprene, pyriproxyfen, temephos and *Bacillus thuringiensis israelensis* (Bti) (WHO 2009a, 2011b, https://www.who.int/pq-vector-control/prequalified-lists/en/).

Key challenges to effective larviciding or pupiciding are the quality of the product and cost of coverage, speed of application, re-application interval, community acceptance, and insecticide resistance. The treatment cycle will depend on the seasonality of transmission, patterns of rainfall, duration of efficacy of the larvicide, and types of larval habitat. Given the long-perceived persistence of many currently used chemicals, it is common to apply two or three applications annually. Intervals between treatment cycles can be shortened if the rate of appearance of new containers outstrips the re-application schedule set by the control team.

The organophosphate temephos is the larvicide that is most widely used for *Ae. aegypti* control. A recent review indicates that there is good, but not universal, evidence of its entomological impact (George *et al.* 2015). For all aquatic habitat interventions, although there are examples of reductions in entomological indices, there is little direct evidence showing that larviciding or pupiciding reduces DENV transmission (Horstick *et al.* 2017). A recent exception comes from a chemical-free community mobilisation trial by Andersson *et al.* (2015), which showed reductions in dengue based on community-driven larval habitat management; serologic evidence of recent DENV infection was 11.3% in treatment clusters versus 14.6% in control clusters. Across all immature *Ae. aegypti* control strategies, however, the biggest challenge is effective implementation (Horstick *et al.* 2017), including coverage (i.e. scaling-up across broad geographic areas, including modern mega-city urban environments), sustainability, and how to most effectively combine immature and adult *Ae. aegypti* control.

Peri-focal treatment

An *Ae. aegypti* eradication plan was implemented in the Americas between the early 1940s and 1970 (Camargo 1967, Reiter 2014). The resulting elimination of *Ae. aegypti* from 22 countries in the region required substantial funding, rigorous training, and a military-style, top-down organisational structure. The most important tool used was 'perifocal treatment' of potential container habitats with DDT. Well-trained operators sprayed the inner and outer surfaces of all potential containers and all other surfaces within a 0.5 m radius of the container (Camargo 1967, Severo 1955). The goal was to kill larvae, ovipositing females and any adults that might rest in and around treated containers. During the pre-plastics era, households relied on a limited number of containers to store water, so many water storage containers were large and easily identifiable. Their scarcity and easy treatment made them particularly well suited for peri-focal spraying. These are the same container attributes that facilitated the effective deployment of predatory copepods for larval control in Vietnam (Kay and Nam 2005).

In the modern environment, which is characterised by crowded, often impoverished urban habitats with myriad containers, peri-focal spraying is no longer as feasible. It is possible, however, that 'skip oviposition' behaviour (i.e. *Ae. aegypti* tend not to lay all of their eggs in a single location, instead they lay portions of their egg batches across multiple containers; Harrington and Edman 2001) increases the probability that a female will contact a treated habitat and die even when coverage is not universal (Reiter *et al.* 2014). The development of new insecticide formulations with long residual effects (Haji *et al.* 2015) may offer an attractive addition to an integrated strategy, especially when specialist teams are already applying larvicides. A pilot implementation of outdoor residual spraying, following the perifocal spraying paradigm, in Malaysia detected a minimum entomological impact on *Ae. aegypti*, with ovitrap indices reduced by 10% compared to the control (Hamid *et al.* 2020). Given the limited entomological effect, high cost associated with houses that have large outdoor areas, and potential impact on non-target organisms, the suitability of an outdoor residual insecticide will depend on local conditions and the vector species.

Adult mosquito control

Chemical control: adulticides

Methods of chemical control that target adult dengue vectors are intended to reduce densities, longevity, and biting behaviour of female *Ae. aegypti* and, thus, reduce the risk of DENV transmission (Table 2, see Table 1 for overall dengue manager recommendations). The diversity of chemical targets that can be used have led to a variety of methods that differ in their modes of application, expected extent of protection (e.g. single premise vs area-wide), deployment (preventive intervention vs outbreak containment), and the human and economic resources needed for proper implementation (Achee *et al.* 2015). Consequently, adulticides can be applied as space sprays outdoors or indoors, residual surface treatments or treated objects (e.g. nets deployed as curtains/screens), and traps.

Human demography and urban environments have changed in important ways since the highly successful vertical implementation of peri-focal DDT spraying, which was performed under the yellow fever eradication campaign in the Americas during the 1950s and 1960s. Widespread and unplanned urbanisation, increased heterogeneity in *Aedes* larval habitats, and greater complexity in building structures all challenged adulticide application coverage, penetration, and

Table 2. Strategies used to control Aedes aegypti *and* Aedes albopictus *with adulticides (ranked from highest to lowest evidence of efficacy).*[1]

Method	Target vector	Application target	Equipment	Insecticides	Persistence	Entomological evidence	Epidemiological evidence
Entomological and epidemiological evidence of *Ae. aegypti* and dengue control, respectively							
Targeted indoor residual spraying (IRS, TIRS)	endophilic *Ae. aegypti*	dark, shady areas indoors, inside wardrobes, under tables and beds, lower walls; surfaces treated to point of runoff.	hand pump pneumatic sprayer with fan nozzle; backpack mister for large buildings such as schools; battery powered electric pump options available	synthetic pyrethroids, carbamates, organophosphates	depends on product: pyrethroids and carbamates up to 3-5 months; novel formulations (pirimiphos methyl) up to 7 months (Correa-Morales *et al.* 2019b)	months of KD of adult populations (Dunbar *et al.* 2019, Ritchie *et al.* 2004, Vazquez-Prokopec *et al.* 2017b)	matched case-control observational studies during dengue interventions (Vazquez-Prokopec *et al.* 2010, 2017a)
Spatial repellent	endophilic *Ae. aegypti*	inside human habitations	passive emanator designed to release a volatile chemical into the air without external heat source	transfluthrin and metofluthrin	formulation-dependent; 2-3 weeks established, 4 weeks under investigation	reduction in adult female *Ae. aegypti* indoor abundance (Devine *et al.*, 2021, AC Morrison unpublished data)	cluster-randomised, double-blind, placebo-controlled phase 3 clinical trial (AC Morrison unpublished data)
Evidence of urban *Ae. aegypti* control, limited evidence of impact on DENV transmission							
Lethal ovitraps (LOs)	gravid *Ae. aegypti*	multiple LOs set at premises	plastic cups or buckets fitted with insecticide treated strips or adhesives	synthetic pyrethroids; adhesives	4-8 weeks	slow reduction of gravid females; must service traps monthly/ bimonthy to sustain	CDC AGOs were associated with decreased chikungunya transmission (Barrera *et al.* 2017, Lorenzi *et al.* 2016)

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Table 2. Continued.

Method	Target vector	Application target	Equipment	Insecticides	Persistence	Entomological evidence	Epidemiological evidence
Outdoor residual spray; peri-focal spray; harbourage spray; barrier spray	*Ae. albopictus* and (to a lesser extent) endophilic *Ae. aegypti*	leaf litter and lower vegetation in shady, forested areas; outdoor container (tires, rubbish, etc.) dumps, bushy fenceline	hand pump pneumatic sprayer with fan nozzle; backpack mister, truck mounted sprayer apply large droplet size to plants and leaf litter	synthetic pyrethroids, carbamates, organophosphates	4-8 weeks depending on product formulations	near elimination of *Ae. albopictus* from treated islands (Muzari *et al.* 2017, Van den Hurk *et al.* 2016). Limited impact on *Ae. aegypti* in Malaysia (10% reduction) (Hamid *et al.* 2020)	impact of peri-focal spraying during yellow fever eradication campaign (Soper 1965)
Indoor space spray	*Ae. aegypti*	dark shady areas inside houses, rooms; must be applied repeatedly (i.e. 3 times weekly) (Gunning *et al.* 2018)	swing fogger (thermal fog); handheld ULV units	synthetic pyrethroids, carbamates, organophosphates	up to 1 week	rapid knock-down but population rebounds within 1 week; retreatment needed 1-2 weeks (Gunning *et al.* 2018, Koenraadt *et al.* 2007)	observational study in Iquitos, Peru, showed significant reduction of dengue incidence following application (Stoddard *et al.* 2014)
Some evidence of urban *Ae. aegypti* control, no evidence of significant impact on DENV transmission							
Insecticide treated window screens	*Ae. aegypti*	windows and doors of houses	screens made of Duranet (long-lasting alphacypermethrin-treated netting material)	synthetic pyrethroids (alphacypermethrin)	1+ year	reductions in adult Ae. aegypti in houses (Che-Mendoza *et al.* 2018, Manrique-Sadie *et al.* 2015)	

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Table 2. Continued.

Method	Target vector	Application target	Equipment	Insecticides	Persistence	Entomological evidence	Epidemiological evidence
Insecticide treated curtains	*Ae. aegypti*	windows and doors of houses	curtains made of insecticide-treated netting material	synthetic pyrethroids (deltamethrin)	ca. 1 year	reductions in *Ae. aegypti* infectations, including declines in dengue-infected females (Kroeger *et al.* 2006, Lorono-Pino *et al.* 2013)	no impact on dengue transmission (Lenhart *et al.* 2020)
Outdoor space spray: truck mounted and aerial	*Ae. aegypti*, *Ae. albopictus*	rapid widespread treatment of outdoor areas	specially equipped airplanes	primarily organophosphates; e.g. naled	<1 week	can achieve rapid knock-down, but needs retreatment within week (Britch *et al.* 2018, Correa-Morales *et al.* 2019a)	limited evidence of combined naled/ Bti spray associated with decreased Zika virus transmission in Miami, FL, USA (Likos *et al.* 2016)

[1] CDC = Centers for Disease Control; AGO = autocidal gravid ovitrap; KD = knock-down; LO = lethal ovitrap; ULV = ultra-low volume spray.

entomological impact (Reiter 2015). Recent and rapid increases of insecticide resistance (Moyes *et al.* 2017), has led to treatment failures (Grisales *et al.* 2013, Vazquez-Prokopec *et al.* 2017b) and further limits the insecticide options that can be used for adulticiding (WHO 2011b, https://www.who.int/pq-vector-control/prequalified-lists/en/). Investment into the development of novel classes of insecticides and non-insecticide-based strategies offer alternative solutions (Flores and O'Neill 2018, Hemingway *et al.* 2006, https://www.ivcc.com/research-development/insecticide-discovery-and-development/).

Presently, the evidence base is weak for the epidemiological impact of adulticide applications on dengue and other *Aedes*-borne viral diseases (Achee *et al.* 2015, Bowman *et al.* 2016). Some adulticides have been assessed for entomological impacts, but entomological metrics do not correlate well with reductions in human infection or disease (Bowman *et al.* 2014, Cromwell *et al.* 2017). Far fewer have been rigorously examined for their capacity to reduce human infection or disease, which is the ultimate goal of vector control (Achee *et al.* 2015, Bowman *et al.* 2016, Esu *et al.* 2010, Pilger *et al.* 2010, Reiner *et al.* 2016). That shortfall will be addressed for novel interventions in well-designed field trials with detailed monitoring of the spatial and temporal distribution of cases and vector control efforts (Manrique-Saide *et al.*, 2020). Results from these studies will substantially increase the vector control evidence base and lead to more effective policy and implementation recommendations (Anders *et al.* 2018, Reiner *et al.* 2016, Wilson *et al.* 2015).

Knowing the vector and its behaviour

The effective use of adulticides against *Aedes* requires an understanding of the local population's abundance and behaviour (particularly resting, dispersal, and feeding behaviour). This must be understood in the context of the local environment where the intervention will be applied (Figure 1). Most dengue control programs target *Ae. aegypti* that rest, blood feed, mate, and reproduce primarily in and around human habitations; i.e. homes and other occupied buildings. *Ae. aegypti* prefers to rest indoors in dark shady areas on objects below 1.5 m of height, such as, wardrobes, closets, under beds/tables, and behind furniture (Dzul-Manzanilla *et al.* 2016, Perich *et al.* 2000). Dark objects are highly attractive to resting male and female *Ae. aegypti*. When access into buildings is restricted by window screening, *Ae. aegypti* seek outdoor-peridomestic habitats where they rest in darker, well shaded sites that are sheltered from wind.

Adult *Ae. aegypti* are typically most active during the early morning (06:00-09:00) and late afternoon (15:00-18:00), although biting can occur throughout daylight hours and occasionally at night in lit rooms (Chadee 1988). Given *Ae. aegypti* seldom disperses beyond 100 m, females can spend their entire lifetime in or around the houses where they emerged as adults (Guerra *et al.* 2014, Harrington *et al.* 2005). Population densities of *Ae. aegypti* are typically low (<10 adults per house), but can occasionally be higher (Koyoc-Cardena *et al.* 2019, Scott *et al.* 2000), and are heterogeneously distributed through time and space (LaCon *et al.* 2014, Scott and Morrison 2003). Low vector density and heterogeneous distribution limit the sensitivity of vector surveillance and entomological quantification of the impact of vector control (Koyoc-Cardena *et al.* 2019, Reiner *et al.* 2016). Epidemiologically, low abundance is compensated for by high frequency of human biting (Scott *et al.* 2000) and marked heterogeneity in the people who are bitten (Liebman *et al.* 2014).

Ae. albopictus is considered a secondary dengue vector, but can be an important DENV vector in some areas; e.g. Europe, Hawaii (Heitmann *et al.* 2018), Japan (Kobayashi *et al.* 2018), and China (Luo *et al.* 2017). In contrast to *Ae. aegypti, Ae. albopictus* generally rests outdoors in leaf litter

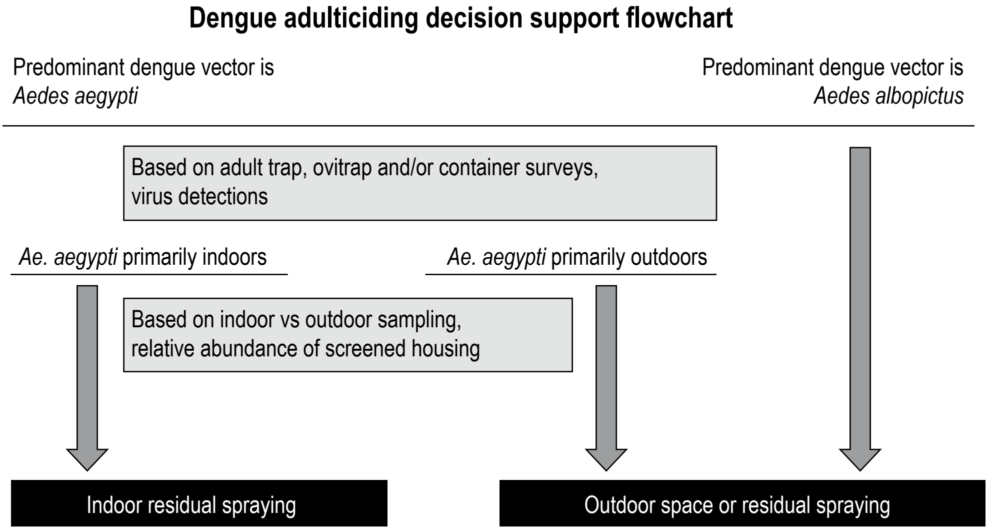

Figure 1. Schematic representation of a decision process for adulticiding strategies using residual insecticides against dengue vectors Ae. aegypti *and* Ae. albopictus. *Note in some areas open housing with minimal wall area (e.g. Thailand; Pant and Mathis 1973, Pant and Yasuno 1971) may preclude indoor residual spraying. Repeated applications of space sprays may be needed.*

under thick sylvan vegetation (commonly referred to as the forest edge mosquito), especially in areas near housing. They blood feed on an array of hosts in addition to humans, have a longer flight dispersal range than *Ae. aegypti*, but are similarly most active during early morning and late afternoon (Richards *et al.* 2006).

Space sprays and their application

Space spraying with adulticides, a mainstay of urban dengue control, can be done outdoors or indoors, as thermal fogs or cold fogs using either hand-held or vehicle-mounted equipment (Reiter 2015, WHO 2009b). Space sprays create a cloud of fine insecticide drops (between 50-100 μm in diameter for low-volume and <50 μm for ultra-low volume) that kill adult mosquitoes on contact. To be effective they must penetrate into human habitations to the places where adult female *Ae. aegypti* are resting or come into contact with them when they are flying. The insecticidal cloud does not create a residual insecticidal film on surfaces and, therefore, is only transient in its killing power. Insecticide droplet size, application rate, indoor penetration, and delivery method are crucial to the effectiveness of space spraying for controlling *Ae. aegypti*. For space sprays to reduce virus transmission they must be applied repeatedly, generally three times at weekly intervals (Correa-Morales *et al.* 2019a, Gunning *et al.* 2018). In situations where vectors are peridomestic and insecticide penetration is not hindered by building construction (e.g. areas where *Ae. albopictus* is a primary vector), truck-mounted ULV, thermal fogging, and aerial spray can provide a rapid yet transient reduction in mosquito populations (European Centre for Disease Prevention and Control 2017). Although there is indirect evidence (Stoddard *et al.* 2014), to date there is no direct evidence from a well-designed trial that a space spray program can significantly reduce DENV transmission (Esu *et al.* 2010).

Indoor space spraying or indoor fogging

Indoor space spraying (ISS) is a recent modification of outdoor space spraying specifically designed to target adult *Aedes* that are biting and resting indoors (Samuel *et al.* 2017). ISS can be carried out any time of the day to rapidly kill flying or resting *Aedes* adults (Samuel *et al.* 2017). Depending on the coverage, insecticide, and formulation used, indoor mosquito populations recover to initial levels soon after an application (~1 week), requiring frequent re-application in order to provide sustained entomological impact (Cavany *et al.* 2020, Gunning *et al.* 2018). ISS can be done with portable hand-carried equipment (WHO 2009b) that can deliver insecticide in 3 forms to control dengue vectors (WHO 2003, 2011b): thermal fogging, low-volume spray (LV) and ultra-low volume spray (ULV) (WHO 2003, 2009a).

In general, ISS is deployed as a reactive approach to the threat of a dengue outbreak; i.e. in response to an increase in reported dengue cases. In some programs, selective ISS treatment of homes within 200-400 m of the home of a diagnosed dengue case is a common practice. This approach is not expected to reduce DENV transmission because by the time a case is detected and a vector control response mounted, DENV will have spread beyond the treated area due to movement of infected people (Stoddard *et al.* 2013).

When a rapid reduction in vector density is essential, such as during a dengue outbreak, broad scale ISS should ideally be carried out across communities every 2-3 days for 10 days (three cycles). Further applications should then be made, as personnel and resources allow, once or twice a week to sustain suppression of the adult vector population. In Iquitos Peru, ISS cycles targeting areas with active dengue transmission were treated over a period of several weeks to months (Stoddard *et al.* 2014). Indirect evidence indicates that ISS applications across broad geographic areas can be effective at temporarily interrupting DENV transmission when promptly implemented in a series of sequential applications in response to the occurrence of humans with symptomatic infections (Stoddard *et al.* 2014, Samuel *et al.* 2017).

Insecticides that are suitable for space spraying as cold aerosols or thermal fogs are provided at the WHO Prequalification Vector Control website (https://www.who.int/pq-vector-control/prequalified-lists/en/). The choice of insecticide formulation for indoor use should be based on its immediate environmental impact, compliance of the community, and information on levels of insecticide susceptibility in local *Ae. aegypti*. Water-based formulations are preferred for indoor use, because they do not leave visible residues or an objectionable smell. Label instructions should always be followed when using insecticides. Operators who carry out house-to-house space spraying using portable equipment should wear appropriate personal protection equipment including facemasks, protective clothing, and gloves.

Outdoor space spraying

Outdoor application of adulticides has been the most widely used emergency control method against *Ae. aegypti* and dengue in the Americas for almost 50 years (World Health Organization 2003). Outdoor space spraying (OSS) was initially recommended in emergency situations, when there was need to suppress an ongoing epidemic. To date, there are no published data indicating OSS by itself results in a significant, sustained reduction in DENV transmission (Bowman *et al.* 2016, Esu *et al.* 2010). Because there have been reports of a rapid increase in pyrethroid resistance in *Ae. aegypti* populations that have been linked to the widespread use of truck-mounted OSS (Moyes *et al.* 2017), program managers should assess the benefits and drawbacks of this methodology for dengue control as well as insecticide resistance management. Despite the lack of supporting evidence, many dengue control programs still rely heavily on OSS. If it is used, guidelines will be needed to optimise it its use within an integrated *Ae. aegypti* management framework.

Vector populations can be transiently reduced over large areas by the use of space sprays released from low-flying aircraft, especially where access with ground equipment is difficult and where extensive areas must be treated rapidly (>1,000 ha). Previous experiences with aerially applied ultra-low volume (AULV) sprays showed limited entomologic and epidemiologic impact, primarily after single applications (Britch *et al.* 2018, Castle *et al.* 1999). In contrast, significant reductions in *Ae. aegypti* abundance after AULV application of naled (dimethyl 1,2-dibromo-2,2-dichloroethylphosphate) in combination with turbine-dispersed Bti, were observed in Miami-Dade, FL, USA after the introduction of Zika virus in 2016 (Likos *et al.* 2016). A randomised controlled trial of AULV performed in Mexico using the organophosphate chloropyrifos showed that efficacy in reducing indoor *Ae. aegypti* abundance increased with each weekly application cycle from 25% after the first spraying to 75% after the fourth spraying (Correa-Morales *et al.* 2019a).

Given the conflicting evidence, carefully designed trials are needed to build the evidence base for assessing the public health impact of AULV. In applying space sprays from the air, careful consideration of meteorological conditions, especially wind speed at spray height and at ground level, the droplet size spectrum obtained at the flying speed of the aircraft and to any tree cover that might prevent droplet penetration at ground level will improve targeting. When aerial space sprays are applied during temperature inversions (i.e. colder air closer to the ground), droplets can be better contained near the ground. Typically, inversions occur in the early morning or in the late afternoon when the ground temperature begins to fall, which corresponds to peak periods of *Aedes* activity. Concerns of the local population about spraying and its impact on non-target species must be considered when deciding to implement AULV. For safety reasons, populated areas should usually be sprayed from twin-engined aircraft. Modern aircraft are fitted with global positioning systems, so the swath coverage can be accurately recorded.

Residual surface spraying

Resting and harbourage sites of adult *Ae. aegypti* can be selectively treated with residual insecticides to provide control for several weeks or even months, depending on the insecticide formulation used. Indeed, the original success of the *Ae. aegypti* eradication campaign in the Americas was largely based on peri-focal spraying with DDT that provided months of control (Soper 1965). There is increased interest in using indoor residual spraying (IRS) to control *Ae. aegypti* and DENV transmission. This shift is supported by recent innovations in intervention deployment, evidence on epidemiological endpoints (Chadee 2013, Reiner *et al.* 2016, Samuel *et al.* 2017), and potential for implementation as a preventive and reactive approach to dengue control (Hladish *et al.* 2018, 2020). For *Ae. albopictus*, outdoor residual spraying (ORS) has proven successful for control where the forest floor and low-lying vegetation that are used as harbourage sites are treated with residual insecticides (Muzari *et al.* 2017).

Indoor residual spraying

IRS is classically understood as the application of long-acting chemical insecticides to the walls and ceilings of all houses and domestic animal shelters in a given area, in order to kill the adult vector mosquitoes that land and rest on those surfaces (WHO 2006). IRS directed specifically at *Ae. aegypti* resting sites is termed targeted IRS (TIRS) to distinguish it from traditional malaria

IRS. For *Ae. aegypti*, areas typically treated in urban housing units include predominant mosquito resting sites, such as walls below 1.5 m, the underside of tables, furniture, and beds, the inside of wardrobes, boxes, and crates, and dark areas corners or areas adjacent to dark objects (Figure 2). Kitchens should be excluded (or minimally treated) owing to the typically relatively low numbers of *Ae. aegypti* that reside there (Dzul-Manzanilla *et al.* 2016) and to minimise potential insecticide contamination of food items (PAHO 2019). Lower walls in toilets and laundry areas that often house water containers should also be sprayed. Locally adapting TIRS to settings with different housing characteristics should be based on assessing the suitability of building structures and materials to being sprayed with residual insecticides and knowing where mosquitoes rest and people gather (Table 1).

Assays in experimental houses show that when TIRS is performed by applying insecticides below 1.5 m to typical *Ae. aegypti* resting sites it achieves the same level of efficacy as the 'classic' spraying of all walls, but requires less spraying time and reduces the amount of insecticide use by more than 30% (Dunbar *et al.* 2019). On average, TIRS of a typical 140 m^2 brick and mortar house (Figure 2) takes approximately 15 min. Hand compression or pneumatic pump sprayers similar to those used for malaria IRS are generally used. Motorised sprayers incorporating electrical (battery or plug-in) motors are also available (Correa-Morales *et al.* 2019b). Fan spray nozzles are preferred, although cone nozzles can be used. Water based emulsifiable concentrates work best because they do not leave a visible residue once dry (PAHO 2019).

Recommended insecticides (https://www.who.int/pq-vector-control/prequalified-lists/en/) should provide several weeks or months of efficacy, depending on the formulation used and the insecticide susceptibility profile of local *Ae. aegypti* populations. Evidence from TIRS programs in Queensland, Australia indicate that TIRS using lambda-cyhalothrin provided ~90% reduction in further dengue transmission in treated houses, an effect that was maintained when >60% of premises within a specific radius of a case house were treated (Vazquez-Prokopec *et al.* 2010, 2017a).

As for all interventions, the efficacy of TIRS is dependent on coverage. Several approaches can be followed to implement TIRS in large urban areas. In non-endemic settings with strong public health resources and robust surveillance systems, TIRS can be used for premises identified through careful contact tracing (Vazquez-Prokopec *et al.* 2017a). Public health nurses can perform phone

Figure 2. An example of indoor resting sites of Ae. aegypti *targeted for TIRS in Merida, Mexico. Areas to treat are (A) underside of black table, back and underside of chairs, and sides of black furniture in distance. In the bedroom (B), the sides of bed frame, black surfaces of bedhead, and walls of closet/wardrobe. Note that the exposed pale walls do not have to be treated.*

interviews on a presumptive dengue case and attempt to identify locations visited during both the exposure period (ca. 4-7 days before symptom onset) and the viremic period (1-2 days before to 10 days post symptom onset). Typically, TIRS focuses on the locations the case visited during the viremic period, because this reflects the time when the infected person could have infected mosquitoes. The goal of TIRS is to kill infected mosquitoes before they complete the extrinsic incubation period (typically 8-10 days) and can transmit virus. Because it may be impractical to treat all contact locations, the highest risk premises are of highest priority for treatment, including residences, workplaces, and premises of friends and family who have been in contact with suspected cases (Vazquez-Prokopec *et al.* 2013). Houses in areas with high risk of virus transmission (i.e. unscreened windows) and known or suspected populations of *Ae. aegypti,* similarly merit careful attention for treatment. Chadee *et al.* (2007) proposed the use of the cardinal point system where the dengue case house and adjacent houses (so-called cardinal points) were identified as the key houses to treat. In Cairns, Australia, houses 50-100 m from the case house are treated with TIRS. Larval control is also conducted at these premises, which often extends further out than TIRS. To minimise selection for insecticide resistance, an approach to consider is the use of larvicides from a different chemical class from the adulticides, such as *S*-methoprene (Dusfour *et al.* 2019, Endersby-Harshman *et al.* 2017). There is potential in the future to use TIRS as a community-based application (do-it-yourself control) by utilising aerosolised residual insecticide formulations (Dzib-Flores *et al.* 2020; Queensland Health).

Because covering large urban environments can be logistically challenging, an alternative to contact tracing, which may be more suitable for many endemic areas, is to apply TIRS pre-emptively in locations reporting persistently high levels of DENV transmission (Bisanzio *et al.* 2018) or potential high-risk premises, such as schools. Recent mathematical modelling projections from Iquitos, Peru, and Merida, Mexico predict significant increases in TIRS effectiveness when interventions are preventively conducted prior to the season of peak virus transmission (Cavany *et al.* 2020, Hladish *et al.* 2018). A cluster-randomised controlled trial is currently ongoing in Merida, Mexico, to evaluate the epidemiological impact of pre-emptive TIRS on dengue and other Aedes-borne viruses (https://www.clinicaltrials.gov/ct2/show/NCT04343521, Manrique-Saide *et al.*, 2020). TIRS may also be suitable for protection of specific household members. For example, in areas of Zika virus transmission where infected pregnant women could transmit virus to their developing foetus.

Outdoor residual spraying, harbourage and barrier sprays

Because the area treated outdoors is usually considerably larger than that treated indoors, mechanised sprayers are often used for ORS. This kind of equipment ranges from motorised backpack misters to truck mounted misters with hose extensions. Outdoor residual sprays can be used to treat heavily vegetated areas where *Aedes*, particularly *Ae. albopictus*, rest or harbour (harbourage spray). Outdoor domestic items such as garden furniture, buckets, tires, abandoned cars, and other potential larval development habitats can be targeted. Barrier sprays are an extension of harbourage spray that include treatment of vegetation, such as, bushes and fence lines to create a barrier to mosquito dispersal. Larval control or source reduction should occur together with ORS (Muzari *et al.* 2017), as part of an integrated vector management strategy. This approach has resulted in the near elimination of *Ae. albopictus* populations in parts of the Torres Strait of Australia (Muzari *et al.* 2017). In Malaysia, however, ORS application led to only a modest reduction in *Ae. aegypti* ovitrap indices, with treatment areas having 10% lower infestation than control areas, reflecting the endophilic behavior of this species (Hamid *et al.* 2020).

Insecticide treated curtains/screens

Insecticide-treated netting can be fitted in houses as curtains or screens to provide *Aedes* control. Insecticide treated curtains (ITCs) can reduce *Ae. aegypti* densities in and around homes. In Thailand, ITCs showed a reduction in immature *Aedes* indices at six months post-deployment (Vanlerberghe *et al.* 2013). In a field trial carried out in Mexico, ITC interventions did not affect indoor adult *Aedes* abundance, but reduced the number of DENV infected female mosquitoes and were associated with lower human infection prevalence in some areas (Lorono-Pino *et al.* 2013). Combining ITCs with targeting productive larval habitats in Mexico (Kroeger *et al.* 2006), Venezuela (Kroeger *et al.* 2006, Vanlerberghe *et al.* 2011), and Guatemala (Rizzo *et al.* 2012) led to reductions in *Ae. aegypti* populations. While multiple studies report impacts on *Ae. aegypti* densities, there is currently no evidence of an epidemiological impact of ITCs (Lenhart *et al.* 2020).

Although ITCs can be implemented in dengue-endemic areas, recent studies revealed challenges related to their handling and sustained usage. A cluster randomised trial in a setting of low *Ae. aegypti* abundance detected no entomological impact (Toledo *et al.* 2015). Housing style can affect the ITC entomological impact, with little efficacy in houses containing large areas open to the outdoors (Lenhart *et al.* 2013). The efficacy of ITCs can also be compromised when curtains remain open or tied back to increase ventilation during the day or when all house entry points cannot be protected. In Iquitos, Peru, a sociological study found that optimal use of ITCs fell dramatically over time (Paz-Soldan *et al.* 2016).

The principle of 'building the vector out' is at the core of effective housing interventions to prevent vector-borne diseases (Lindsay *et al.* 2017, WHO 2017b). The entry of pathogen-transmitting vectors into human habitations can be effectively prevented by screening doors, windows, and eaves of houses, also known as 'Mosquito-proofing' (WHO 1982). Insecticide-treated screening (ITS), to protect houses, was first evaluated in Vietnam in the mid-1990s (Nguyen *et al.* 1996), where significant reductions in house infestations with *Aedes* were observed in comparison to untreated controls. In Merida, Mexico, randomised controlled trials of '*Aedes*-proof houses' that included the use of ITS in doors and windows (Figure 3) showed immediate and sustained (~2 yr)

Figure 3. A door and a window with a pyrethroid-treated screening in Merida, Mexico.

impacts on indoor-female *Ae. aegypti* abundance. It is notable, however, that DENV transmission continues in Singapore despite high building standards (Egger *et al.* 2008, Viennet *et al.* 2016).

Results from trials in Mexico indicate that ITS was viewed positively by the community, with a perceived efficacy on mosquito abundance and biting, and a perceived reduction in other domestic insect pests (Jones *et al.* 2014). Although installation of screens with high quality materials can cost ~$180 for a house with 2 doors and 7 windows, mass production and the potential for impact over several years is expected to increase the cost effectiveness of this intervention (Quintero *et al.* 2017). In a recent entomological cluster randomised trial detection of Zika virus in *Ae. aegypti* was reduced by 85% in clusters with ITS compared to control clusters with no screening or insecticide (Manrique-Saide *et al.*, 2020).

Spatial repellents

Spatial repellents are devices designed to release airborne chemicals at low vapor phase concentration to induce mosquito behaviours that decrease human-mosquito contact, disrupt blood-feeding, and, thus, are intended to reduce human exposure to mosquito-transmitted viruses (Achee *et al.* 2009, Achee and Grieco 2018). Significant entomological reductions have been documented in cluster randomised trials for transfluthrin (AC Morrison unpublished results) and metofluthrin (Devine *et al.*, 2021) emanators. A recently complete cluster-randomised, double-blinded, placebo-controlled phase 3 clinical trial examined the protective efficacy of a transfluthrin-based passive emanator placed inside homes in Iquitos, Peru. Results of the trial indicate a significant protective effect against *Aedes*-borne viruses. Study participants whose houses contained the active spatial repellent intervention were 34% less likely to become dengue or Zika virus infected compared to other study participants that received a placebo product without transfluthrin (AC Morrison unpublished results). Additional research is planned to explore the effect of a product with an increased persistence, the optimal product delivery mechanism, and scaling-up coverage for maximum public health benefit.

Lethal ovitraps

Insecticides or adhesives applied to ovitraps have also been used to trap and kill gravid female *Ae. aegypti*. Studies report that multiple lethal ovitraps (LOs) are needed per premise in order to detect an entomological impact, and they can be set indoors or outdoors. Generally, small to medium sized plastic cups or buckets, typically coloured black or red to enhance attraction to *Aedes*, are fitted with an oviposition substrate (typically cloth or paper-based) that is treated with a residual insecticide or an adhesive (Figure 4).

In addition to an entomopathogenic fungus, the In2Care trap is treated with the insect growth regulator pyriproxyfen. In semi-field (Buckner *et al.* 2017) and field experiments (Seixas *et al.* 2019) exposed adult mosquitoes auto-disseminated pyriproxyfen to other oviposition sites or modified adult traps. Results from the field study indicate that although there was a steady effect on juvenile and adult mosquito populations, more research is needed to better understand how best to use autodissemination as a control tool in urban environments that are often characterised by complex localised spatial heterogeneity (Seixas *et al.* 2019).

LOs often contain an infusion of hay or alfalfa to further attract gravid female mosquitoes, but require servicing every 1-2 months. A database (preferably GIS based) of trap placement should

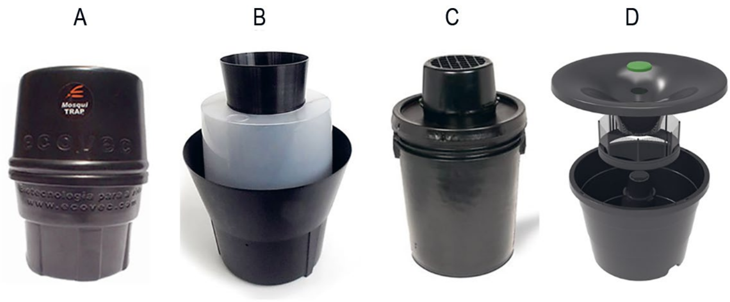

Figure 4. Examples of lethal ovitraps for Aedes *control: (A) mosquiTRAP (Maciel-de-Freitas* et al. *2008), (B) Gravid* Aedes *Trap (GAT) (Eiras* et al. *2014), (C) Autocidal Gravid Ovitraps (AGO) (Barrera* et al. *2014), and (D) In2Care trap (Buckner* et al. *2017). Photos are not set to scale.*

be kept up-to-date, to ensure timely trap servicing and prevent traps from becoming lost. Traps that are not serviced or are discarded can rapidly become larval mosquito development sites.

Several studies indicate that LOs provide significant decreases in gravid *Ae. aegypti* populations (Barrera *et al.* 2014, Rapley *et al.* 2009), and results from Puerto Rico indicate an association between a high density of traps and lower incidence of human chikungunya infection (Barrera *et al.* 2017, Lorenzi *et al.* 2016). The use of adhesives provides an alternative kill strategy, which can be especially useful in targeting insecticide resistant populations.

Safe use of insecticides

Safety precautions for insecticide use, including care in the handling of insecticide products, safe work practices for those who apply them, and appropriate field application should be followed. A safety plan for insecticide application should follow WHO published guidelines (https://www.who.int/water_sanitation_health/resources/vector385to397.pdf, http://npic.orst.edu/health/safeuse.html).

Most ORS products contain residual formulations of pyrethroid insecticides. The high toxicity of these to fish means that great care must be taken to avoid runoff into waterways containing non-target aquatic organisms.

Insecticide susceptibility

As the importance of dengue as a public health problem has increased globally, insecticide-based vector control interventions have become more widely employed.

The heavy reliance on insecticides to control dengue vectors has led to the development of insecticide resistance in many countries across the globe (Moyes *et al.* 2017). Significant levels of resistance to all insecticide classes commonly used for *Aedes* control have been documented, presenting a potentially serious threat to effective dengue vector control. Recent evidence shows that high levels of resistance can lead to significant treatment failures (Grisales *et al.* 2013, Marcombe *et al.* 2011, Vazquez-Prokopec *et al.* 2017b) and that patterns of resistance can be highly variable even at small geographic scales. Insecticide resistance mitigation and management strategies have been proposed for *Ae. aegypti*, but data are lacking regarding their efficacy, particularly under operational conditions (Dusfour *et al.* 2019).

Concluding remarks

A variety of insecticides and application methods can be used to control dengue vectors. These can be deployed across a range of ecological settings with variable infrastructure, expertise, resources, and levels of community participation. Unfortunately, most have not been successful in achieving a significant and sustained impact on DENV transmission. This is now widely recognised, and well-designed trials with epidemiological endpoints will provide a robust evidence base for promising new methods. Properly designed trials of currently available insecticide-based interventions (perhaps with elements of community led campaigns such as source reduction) are urgently needed in order to develop an evidence base for developing more effective public health policy (Wilson *et al.* 2015).

Based on evidence reviewed in this chapter, effective strategies for dengue vector control include the following components.

1. Locally adapted and derived vector control methods are used to fight dengue: Ecological and epidemiological variation are fundamental features of *Ae. aegypti* populations and DENV transmission dynamics. It is unlikely that a single tool or strategy will be successful everywhere. To be successful, vector control will require enhanced intersectorial and interdisciplinary coordination and strong community engagement.
2. Local vectors and their ecologies are well known: The primary urban DENV vector is *Ae. aegypti*. It prefers to rest and blood feed on human blood indoors. Adulticides targeting *Ae. aegypti* in indoor areas will, therefore, be most effective.

   Targeted indoor residual spraying (TIRS) and spatial repellents show promise for reducing dengue and/or Zika. TIRS can, however, be labour intensive and challenging because treatment requires entry into houses. In endemic cities, TIRS implementation as a preventive intervention in high transmission areas is an alternative to large-scale implementation. An improved understanding of optimal product delivery mechanism and minimum coverage for impact in modern urban environments is needed for effective public health application of spatial repellents.

   Most space sprays, aerial and ground, are relatively ineffective in controlling dengue, unless they are repeatedly delivered inside homes. The use of non-residual insecticides applied as a thermal fog or ULV spray outdoors is generally ineffective. In most situations, outdoor sprays are missing the target (i.e. indoor resting *Ae. aegypti*) and only killing for a short period of time. Use of ULV indoors, with repeated applications can overcome these limitations.

   If *Ae. albopictus* is the dominant vector, outdoor application of insecticides may be warranted. Care should be taken to ensure that fogs and ULV sprays are deployed in the optimal manner with reference to wind speed, temperature, and time of day.
3. Insecticide susceptibility of the local vector population is known. Many populations of *Ae. aegypti* are resistant to common insecticides. Without knowledge of local population resistance profiles, an adulticide program risks inefficient use of resources and the potential to exacerbate DENV transmission. A carefully designed insecticide resistance management strategy involving different chemical classes and non-chemical interventions will reduce selection for resistance. Routine insecticide resistance surveillance allows programs to detect resistance and respond to it if it arises.

4. Novel delivery methods have been developed to control *Aedes* populations using residual killing agents. Insecticide treated window screens and curtains and LOs treated with insecticides and adhesives show promise in reducing vector populations. Using current delivery schemes, these methods can be challenging to implement and difficult to maintain over time. Traps require regular servicing to prevent them from becoming *Aedes* larval development sites.
5. Adulticiding is not done in isolation. Adulticiding is most effective when implemented as part of an integrated vector management plan, in partnership with larval control activities.
6. Future dengue control programs include a combination of tools and strategies (Achee *et al.* 2015, Hladish *et al.* 2020, Wilder-Smith *et al.* 2017). Insecticide-based interventions provide the foundation for comprehensive dengue control programs that incorporate vaccines and non-insecticide-based vector control; e.g. source reduction, management of the built environment, and innovations, such as *Wolbachia* (Flores and O'Neill 2018). Although the theoretical benefits of combined approaches are appealing, the details for exactly how this will be done to achieve maximum impact in location-specific contexts remains to be determined.

The findings and conclusions in this chapter are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention. Use of trade names and commercial sources is for identification only and does not constitute endorsement by the Centers for Disease Control and Prevention or the US Department of Health and Human Services.

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5. Insecticide-impregnated screens used under 'multi-target method' for haematophagous fly control in cattle: a proof of concept

Marc Desquesnes[1,2,3], Emilie Bouhsira[4], Piangjai Chalermwong[3], Léa Drosne[1,2,3], Gérard Duvallet[5], Michel Franc[4], Geoffrey Gimonneau[2,6], Yannick René Pierre Grimaud[7], Pierre Guillet[8], Yousif E. Himeidan[9], Philippe Jacquiet[4], Sathaporn Jittapalapong[10], Wycliffe Karanja[9], Emmanuel Liénard[4], Sathaporn Onju[11], Johnson Ouma[9], Jean-Baptiste Rayaisse[6], Roungthip Masmeatathip[11], Ernest Salou[6], Viral Shah[8], Sharif Shukri[4] and Kornkanok Thaisungnoen[3]*

[1]CIRAD, UMR InterTryp, Bangkok, Thailand; [2]InterTryp, Univ Montpellier, CIRAD, IRD, 34398 Montpellier, France; [3]Faculty of Veterinary Medicine, Kasetsart University, 10900 Bangkok, Thailand; [4]Ecole Nationale Vétérinaire de Toulouse (ENVT), 23 chemin des capelles, 31076 Toulouse, France; [5]Université Paul Valery Montpellier3, CEFE, 34000 Montpellier, France; [6]CIRDES, 01 BP 454, Bobo-Dioulasso, Burkina Faso; [7]GDS Réunion, 1 rue du Père Hauck, 97418 La plaine des Cafres, La Réunion, France; [8]AtoZ Textile mills Ltd., P.O. Box 945, Arusha, Tanzania; [9]Africa Technical Research Centre (ATRC), P.O. Box 15500, Arusha, Tanzania; [10]Faculty of Veterinary Technology, Kasetsart University, 10900 Bangkok, Thailand; [11]Faculty of Agriculture at Kamphaeng Saen, Kasetsart University, 73140 Nakhon Pathom, Thailand; marc.desquesnes@cirad.fr

Abstract

Livestock are seasonally subjected to the nuisance of haematophagous flies, such as tabanids and stomoxyine flies. Topical application of insecticides has short term efficacy (a week or so), is expensive, and generates pesticide residues in animal products and environment. Attractive insecticide-impregnated blue fabrics are used for tsetse fly control in Africa; however, they are expensive and were never evaluated for other haematophagous flies. In previous works, we defined specifications of a white and blue screen specifically attracting haematophagous flies, particularly *Stomoxys* spp. In the present study, an assay was carried out in Kantchanaburi Province, Thailand, with around 30 of such screen prototypes, made of a multilayer polyethylene film incorporated with deltamethrin. Screens (also called 'targets') were deployed in 12 test farms, to evaluate the efficacy of a so-called 'multi-target method' (MTM); four control farms were also enrolled. A Vavoua trap was deployed one day/week in each farm to follow-up the density of insects. In the test-farms, during the 4 months post treatment, the mean density of haematophagous flies was significantly and consistently reduced by 63-73% compared to the control group. Laboratory tests indicated that insecticidal activity of these screen prototypes lasted around 3-4 months. However, in the field, significant reduction of fly densities was observed in all test farms up to 7 months after screen deployment, possibly as a consequence of the early impact of the screens on fly population dynamics. The significant effects obtained in test farms provided evidence for the proof of concept that MTM is effective for on-farm control of haematophagous and common flies. Durability of the screens will be increased in the next prototype generation. This innovative control method will be evaluated more extensively and in other livestock and poultry farms.

Keywords: polyethylene film, toxic target, livestock, screens, tabanids, *Stomoxys* spp.

Introduction

Livestock are seasonally subjected to nuisance, bites and blood loss caused by obligatory haematophagous flies, such as tabanids and stomoxyine flies, including *Musca crassirostris* which is highly abundant in cattle (Desquesnes *et al.* 2018). The economic impact of haematophagous flies on livestock is huge, with estimates indicating a loss of 130 kg of milk and 25-60 kg of meat per year, respectively in dairy and feeder cattle (Taylor *et al.* 2012). However, these flies are not only direct pests but also mechanical vectors of a number of pathogens, such as parasites (*Trypanosoma* spp., *Besnoitia besnoiti*), bacteria (*Bacillus anthracis*, *Anaplasma marginale*, *Francisella tularensis*, etc.) and viruses (Equine infectious anemia virus, Bovine leukosis virus, etc.) (Baldacchino *et al.* 2013, 2014) which economic impact must be considered, even if it would hardly be quantified. Very few and poorly efficient methods are available for the control and/or prevention of these haematophagous flies. Keeping animals under permanent protection of buildings or mosquito nets is an option, but it is not convenient for groups of large animals, such as cattle. Chemical or physical repellents, such as smoke, may only ensure limited and temporary prevention. The most employed methods are those that use synthetic insecticides. Insecticide paints or sprays indoor or on farm buildings are used for mosquito control (Mosqueira *et al.* 2010, Schurrer *et al.* 2006). However, for fly control, so far, the most employed method is direct spraying of the insecticides on the animals under contact sprays or fog. These methods have been used as early as in the 1950s, for example in the control of horseflies in cattle using a combination of pyrethrins and piperonyl butoxide (Bruce and Decker 1951). Later, organophosphate preparations were also used (Matthysse 1974). Not only are such sprays costly and of very short-term efficacy (lasting a week or so), they also generate high pesticide residues in animal products and/or byproducts (milk, meat, faeces). Contamination occurs by direct dispersion of insecticide droplets into surface water and by drainage systems or when rain wash-off pesticides from the animals and the run-off find their way into water systems, ending in large environmental contaminations.

An alternative method, developed for the control of tsetse flies in Africa is the use of attractive screens made of insecticide impregnated blue fabrics that are either blue squares (1×1 m) or alternate black net and blue fabric measuring 75×50 cm. A more recent development is the 'tiny target' (25×50 cm) made of small blue fabric panel flanked by a small black net (Lindh *et al.* 2009, Rayaisse *et al.* 2011). Very specific fabrics, mostly made of cotton (making them quite expensive), and dyed with phthalogen blue (a toxic dye now forbidden in Europe (Choudhury 2018)) are considered to be the most efficient in terms of attractivity. Tsetse fly attractivity toward colour is highly selective and only very specific blue fabrics that exhibit a wavelength reflectance around 460nm perform properly (Lindh *et al.* 2012). This method would be very costly, especially if high numbers of screens were needed to control tsetse flies in their natural habitats. However, thanks to the low reproductive capacity of tsetse flies, a very limited number of screens is sufficient to impact their population dynamics (Bouyer *et al.* 2015). Indeed, being larviparous, female tsetse flies produce only one progeny at a time, depositing a third instar larva every 8-12 days (depending on temperature and humidity), thus generating a maximum of 8-10 offspring in a lifetime (Bursell 1963, Wang *et al.* 2013). Blue-black fabric screens are currently used in Africa, especially for the control of riverine tsetse flies. The screens are deployed at intervals of 50-100 m or so along river borders (Tirados *et al.* 2015).

Although the blue-black screens have been used extensively against tsetse flies, they have never been evaluated for the control of tabanids and *Stomoxys* spp., because it is presumable that a very high number of screens would be required to impact their populations. Indeed, stomoxyine flies and tabanids may lay 60-130 and 200-800 eggs at a time, respectively, 8-10 times in a lifetime, for a total of 480-8,000 eggs, respectively (Baldacchino *et al.* 2014, Foil and Hogsette 1994). These flies are, then, highly prolific; it is considered that, for example in tabanids, if only 2% of the female flies oviposit at least once, this would be sufficient to maintain the fly population (Foil and Hogsette 1994). As expected, this population would increase rapidly if more flies and ovipositions occur. Being so prolific, the control of these flies would require the use of more potent tools. It is on the basis of this need that we considered developing toxic screens that can attract and kill tabanids and *Stomoxys* spp. To the best of our knowledge, such efforts have not heretofore been attempted.

In a series of previous developments, we designed, assayed and defined blue and white fabric screens specifically attracting tabanids, *Stomoxys* spp., *M. crassirostris* and other *Musca* spp. These screens did not attract non-target insects, such as butterflies, bees or other pollinators. These so-called 'fly-screens' are made of a white screen 60×60 cm interspersed with a horizontal blue rectangle on the upper part, which wave-length reflectance that peaks at 450-460 nm (Figure 1). However, the use of fabrics presents a number of disadvantages such as high cost, toxic dying procedure, difficult color monitoring and maintenance, high soaking capacities of insecticides (high cost and loss of insecticide), easy wash-off of the insecticide with rains, etc. These challenges experienced with fabrics led us to develop a new type of screen, thanks to a collaborative project implemented by a consortium called *FlyScreen*, that brings together a number of public institutions and a private/industrial partner. These new screens are made of multilayer and multi-functionalised polyethylene plastic film (a patented protected technology), in which a pyrethroid insecticide is incorporated during the polymer extrusion. The attractivity of haematophagous flies by such polyethylene white and blue screens was demonstrated, using sticky films, in previous studies (unpublished). In the present study, these fly-attracting insecticide impregnated screens (also called 'targets') were evaluated in cattle farms, for their efficacy to control haematophagous flies, under a so-called 'multi-target method' (MTM) (a method using multiple targets (20-30) per farm).

Material and methods

Dairy cattle farms

For the purpose of this study, in order to assess the efficacy of MTM in on-farm situation, small to medium size dairy farms were selected from the dairy production area of Nong Pho, Rachaburi Province, central Thailand. Thanks to a local veterinary worker, pre-selected dairy farms were visited, and the farmers issued with a questionnaire concerning the nuisance of flies and the

Figure 1. The 'multi-target method' (MTM): 18-38 screens were set-up around walking areas (A; left) or in the dung drying area (B; right) in dairy farms, Nong Pho, Kantchanaburri, Thailand.

arthropod control practices regularly implemented in the farm. Farms with too low fly activity, or farms systematically / routinely using smoke or insecticide / acaricide sprays were excluded from the study. For the included farms, the historical frequency of insecticides and smoke usage were recorded, but the use of insecticides was 'proscribed' throughout the experiment. In non-rejected farms, an entomological survey was initiated by using Vavoua traps for one day, once in a week for 2-3 weeks before setting up the screens. Farms exhibiting the lowest fly densities were excluded from the study. Selected farms were then randomly assigned into Test and Control groups, taking into account the fly densities, in order to obtain very close densities on average, in the two groups at the beginning of the experiment.

Mean comparisons of farm size (m^2) and number of cows per farm were made amongst Control group and Test group, using T-student test.

Insect trapping, counting and identification

Insect trapping was performed using Vavoua traps, made according to the available recommendations (Laveissiere and Grebaut 1990), using a 100% polyester blue fabric (CR Solon No 41., Chai Rung Textiles, Thailand). This fabric had previously been characterised as the best polyester blue fabric in terms of attractivity to haematophagous flies in Thailand (Onju *et al.*, unpublished results). For stratified flies sampling, one trap was set-up in the best location of each farm, generally in the centre of the farm, for 24 hours each week of the follow-up, from 18th May 2017 to 22nd February 2018. Grease was placed at the lower part of the iron rods used to set up the traps, to avoid interference of ants in the insect catches.

Stomoxyine flies were identified using a reference key (Zumpt 1973) and previous descriptions made in Thailand (Masmeatathip *et al.* 2006). Tabanids were identified using reference keys (Burton 1978, Philip 1960, Schuurmans Stekhoven 1926), and *Musca crassirostris* were identified using a key for *Musca* spp. from Thailand (Tumrasvin and Shinonaga 1978). However, statistics were carried out at the family level for tabanids and genus for *Stomoxys* and *Musca*, with the exception at species level, of *M. crassirostris* (an abundant obligatory haematophagous *Musca* species). Insect counts were reported in table-data files for statistical analyses.

Fly-screens

Multi-layer multi-functionalised polyethylen plastic films 120 µm thick, including deltamethrin (incorporated during the polyethylen extrusion), were produced by AtoZ Textile Mills Ltd. (Arusha, Tanzania) according to a process protected by a patent (Patent pending no. 1856676, deposited on 18/07/18). Screens are made of a white square plastic sheet, 60×60 cm, with a horizontal blue rectangular section (30×50 cm) located in the center and at 5 cm from the top of the screen (Figure 1). Upper and lower parts of the screens are equipped with grooves that allow fixation using a 10 mm diameter plastic pipe (electric sheath). Screens were set-up at 30 cm above the ground or grass level, on bamboo sticks (hammered 80 cm apart) using hay strings; this optimal highness of the screens had been previously studied and validated (Lescure 2014).

Multi-target method

Due to the generally high density of flies inside dairy cattle farms, and to ensure a high probability that flies land on a screen during their flight in the farm, high number of screens, from 20 to 40 screens, were set up per farm. The number of screens to set up in each farm was defined as:

(number of cows × 0.8) ± 20%. More, or less screens might be necessary, according to topographical conditions in each farm. It is the act of deploying multiple targets per farm that we refer to as MTM.

The distance between the screens varied depending on the situation and size of the farms, ranging from 3-5 m in the smallest farms, to 30-50 meters in the largest ones. Screens were deployed at the most visible and easily accessible locations inside the farms, preferably around stables and walking areas (Figure 1A), or, inside the area used to dry cattle dungs (Figure 1B). This was to enhance visibility by insects emerging inside the farm or coming from outside and including special areas that could be considered as 'ways of passage' or 'channels' for the insects. However, the best spots could not always be used since the screens need to stay out of reach of the animals. Indeed, in some preliminary observations, when some screens were reachable by the cattle, the animals tended to smell, lick and chew the screens, thus reducing the efficacy of the screens and compromising the study protocol. When necessary, the grass was cut prior to setting up the screens, and regularly thereafter to keep the screens as visible as possible.

Statistical analyses

To compare farms size, cattle numbers, density of cattle in tests and control groups, and to compare total screen numbers and the mean numbers of screens set-up per head of cattle, we used mean comparisons according to Student t test; a difference was significant when the calculated t value was below the critical 'Tc' value, at the appropriate degree of freedom, with an assumed *P*-value of 0.05.

Insects density analyses were carried out on *Stomoxys* spp., tabanids, *M. crassirostris*, 'haematophagous flies' (*Stomoxys* spp. + tabanids + *M. crassirostris*), 'common flies' (*Musca* spp. at the exception of *M. crassirostris* which was included in 'haematophagous flies'), and 'total flies' (haematophagous flies + common flies). The mean total number of insects trapped in control farms versus test farms were compared before setting up the screens (2-3 weeks of trapping from 18th May until 7th June 2017) and after setting up the screens; numbers of insects from control versus test farms were compared for every 4 weeks periods (i.e. monthly trappings) for up to 9 months. For the comparison of insect densities in test and control farms, the two-way repeated measures ANOVA was used. Before running the ANOVA, and since our data do not have equal sample sizes (number of farms in control and test groups are different) we used the Welch test to check the homogeneity of variance assumptions (hypothesis of homogeneity of variances was accepted if calculated *P*-value was >0.05). In the next step, the mean numbers of insect trapped in serial measures (per periods of 4 weeks) were compared under the different conditions, in control farms and test farms, using 'R program' (R-Development-Core-Team 2005). The mean insect densities were significantly different when the *P*-value was below 0.05 (Schober and Vetter 2018).

Results

Selection of the dairy cattle farms and farm grouping

Thirty-five pre-selected dairy farms were visited with a local veterinarian to select suitable farms for the purpose of the study. Questionnaires revealed that 6 farms had no problem with flies; these farms were generally very clean, and using automatic or systematic manual spraying of water, twice a day, generally linked with milking time. Four farms were treated regularly using insecticides sprays on cattle, 3 farms were treated using slow fires to produce a repellent smoke on a daily basis; these 7 farms were also excluded from the study. Other farms met the selection criteria and fly trapping was initiated in a total of 22 farms. In six of these farms, the insect densities recorded during the first two weeks of the survey were too low to be suitable for this study. Thus, these six were excluded. A total of 16 farms were included in the study. Their mean size was 2,888 m^2 (ranging from 700 to 8,800 m^2) and their mean cattle number was 43.5, ranging from 20 to 60 heads.

These 16 farms were randomly split into 2 groups of 4 farms (Control group) and 12 farms (Test group), taking into account the mean numbers of flies trapped during the first 2-3 weeks of the survey. Fly numbers mean comparisons were made to ensure that the two groups exhibit similar flies' densities before setting up the screens. Only mean densities of *Stomoxys* spp, *M. crassirostris* and common flies were compared. Tabanid' densities were too low to be considered independently. Results from the baseline studies (before setting up the screens) indicated that there were no significant differences in mean densities of flies in the control vs test farms for different types of flies and for all flies considered together (Table 1). Overall, mean fly densities were more or less similar even though slightly higher in test farms than control farms.

Multi-target method screen-setting and maintenance

The screens were set up in the 12 test farms, between 15th and 18th June 2017. In the five smallest farms (<1,200 m^2; mean size 818 m^2) with an average of 32.6 cattle, 18-21 screens (average 20 screens) were deployed at a mean interval distance of 3-8 meters, mainly in the open area (where farmers expose cattle dung under the sun for drying). Some other screens were set up around the stables at a distance of 1-2 meters from the animal shelter, depending on the available space around the stable. Screens were never set up inside the stables and were always kept out of the reach of cattle. The number of screens to set up in each farm (number of cows × 0.8 ± 20%) was respected in all small farms.

Table 1. Means, standard deviations and P*-values of two-way repeated measures ANOVA for comparison of flies trapped in Control (n=4) and Test (n=12) farms before screen-setting (18th May-7th June 2017).*

Flies	Group	Mean	Standard deviation	*P*-value
Stomoxys spp.	Test	60.9	8.7	0.54
	Control	59.6	16.8	
Musca crassirostris	Test	43.5	4.4	0.98
	Control	32.2	11.1	
Hematophagous flies[1]	Test	104.6	8.6	0.68
	Control	91.9	21.7	
Common flies	Test	271.4	30.4	0.98
	Control	205.1	31.3	
Total flies	Test	375.9	30.0	0.88
	Control	328.4	58.3	

[1] 'Hematophagous flies' is the total of *Stomoxys* spp. + tabanids + *M. crassirostris*; 'Common flies' includes all *Musca* spp., at the exception of *M. crassirostris* which is included in 'haematophagous flies' (as an obligatory haematophagous fly (Desquesnes *et al.* 2018)); 'total flies' includes haematophagous flies and common flies.

In the 7 medium and large size farms (1,800-8,800 m^2; mean size 4,054 m^2), with a mean number of 49 cows, between 25 and 38 screens (average 30 screens/farm) were set up, at a mean interval distance of 5-10 meters. For the largest farms (6,320 and 8,800 m^2, with 38 and 60 cattle, respectively), a mean interval distance of 20-30 meters was maintained between the screens. Typical screens-deployments under this MTM are presented on Figure 1. The number of screens to set up (number of cows × 0.8 ± 20%) was respected in all farms, except Farm 6, having 60 cows, which received only 30 screens instead of 38-58, thanks to easy and correct coverage of the space, and Farms 13 and 16, which received respectively 2 and 4 more screens to ensure a better coverage of their land space.

Size of the farms, cattle numbers and numbers of screens set up in each farm are presented in Table 2 with some meaningful meta-data. In total, 311 screens were set up in the 12 test farms, with 406 cows. The MTM was implemented with a little less than one screen per cow (average 0.79±0.10 screen per cow). In other words, a mean of 4 screens for every 5 cows. There were no significant differences in mean farms size (in m^2), number of cows and cow densities between control and test farms.

Table 2. Characteristics of the farms and screen-settings in the test and control farms.

Farm no.	Farm size (m^2)	Number of cows	Cow density (m^2/cow)	Number of screens set up	Screen density m^2/screen	Number of screen/ cattle	Smoke used as repellent	Insecticide sprays frequency
Test farms								
F1	700	27	26	20	35	0.74	+++	+++
F2	700	29	24	21	33	0.72	+++	+++
F3	780	27	29	18	43	O.67	++	0
F4	760	35	22	21	36	0.60	0	0
F5	1,845	36	51	30	62	0.83	+	+
F6	8,800	60	147	30	293	0.50	++	0
F7	6,320	38	166	30	211	0.79	+	0
F13	2,706	24	113	25	108	1.04	++	0
F14	3,710	36	103	25	148	0.69	+	0
F15	1,150	25	46	20	58	0.80	+	++
F16	2,720	35	78	38	72	1.09	0	0
F17	2,275	34	67	33	69	0.97	+	0
Totals	32,466	406		311				
Means (±95% CI)	2,706±1,428	33.8±5.4	73±28	25.9±3.5	97±46	0.79±0.10		
Control farms								
F12	3,300	30	110				0	0
F20	700	20	35				0	0
F21	465	31	15				+	++
F22	680	23	30				0	0
Totals	5,145	104						
Means (±95% CI)	1,286±1,320	26.0±5.2	47±42					

Screens were maintained during the weekly insect-trapping. Servicing of screens consisted in checking and reinforcing the firmness of the strings and sticks and repairing screens that had been torn off either by strong wind or animals. The grass beneath and around the screens was also cut twice a month, depending on the season, to insure full visibility of the screens by the flies, on at least 180°, and, when possible 360° around. All screens lasted 6 months in the farms and were then removed mid-December 2017. However, trappings of insects were implemented for another 3 months, until February 2018.

Dynamics in insect densities in the two groups

Welch tests carried out prior to run the ANOVA, demonstrated that the homogeneity of variance assumptions was acceptable; indeed, before the screens were set up, all *P*-values were above 0.05, ranging from 0.58 for *Stomoxys* spp., up to 0.98 for common flies. The weekly insect catches performed using Vavoua traps are presented on the figures; after screen settings, data were averaged by periods of 4 weeks for representation in the figures. The density of flies at the beginning of the study are the means of weekly trappings made at the end of May-early June 2017, just before the screens were set up. Further on, monthly average of four consecutive weekly trappings were made to represent the monthly trends of fly densities from June 2017 to February 2018. Figure 2 represents the mean apparent densities per trap (ADT) of haematophagous flies in Control (n=4; black interrupted line) and Test group (n=12; grey line). Although the Test group

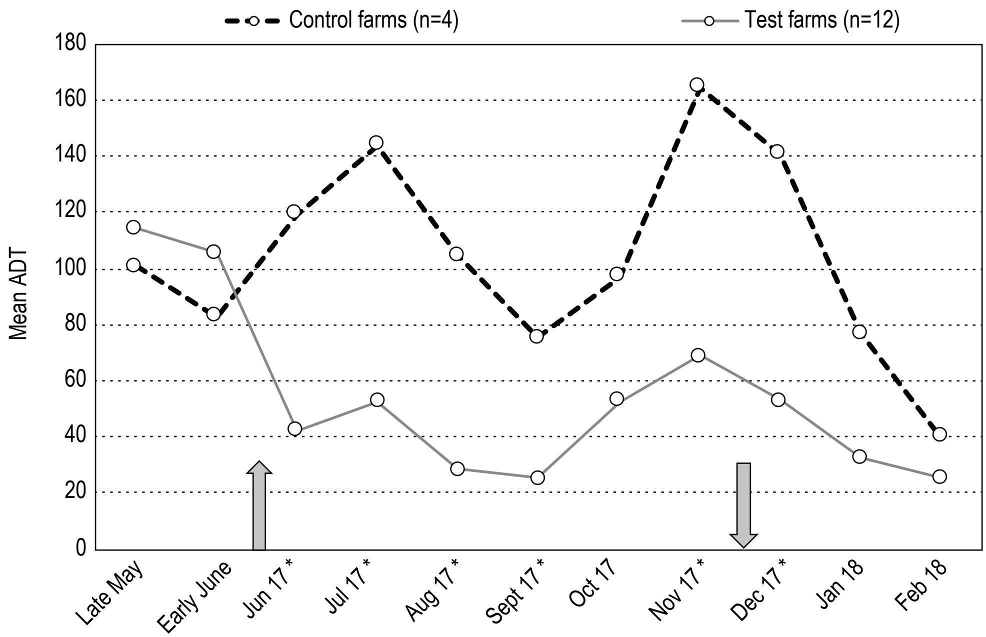

Figure 2. Variations of the average monthly apparent density per trap (ADT) of haematophagous flies in Control farms (black interrupted line) and Test farms (grey line) along the study. Asterisks placed after month-labels are indicating significant difference between Test and Control groups apparent densities; Pointing-up arrow indicates the date of screen deployment (15th-18th June 2017); Pointing-down arrow indicates the date screens were removed (14-15th December 2017).

exhibited slightly higher insect densities than Control group before screens were deployed, the two-way rerepeated ANOVA did not show a significant difference (*P*-values 0.54 for *Stomoxys* spp, 0.98 for 'common flies' and 0.88 for 'total flies'). The two groups were therefore considered as exhibiting similar fly densities before the screens were set up (Table 1, columns 'Before screens setting'). Mean comparisons made before screens-setting and, monthly after screens-setting are summarised in Table 3 for both *Stomoxys* spp., *M. crassirostris*, total haematophagous flies (including tabanids), common flies (*Musca* spp. with the exception of *M. crassirostris*) and total flies. Densities of all flies observingly decreased (Figure 2 and Figure 3) and significantly so (Table 3; all *P*-values <0.05 in June, August and September 2017) in the test farms compared to the control farms just after the screens were set up. Except for *Stomoxys* spp in July, all flies were significantly decreased during the 4 months post treatment (June to September). As shown on Table 4 and Figure 2, in October, the natural decrease of fly populations seems to cancel out the difference between Test and Control groups (all *P*-values >0.05), but significantly lower densities appear again in Test farms in November-December, due to a huge natural increase in fly densities observed in the Control group. From January 2018, the differences between Test and Control groups disappeared, 8 months after screen-setting.

The natural seasonal trend of fly density is shown by the apparent density of the flies in the Control farms, but the trend is different in test farms, although it tends to follow the same pattern especially for *Stomoxys* spp. and as a consequence in haematophagous flies.

Figure 3 is representing the percentage of flies in control farms versus test farms ('mean ADT in test farms' divided by 'mean ADT in control farms'); from 100% flies and more, before screen setting, the percentage of flies trapped in control farms fell down by 63-73% during the first 4 months, and was slowly recovering, reaching only 63% of control farms, 9 months after screen-setting (Feb 2019).

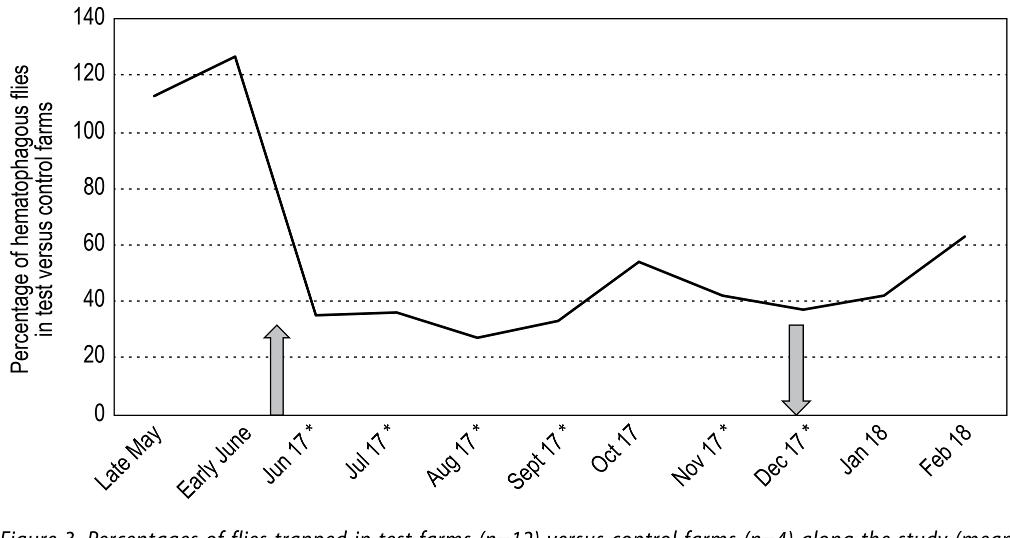

Figure 3. Percentages of flies trapped in test farms (n=12) versus control farms (n=4) along the study (mean apparent density per trap (ADT) in test farms / mean ADT in control farms).

Table 3. Means and P*-values of two-way repeated measures ANOVA for comparison of flies trapped in Control (n=4) and Test (n=12) farms before screen-setting (18th May-7th June 2017) and from June to September 2017.*[1]

	Farms	Before screens setting		Jun 17		Jul 17		Aug 17		Sept 17	
Flies	groups	mean	*P*-value	mean	*P*-value	mean	*P*-value	mean	*P*-value	mean	*P*-value
Stomoxys spp.	Test	61	0.545	22	**0.028**	32	0.140	19	**0.020**	16	**0.017**
	Control	60		68		54		52		44	
Musca crassirostris	Test	44	0.979	20	**0.003**	20	**0.000**	10	**0.000**	9	**0.000**
	Control	32		51		89		52		31	
Hematophagous flies	Test	105	0.676	42	**0.006**	53	**0.002**	29	**0.000**	25	**0.000**
	Control	92		119		144		105		75	
Common flies	Test	271	0.984	67	**0.000**	77	**0.036**	47	**0.000**	55	**0.002**
	Control	205		186		207		148		142	
Total flies	Test	376	0.881	109	**0.000**	130	**0.014**	76	**0.000**	80	**0.001**
	Control	297		306		351		252		217	

[1] Differences between Test and Control farms are significant when *P*-value is <0.05; which is indicated in bold.

Table 4. Means and P*-values of two-way repeated measures ANOVA for comparison of flies trapped in Control (n=4) and Test (n=12) farms from October 2017 to February 2018.*[1]

	Farms	Oct 17		Nov 17		Dec 17		Jan 18		Feb 18	
Flies	groups	mean	*P*-value	mean	*P*-value	mean	*P*-value	mean	*P*-value	mean	P-value
Stomoxys spp.	Test	39	0.082	45	0.071	30	**0.025**	14	**0.045**	9	**0.012**
	Control	77		86		72		36		19	
Musca crassirostris	Test	13	0.384	23	**0.003**	22	**0.004**	18	0.107	16	0.394
	Control	20		77		68		41		21	
Hematophagous flies	Test	53	0.059	69	**0.003**	53	**0.002**	32	0.058	25	0.119
	Control	97		165		141		77		40	
Common flies	Test	67	0.104	125	**0.000**	146	**0.019**	94	0.064	117	0.579
	Control	142		550		394		265		147	
Total flies	Test	120	0.076	194	**0.000**	199	**0.011**	126	0.060	142	0.467
	Control	239		715		535		342		187	

[1] Differences between Test and Control farms are significant when *P*-value is <0.05; which is indicated in bold.

Indeed, in control farms, *Stomoxys* spp. (Figure 4A), and consequently 'haematophagous flies' (Figure 2) exhibit the first peak of activity in end of June-early July, followed by a gradual decrease during the heavy rainy season, reaching a minimum in September and peaking again in October-December. Thereafter, the density declines to a minimum in February, likely due to cool and dry season. In the test farms, the peak of June is completely prevented, either reduced to a very

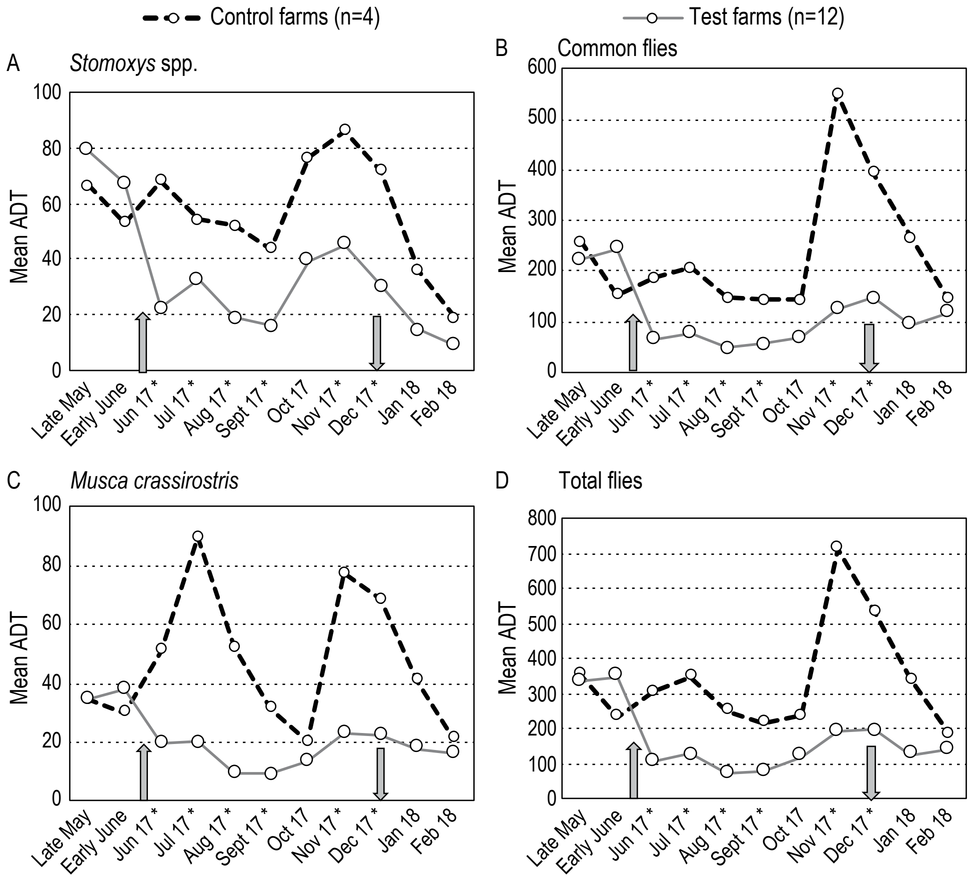

Figure 4. Variations of the average monthly apparent density per trap (ADT) of (A) Stomoxys *spp., (B) common flies, (C)* Musca crassirostris *and (D) total flies, in Control farms (black interrupted line) and Test farms (grey line) along the study. Asterisks placed after month-labels are indicating significant difference between Test and Control groups apparent densities; pointing-up vertical arrows indicate the date of screen deployment (15th-18th June 2017); pointing-down arrows indicate the date screens were removed (14-15th December 2017).*

low level in some farms, or to medium level in others (data not shown), but the general profile of fly dynamics remains the same in all farms, with two conspicuous peaks roughly in July and November (Figure 2 and 4).

In the Control group, *M. crassirostris* density peaks a little later than *Stomoxys* spp., in July to August, and then follows the same trend as *Stomoxys* spp., while common flies have a minor peak in July and a major one in November-December. In the test farms, both peaks of July and November of *M. crassirostris* and common flies in November are almost completely prevented (Figure 4B and 4C).

Overall, fly densities exhibited two peaks, i.e. in July and November. The peaks were clearly brought under control in all test farms, although the second peak of *Stomoxys* spp. was not completely under control. The effect of the treatment seems to disappear completely by January-February 2018, 8-9 months after screen-setting (2-3 months after the screens were removed), when insect populations are naturally decreasing due to the dry season.

Discussion

Although fly density in test farms was slightly higher than in control farms at the beginning of the study, they were very close before the screens were deployed, thus, validating the comparison between the groups. As shown by fly catches (and confirmed by farmer testimonies), there was a reduction of 63-73% in fly densities during the 4 months after the screens were deployed. Despite a slight increase in October (month 5 after screen setting), the fly reduction was still around 60%, up to the seventh month after screens were deployed. At month nine post screen-deployment, the fly density recorded in test farms was still only 37% of the control farms. These values show a medium-term effect of the treatment, quite longer than the toxic activity of the screens which was estimated though a tarsal contact test (Makoundou *et al.* 1995) in laboratory reared *Stomoxys calcitrans*, to be around 4-5 months (data not shown).

The natural trend in fly density observed in the Control group showed two peaks in July and November-December. In the Test group, the first peak is almost completely prevented and the second one is lowered. As a consequence, the effect of the screens can be split into four phases, (1) a first phase for 3-4 months, just after the screen deployment, during which the fly densities in Test group clearly decreases while that of the Control group increases, (2) a natural decrease in fly populations observed in the Control group in October (5 months after screen-setting) during which the difference between Test and Control groups is no more significant, although the all flies density in the Test group is still below that of the Control group (Figure 4D), (3) a huge peak of fly density observed at months 6-7 (November-December 2017) in Control group, and a much lower one in the Test group, thus, making the differences between Test and Control groups significant again during this window of time (likely as a consequence of the early impact of the treatment on fly population dynamic), and (4) a final phase of natural decline in fly density in both groups (January-February 2018), during which the effect of the treatment seems to disappear completely.

Overall, the toxic effect of the screens in the field, as was evaluated in weathering studies carried out on laboratory reared *Stomoxys calcitrans* (data not shown), was estimated to last around 3-4 months. Although the residual effect might extend a little longer, the effect of the screens was expected to last around 4 months in the field. Indeed, the effect of the treatment seems to disappear at month 5 (October), when no significant difference is recorded between Test and Control groups. However, this event coincides with the natural decrease of the fly population shown by the decrease of flies in Control group. Further effects observed in the field might therefore not be due to the killing effect of the screens during the period November-December, but rather because of the early impact of the screens, affecting fly population dynamic for up to 7 months after screen deployment. Considering that the toxic effect of the screens is expected to only the first 3-4 months, a population control of up to 7 months is quite satisfying, in our view. Of course, an extended durability of the toxicity of the screens, lasting for example, up to 12 months, would have a bigger and more sustainable impact on fly densities in the field.

Five farms of the test group (F1, 2, 3, 4, 15) individually showed lower effects than the others, especially for *Stomoxys* spp. (details not provided). In these farms, the effect of the screens was visible for all flies during the 4 months following screens-setting, but not statistically significant for *Stomoxys* spp., and inconsistently significant for common flies, suggesting possible development of insecticide resistance. Supporting a chemoresistance suspicion, the regular use of insecticides in these farms was higher than the average of other farms, including Control farms (Table 2A and 2B), with one farm using insecticide sprays regularly (F15: ++), and two farms using them systematically (F1 & F2: +++); the other two farms (Farm 3 & 4) were not using them, but they are very close neighbours of Farms 1 & 2.

Beside insecticide resistance, other parameters could be considered, possibly contributing to the lower response to the treatment observed in these 5 test farms, in comparison with the others. These farms were smaller in size (818 m^2/4,054 m^2), their mean number of cows was also lower (29/38), but they exhibited a higher density (1 cow/41 m^2) than the other group (1 cow/104 m^2); they received lower mean numbers of screens (20.0/30.1) and thus the number of screens set-up per cow was lower in these farms (0.72) compared to the others (0.84). Considering these observations, it can be hypothesised that a balance between the density of screens and cows needs to be considered in order to optimise the effects of the treatment.

The cost of production of screens produced under this new technology being quite low (around 1 €/screen), the MTM has a real potential to be easily and early adopted by the farmers.

Conclusions

The effect of the insecticide-impregnated screens was obvious as soon as the screens were set up, as was repeatedly mentioned by the farmers, and confirmed by the mean apparent density of flies per trap (ADT) observed in test farms versus control farms; indeed, ADT in test farms fell between 63-73% of the control farms, during the first 4 months after the multiple targets were set up.

The proof of concept of the MTM was demonstrated by this study. Results obtained suggest that, on average, setting-up of around 1 screen per cow could be the optimal rate appropriate for the control of haematophagous flies. Thanks to a reasonable cost of these screens, the MTM has a fair potential for early and large-scale adoption.

Durability of the toxic effects of the screens should be improved in the next generation of screens, with the aim of achieving one-year (12 months) efficacy for practical timeline reasons.

Other farming systems might also benefit from this control method which should be evaluated, for example, in horse, pig and poultry farms.

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Innovative strategies in integrated vector management

Treatment of anopheline breeding site with Bti (photograph: W. Takken)

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6. Peri-domestic vector control interventions using attractive targeted sugar baits and push-pull strategies

Caleb Stica[1], Neil F. Lobo[2] and Sarah J. Moore[1,3,4]*
[1]Ifakara Health Institute, Bagamoyo, P.O. Box 74, Pwani, Tanzania; [2]University of Notre Dame, Department of Biological Sciences, South Bend, IN 46556, USA; [3]Epidemiology and Public Health Department, Swiss Institute of Tropical and Public Health, Soccinstrase 57, 4002 Basel, Switzerland; [4]University of Basel, Petersplatz 1, 4003 Basel, Switzerland; smoore@ihi.or.tz

Abstract

Great challenges to sustained malaria and arbovirus control remain, including transmission by vectors that occur outdoors or outside of sleeping hours, the enormous scale of larval breeding in urban centres and the failure of people to comply with vector control. Furthermore, developing insecticide resistance, shifts in vector dominance and behaviour emphasises the need for new integrated vector management strategies. Behavioural aspects of the mosquitoes' lifecycle, such as mating, oviposition, sugar- and host-seeking, are influenced by olfactory cues in the environment. This chapter focuses on two new technologies that are in development for targeted vector control in and around the home that require minimal compliance from users. Both technologies exploit specific olfactory mechanisms in mosquito genera that could unlock the potential for highly targeted vector control interventions. Attractive targeted sugar baits (ATSB) exploit mosquito sugar-feeding behaviour to deploy insecticides. They use an attractive scent as an olfaction stimulant and a sugar solution as a feeding stimulant mixed with an oral insecticide to induce mosquito mortality upon ingestion. ATSB methods may be deployed as a stand-alone method or integrated with other interventions. They are technologically and operationally simple, low-cost and effective across all major mosquito genera. A major benefit of ATSB is that it targets and kills male and female mosquitoes on emergence from breeding sites and multiple contact points throughout the mosquito's lifetime, increasing the likelihood of reducing the mosquito's lifespan, and thus, its probability of transmitting disease. Push-pull systems exploit mosquito host-seeking behaviour using a combination of spatial repellents and lure and kill strategies to push mosquitoes away from the home or the peridomestic space and into traps that mimic vertebrate hosts. At the moment, the greatest limitation to push-pull systems is the need for CO_2 to attract mosquitoes. Most of the current trials have shown that efficacy of the push-pull strategy is primarily reliant upon the push unit, with only marginally improved efficacy with the addition of the pull unit. This finding could potentially be due to the size of these studies, because community-level protection from malaria using removal trapping has been demonstrated.

Keywords: peri-domestic, vector control, attractive targeted sugar baits, push-pull, malaria, dengue, spatial repellent

Introduction

The World Health Organization (WHO) currently recommended core malaria vector control strategies are indoor residual spraying (IRS) and long-lasting insecticidal nets (LLINs). These interventions have been widely deployed and are highly effective against malaria transmitted by indoor biting or resting vectors (Alonso *et al.* 2017). However, limited interventions are available that control mosquito species that bite outside of sleeping hours, that bite outdoors or that rest outdoors.

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Larval source management (LSM) is effective against indoor and outdoor biting mosquitoes, and is recommended for community control of malaria (WHO 2019) and dengue (WHO 2012a). In addition, the use of repellents and long clothing for personal protection against mosquito bites is recommended (WHO 2016a). House screening, mass trapping and space spraying also have some evidence of effect for dengue control (Roiz *et al.* 2018), and space spraying is frequently conducted during dengue epidemics (Olliaro *et al.* 2018). A number of *Anopheles* mosquitoes transmit malaria, while *Aedes aegypti* and *Aedes albopictus* are the principal vectors of the most common arboviruses, including dengue, chikungunya, Zika, and yellow fever. With a majority of the interactions between disease vectors and human hosts occurring in or around the home (Bern *et al.* 2010, Coluzzi 1999, Coura *et al.* 2014, De Zulueta 1994, Powell and Tabachnick 2013), deployment of interventions that control vectors within the peri-domestic space may present cost-effective means of controlling multiple vector-borne diseases including malaria and dengue.

The current chapter focuses on two new technologies that are coming through the vector control research and development pipeline (Hemingway *et al.* 2016) that may be targeted at the household for peri-domestic malaria and dengue control. The first technology, attractive targeted sugar baits (ATSB) exploit mosquito sugar-feeding behaviour to deploy insecticides (Muller and Galili 2016). Secondly, push-pull systems exploit mosquito host-seeking behaviour using a combination of spatial repellents (Norris and Coats 2017) and lure and kill strategies (Kline 2006) to push mosquitoes away from the home or the peri-domestic space and into traps. ATSB, push-pull and spatial repellent technologies are all currently under review by the WHO Vector Control Advisory Group (VCAG) to determine their public health value for the control of dengue and malaria vectors (WHO 2020b).

Malaria and *Anopheles* control

The scale-up and implementation of IRS and LLINs for vector control since 2000 has resulted in an 18% decrease in global malaria incidence (WHO 2018). However, progress has recently stalled with an increase of 2 million cases globally between 2016 and 2017. Sub-Saharan Africa and India carry approximately 80% of the global malaria burden, with the majority of malaria deaths occurring in sub-Saharan Africa (WHO 2018). IRS and LLINs, are highly effective in the Afrotropical setting (Sinka *et al.* 2016) where the majority of vectors bite indoors late at night when people are asleep and LLINs may be deployed, and vectors often rest inside of buildings (Sinka *et al.* 2010a). Recommendations for malaria vector control prioritise delivering either LLINs or IRS at high coverage and to a high standard, rather than introducing a second intervention as a means to compensate for deficiencies in the implementation of the first (WHO 2019). An estimated 552 million LLINs, were distributed globally between 2015 and 2017, resulting in roughly half of those at risk for malaria in Africa sleeping under a bed net (WHO 2018). IRS is less widely deployed due to the operational complexity of effective delivery. IRS coverage declined from 5% in 2010 to 3% in 2017 due to budget constraints (WHO 2017). As resistance to the pyrethroid insecticides used in vector control has increased, it has become necessary to use new classes of insecticides for IRS that are substantially more expensive (Oxborough 2016). However, even when both LLINs and IRS are deployed together malaria may still persist. A recent randomised controlled trial in Tanzania with high coverage of non-pyrethroid IRS (94%) combined with LLINs (77% reported use) still had a 28% malaria prevalence measured among under five children (Protopopoff *et al.* 2018). The latest dual active LLINs have been evaluated with improved control of malaria observed in areas where they were deployed, although substantial malaria persisted. A trial in Burkina Faso where 99% of children used pyrethroid LLINs, demonstrated a 12% reduction in malaria from 2 episodes per child-year among the conventional pyrethroid net group to 1.5 episodes per child-year in the combination pyrethroid-pyriproxyfen net group (Tiono *et al.* 2018). Two clinical trials of piperonyl butoxide-pyrethroid nets have shown 31% reduction in malaria prevalence in Tanzania sustained for 21 months (Protopopoff *et al.* 2018) and 20% reduction in malaria prevalence in Uganda sustained for 18 months (Staedke *et al.* 2019). Although these trials clearly indicated protection from malaria infections, the reductions reported highlight additional interventions may be needed in high endemic settings to further reduce malaria transmission.

Dengue and *Aedes* control

Over the past five decades dengue has spread rapidly to naïve populations in formerly unaffected regions of the world (Bhatt *et al.* 2013). First time infection generally manifests as a severe flu-like illness, but subsequent infections with a different serotype (or even genotype) can result in severe illness, and are more likely to lead to dengue haemorrhagic fever that can result in death. It is estimated that there are 390 million dengue virus infections per year of which 96 million are clinically significant (Bhatt *et al.* 2013). The number of dengue cases reported to WHO increased over 8 fold over the last 20 years, from 505,430 cases in 2000, to 4.2 million in 2019, while reported deaths between the year 2000 and 2015 increased from 960 to 4,032 (WHO 2020a). Around 70% of the global burden is concentrated in Southeast Asia (Bhatt *et al.* 2013), dengue is endemic in Central America and South America, while increasingly, outbreaks are being observed throughout the African sub-continent and India (Guzman and Harris 2015). Dengue is now present in more than 100 countries, whereas fifty years ago it was present only in nine countries (WHO 2020a). While the majority of vector borne diseases are predicted to decline in the next 25 years, dengue burden is predicted to increase threefold (Foreman *et al.* 2018). This rapid increase is due to demographic and societal changes, importantly rural-urban migration leading to unplanned urban settlements and introducing viruses to new areas. As the global urban population is set to rise to 5 billion by 2030 and urban land area will be 1.2 million km^2 (Seto *et al.* 2012), it is unlikely that dengue will decline without sustained and effective control measures.

The mosquito *Aedes aegypti* is the primary vector of dengue. *Ae. aegypti* has evolved to mate, feed, rest and lay eggs around urban human habitations and flourishes in urban environments closely associated with humans (Powell and Tabachnick 2013). It is a daytime feeder; its peak biting periods are early in the morning and before dusk in the evening. Female *Ae. aegypti* frequently bite multiple people during each feeding period and there is often clustering in dengue cases related to the presence of vectors (Liebman *et al.* 2012). There are a number of effective strategies against the vector focused on larval control including lethal ovitraps, window screening and larval source management with source reduction, biological control with larvivorous fish and copepods, source reduction and social mobilisation to clear breeding sites (Achee *et al.* 2015, Roiz *et al.* 2018). Ultra-low volume (ULV) spraying of insecticides indoors and outdoors is also commonly practiced, although there is limited evidence to support this as a strategy (Achee *et al.* 2015). ULV reduces mosquito densities only in the short term (Gunning *et al.* 2018) and IRS has demonstrated better efficacy for *Ae. aegypti* control (Paredes-Esquivel *et al.* 2016). Throughout the Caribbean and Central and South America vector control programmes conducted in the 1950s (Severo 1955) through to the 1970s almost eliminated *Ae. aegypti* from most of the region by the early 1970s (Slosek 1986). This programme focused on *Ae. aegypti* breeding sites in and around houses. Dichlorodiphenyltrichloroethane (DDT) was sprayed inside and outside water containers near houses and stopped *Ae. aegypti* mosquitoes from laying eggs in the sprayed containers. If the adult mosquitoes were not repelled by DDT, then DDT killed them when they contacted the sprayed surfaces. This program was largely scrapped due to resistance development, donor fatigue and the negative perception of DDT and it was scaled back from elimination to control in 1985 (PAHO

1997). Dengue transmission has also been controlled in Singapore (Hapuarachchi *et al.* 2016, Sim *et al.* 2020) and Cuba (Guzmán 2012) through well organised sustained vector control campaigns based on entomologic surveillance and larval source reduction (i.e. reducing the availability of *Ae.* larval habitats) but this is costly in terms of money and human resources. However, in many regions of the world, interventions are put into place only after the onset of an outbreak (reactive control) or proactive control efforts are not sustained, resulting in little, if any, control of the vector (Roiz *et al.* 2018). Other promising tools for Dengue control include *Wolbachia*, sterile insect technique, lethal ovitraps, and spatial repellents, all of which are now in an advanced stage of development (Achee *et al.* 2015). *Wolbachia* has reduced arbovirus transmission in several trials (Calloway 2020), sterile insect technique has successfully controlled *Aedes albopictus* (Zheng *et al.* 2019), ovitraps have reduced chikungunya transmission (Sharp *et al.* 2019) and spatial repellents have reduced dengue transmission (WHO 2020c).

The challenge of vector behaviour in combatting vector-borne disease

Malaria transmission may persist even with good access to and usage of LLINs or well-implemented IRS due to variability in human and/or vector behaviours (WHO 2014). The implications of malaria vector behaviour for malaria control was documented during the first Global Malaria Eradication Programme where it was observed that some species of mosquitoes had behaviours that allowed them to survive exposure to IRS with DDT (Elliott 1972). It was noted that outdoor resting contributed to this outcome, and had probably existed but not fully characterised before the implementation of mass spraying with DDT in many South American countries. Nonetheless, DDT spraying was highly efficacious and lead to massive reductions of malaria burden in the region (Roberts *et al.* 2000b). The contribution of DDT's spatial repellency action was the primary factor driving the observed malaria reduction by reducing human-vector contact (Roberts *et al.* 2000a). Malaria transmission outside of Africa is mainly mediated by mosquito vectors that tend to feed and rest outdoors and therefore evade core malaria control interventions that are applied indoors, e.g. *Anopheles dirus, Anopheles farauti, Anopheles fluviatilis* and *Anopheles minimus* in South-east Asia (Sinka *et al.* 2011) and *Anopheles albimanus*, *Anopheles albitarsis*, *Anopheles darlingi, Anopheles nunetzovari* and *Anopheles pseudopunctipennis* in South America (Sinka *et al.* 2010b). In sub-Saharan Africa where malaria vectors tend to bite and rest indoors (Sinka *et al.* 2010a), core malaria control interventions are highly effective. However, the recent scale up of LLINs is exerting selective pressure on mosquito populations which can be categorised into (1) changes in relative vector abundance or vector dominance to vectors with more exophagic or opportunistic behaviour; (2) shifts in vector behaviour to earlier evening or morning biting; and/or (3) shifts in vector behaviour to increased outdoor biting (Gatton *et al.* 2013). From 2003 to 2018, there has been a 10% increase in outdoor biting which may be due to selection for vector phenotypes or species with more exophagic or opportunistic behaviour, and the success of current and future LLINs and IRS programmes is expected to contribute to a further increase in the relative contribution to malaria transmission of outdoor-biting mosquitoes (Sherrard-Smith *et al.* 2019). Modelling suggests that even with universal coverage of LLINs and IRS, residual malaria transmission will persist. With universal coverage (all people in endemic areas using LLINs) across Africa, transmission modelling predicts a 10% increase in outdoor-biting, resulting in an increase of 12.2 million (69%) in malaria cases per year. Using a more realistic model of 75% LLIN coverage with declining use over time, a suggested 41 million additional malaria cases due to an increase in outdoor-biting is predicted (Sherrard-Smith *et al.* 2019). For instance, Zanzibar, an archipelago off the coast of Tanzania, had a history of high malaria transmission, but through effective and sustained implementation of vector control interventions beginning in 2003, is now approaching pre-elimination status (Bjorkman *et al.* 2019). Repeated household LLIN distributions coupled with high IRS coverage has resulted in a near 100-fold effect on indoor vectoral capacity, however low-level transmission persists and may be mediated by outdoor biting *Anopheles arabiensis* (Bjorkman *et al.* 2019, Monroe *et al.* 2019b). It is recognised that effective implementation of vector control can result in species replacement (Bayoh *et al.* 2010) and selection for biting outdoors or at times human hosts are available (i.e. not under their nets) (Rund *et al.* 2016, Sougoufara *et al.* 2014). Also, it is known that transmission may be maintained by secondary vectors (Mwangangi *et al.* 2013). As more countries move toward malaria elimination, residual malaria transmission may be mediated by secondary vectors that survive despite high coverage of indoor interventions. The development of long-lasting vector control interventions that can combat outdoor biting or resting malaria vectors and sustain lower receptivity of areas where malaria has been eliminated are a research priority (malERA 2017).

Similarly, arbovirus transmission and its control are highly influenced by vector behaviour. *Ae. aegypti* is an extremely efficient vector with a number of adaptations that make it extremely difficult to control. Spreading from West Africa on slave ships *Ae. aegypti* adapted to breed in containers of water and feed almost exclusively on humans (Bennett *et al.* 2016). It has now spread throughout the globe concentrated in urban centres. *Ae. aegypti* feeds several times in one gonotrophic cycle almost entirely on humans, which facilitates disease transmission. It bites during the day in and around the home making bite prevention difficult. Arboviruses such as dengue, Zika and Chikungunya are also transmitted by *Ae. albopictus* that spread from east Asia and has adapted well to suburban and urban environments with larvae now breeding in man-made containers (Bonizzoni *et al.* 2013). It is an aggressive and opportunistic day time biter with a preference for human blood in urban settings (Faraji *et al.* 2014) that tends to bite and rest outdoors although it has been recorded resting indoors in some locations (Valerio *et al.* 2010). The eggs of *Ae. aegypti* and *Ae. albopictus* are drought resistant (Juliano *et al.* 2002) and a single mosquito will lay eggs in multiple breeding sites (skip oviposition) (Colton *et al.* 2003, Davis *et al.* 2016) making larval source management more difficult. Therefore, with an ample supply of human blood and enormous numbers of man-made breeding and resting sites available *Ae. aegypti* and *Ae. albopictus* can rapidly breed and rebound after vector control efforts (Gunning *et al.* 2018).

The influence of human behaviour on vector borne disease transmission

The transmission of vector borne diseases (and their control) is also highly influenced by human behaviour. Research into human and mosquito behaviour demonstrated that night-time activities including household chores and entertainment during evening hours, as well as livelihood and large-scale socio-cultural events that can last throughout the night increase susceptibility to *Anopheles* mosquitoes (Monroe *et al.* 2019b). During the times in which malaria vectors are active, there are many activities that keep both men and women active in the peri-domestic space, unprotected by bed nets (Monroe *et al.* 2019a) (Figure 1). There are also special risk groups associated with ongoing malaria transmission, such as those who live or work in forests of South America (Recht *et al.* 2017) and Southeast Asia (von Seidlein *et al.* 2019), migrants (da Silva-Nunes *et al.* 2008, Kounnavong *et al.* 2017) and displaced populations (Abdul-Ghani *et al.* 2019). These populations are typically away from permanent housing and exposed to vectors outdoors (Figure 1). Chemoprophylaxis and mass drug administration (MDA) may be additionally used for malaria control, while mosquito bite prevention may be used for malaria and dengue prevention (Wen *et al.* 2016).

Bite prevention for dengue control is very important, especially during virus outbreaks. Daytime biting increases the chance that mosquitoes bite visitors to the house, which is a key mechanism

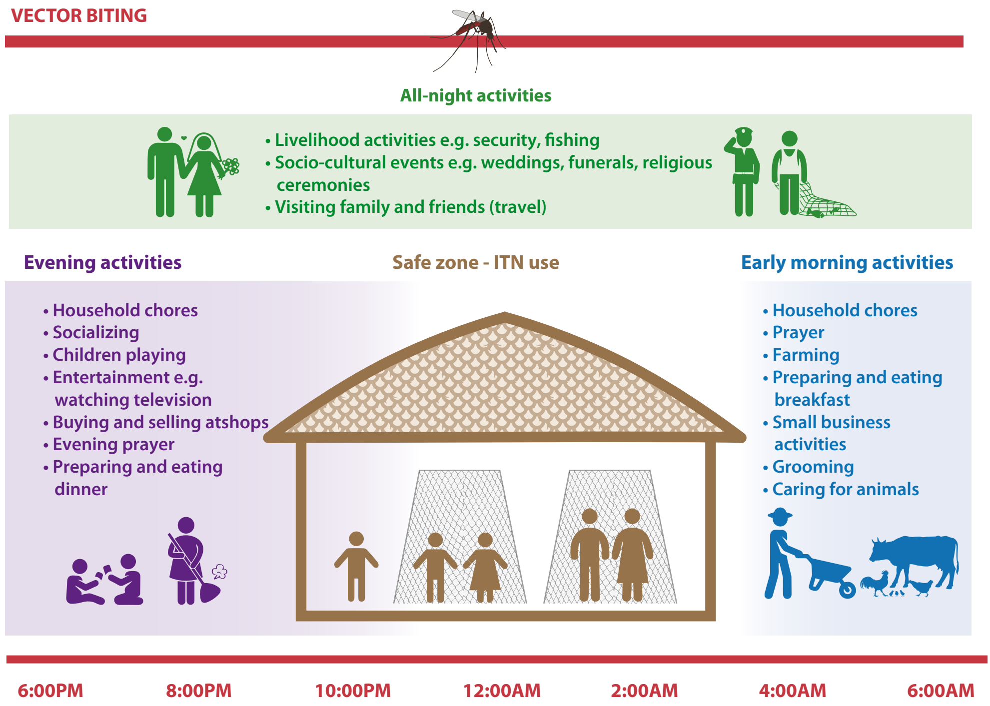

Figure 1. Human activity and protection time during times when malaria vectors are active. From Monroe et al. *(2019).*

that allows dengue to spread rapidly through urban areas despite limited mosquito dispersal (Stoddard *et al.* 2013). Social networks are also key to the spread of dengue, with visits from susceptible residents or infectious visitors carrying new serotypes or immigration of households from non-endemic areas increasing the possibility of disease transmission A study of viral circulation in Colombia showed that external social relationships with people outside of endemic areas generate frequent viral introduction and areas with frequent social contacts can impact immunity through frequent virus circulation (Padmanabha *et al.* 2015). Dengue transmission can be highly explosive locally, even in neighbourhoods with significant immunity in the human population. Variation among neighbourhoods in the density of local social networks, contacts with rural areas and rural-to-urban migration is likely to produce significant fine-scale heterogeneity in dengue dynamics, that interacts with changes in mosquito populations and local immunity to circulating serotypes (Liebman *et al.* 2014). In Dar es Salaam, outbreaks have been associated with neighbourhoods with markets where there is ample mosquito breeding (Mboera *et al.* 2016) and much outdoor, daytime interaction and interaction with people from dengue endemic areas, in the case of the last outbreak the serotype had come from China (Vairo *et al.* 2016). Dengue transmission commonly occurs during the evening when people, especially children, commonly socialise with neighbours on the street or on front porches between 16:30 and 19:30 h, when *Ae. aegypti* are most active (Padmanabha *et al.* 2015). People who spend more time at home are also at greater risk from dengue (Liebman *et al.* 2014) and chikungunya (Sharp *et al.* 2019) as they are exposed to more domestic bites than people who work in offices, for instance.

Human behaviour also impacts on the success or failure of control. For instance, people who have had malaria are more likely to use LLINs (Msellemu *et al.* 2017), or who live in houses where there are mosquitoes (Jumbam *et al.* 2020) but less likely to use them if they do not perceive a risk from malaria (Ahorlu *et al.* 2019). Dengue control is often reliant on human mobilisation to reduce larval breeding (Sim *et al.* 2020) with effective community mobilisation giving cost effective control (Mendoza-Cano *et al.* 2017) and may also be undermined by refusal to comply with spray programs (Gunning *et al.* 2018). Similarly, IRS can be undermined by refusal to allow spray programs access to homes or wall modification post-spray (Opiyo and Paaijmans 2020). Compliance with bite prevention is almost always insufficient and a major hindrance to this technology (Lalani *et al.* 2016). Therefore, as well as considering vector behaviour it is important that new vector control tools are developed to fit as seamlessly as possible with the lifestyle of residents of endemic areas.

Peridomestic spaces

As the most efficient vectors of human disease are strongly adapted to humans (synanthropic); and are therefore most commonly encountered around human dwellings either indoors (Bayoh *et al.* 2014) or in the peri-domestic space (Pollard *et al.* 2020), focusing on the peri-domestic space as an area for delivery of vector control interventions is an effective vector control strategy. However, coverage and sustainability remain a challenge, especially where daytime or outdoor biting occur. Ideally, novel control interventions deployed in this space should kill mosquitoes to provide community protection for users and non-users (Magesa *et al.* 1991) and prevent bites where outdoor transmission is occurring. If they are to kill mosquitoes then they should employ new classes of active ingredients with differing modes of action, be low-cost, sustainable, and safe to humans, non-target organisms and the environment (Vontas *et al.* 2014).

In line with WHO strategy of Integrated Vector Management (IVM), any additional vector control interventions are deployed in parallel with existing control methods (WHO 2012b). IVM strategies are intended to improve the sustainability and cost-effectiveness of vector control interventions by basing them on locally collected evidence, incorporating control of several diseases or several vectors simultaneously, and integrating strategies into the health sector and existing control systems. New control methods that manipulate, and exploit disease vector behaviour at different life and feeding stages will be a beneficial addition to the current vector control toolbox, Figure 2 (Kiware *et al.* 2017). A number of strategies may be employed in the peri-domestic space. Host-seeking mosquitoes can be captured by odour-baited traps, diverted to insecticide treated livestock, or diverted from biting human hosts using topical or spatial repellents and mosquito proofed housing, while mosquitoes in other physiological states may be attracted to targeted sugar baits, or oviposition traps (Kiware *et al.* 2017). In addition, interventions under evaluation by VCAG for arbovirus and malaria control include interventions where mosquitoes are released and interfere with vector survival or vectoral competence in and around the home. These include sterile insect technique (SIT), release of insects carrying a dominant lethal (RIDL) and *Wolbachia* (WHO 2020b), although these are released into an area and spread through the population rather than being applied to the peri-domestic area (Alphey 2014).

Exploiting mosquito behaviour

Behavioural responses of insects to olfactory cues have been exploited by entomologists for more than 200 years since the removal of bark beetles with deliberately felled 'trap trees' (Vite 1989). Mass trapping using odour-baited traps and lure and kill strategies have also been used to manage and even eradicate a number of blood-feeding pest species (El-Sayed *et al.* 2009, El-Sayed

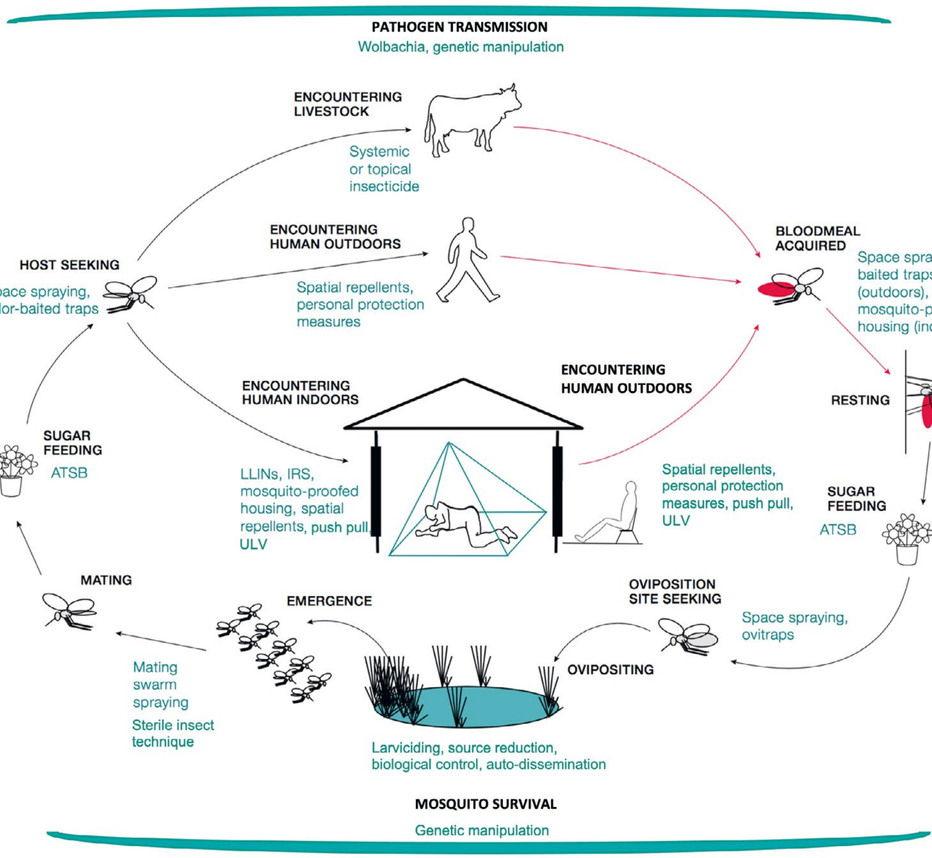

Figure 2. Mosquito life-cycle and potential control intervention target points modified to include peri-domestic protection adapted from (Kiware et al. *2017).*

et al. 2006) including tsetse flies (Torr *et al.* 2005) and salt marsh mosquitoes (Kline 2007). Such behavioural manipulation strategies retain their efficacy because insects rely on olfactory cues for many essential life processes: attractive odours are used to find mates, food and breeding sites (Logan and Birkett 2007), while repellent odours include plant defensive allomones and predatory odours deter oviposition (Van der Goes van Naters and Carlson 2006). In fact, our current best malaria prevention intervention, LLINs exploit mosquito olfactory needs, by turning the bed nets into human baited killing stations, to which resource-seeking vectors are lured and then killed. By using olfactory cues as lures, the selective loss of responsiveness to those cues would have a fitness cost for the insects and resistance is less likely to develop (Lefèvre *et al.* 2009). The field of olfactory neurobiology investigates how insect vectors process odours and this behavioural aspect shows promise as a novel target for vector control interventions. Behavioural aspects of the mosquitoes' lifecycle such as mating, oviposition, sugar- and host-seeking, are influenced by olfactory cues in the environment (Zwiebel and Takken 2004). Animals and plants produce thousands of volatile organic compounds, which are detected by the highly sensitive odorant receptors of mosquitoes that have a highly tuned narrow range of activating odorants specific to their behavioural needs and used to locate vertebrate hosts or sugar sources in the environment (Bohbot and Pitts 2015). Host-seeking behaviour at close-range is influenced by heat, moisture, visual cues, and CO_2, with odours playing a more predominant role at longer distances (Smallegange *et al.* 2011). Identification and exploitation of specific olfactory mechanisms in mosquito genera could unlock the potential for highly targeted vector control interventions including attractive targeted sugar baits (ATSB) and push-pull using odour baited traps.

Attractive targeted sugar baits

ATSBs are based on the 'attract and kill' principle which uses an attractive scent as an olfaction stimulant and a sugar solution as a feeding stimulant mixed with an oral insecticide to induce mosquito mortality upon ingestion. The first baits were made in the 1960s using malathion in sugar (Lea 1965). Based on laboratory data this is an extremely effective strategy because sugars trigger an automatic tactical feeding response causing mosquitoes to ingest the integrated active ingredients in the baits and die. Male and female mosquitoes require a carbohydrate energy source shortly after emergence, and then regularly for the daily activities of flight, mating, fecundity, oviposition, and various other metabolic processes (Foster 1995). This behaviour was largely ignored as a target for intervention development as it was assumed that sugar feeding was relatively rare (Beier 1996). However, it was recognised that soon after emergence mosquitoes seek sugar sources to obtain the energy they need for mating. On emergence both males and females prefer sugar over blood for their first energy source (Foster and Takken 2004). In addition, sugar-feeding increases insemination rates indicating the importance of sugar feeding in mosquito reproduction (Stone *et al.* 2009). There has since been a steadily growing body of evidence that males continue to exclusively sugar feed throughout their lives and females begin a cycle of host seeking, blood-feeding to obtain protein for oogenesis, while periodically sugar feeding throughout their lifespans to increase their energetic reserves, which enhances their lifetime fitness (Stone *et al.* 2011). This is particularly critical if mosquitoes have inadequate energy reserves after emergence from suboptimal larval habitats, since teneral energy reserves are replenished by sugar meals and blood meals (Briegel 1990). Mosquitoes frequently sugar feed on plants found around human homes and select between sugar sources using olfactory cues (Gouagna *et al.* 2010) with preferred plant species contributing to improved survival and fitness (Manda *et al.* 2007). The fitness of mosquito populations and their vectorial capacity (malaria transmission potential) is strongly influenced by the availability of sugar (Gu *et al.* 2011). One study compared sugar rich and sugar poor environments and showed a 250-fold difference in the malarial vectorial capacity of *Anopheles sergentii*, due to greater population size, higher survival rates and shorter duration of the gonotrophic cycle (more frequent blood feeding and oviposition) (Gu *et al.* 2011).

Importantly, the presence of sugar reduces the mosquitoes' probability of blood feeding (Stone *et al.* 2012) and is favoured by females immediately after emergence (Foster and Takken 2004, Impoinvil *et al.* 2004). Both male and female *Anopheles gambiae* (Muller *et al.* 2010) and *Ae. aegypti* (Sissoko *et al.* 2019) mosquitoes feed on sugar and host-seeking female mosquitoes feed on sugar opportunistically, partially feeding before blood feeding (Tenywa *et al.* 2017) or sugar feeding when a blood host cannot be obtained due to the presence of bed nets (Stewart *et al.* 2013). Mosquitoes often take multiple sugar meals throughout their lifetimes to supplement energetic reserves needed to fly to breeding sites (Holliday-Hanson *et al.* 1997). Therefore, adding insecticides to sugar baits has great potential for use in vector control.

Initial ATSB strategies employed local attractive flowering plants sprayed with a combination of sugar, dye, and insecticide, resulting in greater than 90% mosquito population control in arid areas

(Müller *et al.* 2010b) and this was repeated in areas with alternative sources of sugar (Beier *et al.* 2012). In an effort to decrease possible effects on non-target organisms, ATSBs with fruit-based attractant/insecticide combinations were developed (Muller *et al.* 2010). There were concerns about the impact of ATSB on non-target organisms (Qualls *et al.* 2014) and eventually bait stations were developed (Qualls *et al.* 2014). Currently ATSB comprises a bait, attractive to the species of interest (fruit or flower scent), and an oral toxin mixed with sugar as a feeding stimulant with a porous membrane that reduces the availability of sugars to non-target organisms (Figure 3) (Muller and Galili 2016).

The utilisation of a number of oral toxins in ATSB may be highly useful in resistance management. A large number of actives have been used in ATSB from a variety of insecticide classes including bendiocarb (Shin *et al.* 2011); the organophosphates malathion (Lea 1965) and pirimiphos-methyl (Shin *et al.* 2011); fipronil (Allan 2011); the pyrethroids permethrin, cyfluthrin, deltamethrin, bifenthrin, α-cypermethrin, λ-cyhalothrin, D-phenothrin(Shin *et al.* 2011); the neonicotinoids dinotefuran (Khallaayoune *et al.* 2013), imidacloprid and thiamethoxam (Allan 2011); the pyrrole chlorfenapyr (Stewart *et al.* 2013); spinosad (Allan 2011); the endectocide ivermectin (Allan 2011); juvenile hormone analogue pyriproxyfen (Fulcher *et al.* 2014); as well as biopesticides *Bacillus* spp., *Pseudomonas* sp., *Pantoea stewartii* sp. (Lindh *et al.* 2006); *Metarhizium anisopliae* (Ondiaka *et al.* 2015); botanicals including gGarlic oil encapsulated in β-cyclodextrin (Junnila *et al.* 2015), eugenol (Qualls *et al.* 2014); and DNA based technologies RNA interference (RNAi) (Coy *et al.* 2012), siRNA (Mysore *et al.* 2020).

Evidence for attractive targeted sugar baits efficacy

ATSB strategies have been developed and tested in laboratory, semi-field, and field trials in the Middle East, the United States, and Africa, and their efficacy demonstrated against *Anopheles* (Müller *et al.* 2008), *Aedes* (Sissoko *et al.* 2019), and *Culex* (Müller *et al.* 2010c) mosquito populations. Initial field studies looked at *Anopheles* species in arid, sugar-poor environments in Israel (Müller *et al.* 2008), and trials have since expanded to include medically important species of *Aedes* and *Culex* genera in semi-arid, subtropical, and tropical regions of the world with varying degrees of natural sugar source availability (Qualls *et al.* 2015, Revay *et al.* 2014). ATSB formulations have been made from locally sourced sugars and active ingredients or acquired from outside sources,

Figure 3. The stepwise development of attractive targeted sugar baits from concept to product.

depending on the study. Researchers have tested the efficacy of numerous active ingredients and combinations in the laboratory and field setting (Table 1) all with similar results on mosquito populations, as outlined below.

Anopheline

The majority of research into the utility of ATSB as a vector control mechanism has been focused on malaria and the control of Anopheline mosquitoes. Over the past decade, the majority of ATSB research has been ongoing in Israel into control of the primary malaria vectors found in the region. However, a recent field trial in Mali has presented the best evidence to date of the efficacy of ATSBs (Traore *et al.* 2020). A 14 village cluster randomised entomological trial was conducted in 2017 in Mali where the dominant mosquito species were *Anopheles coluzzii* and *An. gambiae* s.s. Seven villages, were allocated to ATSB and seven were control villages. All of the villages had >90% LLINs coverage and no other anti-mosquito interventions. Around 45% of mosquitoes were identified as sugar feeding and the availability of bait stations lowered the feeding on natural sources. In the control site the mean number of females feeding on ATSB ranged between 17 and 35% and males feeding on ATSB ranged between 23 and 40%. Mosquito density and survival was dramatically reduced by ATSB (Figure 4). This resulted in a reduction in entomological inoculation rate (EIR) of 77.76 to 100% indoors and 84.95 to 100% outdoors in monthly mean of EIRs.

ATSBs have also shown impressive results against cistern-dwelling *Anopheles claviger* – decreasing populations by 10-fold (Müller and Schlein 2008) and showing >90% reduction in *An. sergentii* populations using 0.04% spinosad bait stations (Müller *et al.* 2008).

In 2012, research was performed to compare the relative efficacy of sugar baits in sugar-rich environments compared to sugar-poor environments using ATSBs with 1% w/v boric acid sprayed on non-flowering vegetation (Beier *et al.* 2012). It was demonstrated that a single spray application virtually eliminated the entire population of male *An. sergentii* and reduced the female population by over 95%, changing the population age structure so that there were fewer older females, in the same way that IRS is known to do. While population reduction was observed in both types of environment, the decline was more gradual in the resource-rich environment taking 4 weeks compared to 2 weeks in the resource-poor environment. These findings are similar to trials led by

Table 1. Preferred product characteristics for attractive targeted sugar baits and push-pull strategies.

	Essential	Desirable
Mode of action	Breaks human-vector contact	Kills vectors, resistance management
Target population	Peri-domestic space (indoors)	Indoors and outdoors
Target species	*Anopheles* and *Aedes* vectors of malaria and dengue	Secondary vectors/vectors of other diseases, e.g. leishmaniasis
Efficacy	70%	100%
Compliance	Minimal compliance needed	
Persistence	6 months	>6 months
Application	Simple to apply, easy to transport	Can also be used away from home
Safety	Safe for humans and non-targets	
Disposal	No greater environmental harm than standard of care for other vector control products	
Shelf life	2 years	>2 years

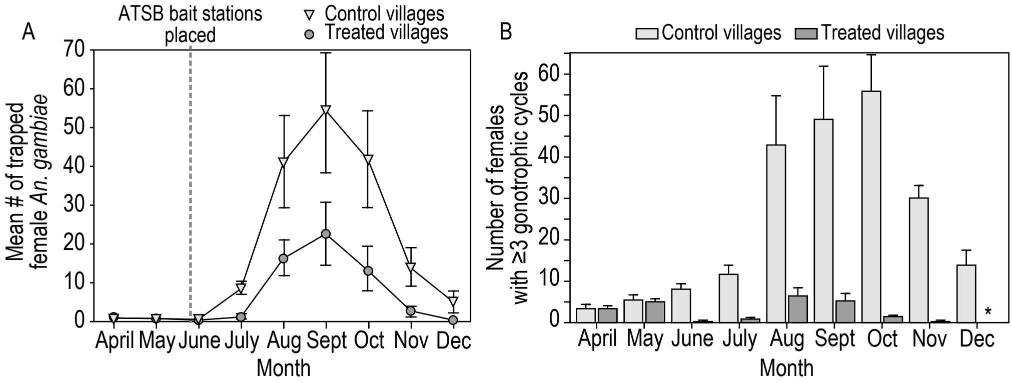

Figure 4. (A) The impact of attractive targeted sugar baits (ATSB) on indoor female Anopheles gambiae *density and (B) the impact of ATSB on the proportion of mosquitoes that lived through three gonotrophic cycle (approximately 9 days) (Traore* et al. *2020). * Absence of mosquitoes.*

Revay *et al.* (2015) which found a decrease in mosquito biting rates, and a 97.5% population drop in *An. sergentii* populations.

Additional field trials have been conducted in Africa on the *An. gambiae* s.l. complex. In Mali, Muller *et al.* (2010c) used 1% w/v boric acid ATSB sprayed on vegetation near mosquito breeding and resting sites as well as surrounding human habitations. After a single spray application, there was a 90% reduction in male and female *An. gambiae* s.l. populations, with a rapid decline over the first week following spraying and then stabilisation at low levels, with most females that remained alive after spraying being too young to transmit malaria.

In 2015, another field study in Mali using the same active ingredient demonstrated a 90% reduction in female and 93% reduction in male *An. gambiae* s.l. using indoor bait stations (Qualls *et al.* 2015). This study used dye in the stations to establish that a high proportion of the local mosquito population was making daily ATSB station contact, resulting in multiple active ingredient exposures throughout their lifespan. In Tanzania, laboratory studies utilised three ATSB formulations, 2% w/v boric acid, 1% v/v tolfenpyrad, or 0.5% v/v chlorfenapyr, looking at their efficacy against resistant populations. All treatments resulted in >90% mortality in pyrethroid susceptible *An. gambiae* s.s. and pyrethroid resistant *An. arabiensis* (Stewart *et al.* 2013). The same study demonstrated 41-48% mortality in wild, pyrethroid-resistant *An. arabiensis* populations in experimental huts using indoor ATSB stations. The indoor ATSB was tested in conjunction with a mosquito net, and it is uncertain if host-seeking mosquitoes would show preference for an ATSB station over a blood meal without a barrier mechanism in place, but it is hypothesised that the net causes the mosquito to expend a large amount of energy and then is diverted to a sugar source (Stewart *et al.* 2013). This synergism between a bed net depleting mosquito energy reserves and increasing their likelihood to subsequently sugar-feed was previously demonstrated by Stone *et al.* (2012) in a mesocosm study. In Tanzania, a semi-field study conducted by Tenywa *et al.* (2017) deployed a homemade ATSB made from 1.5 l water bottles cut in half, black cloth, and 0.01% ivermectin, which demonstrated a 95% mortality at 48 h of *An. arabiensis* (Tenywa *et al.* 2017). This study was also the first to demonstrate that this population showed no preference between fruit juice and 10% sucrose solution, enabling low cost ATSB formulations, and that the mosquitoes showed a preference for bait stations that offered a resting place. Finally, Tenywa *et al.* (2017) observed that in the experimental hut trial, when mosquitoes entered huts and where unable to blood-feed due to mosquito nets protecting human hosts, they were more likely to fully sugar-feed on indoor bait stations as they were unable to reach the blood meal source. This finding further supports the hypothesis of Stewart *et al.* (2013) of mosquito sugar seeking when unable to reach a blood meal and strengthens the body of evidence for the efficacy of integrated vector management and use of several vector control interventions in parallel.

Limited studies have been performed on ATSB against *Anopheles* mosquitoes outside of malaria-endemic areas. However, Qualls *et al.* (2014) performed a combined laboratory and field study in Florida and found that 0.1% w/w eugenol produced almost complete mortality in *Anopheles quadrimaculatus* in the lab, and at 3 weeks post field application, 0.8% w/w eugenol demonstrated a >50% reduction for *Anopheles crucians* (Qualls *et al.* 2014).

Aedine

The majority of research has taken place in the United States, concerning *Ae. albopictus* in the state of Florida. Qualls *et al.* (2012) demonstrated that mosquitoes resting in or emerging from cisterns, a majority of which were *Ae. albopictus*, will readily feed on a sugar bait (90%), irrespective of species, sex or developmental stage (Qualls *et al.* 2012). This finding set the stage for further research into the addition of active ingredients into sugar baits targeting *Aedes* populations. In 2013, Naranjo *et al.* used ATSBs with 1% w/v boric acid against *Ae. albopictus* populations in tropical Florida, which demonstrated a 95% mortality in the laboratory and approximately a 50% population reduction in field trials (Naranjo *et al.* 2013). Field collections also showed a reduction in mosquitoes measured by ovitraps suggesting that the sugar baits may have affected females before they fed or laid eggs. In 2014, ATSB with 0.8% w/w eugenol as the active ingredient decreased *Ae. albopictus* populations by 88% at 4 weeks post-treatment (Revay *et al.* 2014). Fulcher *et al.* (2014), trialled the addition of 1 mg/l pyriproxyfen to the 1% w/v boric acid ATSB spray formulation, again against *Ae. albopictus* mosquitoes. Their theory was that this formulation could exploit environmental rain conditions, as the run-off will drain into breeding sites and act as a larvicide. Laboratory trials resulted in 60-100% adult mortality and 80-100% emergence inhibition in habitats near to the sprayed vegetation. Scott-Fiorenzano *et al.* (2017) also studied *Ae. aegypti* and *Ae. albopictus* populations in Florida and their response to dual attractant ATSB with 1% w/v boric acid and host kairomones, finding that attraction was increased in laboratory studies, but the addition did not enhance the efficacy of the ATSB (Scott-Fiorenzano *et al.* 2017). A further study in Florida by Qualls *et al.* (2014) determined that ATSB with 0.1% w/w eugenol produced almost complete mortality in *Ae. aegypti* in the lab and 0.8% w/w eugenol showed >70% reductions in field studies, 3 weeks post-application of *Aedes atlanticus* and *Aedes infirmatus*.

A few field trials have also been conducted in Africa on *Ae. aegypti* populations with similar results to those observed in the United States. Laboratory studies of ATSB with low-risk 1000 mg/l dinotefuran in Morocco, observed a >80% 24-hour mortality in *Ae. aegypti* (Khallaayoune *et al.* 2013). However, whether this could be reproduced in an urban setting with abundant human hosts has been debated since *Ae. aegypti* females are found to take multiple blood meals in a single gonotrophic cycle (Scott *et al.* 2000) and are less likely to feed on sugar than other species (Olson *et al.* 2020). However, a recent trial in urban Mali using ATSB spray with microencapsulated garlic oil conducted in sugar-rich and sugar-poor environments demonstrated that *Ae. aegypti* were feeding frequently on sugar (Sissoko *et al.* 2019). The study was conducted in both sugar-rich environments where ATSB was sprayed on non-flowering vegetation and in sugar-poor environments where it was sprayed on artificial structures and buildings. Similar to findings with *Anopheles*, a significant reduction in female landing/biting starting at 5 days post-application was observed, but the effect was more pronounced in sugar poor-areas with a 70-fold decrease in trapped females compared to pre-treatment, and in sugar-rich, a 10-fold decrease (Sissoko *et al.* 2019). Similar to what has been seen among *Anopheles* mosquitoes, these findings highlight the differences that are observed when there are competing natural sugar sources.

Culicine

Limited studies have been performed to investigate the impact of ATSBs and culicine control, however, many of the studies previously mentioned collected culicine species in their field trials. *Culex pipiens* showed a decrease of 80% and >50% decrease in blood feeding for 18 days after spraying 0.04% spinosad ATSB on *Tamarix jordanis* trees in Israel (Müller and Schlein 2008). A second study also confirmed these results with spinosad ATSB sprayed onto vegetation near larval habitats of *Cx. pipiens* again causing an enormous decrease in the population and the average age of adult mosquitoes, with only 3% of those captured after spraying being multiparous (Müller *et al.* 2010c). In 2013, Khallaayoune *et al.* (2013) demonstrated that in lab and field studies of ATSB with low-risk 1000 mg/l dinotefuran produced 24-hour mortality of *Culex quinquefasciatus* greater than 80% and in the field, *Culex perexiguus* had greater than 70% population reduction 3 weeks post-application. In Tanzania in 2013, trials used ATSB with 2% w/v boric acid, 1% v/v tolfenpyrad, or 0.5% v/v chlorfenapyr, and all treatments resulted in >90% mortality in pyrethroid-resistant *Cx. quinquefasciatus* in the lab and 36-43% mortality in wild, pyrethroid-resistant *Cx. quinquefasciatus* populations in experimental huts (Stewart *et al.* 2013).

Benefits of attractive targeted sugar baits

ATSBs are a promising addition to the vector control toolbox that offer an additional means of controlling mosquitoes with low doses of insecticides. As the insecticides are ingested by the mosquito a broad range of insecticides may be used of a wide range of classes as well as integrating bacteria or double-stranded RNA (dsRNA) into toxic sugar baits. ATSB methods can work as a stand-alone method of mosquito control or in conjunction with other mosquito control methods and may be used for outdoor mosquito control in the peri-domestic space. ATSB has been shown to be technologically and operationally simple, low-cost, highly effective across all major mosquito genera, does not require human compliance, and bait stations are readily deployable. ATSBs provide an alternative to the contact insecticides used in LLINs or IRS and bypass common problems, such as excito-repellency and insecticide resistance. A major benefit of ATSB is that it targets and kills mosquitoes on emergence from breeding sites and multiple contact points throughout the mosquito's lifetime, increasing the likelihood of reducing the mosquito's lifespan, and thus, its probability of transmitting disease. Importantly, it kills both male and female mosquitoes. ATSB can be used with multiple classes of oral insecticides that are rarely used for public health purposes (Table 1) and show no signs of cross-resistance, which makes this strategy ideal for the management of current pyrethroid-resistant mosquito populations.

Modelling studies have shown that ATSB exposure rates of approximately 36% of those used in Mali has an equivalent reduction in malaria transmission as 80% IRS coverage (Marshall *et al.* 2013). Modelling showed that optimum deployment could be targeted at larval habitats, resting sites and sugar sources and that around three times more bait stations would be needed to control malaria in sugar rich environments than in sugar poor environments (Zhu *et al.* 2015). Furthermore, modelling work showed that the deployment of ATSB may also slow the development of behavioural resistance to indoor control interventions such as LLINs through killing all mosquitoes in the population (Stone *et al.* 2016), and the wide range of insecticides that may be used offer an excellent means of insecticide resistance management.

Potential issues

Specific spatial and temporal conditions must be considered with implementation of control measures. Bait stations have been shown to work well in arid and semi-arid environments, while in tropical environments, ATSB must outcompete natural plant sugar sources, and most likely will work best in arid and semi-arid environments where natural flowering plants are sparse. However, ATSB strategies have been shown to work, even in sugar-rich environments, but results take longer to realise as mosquitoes are also feeding on natural plant sugar sources. Seasonality must be taken into account with all forms of ATSB application. There is a concern of ancillary effects on non-target organisms, especially pollinators. Numerous studies have shown that the effects to non-target orders of insects are minimal when ATSB is sprayed on non-flowering vegetation, with bait stations showing the least effect as a result of product designed protective grids allowing only target organisms to reach the solution (Fiorenzano *et al.* 2017). Secondary effects on non-target predatory insects have been studied by feeding them on ATSB engorged mosquitoes, and no ill effects were observed (Fiorenzano *et al.* 2017, Revay *et al.* 2015). Further research is needed on additional possible non-target species found in other ecological zones and as different ATSB formulations are tested, to ensure that unintended impacts are minimised. It is important that researchers be mindful of the active ingredients that are incorporated into ATSB formulations. The scientific community must decrease the possibility of selection pressure for specific active ingredients by studying and employing classes with different modes of action that are not being used in current vector control programs. We must learn from the errors made in the recent past with the almost total reliance on pyrethroid insecticides as a 'monotherapy' for vector control.

The future of attractive targeted sugar baits

Current studies have established the ability of ATSB to decimate populations of mosquitoes in laboratory and field trials. Their potential impact in the peri-domestic space and control of exophagic mosquito populations through the exploitation of mosquito's natural need for sugar makes an excellent addition to the current vector control tool box that would be extremely beneficial to vector control programs worldwide. The potential of ATSB is just beginning to be realised, and several improvements and modifications are on the horizon. ATSB with mixtures of multiple insecticides or novel insecticide classes may help minimise resistance development. ATSB spraying may be effective in large-scale rice cultivation areas, as rice plants do not provide a source of sucrose for mosquitoes but do provide breeding sites (Müller *et al.* 2010b). The addition of larvicides to ATSB which mosquitoes will carry to or excrete at breeding sites after sugar-feeding has a potential added benefit that merits further research since pyriproxyfen in ATSBs can be faecally disseminated into mosquito breeding sites through adult *Ae. albopictus* ingestion and excretion, inhibiting mosquito emergence by 57% (Scott *et al.* 2017). Optimisation of bait stations is also required. Maximising the attraction of baits will improve the effectiveness of baits, especially in resource-rich environments. Mosquitoes use olfactory cues to discriminate between diverse species of plant sugar sources in their environment (Müller *et al.* 2010a) based on beneficial volatile organic compounds (Nyasembe *et al.* 2018). Some cues are species-specific, but *Ae. aegypti* and *An. gambiae* s.l. use both β-myrcene and (E)-β-ocimene as primary chemicals to determine if plants are a potential nutrient source (Nyasembe *et al.* 2018). As with host cues, the response of mosquitoes to these volatiles is dose dependent (Hao *et al.* 2013, Meza *et al.* 2020).

Identification of optimal cues, the correct concentrations and possibly development of a synthetic attractant blend Incorporation of these specific chemical components into ATSB formulations could increase their efficacy, especially in sugar-rich areas.

Push-pull

Push-pull systems utilise stimuli to modify the behaviour of vectors by repelling or pushing vectors away from a protected resource (human host, house, breeding site, etc.) while attracting or pulling them to a concentrated trapping or removal point (Cook *et al.* 2007). The concept of push-pull was developed in 1987 by Pyke *et al.* (1987) for use in the agricultural industry, and used against cotton crop pest populations, in an attempt to decrease reliance on insecticides and developing resistance by luring insects away from crops and to a secondary resource in the area for the pest to attack in place of the protected resource (Pyke *et al.* 1987). Push-pull systems have since been used extensively in the agricultural arena with success and this has shown its potential to be incorporated into the control of medically important vector species. In relation to public health, several lab and field studies have been conducted to demonstrate the efficacy and functionality of push-pull strategies for vector control.

Mosquitoes are attracted by a mixture of chemical cues to locate sites for oviposition, mating, sugar foraging, and their preferred host when seeking a blood meal (Zwiebel and Takken 2004). Mosquitoes use a combination of visual cues, upwind flight, and olfactory stimuli to locate a host for blood-feeding (Takken and Knols 1999). A large body of research has been devoted to the identification of semiochemicals (in particular kairomones) that are released by human hosts in breath, sweat and skin emanations in an attempt to exploit them to our advantage in vector control strategies (Verhulst *et al.* 2010). Close range host-seeking behaviour is influenced by visual stimuli, heat and moisture (Hawkes *et al.* 2017), at medium range the metabolites of bacterial decomposition such as short chained carboxylic acids (Knols and De Jong 1996) with CO_2 activating and attracting mosquitoes over long range at distances up to 70 m away (Gillies and Wilkes 1968). Humans differ in their level of attractiveness to mosquitoes (Mukabana *et al.* 2002) based on the specific mixture of emanations that they exude, which is mediated by metabolites released by skin bacteria (Verhulst *et al.* 2010) as well as infection with malaria (De Boer *et al.* 2017). Whilst foraging for a resource, an insect roams throughout the landscape and exhibits non-directional movement termed kinesis (White 2007). Once an insect detects a sufficient concentration of behaviourally-active odour, it exhibits taxis, directional orientation towards an attractive stimulus (positive taxis) or away from a repellent stimulus (negative taxis) (White 2007). A simplified and quantitatively tractable description of the full host-seeking cycle was described by Okumu *et al.* (2010) and used to assess potential impacts of odour-baited mosquito traps in different epidemiological and ecological scenarios in Africa (Okumu *et al.* 2010). The process was depicted deterministically as consisting of two sequential phases, i.e. an initial phase of non-host oriented kinesis, during which the vectors are in random flight paths before they encounter or detect any cues, followed by a phase of host oriented taxis, when the mosquitoes have detected the host cues and move directionally towards the source of those cues, towards the host. In order for a lure to be practical it must be perceived by a high proportion of target insects in the zone of deployment and be able to outcompete natural sources of attraction (El-Sayed *et al.* 2006, Miller *et al.* 2010). By increasing the distance over which the lure may be perceived and elicit a response – the range of stimulation (Wall and Perry 1987) – the probability of an insect encountering a lure is increased (Byers 2009). This has been termed 'findability', and is important to maximise cumulative numbers of insects caught (Miller *et al.* 2010). Since most haematophagous insects feed on highly mobile and often dispersed hosts, they have developed the ability to detect odours from both short range (0-20 m) as well as long range (>20 m) (Gibson and Torr 1999).

Personal protective measures, such as topical repellents, prevent malaria (Hill *et al.* 2007) and effectively prevent outdoor-bites (Goodyer *et al.* 2010), but mosquitoes are not killed, and can move from protected to unprotected individuals (Maia *et al.* 2013). From a programmatic disease control perspective, where coverage of interventions is generally imperfect, movement of mosquitoes from protected to unprotected individuals is undesirable, and mosquito kill is preferable in order to protect both users and non-users of an intervention (Howard *et al.* 2000). Therefore, combining 'trap and lure' strategies that have been successful in the control of malaria (Homan *et al.* 2016) with a strategy to reduce human-vector contact inside of homes and in the peri-domestic space should be beneficial to control malaria (Menger *et al.* 2014) and dengue (Salazar *et al.* 2012).

Evidence for 'push' efficacy

The 'push' component typically consists of a spatial repellent, an active ingredient at sub-lethal level, that vaporises and disseminates into the surrounding environment to create a 'bite free space' (Achee *et al.* 2012). Several such active ingredients have been tested, and the most common are: volatile pyrethroid insecticides (d-allethrin, prallethrin, flumethrin, metofluthrin, transfluthrin, and meperfluthrin (Bibbs *et al.* 2018)), and botanicals or essential oils, such as catnip oil (Bernier *et al.* 2005), para-menthane-3,8-diol (PMD) and 1 delta-undecalactone (dUDL) (Menger *et al.* 2014), linalool (Kline *et al.* 2003). Other studies have been conducted to determine the most effective 'push' formulation strategies. Tainchum *et al.* (2013) evaluated repellent-treated fabric placed in the interior perimeter of experimental hut openings compared to placing irritant-treated fabric at preferred indoor resting locations, in hopes of exploiting the endophilic behaviour of *Ae. aegypti*. This study demonstrated that *Ae. aegypti* preferentially rest on dark surfaces which can influence spatial repellent treatment applications in push-pull efforts. Manda *et al.* (2013) tested various sub-lethal concentrations and treatment surface areas of pyrethroid insecticides, alphacypermethrin, lambda cyhalothrin, and deltamethrin in experimental hut trials located in both Peru and Thailand, suggesting that sub-lethal, focal applications of these insecticides has the potential to reduce human-vector contact inside treated homes (Manda *et al.* 2013). Other work with targeted application of pyrethroids involves application of transfluthrin push to the eaves of houses. In sub-Saharan Africa the primary vectors *An. gambiae* s.s., *Anopheles funestus* and *An. arabiensis* prefer to enter houses through the eaves (Lindsay and Snow 1988). Videography has shown that mosquitoes that passed through the eave spent more than 80% of the observed time within 30 cm of the eave (Spitzen *et al.* 2016). It is therefore an excellent place to apply spatial repellents. Five pyrethroid spatial repellents (prallethrin, flumethrin, metofluthrin, transfluthrin, and meperfluthrin) were evaluated in the laboratory setting for their efficacy against *Ae. albopictus*, *Ae. aegypti*, *Cx. quinquefasciatus*, and *An. quadrimaculatus* and found metofluthrin, transfluthrin, and meperfluthrin to be potential candidates for adulticidal spatial repellent activity (Bibbs *et al.* 2018). Swai *et al.* (2019) demonstrated that 1.5% transfluthrin-treated eave ribbons (33 g transfluthrin) provided an approximate 5 m of protection in semi-open shacks in rice farms, against indoor and outdoor biting *Anopheles*, *Culex*, and *Mansonia* species (Swai *et al.* 2019). Using higher doses of transfluthrin gives longer duration of effect and induces mortality among mosquitoes which may result in a community effect (Mwanga *et al.* 2019). Eave ribbons treated with 0.25 g/m^2 transfluthrin have recently been shown to offer protection for users (83% indoor and 62% outdoor) and with at least 80% community coverage, and non-users (57% indoor and 48% outdoor) against *Anopheles* mosquitoes in a semi-field study (Mmbando *et al.* 2019). This is the first study to test and demonstrate that employment of a push-only strategy can potentially offer community-wide protection and limit diversion to non-users, but these findings must be assessed in field trials to establish their validity. It should be noted that spatial repellents are under review at VCAG as a stand-alone intervention, as well as a component of push-pull strategies (WHO 2020b). A number of trials have demonstrated that transfluthrin or metofluthrin spatial repellents have public health impact, reducing malaria when delivered through mosquito coils (Hill *et al.* 2014, Syafruddin *et al.* 2014); reducing malaria (Syafruddin *et al.* 2020) and arboviruses (WHO 2020c) delivered through passive emanators.

Evidence for 'pull' efficacy

The 'pull' component functions to attract and concentrate vectors in another location to facilitate trapping and prevent return to the protected resource (Luntz 2003). Several traps have been developed for gravid mosquitoes that are under review by VCAG (WHO 2020b). However, push-pull systems use 'pull' components for host seeking mosquitoes that employ synthetic lures that mimic attractive human odours and excretions associated with a trapping and/or killing mechanism. Numerous odour combinations have been employed in laboratory and field trials that are excreted by humans or are bacterial metabolites of the human skin biome (Takken and Verhulst 2017). The most attractive compounds identified to date are lactic acid, ammonia, 3-methyl-1-butanol, 3-methyl-butanoic acid and tetradecanoic acid (Van Loon *et al.* 2015). It is important to note that the response of mosquitoes to these volatiles is enhanced by carbon dioxide (Van Loon *et al.* 2015). Considering the fact that the attractive radius 'findability' of traps as well as the attractiveness of blends used to attract mosquitoes are both enhanced by CO_2 (Van Loon *et al.* 2015), the ability to produce CO_2 for trapping at scale is a major limitation of this technology. There has been some progress with the identification of 2-butanone as a potential replacement for CO_2 in traps (Mburu *et al.* 2017, Turner *et al.* 2011). Furthermore, there are a wide array of traps that have been tested for adult host seeking mosquito collection, such as BG-Sentinels (BGS) with BG-lure and other blends (Visser *et al.* 2020), BG malaria trap (Mmbando *et al.* 2019), and Suna Trap (Hiscox *et al.* 2014). To complicate matters further, the positioning of the trap also seems to play a crucial role in the success of mosquito trapping strategies (Hiscox *et al.* 2014, Mmbando *et al.* 2019). Hawkes *et al.* (2017) demonstrated that the Host Decoy Trap (HDT), which use visual, thermal and olfactory stimuli, trapped approximately 10 times more *An. gambiae* that human landing catches (HLC), the current 'gold standard' trapping method, demonstrating its potential as a possible 'pull' for vector control interventions (Hawkes *et al.* 2017).

Push-pull system efficacy against Anopheles

In some areas push-pull may be mediated by the presence of livestock. Iwashita *et al.* (2014) explored the utility of 'zooprophylaxis' as a pull mechanism for *An. arabiensis*, *An. gambiae* s.s., and *An. funestus* s.s. species with ITNs as the push component of the system, in Kenya (Iwashita *et al.* 2014). For all three species ITNs reduced the probability of finding a blood fed mosquito and the presence of cattle reduced human feeding among *An. arabiensis,* but not *An. gambiae* s.s. or *An. funestus* s.s. In this case, cattle presence may act as a passive pull mechanism for malaria vectors in areas with high ITN coverage.

In Belize, Wagman *et al.* (2015) conducted a field trial in experimental huts against *An. albimanus* and *Anopheles vestitipennis* with a 'push' of transfluthrin-impregnated nylon strips and a 'pull' of CDC Miniature Light Traps baited with worn cotton socks to provide human odour (Wagman *et al.* 2015). The combined push-pull reduced mosquito house entry by 39% for *An. vestitipennis* and 54% for *An. albimanus*. The set-up increased the number of *An. vestitipennis* collected outdoor by

48% with no effect on *An*. *albimanus* compared to the pull-only setup, with a very similar result to using the push, transfluthrin spatial repellent, alone.

Verhulst *et al.* (2011) determined that in push-pull systems against *An*. *gambiae* s.s., a synthetic blend of the human foot bacterial volatiles of 3-methyl-1-butanol in the 'pull' and 2-phenylethanol as the 'push', showed great promise in laboratory and semi-field studies (Verhulst *et al.* 2011). This finding was further developed by Menger *et al.* (2014) in a semi-field trial against *An*. *gambiae* s.l. (Mbita strain) with the 'pull' of Mosquito Magnet X (MM-X) traps and a combination of CO_2 and nylon strips impregnated with 2.5% v/v ammonia, 85% w/w L-(+)-lactic acid, 0.00025 g/l tetradecanoic acid, 0.000001% v/v 3-methyl-1-butanol and 0.001% v/v butan-1-amine and the 'push' using MM-X traps hanging from experimental hut roofs with the suction turned off and repellents applied to identical nylon strips impregnated with para-menthane-3,8-diol (PMD), catnip oil, or delta-undecalacton (dUDL) (Menger *et al.* 2014). The design of this experiment was elegant, demonstrating the relative contributions of push-only, pull-only, and push-pull combination strategies that have been since replicated in several studies of push-pull. In this experiment, all treatment strategies significantly reduced the number of mosquitoes entering the experimental huts, and the dUDL push-pull producing the greatest reduction in mosquito house entry (95.5%)(Verhulst *et al.* 2011). While this study shows the promise of push-pull for *Anopheles* control and highlights potential attractants and repellents of interest, the specific strategy itself is not practical in rural settings

Menger *et al.* (2015) then went on to conduct a small-scale field trial of a push-pull system in western Kenya against malaria vectors using a 'push' of microencapsulated dUDL-impregnated fabric and a 'pull' MM-X trap with a five-compound attractant of synthetic human kairomones and CO_2 (Menger *et al.* 2015). All interventions (push-only, pull-only, and push-pull) resulted in a 50% reduction in home entry of *An*. *gambiae* s.l. and *An*. *funestus*. This study also modelled a large-scale implementation of this push-pull strategy, with 67% bed net coverage, and predicted significant reduction in entomological inoculation rate (EIR) with implementation of either push-only or pull-only, with the strongest reductions (up to 20-fold) in the push-pull combined method. However, while this trial showed efficacy against wild mosquito populations, the authors emphasise that a long-lasting spatial repellent impregnated in eave screens would provide a combined vapour repellent and physical barrier that would prove much more beneficial to vector control programmes. Menger *et al.* (2016) went on to look at the effect of an eave screening approach alongside the push-pull strategy, and found that with all *Anopheles* species tested, eave screening alone or in combination with a baited trap reduced mosquito house entry by 61-99%, with the addition of a repellent to be of limited beneficial value (Menger *et al.* 2016). The authors also observed the utility of odour baited traps for removal trapping of outdoor mosquitoes. This assessment proved to be correct after Homan *et al.* (2016) conducted a large step wedge trial using solar-powered odour-baited mosquito trapping systems (SMoTS) in Western Kenya. Among users of the system malaria prevalence measured by rapid diagnostic test was 23.7% (1,552 of 6,550 people), which was 29.8% (95% CI 20.9-38.0) lower than among non-users (prevalence 34.5%; 2,002 of 5,795 people).

Push-pull system efficacy against Aedes

There has been some success in luring *Aedes* to oviposition traps (ovitraps) that mimic their preferred breeding sites (Davis *et al.* 2016, Paz-Soldan *et al.* 2016, Sharp *et al.* 2019). Because *Ae. aegypti* is highly anthropophilic (Scott *et al.* 2000) it could be controlled through a lure that mimics a human host. Most push-pull strategies for *Ae. aegypti* have utilised the previously established

BG-Sentinel (BGS) (Biogents AG, Regensburg, Germany) mosquito trap for the capture of adult *Aedes* mosquitoes, which mimics human convection currents, provides an olfactory cue if used with a lure and a visual cue in its black and white contrast to attract the mosquito (Obermayr *et al.* 2012, Salazar *et al.* 2013). Salazar *et al.* (2012) performed a mark-release-recapture experiment with adult female *Ae. aegypti* in the semi-field setting in Thailand, using a BGS with a BG-Lure to determine the feasibility and efficacy of its use (Salazar *et al.* 2012). The study determined that *Ae. aegypti* mosquitoes were most likely to be host-seeking in the morning hours between 05:30 and 09:30 and that placement of at least 2 BGS traps in the peri-domestic space captured the highest number of mosquitoes, approximately 86% of those released, with the placement of 3 or 4 traps having little difference in effect. Salazar *et al.* (2013) conducted a similar experiment with the addition of a 'push' component consisting of DDT and transfluthrin treated fabric positioned on interior walls or metofluthrin mosquito coil and a BGS with lure for mosquito collection, demonstrating that this addition did not decrease the efficacy of the BGS as the trapping component (Salazar *et al.* 2013). In Tanzania, a semi-field evaluation of a push-pull system using a push of free standing transfluthrin passive emanators (FTPE) made from hessian strips treated with 5.25 g of transfluthrin active ingredient and a pull using Biogents-Lure (BGL) and carbon dioxide as a pull (Tambwe *et al.*, 2020). The BGL is a synthetic lure consisting of lactic acid, caproic acid and ammonium bicarbonate dispensed via granules. The efficacies of FTPE and BGS alone and in combination were evaluated by human landing catch. Two FTPE had a protective efficacy (PE) of 61.2% (95% confidence interval (CI): 52.2-69.9%) against the human landings of *Ae. aegypti*. The BGS did not significantly reduce mosquito landings; the PE was 2.1% (95% CI: -2.9-7.2%). The push-pull provided a PE of 64.5% (95% CI: 59.1-69.9%). However, there was no significant difference in the PE between the push-pull and the two FTPE against *Ae. aegypti* (P=0.30). The FTPE offered significant protection against *Ae. aegypti* at month three, with a PE of 46.4% (95% CI: 41.1-51.8%), but not at six months with a PE of 2.2% (95% CI: -9.0-14.0%).

Benefits of push-pull

Push-pull may be a useful addition to the vector control toolbox as it offers personal protection to individuals outside of sleeping hours and can be deployed where people sleep outdoors. Personal protective measures, such as topical repellents, prevent malaria (Hill *et al.* 2007, 2014) and effectively prevent outdoor-bites (Goodyer *et al.* 2010), but mosquitoes can move from protected to unprotected individuals (Maia *et al.* 2013). In addition, existing personal protection measures require frequent re-application and users forget to comply with the intervention, effectively negating its protection; thus, long-lasting tools with minimal need for behaviour change are preferred by users (Sangoro *et al.* 2014) and are essential to support the required scale of cost-effective coverage of any intervention. The push components tested in several studies have high efficacy lasting several months that will make them highly attractive to users. Furthermore, push-pull systems using solar power may give households substantial benefits beyond just vector control through providing power for a light and phone charging (Homan *et al.* 2016). Should a successful push-pull combination be developed it will improve protection in the immediate peridomestic spaces, and also in the community at large, presumably by offering the diverted mosquitoes an alternative pseudo-host option thus removing them completely from the transmission cycle.

Potential issues

Studies have found that some push-pull systems do not necessarily work through synergism but independently through their complementary functions when employed in parallel, as mosquitoes that are pushed away do not have an increased chance of being pulled to the trap (Mmbando *et al.* 2019), while others work synergistically (Menger *et al.* 2015). The result measured depends on the individual components used. At the moment the greatest limitation to push-pull systems is the need for CO_2 to attract mosquitoes. Most of the current trials have shown that push-pull strategy efficacy is primarily reliant upon the push unit, with most studies demonstrating only marginally improved efficacy with the addition of the pull unit. This finding could potentially be due to the size of these studies, while in large-scale field trials a level of community-protection may be observed amongst both users and non-users as was seen in the SolarMal trial where 'pull' units applied at community scale did reduce clinical malaria (Homan *et al.* 2016). However, further research into an improved 'pull' component is necessary alongside larger-scale field trials in varied geographic regions.

The future of push-pull

Active ingredients that are incorporated into push-pull strategies should not be dependent upon currently utilised classes of insecticides and further research into novel modes of action is warranted. The introduction of novel active ingredients to which there is no resistance can prove useful against resistant mosquito populations (WHO 2016b). Research has demonstrated that exposure to neurotoxic compounds, such as insecticides, can cause mosquitoes to rest or seek shelter (Cohnstaedt and Allan 2011), and thus the success of a push-pull system is contingent on the 'push' component not overly impeding the mosquito's ability to seek an alternative host or 'pull' component. Therefore, it is essential that the 'push' and 'pull' complement each other even if they are not working entirely in a synergistic relationship. Novel vector control interventions should be low-cost and easily applicable in a variety of settings, able to operate in synergy with current control methods and utilise novel, environmentally friendly active ingredients with different modes of action (Vontas *et al.* 2014). Push-pull systems can be deployed in the peri-domestic space and decrease mosquito population density, human-vector contact and, ultimately, pathogenesis potential. Additional research into this vector control strategy is necessary to realise it full potential, focusing on cost reduction of components and development of long-lasting attractants.

Conclusions

To incorporate new vector control interventions into national vector control programmes, it is essential that an integrated vector management strategy be employed. The current WHO-recommended core malaria vector control interventions, LLINs and IRS, have proven to be effective vector control measures following the increase in their implementation over the previous decades. However, these interventions primarily focus on endophilic vector populations, leaving a large protection gap in the peri-domestic space. Similarly, control of arboviruses through larval source management is often difficult to achieve so the implementation of tools that target the adult mosquito will be advantageous for sustained disease control. Furthermore, developing insecticide resistance, shifts in vector dominance, and behavioural changes only emphasises the need for novel IVM strategies. *Wolbachia* may fill some of these gaps, especially for arbovirus control and on the horizon are genetic manipulation strategies. In the meantime, ATSB and push-pull systems which exploit the sugar- and host-seeking behaviours of mosquitoes show promise as new vector control interventions. They may be more socially acceptable and easy to deploy than genetic manipulation or large-scale larval source management. They require lower human compliance than interventions, such as topical repellents or LLINs, and show promise for their future employment in peri-domestic spaces and possibly for use by mobile populations. Several large community-based trials are ongoing to evaluate ATSB, to demonstrate the public health impact, which is required for WHO approval and full realisation of the potential impact of these control strategies in controlling disease vectors. Scale up of push-pull is not yet on the horizon although it is a vibrant area of research.

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7. Mass mosquito trapping for malaria control: past successes and future directions

Alexandra Hiscox[1,2] and Willem Takken[2]*
[1]ARCTEC, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom; [2]Laboratory of Entomology, Wageningen University & Research, P.O. Box 16, 6700 AA Wageningen, the Netherlands; alexandra.hiscox@lshtm.ac.uk

Abstract

In the context of increasing levels of insecticide resistance, changes in mosquito biting behaviour and drug resistant malaria parasites, mass mosquito trapping for malaria control forms a promising tool to complement long-lasting insecticide-treated nets and indoor residual spraying. Laboratory studies led to the development of synthetic odour baits to lure host-seeking mosquitoes, and these baits have been incorporated into odour-baited trapping systems which have been evaluated under semi-field and field conditions in East Africa. On Rusinga Island, western Kenya, the first ever field evaluation of mass mosquito trapping for malaria control took place between 2012 and 2015. The results showed that mass trapping is associated with reductions in *Anopheles funestus* populations of 70% corresponded with a 30% reduction in malaria cases among people living in households with the trapping systems, compared to people living in households yet to receive traps. The success of this intervention leads to questions about the next steps in trap development and the feasibility of using traps in a malaria control or elimination context. Development of next generation traps which are cheaper, more durable and require less user-maintenance would take this technology one step closer to a policy recommendation. Adaptation of odour baits and traps to attract malaria vectors in other regions would be advantageous. Combining solar-powered traps with rural electrification programmes forms a promising pathway for the distribution of trapping systems, and expanding the scope of the intervention to include a spatial repellent in a push-pull set-up could increase the efficacy of traps and the degree of personal protection provided. Learning from past successes in mass trapping for vector control leads to exciting prospects.

Keywords: *Anopheles*, malaria, mass trapping, mosquito, odour-baited trap, vector control

Introduction

The need for innovative vector control tools

New, innovative vector control tools are required to alleviate pressure on the use of insecticides in regions where mosquitoes are developing, or are already highly resistant, to insecticides. In an era of a renewed drive toward malaria eradication new tools are essential to target malaria vectors which feed outdoors as well as during the early evening and morning hours. In these settings, long-lasting insecticidal nets (LLINs) and indoor residual spraying do not provide complete protection against mosquito bites.

Innovative vector control tools should be capable of controlling mosquitoes of more than one genus, providing a more efficient use of limited resources. Recent and ongoing outbreaks of dengue, yellow fever and Zika, as well as concerns about newly emerging vector-borne diseases

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encourage the development of tools to control anopheline and culicine mosquitoes in both urban and rural environments.

The concept of mass trapping for vector control

Mass trapping is the principle by which daily removal trapping of a disease vector, such as the malaria vector *Anopheles gambiae s.s.*, leads to a gradual reduction in vector population size and a corresponding reduction in biting pressure. Fewer bites lead to fewer opportunities for transmission and an eventual reduction in disease. The concept of mass trapping to control a vector-borne disease is not in itself new. Control of Human African trypanosomiasis and cattle trypanosomiasis in countries of sub-Saharan Africa, including Zimbabwe, Uganda and Kenya (Kuzoe and Schofield 2004), was achieved through suppression of tsetse populations using insecticide-treated traps and targets, together with insecticide-treatment of cattle and the sterile insect technique. Daily removal of a portion of the adult tsetse population led to reductions in tsetse populations of over 98% in only one month in Mali (UCLT 2004), 99% after 4 months in Uganda (Lancien 1991) and up to 99.7% over 8 months in Côte d'Ivoire (Laveissière *et al.* 1986).

Control of tsetse flies using traps and targets proved effective due to the low reproductive rate of the fly, as well as the ability to attract flies using low-cost, coloured targets which could be deployed by members of the local population with a good knowledge of tsetse locations. Applying the same approach to mosquitoes is a more complex challenge, but models (Okumu *et al.* 2010) have indicated that under the right conditions, using odour-baited traps, mass trapping could be feasible. Okumu and colleagues predicted that traps could be effective if they were used to complement, not replace, existing methods such as LLINs. The traps would need to be attractive to a wide range of malaria vectors, and models indicated that the traps would need to be more attractive than humans (Okumu *et al.* 2010). This could be achieved through; the use of highly attractive odour baits, by positioning traps so that they are more available than a human host (strategic positioning), and by reducing the availability of humans through the use of LLINs. By daily removal trapping of mosquitoes, vector density would be reduced, leading to lower biting rates and a decline in EIR and disease transmission.

The development of odour-baited traps for malaria vector control

To design an effective trap for mass trapping of host-seeking malaria vectors, a strong basis in fundamental research was required. Over recent decades, a combination of laboratory, semi-field and field studies have increased our understanding of mosquito host-seeking behaviour and an overview of these studies is made below. Advances in molecular biology, gas chromatography mass spectrophotometry (GC-MS) and electroantennography (EAG) have supplemented data gathered during bioassays to build a picture of how malaria vectors find their human hosts (Verhulst *et al.* 2009). It is now well understood that mosquitoes are attracted to their hosts by a combination of carbon dioxide, odour cues and heat from the body (McMeniman *et al.* 2014, Spitzen *et al.* 2013, Van Breugel *et al.* 2015). The specific composition and concentration of these odours and CO_2 varies between host species as well as between individuals of the same species (Verhulst *et al.* 2010). Identification of an optimal blend of attractants which is at least as attractive as a human, and recreation of this blend in a universally attractive synthetic lure could provide a means of attracting mosquitoes to traps for the purposes of mass trapping for malaria control.

Development of a synthetic odour-bait to lure malaria vectors

The discovery of CO_2 as a universal mosquito flight activator and attractant (Van Thiel and Weurman 1947) was followed by the later discovery of a range of other attractants; lactic acid, ammonia, acetone, carboxylic acids, 1-octen-3-ol, 3-methyl-1-butanol and butan-1-amine (Acree *et al.* 1968, Braks *et al.* 2001, Knols *et al.* 1997, Mukabana *et al.* 2012, Smallegange *et al.* 2005, 2009, Takken *et al.* 1997, Van Loon *et al.* 2015). The identification of individual attractants created a basis for the development of a synthetic odour bait which combined different chemicals at the most appropriate concentrations for host-seeking malaria vectors, in particular members of the *An. gambiae* and *Anopheles funestus* complexes. Under laboratory conditions, a high-throughput bioassay screening of attractive odours at varying concentrations, and in different combinations, led to the development of a five-component attractive blend of odours, named the Mbita-5 blend (MB5) (Menger *et al.* 2014). This blend was taken forward as the lure in odour-baited traps for trapping of *An. gambiae* s.l.

Tests using a 10-component bait (the Ifakara blend, IB1) showed that the bait could attract *An. gambiae* consistently for a year under semi-field conditions when a single lure was used overnight, once per week for 52 weeks. Between uses the lures were stored at 4 °C. The duration of attraction is thought to be due to colonisation of the baited nylon strips with bacteria and release of bacterial volatiles which were attractive to mosquitoes (Mweresa *et al.* 2015).

Laboratory screening of *Anopheles coluzzii* responses to the MB5 blend demonstrated that CO_2 played a vital role in attraction of malaria vectors (Van Loon *et al.* 2015). While the use of CO_2 to supplement an odour blend is a straightforward process in the laboratory, taking the odour blend to the field required a CO_2 source that was readily available under field conditions. Work by Smallegange and Mweresa (Mweresa *et al.* 2014, Smallegange *et al.* 2010) demonstrated that fermentation of sugar or molasses by yeast could provide a cheap and readily available source of CO_2 for small-scale use in trapping for monitoring purposes. Mass trapping would require the deployment and daily use of thousands of mosquito traps. Under this scenario, the use of CO_2 produced by fermentation would no longer be feasible due to the cost of raw ingredients, need for daily replenishment and a requirement for disposal of the by-products of this fermentation.

During electrophysiology screening experiments to identify chemicals capable of eliciting prolonged activation of CO_2-sensing neurons, Turner *et al.* (2011) discovered that 2-butanone is a dose-dependent activator of the cpA neuron in species of three genera (*An. gambiae, Aedes aegypti* and *Culex quinquefasciatus*). In this study, the temporal pattern of cpA neuron activation was indistinguishable from the pattern elicited by CO_2.

Under semi-field and field conditions in Kenya, Mburu compared attraction of *Anopheles arabiensis* and *An. gambiae s.s.* mosquitoes to traps containing the MB5 blend supplemented with CO_2 and with 2-butanone. Under semi-field conditions where traps were in relatively close proximity to one another the blend supplemented with CO_2 was more attractive than the blend supplemented with 2-butanone. However, inside separate houses under field conditions, Mburu found that traps containing the MB5 blend and 2-butanone were equally attractive to *An. gambiae* s.l., *An. funestus* and *Culex* species as traps containing MB5 plus CO_2. These results suggested that 2-butanone could form a suitable replacement for CO_2 under field conditions.

Specification for an odour-baited trap for mass mosquito trapping

With the development of a synthetic human odour mimic and a viable replacement for CO_2 in the field, focus shifted to the development of an odour-baited trapping system for use in large-scale trials to measure the effectiveness of mass mosquito trapping for malaria control. An ideal odour-baited trap would capture vector mosquitoes while not being attractive to non-target organisms. It would require minimal user-interaction, be robust enough to withstand continuous exposure to heat, rain, humidity and dust, should not require a power source to disseminate the odour lure or trap the mosquitoes that enter, should be insecticide-free and available at low-cost.

The evaluation of mass mosquito trapping for malaria control

Between 2012 and 2015 the first field trial to evaluate the impact of mass mosquito trapping for malaria control took place on Rusinga Island, western Kenya. The study (SolarMal) deployed the newly developed Suna trap (Hiscox *et al.* 2014) baited with the MB5 bait plus 2-butanone to over 4,000 households (a population of 25,000 people) and measured clinical incidence, malaria parasite prevalence, mosquito densities and social acceptance as outcomes (Hiscox *et al.* 2016). Data from intervened areas were compared against areas with only the national malaria control programme strategy in place (LLINs and case management). The Suna trap was selected for this study as it was more robust than existing odour baited traps (e.g. the MM-X trap which is not UV-resistant) and could be readily baited with an odour lure for use outdoors, unlike the CDC light trap which is designed to be positioned beside a human host sleeping beneath a bed net.

New tools require new study designs; a stepped-wedge cluster-randomised trial

This novel approach to malaria control required a new approach to study design in order to measure the impact of the intervention. It was anticipated that trapping would have the greatest impact when traps were rolled out to all households on Rusinga Island (measuring approx. 44 km^2). However, there was a need to maintain a contemporaneous control to adjust for the effect of seasonality on parasitological and entomological outcomes in the analysis. A stepped-wedge study design was modified to allow for clustering of the intervention over mosquito flight distances so that the final study employed a stepped-wedge cluster-randomised study design (Silkey *et al.* 2016). In this approach the intervention was rolled-out to nine clusters, of approximately 450 households each. The order of the roll-out was drawn from nine randomised sequences during a community ballot held on the island (Oria *et al.* 2014). From mid-2013 until mid-2015, mosquito traps were installed at a rate of around 50 households per week until all households on the island had received the intervention.

Outcome data were collected through a system of health- and demographic surveillance (HDSS) (Homan *et al.* 2015), where all households on the island were visited three times per year by trained data collectors using an electronic data-capture system. During household visits, members of the households were asked whether they had experienced fever during the two weeks, and during the two days prior to the visit and whether they were experiencing fever at the time of the visit. If the study participant reported fever at any of these times, an in-ear measure of body temperature was taken and anyone experiencing fever was tested for malaria using a rapid diagnostic test (RDT). Those scoring positive were recorded as suffering from clinical malaria and provided with appropriate treatment. Malaria parasite prevalence surveys were conducted in a randomly selected 10% of the population three times per year, with participants tested for malaria using RDTs irrespective of symptoms. Mosquito surveillance took place on a rolling basis in random samples of 80 households, randomly selected from the study population at the start of each round of surveillance. Mosquitoes were sampled from inside and outside each household using MM-X traps baited with the MB5 blend plus CO_2 produced through yeast and molasses fermentation. Suna traps were not used for monitoring because baseline data collection commenced prior to the production of the first batch of Suna traps. Sociological outcomes, including existing knowledge, attitudes and practices towards malaria control, as well as reactions to the new SMoTS technology, were recorded through in-depth interviews and focus group discussions.

Rural electrification and power supplies for mosquito traps

The ideal specifications for a mosquito trap included a trap without a requirement for power. To-date an effective power-free trap for luring host-seeking mosquitoes has yet to be developed. During the Rusinga trial, Suna traps required a source of electricity to power a fan inside the trap. This fan created a counter-current airflow which facilitated the release and spread of attractive odours from the bait in to the environment and an in-flow of air to draw host-seeking mosquitoes in to the trap once they came within range of the inlet funnel. Use of these traps in a rural environment required the development of an innovative solution to providing power – the solar-powered mosquito trapping system (SMoTS) (Figure 1).

Each SMoTS consisted of one odour-baited Suna trap suspended immediately outside the house, with the fan section 30 cm above ground level (Hiscox *et al.* 2014). The trap was powered using solar energy generated by a 20 Watt-peak solar panel on the roof of the house, supplying a 12-volt battery inside the house. In addition to powering the Suna trap, each solar powered system provided a source of electricity for two indoor LED lights and a mobile phone charging point (Oria *et al.* 2015). All households were encouraged to continue using LLINs provided to them through national distribution programmes.

Results of the study

Over the course of the intervention period parasitological and entomological findings were recorded. The results of a contemporaneous analysis revealed that populations of *An. funestus*, the major malaria vector on Rusinga Island, were reduced by 69% in areas with SMoTS (intervened) compared to areas of the island which were yet to receive the SMoTS (not yet intervened) (Homan *et al.* 2016). Populations of *Culex* mosquitoes were 34% lower in intervened areas over the course

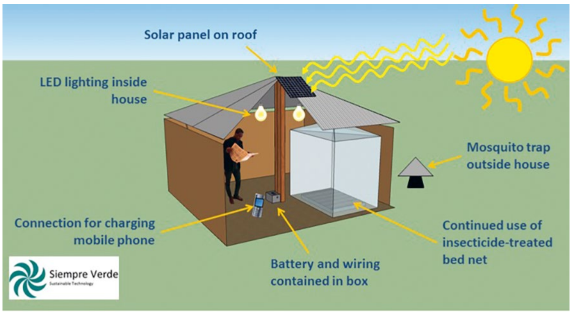

Figure 1. Diagram of a solar-powered mosquito trapping system (SMoTS) installed in a house with a long-lasting insecticidal net. Figure reproduced from Oria et al. *(2014).*

of the intervention period. *An. gambiae sensu stricto* and *An. arabiensis* populations were low throughout the trial and an effect of the intervention was not observed for the *An. gambiae* complex.

During the intervention period a total of 23 clinical malaria cases were recorded in clusters with SMoTS and 33 cases were recorded in clusters yet to receive SMoTS. With wide confidence intervals, this difference in the number of cases was not significantly different. A contemporaneous comparison of malaria parasite prevalence (recorded by RDT in cross-sectional surveys and not based on reported symptoms) showed a statistically significant 30% reduction in the prevalence of malaria parasites among people living in households with SMoTS (n=6,550 participants, prevalence 23.7%) compared to those living in households which were yet to receive SMoTS (n=5,795 participants, prevalence 34.6%, 95% CI for effect size = 20.9-38.0%, P<0.001). The overall conclusion of the study was that mass mosquito trapping using solar-powered mosquito trapping systems could be effective in reducing malaria vector populations and malaria prevalence (Homan *et al.* 2016).

Semi-structured questionnaires were used to guide interviews in 24 households where SMoTS had already been installed for six months at the time of the interview. The respondents indicated that indoor electrical lighting was a strong motivator for using the system and that the lighting reduced or eliminated expenditure on kerosene (Oria *et al.* 2015). Household visits, including observations of whether traps were well maintained and functioning, suggested that only one third of those responding were regularly maintaining their trap, but 6 of 24 respondents did report that they no longer heard sounds of mosquitoes in their home. Further evidence of the perceived benefits of lighting and emphasis placed on this asset were seen in requests for technical assistance in maintaining/ repairing the systems. Faults with lighting were most commonly reported, and faults with traps were under-reported.

The Rusinga Island study concluded with one round of surveillance at complete intervention coverage, at which point there was no longer a contemporaneous control for measurement of intervention impact. It was therefore not possible for the researchers to determine whether mosquito populations and malaria transmission continued to decline over time with subsequent months of island-wide intervention coverage.

Future directions

Development of odour baits and trapping systems for surveillance and control

From the laboratory to the field, substantial progress has been made in the development of synthetic lures and odour-baited traps for trapping of host-seeking malaria vectors. The Rusinga Island study demonstrated for the first time that mass trapping can lead to reductions in mosquito populations and malaria prevalence, but research and product development continues to improve on the approach.

Prior to the field trial, preliminary experiments were conducted to optimise the placement of odour-baited traps outside houses above ground level (Hiscox *et al.* 2014) but subsequent research is increasing our understanding of mosquito flight patterns around houses and traps. Through 3D flight tracking, we now understand more about the way in which a mosquito approaches a house with an open eave (Spitzen *et al.* 2017) and a trap (Cribellier *et al.* 2018) and how we can use this knowledge to strategically orient and position traps in the domestic environment to increase mosquito responses and trapping efficiency. In addition, this knowledge can be used to modify house design and/or trap design. Models of mosquito flight paths and host-seeking behaviour suggest that targeted positioning of odour-baited traps by placing them between breeding sites and houses could lead to interception of mosquitoes before they reach people (Okumu *et al.* 2010) but these theories must be tested in the field.

A critical element on the pathway to the development of a trap that can compete with the odour of a human, is the identification of an effective replacement for CO_2. While 2-butanone was effective under field conditions in Kenya (Mburu *et al.* 2017), in short-range experiments under semi-field conditions, trap capture rates were significantly higher for traps using CO_2. For wide-scale adoption of traps for mosquito control there is also a need to increase the longevity of odour baits so that they need less frequent replacement. During the Rusinga study, data was not captured on the longevity of odour baits and further studies are needed. Frequent bait replacement requires behaviour change and leads to increased supply-chain complexity and additional distribution costs. Universal baits should be developed for a range of malaria vectors, including those which are currently regarded as secondary vector species. Malaria eradication will require control of these species which are responsible for outdoor as was as early evening and early morning transmission.

It is recognised that malaria eradication will require substantial financial investment and that the cost of malaria elimination is likely to be greater than the routine cost of control, though the ultimate gains of elimination should outweigh the cost (Patouillard *et al.* 2017, Shretta *et al.* 2016). In order for traps to be incorporated into policy recommendations, and for mass trapping to be integrated with national malaria control programmes, traps must become more cost-effective. Substantial savings could be made through scaled up mass production of traps and through the development of trapping systems which do not require an external power source. However, it is important to note that the Rusinga study provided evidence that motivation for adherence to the use of trapping systems may derive from value placed on household electrification.

As well as the development of trapping systems for the removal of host-seeking malaria vectors, the past decade has seen a renewed interest in the development of traps for mosquito monitoring and surveillance. New monitoring traps aim to replace the human landing catch with a standardised, odour-baited trap. The Microsoft Premonition project includes exciting developments in this field, with the invention of so called 'robotic field biologists' capable of trapping only a specific species of interest based on wing-beat frequencies (Microsoft News Center 2016). The use of infrared technology by Biogents AG, Regensburg, Germany, has enabled traps to be fitted with sensors to detect individual mosquitoes entering a trap and to identify the species, with data uploaded to the cloud in real-time for immediate analysis (Biogents AG). Further adaptations to a trapping system could be made through the use of additional cues, including sound (Johnson *et al.* 2018), heat (Abong'o *et al.* 2018, Hawkes *et al.*, 2017, Zhou *et al.* 2018), light (Hiscox *et al.* 2014, Mwanga *et al.* 2019) or other visual stimuli (Abong'o *et al.* 2018), and the next generation of mosquito traps should consider incorporating these elements. Advances in 3-D printing technology are also an exciting leap forward in our ability to create and quickly test trap prototypes. 3-D printing technology could also provide a means to create and produce traps locally at lower cost compared to large-scale factory manufacture (Hoshi *et al.* 2019). For any of these newly developed traps to be useful for mass trapping, the cost of production, distribution and maintenance should be low, reliance on an external power supply should be minimised and odour blends should be universally attractive and long-lasting.

Combining traps with spatial repellents (push-pull)

The effect of an odour-baited trap requires mosquitoes to enter the trap at some point in their lifecycle, preferably before biting a host. The likelihood of mosquito capture can be increased through developments to the trap as described above (e.g. more attractive bait, additional cues). But attraction to a trap could also be increased by reducing the relative availability of human hosts. In the Rusinga study the relative availability of human hosts was reduced through the continued use of LLINs by study participants. Alternate approaches to reducing host availability using spatial repellents are under development. Push-pull refers to the combined use of a repellent to 'push' mosquitoes away from a host species and a trap to 'pull' them away from the preferred host and remove them from the environment. While both single interventions should offer protection against bites, the hope is that a combination of these two tools would lead to a synergistic effect whereby trapping efficacy is greater when used in combination with a spatial repellent than when used in isolation. The push-pull approach has been extremely successful for the control of agricultural pests (Khan *et al.* 2008, 2014) and studies in Kenya and Tanzania have demonstrated that this approach can be effective for malaria vectors too (Menger *et al.* 2014, 2015, 2016, Mmbando *et al.* 2017, 2019).

Odour-baited traps for malaria vectors outside sub-Saharan Africa

Outside of sub-Saharan Africa there is limited evidence for the development or testing of lures designed specifically for host-seeking malaria vectors. Experiments using odour-baited traps have largely been conducted to compare trap performance for monitoring purposes. In the Southwest Pacific, Van de Straat *et al.* (2019) evaluated the MB5 blend, BG lure and a human-worn sock in traps for monitoring of *Anopheles farauti*. It was concluded that fan-powered traps including CO_2 could be an effective tool for monitoring of this species group, but that odour-baits would need to be tailored to the target species (Van de Straat *et al.* 2019). In Suriname a combination of CO_2 plus a synthetic lure (MB5 or BG lure) in fan-powered traps was effective in capturing *Aedes aegypti* and *Culex* mosquitoes (Visser *et al.* 2020). In Southeast Asia, Tangena *et al.* (2015) compared a range of odour-baited traps against human landing catches for monitoring of host-seeking mosquitoes in rural villages. In this setting mean catch sizes of *Aedes, Anopheles* and *Culex* mosquitoes were substantially lower in battery-powered traps (CDC light trap with worn sock, Biogents sentinel trap with BG lure and Suna trap with MB5 blend) compared with humans in a human landing catch or human-baited double-net trap (Tangena *et al.* 2015). Further investigation is needed to estimate the potential for mass trapping of malaria vectors in South America, Southeast Asia and the Southwest Pacific. Whether mass trapping is a viable option will depend on a range of factors including; the availability of a lure and trap to capture the locally important malaria vectors, the location of biting (e.g. mass trapping for control may not be feasible where malaria infections are most commonly acquired in the forest). Mass trapping is most likely to be effective in areas where there are one or two key malaria vectors and the behaviour of these mosquitoes is predominantly anthropophilic. In areas where a range of different species are important for malaria transmission and where vectors exhibit a range of host preferences, lures and traps would need to be universally attractive.

Scale-up of mass trapping

It is vital that the investment in the development of trapping systems in the lab and under semi-field and field conditions is conducted with parallel consideration of how systems could be scaled up and incorporated in to control programmes. Trapping systems should be cost-effective and durable, and consideration should be given to distribution models for this type of approach. Should mass trapping be considered as a top-down, government-led intervention, or would incorporation with rural electrification permit a hybrid model whereby end-users could contribute to the cost of systems?

Conclusions

Mass trapping for mosquito control is a promising tool for use in specific settings where vectors are attracted to the lures and trapping systems used and where existing tools (e.g. LLINs, indoor residual spraying (IRS)) are already rolled-out to maximum coverage. Trapping could be used to complement existing tools such as LLINs and IRS but further developments of trapping systems to reduce costs and increase performance are necessary before this approach is scaled-up.

Mass mosquito trapping is an excellent example of the type of framework outlined by the Global Vector Control Response (GVCR) (WHO 2017). Mass mosquito trapping programmes include the foundational elements of the GVCR by increasing basic- and applied research and innovation, as well as enhancing vector control and capacity. Programmes such as the Rusinga study are a good example of strengthening inter-and intra-sectoral action and collaboration as well as engagement with communities. Traps developed for control should also form tools that can be used for enhancing vector surveillance and monitoring of interventions and we encourage discussions between academia, industry, non-governmental and governmental agencies to scale-up and integrate trapping with existing approaches as well as new approaches under development. The hope is that mass trapping will eventually become integrated with national control programmes as an effective, locally adapted and sustainable tool for vector control.

Ethics

This chapter describes the findings of published work for which the appropriate ethical approvals were obtained.

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8. Larval source management for malaria control: prospects for new technologies and community involvement

Constantianus J.M. Koenraadt
Laboratory of Entomology, Wageningen University & Research, P.O. Box 16, 6700 AA Wageningen, the Netherlands; sander.koenraadt@wur.nl

Abstract

Tackling the aquatic stages of anopheline malaria vectors is a key element in integrated vector management (IVM) programmes. The first large trials with *Bacillus thuringiensis* var. *israelensis* (*Bti*) as a novel biological control agent demonstrated that its impact can be highly effective, but context dependent. To better understand this dependency, there is a need to answer fundamental questions on mosquito larval ecology. At the same time, new technologies enter the stage, e.g. drones for delivery of *Bti* and approaches with genetically modified (GM) mosquitoes, that can aid field control operations. Such developments are promising, but any larval source management (LSM) programme also needs the involvement of communities from the very start in order to implement sustainable programmes. In this chapter, progress in answering fundamental questions on larval ecology is reviewed and recent examples that specifically aimed to assess the feasibility of involving communities in IVM programs for malaria control are discussed.

Keywords: larval source management, vector control, community engagement, malaria

Background and rationale

Despite tremendous efforts to curb malaria morbidity and mortality, further progress in malaria control has slowed down recently, and new tools are needed to help reduce the impact of this debilitating disease. Both long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) have been the mainstay in vector control efforts (Bhatt *et al.* 2015), but insecticide resistance and the slow market entry of new formulations have hampered further progress (Hemingway 2018). In addition to resistance, also the implementation of LLIN programmes presents major challenges. Over the years, it has become clear that community engagement strategies play an essential role in the roll-out and scale-up of interventions. Although there is large variation by country, the World Health Organization currently estimates LLIN coverage, i.e. the proportion of households owning at least one LLIN, at 72%. However, this does not imply that all household members have access to a net, because only 40% of the households in sub-Saharan Africa have sufficient nets for all occupants (WHO 2019). In other words, possession of a net does not guarantee its actual use, and multiple studies have in fact reported on the improper use and even misuse of nets (Eisele *et al.* 2011, Minakawa *et al.* 2008, Okumu 2020). In such a case, it is essential that effective communication messages are delivered so that people understand why they should use a net and how to properly install it for protection at night.

Although insecticide-based approaches are the core of the current global malaria control efforts, alternative approaches are needed that tackle the resistance problem and that offer more sustainable solutions (Hemingway 2017, Koenraadt and Takken 2018, McGraw and O'Neill 2013). Several tools and technologies are available for this in our toolbox (Takken and Knols 2009, Williams *et al.* 2018). Whereas some of them, such as house screening, already have a longer history of proven efficacy (Kirby *et al.* 2009, Lindsay *et al.* 2002), others are relatively new and are still undergoing evaluation of their epidemiological impact, such as odour-based removal trapping of adult malaria vectors and genetic modification to replace malaria vector populations with strains that are refractory to the malaria parasite (Alphey *et al.* 2002, Homan *et al.* 2016, McGraw and O'Neill 2013). All the above described strategies target the adult stages of the malaria vector and do not take the source of malaria vectors into account. There is great potential to also include the management of larval sources in vector control programs. Besides the fact that there is a need to quantify the epidemiological impact of larval vector control (Williams *et al.* 2018), there is also a need to evaluate how communities can be involved in such programs, as many of the larval breeding sites can be found in the peri-domestic environment or are the result of agricultural activities, such as drainage and irrigation (Killeen *et al.* 2002, Mukabana *et al.* 2006).

Larval source management involves the manipulation, alteration or management of water sources that could harbour the immature, aquatic stages of malaria vectors. Central to this concept is the fact that control takes place at the earliest life stage possible and, in this way, it contributes to the reduction of adult vector populations. Moreover, in their adult stage, disease vectors display a variety of behaviours, such as indoor versus outdoor feeding and resting. Also, host feeding preferences vary widely, which leads to a wide diversity of niches that mosquito vectors occupy. As a result, conventional control tools may not always affect the adult mosquito, and control efforts aimed at the adult stages may thus be jeopardised. For example, indoor residual spraying affects those mosquitoes that feed and/or rest inside, whereas outdoor feeding mosquitoes are missed and will still be able to sustain malaria transmission (Sherrard-Smith *et al.* 2019).

As control of the larval breeding sites is indiscriminate of the feeding and resting behaviours of the adult forms later in life, it would thus ensure that vector populations are reduced in both the indoor and the outdoor environment, thereby contributing to more efficient malaria elimination efforts. Recently, some interesting insights in the genetic make-up and diversity of larval versus adult *Anopheles gambiae s.s.* have been obtained that support this notion. Riehle *et al.* (2011) noted that the genetic composition of larval *An. gambiae s.s.* populations, based on unbiased sampling of larval habitats, was different from the genetic composition of adult *An. gambiae s.s.* collected indoors. Clearly, a genetic sub-group existed that was represented in the larval stage, but that was absent in the indoor sampled adult mosquitoes. This suggested that this subgroup is exophilic and not captured with conventional indoor trapping techniques. Further isolation of this exophilic sub-group (named GOUNDRY) revealed that it is actually more susceptible to *Plasmodium falciparum* infection than its endophilic counterpart (the ENDO subgroup of *An. gambiae s.s.*). These genetic complexities are a good example of how vector population dynamics may complicate efforts to control malaria, but also demonstrate the added value that larval source management may have in terms of the selective pressures that it has in comparison with adult vector control (Crawford *et al.* 2016).

Fundamental aspects of larval ecology of malaria vectors

For successful implementation of larval control programmes, it is essential to have a thorough understanding of ecological factors that affect the development and survival of malaria mosquito larvae in their aquatic habitats. Of the 462 formally named species belonging to the *Anopheles* genus, approximately 70 are actually involved in the transmission of malaria (Hay *et al.* 2010, Massey *et al.* 2016). Larvae of these anopheline species can be found in a wide diversity of habitats, ranging from small, temporary pools and puddles to large, more permanent water bodies. Some of these sites can be fully exposed to the sun, e.g. sites in which *Anopheles coluzzii* breeds in Africa, whereas other malaria vector species prefer forested, and hence more shaded sites, e.g. *Anopheles dirus* in Asia. The aquatic life cycle of all these species starts when a gravid female mosquito deposits her eggs on or very near the water (Minakawa *et al.* 2001).

Various cues originating from the aquatic habitat play a role in the detection and subsequent selection of the site for oviposition. These include visual cues, e.g. site tone, as well as chemical cues, i.e. volatile infochemicals (Blackwell and Johnson 2000, McCrae 1984). Some of these chemical cues are likely to have a bacterial origin, and may hence indicate the suitability of the site in terms of bacterial food availability for the developing offspring (Sumba *et al.* 2004). One particular volatile compound derived from water infused with soil from a natural breeding site that shows strong attraction towards gravid female mosquitoes is cedrol (Lindh *et al.* 2015). Both in a laboratory and in a field setting, this compound elicited strong egg laying responses from gravid female *An. gambiae s.s.*. Other cues may emanate from conspecific larvae already present in the breeding habitat, and these can either have an attracting or a repelling effect. Recently, it has been established that two volatiles, nonane and 2,4-pentanedione, are released by early stage *An. coluzzii* larvae, and these volatiles may indicate the suitability of the site for development of the offspring of the ovipositing female (Schoelitsz *et al.* 2020). The same study reported that the presence of conspecific, late stage (fourth instar) larvae was associated with the release of two repellent volatile compounds, dimethyl disulfide and dimethyl trisulfide (Schoelitsz *et al.* 2020). These compounds may signal a predation risk to the gravid female, because it is known that older *An. coluzzii* larvae can cannibalise on their younger conspecifics or negatively affect their development rate. These effects seem to be mostly mediated by limitations in food and space for the larvae (Koenraadt and Takken 2003, Koenraadt *et al.* 2004).

Once eggs have been deposited, they may face conditions that are detrimental to their survival and development, such as prolonged drought which causes dehydration, or intense rains which results in the flushing of eggs. In comparison with other mosquito genera, in particular *Aedes*, the eggs of *Anopheles* have a limited capability to survive dry periods. For eggs of *An. gambiae* s.l. this has been estimated at 12-16 days (Beier *et al.* 1990, Holstein 1954). Interestingly, if eggs are not directly floating on the water surface, but are rather stuck on the wet mud surrounding an aquatic habitat as a result of prolonged drought, larvae do have the capability to emerge from these eggs and crawl a short distance of a few centimetres towards the actual water body and continue their development (Koenraadt *et al.* 2003, Miller *et al.* 2006). Interestingly, finding eggs on wet mud may actually not be 'accidental', as there is evidence that eggs are more likely to be found outside than inside water puddles (Miller *et al.* 2006). In addition to survival in the egg stage, the different larval stages can survive up to a maximum of three to five days if they end up on damp soil as a result of an aquatic habitat completely drying out (Koenraadt *et al.* 2003). The above described findings on drought resistance and survival have important implications for larval control strategies, as they all suggest that interventions should not only target water bodies themselves, but also recently dried out habitats to ensure a maximum reduction in adult mosquito numbers.

As discussed above, the dry season may have detrimental effects on the population dynamics of the larval stages of *An. gambiae*. Although this species also breeds in water bodies that are the result of human activity, such as water-filled brick pits, cattle drinking sites and borehole run-off, the onset of the rainy season results in numerous, temporary pools and puddles that support the development of large numbers of *An. gambiae* larvae (Coetzee *et al.* 2000). Interestingly, rains that are too intense could result in the flushing of larvae or in the ejection of larvae from their breeding site. As a consequence, nightly losses for the different developmental stages have been estimated at 5 and 18% for the younger (L1) and older (L4) larval stages, respectively (Paaijmans *et al.* 2007). Remaining larvae can experience high levels of competition, which in the most severe circumstances, can result in predation of conspecifics, or in delayed development and increased mortality (Koenraadt and Takken 2003). The outcome of competition can be different for the different species of the *An. gambiae* complex. In places where both sibling species are sympatric, *Anopheles arabiensis* is the more dominant species during the dry season as it is generally more drought resistant, while the relative abundance of *An. gambiae* increases during the wet season (Kirby and Lindsay 2003, Koenraadt *et al.* 2004). This can be explained by the differential sensitivity of the two species to high temperatures, with *An. arabiensis* adults being able to withstand higher temperatures and express higher survival at higher temperatures (Kirby and Lindsay 2003). In addition, differences can be explained by the asymmetric levels of competition between the two species in their aquatic habitats: *An. gambiae s.s.* generally is a better competitor, as evidenced by the fact that larvae of *An. arabiensis* had an extended development time in mixed sibling species populations. Also, mortalities of *An. arabiensis* were higher than those of *An. gambiae s.s.*, although latter effects depended on habitat size (Paaijmans *et al.* 2009).

In conclusion, numerous fundamental aspects on the larval ecology of malaria vectors have been unravelled in the past decades. In particular the identification of key chemical compounds that stimulate oviposition behaviour (cedrol, nonane and 2,4 pentanedione) offers opportunities for exploitation in attract-and-kill strategies. This, however, requires careful testing of formulations that combine attractant and lethal compounds, as the lethal compounds should not exert a strong repellent effect. This would simply negate the positive effect of the attractant. For example, it has been shown that the larvicide temephos has a strong deterrent effect on gravid *An. gambiae* s.l. females, but not on gravid *Culex quinquefasciatus*. On the contrary, *Bti* did not cause any repellent effects on oviposition (Mwingira 2020), making it a more suitable candidate in attract-and-kill strategies that target the larval stages. As an alternative to temephos and *Bti*, a large list of plant-derived compounds has been evaluated for their larvicidal effects against various *Anopheles* species. These compounds either exert direct toxic effects, act as mimics of insect growth regulators, or are used as essential oils that interfere with oxygen uptake of the aquatic larvae (reviewed in Muema *et al.* 2017). Similarly, plant-derived compounds can also have a repellent rather than a toxic effect. These are flavours and fragrances of plant essential oils that are categorised as monoterpenes, sesquiterpenes and aliphatic chemicals. Such compounds could thus be incorporated in push-pull strategies, in which the repellent compound is used to deter gravid females away from specific locations and lure them to other locations where their offspring will not be able to complete development. Sufficient opportunities thus exist to develop effective attract-and-kill formulations. When used wisely, e.g. in rotational schemes, these strategies would also reduce the selective pressure on resistance development.

New technologies in larval source management

Long before the formal identification of *Anopheles* mosquitoes as vectors of *Plasmodium* parasites by Ronald Ross and others in the late 19th century, people were already aware of the association between 'periodic fevers' and the proximity of swampy areas. Without the availability of tools to identify disease causing organisms, which took a major flight with the development of the microscope by van Leeuwenhoek in the late 17th century and the germ theory of Louis Pasteur and Robert Koch, people ascribed their fevers and sickness to *miasmas* or noxious forms of bad air (Dobson 2007). Numerous descriptions of the devastating impacts of malarial fevers can be found in the historical texts of Egyptian, Greek, Roman and Chinese writers, and date back to several centuries B.C. As a consequence of the awareness of this association, the first forms of larval vector control were already undertaken through, for example, drainage of swamp areas and the implementation of sanitary measures, such as cleaning sewers and pumping bilge water out of ships (which constitutes a potential breeding spot for *Aedes aegypti*). Of course, we can only speculate about the actual impact of these control measures, as the scientific evidence of these historical programmes is simply lacking.

The first well-described trial of a malaria vector intervention was carried out in Italy by Angelo Celli among railway workers, and included the combination of house screening, whitewashing of internal walls, burning of specific powders (most likely including pyrethrum) and the use of protective clothing (Ferroni *et al.* 2012). Malaria was contracted in 92% of the people in the control arm, whereas only 4% contracted malaria in the intervention arm of the trial. Although these intervention techniques were seemingly simple and straightforward to carry out, the example also demonstrated the logistical and analytical challenges of combining interventions, and the need for intersectoral collaboration, as in this case railway workers were the targeted group. In addition, Celli recognised the importance of public education and the role of the living conditions of affected communities in tackling the disease. Interestingly, Celli noted that interventions were sometimes met with apathy, ignorance and prejudice, and trial participants commented that they were not wild animals and did not want to sleep in cages (Ferroni *et al.* 2012), highlighting the need for community involvement in vector control programmes. The work by Celli can thus be considered as an example of an integrated vector management strategy *avant la lettre*.

Many of the above described older techniques, such as drainage, house screening and personal protection (e.g. bed nets), are still part of malaria vector control efforts today. At the same time, many new vector control technologies have been developed and added to our toolbox (Takken and Knols 2009), including the development of lure-and-kill strategies based on host-derived odours (e.g. traps and eave tubes (Homan *et al.* 2016, Knols *et al.* 2016)), the development of biological control (e.g. natural enemies and organisms pathogenic to the larval and adult stages (Bukhari *et al.* 2013)), and the advancement of genetic based approaches (e.g. release of insects carrying a dominant lethal, or RIDL (Phuc *et al.* 2007)). Here I will highlight new developments in a selected number of tools that specifically target the larval stages of malaria vectors, and further elaborate on how they can be taken up in LSM programs.

The potential of *Bacillus thuringiensis* var. *israelensis* (*Bti*) and other *Bacillus* preparations (e.g. *Bacillus sphaericus*) for the biological control of African anophelines has been recognised since the early 1980's (Pant *et al.* 1981). This took a major flight with the evaluation of its impact within large-scale epidemiological field trials in different ecological settings (reviewed in Derua *et al.* 2019). These trials demonstrated significant reductions in the prevalence or incidence of malaria in, for example, the urban environment of Dar es Salaam, Tanzania (Geissbühler *et al.* 2009), and the highlands of western Kenya (Fillinger *et al.* 2009). In the floodplains of the Gambia, however, the impact of the application of *Bti* to larval breeding sites on malaria was not observed, most likely through the abundance of large riverine areas with extensive flooding, which resulted in highly mobile and also inaccessible sites (Majambere *et al.* 2010). One option to tackle this challenge is the use of drones to deliver the biolarvicides to water bodies. Various trials are currently underway to evaluate the feasibility and cost-effectiveness of this approach. Regardless of their usefulness in the actual application of *Bti*, drones may also greatly aid in the mapping and identification of potential breeding sites, and could thus contribute to more efficient LSM (Carrasco-Escobar *et al.* 2019, Hardy *et al.* 2017).

Methods that cause the asphyxiation of larvae have been in use since the very first vector control attempts and were mostly based on the application of mineral and paraffin oils to the water surface. Similarly, various monomolecular surface films have been developed and tested in different ecological settings with variable effects (reviewed in Nayar and Ali 2003). A downside of these surface films is that when they are applied in the open field, they may break up as a result of wind and vegetation present in the water, and hence lose their effectiveness. However, newer formulations, such as Aquatain, have a higher resistance against these disturbances (Bukhari and Knols 2009, Mbare *et al.* 2014). A field trial in rice fields in Kenya demonstrated a strong reduction in the aquatic stages of anopheline and culicine larvae. Moreover, the product reduced water loss due to evaporation. Importantly, no negative effects on non-target organisms were observed and also the development of rice plants and the rice yield were not affected (Bukhari *et al.* 2011). Despite their proven efficacy in entomological field trials, these types of products have not yet been incorporated to their fullest extent in LSM programs. Randomised controlled trials, following the guidelines of the Vector Control Advisory Group (VCAG) of WHO, are needed in order to demonstrate the impact of monomolecular surface films on malaria incidence or prevalence, and thus to demonstrate the public health value of such a new intervention.

A relatively new player in the field is the use of RNA interference as a mechanism to silence genes that are essential in the development of *Anopheles* larvae, and that induce mortality as a result. The idea is to expose larvae to RNAi nano-particles that are incorporated in larval food, which is ingested during development (Zhang *et al.* 2010, 2015). The technique has been further developed by genetically engineering of *Saccharomyces cerevisiae* (baker's yeast) to express short hairpin RNA that silences neural development genes. The yeast thus acts as the food source as well as an RNAi delivery platform, and could thus be considered an RNA pesticide. Proof of concept of this tool has been provided for a number of disease vectors, including *Ae. aegypti*, *Aedes albopictus*, *Culex quinquefasciatus* and *An. gambiae* (Mysore *et al.* 2017, 2019). The concept opens up a plethora of opportunities to specifically target genes that are essential in the development of the pest species, and it may thus be less vulnerable to insecticide resistance than other strategies. Nevertheless, the approach will require a substantial amount of regulatory approval, as it will be considered a genetic modified organism (GMO) that will be released in the open field (Lopez *et al.* 2019). As such, it is likely that the tool will not be available for LSM programmes any time soon.

Role of communities in malaria vector control

In the scientific literature, one may come across many different terms that are used to describe the roles and levels of involvement of communities in (vector-borne) disease control. These include, among others, 'community participation', 'community engagement', 'community mobilisation', 'community sensitisation' and 'community empowerment'. The types of activities and tools that describe the role of communities are highly diverse and are culture and context dependent. They range from school-based education programmes and focus group discussions to the provision of incentives and health care insurance. All of these have the aim to provide communities with a more active role in an intervention programme (e.g. in decision making), rather than undergoing a certain intervention without any input. The ultimate aim of these activities is to increase the uptake and coverage of an intervention so that maximum impact on disease reduction is achieved.

A search on PubMed to quantify the attention in the scientific literature for community participation and vector control (using 'vector AND control AND community AND participation' as keywords, search date: July 2020) revealed 429 publications. Of these, the majority focused on malaria (33%) and dengue (31%). Other vector-borne diseases received far less attention in the scientific literature, with leishmaniasis (1.4%) and onchocerciasis (1.6%) as the two vector-borne diseases with the least publications on community participation. Of the 140 malaria-related studies on community participation, 19 were qualified as a 'review'. Interestingly, eight were labelled as 'randomised controlled trial'. In most cases, community participation or engagement strategies were in that case included in the study of vector control interventions, such as IRS (e.g. Keating *et al.* 2011), insect growth regulators (e.g. Yapabandara *et al.* 2001), larvivorous fish (e.g. Fletcher *et al.* 1992) or the combination of larval source management and house improvement (McCann *et al.* 2017). None of the identified studies included a comparison in which the effect of community participation by itself was evaluated at an epidemiological level. In other words, the studies did not include intervention arms evaluating a vector control tool with and without community participation. This probably uncovers the weakness of community participation in integrated vector control efforts: there is no good handle on the quantitative impact of community participation on epidemiological outcomes of malaria. One could argue that that may be an unrealistic appeal, especially because of the logistical complexities of such a study, but without any assessment, we remain in the dark about the true value of engaging communities in vector control. As mentioned, many different approaches exist to involve communities as stakeholders in a vector control program, but in recent years, also in this field innovative approaches have been tested and evaluated. A few of these will be highlighted here.

Because farming activities, such as rice irrigation and drainage construction, are strongly associated with malaria risk, involving farmers in vector control efforts has received much attention in the literature. The so-called Farmer Field School is an approach that has been successfully implemented in crop protection programs, and it has been argued that a similar approach can also be used for malaria vector control (Van den Berg and Knols 2006). The Farmer Field School provides a form of education that uses experiential learning methods with the aim to increase farmers' expertise. The concept is that groups of farmers meet at regular (e.g. weekly) intervals, take observations and sample populations and characteristics of harmful and beneficial organisms, plants, soil and environmental conditions. Such data are analysed and discussed and can lead to decision-making on experimental action to be evaluated the following week. In the case of malaria vector control, this could for example result in improved drainage channels with less standing water which, on its turn, results in reduced vector populations and hence reduced transmission of disease. In addition, besides these direct effects, also more indirect effects can follow. For example, increased profit because of better water management can result in better housing and nutrition, resulting in less disease. Also increased awareness and less use of (agro)insecticides and hence reduced selective pressure for insecticide resistance can positively affect malaria control efforts in this way (Van den Berg and Knols 2006). Ideally, the curricular activities on mosquito ecology are incorporated into ongoing Farmer Field School programs on crop management, so that an integrated pest and vector management (IPVM) approach can be rolled out. Ecologists at African institutions can play an important role in this, and thus need the full support at academic level to train the next generation of trainers and practitioners (Mukabana *et al.* 2006).

Whereas Farmer Field Schools are specifically aimed at a particular profession, other approaches, such as the Open Space technique, aim to elicit the attention of communities at large. By formulating provocative 'calling questions' prior to public meetings, those interested in a specific topic, e.g. malaria control, come together at a specific Open Space meeting venue. Rather than having a pre-set agenda in this approach, topics for discussion will be collected and determined during a first round of brainstorming. This is followed by group discussions during which participants can move freely from one topic to the other so as to promote 'cross-pollination'. The Open Space technique is a bottom-up approach that is frequently implemented in company settings, for example when companies need to re-organise and to go through a change process collectively. This approach was also tested in a public health/malaria context in Rwanda (Ingabire *et al.* 2014). Two Open Space meetings engaged the local community in the malaria problem and resulted in community-formulated, sustainable suggestions for malaria control. One consisted of the formation of 'community malaria action teams' (CMATs), which aimed to deliver malaria prevention messages at village level. The other suggestion was the implementation of a mosquito LSM program in the rice fields using biological substances, in this case *Bti* (Ingabire *et al.* 2016). Evaluation of the 6-month LSM trial revealed that community awareness and support for LSM increased. A high effectiveness of *Bti* in terms of mosquito abundance and nuisance biting was perceived by the community (Ingabire *et al.* 2017), and later also confirmed in independent entomological surveys (Hakizimana 2019). Especially this community perception is critical for the success of a control programme, because without it, interest and motivation can rapidly wane, resulting in only short-term benefits of the intervention.

Vector surveillance constitutes an essential part of malaria control programmes and is often performed by well-trained staff at local, regional or national level. It needs to be performed repeatedly, so as to obtain an idea of the temporal dynamics in vector populations. It also requires high spatial coverage so as to identify areas that are most at risk of malaria transmission, which could then be specifically targeted with (vector) control tools. The need for informative data that have a high temporal and spatial resolution represents challenges, because often the number of staff and available budget is limited. The consequence is that specific transmission areas may be overlooked or that peaks in transmission may not be detected in a timely fashion. The question is whether such gaps in surveillance could be solved by involving the general public in the reporting of mosquito bionomic data (Bartumeus *et al.* 2018). If set-up rightly, such a 'citizen science' approach may generate a large amount of relevant entomological data, while at the same time engaging and educating communities about malaria (vector) biology. This approach has been successfully implemented in several developed countries for the surveillance of native and invasive mosquito species (reviewed in Kampen *et al.* 2015) and is considered an important tool for the detection of (invasive) vectors and their associated diseases by the European Centre for Disease Prevention and Control (ECDC 2014). The question remains whether the same approach can also be used to enable 'passive' monitoring of *Anopheles* mosquitoes involved in the transmission of malaria in rural African settings.

In a recent study from Tanzania, groups of volunteer participants were asked every month to rank areas around their villages from low to high outdoor-biting mosquito density based on their own knowledge and experience (Mwangungulu *et al.* 2016). This ranking was then validated with actual mosquito abundance reported from odour-baited traps. Results showed that such community knowledge and experience was a reliable means for identifying areas with true low or high mosquito densities, and this simple low-cost tool could thus guide large-scale implementation of mosquito control operations (Mwangungulu *et al.* 2016). Similarly, a 1-year citizen science project was set-up in five villages in southern Rwanda with the aim to contribute to malaria mosquito surveillance (Asingizwe *et al.* 2018, Murindahabi *et al.* 2018). In that study, a bottom-up approach was chosen by involving communities in the design of the citizen science program. This involved both the technical aspects (e.g. which trapping tool to use), as well as the social aspects of the program (e.g. how to organise data collection and reporting (Asingizwe *et al.* 2019)). On a monthly basis, data were collected on mosquito nuisance, numbers of mosquitoes in a hand-made trap and confirmed malaria cases in the household. Results showed significant correlations among reported nuisance, actual mosquito numbers and malaria cases, although these were strongly dependent on time (i.e. seasonal) and space (i.e. village vs sector level) (Murindahabi 2020). Collectively, the results from Tanzania and Rwanda suggest that by involving citizens in the reporting of observations, one could quickly 'scan' a larger area for potential hotspots of disease, and initiate further in-depth entomological surveillance. In other words, citizens could be the ears and eyes via which the malaria situation is monitored and eventually controlled.

Of course, in such a research project setting, it is relatively easy to keep villagers motivated to participate. Experimental projects generally do not last that long, and the challenge is to design programmes that are sustainable in the long run, particularly in terms of acceptability and participation, and that have high quality data and visible impact on the problem under study (Mboera *et al.* 2014, Rubin *et al.* 2020). After the study in Rwanda, volunteers showed significantly more involvement in malaria-related activities and had higher acceptance rates of IRS, which both could be considered as indicators of success of the project (Asingizwe *et al.* 2020). With regards to participation rates, these depend on numerous factors such as perceived severity of the malaria problem, perceived barriers and subjective norms. They are also determined by the (perceived) ease of use of reporting systems. The studies in Tanzania and Rwanda both used paper-based reporting systems. This approach could be more streamlined if data were to be collected via e.g. smartphone applications. Such digital approaches have already shown a lot of promise in the monitoring of invasive species in Europe, and even demonstrated that the citizen science approach picked up new invaded territories of the Asian tiger mosquito (*Aedes albopictus*) earlier than the traditional approach using oviposition traps (Palmer *et al.* 2017).

Conclusions

Innovations in larval vector control are a cornerstone in the global fight against malaria, and these include, among others, novel formulations of biological larvicides, RNA pesticides, monomolecular surface films, and attract-and-kill approaches based on volatile infochemicals. These innovations are often inspired by new knowledge in the (chemical) ecology, physiology and genomics of mosquito larvae. Therefore, it remains of utmost importance to keep investing in basic research as part of the Global Vector Control Response (WHO 2017). Implementation of these novel tools requires the involvement of communities from the very start of a control programme. Several new approaches have been evaluated recently (e.g. the Farmer Field School, Open Space, and citizen science) that specifically address ways of involving communities and keeping them motivated to contribute to the programme. Also, a toolbox of community-engagement approaches thus exists that can be used to effectively integrate new solutions into ongoing malaria control programs. Selection of approaches that have optimal local impact on malaria will be context and culture dependent, and this will require extensive collaborations across multiple sectors.

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Intersectoral collaborations

Community workshop about the use of solar-powered mosquito trapping (photograph: W. Takken)

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9. Intersectoral collaboration and action in dengue vector control in Asia based on an eco-bio-social perspective

Pattamaporn Kittayapong[1,2]
[1]Center of Excellence for Vectors and Vector-Borne Diseases, Faculty of Science, Mahidol University at Salaya, Nakhon Pathom 73170, Thailand; [2]Department of Biology, Faculty of Science, Mahidol University, Bangkok 10400, Thailand; pkittayapong@gmail.com

Abstract

Complexity in the emergence of vector-borne diseases involves several components in the eco-bio-social perspective. This makes it difficult for vector-borne disease control to be based solely on one organisation working on vector reduction. Dengue in particular involves (1) ecological components, such as the increase of breeding sites through changing a landscape (from rural to urban) and expansion of the range of mosquito habitats through climate change; (2) biological components, which mainly include human-vector-virus evolution and interaction in disease transmission; and (3) socio-economic components, such as insufficient household income and inadequate public health service. It is obvious that intersectoral collaboration with all relevant sectors to address these integrated components is one of the key criteria for successful vector-borne disease control. Intersectoral collaboration related to dengue has been mostly conducted when dengue control is in action, in order to enhance interventions aimed at vector control. In this chapter, different approaches of intersectoral collaborations and actions to control dengue in Asian countries by suppressing *Aedes* mosquito vectors will be highlighted. A few case studies include intersectoral collaboration for integrated vector management and innovative vector birth control. Based on the Asian experience, achieving intersectoral collaboration mainly involved the following key factors: (1) financial or technical support from within and outside participating sectors; (2) a clearly defined common interest which benefit all sectors; (3) a division of workload and joint management to achieve a common goal; (4) consistent coordination and communication among partnered sectors; (5) adaptability and flexibility in management; and (6) capacity building for sustainable intersectoral partnership.

Keywords: intersectoral collaboration, eco-bio-social, dengue, vector control, Asia

Complexity in dengue emergence and the need for intersectoral collaboration

Dengue is an important vector-borne disease. Dengue incidences have increased in magnitude globally. Using cartographic approaches, 390 million dengue infections per year were estimated in the recent past (Bhatt *et al.* 2013). This disease can spread through the bites of *Aedes* vectors that are distributed throughout the tropics and subtropics. *Aedes aegypti*, the major vector, breeds and lives in or near human habitations, while *Aedes albopictus*, a minor vector, is found in the household surroundings, gardens, or nearby forested areas. Eliminating and/or managing breeding habitats, which mostly are artificial man-made containers, have proven to be the most effective ways to reduce the abundance of the mosquito vectors and the diseases they transmit. Controlling dengue currently relies on controlling the *Aedes* mosquito vectors and depends mainly on the use of insecticide sprays in households and surroundings, and larvicide application in breeding containers.

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The situations that lead to dengue emergence are complex. These involve ecological, biological, and social factors. These factors together are often referred to as eco-bio-social factors in different contexts. Climate change and landscape change are good examples of ecological factors influencing dengue emergence. Increase in temperature, as the outcome of climate change, is likely to result in an increase in the range and distribution of mosquito vectors and hence the spread of the diseases they transmit (Caminade *et al.* 2019). Changing landscape from rural settings to urban cities increases the breeding habitats of the dengue vectors (Higa 2011). In addition, vector-virus evolution and interaction to enhance disease transmission is one of the important biological factors. Female mosquitoes generally acquire the virus from an infected host during blood feeding. The virus then is replicated in the gut and disseminated to the salivary glands before it is released into the saliva, where it is transmitted to the host during subsequent feeding. Rückert and Ebel (2018) reviewed and summarised how virus-mosquito interactions were critical for these viruses to become global pathogens at molecular, physiological, evolutionary, and epidemiological scales. Socio-economic factors also play an important role in how dengue emerges. Poor living condition with inadequate public health services are the important factors leading to vulnerability to dengue infections among human populations (Figure 1).

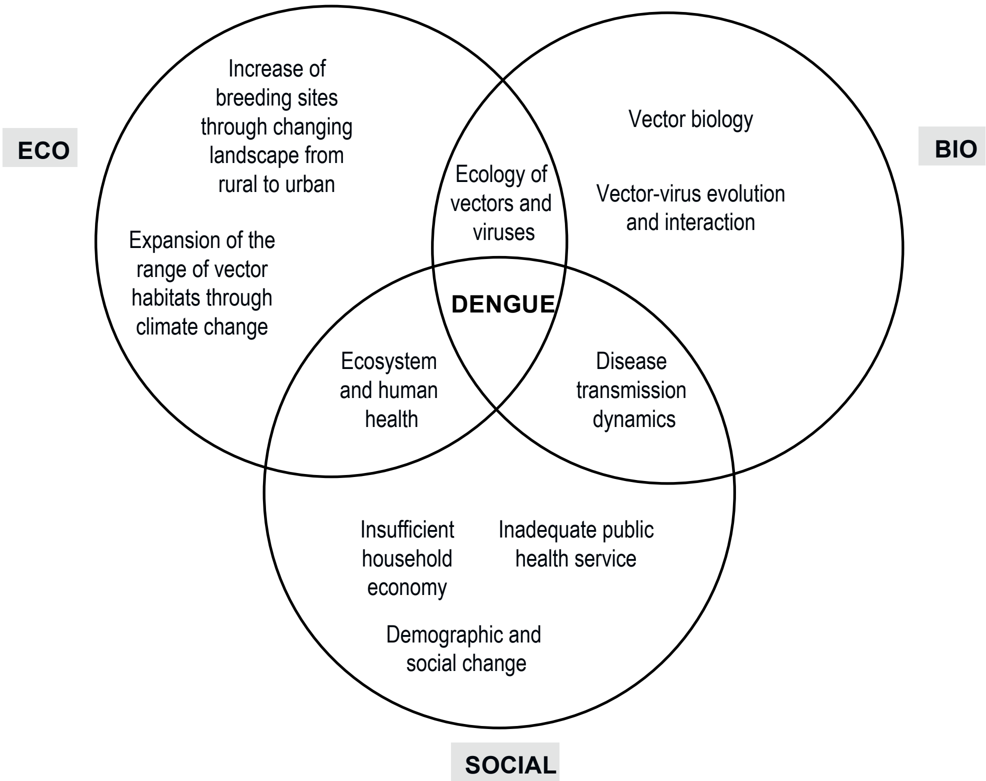

Figure 1. Eco-bio-social framework demonstrating the factors associated with dengue emergence (modified from Tana et al. *2012a).*

Intersectoral collaboration and action in Asia

Research on intersectoral collaboration and action in Asia originated from a collaborative effort of the World Health Organization/Special Programme for Research and Training in Tropical Diseases (WHO/TDR) and the International Development Research Centre (IDRC), Canada, in order to jointly develop an initiative entitled 'Eco-Bio-Social Research on Dengue in Asia' (2006-2010). This initiative was launched with a call for research proposals in Asia in 2006, and led to research activities on this topic in six Asian countries, namely India, Indonesia, Myanmar, Philippines, Sri Lanka and Thailand (Sommerfeld and Kroager 2012). Within each participating country, multi-disciplinary research teams representing different sectors were formed. Most of the teams included those from local public health offices, communities, hospitals, schools, universities, NGOs, etc. who worked together to analyse dengue situations in their selected neighbourhoods during the first phase and to eventually develop intersectoral, community-based interventions in the second phase (Abeyewickreme *et al.* 2012, Arunachalam *et al.* 2012, Espino *et al.* 2012, Kittayapong *et al.* 2012, Tana *et al.* 2012b, Wai *et al.* 2012). Intersectoral partners and actions taken for dengue vector control from each Asian country project are summarised in Table 1. These individual projects shared the common goal of integrating intersectoral collaboration and community involvement with the uniqueness and variations associated with the country context.

Table 1. Intersectoral collaboration and actions taken for dengue vector control in the six Asian countries that participated in the WHO/TDR-IDRC Eco-Bio-Social Initiative on Dengue Research in Asia (2006-2010).

India, Chennai	Indonesia, Yogyakarta	Myanmar, Yangon Townships
1. Women self-help group (SHG): – awareness raising 2. Schools: – school-based health education materials, street health ambassador – student-initiated public awareness campaigns 3. Hospitals: – health education material distributed by ward volunteers 4. Health authority: – mobilisation and coordination	1. Community self-help group: – solid waste management and recycling 2. Schools: – school-based awareness raising 3. Health Authority: – health education materials distributed by home visit 4. NGO: – mobilisation and coordination	1. Thin-Ga-Ha (friendship) group: – implementing dengue vector control and environmental sanitation 2. Hospitals: – awareness raising by ward volunteers (Yatkwet cetana-wundan) 3. Health authority: – mobilisation and coordination
Philippines, Muntinlupa City	**Sri Lanka, Gampaha District**	**Thailand, Chachoengsao Province**
1. Barangay health care workers: – trained as outreach workers to inspect breeding containers 2. Health authority: – solid waste management – educational DVD on dengue distributed – mobilisation and coordination	1. Community health volunteers: – community mobilisation – labour sharing (Shramadarma) 2. Schools: – school-based health education 3. Environment authority: – improved solid waste collection – promote home gardening 4. University researchers: – mobilisation and coordination	1. Ecohealth volunteers: – selected among community health volunteers and were trained to conduct vector control activities 2. Health authority: – mobilisation and coordination 3. University researchers: – consultation and coordination

After completion of the eco-bio-social initiative, IDRC had launched another ecohealth-based initiative, in collaboration with the Canadian International Development Agency (CIDA), the Australian Agency for International Development (AusAID), and the Global Health Research Initiative (GHRI). This initiative was named Ecohealth-Emerging Infectious Diseases (EcoEID), in order to promote the application of an ecosystem-based approach to health in Southeast Asia. One of the funded projects entitled 'Application of an Eco-Bio-Social Approach to Emerging Infectious Diseases in the Southeast Asian Global Outreach Hotspots' used dengue as a proxy or an example disease in six tourist sites in Cambodia, Indonesia, Lao PDR, Philippines, Thailand, and Vietnam. Each country project promoted intersectoral collaboration, especially in community-based prevention and control of dengue vectors (Kittayapong *et al.* unpublished data).

Intersectoral partnership in the EcoEID projects varied according to the local situation of each selected tourist site. Most of the partners included international organisations, relevant government authorities (such as health and environmental sectors), different levels of communities, private sectors, and NGOs. Table 2 identifies and compares the intersectoral partners that participated in the risk reduction of vector-borne and zoonotic diseases in the six tourist settings in Southeast Asia. The total partners/sectors ranged from five in Bali, Indonesia to nine in Koh Chang, Thailand. It was noticed that local administrative authorities and health workers were involved in all settings, whereas only two NGOs were involved from the six participating countries.

From 2011-2013, the WHO Center for Health Development in Kobe conducted a study at the local government level, in order to understand the role of local governments in promoting intersectoral collaborations and actions (Rantala *et al.* 2014, WKC 2012, 2013). It was found that intersectoral collaboration promoted by local governments mostly involved issues that were not related to dengue control. The study showed that only two out of 25 case studies around the world reported intersectoral collaboration related to specific issues of dengue control, i.e. one

Table 2. Intersectoral partners participated in the Ecohealth-Emerging Infectious Diseases (EcoEID) Initiative (2011-2015) in an attempt to reduce the risk of vector-borne and zoonotic diseases in the selected Southeast Asian tourist settings.

Partner	Cambodia, Siem Reap	Indonesia, Bali	Lao PDR, Vang Vieng	Philippines, Palawan	Thailand, Koh Chang	Vietnam, Cat Ba Island
Local admin. authority	X	X	X	X	X	X
Tourism authority	X		X	X	X	X
National park/forest authority	X		X		X	X
Hotel/resort owner			X	X	X	X
Health worker	X	X	X	X	X	X
Animal health worker	X	X	X	X	X	
Environment/climatic authority	X		X	X	X	X
School	X	X	X	X		X
Union		X	X	X	X	X
NGO	X				X	

in Cuba and another one in Mexico (Rantala *et al.* 2014). The study reported by Sanchez *et al.* (2009) in Havana, Cuba indicated that intersectoral coordination led by local municipalities clearly improved dengue vector control in the study communities. In addition, they found that even better results were obtained when intersectoral coordination was combined with community empowerment, which targeted five participatory processes, i.e. capacity building, community dengue surveillance, social communications, behavioural change, and participatory evaluation.

An experience from the EcoEID initiative, with dengue as a proxy or an example disease in the Southeast Asian countries, indicated that local governments were the key partners in intersectoral collaboration, and on-site actions were conducted through these grass-root governmental units (Table 3). For example, implementation of garbage collection points to reduce the plastic waste that are important breeding sites for *Aedes* vectors on Koh Chang Island in Thailand was conducted by the local municipality in collaboration with the hotels/resorts located on the islands (Kittayapong *et al.* unpublished data). Another example of collaboration between local government authorities and hotels/resorts involved an establishment of the Ecohealth-Hotel Network on Cat Ba Island, Vietnam. The local government authority provided training for dengue vector control and gave an Ecohealth Certificate to hotels/resorts that were proved free of dengue vector breeding sites (Nam *et al.* unpublished data). An example of unique dengue prevention solutions being implemented by local governmental authorities in Palawan, Philippines involved prohibiting the use of bamboo fences, which were found to be an important breeding site of *Aedes* mosquito vectors (Espino *et al.* unpublished data).

One outstanding intersectoral action at the local level involved collaboration among local governments and community workers to integrate dengue surveillance with dog bite case reports in Bali, Indonesia, where both dengue and rabies are prevalent. The integrated disease surveillance was based on the fact that (1) the larval workers affiliated with the Public Health Office had routinely conducted larval surveys in the communities in order to prevent dengue; and (2) dog bite cases were usually not found through community surveys but by direct reports from the victims to the Animal Health Offices. Therefore, the combined disease surveys could report more dog bite cases in the communities and eventually reduce rabies. In addition, dengue surveillance was more active with additional support from the Animal Health Office. The collaboration resulted in a memorandum of understanding signed by local public health and local animal health officials and obviously improved the efficiency of both activities (Tana *et al.* unpublished data).

The common achievement or outcomes across sites involved in the intersectoral collaboration and community-based action of the EcoEID in Southeast Asia can be summarised as follows: (1) a demonstrated relationship between climatic factors and/or land use and disease incidence in tourist settings; (2) acquisition of eco-bio-social baseline knowledge, for example, vector surveillance and/or disease surveillance and household interview information in tourist settings; (3) strengthened active surveillance systems for selected vector-borne and zoonotic diseases; (4) stakeholder mapping and meetings which led to multisectoral collaborations and activities that either improved disease surveillance and/or reduced disease risk in the selected tourist settings; (5) demonstrated application of the Ecohealth or Eco-Bio-Social approach in community-based prevention and control programmes in the selected tourist settings. Table 3 demonstrates the local organisations and actions during the EcoEID project implementation phase in the six participating Southeast Asian countries.

Since 2014, the International Atomic Energy Agency (IAEA) launched an initiative aiming at controlling the *Aedes* mosquito vectors causing dengue, chikungunya, and Zika in Asia-Pacific,

Table 3. Intersectoral collaboration and action in dengue control in the six tourist settings in Southeast Asia during the implementation of the Ecohealth – Emerging Infectious Diseases (EcoEID) Initiative (2011-2015).

Cambodia, Siem Reap	Indonesia, Bali	Lao PDR, Vang Vieng
1. Local health office and communities: – organisation of multi-sectoral meeting for planning dengue vector control intervention – implementation of community health education on-site to educate local communities	1. Local public health office and local animal health office: – development of survey instrument, standard operating procedures, and integrated disease surveillance mechanism – integrated surveillance of dengue vectors and dog bites to increase intersectoral collaboration; increased disease surveillance efficiency and reduce costs	1. Local health office and communities: – strengthening local dengue and vector surveillance system – implementation of vector control activities at the household level using larviciding and spraying 2. Local health office and local hotels/resorts: – training with certificate on vector-borne diseases and vector control
Philippines, Palawan	**Thailand, Koh Chang**	**Vietnam, Cat Ba Island**
1. National dengue prevention and control programme (NDPCP): – enhanced dengue surveillance and nomination as one of the 11 dengue sentinel sites 2. Research institute for tropical medicine (RITM): – initiative for integrated vector-borne disease surveillance to increase intersectoral collaboration; increased disease surveillance efficiency and reduced costs 3. Local health office and city authorities: – reduction of breeding sites with highlight on local policy to prohibit the use of bamboo (major breeding sites) as fences	1. Local public health office and health volunteers: – establishment and training of Ecohealth volunteers to improve dengue vector surveillance 2. Local public health office and migrant communities: – organisation of health education and intervention to reduce breeding sites in migrant villages – organisation of questionnaire interview, which led to understanding behavioural enhancement of disease spread due to lack of treatment and continued working of sick labourers 3. Local municipality: – implementation of garbage houses to reduce breeding sites	1. Local health office and local hotels/resorts: – establishment of Ecohealth-hotel network, with certificate for breeding site-free hotels 2. Local health office and community households: – establishment of Ecohealth-houses, with monthly visit to inspect breeding sites by local health officers

with an emphasis on the use of the sterile insect technique based on irradiation. The first regional initiative, IAEA/TC/RAS5066 (2014-2017), led to networking and knowledge sharing among 14 participating countries in the Asia-Pacific. In 2018, another regional project, IAEA/TC/RAS5082 (2018-2021), was launched with a coordination and consultative meeting in Bangkok, Thailand, involving participants from 14 regional countries. The aim of the project was to manage and control *Aedes*-transmitted diseases using the area-wide sterile insect technique. The lessons learned from previous eco-bio-social and EcoEID initiatives in Asia indicated that both intersectoral collaboration and community participation were very useful and were essential to successful implementation of such a technology. For example, the sterile insect technique applied in combination with the *Wolbachia*-induced incompatible insect technique in Thailand used both intersectoral collaboration and community engagement as key strategies. The pilot project in semi-rural settings demonstrated the first proof-of-concept in suppressing populations of *Ae. aegypti*, the major dengue vector. The outcome was a significant reduction of female mosquitoes per household, up to 97%, after a 6-month open release of sterile males. The implementation was conducted through the intersectoral collaboration of different governmental units, as well as strong public/community engagement (Kittayapong *et al.* 2019). The intersectoral partners for this particular project were as follows: (1) an international organisation; (2) local government authorities; (3) local administrative authorities; (4) community health workers; (5) household owners; (6) local schools; and (7) the national media. The proof-of-concept for disease reduction at a larger scale requires even more intersectoral collaboration and division of workload in order to achieve the common goal. Table 4 shows an example of intersectoral governmental units and the division of workload among different units involved in the collaborative project to control dengue, using a combination of the sterile insect technique and the *Wolbachia*-induced incompatible insect technique in Bangkok, Thailand.

Table 4. Intersectoral collaboration and division of workload for the collaborative project to control dengue using the combined sterile insect technique and Wolbachia*-induced incompatible insect technique in Bangkok, Thailand.*

No	Activities	Institution in charge
1	Study site selection	All institutions
2	Public/community engagement	All institutions
3	Study on knowledge and perception, acceptability and social impacts	Faculty of Social Sciences and Humanities, Mahidol University (MU)
4	Study on environmental impacts	Faculty of Veterinary Science, Kasetsart University (KU)
5	Mass-rearing of mosquitoes	Faculty of Science (CVVD), MU
6	Mosquito sterilisation by irradiation	Thailand Institute of Nuclear Technology (TINT), MOST
7	Entomological baseline study and quality control of sterile male production	Faculty of Science (CVVD), MU and Department of Medical Science, MOPH
8	Transportation of sterile males to the release sites	Faculty of Science (CVVD), MU
9	Drone release of sterile males	Defence Technology Institute (DTI) in consultation with the Royal Thai Air Force and the International Atomic Energy Agency (IAEA)
10	Coordination with local communities/ accompany the research team to the sites	Bangkok Metropolitan Administration (BMA)
11	Recording coordinates and production of GIS maps	Department of Medical Science (DMSC)
12	Entomological monitoring and evaluation	Department of Disease Control (DDC) and Department of Medical Science (DMSC), Ministry of Public Health (MOPH)
13	Epidemiological monitoring and evaluation	Department of Disease Control (DDC) and Bangkok Metropolitan Administration (BMA)
14	Data analysis and result dissemination	All institutions

Key factors for achieving intersectoral collaboration

Based on the results of multi-country initiatives to control dengue vectors in Asia, the key factors leading to successful achievements via intersectoral collaboration were identified, and six important key factors were highlighted. First, *financial or technical support* from within and outside participating sectors have to be obtained. Financial support was obtained from both national and international sources in all example multi-country projects that used intersectoral collaboration. The main funding sources were from international funding agencies. Therefore, the sources of funding for collaborative efforts should be identified before initiating intersectoral collaboration. Second, it is necessary to clearly define the *common interest* that benefits all collaborating units, either government or non-government. Without common goals, it is difficult to keep up active intersectoral collaborations. Third, to achieve common goals, all partners need to have *clear roles* and workloads that are divided and, if possible, jointly managed among participating sectors in order to achieve common goals. Fourth, *consistent communication* among partnered sectors by active coordinators is necessary in order to take actions that achieve the common goals. Fifth, *adaptability and flexibility in management* is an important key factor which should increase the efficiency of intersectoral collaboration. The last key factor leading to a sustainable intersectoral partnership is *capacity building* of participating sectors.

A systematic review of 50 studies that applied intersectoral collaboration in vector-borne disease control and prevention by Herdiana *et al.* (2018) clearly showed more or less the same important key factors. This review identified six factors influencing the effectiveness of intersectoral collaboration. Among the six factors, i.e. approach, resources, relationships, management, shared vision, and type of organisation, only the last one was less influential (Herdiana *et al.* 2018). The first five identified factors were more or less aligned with the lessons learned from the dengue vector control initiatives in Asia, while the last one was different. Our experience indicates that capacity building of the participating sectors enhances effective outcomes and should be promoted whenever intersectoral collaboration is implemented, in order to achieve a long-term sustainable partnership.

Conclusions

Several examples of dengue prevention and control in multiple countries in Asia indicate that intersectoral collaboration is an important component leading to successful interventions to reduce dengue vectors and the diseases they transmit. Recently, intersectoral collaboration was highlighted as one of the four important pillars of action to reduce the human burden caused by vector-borne diseases in the Global Vector Control Response 2017-2030, approved during the 70th session of the World Health Assembly (WHO, 2017). Therefore, intersectoral collaboration alone, or intersectoral collaboration combined with community participation, should be considered important components and be applied in practice by all sectors responsible for dengue vector control, in order to increase efficiency in reducing the burden of vector-borne diseases, especially dengue.

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10. Health impact assessment: a tool for intersectoral collaboration

Martin Birley[1*] *and Robert Bos*[2]
[1]BirleyHIA, Consultants in Health Impact Assessment, 7 Manley Close, Hartrigg Oaks, New Earswick, York YO32 4DN, United Kingdom; [2]Independent Consultant, Public Health, Environment, Water & Sanitation, Route du Creux-du-Loup 10, 1285 Sézegnin, Switzerland; martin@birleyhia.co.uk

Abstract

The benefits and logic of intersectoral collaboration have been reiterated at regular intervals and substantial experience has been gained in what works and what doesn't. One of the iterations was the joint WHO/FAO/UNEP/UNCHS Panel of Experts on Environmental Management for Vector Control. This chapter starts by summarising that experience. We learned that successful intersectoral collaboration depends on vested interests, external pressures, strong institutional arrangements and suitable instruments. Health impact assessment (HIA) has proved one of the most successful instruments and we describe its procedures and methods in some detail. Although HIA is completely general, it includes the management of vector-borne diseases (VBD). In countries where VBD are of major public health importance, they make up a large part of the fraction of the increased disease burden attributable to development projects. HIA assists planners and decision-makers in non-health sectors, such as water resource development, energy, transport, mining or agriculture, to anticipate the health impacts and opportunities of their plans and projects. A set of recommendations can then be formulated to protect and promote health. These recommendations can be arranged in a hierarchy and this includes healthy engineering design. We identify different types of intersectoral collaboration and suggest where intervention points lie during development project planning. Reference is made to the health and safety performance standards of the lending institutions, and national planning and environmental regulations. There is still a global lack of capacity to carry out HIA to an acceptable standard and we summarise some of the causes and consequences. We provide two recent examples of intersectoral collaboration. The first example is a recently completed programme of the Asian Development Bank that focused on malaria and other communicable disease threats. The second example concerns the procedures used by multinational corporations and often referred to as environmental, social and health impact assessment (ESHIA). We conclude with a brief summary of future directions.

Keywords: health impact assessment, healthy design, healthy operation, EIA, ESIA, ESHIA, HIA

Introduction

The Global Vector Control Response (GVCR) strategy has four major components or pillars (WHO 2017). The first pillar recognises the need for inter-and intra-sectoral action and collaboration. This is interpreted as coordination of vector control activities within the health sector, at all levels, and between health and nonhealth sectors. Examples include designing irrigation schemes with self-draining hydraulic structures to eliminate the breeding of mosquito vectors (malaria) and intermediate host snails (schistosomiasis); formulating plans for the management of large reservoirs of hydropower or multipurpose dams (known as 'rule curves') to reduce the breeding of mosquitoes and snails along the reservoir shores and downstream of the dam (Jobin 1999, World Commission on Dams 2000); designing dams with duplicate spillways to avoid the breeding of blackflies in onchocerciasis-prone regions; managing livestock in areas where mosquito vectors are zoophilic (zoo-prophylaxis); and, taking into account the breeding habits of dengue vectors (*Aedes* spp.) when planning urban development and designing houses. The other pillars of the GVCR are discussed in many chapters of this book.

Intersectoral collaboration has long been an aspiration for many areas of public health but has often proved elusive. It featured predominantly in the WHO strategy of Health for All by the Year 2000 which emerged from the 1978 WHO/UNICEF Alma Ata Declaration on Primary Health Care (WHO 1978, see article VII point 4). For many years, WHO HQ had a unit called 'Intersectoral Action for Health' in its Strengthening of Health Services Division. In brief, it is a concept loved by all, funded by no-one – the fact that it requires financial resources, a policy and legal framework with clear decision-making criteria and staff trained in performing negotiations in a multi-disciplinary framework proves challenging in most resource-limited environments. It has been most successful in its upstream, strategic form (taking health into account in policies of all sectors). Yet, it comes in many forms and applies to different levels. This chapter focuses on the use of a specific tool called health impact assessment (HIA) that has the potential to regulate the impact of economic development projects from any sector on the health of communities and to provide a framework for intersectoral action. Large investments continue to be expected to achieve the sustainable development goals (SDG) targets (Anonymous 2016), especially in countries where vector-borne diseases are prevalent. This situation provides opportunities to address vector-borne disease challenges in the context of major infrastructure developments for transport, energy generation, food production and human settlements.

Motivation and, counter-intuitively, vested interests are principal drivers behind successful intersectoral collaboration. One of the earlier examples of a programme to promote intersectoral collaboration was the Joint WHO/FAO/UNEP/UNCHS Panel of Experts on Environmental Management for Vector Control (PEEM). This programme was initiated in 1980 through Arrangements under an existing Memorandum of Understanding between the World Health Organization, Food and Agriculture Organization of the United Nations and United Nations Environment Programme. The United Nations Centre for Human Settlements (UNCHS, now known as UN-Habitat) joined PEEM later, in 1989. Memoranda of understanding can be an effective mechanism to achieve agreement on roles, responsibilities and resource allocations in support of intersectoral action.

PEEM is an example of intersectoral collaboration between UN agencies. In the post-Second World War period, UN specialised agencies were established along sectoral boundaries, and this continues to be reflected in their governance structure – the highest policymaking body of the WHO is the World Health Assembly, the annual gathering of ministers of health of all Member States in Geneva; similarly, at the biennial FAO Conference, ministers of agriculture establish the Organization's policies and programmes. Clearly such silo-ed governance structures are not conducive to the promotion of intersectoral approaches – rather, in practice they guarantee a focus on the core business in a sector. Policy statements by UN governing bodies seldom go beyond paying lip service to the concept. Depending on the issue at stake, intersectoral collaboration can be at its most useful at different levels: between international agencies, between ministries and other agencies at the level of national government, or to tackle local health issues through metropolitan, provincial, municipal or district levels.

At the international level, PEEM focused on the relationship between water resource development and management programmes and the associated risk of vector-borne disease transmission. The three agencies found each other in this collaborative framework motivated by converging interests and concerns. In WHO, the collapse of the Global Malaria Eradication programme at the end of the 1960s had left a traumatic hiatus in the tropical disease control strategy and an aversion to the militarily organised activities of house spraying with residual insecticides that were the hallmark of the eradication programme. There was a level of nostalgia for the pre-WWII 'naturalistic approaches' such as housing design, land use planning, and water management in agriculture, when professionals from different sectors worked together in different settings. As a result, there was a revival of interest in environmental management for vector control (FAO 1987, WHO 1982). FAO was concerned about the public health risks associated with irrigated agriculture. It predicted a need to rapidly expand irrigated agriculture, particularly in Africa, to keep up with food demands of a growing population. By the late 1970s there were many well-documented case studies of detrimental impact of irrigation on malaria, filariasis, schistosomiasis and Japanese encephalitis which fed these concerns. Compared to WHO and FAO, UNEP was a relatively young organisation (it was established in 1974) and one of its main agenda items was the reduction of reliance on pesticides, in agriculture and in public health – hence their strong interest in promoting environmental management approaches. Around these themes, the agencies got together in PEEM.

Annual Panel meetings with technical discussions on relevant themes were complemented by many intersectoral workshops to consider irrigation systems, water reservoirs, and water supply and sanitation systems. Over the 15+ years of its existence PEEM generated a large volume of unique, multidisciplinary information which continues to be valid and of value. Several publications resulted, including a set of PEEM guidelines. One of these was a publication entitled 'Forecasting the vector-borne disease implications of water resource development' (Birley 1991). This was later generalised to consider all the potential health impacts of any kind of economic development project in any setting. The term forecasting was changed to assessment, emphasising that this is a management tool, not a scientific endeavour (Birley 2011). HIA is now well recognised in the impact assessment community. It remains more marginal with the public health community, where medical service delivery continues to take precedence over primary prevention.

PEEM gradually phased out in the mid-1990s when the UN agencies were hit by acute resource constraints and their agendas, workplans and budgets retracted to activities related to their respective core mandates. Yet activities set in motion have continued, such as health impact assessment, multidisciplinary research looking at the public health-agriculture nexus in various CGIAR institutions, and spin-offs such as the links between public health and biodiversity (Anonymous n.d., CGIAR n.d.; IFPRI n.d.).

Definition and components of health impact assessment

HIA is a tool that can be used at the planning stage to identify the most significant positive and negative health impacts of an economic development policy, programme, strategy, or project (Asian Development Bank 2018a, Birley 2011, Quigley *et al.* 2006). It is an assessment of the future consequences of a proposed development policy, programme or project on the health of a population. It takes account of the distribution of impacts between different community groups. The objective is to make justifiable recommendations to safeguard vulnerable communities and enhance health opportunities. The recommendations can affect the planning, design, construction, commissioning, operation and decommissioning of projects. During the design and construction of infrastructure projects there is a unique opportunity to apply environmental methods for vector control that would otherwise be too expensive to retrofit. HIA is a powerful tool for advocating healthy design.

The rationale of HIA underlines its value to promote intersectoral collaboration. Basically, HIA tries to prevent the transfer of hidden costs of development to the health sector. These costs can amount to millions of US dollars. A notorious example is that of Japanese encephalitis (JE) outbreaks in system H of the Accelerated Mahaweli Development Project in Sri Lanka (Peiris *et al.* 1992). Intensification of irrigated rice production coupled to the promotion of pig rearing as a secondary source of income (rice fields being the natural habitat for JE vector propagation – *Culex tritaeniorrhynchus* – and pigs being the JE virus' amplifying hosts) led to serious outbreaks and cost the Sri Lankan Government millions of dollars in vaccination campaigns. In addition, HIA provides the convincing evidence of how plans and actions lead to adverse health impacts and how changes to these plans and actions can contribute to their reduction or elimination. Thirdly, a good HIA will also highlight health opportunities: the design and operational options that contribute to improving community health. In this way it represents an important tool for actors in other sectors to boost their social responsibility image. HIA provides an opportunity for building consensus about how the design and implementation of a project could affect human health.

In method and procedure, HIA is holistic: recognising that health is determined by many interconnected factors. It gives equal weight to communicable diseases, non-communicable diseases, injuries, nutritional disorders, and mental well-being. Vector-borne diseases, as a subcategory of communicable diseases, form part of the assessment. The broadest WHO definition of health is normally assumed: a complete state of physical, social and mental well-being, and not merely the absence of disease and infirmity (WHO 1948). Spiritual well-being is also included in some contexts.

HIA provides a systematic approach. It subdivides the assessment into well-defined procedural steps, many emulating those of environmental impact assessment (EIA). The procedures include concepts like screening, scoping, gathering evidence, community engagement, prioritisation, mitigation and monitoring. The method focuses on changes in the determinants of health rather than on health outcomes.

Determinants of health

The determinants of health are those factors that jointly lead to health status. They are a generalisation of the terms used in malaria control: vulnerability of the individual, receptivity of the environment, and vigilance of all the institutions responsible for safeguarding health. The individual determinants of health include genetics, age, sex, education, and socio-economic status. The environmental determinants of health include both the physical environment and the social environment. Physical environment includes both the natural and built environment. Examples of these are vector breeding sites and exposure to vectors. The social environment includes poverty, inequality and economic conditions. There is usually a social gradient in health where community health status is correlated with socio-economic status (Marmot 2008). The institutional determinants of health include the various public bodies with a mandated responsibility for safeguarding health or providing medical treatment. In addition to the Ministry of Health, these include the police and fire service, the public utilities, the traffic regulation system, the educational system and the courts. The determinants of health can be categorised as those that can be changed by the project, such as vector breeding sites and socio-economic poverty, and those that cannot be changed by the project, such as the current genetic make-up of project affected communities.

In the context of the SDG, the operational framework for development until 2030, sustainability is defined by three pillars: economic, social and environmental factors. The latter two can be easily and directly linked to the environmental and social determinants of health referred to above. Economic factors frequently have been presumed part of the social indicators. At a macro level we know that poverty and ill-health are two sides of the same coin and mutually re-enforce one another. Economic regulations related to trade policies, and the adverse impact of certain tariffs on the health status of vulnerable groups are examples; also in rural areas where vector-borne diseases are prevalent, their transmission is often reduced in the wake of major infrastructural improvements that provide people with more money to spend (on medicines, mosquito nets, improved water and sanitation facilities and other health related items). The debate on how to accommodate economic determinants of health in HIA is still on-going.

Scope

The scope of the HIA has both geographical and temporal dimensions. Many economic development projects have a specific geographical location, or locations. A distinction can be made between health and safety issues that arise within the boundaries of the project, and health and safety issues that lie outside the boundaries of the project. Occupational Health and Safety is under the management of the project and generally not included in HIA. Those risks are assessed separately using the tools of health risk assessment (HRA). HIA focuses on the community who are outside of the project boundaries and who do not automatically benefit from occupational health and safety measures.

The physical boundaries of HIA will often differ from those of an Environmental Impact Assessment of the same project. The movement of people (temporary labour, camp followers) is included in order to avoid non-immune people from being placed in a malarious area, or to prevent diseases prevalent in the project area from spreading to communities outside of the direct project sphere. In Kenya in the 1970s an irrigation project in the Bura River basin had to be abandoned after the workers, brought in from non-malarious highland areas, and their family members started dying of malaria (D. Smith, personal communication); in Ethiopia, schistosomiasis was shown to have spread to areas where the disease was not present before by temporary agricultural labourers who had gone to infected areas for the sugar cane harvest, and took the infection back to their communities of origin (Kloos 1985).

In data analysis, boundaries may also be an obstacle: data on determinants of health may be collected within natural boundaries (i.e. a river basin) while health data may be organised along administrative boundaries (districts, counties or provinces). These discrepancies will affect the feasibility of productive intersectoral collaboration between the health and environment sectors.

The temporal dimensions of the project include the specific phases of construction, operation, and decommissioning. The health impacts of each phase are likely to be different. For example, during construction there may be a large increase in vector breeding sites associated with water containers and indentations on muddy ground. A large construction labour force may be required, and these generally consist of mobile men with money. They may live in construction camps for several years and buy goods and services from the local community, including food, alcohol, drugs and commercial sex. The interaction between the construction labour force and the local community may give rise to a range of specific health impacts, including sexually transmitted infections, traffic injuries, and communal violence. The construction labour force is often accompanied by many camp followers, or squatter communities. These may construct temporary houses without proper water supplies, sanitation, barriers to vector contact, or access to medical services. The influx can distort the local market for basic foods and rental accommodation, leading to price inflation. Those excluded from the project may experience a reduction in their food supply, leading to undernutrition.

The operational phase of the project may have a different community mix and a different set of health determinants. For example, there may be emissions of relatively toxic materials to air, water, or soil. The use of pesticides in agricultural projects may lead to intentional and unintentional poisoning. For example, agricultural households may store concentrated pesticides in their kitchens in unmarked containers. The indiscriminate use of pesticides in agriculture has been proved to have a major impact on resistance in human disease vectors, for example cotton field spraying promoting resistance in *Anopheles albimanus* (Georghiou 1972, Reid and McKenzie 2016).

The decommissioning or abandonment phase of the project may occur 50-100 years in the future. There may be land contaminated with unknown chemicals, pooling of water, overflowing drains, dangerous holes and crumbling buildings.

The contextual determinants of malaria and the complexity of their interactions were reviewed by a group of experts in 1999 (Casman and Dowlatabadi 2002), and this review produced a comprehensive global picture of how developments led by other sectors have influenced the transmission patterns of the disease.

Community groups

There are usually a range of different community groups that are affected by the project. Each group may experience different kinds of health impacts during different phases of the project. These groups include the workforce and their families; subcontractors and their families; local service providers, such as police, teachers and nurses; secondary industries, such as taxis and stores; project managers and their families; and peripheral communities. Some communities may be migrants from areas where certain communicable diseases are common or absent. For example, people may migrate from an area without malaria to an area with endemic malaria.

Large-scale economic development often requires the involuntary displacement and resettlement of large numbers of people. It has been estimated that over 40,000,000 people have been displaced by the construction of large reservoirs (Scudder 2012). International norms now require these resettled communities to have a minimum standard of housing and livelihood. These standards are unlikely to protect the community adequately from vector-borne diseases.

Measuring the significance of health impacts

The significance of a health impact is often inferred from the likelihood and severity of a change in health attributable to the project. Each of these may be ranked into five categories to form a risk assessment matrix (Birley 2011). A change with high likelihood and severity is unacceptable. A change with low likelihood and low severity is acceptable. In between these extremes there are judgements to be made. Significant changes are mitigated. Mitigation measures should be enough to reduce likelihood and/or severity to an acceptable level.

Management plan

A public health management plan (PHMP) is an integral part of any HIA. The analysis carried out in the HIA of how changes in health determinants translate into lower or higher risks, and what health opportunities a specific project offers is the basis for this PHMP. A good PHMP will highlight the options for planning, design, construction and management measures that the non-health sectors responsible for the project could adopt. The design measures addressing vector-borne disease risks deal with ways to minimise or eliminate the creation of breeding places. They may be of an environmental engineering nature and in terms of vector control are referred to as environmental modification. The operational measures focus on best practice, for example in water management, to reduce or eliminate vector breeding, and is referred to as environmental manipulation. The PHMP provides the framework for intersectoral action.

Role of health sector

The role of the health sector in HIA is a regulatory one. This starts with the planning of an HIA, where ideally the Ministry of Health (MOH) takes part in the screening and scoping process, and ensures health is mentioned explicitly in the terms of reference for the assessment (TOR). The MOH then appraises the HIA according to strict criteria and reviews the associated PHMP.

The negotiations stage in the HIA process is critical for intersectoral action – this is when (human and financial) resource allocation takes place, and roles and responsibilities are agreed upon. The PHMP is, in principle, an intersectoral plan. It is therefore important that the institutional arrangements for its implementation are nailed down in a memorandum of understanding (MoU) or other legally binding document. This document will be the basis for compliance testing. Compliance by the non-health sectors to implement the design and operational measures are recommended and agreed. There must also be compliance by the MOH to ensure funding is not diverted back to the health sector to build hospitals and clinics rather than take preventive measures, and to ensure the MOH delivers on its monitoring and evaluation responsibilities laid down in the PHMP. The outcome of these negotiations is at the core of subsequent intersectoral action. Once the PHMP takes effect, the MOH will have to monitor compliance by the other sectors to implement their activities in accordance with the agreed PHMP. There should be regular surveillance of the health status in the affected communities to provide an early warning system for the emergence of unexpected health impacts.

The regulatory role of the MOH can be at national, provincial or even local government level. It is particularly important in urban settings where development is at its most accelerated. The municipal health authorities should have a role in the planning, development and operations of departments dealing with infrastructure. In this regulatory role, the intersectoral nature of interventions in the development process must be all-pervasive.

Some types of intersectoral collaboration

Intersectoral collaboration may be achieved by different means including those listed in Table 1.

Simple collaboration is the least likely option because institutions and divisions have competing objectives, limited budgets and differing influence. HIA provides a tool for intersectoral collaboration based on due diligence, legislation and regulation. It does not depend on different sectors wanting to collaborate and this promises to be a more stable solution. Simple collaboration

Table 1. Some types of intersectoral collaboration.

Type	Ministry of Health (MOH) role and health impact assessment (HIA)
Performance standards	The international lending agency requires certain safeguards to be in place to protect human health before funds are released, as part of due diligence (IFC 2012). HIA provides a tool for ensuring that performance standards are met. The HIA is administered through the MOH in coordination with the EIA authorities.
Legislation and regulation	The MOH is instrumental in creating laws and regulations that safeguard health. This should include a legal and regulatory framework for HIA methods and procedures.
Statutory consultees	The MOH must comment on and approve proposals that are submitted to a planning process. The proposal includes some sort of HIA statement.
Environmental Impact assessment (EIA)	The MOH works with the Ministry of the Environment to require quality impact assessments with suitable mitigation measures to safeguard and enhance human health. In many countries this is HIA as part of EIA.
Stand-alone Health Impact Assessment	Governments may formulate regulations requiring that a proposal receives an HIA and the proposal is approved or amended accordingly. Such requirements should be defined by clear criteria. The regulations and HIA are administered by the MOH.
The judicial	Opponents of an economic development project may take their case to court and argue that an increased health risk is a violation of their human rights (Meason and Paterson 2014, Salcito et al. 2014, UN 2017). The MOH may have multiple roles. An HIA may be commissioned to oppose or support the project.
Memorandum of understanding	The MOH works with one or more other ministries to create written MoUs that define when and how intersectoral collaboration is triggered. The MoU may specify HIAs.
Simple collaboration	There is a joint decision-making body with representatives from the MOH and one or more other ministries. There is a shared budget and an HIA is commissioned.
Informal collaboration	Government officers in different departments with different skills consult personal acquaintances informally and acquire new ideas.

will only become part of the development landscape of a country if leadership at the highest level decides to make it a rule rather than an exception, or if there are enlightened spirits in the leadership of two or more ministries that see the value of collaboration over competition. In any case, such collaboration remains linked to personalities rather than government structures and is therefore inherently unsustainable.

Figure 1 illustrates some of these procedures where money flows from an international lending agency into non-health ministries for the purposes of economic development projects. The circles represent critical control points where changes can be made to project proposals in order to protect or enhance human health through intersectoral action.

Clearly, the head of government (President or Prime Minister) is in a position from where he or she can instigate, stimulate or impose intersectoral collaboration. An example comes from Lao PDR, where controversies over the Nam Theun 2 hydropower dam focused attention on the health impact of this major infrastructure project. A Prime-Minister's Decree (2006) then ordered HIA to be compulsory for major development projects, which in turn allowed the Minister of Health to establish an HIA unit within the Ministry with intersectoral links to other ministries (Ministry of Health, Department of Hygiene and Prevention 2010). Ministries of finance hold the purse strings to government budget. In the field of drinking water supply and sanitation, 'Sanitation and Water for All' (an international NGO) has organised meetings during the traditional 'spring meetings' of finance ministers at the World Bank, to prime them to the need for enhanced investments to achieve the SDG6 (water and sanitation) targets. This has been a successful strategy (personal observation). The economic rationale for HIA (minimising the transfer of hidden costs to the health sector) would make a strong argument for this target group. At the national level, various government structures exist where different sectors meet regularly. Economic Development Councils are usually mandated to test proposals for development against macro-economic policies, and they could also include the costs of proposed projects to the environment and to health in their analyses – these are now frequently still treated as externalities. In environmental protection councils, HIA's could be reviewed alongside EIA's, or various forms of merging different types of impact assessment could be explored. In National Councils for Science and Technology, multidisciplinary research could be promoted to strengthen the evidence base for HIAs. Figure 1 captures some of the decision-making associated with project development. Key intervention points, indicated as circles, are opportunities for intersectoral collaboration.

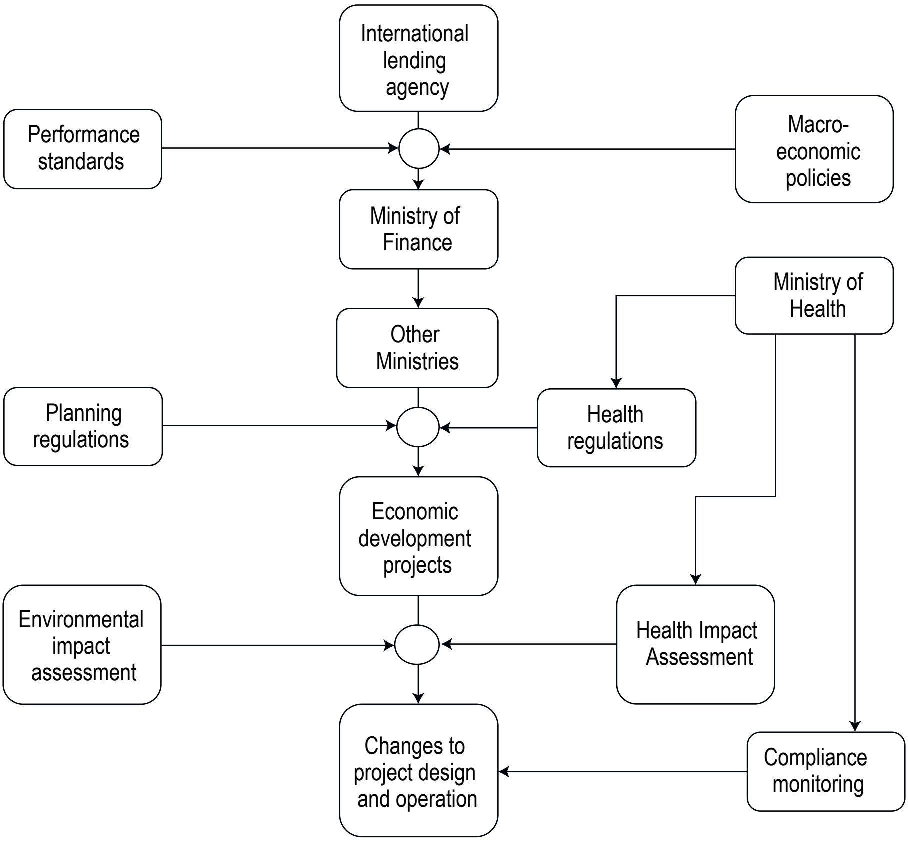

Figure 1. Some of the intervention points (indicated as circles) for influencing whether economic development projects affect human health.

Mitigation hierarchy

When a health impact has been judged significant, mitigation measures are recommended in order to reduce the impact to an acceptable level. These measures can be arranged into a hierarchy (Table 2). Items higher up in the hierarchy should be implemented first. Poorly designed mitigation measures frequently call for health education and more hospitals. A community should not be expected to change their behaviour because they are going to be exposed to an economic development project that increases health risks. Nor should it be taken for granted that economic benefits bestowed upon communities as a result of development project will trickle down to the household level and automatically result in household decisions to spend more on health.

Health should be protected by project design and operation. The cardinal rule of mitigation is to put multiple barriers in place, so that health is safeguarded even if one or more barriers fail. For example, multiple barriers for malaria control include:
- environmental engineering measures;
- water management practices;
- settlement location;
- housing improvement;
- distribution of livestock in relation to human settlements;
- provision of insecticide treated nets;
- rapid diagnosis and effective treatment;
- poverty reduction and gender empowerment (enables people to protect themselves and their families);
- deploying new vector control technologies.

Similar considerations apply to health enhancements. Enhancement is about maximising the health benefits of the project and identifying opportunities for improving the health of affected communities (Asian Development Bank 2018a). For example:
- using social investment to further improve the quality of life of affected communities or to support existing plans and programs by the public sector;
- providing vocational training to increase the employability of local workers;
- improving access to social services;
- promoting secondary industry;
- improving safe water supplies and waste disposal.

Table 2. The mitigation hierarchy and a vector-borne disease example.

Hierarchy	How	Vector-borne disease example
Avoid	Design out	Choose vector free localities for settlements, design out vector breeding
Stop at site	Management	Remove breeding sites
Reduce human contact	Personal protection	Insecticide treated nets and training in their use, repellents, poverty reduction
Repair	Medical treatment	Rapid diagnosis, surveillance, and effective treatment
Compensate	Finance and insurance	Provide funding to the medical sector to cope with additional medical demands

There is no universal health enhancement hierarchy equivalent to the mitigation hierarchy. Table 3 is a suggestion.

Healthy engineering design

The engineering design process is central to any large infrastructure project. It is methodical, highly iterative, and team based. It includes conceptualisation, feasibility assessment, establishing design requirements, outline design, preliminary design, detailed design, and execution planning. During this process the benefits, constraints, and costs of a wide range of options are reduced to a deliverable and detailed final design. It generally includes a high-level risk register or equivalent that is refined at each iteration. There is an opportunity to look at the potential environmental, social and health impacts of each iteration with increasing specificity and depth. Recommendations can then be made and fed back into the engineering design for the next iteration. If an HIA can be included in each iteration there is an opportunity to direct the design towards improved vector control technologies.

Experience shows that adverse vector-borne disease impacts of hydraulic infrastructure projects can often be traced back to cost-saving. Internal rate of return (IRR) is the interest rate at which the net present value of all the cash flows (both positive and negative) from a project or investment equal zero. It is used to evaluate the attractiveness of a project or investment. If the IRR of a new project exceeds a company's, investor's or lending agencies' required rate of return, that project is desirable. If IRR falls below the required rate of return, the project should be rejected. The reality of irrigation development in Africa South of the Sahara is, for example, that it is hard to achieve an IRR on investment. A positive IRR can often be achieved by cutting certain components or by phasing their implementation over a long period of time. There are various examples of irrigation schemes where the elimination of a drainage component led to serious malaria or schistosomiasis outbreaks. For example, schistosomiasis was associated with irrigation development without proper drainage in the Middle Awash Valley of Ethiopia (Kloos 1985, Kloos and Lemma 1977). In

Table 3. A health enhancement hierarchy with some examples (Asian Development Bank 2018a).

Hierarchy	Examples
Permanent modifications	Benefits that last the length of the project, such as roads with space for non-motorised users; parks and recreational facilities included in urban housing projects; hydraulic structures that are mosquito-breeding proof; vector proof housing
Enhancing equity	Ensuring that disadvantaged groups benefit, such as protecting and widening livelihoods; creating healthy choices, such as making the public realm attractive to users
Repeated actions	Maintenance and repair of project structures, including removal of vector breeding sites
Promoting healthy behaviour	Targeted health promotion campaigns, such as healthy eating, physical activity, protected sex, and use of insecticide treated bed nets
Enhancing medical care	Sustainable improvements to public clinics, that continue to function when project-related finance is removed, including rapid diagnosis and treatment of vector-borne diseases

the 1960s, engineers labelled the drainage component of an irrigation project in the Philippines as a public health component – an externality. The public health component would not be part of the calculations for the IRR – yet these tactics came back to haunt them when the health authorities pointed out that with the amount budgeted it would be far cheaper to permanently install a case detection and treatment programme for the disease in question (schistosomiasis) (D Bradley, personal communication).

Capacity building

There is a global lack of capacity to carry out HIA to an acceptable standard. It is often done by gifted generalists who have no specific training in health or vector-borne disease control. Such generalists rely on easy access to guidelines, textbooks, and manuals. They also rely on direct communication with suitable specialists, when they can identify them.

In other instances (for example, the construction of hydropower dams in eastern Anatolia, Turkey (personal observation)), the HIA was commissioned from a vector-borne disease specialist (main fears were for malaria and schistosomiasis to spread) whose report focused narrowly on the vector-borne disease outlook without taking the range of other dam-related health issues in that region into account. In general, if the HIA team is not multidisciplinary, then the HIA report will have a strong bias towards strengthening of health services.

The entire process of identifying a need for an HIA, commissioning it, doing it, reviewing it, and acting on the recommendations requires different kinds of competence. These have been captured in a competency framework and suitable training courses have developed (Birley 2011).

When a decision is made to recommend vector control as a mitigation measure, the default solution is to outsource to a local pest control company. Such companies are usually equipped to spray insecticides. They may not be equipped to check for insecticide resistance, undertake species identification, or to sample larval habitats. They may not be familiar with the principles of environmental management, or housing design, for vector control. They may understand the value of insecticide treated nets.

If resettlement villages are part of a project, the default solution may be to outsource to a town planning company. The result may be a reticulated water supply, flush toilets, mains electricity, and solid waste collection. But the houses are unlikely to be designed to exclude vectors. The resettled villagers maybe expected to pay the monthly charges for the utilities but have neither the income nor the experience to do so.

As the above examples illustrate, lack of capacity is a root cause of absent HIA practice or poor HIA performance. Creating an enabling environment should be the first target of any HIA capacity development efforts. Clear policy, legal and regulatory frameworks for HIA should guide procedures, and they should be aligned with similar frameworks for EIA and for sustainable development. For HIA, key actors are the Ministry of Health (as the national public health authority) and the environmental authority responsible for impact assessment. Staff in these two agencies need specific HIA training, focused on generating knowledge and expertise. Their skills need to be developed so they can successfully engage in intersectoral dialogue and negotiation. To sustain a human resource base for HIA, competency frameworks and staff performance standards (linked to regular appraisal) are essential. A problem-based learning kit was developed and tested by

PEEM in the 1990s and has served as the source for the development of custom-made training programmes in different parts of the world (Bos *et al.* 2003).

An Asian example of using health impact assessment to support intersectoral development

The Asian Development Bank (ADB) created the Regional Malaria and Other Communicable Disease Threats Trust Fund in 2013. Its remit was to support, for a five-year period, the ADB's developing member countries to develop multi-country, cross-border, and multisector responses to urgent malaria and other communicable disease issues (Asian Development Bank 2018b). The fund had a total budget of about $29,000,000. The associated projects were intersectoral. According to the final report, the key achievements were as follows.

1. galvanised malaria elimination leadership at the highest level and provided decision support for accountability;
2. introduced innovative mechanisms for malaria elimination financing and donor collaboration;
3. supported regulatory and disease control bodies to work more effectively, strengthen post-market surveillance of anti-malarials, and to collaborate with regional counterparts;
4. convened partners within countries and across borders to work toward the common goal of eliminating malaria;
5. stimulated the appetite for transformational digital interventions and improved capacity, resulting in increased surveillance and automated reporting of malaria and communicable diseases;
6. strengthened the role of HIA for malaria prevention in infrastructure projects and special economic zones in border areas.

Item 6 focused on increasing capacity to apply HIA in infrastructure projects in the five countries of Southeast Asia. The specific outcomes of item 6 included the following:

- three countries with country HIA guidelines developed;
- one regional HIA framework for special economic zones developed;
- HIA training modules developed;
- four countries with staff trained in HIA;
- four countries integrated HIA curriculum integrated public health and environmental programs;
- a regional network of HIA experts and universities established;
- three countries with intersectoral coordination on HIA;
- three countries with HIA policies in place or developed;
- four ADB supported infrastructure projects in malaria endemic areas applied HIA;
- ADB HIA tools developed including sourcebook and checklists;
- thirty ADB staff trained in HIA;
- HIA tools integrated into ADB processes.

One of the outcomes was the development and publication of the 'Good Practice Sourcebook on Health Impact Assessment' (Asian Development Bank 2018a). This publication represented a new iteration of ADB's concern about health impacts. The first iteration was 'Guidelines for the Health Impact Assessment of Development Projects' (Birley and Peralta 1992), associated with the PEEM project outlined in the introduction. The second iteration was 'A Primer on Health Impacts of Development Programs' (Peralta and Hunt 2003) considering health impacts sector by sector.

The sourcebook makes many references to the control of vectors and vector-borne disease in infrastructure projects. It also draws the reader's attention to other publications including one on preventing disease through healthy environments (WHO 2016). This publication suggests that:
- about 42% of the malaria burden in Asia is amenable to environmental management;
- environmental manipulation can reduce the malaria risk by about 88%;
- environmental modification can reduce the malaria risk by about 80%;
- environmental methods can be non-toxic, relatively easy to apply, cost-effective, and sustainable.

The role of the private sector

Many countries manage their economic development goals by licensing projects to the private sector. This is particularly the case in the extractive sectors including oil and gas and mining and minerals. A country may retain a 51% share of the project but allocate operational control to a multinational corporation. Many multinational corporations in the extractive sector have adopted Environmental, Social and Health Impact Assessment (ESHIA) as a standard planning tool. They have done so to maintain their reputation and their social license to operate (Birley 2005, 2011). In addition to budgets for mitigating the unintended impacts of their projects, these corporations often have social investment budgets for providing general enhancements to the well-being of the population.

Oil and gas projects in West Africa provide an example. These are very large projects that may require a construction workforce of 5,000 men for several years. They can be in areas with endemic malaria, an unknown potential for transmission of viruses that cause dengue, Zika fever and other arboviral disease, as well as a range of other communicable and non-communicable diseases. They attract large communities of squatters and create substantial economic inequalities in areas with high levels of poverty. They often require involuntary resettlement.

The multinational corporation usually tenders the ESHIA to multinational environmental consultancies. These are full of intelligent generalists with experience of conducting EIAs. Their knowledge of HIA is often limited and they may subcontract this to appropriately qualified subcontractors.

As with other economic development projects, there is a unique opportunity to include environmental methods for vector control in the design and operation of the project. The budget comes from the multinational corporation that owns the project.

The future

The impacts discussed in this chapter can be regarded as direct impacts of policies, plans and projects. There are, in addition, cumulative impacts that arise at local, national and global levels (Asian Development Bank 2018a, Birley 2011). For example, a set of development projects may be built on an industrial development site, owned by different sectors and corporations. There are likely to be cumulative local impacts such as pollution of the air shed, excess traffic, and inadequate waste disposal. More pressing still, are the challenges associated with global social and environmental change. These include the climate emergency and the growing scarcity of water supplies. Transformative global change is required to adapt to these challenges (IPCC 2012), but such change is not forthcoming. The mitigation measures built into new infrastructure development projects need to take account not only of the local impacts but also of the consequences of climate breakdown.

Conclusions

Over the past 30 years the HIA tool has grown from obscurity to mainstream but technical competence and capacity have not kept up. Opportunities for anchoring the tool more firmly arise sporadically and continue to grow. One of the challenges has been to ensure that the various stakeholders have an appropriate level of understanding of HIA and of the available vector control technologies. These stakeholders include financiers, project owners, engineers, environmental impact assessors, planners and medical workers.

Nevertheless, HIA thus far has proved to be the only viable entry point into sustainable intersectoral collaboration. The motivation of other sectors to engage fluctuates with the economic tendencies – when economies are up, social responsibility and sharing resources with other sectors to get full credit for the results are great motivators. After an economic downturn, sectors return to their core business and intersectoral programmes are the first ones to be cut back. This is exactly what happened to the Joint WHO/FAO/UNEP/UNCHS PEEM during the financial crisis that hit the UN in the mid-1990s – agencies withdrew their support and returned to sectoral business.

Equally important, perhaps, in the context of this textbook is to determine what knowledge the vector control community requires about intersectoral collaboration, development finance, engineering, planning, EIA, and HIA. Vector bionomics, insecticide resistance and genetic manipulation of vectors are all highly interesting topics for the medical entomologists, but in order to get a seat at the table where design issues of a project are decided, or where the resources for project activities are allocated, the vector control community will have to develop the skills and vocabulary that will make them be heard in the development debate.

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11. Integrated vector management for control, elimination and prevention-of-reintroduction of malaria in Sri Lanka: a historical review

Henk van den Berg[1], Gamini Manuweera[2] and Manonath Marasinghe[3]*
[1]Visiting Scientist, Laboratory of Entomology, Wageningen University, P.O. Box 16, 6700 AA Wageningen, the Netherlands; [2]Chemicals and Health Branch, United Nations Environment Programme, International Environment House 1, Chemin des Anémones 11-13, 1219 Châtelaine, Switzerland; [3]Anti-Malaria Campaign, Ministry of Health, 555/5 Elvitigala Mawatha, Colombo 00500, Sri Lanka; vandenberg.henk@gmail.com

Abstract

A review of malaria vector control in Sri Lanka was conducted to understand how the country successfully transitioned from control of malaria to elimination over the past century, and how vector control is being used to prevent the reintroduction of malaria. The case study is expected to provide examples and lessons learnt to other programmes or countries. Malaria vector control in Sri Lanka has faced major challenges of sudden and unstable transmission, insecticide resistance, movements of settlers and refugees, and programme fatigue. Early on, the importance of vector ecology and environmental factors in malaria epidemics was recognised, and in response, vigilance units were set up at periphery level. After intense indoor residual spraying campaigns with DDT (1950s and 1960s) and, subsequently, malathion failed to end malaria (1970s), pesticide policy was developed in the 1980s, and a routine system of monitoring of insecticide resistance was incorporated into the malaria control programme. This system was the basis for a proactive scheme of rotation and mosaics of insecticide applications to manage resistance. Entomological and epidemiological surveillance data were used to stratify malaria incidence, identify high-risk groups or locations, and plan appropriate interventions, including larval vector control. The programme adapted to changing epidemiological circumstances. After Sri Lanka was certified malaria-free in 2016, the system of surveillance and control was reoriented, with malaria risk mapping providing the basis for decisions on proactive vector control in receptive and vulnerable locations. The vector control programme has been disease-specific, but in recent decades the entomological expertise has regularly been shared with the dengue control programme, which is an example of integrated vector management. Further coordination on vector surveillance and control between programmes will be vital to improve the efficiency, effectiveness and financial sustainability of operations.

Keywords: entomological surveillance, insecticide resistance, inter-sectoral collaboration, malaria elimination, vector control

Introduction

When well implemented, vector control can lead to drastic reductions in the burden of vector-borne diseases, as demonstrated in various historic examples (WHO 2017). Vector control has been emphasised as being key to the prevention and elimination of vector-borne diseases, as presented in its global strategic framework on integrated vector management (IVM). More recently, WHO launched the Global Vector Control Response (GVCR), which was based on the principles of IVM (WHO 2004, 2017). The IVM approach seeks to make vector control more effective, efficient and sustainable, and relies on functional intersectoral collaboration, evidence-based decision making and an integrated approach to implementation (WHO 2012b, 2016).

Despite international policy support for IVM, the uptake at country level has reportedly suffered from insufficient political buy-in necessary for the reorientation of vector-borne disease control programmes (Alonso *et al.* 2017, WHO 2017). Apparently, the transition towards an IVM approach has been a major challenge for countries with a centralised and linear management structure for vector control.

Recent studies in Africa have suggested that only few countries made significant advancements in IVM over the past decade (Chanda *et al.* 2015, 2017, Mutero *et al.* 2015, Okia *et al.* 2016); the majority of countries have been struggling to implement IVM because of challenges to establish intersectoral collaboration and limited entomological capacity (Chanda *et al.* 2017).

One of the key elements of IVM is an integrated approach, implying the integration of vector control methods (chemical, non-chemical) and addressing several diseases, where appropriate (WHO 2012b). Countries have been applying IVM principles mainly to the control of malaria alone (Chanda *et al.* 2017), whilst the toolbox of malaria vector control interventions has been very limited, with only two vector control methods, insecticide-treated nets and IRS, recommended as core interventions for malaria control (WHO 2019).

Important contemporary questions about IVM are: how does a country transition towards IVM? Which existing factors enable IVM? How is intersectoral collaboration established? And, how can vector control adapt to epidemiological changes? Such questions, which are inevitably embedded within local environmental and institutional context, require in-depth studies on a case-by-case basis.

The objective of this study is to provide better understanding into the decision, practices and organisational structures in relation to disease vector control. Sri Lanka was selected for historical review, as a country with a long history of malaria vector control, having successfully eliminated malaria, whilst diseases such as dengue continue to cause a public health burden. The study could provide lessons learnt on successes or failures for the benefit of other programmes or countries. Some parts of this study have been used in the context of preparing a road map for the development of alternatives to DDT under the Stockholm Convention (UNEP 2019).

Sri Lanka is an island country in South Asia, with 25 districts organised into nine provinces, and a contemporary population of 21 million. Sri Lanka has a tropical climate, and can be divided into a dry, intermediate and wet zone (Figure 1). In the past, malaria has been endemic in the dry and intermediate zones, where peak transmission occurred mostly during the rainy season. Conversely, in the wet zone, malaria has been epidemic during dry spells. Major malaria epidemics in Sri Lanka have coincided with periods of drought in El Niño years (Bouma and Kaay 1996).

Several phases in malaria vector control can be identified in Sri Lanka history, starting with interventions from 1940, followed by the first Global Malaria Eradication Programme, and subsequent phases of malaria control, leading to malaria elimination, and the post-elimination phase (Table 1).

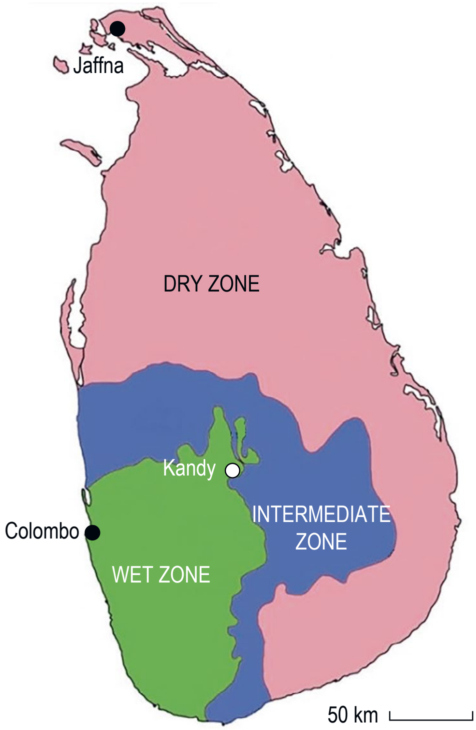

Figure 1. Map of Sri Lanka, showing three climatic zones (adapted from Punyawardena 2007).

Table 1. Phases of malaria vector control in Sri Lanka.

	Phase	Period	Result
I	Early malaria control	1911-1955	Control
II	DDT indoor residual spraying during Global Malaria Eradication Programme	1955-1969	Pre-elimination
III	Switch to malathion for indoor residual spraying	1969-1980	Pre-elimination
IV	Pesticide regulation and insecticide rotations	1980-2009	Control
V	Period until certified elimination of malaria	2009-2016	Elimination
VI	Prevention of reintroduction of malaria	from 2016	Post-elimination

Early malaria control (1911-1955)

The anti-malaria campaign (AMC) was established in 1911 under the line Ministry of Health, with the task of malaria control. After some years, *Anopheles culicifacies* was incriminated as malaria vector in Sri Lanka (Carter 1930). Early vector control methods included draining and filling of water bodies and clearing of forests.

The importance of *An. culicifacies* as malaria vector became evident through the major malaria epidemic of 1934-35, causing an estimated 5.5 million cases and 80,000 deaths on a national population of 5.4 million (Briercliffe 1936). This vector is most prevalent in the dry zone, where it prefers to breed in shallow pools with clear water exposed to sunlight, such as sand and rock pools in river beds, river margins, irrigation channels, and wells.

In 1934, however, an exceptional drought shifted the breeding of this vector to the wet zone. Major rivers and their tributaries in the wet zone were reduced to small streams, leaving numerous pools in their sandy and rocky riverbeds over long distances flanking human habitation. This provided favourable breeding conditions for *An. culicifacies* resulting in exceptionally high vector mosquito densities recorded inside people's homes (Briercliffe 1936). These facts, together with a non-immune human population, whereby infected persons exhibited high gametocyte densities in their bloodstream to be picked up by the biting vectors, were conducive for a very sudden and disastrous epidemic (Briercliffe 1936).

Around that same period, sanitary engineers experimented with environmental modification to reduce pool formation in river beds (Worth 1937). However, there are no reports that environmental modification of river beds was ever implemented beyond the pilot scale.

'Vigilance units' were set up following the 1934-35 epidemic, to examine and report on the breeding of *An. culicifacies* in rivers and streams in the epidemic zone (Gunaratna 1956). From 1940, vigilance units also involved the collection of adult mosquitoes and detection of malaria cases, with a focus on the adult vector in the epidemic zones and on case detection in the endemic zone.

In 1946, indoor residual spraying with DDT was introduced, and larval control methods were stopped because they were no longer considered necessary. Indoor residual spraying with DDT was followed by a sharp reduction in the number of malaria cases, and a drop in mortality, despite weather conditions known to favour malaria outbreaks (Rajendram and Jayewickreme 1951). This positive result provided confidence that malaria transmission could be interrupted (Karunaweera *et al.* 2014). During this post-WWII period, the country experienced substantial improvements in living standards and health care (Langford 1996), which may also have influenced the observed pattern in malaria incidence.

Elsewhere, in Greece, DDT spraying achieved almost complete interruption of malaria transmission in selected areas in the 1950s. This outcome was important for the launch of the Global Malaria Eradication Programme (GMEP) in 1955. Nevertheless, the local vector in Greece developed resistance to DDT (Livadas and Georgopoulos 1953). This experience contributed to the notion that the intensive spraying to eradicate malaria, with strong external support, should be a time-limited effort of 4 or 5 years (Spielman *et al.* 1993).

DDT indoor residual praying during Global Malaria Eradication Programme (1955-1969)

Sri Lanka joined the global malaria eradication programme (GMEP) in 1956 (Karunaweera *et al.* 2014). Sri Lanka was selected as one of the first 'pilot' countries of the GMEP, with an 'attack phase' of the eradication programme from 1958-1963. During these five years, malaria incidence dropped further to merely 17 cases in 1963 (Figure 2), 11 of which were imported. The intensive spraying

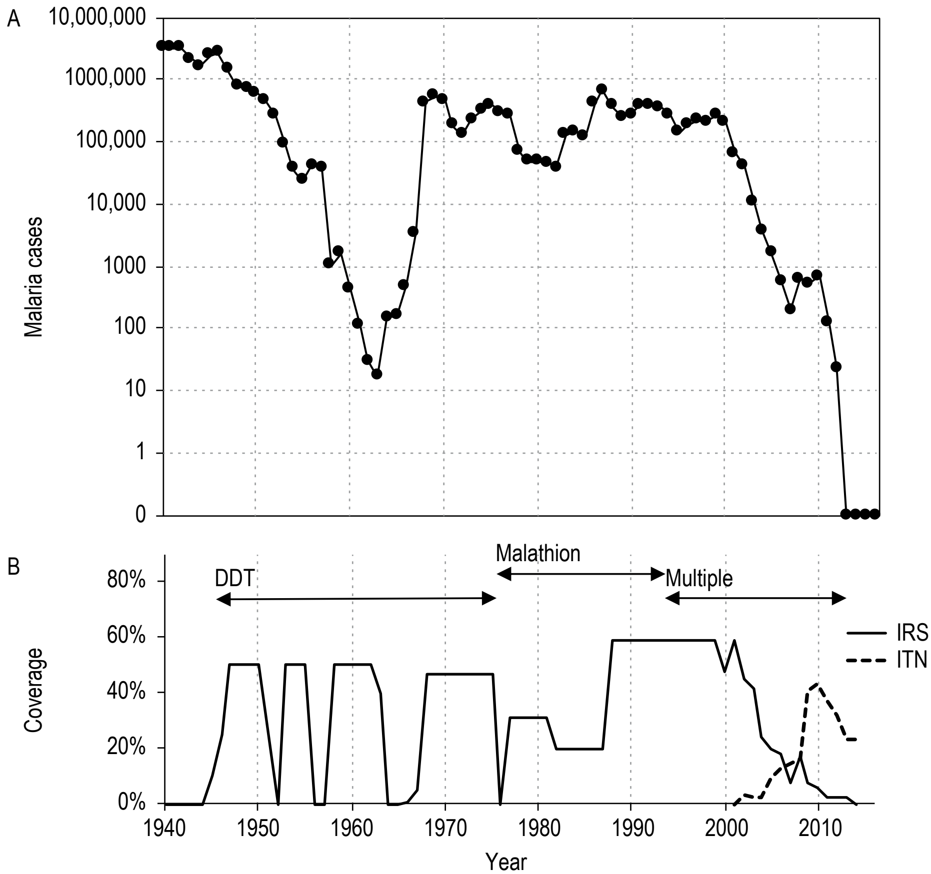

Figure 2. (A) Local cases of malaria (on the logarithmic scale), and (B) percentage at-risk coverage by the two core vector control interventions, indoor residual spraying (IRS) and insecticide treated nets (ITNs) during the past 80 years. Use of DDT, malathion and multiple insecticides used for IRS is indicated. For IRS coverage data prior to 2000, the plateau levels are approximations (source: Anti-Malaria Campaign, Ministry of Health, Colombo).

campaign was stopped following the transition from the attack phase to the consolidation phase of the GMEP.

However, soon after cessation of spraying, several active foci of transmission were detected. These were identified as areas with slash-and-burn agricultural settlements, development projects and gem mining activities (Fernando and Warusavithana 2011). One extensive area of water-filled gem pits and a nearby pilgrimage site, drawing people from all over the country, most likely facilitated the further spread across the country. Aided by population movements and a stepped-down surveillance system after spraying was stopped, a sharp resurgence of malaria incidence took place in the absence of vector control interventions, reaching over 500,000 cases in 1969. Hence, the eradication of malaria had failed.

DDT spraying was gradually resumed, supplemented in some areas with lindane to overcome temporal shortage of DDT (Fernando and Warusavithana 2011, Rajendram and Jayewickreme 1951). However, despite spraying, the number of cases did not decline. DDT resistance was first detected through susceptibility testing in 1969, and subsequent tests indicated that resistance was spreading (Clarke *et al.* 1974).

Switch to malathion for indoor residual spraying (1969-1980)

The next phase was marked by a switch from DDT to malathion. To verify whether the efficacy of DDT was reduced, the AMC commissioned a field study, from 1973-75. An independent evaluation team with international representation concluded that DDT resistance was one of the main reasons for the resurgence of malaria (Fernando and Warusavithana 2011); other reasons were poor coordination with general health services and poor community acceptance of IRS. Instead of DDT, the team recommended malathion for use in IRS, to be used within a time-limited schedule considering the previous experience with the development of insecticide resistance. By 1976, DDT resistance had become widespread (Fernando and Warusavithana 2011), and in the same year, DDT was banned from all uses in Sri Lanka.

A second field trial was conducted in 1975-77, to demonstrate the effectiveness of malathion. The results showed a reduction in malaria in the sprayed village compared to the outside control villages (Fernando and Warusavithana 2011). In addition, susceptibility tests from samples at nine sites throughout the country indicated that resistance to malathion in *An. culicifacies* was non-existent.

It was recognised that concurrent use of the same insecticides for public health and in other sectors, notably agriculture, might accelerate the development of resistance in malaria vectors. Therefore, to preserve the efficacy of malathion (and fenitrothion, as alternative insecticide) for as long as possible, the evaluation team recommended that they should be banned for all other purposes except for IRS. These results and recommendations were promptly adopted. In April 1976, an intersectoral decision was taken jointly by the ministers of health and agriculture that import of malathion (and fenitrothion, as alternative to malathion) for agricultural purposes would be prohibited, and later on, legal status was given through an Act of Parliament.

In the late 1970s, IRS with malathion was gradually introduced into the endemic districts to replace DDT. The DDT-spray teams were re-engaged and re-trained, including on chemical safety precautions of the acutely toxic organophosphate insecticides.

Gaining substantial international support for procurement of insecticides and spray equipment, an intensive IRS spraying campaign was implemented over a 5-year period (1977-82), with 2-4 applications per year. In view of the biting and resting habits (e.g. time and habitat of biting and resting) of the main vector *An. culicifacies*, temporary structures, settlements and animal sheds were included in the spraying programme (Fernando and Warusavithana 2011). Also, a small component on chemical larviciding, using temephos, was included in the program.

Over the 5-year period, an impressive 85% drop in malaria cases was achieved. However, malathion resistance was detected in 1982 (Herath *et al.* 1987). To delay the build-up of malathion resistance, and reduce input costs, the intensity of application was scaled-down after 1982. IRS was fine-tuned according to a stratification of malaria risk in each area, with malathion applied 0, 1, 2 or 4 times per year, or as focal application.

Unfortunately, malaria incidence went up once again, from 38,000 in 1982 to more than 100,000 cases in 1983, reaching almost 700,000 cases in 1987. This alarming trend was largely attributed to the development of large irrigation schemes during the 1980s. Malathion was still considered effective at this time, despite a slowly increased resistance frequency (Herath *et al.* 1987). Over one million settlers, most of whom non-immune for malaria, moved into the newly cleared irrigation areas located within the malaria-endemic zones. The settlers were initially living in temporary housing not adequately covered by IRS. Despite the introduction of various mitigation measures, including provision of prophylactic medication to new settlers, and gradual establishment of medical institutions, a new malaria epidemic was inevitable (Jayawardene 1993). At this time, *Plasmodium falciparum* parasite resistance against the first-line drug, chloroquine, was beginning to develop.

To make matters worse, some operational shortcomings in malaria control were identified. After malathion had been successfully used for 5 years, there was mounting evidence of refusal of malathion for indoor residual spraying by householders. Apparently, the acceptability of the strong odour emitted by malathion had been overlooked. Also, morale among spray teams had sunk, along with the quality of supervision. A side-effect was that the unauthorised use of malathion by farmers became a widespread problem, leading to reduced quantities available for IRS (Fernando and Warusavithana 2011). Some years later, in 1989, malathion resistance had increased, and by 1995, almost all areas tested showed high levels of malathion resistance.

The civil conflict in the North and East (1983-2009) adversely affected the malaria situation. Access became severely restricted, and the supply chain of medication and insecticides was regularly broken up, thus disrupting the malaria control programme in conflicted-affected areas (Fernando and Warusavithana 2011). These areas, which previously had low incidence levels, suddenly became malaria hotspots, thus shifting the country's centre of gravity of malaria.

Hence, the intensive spray campaign with malathion did not bring the target of malaria eradication much closer.

Pesticide regulation and insecticide rotations (1980-2009)

More constructive progress was made after pesticide legislation was established in 1980, with further additions to the legislation made in 1983 and 1985. Under the Control of Pesticides Act, the import, packaging, labelling, storage, formulation, transport, sale, and use of pesticides started to be regulated. The Act was administered by the Registrar of Pesticides which, like in most countries at risk of vector-borne diseases (Matthews *et al.* 2011), was housed within the Ministry of Agriculture. This authority was responsible for approval of pesticide products, regulating the purposes and conditions of use of each product. A Pesticide Technical and Advisory Committee with representatives from related agencies, including the Ministry of Health, served as advisory body. Moreover, pesticide analysts were designated, enforcement officers appointed, and pesticide imports controlled.

With devolution of administrative powers of government in 1989, the malaria control programme was radically changed. The implementation and logistics of the malaria control programme were transferred from AMC to the provinces and districts, thus increasing local accountability of the program. Technical leadership, including policy, guidelines and monitoring, remained with the AMC at national level.

The decentralised programme continued to rely on IRS for vector control. After village-level trials in 1993-94 had shown reduced efficacy of malathion, this insecticide was replaced by lambda-cyhalothrin and fenitrothion in Kurunegala and Puttalam Districts, respectively. In these two districts, the change in insecticide choice was followed by a major decline in malaria cases from 1993-96 (Fernando and Warusavithana 2011). Consequently, the pyrethroid lambda-cyhalothrin and the organophosphate fenitrothion were added to the insecticide arsenal for malaria control.

Insecticide rotations

In line with the contemporary international guidance, a new strategy was implemented whereby chemically unrelated or partially-related insecticides were used in a rotational and mosaic scheme of IRS. The aim was to delay the development of resistance and reduce malaria transmission, by using different insecticides in adjacent areas and by alternating the use within each area. The insecticides used were the organophosphates malathion and fenitrothion and the pyrethroids bifenthrin, cyfluthrin, deltamethrin, etofenprox, lambda-cyhalothrin. Malathion and fenitrothion were last used in 2001 and 2009, respectively. From 2009, only pyrethroids were used for IRS.

Susceptibility tests on *An. culicifacies* and on secondary vector *Anopheles subpictus* have been conducted routinely since 1991 in more-or-less fixed sentinel sites across the island. This provided an evidence base for decision making on the insecticides selected at district level. Analysis of the available data suggested that the rotational spray regimen has likely delayed the development of resistance, and avoided widespread resistance against the new insecticides (Kelly-Hope *et al.* 2005). Nevertheless, data from annual reports from 2012 and 2015 indicated high resistance in *An. subpictus* against bifenthrin, cyfluthrin, deltamethrin and permethrin was becoming widespread at the tested sites, whereas *An. culicifacies* remained mostly susceptible to the pyrethroids, with the exception of a few sites with moderate resistance to permethrin or cyfluthrin. A possible explanation for this difference between the two species is that *An. subpictus* is known to breed more than *An. culicifacies* in rice irrigation systems, and will thus be more exposed to agricultural use of the same or related insecticides (Kelly-Hope *et al.* 2005).

Evidence base for interventions

A range of entomological studies were conducted in Sri Lanka in the 1990s and 2000s, which generated valuable evidence on larval breeding ecology, vector incrimination, host preference, biting behaviour, and resting behaviour.

Long after *An. culicifacies* had been pinpointed as malaria vector in Sri Lanka, field studies reported as many as ten anopheline species found to be infected with human parasites, thus having potential as malaria vector (Mendis *et al.* 1990, Mendis *et al.* 1992, Ramasamy *et al.* 1992). *An. culicifacies* was singled out as the principle vector in most areas, but *An. subpictus* and *Anopheles annularis* were incriminated as main vectors in specific settings of irrigated agriculture, such as rice fields.

Breeding preferences of malaria vectors were rather well described, owing to several detailed larval surveys. A study in a natural stream, which was part of a reservoir cascade irrigation system, indicated that fortnightly flushing of the stream would eliminate most breeding sites of *An. culicifacies* (Konradsen et al 1998, Matsuno et al 1999). However, engineering-based interventions have not been adopted in the malaria control programme (Konradsen *et al.* 2000). Studies on larval control using insect growth regulator pyriproxyfen in gem pits demonstrated the local reduction of adult vectors and malaria incidence (Yapabandara *et al.* 2001), underpinning the importance of this intervention for the programme.

Peak biting of the main vectors *An. culicifacies* and *An. subpictus* was found to be during the early and late evening (Amerasinghe and Indrajith 1995, Dewit *et al.* 1994), a behaviour which could suggest moderate suitability of insecticide-treated nets to reduce transmission. *An. culicifacies* and *An. subpictus* have shown to bite both indoors and outdoors and, after a bloodmeal, commonly rest inside houses and animal sheds, suggesting that they are reasonable, but not perfect, targets for IRS. *An. culicifacies* feeds both on humans and animals, and can be found far away from human habitation. *An. subpictus* feeds mostly on animals. Despite these zoophylic feeding habits, it was found that females of both vector species commonly took multiple bloodmeals per cycle of egg production, suggesting their efficiency as vectors of disease pathogens (Amerasinghe and Amerasinghe 1999).

New interventions

From the late 1980s, the AMC made permethrin available to aid in the treatment of commercially available bed nets, but the scale of these early activities is unknown. Then, with external support, insecticide-treated nets (ITNs) started to become distributed from 1999, and long-lasting insecticidal nets became available from 2002 (Abeyasinghe *et al.* 2012). Studies indicated above 80% use compliance to ITNs (Fernando and Warusavithana 2011, Whidden *et al.* 2015).

Moreover, in special transmission settings, around army camps and the camps of displaced persons and during open air religious festivals, space spraying was conducted in addition to IRS for an immediate killing effect on malaria vectors to reduce outdoor biting (AMC 2016).

In addition, from 2001, a novel approach to vector control was implemented that used 'farmer field schools' for active participation of farming communities in the control of vectors breeding in irrigated rice environments in addition to prevention and control of agricultural pests (Van den Berg and Knols 2006, Yasuoka *et al.* 2006b). This approach, which was labelled 'integrated pest and vector management' (IPVM) was a collaboration between the Department of Agriculture, Mahaweli Authority and AMC (Van den Berg *et al.* 2007). Available evidence suggested that the IPVM approach suppressed anopheline densities (Yasuoka *et al.* 2006a). AMC continued supporting IPVM into the malaria elimination phase as a method to reduce malaria receptivity in rice-growing areas.

Period until certified elimination of malaria (2009-2016)

After the civil conflict in the North and East, which had lasted over 30 years, had been resolved in 2009, the country aimed for malaria elimination once again (AMC 2016). The objectives were to interrupt transmission of *P. falciparum* by 2012 and *Plasmodium vivax* by 2014. Malaria incidence had remained relatively high in the districts in the North and East that had been affected by the conflict, and that were rehabilitated from 2009. In these districts, malaria control operations and human resources were gradually restored over a period of four years.

The epidemiological surveillance system was stepped-up country-wide. Previously, surveillance included passive and active case detection. This system was further strengthened with active case detection in receptive areas and among vulnerable populations, using house-to-house visits and mobile malaria clinincs, to detect cases not reporting to health facilities (Wickremasinghe *et* *al.* 2014). AMC also started classifying cases as locally-acquired (indigenous) cases and imported cases. Slowly, it was observed that indigenous cases declined while the proportion of imported cases increased (AMC 2016). The intensity of surveillance was increased to detect the last indigenous cases. Most of the last indigenous cases were among military personnel stationed in camps near forested natural habitats where the main vector *An. culicifacies* bred.

The entomological surveillance was conducted through routine sampling at sentinel sites. In addition, high-risk areas were regularly spot-checked, and case-based entomological surveillance carried out, sampling larval occurrence, adult mosquito behaviour, and insecticide susceptibility. Resistance data were entered into a national database on insecticide resistance and used for selecting insecticides for IRS (AMC 2016).

Vector control activities and entomological surveillance outcomes were discussed at monthly review meetings, where regional malaria officers reported and planned on their vector surveillance and vector control activities, and reported on notified malaria cases. This mechanism enhanced coordination on surveillance and control between the districts and the central task force. District data were entered into a national database which has been reviewed every six months at AMC (AMC 2016).

Coverage of populations with IRS had been much reduced since the previous phases of malaria control. Macro-level stratification was conducted to tailor IRS, and spray frequencies (1-2× annually), according to malaria risk in each stratum. As the number of indigenous malaria cases declined, IRS was gradually phased out, being replaced with insecticide-treated nets, which were provided with international funding support (Abeyasinghe *et al.* 2012) (Figure 2). IRS and ITNs were increasingly targeted to receptive areas and among vulnerable populations (Wickremasinghe and Newby 2016), including gem miners, 'chena' settlements (slash-and-burn agriculture), military premises and other mobile sections of society.

In the final years before elimination, insecticide-treated nets were used as main vector control intervention, targeted to receptive areas and vulnerable populations.

Additional interventions were aimed at the vector's larval stage. This included larviciding (mainly using temephos), environmental modification, integrated pest and vector management, and use of larvivorous fish. Based on data from entomological surveillance and past malaria incidence, these interventions were targeted to gem mining areas (with most gem pits 1.5 m in diameter and 1 m in depth) (Yapabandara and Curtis 2004), river beds bordering human habitation, irrigated rice systems, and locations of detected cases. In particular, the filling of numerous abandoned pits in gem mining areas may have had an important contribution to the elimination of malaria.

The system of early detection and treatment of cases, together with entomological surveillance and proactive vector control, eventually interrupted malaria transmission (Senaratne and Singh 2016). The last indigenous cases were detected in October 2012, and without a relapse of malaria cases, Sri Lanka was certified malaria-free by the WHO in 2016.

Prevention of reintroduction (from 2016)

Present-day Sri Lanka is in the post-elimination phase for malaria. The AMC and its partners are implementing a national plan to sustain the malaria-free situation to prevent reintroduction. Interventions include the screening of passengers at points of entry and provision of access to prophylactic chemotherapy for citizens travelling to malaria-endemic countries. The country is also in the process of realigning its entomological surveillance and vector control activities to the new situation.

In 2017, the AMC developed and adopted a strategy and action plan on IVM. The purpose was to ensure that receptivity to imported malaria cases is reduced, particularly in highly vulnerable locations. 'Receptivity' implies the potential for malaria outbreaks; 'vulnerability' implies the risk of importing malaria from nearby malaria-endemic populations (Smith *et al.* 2009). After the plan was completed, a process of adaptation took place whereby the system for vector surveillance and vector control was adapted to the requirements for the post-elimination phase of malaria (AMC 2014, 2016).

Vector surveillance

Over the past decades, the AMC has operated an entomological surveillance system in malaria-endemic and at-risk districts. On average, a district-level team sampled two sentinel sites and 2-3 spot check sites per month. In the prevention-of-reintroduction phase, sustained vigilance is of the essence, and entomological surveillance continues play a vital role to provide local parameters on vectorial capacity needed to assess malaria risk. Late 2017, a reorientation workshop on entomological surveillance was conducted for staff from the districts. A critical assessment of sampling methods and techniques was carried out to adjust the entomological surveillance to the post-elimination phase. The new system included four types of surveillance: routine and extended routine sentinel sites, proactive spot checks, larval surveys and reactive spot checks. Moreover, the frequency of each sampling technique was reoriented to each type of surveillance. The sentinel sites was reduced and the number of spot checks increased, thus, adapting the system to the identification of high receptivity sites as the basis for proactive vector control action. In accordance with these adaptations made, national guidelines for entomological surveillance have been revised, and staff trained.

Decision support

During the malaria elimination phase, vector control operations were mainly guided by the localities where malaria cases were detected. However, in the absence of indigenous malaria cases since 2012, vector control was gradually guided by malaria risk, which is the combination of receptivity and vulnerability.

In 2016, AMC has piloted malaria risk mapping in one district, by producing overlays of maps for receptivity and vulnerability to malaria. Support for a GIS expert was provided by the Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM). The receptivity was modelled by using local estimates of vectorial capacity, remote sensing data on water surface area and land use, demographic data, and monthly meteorological data (particularly to forecast vector proliferation in the wet zone during droughts). Vulnerability was determined from GPS-referenced Annual Parasite Index (API) data available in historic records, supplemented with local information on vulnerable populations (e.g. communities with exchanges to India, migratory populations, foreign workers, tourists).

Risk mapping was extended to the entire country, using entomological data, historic case data, as well as locally obtained environmental data; remote sensing could not yet be scaled up after the pilot project. Initially, mapping was conducted at the level of Medical Officer of Health area, which is a regional health administrative division serving a minimum population of 50,000 with large variability in size. However, the initial mapping produced malaria risk data that were too course-grained for vector control response action.

In 2019, fine-grained mapping of malaria risk was started at the smallest administrative unit, the Grama Niladhari (GN) division (average population 1,500). Once finalised, AMC plans to routinely update the available risk maps to capture the dynamics in vulnerability and receptivity. However, AMC is facing the challenge of completing and, subsequently, updating, the maps of all 14,000 GN divisions for the entire country, but has started with areas pre-selected as the most vulnerable.

Interpretation of the data is done by regional teams in order to establish three risk levels of malaria risk: low, moderate and high-risk areas, while technical inputs are provided in monthly review meetings at central level. Within GN divisions with moderate or high malaria risk, foci of few km^2 with high receptivity and vulnerability will be identified. These fine-grained maps and high-risk foci on malaria risk provided decision support for vector control activities at periphery level.

Vector control action is used proactively in high-risk focus locations and at sites where imported and introduced cases occur, having considered the entomological surveillance data. Vector control action consisted of ITNs and IRS, in combination with supplementary control methods such as larviciding and environmental modification and manipulation. So far, proactive vector control action has been targeted only at focus locations with potentially high malaria risk, but without proper risk assessment. This information-based system will help to improve the effective and efficient use of limited resources where and when most needed (Kelly *et al.* 2012). AMC plans to develop appropriate proactive vector control strategies tailored to moderate risk areas, and to revise vector control guidelines.

A new chapter in Sri Lanka's history of malaria vector control was the recent detection of *Anopheles stephensi*, an important malaria vector in urban areas in India and the Middle East. This invasive species, which likely entered into Sri Lanka from India, was first detected in 2016 and soon detected in five more districts in the North and East of Sri Lanka (Dharmasiri *et al.* 2017, Surendran *et al.* 2018). This urban malaria vector was seen as a potential threat to Sri Lanka's malaria elimination status. Since 2017, AMC attempted to eliminate this introduced species through a combination of IRS, ITN and larval control. Soon, however, bioassay testing revealed that this species was highly resistant to the adulticides being used in Sri Lanka. Hence, the strategy was altered to the use of larvivorous fish, chemical larviciding (using temephos) and environmental modification, depending on the larval habitat. Since then, the vector has reportedly been suppressed to undetectable levels in three districts. This species still prevails at low densities in the three other districts, where it could increase following favourable weather.

Coordination on vector-borne diseases

In Sri Lanka, the control, elimination and prevention-of-reintroduction of malaria has been conducted largely as a disease-specific programme. Arguably, the single-disease focus may have been a factor in achieving the successful elimination of malaria. However, the value of establishing functional coordination with other vector-borne disease programmes has recently become more apparent. Whilst malaria has been eliminated, several other vector-borne diseases are increasing. The malaria teams in the districts have entomological skills and resources that are required for control of other vector-borne diseases.

Dengue epidemics have in the past two decades become progressively more severe, causing a substantial public health burden, with a particularly large outbreak occurring in 2017 (Rathnayake *et al.* 2018). In the past, the AMC was leading vector surveillance and control of dengue, but in 2005, a separate National Dengue Control Unit was established in the Ministry of Health. An urgent need was identified for dedicated entomological staff for dengue control at central and periphery level (Tissera *et al.* 2016), but reportedly, this need has not yet been fully filled. Over the years, malaria staff from the AMC in the districts have been providing their assistance to their counterparts in the dengue unit with respect to the sampling, species identification, and identification of breeding sites of dengue vectors. Malaria staff have assisted in the routine vector surveillance and reactive vector control response to localised dengue outbreaks. In some regions dengue vector control is predominantly done by the malaria control teams. An addition with the detection of *An. stephensi*, which shares common breeding sites with dengue vectors, a common platform for larval surveillance and reporting has been used.

A Presidential Task Force for dengue control was established in 2010 with multisectoral participation, seeking to mobilise communities and other partners in source reduction to control the dengue vector. However, this multisectoral task force has not yet taken on board vector-borne diseases other than dengue.

At the time of writing, activities to explore options, mechanisms and administrative arrangements for improving the efficiency and sustainability of surveillance and control operations between the programmes on dengue and malaria are yet to begin. Full integration of the malaria and dengue programmes is not considered desirable by the AMC. As an integrated programme, resource allocation would likely prioritise the disease with the highest public health burden, at the expense of preventing the reintroduction of malaria. Rather, there is a need for improved coordination and sharing of information and resources between the dengue and malaria programmes at district level; this would increase efficiency and contribute to financial sustainability for the prevention-of-reintroduction of malaria. With upscaling of larviciding and space spraying for dengue vector control, the need for a common policy on the use of insecticides for the malaria and dengue programmes is increasingly felt.

Cutaneous leishmaniasis is an emerging disease in Sri Lanka (Siriwardana *et al.* 2019). The recent increase in cases is possibly associated with the termination of IRS against malaria, because elsewhere, IRS has been shown to be effective against cutaneous leishmaniasis (Faraj *et al.* 2016). Routine vector control operations specifically targeting the sandfly vectors of leishmaniasis have not yet been planned. The AMC is the designated authority for control of leishmaniasis, which suggests there is good prospect for effective coordination on vector surveillance and control between malaria and leishmaniasis. But the evidence base on the transmission and effectiveness of vector control methods is a perceived gap that must be bridged.

The AMC teams in the districts also assist in the control of other vector-borne diseases for which no or inadequate dedicated entomologists are available, including for Japanese encephalitis, schistosomiasis and lymphatic filariasis.

Hence, the AMC has reoriented the vector surveillance system and the decision support system for vector control to the prevention-of-reintroduction phase. The AMC continues to hold monthly review meetings for its district staff at central level as an essential forum for two-way feedback.

Discussion

The Sri Lankan example presents several best practices and lessons learnt in relation to IVM. Early on, an enabling factor in malaria control has been at the policy front. Pesticide policy and regulation have been pivotal in facilitating the changes in the methods of malaria vector control. When DDT resistance had become widespread, it was banned for all uses. The Malathion Control Act effectively prohibited the use of malathion for uses outside of public health. The policy change was made on the basis of field studies demonstrating effectiveness of malathion and showing control failure of DDT. The absence of a pesticide manufacturing sector in Sri Lanka meant that there was no direct economic pressure that might have influenced the policy decision on malathion (Pearson *et al.* 2013).

After the Control of Pesticides Act was enacted in 1980 and fully implemented in 1984, the regulation of pesticides was reinforced. The process of registration submitted insecticide products for malaria control to local tests on suitability and bio-efficacy (Manuweera 2007). Moreover, insecticides were screened for their safety to human health and the environment. The Pesticide Registrar, with representation in each district, monitored pesticide regulatory activities, including the local availability, purpose of use and conditions of use of available pesticide products. The Pesticide Act and regulatory system thus played a crucial role in the monitoring and control of insecticide efficacy and resistance in public health and agriculture.

Pesticide policy and regulation played a role not only in malaria control and agriculture, but also in reducing pesticide self-poisoning, which has been a problem in Sri Lanka accounting for an important part of suicides. In 1995, all WHO Class I pesticides were banned for import or sale, and in 1998, endosulfan was banned. These bans coincided with a sharp decline in suicide rates, indicating that strict pesticide regulatory control can have a positive effect on reducing pesticide self-poisoning, without compromising agricultural production (Gunnell *et al.* 2007, Manuweera *et al.* 2008)

Surveillance has been a strength throughout the Sri Lankan programme. Back in the 1930s, vigilance units effectively integrated the epidemiological and entomological surveillance, and were used to improve targeting of vector control operations. As malaria incidence declined, and DDT spraying gradually withdrawn, the vigilance units were expanded. Upon detection of foci of transmission, the vigilance units would eliminate these foci by spraying, assisted by drug administration (Gunaratna 1956). Unfortunately, during the attack phase of the eradication campaign, in 1958-63, when malaria elimination was in sight, entomological surveillance was weakened, and lost its integration with epidemiological surveillance.

Over the years, the AMC has continued to conduct entomological surveillance on a routine basis, using a number of traditional techniques to sample larval occurrence, adult mosquito biting and resting behaviour, and annual testing of insecticide susceptibility. Also, a relatively efficient epidemiological surveillance system has been in place. This system included case detection at medical institutions, and several active case detection programmes in receptive areas and among vulnerable populations, through house-to-house visits and mobile malaria clinics, to detect cases not reported to the health system (AMC 2016). Prompt treatment helped reduce the parasite reservoir and the chance of transmission. The surveillance system, with strengthened capacity since 2010 (Wickremasinghe and Newby 2016), has facilitated the successful elimination of malaria. Epidemiological and entomological surveillance have been closely connected at the district level. Suspected or diagnosed cases were notified directly to the district malaria team, and to central level, for rapid response action. Moreover, the malaria team was involved in active case detection programmes.

The emergence and spread of insecticide resistance has long been a threat to malaria vector control in Sri Lanka. The 'mono-therapy' of IRS, first using DDT, and later on malathion, lead to high resistance levels, which were acknowledged only after interventions failed to reduce malaria cases. Simultaneous use of DDT in public health and agriculture, including in irrigated rice (Sumith 2016), was thought to have contributed to DDT resistance levels. Initial steps in resistance management in the 1970s were the timely switch to malathion, setting aside fenitrothion as alternative, and the registration of these pesticides for use in public health only. Nevertheless, considering the intensity at which malathion was applied, a gradual development of malathion resistance was inevitable.

Progressive steps in resistance management were the use of insecticide products within a rotational and mosaic scheme of IRS, and the shift from blanket application to need-based application of IRS according to malaria risk strata. More recently, these methods have been promoted by the WHO (WHO 2012a). The insecticide scheme was proactive, aiming to reduce selection pressure on the vector. The scheme was informed by insecticide susceptibility testing of samples from sentinel sites, producing time-series data managed in a national database. Insecticide susceptibility testing was a routine activity incorporated into AMC's programme – not an add-on research activity. After the bioassays indicated evidence of resistance, the insecticide application scheme was adjusted accordingly. The system was not without fault because malathion continued to be used for a number of years after widespread resistance in malaria vectors had become evident.

There are indications that the resistance management practices have contributed to the decline in malaria incidence in Sri Lanka (Kelly-Hope *et al.* 2005). In this respect, an example is provided to malaria-endemic countries that are in the process of capacity building to monitor and manage insecticide resistance (Mnzava *et al.* 2015). In the final years towards malaria elimination, long-lasting insecticidal nets gradually replaced IRS. At that time, IRS depended on pyrethroids while the same insecticide class was used in nets. Whilst pyrethroids are not recommended for use in IRS where there is high insecticidal net coverage because this may accelerate resistance development (WHO 2012a), the phasing-out of IRS and phasing-in of nets apparently averted this dilemma.

Data on local receptivity and vulnerability of populations were used to stratify malaria risk amidst a changing epidemiology of malaria. The Sri Lankan example thus demonstrated how surveillance data provided the basis for targeting of interventions. Moreover, the vector surveillance system and the decision support system for vector control have recently been reoriented to the prevention-of-reintroduction phase.

An enabling factor to successful elimination of malaria has been that the AMC has consistently managed competent and well-resourced malaria teams at the decentralised level, with coordination provided through monthly review meetings and regular refresher training courses. In a medium-sized country like Sri Lanka, central-level coordination was functional. A national database served its purpose of providing prompt feedback advice to districts, for example, about insecticide management, or about high-risk locations needing proactive response action. However, in countries larger than Sri Lanka, an efficient management structure might be possible only at sub-national or provincial level.

Large-scale development projects on irrigated agriculture, as well as economic activities on gem mining, have clearly demonstrated the risk these activities pose to human health, by causing epidemics of malaria, and by maintaining residual transmission in pre-elimination settings. Consequently, a lesson learnt is that intersectoral collaboration which includes health impact assessment is critical to any project that causes environmental changes.

The Sri Lankan case indicates that research has benefited malaria vector control in various ways, but also pinpoints missed opportunities of data utilisation. Entomological studies verified the suitability of IRS and ITNs in targeting the main vector *An. culicifacies*, but have also indicated the limitations because of vector characteristics of partly outdoor biting and resting behaviour, biting during the early evening, and preference to feed on animals. This knowledge resulted in the adaptation to extend IRS to temporary structures, settlements and animal sheds. Also, additional vector control methods that targeted the larval stage were seen as critical in specific settings. When the Mahaweli irrigation schemes were being developed, entomological and sociological studies clearly influenced malaria control interventions and operations in the newly cleared and populated areas. Moreover, the incrimination of *An. subpictus* and *An. annularis* as main vectors in irrigated rice farming helped redirect vector control operations, which included the integrated pest and vector management approach. Studies on larval control in gem pits demonstrated the importance of this intervention for the programme. Conversely, studies on the modification and periodic flushing of river streams, a promising vector control intervention, did not result in engineering-based interventions for malaria control, probably because of lack of intersectoral collaboration.

Coordination between vector-borne disease control programmes is only recently attracting attention. The incidence of dengue and cutaneous leishmaniasis have increased, but human and technical resources for entomological surveillance remain with the malaria programme. However, high-level advocacy will be essential to obtain 'buy-in' into the IVM concept among other partners to strengthen collaboration between vector-borne disease control programmes and between sectors.

Conclusions

Over the past century, malaria vector control in Sri Lanka has faced challenges of sudden and unstable transmission, insecticide resistance, movements of settlers and refugees, and, at times, programme fatigue. Good practices that contributed to the country achieving malaria-free status include intersectoral agreement over pesticide policy, a routine system of monitoring of insecticide resistance incorporated into the programme, and a proactive scheme of rotation and mosaics of insecticide applications to prevent resistance development.

Equally important, entomological and epidemiological surveillance, and research outputs, generated information that was quite effectively used by the programme to stratify malaria incidence, identify high-risk groups or locations, and select and target appropriate interventions. Programme response to emerging threats was sometimes delayed, or overlooking the role of the community. But in several ways, the island state was ahead of its time, providing a valuable example in good practices and lessons learnt to other countries that are still fighting malaria.

After elimination of malaria, the long-established system of vector surveillance and control was reoriented to the changed epidemiological situation. Sentinel sites were adjusted, sampling methods changed, and staff trained on the new methods and procedures. Malaria risk mapping was developed, and refined, to provide the basis for decisions on proactive vector control. The Sri Lankan programme has always been disease-specific, which may have been part of its strength. However, now that malaria has been eliminated, and 'prevention of reintroduction' is supported by policy, a more systematic coordination in entomological surveillance and vector control between programmes of malaria, dengue and leishmaniasis could improve the efficiency, effectiveness and financial sustainability of operations. Coordination should be by sharing of resources and infrastructure for surveillance and interventions at the district level.

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12. Outbreaks of arboviruses, biotechnological innovations and vector control: facing the unexpected

Christophe Boëte
ISEM, Univ Montpellier, CNRS, EPHE, IRD, Place Eugène Bataillon CC65, 34095 Montpellier, France; christophe.boete@umontpellier.fr

Abstract

Outbreaks of arboviruses have occurred in the last decades in many places around the world and a variety of responses have been taken in order to control them. Responses ranged from vaccination campaigns to the use of conventional vector control methods. Innovative approaches relying on biotechnological novelties, often still under development, have been considered despite the lack of solid evidence of their efficacy. While discussing these different aspects of the fight against vector-borne diseases with a focus on the context of outbreaks, this chapter considers the social and ethical aspects related to both the rhetoric and the discussion about the implementation of new and innovative approaches.

Keywords: *Aedes*, delay, emergence, hype, mosquito, risk, Zika

Introduction

A number of outbreaks of emerging or re-emerging arboviruses has been hitting populations worldwide in the last two decades in an unusual diversity and magnitude. They have been fought with a number of different tools, mainly in order to control the vectors. Even though some of these methods are well known for their efficiency when properly deployed, the difficulties experienced in the management of these epidemics have led, in some circumstances, to consider novel methods relying on biotechnological innovation. This occurs even while the measures are still under development and are lacking the required insight for their efficient use in public health. It appears then important to question the associated infatuation with a particular method and to look back at past achievements in the control of vector-borne diseases.

A bit of history

When considering innovations and the difficulties we are facing in the control of vector-borne diseases it seems indeed reasonable to look at what we can learn from history and especially from the success in the fight against vector-borne diseases obtained with proven, scalable and efficient vector control methods and tools. Not only the classical example of the eradication of the malaria mosquito *Anopheles gambiae* from the north-eastern part of Brazil quickly comes to mind (Killeen 2003, Killeen *et al.* 2002), there are also a number of other examples where populations of *Aedes* spp. have been drastically reduced, especially in Latin America and the Caribbean (Gorgas 1901, 1905). When looking at the map of Latin America (Figure 1) indicating the fluctuation of the presence of the yellow fever mosquito *Aedes aegypti* over 80 years (Gubler 2011), it appears clearly that while this vector was largely absent from a number of countries at the beginning in 1970, it has now reinfested a large part of the region, even being present in places where it was not detected in the nineteen thirties. This has obviously been associated with the presence and spread of dengue haemorrhagic fever in the sub-continent (Figure 2).

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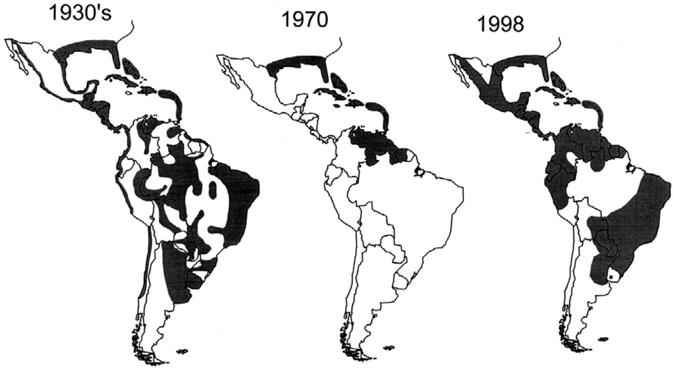

Figure 1. The distribution of Aedes aegypti *in the Americas between the 1930's and 2015.*

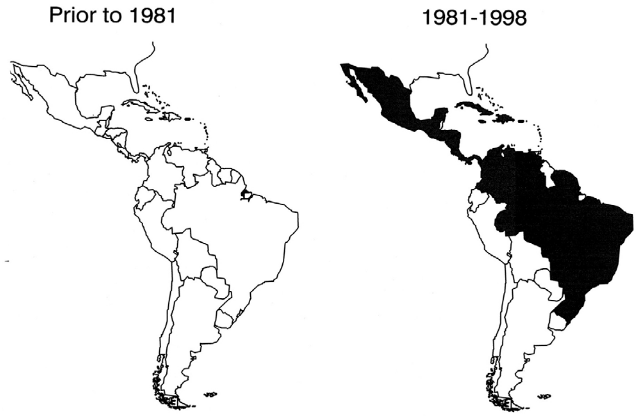

Figure 2. The spread of dengue haemorrhagic fever in the Americas.

What are outbreaks?

Outbreak or epidemic

Disease outbreaks or epidemics are localised increases in the numbers of cases of illness that are clearly in excess of normal expectancy. While an outbreak is usually limited to a small focal area, an epidemic covers larger geographical areas and may have more than one focal point. The number of cases that defines an outbreak depends on past patterns of the disease, the mode of transmission, contact and case fatality rates and potential spread to other areas (WHO 2012).

Worldwide alerts

Even when confined in space and time, outbreaks and epidemics tend to be of global concern. An overview of the online platform Health map (http://www.healthmap.org/en/) and a search on the number of alerts on a group of arboviruses (dengue, chikungunya, Zika, yellow fever, Rift Valley Fever, West Nile Virus) generate more than one hundred hits. It reveals the presence of information being reported in the media about these viruses during about four weeks in May/June 2019 (Figure 3). Note that the presence of a dot in Siberia does not indicate the emergence of any of those viruses in this part of the world but the fact that the newspaper 'Siberian Times' published an article warning Russian travellers about the risk of dengue infection in Thailand (Skarbo 2019). While this map aggregates information, this does not reflect the location of an epidemic or an outbreak but the importance with which a given outbreak is reported in online sources. Clearly, concerns about the emergence or re-emergence of vector-borne diseases are global.

Arboviral outbreaks

As mentioned earlier, over the last decades numerous outbreaks of arboviral disease have been hitting human populations worldwide. Dengue outbreaks have occurred in Latin America, in South-East Asia and in the Indian Ocean. More recently the chikungunya virus has emerged in the early 2000s with several epidemics in Reunion Island in 2005-2006 (Josseran *et al.* 2006, Weaver and Lecuit 2015) and again in 2009-2010 before reaching the West Indies in 2014 and the Americas (Chen *et al.* 2016). Despite the existence of an efficient vaccine for many years, yellow fever outbreaks continue to occur as in the Omo Valley in Ethiopia in 2012-2014 (Mulchandani *et al.* 2019) and more recently in Angola in 2016 (Woodall 2016).

Among the recent arboviral emergences, the Zika epidemic is, with little doubt, the one that has been the most reported, the most discussed and probably the most frightening. While first detected on the island of Yap in 2007 (Duffy *et al.* 2009), and next in French Polynesia (Cao-Lormeau *et al.* 2014), it has been of major concern when it was associated with neurodevelopmental abnormalities in

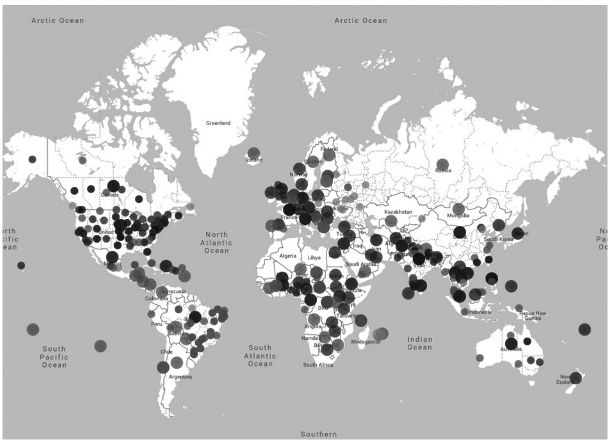

Figure 3. Representation of the global alerts on the presence of several arboviruses (dengue, chikungunya, Zika, yellow fever, Rift Valley Fever, West Nile Virus) in any online sources. The map represents a study done for a period of one month during May and June 2019.

new-borns in the northern part of Brazil in 2015 (Rasmussen *et al.* 2016, Rodrigues 2016). This has even led, in February 2016, to a declaration of Public Health Emergency of International Concern by the World Health Organization (WHO 2016).

The delay

One of the major issues with any outbreak is that it calls for a collective action in the timeliest manner as possible in order to reduce both the spatial and the temporal extension of the disease. This corresponds then to reducing the delay before a collective action is undertaken. As already mentioned in the case of responses to global disease outbreaks (Hoffman and Silverberg 2018), the nature of the delay can be of two types: (1) a delay between the emergence of an outbreak' index case and the detection of the outbreak by health care providers or public health authorities or (2) a delay between the outbreak' detection and the widespread recognition of it as an international concern.

In order to minimise this delay, there is a need for a rapid response as stated in the COMBI document (Communication for behavioural impact – A toolkit for behavioural and social communication in outbreak response) (WHO 2012) and this largely relies on social mobilisation. This is defined by the WHO as 'the process of mobilising all societal and personal influences with the aim of prompting individual and family action'. It is also based on the promotion of the outbreak control with the idea of mitigating the social disruption by communicating with the public in ways that build, maintain and restore trust. Overall, speed of reaction to an outbreak is critical but this should be done in a manner that does not erode the trust of the public nor the expected social mobilisation.

Responses to the outbreak(s)

When considering the responses to several recent arboviral outbreaks it is interesting to look at the differences of the discussion and rhetoric about outbreak management and vector control (Figure 4).

Figure 4. Responses to different outbreaks of arboviral diseases that have occurred in the last 20 years.

Yellow fever in Angola

When the yellow fever outbreak hit Angola in 2015, the major strategy against it was centred on vaccination. Indeed, the disease started to spread in the capital city, Luanda, at the end of 2015 and then to five provinces of the country as well as to several other African countries (Democratic Republic of Congo, Kenya and Morocco) as well as to China because of returning unvaccinated Chinese workers (Boëte 2016). Given the vaccine shortage leaving a high risk of expansion of the disease, an interim solution was suggested with the use of a one-tenth-dose vaccination (Monath *et al.* 2016). Not only was this evidence of a lack of adequate means in front of an epidemic with a pathogenic agent known since decades, but also the lack of an efficient regional coordinated plan to ensure a quick reaction toward an epidemic.

Chikungunya in Reunion Island

Chikungunya emerged in Reunion Island in 2005 (Josseran *et al.* 2006) and, in the absence of a vaccine, the response has been on vector control with a variety of tools and methods: the removal of breeding sites, the use of larviciding as well as the killing of adult mosquitoes with fumigation.

Dengue in Reunion Island

When dengue fever started affecting Reunion Island in 2018, the answer was very similar to the one against the earlier 2005 chikungunya outbreak and focused again on vector control.

Zika in Brazil

Similarly to other outbreaks, a variety of tools aiming at reducing both the larvae and the adult populations of mosquitoes has been used in the context of the Zika outbreak in Brazil. However, contrary to other recent outbreaks, there also has been a strong interest for novel and innovative approaches and two of them received particular attention: the use of 'release of insects carrying a dominant lethal' (RIDL) (partially-sterile) mosquitoes developed by the British company Oxitec, and the use of *Wolbachia*-infected mosquitoes (Yakob and Walker 2016). In the first case, the idea behind this approach is the theoretical reduction in density of the *Ae. aegypti* population (Atkinson *et al.* 2007) while in the second situation the idea is to replace the local species of mosquitoes by *Wolbachia*-infected mosquitoes purportedly unsuitable for Zika replication (Caragata *et al.* 2016).

As the global concern around Zika arose in 2016, it was important to measure how much evidence was available about the potential efficiency and deployment of such technologies at that particular time.

Innovations: do we have (enough) solid evidence?

Wolbachia *infection in mosquitoes*

There is much hope for the potential use of *Wolbachia* in the fight against dengue with the approach limiting (or partially blocking) the replication of the virus (Moreira *et al.* 2009). Since several years, there is indeed evidence of the negative impact of the infection of mosquitoes that carry the *Wolbachia* strain *w*Mel on dengue replication in both *Ae. aegypti* (Walker *et al.* 2011) and *Aedes albopictus* (Blagrove *et al.* 2012). Some of this information was already available and peer-reviewed at the time of the Zika epidemic in Brazil. At the same time, there was also contrary evidence published on the impact of the *Wolbachia* strain wAlbB on the replication of the West Nile virus in *Culex tarsalis* (Dodson *et al.* 2014).

Disturbingly, however, there was no evidence of a positive or negative impact of *Wolbachia*-infected *Ae. aegypti* on the replication of the Zika virus at the time of the epidemic. That information became available only later in the year (Aliota *et al.* 2016, Carneiro Dutra *et al.* 2016).

Release of genetically modified partially-sterile mosquitoes

Regarding the other approach considered by Yakob and Walker (2016), the efficacy of genetically modified (GM) partially-sterile mosquitoes OX513A developed by Oxitec to control the Zika epidemic, was also not backed up by solid data. There was no evidence at that time of any positive impact of their use at curbing the number of cases of infected persons in any arboviral epidemic. Note that these genetically-modified mosquitoes are often presented as a sterile insect technique, including by its promoters (Lacroix *et al.* 2012), while in fact, they are able to produce viable offspring. Most of the progeny of an OX513A male does indeed not reach adulthood because late stage larvae or early stage pupae are designed not to survive in the absence of tetracyclin (an antibiotic). However, studies have shown that about 3 to 5% of the progeny of females that have mated with GM OX513A males survive in laboratory experiments (Phuc *et al.* 2007). To make matters worse, a recent study has even shown the introgression of the transgenic population of OX513A males into the wild population in Brazil (Evans *et al.* 2019) increasing the genetic variability of the target population. The only study conducted in Brazil at the time of the Zika epidemics was one whose results were reported by Carvalho *et al.* (2015). While the study was presented as the suppression of a field population of *Ae. aegypti* in the suburb of Juazeiro, Bahia, Brazil, a detailed analysis of the data and especially the ones presented in the supplementary section reveals a different and less satisfying situation for a number of reasons (Boëte and Reeves 2016) (Figure 5). In fact, Carvalho *et al.* (2015) do not compare the adult density in the treated area with the untreated one. There is no direct information about the adult density in the control area. Another disturbing point about the methodology is a change in the methods for the monitoring of the adult mosquito populations during the experiments with aspiration being used in the beginning and mosquito traps later. In their re-analysis of the data, Boëte and Reeves (2016) have presented the estimates of the adult population size for males and females (Figure 5A) as well as comparing the frequency of egg positive traps (ovi-index) in the two release areas as well as in the no-release area (control) (Figure 5B) (Boëte and Reeves 2016). This latter graph clearly shows that the *Ae. aegypti* population not only decreased in the two release areas but also in the control one. This highlights the fact that the release of the OX513A partly sterile mosquitoes did not solely lead to a major decrease in mosquito density, making it less efficient than it seemed.

Another important comment regarding the RIDL[1] approach is the statement by the WHO's Vector Control Advisory Group (VCAG) claiming that 'Results from epidemiological trials remain the primary missing information for assessment of the public health value of this product. Epidemiological studies must be carried out to assess the public health value of reducing vector populations through the application of OX513A' (WHO 2017a).

Clearly, recommending the use of these two innovative and under development approaches against Zika appeared as rushing towards methods that at the time had been imperfectly tested.

[1] Recently Oxitec has withdrawn the RIDL technology for further use (source: WHO-VCAG) while currently developing a daughter-killing approach against mosquitoes.

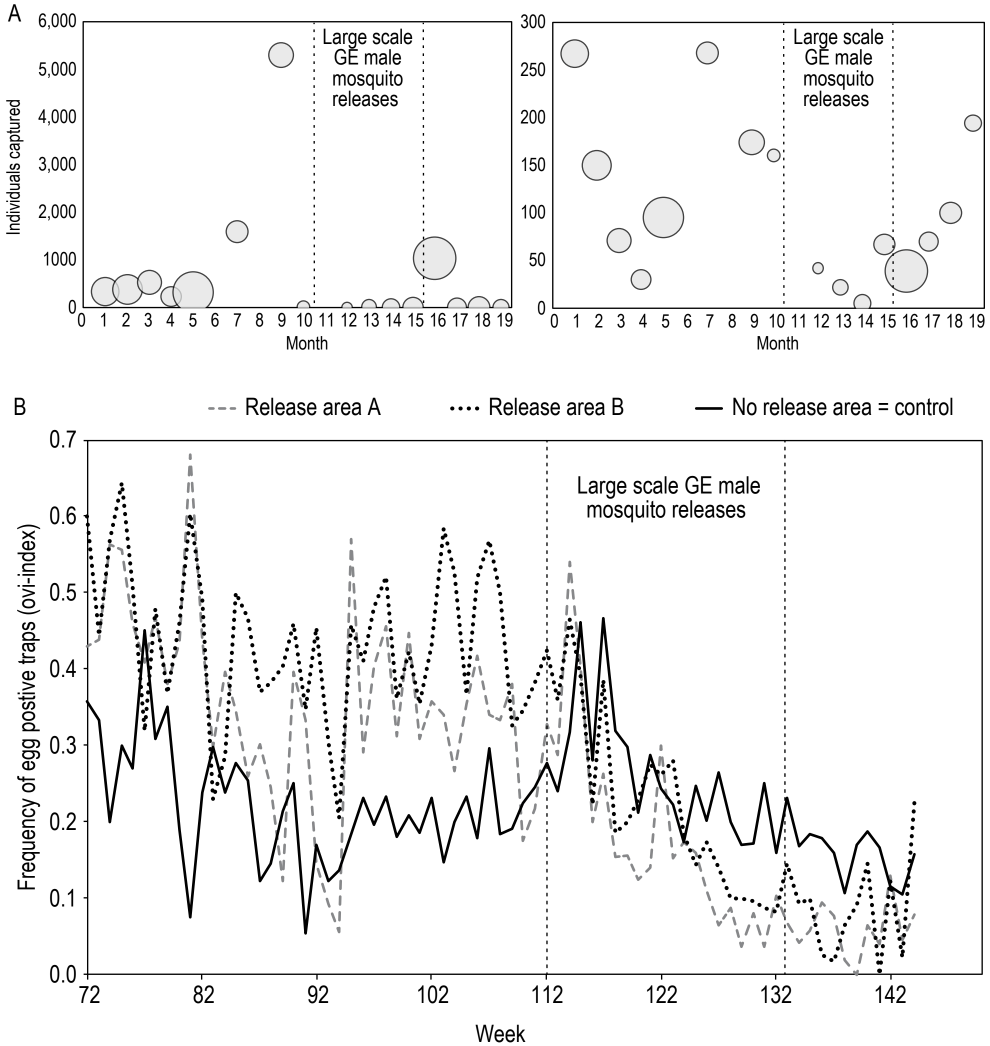

Figure 5. Re-presented data from the largest trial of 'release of insects carrying a dominant lethal' (RIDL) mosquito population suppression in N.E. Brazil. (A) Data from the only RIDL trial to make direct estimates of adult population size. Datapoint size is scaled by monthly collecting effort. The reported value of 95% adult suppression was calculated using only the wild male data (and the frequency of genetically modified males, not shown). (B) Egg trap data providing the basis for the reported 81% population suppression. Note that while the estimates of population size based on egg traps have equivalent control data, the estimate of adults does not. This figure is based on an illustration from Boëte and Reeves (2016).

The absence of solid evidence is not only obvious for their entomological and epidemiological efficacy but also for the associated unevaluated consequences at the population level.

Why the obsession?

If the fight against Zika in Brazil was associated with some interest for tools whose evidence about their efficacy was not clear at that time, one might wonder if this is related to the limitation of our ability to deploy efficient tools for *Aedes* management. It may also well be associated with the lure of the novelty and its associated hype. Clearly, this infatuation for recent and 'modern' unproven approaches is not innocuous and the lack of evidence around them goes along with several risks.

Which risks?

Besides the most obvious risk associated with the use of an inefficient tool with which the problem cannot be fixed while it is expected to do so, there are also a number of other major flaws. An incomplete assessment of the tool considered can indeed lead to a premature implementation of the technology and the deployment of interventions that can be, at minimum, ineffective or, at worse, be the source of other problems that need to be solved because the associate risks have not been accurately evaluated. Speed towards the implementation of mis-evaluated approaches could also be easily associated with misinformed policy debates about the real and objective benefits and risks. Of course the risks associated with innovation is clearly not a novel topic in the area of vector control as it has already been the subject of numerous reports and publications dedicated to GM mosquitoes (Lavery *et al.* 2008; WHO/TDR & FNIH 2014). However, some reports were published after the release of such mosquitoes by Oxitec in the Cayman Islands in the fall of 2009.

As this release took many scientists and the public health world by surprise, since then a number of reports about the ethics of GM mosquitoes as well as guidelines for their safe and responsible use have appeared, demonstrating that the scientific world and international organisations consider the potential risk associated with the introduction of new technologies (WHO/TDR & FNIH 2014, James *et al.* 2018); this has led to a different approach to the technology with no release yet until a range of criteria have been met (NASEM 2016; Johns Hopkins Center for Health Security 2020).

However, and apart from the technical aspects of deploying a tool despite lack of evidence, there is also a risk of creating a gap between the promises and the deliveries by not fulfilling the expectations. There is also a real danger to favour or increase the loss in public trust. This clearly does not get along with the recommendations by the WHO where trust is considered paramount in the response to an outbreak (WHO 2012).

Finally, another important risk, which may be overlooked by innovators, is the harmful diversion of research resources as discussed many years ago with the question of the value of investment in genomics in the fight against malaria (Curtis 2000).

Novel tools: which requirements before application?

In the case of an outbreak it has been seen earlier that minimising the delay between the emergence or the detection and the collective action is essential. This can then easily lead to haste in favour of novel and so-called promising tools. There are however a couple of requirements that should not be overlooked even in such pressing conditions. Among the most obvious ones, the efficacy is key and it should not only be at the entomological level but also at the epidemiological one. One should keep in mind that the VCAG recently requested two trials with entomological and epidemiological endpoints in contrasted epidemiological settings when evaluations of novel tools for vector control are conducted. As a corollary, the effectiveness of proposed tools should enter the equation because cost is often an issue for countries affected by vector-borne diseases. Considering again the case of the patented GM OX513A mosquito by Oxitec, the question of cost remains quite vague with important variations in the estimation of the cost per person per year ranging for a 2-year programme from 10 USD/person/year to more than 40 USD/person/year (Alfaro-Murillo *et al.* 2016, Meghani and Boëte 2018, Notimérica 2015). While this may be related to different contexts, situations or economy of scale, such discrepancy remains troubling and does not help concerned communities and public health authorities to take informed and accurate decisions.

As seen earlier as a major point according to the COMBI document dedicated to the fight against outbreaks (WHO 2012), trust is crucial when a novel tool is considered for implementation; its corollary being the acceptability by the population.

Obviously the question of trust and acceptability leads to several other points: the way risk assessments are performed but also how the deliberations and decision-making process are conducted at the community level (Meghani and Boëte 2018).

Zika outbreak: what was the unexpected?

When considering the Zika epidemic of 2015-2016, the real unexpected aspect of it was the emergence of neurodevelopmental abnormalities with many microcephaly cases occurring in Brazil and the magnitude of their occurrence in the northern part of the country. Less surprising is the vector of Zika, the yellow fever mosquito *Ae. aegypti*. It is not an unknown vector of arboviral diseases and, even worse, it has been responsible for several outbreaks of dengue haemorrhagic fever as well as outbreaks of chikungunya in Brazil in recent years (Nunes *et al.* 2019).

What seems then essential here is to refrain from undermining the existing tools we have to conduct vector control actions even if they are imperfect or challenging to use. This is sadly an old tune we read too often in papers, especially when these latter ones present biotechnological development even without a potentially efficient use in vector control in the near future. Another major point is that vectors and vector-borne diseases management are not the only challenges populations often have to face. As shown for Zika as for many other vector-borne diseases, they tend to affect more often the poorest of the poor (Human Rights Watch 2017). When considering Brazil with about seven million houses with no access to rubbish- and waste collection and 10 million houses with no access to clean water (Henriques *et al.* 2016), there is some doubt that use of a repellent for personal protection twice a day can be a sustainable solution, as stated by Gómez *et al.* (2018).

This calls not only for a questioning the health policies but also for major socio-economic changes able to alleviate the burden of vector-borne diseases among other challenges human populations are faced with. Addressing them would permit to avoid the too often use or promises of a technological fix.

Novel tools: what do professionals expect?

When considering the use and implementation of novel tools in the particular context of an outbreak, it is interesting to notice that the incentive to use them usually arises from members of the academic world or from developers of such novelties. If referring to the recommendations presented in the WHO report 'Global Vector Control Response 2017-2030' (which is not specifically dedicated to the context of outbreaks) it emphasises the success of the existing strategies of vector control in the global health agenda and the importance of building on broad experience in favour of existing tools in a process favouring the consultation with the affected communities (WHO 2017b). Regarding innovative tools, this report recognises their importance but also recommends that their development follows the recommendations of the VCAG and that the efficacy on vectors and on human infection should be strongly supported by evidence, which is too often not the case apart from long-lasting insecticide-treated mosquito nets (LLINs) and indoor residual spraying (IRS).

Drawing a parallel with a recent Delphi survey (unpublished data, C. Boëte) focusing on the perception of experts in the field of malaria control with a particular focus on emergency settings might be useful too. Even if outbreaks are not equivalent to emergency settings as defined by the WHO (Wisner *et al.* 2012) it is informative to notice that the favoured novel tools for the control of malaria both in emergency settings and in non-emergency settings are mostly next-generation LLINs and IRS whereas high-tech approaches (sterile insect technique via irradiation, genetic modification of insects for population replacement or suppression) receive a much weaker support. Clearly, this highlights the fact that the recommended approaches are the ones in the continuity of the existing tools and their amelioration over disruptive ones. While there is most likely a balance between on the one hand, the amelioration of available tools and the way we use them and, and on the other hand, the innovation of new tools, there is also a need for honesty and reservation when discussing promising results and their potential applications.

Conclusions: next emergence … the unexpected

If vector control remains the first choice when fighting vector-borne diseases, we should keep in mind a very simple aspect of vector control: tackling a vector species can affect the transmission of more than one virus. As a serendipitous fact, keeping *Ae. aegypti* under control when trying to avoid dengue epidemics can well limit the occurrence and the spread of a Zika outbreak.

This is clearly valid for a number of known (or unknown) arboviruses and their vectors and especially for the future potentially emerging or re-emerging and invading ones that one can hardly and reasonably pick up from a list (Figure 6) of the (more or less known and characterised) usual suspects.

Figure 6. Representation of various arboviruses and their potential vectors that may be (or not) involved in the potential emergence of a vector-borne disease outbreak in the future.

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Conclusions

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13. Global Vector Control Response – supporting the pillars

Willem Takken[1], *Constantianus JM Koenraadt*[1*], *Jeroen Spitzen*[1] *and Raman Velayudhan*[2]
[1]Laboratory of Entomology, Wageningen University & Research, P.O. Box 16, 6700 AA, Wageningen, the Netherlands; [2]Veterinary Public Health, Vector Control and Environment unit (VVE), Department of Control of Neglected Tropical Diseases (UCN/NTD), World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland; sander.koenraadt@wur.nl

From the chapters in this volume it is evident that, in spite of remarkable progress in the control of vector-borne diseases (VBDs), these diseases continue to place a huge burden on human societies across many geographic regions. Although VBDs are transmitted by a large and diverse group of arthropod species (Mullen and Durden 2018), mosquitoes are without doubt the group that receives most attention because of the huge impact mosquito-borne diseases poses on many different aspects of societies.

With the realisation that interruption of pathogen transmission would be the most effective way of VBD control (Anderson and May 1992, MacDonald 1957), the introduction of insecticides in the 20th century created expectations that VBDs could be effectively controlled and even eliminated. More than 50 years later, it is realised that this expectation was too optimistic. Recurring developments of insecticide resistance and financial and logistical constraints for efficient roll-out of control programmes have led to a growing awareness that different strategies are required. This was made more explicit by the simultaneous emergence of *Plasmodium* drug resistance (Menard and Dondorp 2017), leaving the world without effective tools with which to combat malaria. To date, only two of these mosquito-borne diseases can be prevented by vaccination: yellow fever and Japanese encephalitis. As with insecticides, however, financial and logistical constraints sometimes lead to situations where the vaccines arrive too late to prevent an epidemic (Sérié *et al.* 1968). It is remarkable that both vaccines were developed and introduced already in the nineteen thirties, but that since then no other vaccines for mosquito-borne diseases became available. In recent years, though, significant progress has been made in the development of vaccines for a number of mosquito-borne diseases. For example, in 2016 for the first time a vaccine for dengue became available, but its use is restricted to people who have had dengue once and in non-immunes the vaccine may even increase the risk of severe dengue (Macias *et al.* 2020). The recent phase III trial of a malaria vaccine in three African countries is a breakthrough, but efficacy- and health concerns still remain (https://www.bmj.com/content/368/bmj.l6920.full). Vaccines for chikungunya and Zika are under various phases of development, but it is not clear when these may become available (Schrauf *et al.* 2020). Until vaccines for these diseases are effective, safe and widely available, vector control is the only effective tool for arboviral disease prevention.

The 2015-2016 Zika outbreak in South America triggered a radical switch in classical VBD control. With strong support from the Director General, the World Health Organization assembled an international group of experts with the task to develop a comprehensive approach for the control of VBDs: the Global Vector Control Response (GVCR) which includes incorporation of novel and innovative tools. This response, based on four pillars, makes a convincing plea for a radically different approach to VBD control: intersectoral collaboration, community engagement, monitoring, surveillance and evaluation, and integration of tools and approaches, supported by novel and innovative research, are the principle drivers that should lead to a reduction of the VBD disease burden (WHO 2017).

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It is noteworthy that the GVCR was unanimously adopted by the World Health Assembly in its 70th session in May 2017. Since then, WHO has engaged on a programme to roll out the GVCR in all regions, with the specific mandate to strengthen intersectoral collaboration and community engagement. These aspects of the GVCR were in full development at the time of the first GVCR conference in 2019. The state-of the art of the various aspects of the GVCR were presented and discussed during the conference. Section 1 of this book covered scaling up and integration of tools and approaches based on the current and future use of insecticides (Chapters 2, 3, 4 and 5). Section 2 presented examples of innovative strategies, with a strong emphasis on integrated vector management (IVM). Section 3 discussed examples of intersectoral collaboration and community engagement.

Insecticides

Insecticides continue to play a large role in the prevention and control of malaria. The global distribution of insecticide-treated bed nets in 2000 as the main pillar of malaria prevention and control, has indeed led to a large and significant decrease in malaria morbidity and mortality (Cibulskis *et al.* 2016). The unwanted side effect of this global programme, however, has caused the very high levels of insecticide resistance that render the LLINs less effective (Okumu and Finda, Chapter 3). One could argue that this appears as a repeat of the 1955-1969 malaria eradication effort, where increased levels of resistance to DDT were among the factors that led to abandonment of the programme (Gabaldon 1969, Nájera *et al.* 2011). There is, however, a major difference with the previous campaign. The 1950s global campaign ran aground in the mid 1970s not only because of insecticide resistance, but also for lack of funds and logistical difficulties when it was rolled out in least developed countries. There, was also the lack of staff trained in the many different aspects of malaria control.

Today, the situation is radically different: international donors are committed to support the programme for the foreseeable future, and a large number of young people have received training in VBD control at all levels. Most malaria-endemic countries have a national malaria control strategy, with a national team of experts who can provide direction and leadership. Indeed, monitoring and evaluation has shown high levels of insecticide resistance (WHO 2019). Innovative research is expected to produce new classes of insecticides, while at the same time the concept of integrated control with less reliance on insecticides, is being introduced (Wilson *et al.* 2020). Okumu and Finda (Chapter 3) make a plea to conduct epidemiological trials with untreated bed nets, suggesting that modern nets of strong quality can provide sufficient physical protection against mosquito bites, leading to significantly less malaria. This approach, combined with other, innovative tools may open the way to insecticide-free malaria control which would be revolutionary after more than 100 years of reliance on these compounds (Wilson *et al.* 2020) and possibly prevent derailment of the malaria eradication campaign, as suggested by Hemingway *et al.* (2016).

Innovative strategies in integrated vector management

In contrast with malaria control, which continues to rely heavily on insecticide-based tools (see above), the control of arboviral disease focuses currently on highly innovative strategies and tools. Historically, insecticides played a major role in the control of the main vector *Aedes aegypti* and led indeed to the temporary disappearance of this vector in South America (Chapter 4) and Gubler (1989). Besides insecticide resistance, environmental and logistical reasons have led to less reliance on insecticides for the control of *Ae. aegypti* in favour of highly innovative and advanced technologies. The discovery that *Wolbachia*-transfected *Ae. aegypti* are refractory to dengue virus (Flores and O'Neill 2018, Moreira *et al.* 2009), as well as a population suppression approach with a self-limiting gene provide alternative, more sustainable interventions for dengue control programmes (Alphey *et al.* 2013, Patil *et al.* 2018, Qsim *et al.* 2017). The potential success of these technologies provides hope that in the not-too-distant future *Aedes*-borne arboviral diseases can be controlled more effectively than at present.

Until recently most mosquito-borne disease control programmes focused on the control of indoor-biting and resting vector populations. In spite of some highly successful control methods and decline in vector densities, disease incidence and prevalence, however, were not declining sufficiently, suggesting ongoing transmission elsewhere. These residual transmission foci were largely found to occur in the peri-domestic space and caused by various factors: intensive and longtime exposure to insecticides had led to selection for mosquitoes that preferentially fed outdoors (Moiroux *et al.* 2012, Russell *et al.* 2011, Sougoufara *et al.* 2014). Also, it was found that fractions of mosquitoes were naturally feeding outdoors, but had been overlooked or 'missed' in the historical monitoring and surveillance programmes which focused primarily on indoor biting and resting mosquitoes (Killeen 2014, Monroe *et al.* 2020, Riehle *et al.* 2011). To tackle outdoor populations, push-pull systems as well as toxic sugar baits are under development (Chapter 6). Another tool, with already proven epidemiological effectiveness, is the use of odour-baited traps that intercept and kill mosquitoes outdoors before they have had a chance to bite (Chapter 7). It has furthermore been realised that killing the vectors in their breeding sites may be more effective than focusing on adult vectors, as this prevents the building up of adult populations. For malaria, recent larval control methods have proven to be effective (Chapter 8). Many dengue control programmes include larval control, but it is unclear if these have led to significant epidemiological outcomes and hence, it is recommended to include adult control (Chapter 4).

From these encouraging developments it can be concluded that novel and effective vector-control tools are in an advanced stage of development, to be added to the toolbox of integrated vector management, with a lower dependence on insecticides and leading to higher sustainability.

Genetic tools for vector-borne disease control have in the last decade received much attention as they may lead to ways in vector control that do not require insecticides, with gene drive systems being among the most promising technologies for future vector control (Hammond *et al.* 2016, Wang *et al.* 2017). As these tools need to pass ethical and regulatory approval before they can be tested in the field (James *et al.* 2018), they have not been included in this volume.

Intersectoral collaboration and community engagement

The heavy burden on human health caused by vector-borne diseases has historically been well recognised and in efforts to lower this burden, disease-endemic countries, often with assistance from WHO, numerous international organisations and NGOs, run government-led control programmes with the aim to reduce the burden of disease caused by VBDs. In most countries the Ministry of Health (MoH) has a central role in initiation, decision making and execution of these programmes. This approach often leads to a vertical programme with little or no involvement of other government ministries, national and international organisations or the private sector (Herdiana *et al.* 2018). Allocation of funds independently to the partners for implementing vector control further augments the success of intersector collaboration. To improve the effectiveness of VBD prevention and control, collaboration between the health and non-health sectors is strongly encouraged (Chapters 9, 10 and 11). For example, in urban centres, water management cannot be arranged without interaction with the Ministry of Public Works or Housing. In rural areas, farming systems can, unwittingly, contribute to high VBD risk (Jaleta *et al.* 2013, Mutero *et al.* 2004), and farmers, (water)engineers and plant production experts need to be involved in redesigning farming systems to reduce this risk. Deforestation and/or reforestation can also affect populations of arthropod vectors (Lima *et al.* 2017, Nava *et al.* 2017), and collaboration between the MoH and the Ministry of the Environment can lead to different approaches for risk reduction. With the growing awareness of the importance of community engagement (see below), organisations and departments that engage in the social aspects of public health are increasingly involved in the rolling out of VBD control. A clear example of this involvement is the use of insecticide-treated bed nets for malaria control: the success of this programme depends strongly on social workers or village health workers who engage with community members and householders to explain the importance of bed net use (Bashar *et al.* 2012, Ingabire *et al.* 2015). For these reasons, the GVCR has placed intersectoral collaboration as the first pillar supporting the response (WHO 2017). More and intensified collaboration between the various sectors associated with VBD risk and mosquito production is required for more effective prevention and control of VBDs (Chapter 10).

As communities are the primary stakeholders in a VBD control programme, members of the community should be involved in the design of an intervention whether with classic, well-known methods as well as when novel tools will be used. In this way acceptance for and compliance with the measures being taken can be assured. Whereas clinical care, drug treatment and vaccination are done by well-trained and expert staff and which are primary health care interventions, where community members cannot be actively involved, this is different when vector control activities are required. Vector control requires action in the field: mosquito surveillance, house improvement, bed net distribution, *Bti* treatment of water bodies and setting up mosquito traps are among the activities where members of the local community should be involved (Chapters 9 and 11).

Chapter 8 demonstrated that, besides innovations in new vector control tools, also novel approaches for involving communities in vector control (e.g. the Farmer Field School, Open Space, and citizen science) have been developed and evaluated recently. A toolbox of community-engagement strategies thus exists and can be used to effectively integrate new tools into ongoing vector control programmes (Wilson *et al.* 2019). Which approach works best will of course be context and culture dependent, and this will require extensive collaborations across multiple sectors.

Research and development are expected to contribute to more sustainable, effective VBD control tools (GVCR2017). Novel tools should be tested solidly and having passed the appropriate regulatory procedures before they can be applied in a disease control programme (James *et al.* 2018). When innovative approaches involving genetic modification, gene drive or transfection are proposed, these can meet with strong resistance from the community and even prevent the application of these technologies. Resistance by communities often results from a lack of understanding of the mechanisms of the proposed intervention, such that communities perceive that the interventions lead to increased health risks (Ernst *et al.* 2015, WHO 2020, Wilke *et al.* 2018). Early involvement of target communities is therefore essential to ensure support and prevent long delays in the approval of such tools (Chapter 12).

Conference workshop

The conference not only discussed the various GVCR topics with experts, but also participated actively in an interactive workshop to provide new ideas and suggestions how the GVCR could be further strengthened and become a widely accepted strategy for integrated vector control. The workshop was divided in eight themes, and each group considered the Goals, Current Challenges, Potential solutions and Value for stakeholders for the theme they had been assigned. The outcome of the workshop is presented in the Appendix to this book.

Conclusions

The various chapters in this volume of ECDV provide state-of-the-art, in-depth information to advance the actions laid out in the Global Vector Control Response. In this book mosquito-borne diseases and their vectors are dominant, with focus on malaria and dengue. It is realised that a large number of other VBDs are vectored by arthropods such as flies, fleas, gnats, lice, assassin bugs and ticks. We hope that the strategies for VBD control as described in this book will be used for integration across multiple diseases as outlined by Golding *et al.* (2015). As vector-borne diseases will not disappear on their own, the GVCR provides a novel and practical pathway towards reduction of the heavy burden these diseases inflict on human societies.

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Appendix. Challenges and opportunities

The various chapters in this volume are written by experts who were invited to provide an overview of the state of the art of the multiple aspects of vector control. Their views and presentations were discussed by the participants of the 2019 conference on the Global Vector Control Response (Figure S2). At the end of the conference, participants were invited to join a workshop on the challenges and opportunities that may arise within the different 'pillars of action' as identified by the World Health Organization (Figure S1). Eight themes from the GVCR were discussed in small groups (two groups per theme): (1) capacity building; (2) public-private partnership; (3) community engagement; (4) integrated vector management; (5) monitoring and surveillance; (6) regulatory issues; (7) linkage with sustainable development goals; and (8) research. Each group discussed the assigned team according to four topics: (1) goals; (2) current challenges; (3) potential solutions; and (4) value for stakeholders. In the final conference plenary each group presented the outcome of their discussions. The summary statements of the workshop groups are presented here, and provide numerous suggestions for the improvement and further rolling-out of the GVCR, as discussed in Chapter 13.

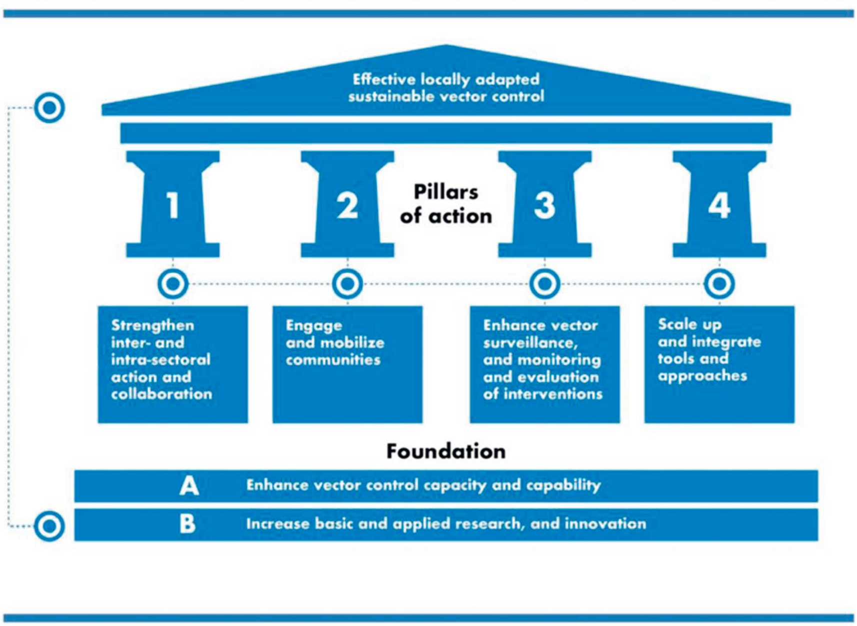

Figure S1. Pillars of action as identified by the World Health Organization, 2017.

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1. Capacity building

A. What are the goals	B. What are the current challenges
• Sufficient vector-borne disease experts at the right place and time • Linking supply and demand • Building on all levels (district-regional)(technicians-PhD's) • Multi-disciplinary education (epidemiology-entomology) • Sustainability (retain and update)	• Not enough vector-borne disease experts and units • Difficulties in retention of vector-borne disease experts • Gender and diversity balance (equity) • Limited funding and competition for funding (training ⇔ implementation) (specialism ⇔ generalism) • Lack of political commitment and involvement • Regional leadership and knowledge exchange missing • Data management (storing and sharing) • Access to internet/knowledge • Integration across VBD's (programmes/funders/...) → how to address prevalent VBDs simultaneously?
C. Potential solutions	**D. Value for stakeholders**
• Assessment, plan and monitoring & evaluation (M&E) • Clear career pathway for entomologists • Integrated surveillance (not just malaria) • Lobbying funders and legislatives (packaging) • Leadership by regional networks: universities, WHO, research and industries → standardisation of control, mobility of fieldworkers, licensing and certification • Multi-disciplinary education (epi-ento) • GVCR courses by stakeholders: industry (training of staff supervisors), universities, ... • Training for free/at distance • Fellowships for non-academic entomologists • Community engagement and training	• Population at risk: better health and income • Tourism, agriculture and transport sector: economic gain • Governments: fast response to outbreaks • Vector control industry: partnerships for product development and testing • Universities: funding, relevance, partners on ground • Funders: better surveillance and risk assessment

2. Public-private partnership

A. What are the goals	B. What are the current challenges
• Eradicate malaria and reduce other vector borne diseases • More collaborations between P&P → speeding up innovation (roll back Aedes) • Intersectional databank → knowledge dispersal	• Lack of trust and understanding (gossip) • Conflict of interest • Operational challenges: legal, bureaucracy • Availability of reliable partners • Sustainability of consortia • Lack of funding
C. Potential solutions	**D. Value for stakeholders**
• Education • Best practices • Matchmaking • Capacity building • Political advocacy	• Public protected from disease (vulnerable group) • Researchers and young professionals • Private companies • Global donors • Governments

3. Community engagement

A. What are the goals	B. What are the current challenges
• Always engage local communities in decision making and create political goodwill • Identify natural networks • Give guidance on the practical frameworks • Identify communication tools and incentives (financial (generated by communities), health, education)	• Ensuring durability of community activity • Community motivation and acceptance • Need for interdisciplinary & intersectoral collaboration (community as a sector + political goodwill) • Facilitation of 'spread' (gets viral) • Lack of priority and donor-driven research
C. Potential solutions	**D. Value for stakeholders**
• Planning of work in phases and thinking in long term • Early stage assessment of acceptability of new tools • Incentives based on community need • Institutional arrangements • Document and disseminate • Prioritise during conceptualisation, provide resources and engage with social scientists • Community-driven research	• Community cohesion and ownership • Realistic and durable implementation for scale up • Improved health → economic gains • Outbreak preparedness • Integrated multidisciplinary approach

4. Integrated vector management

A. What are the goals	B. What are the current challenges
• Adopt IVM as mentioned in GVCR • Find cost effective solutions • Find feasible solutions • Find sustainable solutions	• Vector problem is wicked • Lack of evidence of potential solutions • Allocation of funds to other issues • Lack of capacity • Lack of motivation
C. Potential solutions	**D. Value for stakeholders**
• Stimulate research implementation • Conduct research to generate cost-effectiveness estimates • Develop business-cases • Educate bottom up and top down • Find incentives • Use a 'systems' approach	• At policy level • Evidence based policy • Biggest bang for your buck / return to you • Lower disease burden • At operational level • Compliance from other stakeholders • Appreciation • Fewer vectors • At individual level • Improved health • Reduced risk • Less nuisance

5. Monitoring and surveillance

A. What are the goals	B. What are the current challenges
• Integrated systems to deliver: • Appropriate coverage (space and time) • Appropriate quality • Actionable (can the information be used) • Sustainable surveillance structures • Targeting all the vectors, not only the 'usual suspects' and key indicators • Optimal ignorance (enough knowledge but not too much)	• Perception and awareness of the importance of surveillance and monitoring • Lack of protocols & tools for all situations and thus the adaptability of them • Measuring the wrong indicators for vector distribution and their contribution to disease transmission • Resource allocation, not only investments in new tools • Career structure for sustainable surveillance and monitoring infrastructure • Lack of fundamental knowledge on vector behaviour • Capacity building (trained people, infrastructural support, data action plan and data literacy ...) • Limited understanding of amount/scale needed • Knowledge transfer and ownership
C. Potential solutions	**D. Value for stakeholders**
• Decision framework for implementing surveillance and monitoring for any situation • Guidance on sample strategies and tools for vectors behavioural indicators • Intersectoral coordination & participation • Advocacy for surveillance and monitoring of vectors (role for the likes of PAMCA?)	• Reduce disease burden • Preparedness for vector-borne disease outbreaks • Improved cost-effectiveness • Improved fundamental knowledge • Evidence based vector-control • Reduced risks for environmental and human health • Reduced selection for insecticide resistance • Lead to more ownership and independence

6. Regulatory issues

A. What are the goals	B. What are the current challenges
• Timely/expedited access to quality-assured vector control products • Prevent creation of receptive environments for vector proliferation and biting • Link regulatory bodies with vector control programs • Clear legislation and enforcement	• Poor intersectoral collaboration (ministries) • Lack of political will • Non-transparant regulatory processes and requirements (+ diversity of systems) • Ignorance of prequalification • Requests for repeated tests or data • Novel VC tools or products not understood • Lack of community participation and feedback on vector management
C. Potential solutions	**D. Value for stakeholders**
• Establish intersectoral-steering committees • Establish political will, recognising the problem (GVCR) at high political level (ALMA, AU, APMEN, RBM) • PQ: identify what it is, establish partnerships with regulators (2-ways) • Modernise application systems (contact, fees, timelines) • Build capacity of environmental health inspectors • Build capacity of country regulatory authority	• Populations benefit rapidly from effective approaches to combat vector-borne diseases • Manufacturers can market products • Reduction of vector populations across borders

7. Linkage with sustainable development goals

A. What are the goals	B. What are the current challenges
• To mainstream Global Vector Control Response into SDGs[1] • Benefits of this approach include: • To help generate resources • Expansion of the use and impact of vector control activities with the ultimate benefit of reducing levels of disease, improving well-being and fostering processes of development	• Within GVCR 'community' many are unaware of the SDG's, let alone the targets ... we know specific ones (e.g. 3.3, but not much else) • Diverse intellectual group within vector control • Similar silos within UN agencies and Ministries of Health • Not sure where the social scientists fit in here – but they are circling on the outside and need to be incorporated as well! • Knowledge gaps • Many unknowns, and it is important to recognise what we don't know e.g. resistance to insecticides, vector species composition, variations indoor/outdoor biting, etc. • Fragmented research • Community engagement • Capacity of countries for M&E • Funding
C. Potential solutions	D. Value for stakeholders
• Demonstrate impact to different types of audience: programme managers, academics, WHO, local communities • Researchers • Develop detailed case studies with clear examples of the multiple benefits of a GVCR integrated, holistic approach • Demonstrate how programmes might adapt and respond to political, social issues • Programmatic levels (WHO, NGOs, PPPs, MoH's) • Globally: GVCR alliance of stakeholders; provide OECD documents for regulators; provide examples of the value-added • Nationally: Country ownership: need a committee from highest level, PM's office; more and better communication with 'communities;' improve surveillance and evidence base • Local communities • Identify processes that enable communities to adapt approach to local environmental, political & social context	• National and sub-national endorsement of GVCR • Establish increased inter-sectoral participation • Generate resources • Social and economic benefits of vector control • Declines in disease, morbidity and mortality • Strengthens economies & facilitates development

[1] An unintended benefit of endeavours to mainstream GVCR for SDGs is that it creates intellectual- and policy spaces for inter-sectoral and multi-disciplinary collaborations.

8. Research

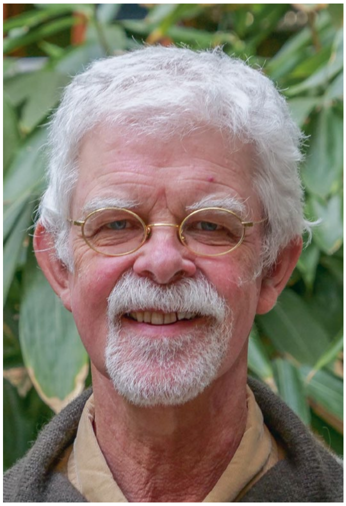
A. What are the goals	B. What are the current challenges
• Research to develop/implement multisector research (e.g. One Health) • Research from baseline to effective implementation with measurable impact • Research framework to assess multiple integrated tools • Methodology research to map stakeholders, community sentiments and network	• Regulatory capacity and capability in an independent and transparent manner • Absence of a harmonised set of ethical principles supported by WHO and OIE • Difficulty in measuring and linking relevant entomological parameters for epidemiological outcomes • Cost-effectiveness of research
C. Potential solutions	**D. Value for stakeholders**
• Awareness and political commitment for building capacity on regulation • Training and harmonisation in ethics • Technical: access to efficient tools + conceptual framework to evaluate the outcome of a programme with multiple tools • Unified metric for cost comparison	• Credible and independent oversight of novel tools • Accelerate the research process (cost-effectiveness) and research participation • Better design in combination with IVM programme • Improvement of decision-making and maintenance of best quality tools and improved access to resources for research

Figure S2. Participants of the 2019 conference on the Global Vector Control Response. Photo credits: Guy Ackermans.

About the editors

Constantianus J.M. (Sander) Koenraadt (1975) is Associate Professor at the Laboratory of Entomology of Wageningen University & Research, the Netherlands in the area of Biology and Control of Disease Vectors. He studied biology at Wageningen University and earned his PhD from the same institute in the field of medical entomology. For this, he carried out field work on the impact of environmental change on malaria risk in Kenya. After this, he joined the University of California, Davis, USA, for which he led a project on dengue risk in rural Thailand. After living and working in Thailand for 2.5 years, he moved to Cornell University (Ithaca, NY, USA) to work on the ecology of genetically modified *Aedes aegypti* for dengue control and the ecology of West Nile virus vectors. At present, he is involved in several research programs on the risks of emerging vector-borne diseases in Europe (Zika, West Nile and tick-borne encephalitis) and on the possibilities for malaria elimination in Rwanda. He enjoys sharing and communicating his science to the general public. For this, he writes for a popular Dutch blog on the developments in nature in relation to blood-feeding insects and manages several projects to evaluate the role of 'citizen science' in the surveillance of disease vectors.

Jeroen Spitzen (1978) is a teaching/research associate at the Laboratory of Entomology of Wageningen University & Research, the Netherlands. In a team with Willem Takken and Sander Koenraadt, he has been active in many behavioural ecology studies related to disease vectors since 2002. In 2018 he obtained a PhD degree based on his research on the flight behaviour of host-seeking malaria mosquitoes. His enthusiasm is triggered by the challenge to find and implement sustainable, effective control tools to combat disease transmitting arthropods. Studying their ecology and behaviour contributes to the innovation of vector control tools. Currently, the obtained fundamental knowledge is exploited in the design of mosquito traps and the redesign of houses, to prevent mosquitoes from entering. For his research, Jeroen collaborates with groups for studies on flight dynamics and has established several partnerships to evaluate findings in field settings in Malawi, Kenya, The Gambia and Tanzania.



Willem Takken (1951) is professor in Medical and Veterinary Entomology at Wageningen University & Research, the Netherlands. He studied in Wageningen and obtained his PhD degree in 1980 based on research on the biology and feeding behaviour of tsetse flies. He worked in several African countries on the control of animal trypanosomiasis. Upon his return to Europe, he was appointed as lecturer at the Laboratory of Entomology in Wageningen, where he introduced medical and veterinary entomology to the Wageningen academic society. His work involved mosquito-host interactions, in particular the host-seeking behaviour of malaria mosquitoes. He later expanded this work to include field research in Tanzania, Kenya, and other tropical countries. With the increasing attention to the increasing risk of neglected tropical diseases, in the last decade his work switched to the application of innovative, practical technologies for vector control. This included the ecology of mosquitoes, biological control of mosquitoes and the impact of environmental change on malaria vectors. In Europe, Willem studied the ecology of Lyme disease vectors and vectors of other, emerging infectious diseases. He emphasises collaboration with other institutions, and has an extensive network of national and international collaborators. He serves on several editorial boards and advisory committees. Willem retired from Wageningen University & Research in 2019, and continues as consultant for Public Health Entomology programmes as well as participates in the publication of relevant research.

Picture credits: Hans Smid

Contributors

Martin Birley

BirleyHIA, Consultants in Health Impact Assessment, 7 Manley Close, Hartrigg Oaks, New Earswick, York YO32 4DN, United Kingdom
martin@birleyhia.co.uk

Christophe Boëte

ISEM, Univ Montpellier, CNRS, EPHE, IRD, Place Eugène Bataillon CC65, 34095 Montpellier, France
christophe.boete@umontpellier.fr

Robert Bos

Independent Consultant, Public Health, Environment, Water & Sanitation, Route du Creux-du-Loup 101285 Sézegnin, Switzerland
robert.bos53@gmail.com

Emilie Bouhsira

Ecole Nationale Vétérinaire de Toulouse (ENVT), 23 Chemin des Capelles, 31076 Toulouse, France
emilie.bouhsira@envt.fr

Piangjai Chalermwong

Faculty of Veterinary Medicine, Kasetsart University, 10900 Bangkok, Thailand
joy_piangjai@hotmail.com

Marc Desquesnes

CIRAD, UMR InterTryp, Bangkok, Thailand
InterTryp, Univ Montpellier, CIRAD, IRD, 34398 Montpellier, France
Faculty of Veterinary Medicine, Kasetsart University, 10900 Bangkok, Thailand
marc.desquesnes@cirad.fr

Gregor J. Devine

Mosquito Control Laboratory, QIMR Berghofer Medical Research Institute, Locked Bag 2000, Royal Brisbane Hospital, Herston, QLD 4006, Australia
greg.devine@qimrberghofer.edu.au

Léa Drosne

CIRAD, UMR InterTryp, Bangkok, Thailand
InterTryp, Univ Montpellier, CIRAD, IRD, 34398 Montpellier, France
Faculty of Veterinary Medicine, Kasetsart University, 10900 Bangkok, Thailand
lea.drosne@agroparistech.fr

Gérard Duvallet

Université Paul Valery Montpellier3, CEFE, 34000 Montpellier, France
gerard.duvallet@univ-montp3.fr

Marceline F. Finda

Environmental Health & Ecological Sciences, Ifakara Health Institute, P.O. Box 53, Ifakara, Tanzania
School of Public Health, University of the Witwatersrand, 1 Smuts Avenue, Braamfontein 2000, Republic of South Africa
lfinda@ihi.or.tz

Michel Franc

Ecole Nationale Vétérinaire de Toulouse (ENVT), 23 Chemin des Capelles, 31076 Toulouse, France
m.franc@envt.fr

Geoffrey Gimonneau

InterTryp, Univ Montpellier, CIRAD, IRD, 34398 Montpellier, France
CIRDES, 01 BP 454, Bobo-Dioulasso, Burkina Faso
geoffrey.gimonneau@cirad.fr

Yannick René Pierre Grimaud

GDS Réunion, 1 rue du Père Hauck, 97418 La plaine des Cafres, La Réunion, France
yannick.grimaud@hotmail.fr

Pierre Guillet

AtoZ Textile mills Ltd., P.O. Box 945, Arusha, Tanzania
guilletpf@gmail.com

Yousif E. Himeidan

Africa Technical Research Centre (ATRC), P.O. Box 15500, Arusha, Tanzania
yousif@vectorhealth.com

Alexandra Hiscox

ARCTEC, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom
Laboratory of Entomology, Wageningen University & Research, P.O. Box 16, 6700 AA, Wageningen, the Netherlands
alexandra.hiscox@lshtm.ac.uk

Philippe Jacquiet

Ecole Nationale Vétérinaire de Toulouse (ENVT), 23 Chemin des Capelles, 31076 Toulouse, France
p.jacquiet@envt.fr

Sathaporn Jittapalapong

Faculty of Veterinary Technology, Kasetsart University, 10900 Bangkok, Thailand
jittapalapongi@gmail.com

Wycliffe Karanja

Africa Technical Research Centre (ATRC), P.O. Box 15500, Arusha, Tanzania
karanjawm@yahoo.com

Pattamaporn Kittayapong

Center of Excellence for Vectors and Vector-Borne Diseases, Faculty of Science, Mahidol University at Salaya, Nakhon Pathom 73170, Thailand
Department of Biology, Faculty of Science, Mahidol University, Bangkok 10400, Thailand
pkittayapong@gmail.com

Immo Kleinschmidt

MRC International Statistics and Epidemiology Group, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom
Department of Pathology, School of Health Sciences, University of Witwatersrand, 7 York Road, Parktown, Johannesburg, South Africa
immo.kleinschmidt@lshtm.ac.uk

Constantianus J.M. Koenraadt

Laboratory of Entomology, Wageningen University & Research, P.O. Box 16, 6700 AA, Wageningen, the Netherlands
sander.koenraadt@wur.nl

Audrey E. Lenhart

Entomology Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, 1600 Clifton Road, MS G-49, Atlanta, GA 30329, USA
ajl8@cdc.go

Emmanuel Liénard

Ecole Nationale Vétérinaire de Toulouse (ENVT), 23 Chemin des Capelles, 31076 Toulouse, France
e.lienard@envt.fr

Neil F. Lobo

University of Notre Dame, Department of Biological Sciences, South Bend, IN 46556, USA
nlobo@nd.edu

Pablo Manrique-Saide

Unidad Colaborativa para Bioensayos Entomologicos, Departamento de Zoologia, Universidad Autonoma de Yucatan, Km. 15.5 Carretera Mérida-Xmatkuil s.n., Merida, Yucatan, C.P. 97315, Mexico
msaide@correo.uady.mx

Gamini Manuweera

Chemicals and Health Branch, United Nations Environment Programme, International Environment House 1, Chemin des Anémones 11-13, 1219 Châtelaine, Switzerland
gamini.manuweera@un.org

Manonath Marasinghe

Anti-Malaria Campaign, Ministry of Health, 555/5 Elvitigala Mawatha, Colombo 00500, Sri Lanka
manonathmarasinghe@yahoo.com

Roungthip Masmeatathip

Faculty of Agriculture at Kamphaeng Saen, Kasetsart University, 73140 Nakhon Pathom, Thailand
fagrrtm@ku.ac.th

Sarah J. Moore

Ifakara Health Institute, Bagamoyo, P.O. Box 74, Pwani, Tanzania
Epidemiology and Public Health Department, Swiss Institute of Tropical and Public Health, Soccinstrase 57, 4002 Basel, Switzerland
University of Basel, Petersplatz 1, 4003, Basel, Switzerland
smoore@ihi.or.tz

Fredros O. Okumu

Environmental Health & Ecological Sciences, Ifakara Health Institute, P.O. Box 53, Ifakara, Tanzania
School of Public Health, University of the Witwatersrand, 1 Smuts Avenue, Braamofontein 2000, Republic of South Africa
Institute of Biodiversity, Animal Health & Comparative Medicine, University of Glasgow, G12 8QQ Glasgow, United Kingdom
School of Life Science and Bioengineering, Nelson Mandela African Institution of Science & Technology, P.O. Box 447, Arusha, Tanzania
fredros@ihi.or.tz

Sathaporn Onju

Faculty of Agriculture at Kamphaeng Saen, Kasetsart University, 73140 Nakhon Pathom, Thailand
camba-11@hotmail.com

Johnson Ouma

Africa Technical Research Centre (ATRC), P.O. Box 15500, Arusha, Tanzania
johnson@azpfl.com

Jean-Baptiste Rayaisse†

CIRDES, 01 BP 454, Bobo-Dioulasso, Burkina Faso
† Deceased

Scott A. Ritchie

Australian Institute of Tropical Health & Medicine, James Cook University, 1/14-88 McGregor Road, Smithfield QLD 4870, Australia
scott.ritchie@jcu.edu.au

Mark Rowland

Department of Disease Control, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom
mark.rowland@lshtm.ac.uk

Ernest Salou

CIRDES, 01 BP 454, Bobo-Dioulasso, Burkina Faso
salouernest@gmail.com

Thomas W. Scott

Department of Entomology and Nematology, University of California Davis, 367 Briggs Hall, One Shields Avenue, Davis, CA 95616, USA
twscott@ucdavis.edu

Viral Shah

AtoZ Textile mills Ltd., P.O. Box 945, Arusha, Tanzania
viral@azpfl.com

Sharif Shukri

Ecole Nationale Vétérinaire de Toulouse (ENVT), 23 Chemin des Capelles, 31076 Toulouse, France
s.sharif@envt.fr

Jeroen Spitzen

Laboratory of Entomology, Wageningen University & Research, P.O. Box 16, 6700 AA, Wageningen, the Netherlands
jeroen.spitzen@wur.nl

Caleb Stica

Ifakara Health Institute, Bagamoyo, P.O. Box 74, Pwani, Tanzania
sticacaleb@gmail.com

Willem Takken

Laboratory of Entomology, Wageningen University & Research, P.O. Box 16, 6700 AA, Wageningen, the Netherlands
willem.takken@wur.nl

Kornkanok Thaisungnoen

Faculty of Veterinary Medicine, Kasetsart University, 10900 Bangkok, Thailand
kornkanok.tha@gmail.com

Henk van den Berg

Visiting Scientist, Laboratory of Entomology, Wageningen University, P.O. Box 16, 6700 AA Wageningen, the Netherlands
vandenberg.henk@gmail.com

Gonzalo M. Vazquez-Prokopec

Department of Environmental Sciences, Math & Science Centre, Emory University, 400 Dowman Drive, Atlanta, GA 30322, USA
gmvazqu@emory.edu

Raman Velayudhan

Veterinary Public Health, Vector Control and Environment unit (VVE), Department of Control of Neglected Tropical Diseases (UCN/NTD), World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland
velayudhanr@who.int

Reviewers

The editors greatly acknowledge the following reviewers:

Nicole L. Achee

Eck Institute for Global Health
Department of Biological Sciences
239 Galvin Life Science Center
Notre Dame, Indiana 46556, USA
Email: nachee@nd.edu

Leonard E.G. Mboera

Emerging and Vector-borne Diseases
SACIDS Foundation for One Health, Sokoine University of Agriculture
P.O. Box 3297, Chuo Kikuu, Morogoro, Tanzania
Email: leonard.mboera@sacids.org

Raphael N'Guessan

London School of Hygiene and Tropical Medicine
Faculty of Infectious and Tropical Diseases
Department of Disease Control
Based at Institut Pierre Richet (IPR), Bouake, Côte d'Ivoire
Email: raphael.n'guessan@lshtm.ac.uk

Alongkot Ponlawat

Chief, Vector Biology and Control Section,
Department of Entomology,
USAMD-AFRIM
Bangkok, Thailand 10400
Email: alongkotp@afrims.org

P. Marijn Poortvliet

Strategic Communication Group,
Wageningen University,
PO Box 8130, 6700 EW Wageningen,
The Netherlands
Email: marijn.poortvliet@wur.nl

Julie-Anne A. Tangena

Liverpool School of Tropical Medicine
Pembroke Place Liverpool
L3 5QA, UK
Email: julie-anne.tangena@lstm.ac.uk

Sonthaya Tiawsirisup

Animal Vector-Borne Disease Research Unit,
Veterinary Parasitology Unit, Department of Veterinary Pathology,
Faculty of Veterinary Science, Chulalongkorn University,
Bangkok 10330, Thailand
Email: sonthaya.t@chula.ac.th

Hans Verhoef

Division of Human Nutrition and Health,
Wageningen University,
P.O. Box 17, 6700 AA, Wageningen,
The Netherlands
Email: hans.verhoef@wur.nl

Anne L. Wilson

Liverpool School of Tropical Medicine
Pembroke Place Liverpool
L3 5QA, UK
Email: anne.wilson@lstmed.ac.uk