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Measuring, manipulating and exploiting behaviours of adult mosquitoes to optimise malaria vector control impact

Gerry F Killeen, John M Marshall, Samson S Kiware, Andy B South, Lucy S Tusting, Prosper P Chaki, Nicodem J Govella

ABSTRACT
Residual malaria transmission can persist despite high coverage with effective long-lasting insecticidal nets (LLINs) and/or indoor residual spraying (IRS), because many vector mosquitoes evade them by feeding on animals, feeding outdoors, resting outdoors or rapidly exiting from houses after entering them. However, many of these behaviours that render vectors resilient to control with IRS and LLINs also make them vulnerable to some emerging new alternative interventions. Furthermore, vector control measures targeting preferred behaviours of mosquitoes often force them to express previously rare alternative behaviours, which can then be targeted with these complementary new interventions. For example, deployment of LLINs against vectors that historically fed predominantly indoors on humans typically results in persisting transmission by residual populations that survive by feeding outdoors on humans and animals, where they may then be targeted with vapour-phase insecticides and veterinary insecticides, respectively. So while the ability of mosquitoes to express alternative behaviours limits the impact of LLINs and IRS, it also creates measurable and unprecedented opportunities for deploying complementary additional approaches that would otherwise be ineffective. Now that more diverse vector control methods are finally becoming available, well-established entomological field techniques for surveying adult mosquito behaviours should be fully exploited by national malaria control programmes, to rationally and adaptively map out new opportunities for their effective deployment.

INTRODUCTION
Malaria vector control with long-lasting insecticidal nets (LLINs) or indoor residual spraying (IRS) has been remarkably successful over recent years, accounting for most of the 663 million cases and 4 million deaths averted since 2000.1,2 LLINs and IRS have been most effective in regions of high transmission where local vectors like Anopheles funestus and A. gambiae in Africa, or A. punctulatus and A. kolisi in the Pacific, exhibit...
human-feeding, indoor-feeding and indoor-resting behaviours that are vulnerable to attack with LLINs and/or IRS.\textsuperscript{3–5} However, LLINs and IRS are poorly suited to tackling the much larger number of important vector species that avoid fatal contact with these products by feeding outdoors, by frequently feeding on animals, resting outdoors or foraging briefly and cautiously within houses when they do enter them.\textsuperscript{3 5 6} Thus, for many high-risk populations, elimination of \textit{residual malaria transmission} is unattainable, even with full universal coverage of highly effective LLINs and/or IRS, using active ingredients to which the local vectors are fully susceptible.\textsuperscript{3 6 7}

However, a number of rejuvenated, repurposed and entirely new vector control methods are now emerging that can address residual malaria transmission by complementing, and even superseding, current LLIN and IRS technologies.\textsuperscript{8} It is therefore time to be more optimistic, and urgently rethink how we look at malaria vector behaviours. Specifically, we need to start viewing phenomena like outdoor feeding, feeding on animals and early exit from houses as missed opportunities for rational deployment of new interventions, rather than merely obstacles to success with existing IRS and LLIN options.

**Turning problems into opportunities**

Fortunately, many behaviours that render vectors resilient to IRS and LLINs also make them vulnerable to emerging new alternatives. New or improved vector control strategies for dealing with residual transmission are now emerging that exploit specific, quantifiable, vulnerable behaviours of adult mosquitoes, the first three of which were previously viewed as problems rather than potential solutions: (1) exclude, repel or kill adult vectors attempting to feed or rest inside houses; (2) repel, incapacitate or even kill adult mosquitoes when they attack people outdoors; (3) kill adult mosquitoes when they attack livestock; or (4) kill adult mosquitoes when they feed on sugar; (5) kill adult mosquitoes when they aggregate as mating swarms within human settlements.\textsuperscript{8}

Taking the example of mosquitoes like \textit{A. arabiensis} or \textit{A. darlingi}, which can persistently forage indoors despite high coverage of LLINs or IRS\textsuperscript{9 10} by avoiding extended contact with treated surfaces,\textsuperscript{11–14} this frustrating behaviour also provides convenient opportunities for preventing them from entering houses with traditional screening methods.\textsuperscript{15} Being more ambitious, it should even be possible to deliberately target them when they attempt to enter houses, with either entry traps\textsuperscript{16} or improved insecticides delivery formats.\textsuperscript{17–19}

Similarly, where vectors like \textit{A. farauti} or \textit{A. epiroticus} frequently attack people while they are active outdoors, this can be viewed as an unexploited opportunity to target them by protecting humans with insecticide-treated clothing\textsuperscript{20} or new, long-lasting vapour emanator formulations of volatile insecticides\textsuperscript{22–24} that can debilitate\textsuperscript{25} or even kill\textsuperscript{26} vectors. Even vectors like \textit{A. arabiensis}, which can feed often enough on humans to mediate intense transmission but extensively enough on cattle to be resilient against attack with IRS, LLINs or any other insecticidal personal protection measure for humans,\textsuperscript{27} may be tackled by deliberately targeting insecticides to these alternative blood sources. Where zoophagy predominantly results in frequent feeding on livestock rather than wild animals, veterinary formulations of topical or systemic insecticides (the latter are often referred to as endectocides) may be deployed, which are far more affordable, acceptable and long-lasting than available formulations of the same active ingredients for humans, through delivery systems that already exist in many low-income countries.\textsuperscript{28}

**Manipulating vector behaviours to create new intervention opportunities**

Furthermore, previously unusual behaviours of adult mosquitoes often become vital to their continued survival following deployment of interventions targeting more common behaviours, creating measurable new opportunities for complementary additional approaches to target these engineered vulnerabilities.

For example, in an east African setting with which we are particularly familiar, \textit{A. arabiensis} historically fed predominantly indoors on humans despite their preference for cattle, because at that time cattle were scarce while people were both abundant and unprotected.\textsuperscript{29 30} Following scale-up of LLINs, anthropophagic \textit{A. funestus} became far more scarce and \textit{A. gambiae} almost disappeared but \textit{A. arabiensis} persisted\textsuperscript{31 32} by exhibiting three behaviours which protect it against LLINs, as well as render it remarkably vulnerable to complementary measures: (1) increased feeding outdoors in the early evenings when people are active and unprotected by nets\textsuperscript{33} where they could now be targeted with insecticide-treated clothing\textsuperscript{20} or vapour-phase insecticides;\textsuperscript{22–24} (2) although they avoid fatal contact with LLINs when they do enter houses,\textsuperscript{12 13} the fact is that bed nets force mosquitoes to enter twice as many houses to obtain the blood they need.\textsuperscript{10} This phenomenon of repeated house entry could therefore be exploited to kill them more effectively than would otherwise be possible, by applying additional insecticides inside houses by spraying them on the walls as IRS (figure 1), or by targeting them to entry points with eave tubes\textsuperscript{19} or exit points with eave baffles;\textsuperscript{17} and (3) half of their blood meals are now obtained from unprotected cattle\textsuperscript{34} that do not use nets but could be readily treated with long-lasting veterinary insecticide formulations.\textsuperscript{28}

As illustrated mechanistically in figure 2, such layering of interventions in a logical sequence can enable rational manipulation and exploitation of mosquito behaviour patterns, sometimes referred to as ‘push–pull’ strategies\textsuperscript{35–38} that originate from the agriculture sector.\textsuperscript{39} Such altered postintervention behavioural patterns create new opportunities for targeting outdoor-feeding vectors with insecticide clothing treatments,\textsuperscript{18 19}
Monitoring purposes is essential because the heritable behavioural preferences of vector populations can change in response to selection pressure exerted by selectively targeted interventions. Beyond the simple, instantaneous plasticity assumed in figure 2 that can be described as behavioural resilience, mosquitoes can also evolve behavioural resistance in the true sense, exhibiting altered patterns of innate feeding preferences over the longer term.

The observations of highly plastic blood-feeding behaviours by *A. arabiensis* in southern Tanzania, as described above, represent neither an isolated example nor a new paradigm, and figure 2 could well be described as a ’glass-half-full’ reinterpretation of our previous simulations of these same behavioural processes. Indeed, this narrative for our local *A. arabiensis* population is just one out of hundreds of similar historical and contemporary examples reported for numerous vector species all across the tropics. In fact, even the more anthropophilic African species *A. coluzzii*, *A. gambiae* and *A. funestus* have recently been observed to persist following LLIN/IRS scale-up by switching to feeding on animals.

**Exploiting the full potential of existing entomological field techniques**

Most of the survey methods required to measure mosquito behaviours and enable optimal intervention selection (table 1) have been available for decades in practical low-technology formats that are accessible and affordable to national control and elimination programmes. While much more advanced laboratory techniques are now available for identifying which hosts mosquitoes obtain blood from, assuming that 90% of all attacks on humans would occur indoors in the absence of any protection measure (*πh,i,0=0.9*), IRS, indoor residual spraying.

Figure 1 An illustration of how high coverage with bed nets can enhance the impact of a second domestic vector control measure with insecticides, such as IRS, by forcing mosquitoes to visit far more houses than they normally would. (A) A schematic representation of how reducing the availability of human blood (*Z*) with 80% human usage (*Uh=0.8*) of bed nets (N) can double the number of encounters (E) with humans required by *Anopheles arabiensis* to obtain a blood meal, relative to baseline conditions with no nets (O). Estimated coverage of the mosquito population (*CM*) with exposure to insecticide delivered through IRS, at varying levels of house coverage (*CH*). Mosquito population coverage is expressed as the proportion of mosquitoes exposed to insecticide per feeding cycle and calculated by expressing equation 8 of a previously published model using the same notation as the model of *A. arabiensis* early-exit behaviour, assuming that 90% of all attacks on humans would occur indoors in the absence of any protection measure (*πh,i,0=0.9*).

IRS, indoor residual spraying.

Insecticide vapour emonators and/or veterinary insecticides that would previously have been ineffective. These intervention options can therefore be expected to have a much greater impact on residual transmission as second-line and third-line measures to supplement LLINs in an elimination programme than they ever could on baseline transmission as the first-line measure in a control programme. Interestingly, a similar rationale may even be applicable to enhance the impact of attractive toxic sugar baits, because mosquitoes with less access to blood often maintain their increased energetic requirements by consuming more sugar.

As each layer of intervention tackles the fraction of transmission it is best suited to, the altered characteristics of the remaining residual transmission should be reassessed entomologically, to identify the new opportunities that emerge as the remaining fractions become progressively more vulnerable to well-chosen complementary strategies. Continuous, or at least regular, remeasurement of these behavioural metrics for monitoring purposes is essential because the heritable behavioural preferences of vector populations can change in response to selection pressure exerted by selectively targeted interventions. Beyond the simple, instantaneous plasticity assumed in figure 2 that can be described as behavioural resilience, mosquitoes can also evolve behavioural resistance in the true sense, exhibiting altered patterns of innate feeding preferences over the longer term.

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A schematic illustration of how sequential layers of vector control interventions against particular fractions of blood-feeding mosquitoes can create measurable opportunities for complementary approaches to achieve increasingly dramatic impacts on vector survival and residual transmission. This illustration is based on the well-characterised example of *Anopheles arabiensis* in southern Tanzania, as described in the section entitled *Manipulating vector behaviours to create new intervention opportunities*. We provide a simple online interactive graphical model (https://andysouth.shinyapps.io/coverage1/) allowing the reader to investigate the implications of combining interventions targeting different behaviour patterns under different baseline scenarios of proportional feeding indoor and on humans. The source code (in the statistical language R) is also provided so that the reader can run offline (https://github.com/AndySouth/coverage). LLIN, long-lasting insecticidal net.

<table>
<thead>
<tr>
<th>Technology</th>
<th>Human indicator</th>
<th>Entomological indicator</th>
<th>Niche</th>
<th>Challenges</th>
</tr>
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<tbody>
<tr>
<td>Physical mosquito proofing of</td>
<td>At least partially sedentary lifestyles and sleep indoors</td>
<td>At least one-third of historical or current human exposure to vectors occurs indoors</td>
<td>Almost ubiquitous</td>
<td>Establish systems for promotion and subsidisation of affordable materials</td>
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<td>Residential housing</td>
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<tr>
<td>Temporary or mobile shelters</td>
<td>At least partially migrant lifestyles and sleep in shelters</td>
<td></td>
<td>Almost ubiquitous</td>
<td>Develop locally appropriate, affordable prototype products</td>
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<tr>
<td>Traps or insecticide-treated window screens</td>
<td>Sleep indoors or inside shelters</td>
<td>At least one-third of historical or current human exposure to vectors occurs indoors</td>
<td>Almost ubiquitous</td>
<td>Establish systems for promotion and subsidisation of affordable materials, including insecticide retreatments, developing locally appropriate, affordable prototype products</td>
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<tr>
<td>or eave tubes or eave baffles for killing</td>
<td></td>
<td>and at least one-third of blood meals are obtained from humans</td>
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<td>mosquitoes attempting to enter houses or</td>
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<td>shelters</td>
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<td>Insecticide-treated clothing or emanators</td>
<td>Outdoor activities common during hours of darkness</td>
<td>At least one-third of current human exposure to vectors occurs outdoors</td>
<td>Almost ubiquitous</td>
<td>Reformulation of volatile pyrethroids to maximise affordability, durability and safety</td>
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<td>for vapour-phase repellent, incapacitant and/or</td>
<td></td>
<td></td>
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<td>Development of products with non-pyrethroid active ingredients</td>
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<td>lethal insecticide</td>
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<tr>
<td>Insecticide treatments for livestock</td>
<td>Livestock ownership</td>
<td>At least one-third of vector blood meals are obtained from identified livestock species</td>
<td>Almost ubiquitous</td>
<td>Identify products which most effectively perform both their primary veterinary function and kill locally important malaria vectors</td>
</tr>
<tr>
<td>Insecticidal sugar baits</td>
<td>None known</td>
<td>Most vectors can be labelled with dyed baits lacking insecticide or killed by baits including insecticide</td>
<td>Unknown</td>
<td>Identify best available products and bespoke prototypes, map out geographic extent and variability of high sugar feeding rates and corresponding potential for impact, identify consistently optimal environmental targets and delivery strategies, demonstrate lack of environmental impact on non-target species of arthropods, pollinators in particular</td>
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Continued
targetable behaviours, including aggregation into mating swarms. However, many vector species exhibit considerable plasticity in these traits, so that each can adapt instantaneously and opportunistically to local, fine-scale heterogeneities in the availability of environmental resources. Many mosquito species have been observed to exhibit both extremes of human feeding versus animal feeding, indoor-feeding versus outdoor-feeding and indoor-resting versus outdoor-resting behaviours (figure 3). The ideal, but probably unachievable, optimal balance of vector control interventions can therefore vary greatly between neighbouring villages, or even within a single village. Of course, human beings are essential to malaria transmission, and also exhibit important plastic behavioural variations between individuals, families and communities that are driven by necessity, opportunities, culture and idiosyncrasy. Heterogeneities of mosquito and human behaviours (figure 3) create a complex interplay of local, vector control interventions and the transmission environment that is difficult to predict and control. Fortunately, the extremes of variation in each behavioural plasticity in these traits so that each can adapt instantaneously and opportunistically to local, fine-scale heterogeneity. Each vector species exhibit considerable plasticity in these traits, so that each can adapt instantaneously and opportunistically to local, fine-scale heterogeneities in the availability of environmental resources. Many mosquito species have been observed to exhibit both extremes of human feeding versus animal feeding, indoor-feeding versus outdoor-feeding and indoor-resting versus outdoor-resting behaviours (figure 3). The ideal, but probably unachievable, optimal balance of vector control interventions can therefore vary greatly between neighbouring villages, or even within a single village. Of course, human beings are essential to malaria transmission, and also exhibit important plastic behavioural variations between individuals, families and communities that are driven by necessity, opportunities, culture and idiosyncrasy. Heterogeneity of mosquito and human behaviours (figure 3) create a complex interplay of local, vector control interventions and the transmission environment that is difficult to predict and control. Fortunately, the extremes of variation in each behavioural

Table 1

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<td>Insecticidal aerosols or fogs targeted at mosquitoes when they disperse, rest or form mating swarms</td>
<td>None known</td>
<td>Most vectors can be labelled by dyed with formulations lacking insecticide or killed by formulations including insecticide</td>
<td>Possibly west and central Africa</td>
<td>Identify best available products and bespoke prototypes; Map out geographic extent and variability of swarming within human settlement and corresponding potential for impact; Identify consistently optimal environmental targets and delivery strategies; Demonstrate lack of environmental impact on non-target species of arthropods</td>
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The indicators, prioritisation threshold values and niches for application of these vector control technologies are synthesised from a previous detailed review and modelling analyses. For referenced discussion of the methodology required to survey each indicator, see the first paragraph of the section entitled Exploring the full potential of existing entomological field techniques.
However, in order for control programme managers and product developers to confidently rely on such ‘cheap and cheerful’ entomological indicators, they must first be rigorously evaluated across diverse settings in terms of their epidemiological predictive power. While the theoretical evidence base emphasising the importance of such behavioural measurements has become stronger in recent years, direct empirical field assessments of their predictive value and generalisability are now urgently needed. To the best of our knowledge, no wide-scale, multisite assessment of the epidemiological relevance of any behavioural indicator other than the human blood index has ever been conducted, but some examples from single-site studies give an encouraging idea of how this might be achieved and what kind of predictive values they may yield (figure 4).

**Restoring the problem-solving traditions of malaria vector surveillance**

Developing and evaluating a simple set of affordable, practical, scalable entomological indicators of vector control opportunities will require considerable consensus and funding investment; it will also need a new generation of entomologists to embrace the quantitative ethos of what was once known as epidemiological entomology and update the underlying science. After decades

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**Figure 3** Examples of extremely heterogeneous behavioural outcomes, which arise from behavioural plasticity of malaria vector mosquitoes and their human victims, and occur across the full range of spatial scales that are relevant to vector control intervention selection. (A) Specimens of blood-fed, indoor-resting *Anopheles arabiensis* sampled from 12 different locations within a single village in northern Tanzania yielded estimates for the proportion of blood meals obtained from humans, which are distributed across the full possible range of values. (B) The estimated fraction of *A. arabiensis* which rest indoors after feeding (reported originally as the estimated usage rate for indoor resting sites per feeding cycle) varies across a range of more than 300-fold in 21 distinct villages surveyed all across Africa. (C) Variations of only 1–3 hours in the times at which people go indoors for the evening and leave the house in the morning, among 9458 occupants of houses with well-screened windows and ventilation points in a single African city, result in derived estimates for the proportion of remaining residual transmission exposure that occurs outdoors (assuming that a 90% protective effect of the screening is accounted for as previously described) which are widely distributed across most of the full range of possible values.
of stagnation and excessive reliance on prescriptive global policies, it is high time to restore the historically creative traditions of malaria vector surveillance and control, which have yet to fully recover from the naïve adoption of IRS as a vector control panacea by the GMEP 60 years ago:

A serious consequence of that exaggerated confidence was the belief that the wide experience and knowledge of the old malariologists was superfluous and even counter-productive, particularly if they persisted in modifying the eradication strategy locally. Therefore, eradication campaigns were entrusted to new, preferably young ‘malarologists’, trained in ‘Malaria Eradication Training Centres’ established by WHO in several countries.77

Before DDT, malariologists were trained to be problem solvers; after DDT malariologists were trained to be solution implementers.78

The WHO has recently provided laudable leadership and direction by finally embracing a much more inclusive, developed, diversified and adventurous, but nevertheless rational, approach to malaria vector control.6 This historic recent policy revision now encourages locally tailored, programmatic development of a much wider variety of malaria vector control interventions on a biologically rational basis.6 Those of us responsible for surveillance of malaria vector mosquito populations must now respond to this unprecedented formal broadening of our mandate. Sustainable entomological surveillance platforms are urgently needed that go beyond merely reporting physiological resistance to insecticides as the sole explanatory predictor of vector control impact. National and regional surveillance teams should now creatively and adaptively apply long neglected entomological techniques, to routinely measure targetable vector behaviours as a means to inform intervention choice and maximise impact.

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