
Entomological Surveillance as a Cornerstone of Malaria Elimination: A Critical Appraisal

Gerry F. Killeen, Prosper P. Chaki, Thomas E. Reed,
Catherine L. Moyes and Nicodem J. Govella

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.78007>

Abstract

Global capacity for developing new insecticides and vector control products, as well as mathematical models to evaluate their likely impact upon malaria transmission has greatly improved in recent years. Given that a range of new vector control products are now emerging that target a greater diversity of adult mosquito behaviours, it should soon be feasible to effectively tackle a broader range of mosquito species and settings. However, the primary obstacles to further progress towards more effective malaria vector control are now paucities of routine programmatic entomological surveillance, and capacity for data processing, analysis and interpretation in endemic countries. Well-established entomological methods need to be more widely utilized for routine programmatic surveillance of vector behaviours and insecticide susceptibility, the effectiveness of vector control products and processes, and their impacts on mosquito populations. Such programmatic data may also be useful for simulation analyses of mosquito life histories, to identify opportunities for pre-emptively intervening early in the life cycle of mosquitoes, rather than targeting transmission events occurring when they are older. Current obstacles to more effective utilization, archiving and sharing of entomological data largely centre around global inequities of analytical capacity. These prohibitive and unfair imbalances can be addressed by reorienting funding schemes to emphasize south-centred collaborations focused on malaria-endemic countries.

Keywords: malaria, entomological surveillance, mathematical modelling, capacity strengthening, vector control

1. Introduction

Elimination of malaria parasite transmission from most of the tropics will require scalable, affordable new vector control interventions, which improve upon long-lasting

insecticidal nets (LLINs) and indoor residual spraying (IRS) for population suppression of mosquitoes which feed or rest indoors, and also extend control of adult mosquitoes outdoors [1–3]. However, the greatest challenge that lies ahead is defining exactly which of these intervention options is necessary and optimal [4] in each of the diverse vector systems that support malaria transmission across the tropics [5–7]. Product developers and manufacturers need a manageably short list of ecologically-defined target product profiles to work with, based on quantitatively characterized traits of wild vector populations [6, 8]. Assuming an adequate arsenal of diverse and mutually-complementary vector control strategies can be made available [2, 3], malaria control programmes will then need to select the most effective subset of these options that they can afford and realistically implement [9], based on longitudinal, nationally-representative surveys of key behavioural and physiological traits [6–11].

As a result of long-term investments in the industrial development pipeline initiated over a decade ago [12], a diversity of new insecticide formulations for malaria vector control products are coming onto the market and entirely new insecticide classes will soon follow [13, 14]. It is also encouraging that a growing diversity of new or repurposed vector control methods are emerging which either use insecticides more efficiently and effectively, or even do entirely without them [2, 3]. Indeed, a range of new vector control technologies are now emerging for tackling a much wider range of mosquito behaviours and species in more diverse tropical settings [2, 3].

2. Knowledge and methodology limitations to improved vector control products and practices

Several detailed models of malaria transmission have been independently developed over the last decade, and integrated into collaborative ensemble platforms [15–21] that have successfully informed global policy [22]. However, as these models develop and improve, further progress is increasingly limited by lack of knowledge rather than global mathematical capacity:

Differences in the predicted impact size arise due to the different assumptions made about malaria transmission in each model, which represent realistic uncertainties in our understanding of this process [22].

...assessment of the consequences of uncertainties in parameter values, are generally much more time-consuming and challenging than the modelling itself [23].

Unfortunately, knowledge and data are most limiting in relation to the underlying entomological input parameters that these mathematical models are most sensitive to [24]. While the blood-stage dynamics of malaria parasites in humans are now simulated based on hundreds of observed time courses for individual human infections, and calibrated against tens of thousands of malaria prevalence data sets from the field, epidemiologically important variability in survival demographics between different mosquito populations [25] remains to be captured in commonly-used malaria transmission models. Given the

central importance of mosquito survival and gonotrophic cycle duration as targets for many vector control measures [24], it is remarkable that we know little about foraging and mortality processes occurring outside the artificial indoor environment of experimental huts (**Figure 1**). Only a handful of sites exist globally for which estimates of local vector survival, host preference, biting pattern, and adult emergence rates are all available, so that malaria transmission models can be explicitly tailored to the dynamic properties of local vector populations [26]. Indeed, several independently formulated families of models rely heavily on a single village in southern Tanzania for several of their most important vector parameter estimates [4, 15, 27, 28].

Many of the biggest knowledge gaps relating to malaria vector biology arise from our inability to observe, track or label mosquitoes over large, important parts of their life cycles that occur outdoors. Crucially, the outdoor environment represents a refuge for mosquitoes from currently prioritized indoor-targeted interventions like LLINs and IRS. Important limitations to existing entomological methodology includes: (1) representative sampling of outdoor-resting, blood-fed mosquitoes for surveying host choice, especially beyond the peri-domestic environment; (2) observing, tracing or tracking mosquitoes when they are not host-seeking, especially outdoors; (3) quantifying and mapping participation of males and females in mating swarms; (4) quantifying and mapping of oviposition behaviour and; (5) mapping dispersal between emergence, mating, feeding, resting, and oviposition sites.

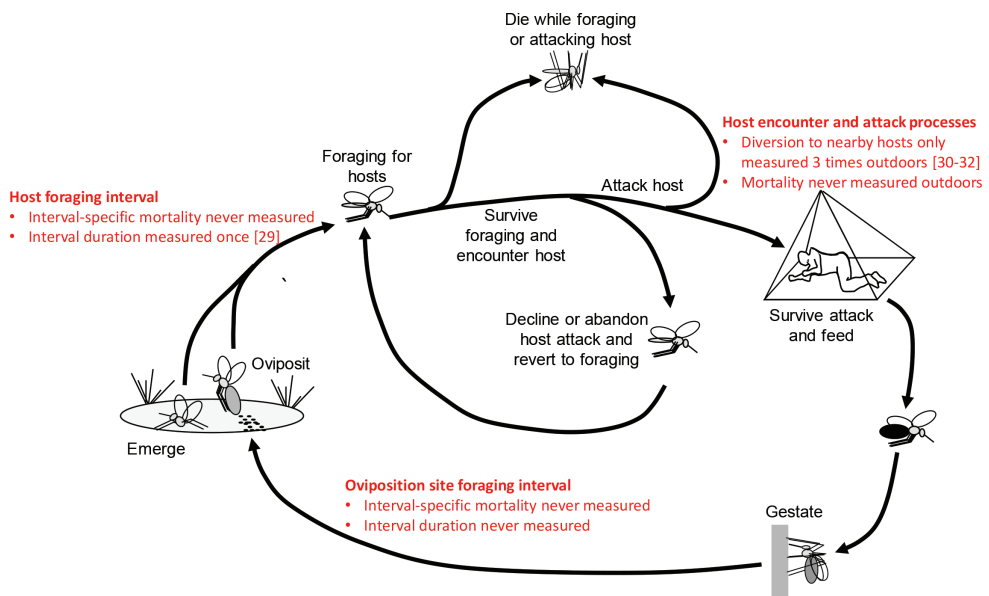


Figure 1. A schematic illustration of major gaps in knowledge about even the most simplistic conceptual model of a mosquito life cycle that are relevant to interventions targeting human-feeding mosquitoes. For simplicity, some common mosquito life history processes excluded, viz., include feeding on animals, feeding upon sugar, swarming and mating. Source: Ref. [29–32].

3. Underutilization of existing methodology for informing malaria vector control programmes

While the methodological limitations described above merit investment, a far bigger limitation is underutilization of long-established and widely-accepted methodologies to inform vector control product development, deployment and assessment. It is remarkable just how few study sites are available with consistently-collected, long-term legacy data that capture longitudinal trends for coverage with important interventions along with both entomological (human biting rate, sporozoite infection prevalence, entomologic inoculation rate) and epidemiological (parasitological incidence and prevalence, as well as disease burden) outcomes to enable satisfactory analysis. Dielmo is a rare exception on the vast continent of Africa, where the same entomological methods for monitoring vector population densities and malaria inoculation rates have been continuously applied in a consistent manner for more than two decades [33]. More recently, these vector population dynamics surveys have been supplemented with repeated characterisations of behavioural interactions between humans and mosquitoes [34]. These additional measurements of human exposure distribution across indoor and outdoor environments at different times of the day certainly help explain why robust residual transmission persists, and reveals worrying signs of a worsening situation [34, 35].

While this intensively studied village provides a valuable illustration of how informative such longitudinal surveillance can be, it is not necessarily representative of other parts of Senegal, much less any other country in Africa [35]. National malaria control or elimination programmes all need their own, nationally-representative set of surveillance sites like Dielmo, where malaria transmission is continually and indefinitely monitored using consistent methods. Such platforms are needed to reliably monitor the dynamics of malaria vector populations and transmission intensity across all major ecological and epidemiological strata, so that the limitations and failures of interventions can be identified, distinguished (**Figure 2**), investigated and responded to.

Looking more broadly at programmatically-relevant entomological measurements, insecticide susceptibility testing is now widespread, but measurements of important mosquito and human behaviours are remarkably sparse (**Figure 3**). The species identity of blood hosts that mosquitoes feed upon has long been recognized as a crucial determinant of malaria transmission intensity and an indicator of intervention impact [6, 36–39]. Although adequate field and laboratory methodology for surveying the blood meal choices of most vector species have been available for over 50 years, species-specific reports of this metric remain remarkably scarce for all but a few key vector species (**Figure 3B**). The principles of how to weight indoor and outdoor human landing catch data in proportion to survey results for where people spend each time of the night were first outlined by Garrett-Jones in 1964 [40], yet today less than a dozen such estimates of how human exposure is distributed have been reported, in most cases for undifferentiated mixtures of vector complexes or groups (**Figure 3C**). Only

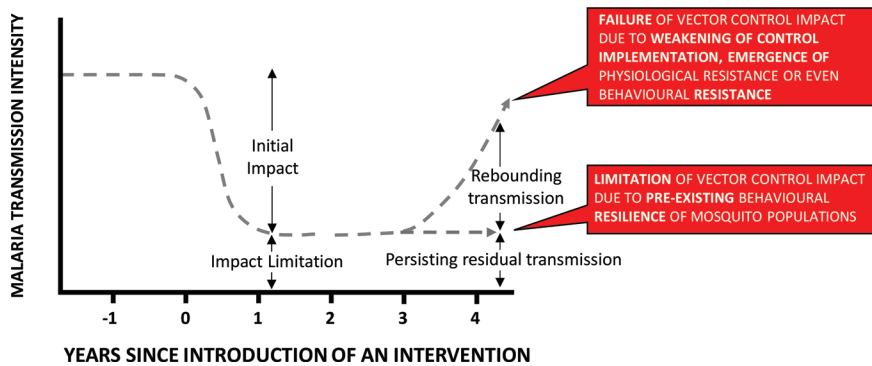


Figure 2. A schematic illustration of how the different trajectories of intervention limitations and failures can be captured and distinguished through longitudinal surveillance of vector population and transmission dynamics (adapted from [6]).

two of the four villages for which a full minimum set of parameters for modelling malaria transmission based on local measurements (**Figure 3D**) relate to a single species, neither of which relied on disaggregation of species-specific data, because only one sibling species from within the relevant complex was abundant.

There are also limitations to the quality of data collection, archiving and analysis that result in most available entomological measurements being reported at the level of species groups or complexes, rather than disaggregated on a species-by-species basis. For example, despite clear evidence for differences among species in both the mechanisms of insecticide resistance and in the prevalence of resistance phenotypes [41–44], the species-specific data presented in **Figure 3A** represents only 27% of the total available [45]. The remaining 73% of archived data represent aggregated mortality rates for mixtures of two or more undifferentiated species [45]. In some cases, species-level classification simply was not conducted. In others, species identification was conducted but the bioassay results were only provided for the pooled species. In other examples, the species data was compromised because only a subset of the mosquitoes assayed, for example only bioassay survivors, were identified to the species level. This lack of species-specific data reduces the power to investigate trends in insecticide resistance and to detect associations between resistance in wild vector populations and malaria transmission experienced by the human population. The data in **Figure 3B** represents only the small fraction (12%) of all available data on human blood indices that unambiguously relates to a single species rather than an undifferentiated mixture of two or more. Only three [46–48] of the small handful of estimates for the proportion of human biting exposure occurring indoors or while asleep (**Figure 3C**) relate to a single, clearly identified and disaggregated species.

Generic (e.g., Microsoft Access®) or freely available (e.g., mySQL®) relational database applications have been adopted as standard tools and used ubiquitously by almost all epidemiologists and field biologists for decades, but medical entomologists generally lag far behind, especially in low income countries. If links between data fields are lost they cannot

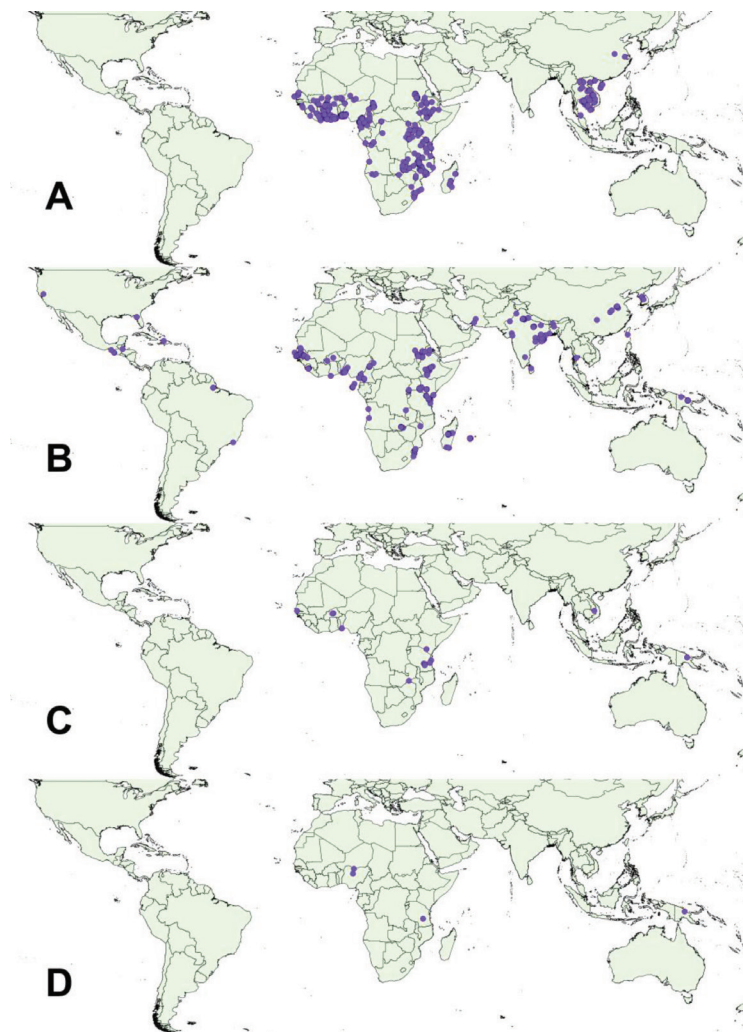


Figure 3. The global distribution of reported measurements for (A) insecticide resistance, (B) the proportions of bloodmeals obtained from humans, (C) the proportion of human exposure to bites occurring indoors, for *Anopheles* vectors of malaria, and (D) the only four locations, we are aware of, where estimates for the mean adult biting density, survival and human blood index for even a single vector, as well as human population size and infectiousness are all available, so that malaria transmission and control can be modelled in a site-specific manner based on local estimates of these parameters. Panels A and B respectively represent the species-specific subset of all insecticide susceptibility bioassay [45] and human blood index [7, 49] data collated by the time they were most recently published as dataset summary reports. The studies represented in Panel C include only three reports of species-specific estimates [46–48] for the proportion of human biting exposure occurring indoors, with the remaining handful all relating to undifferentiated mixtures of species in a complex or group [34, 50, 51]. Panel D represents only four locations in only three countries (Nigeria, Tanzania, Papua New Guinea), all of which were small rural villages with intense transmission and anthropophilic vectors (otherwise at least some of these parameters would probably have been impossible to measure), but nevertheless yielded remarkably different vector-parasite demography patterns and suitability for various complementary vector control measures beyond LLINs and IRS [26, 52].

be reinstated and the utility of the unlinked data is severely reduced. The most obvious and common example is a collection of morphologically indistinguishable mosquitoes that are used in an insecticide bioassay, then separated into live and dead mosquitoes, and tested for species and sporozoite infection. If unique identifiers are not assigned to each mosquito and linked to data on bioassay survival, species, sporozoite presence and blood meal for that individual mosquito, then any analysis of the relationships among species, insecticide susceptibility, infection and blood meals is severely hampered. Too often, all that is reported is the sporozoite rate, species composition, etc., for the whole sample, i.e., the aggregate value for all the mosquitoes in the original collection even though they comprise a mixture of two or more different species. This is probably the single most important limiting factor when it comes to species-specific measurements for the variables that matter most, or the interactions between them.

In addition to being so limited in quantity and quality, the utility of existing vector bionomic data is also compromised by the fact that it has mostly been collected haphazardly and opportunistically with project-based research funding. As a result, it has typically been collected on scales varying from villages to districts, over only a few years at a time. Different research studies in any given setting typically have different objectives that often necessitate different sampling and trapping approaches, so collating data sets from multiple projects often yields a patchwork of data with substantial temporal gaps and methodological inconsistencies that confound unambiguous interpretation [6–8, 11].

4. Addressing data deficits through programmatic entomological surveillance platforms

The latest guidelines from WHO for entomological surveillance, monitoring and evaluation offer an excellent new framework for comprehensively applying existing field and analytical methods, and for conducting operational research into improving their use practices in the future [53]. In order for national programmes to make evidence-based decisions about what vector control measures to deploy, and evaluate their ongoing impact, the remarkably diverse arsenal of entomological methods already at our disposal [54] now need to be adapted to programmatic surveillance platforms that are nationally representative of all major ecological and epidemiological strata in the country [6–8, 11]. Such programmatic platforms should emphasize the absolute minimum number of essential entomological metrics, with strong data quality control and assurance processes to maximize confidence and minimize ambiguity of interpretation (**Figure 4**).

Data quantity and quality obviously trade off against each other, especially when working across very large geographic areas, so it is often necessary to select the smallest number of surveillance sites required to adequately represent all major epidemiological and ecological strata in the country. Based on our experience, a minimum of five surveillance sites per stratum is suggested to adequately capture variation within each stratum. The recent WHO guideline of one sentinel site per million people [53] also represents a good benchmark that

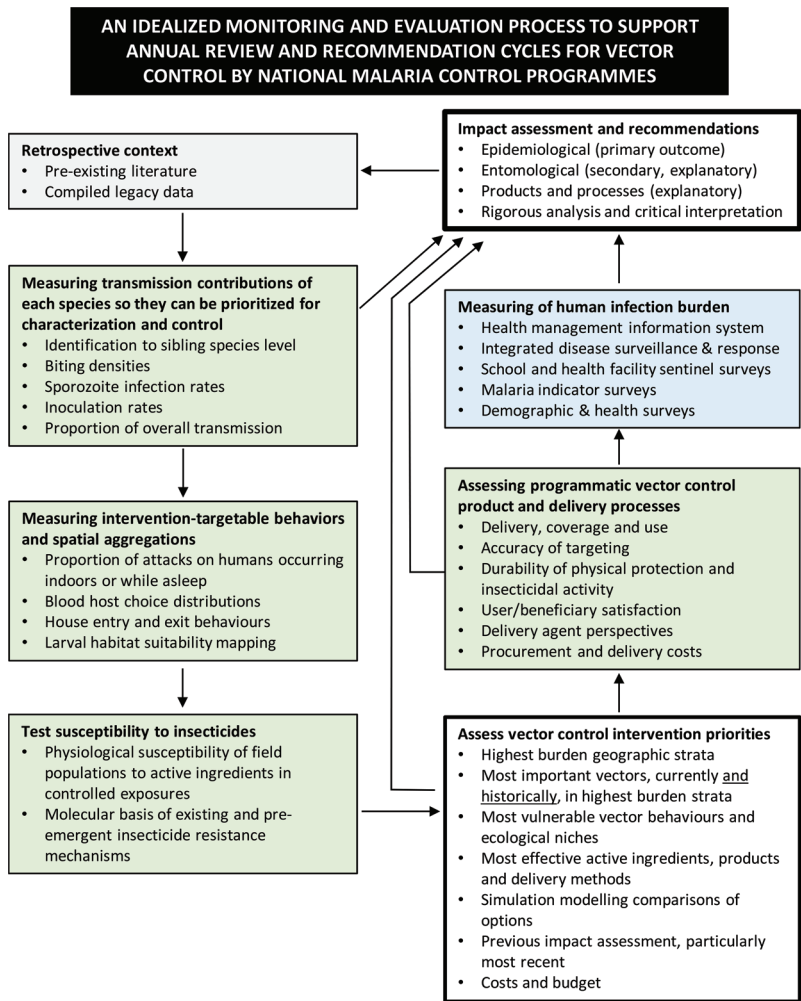


Figure 4. A suggested flow diagram for cyclical collection and assessment of programmatic surveillance data to inform malaria vector control on national scales. Formal annual review cycles may be supplemented by *ad hoc* review meetings at short notice, whenever surprising or alarming trajectories are observed through ongoing data monitoring.

can be modified according to need by countries that are particularly large, small or diverse. In addition to routine surveys of established surveillance sites, *ad hoc* spot checks and focus investigations are also recommended as ways to further improve vector surveillance and control [53]. Additionally, much more intensive, finer-scale surveillance of vector population dynamics is required wherever pro-active mosquito abatement methods, specifically larvicide application or space spraying, are deployed. These vertically-managed methods for delivering insecticides across large areas need to be repeated on a regular basis, often as frequently as every week. In order for mosquito population density measurements to be useful for monitoring purposes, they need to be collected at spatial scales fine enough to identify

operational coverage gaps as soon as they arise. Entomological monitoring to inform daily operations of such area-wide insecticide applications therefore need to be repeated on a correspondingly regular basis, and on geographic scales approximately matched to the scale at which insecticide application succeeds or fails. While active larval searches can be useful for monitoring the effectiveness of insecticide applications, they are prone to large observational biases, especially towards over-representing the most obvious and accessible habitats most likely to be effectively covered. Adult mosquitoes, however, fly and gravitate towards stimuli so they can be passively monitored with traps. Adult mosquito density measurements are therefore a far more reliable way to verify impact and inform operational implementation of larviciding or space-spraying programmes that actively deliver relatively short-lived insecticides across large areas. For such pro-active area-wide interventions, much higher spatial and temporal resolution is required than for more passive human-targeted approaches like LLINs and IRS, which rely on mosquitoes being attracted to protected individuals and households.

National surveillance platforms need to not only monitor the most useful predictors and indicators of successful vector control, but also the products and delivery processes that are essential to achieving impact in practice. Biologically-rational selection of an optimal overall intervention approach, such as LLINs, IRS or larviciding, does not in itself guarantee success. First, it is essential that the most efficacious products within that class are procured, and that they are then effectively delivered. WHO pre-qualification and centralized procurement help target investments towards reliable products. Subsequently, laboratory-based efficacy testing of products sampled from various stages of the supply chain are an invaluable means to quality assure, and even quality control, product supplies. However, beyond successful procurement and supply, it is also essential to ensure that vector control products are satisfactorily delivered and remain effective over the lifetimes required of them. While the coverage of area-wide, frequently re-applied products like larvicides can be difficult to quantify objectively [55, 56], coverage indicators for human-targeted measures like LLINs and IRS can be readily incorporated into questionnaires for routine epidemiological surveys. Reliable, standardized methodology has long been available for measuring the extent and durability insecticidal activity of walls, roofs and ceilings treated with IRS, and have been applied to great effect across multi-country scales, to demonstrate programmatically-relevant variations in product performance [57]. Standardized methods for assessing the physical and insecticidal durability of LLINs reveal similarly important variations in performance, including some notable shortfalls relative to the requirements for recommendation of a '3-year net' [58]. Regardless of how well they are developed, manufactured and tested before they are delivered, products do not always 'do what they say on the tin', so their effectiveness in the field needs to be regularly assessed and re-assessed on nationally representative scales.

5. Directly interpretable entomological metrics of mosquito behaviours, insecticide susceptibility, intervention effectiveness, and intervention impact

Entomological monitoring to inform routine programme implementation needs to yield measurements that can be directly and informatively interpreted, so that those collecting the

data in the field can readily use and quality control it. As discussed in the section that follows, simple summary metrics of mosquito behaviour and insecticide susceptibility do have limitations that need to be addressed with simulation models, but nevertheless need to have decision-making value in their own right.

Despite their limitations, existing simple insecticide bioassays provide an excellent example. Some insecticides can induce delayed but nevertheless invaluable mortality among mosquitoes that are classified as highly resistant based on the 24-hour holding period traditionally used in standard susceptibility assays [59]. Nevertheless, complete and rapid mortality within a day of exposure can only be a good thing and favours the selection of an insecticide verified to do so. Once interventions like LLINs or IRS have been deployed, it is always encouraging if they can be verified to exhibit durable insecticidal efficacy in the field, using well-established cone or wire ball assays with fully-susceptible insectary-reared mosquitoes.

For measuring impact, reduced biting densities and sporozoite prevalence rates can be directly interpreted as indicators of intervention success. Also, vector population rebounds can be identified by directly examining simple graphs of longitudinal trends in density and infection prevalence (**Figure 2**). Any such suspected intervention failure should trigger careful examination of all the above vector behaviour and insecticide susceptibility metrics, as well as indicators of effective vector control products and delivery processes in the field.

On the behavioural front, high estimates for the proportion of human exposure to mosquito bites occurring indoors is always an encouraging indicator that LLINs should at least provide strong personal protection [6]. They may also achieve vector population control if they are also susceptible to the insecticidal active ingredients and obtain a large proportion of blood meals from humans [1, 6–8]. Once high LLIN use has been achieved, high proportions of residual transmission may occur outdoors, and the vector may become more reliant upon livestock as a source of blood, indicating that spatial insecticide emanators or veterinary endectocides may be considered as possible supplementary interventions [7]. While surveys of bloodmeal sources among samples of engorged mosquitoes are always biased to over-represent the indoor-resting and human-feeding fraction of the vector population [36, 37], very high estimates of the human blood index are nevertheless a strong indicator of both vectorial capacity and vulnerability to attack with human-centred approaches [1, 6–8, 38]. Conversely, where large proportions of blood meals are found to originate from livestock, this is an encouraging indicator that veterinary formulations of endectocides could be useful as a supplementary vector control tool [6–8].

Perhaps the most important reason for entomological surveillance data to be readily and directly interpretable is so that data interrogation begins with the front-line staff who collect it in the field. The closer to the point of collection that data is examined and interpreted, the sooner it is acted upon and the sooner it is queried for completion and correctness. Even within our specialized research groups, we have recently achieved huge improvements in entomological data quality simply by having it entered by the people who collected it on the day it was recorded. Entomological surveillance indicators that can be directly and intuitively interpreted in the field are much easier to quality control and quality assure, especially through decentralized data collection platforms.

Appropriate graphical tools are particularly important for helping programme staff to accurately interpret data. For example, many entomologists directly interpret the results of indoor and outdoor human landing catches without weighting these biting rate measurements in proportion to estimates of where people spend various times of the night (**Figure 5A and B**). This common misinterpretation is even endorsed by the latest WHO guidelines [53], which recommend numerical expression in the form of an *endophagy index*, comprising the mean indoor biting rate divided by the sum of the mean indoor and outdoor biting rates. This approach usually grossly overestimates the outdoor fraction of transmission exposure because participants in human landing catches behave in a deliberately misrepresentative manner, spending an average of half their time indoors and half outdoors across all times of the night. In the vast

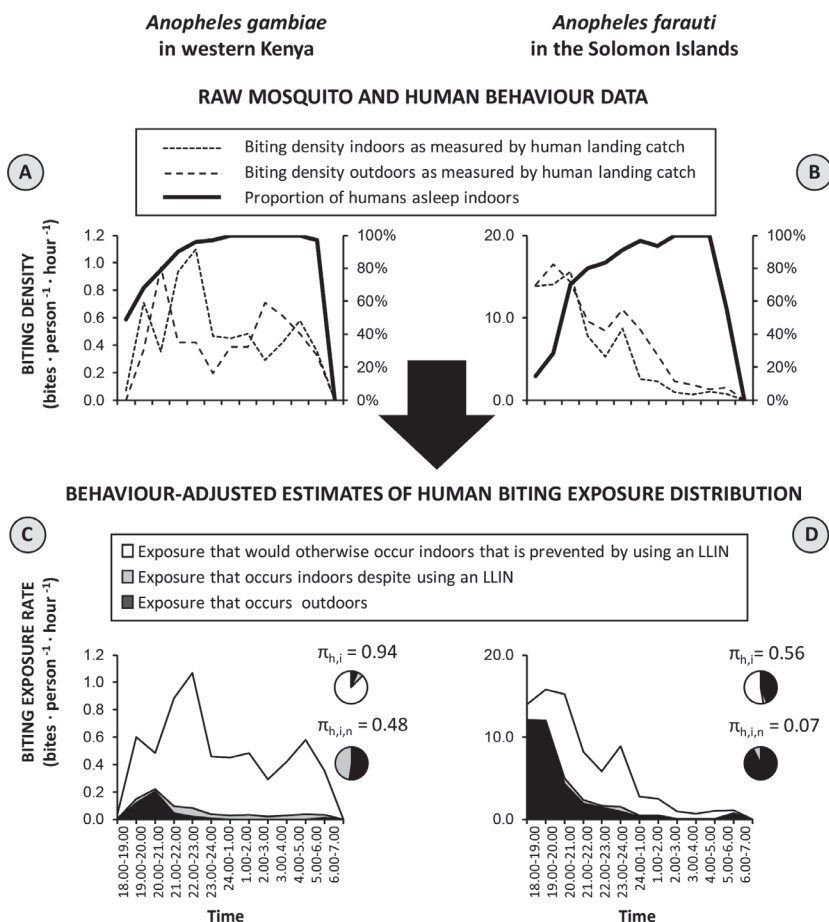


Figure 5. Two examples of how raw mosquito and human behaviour data must be combined with simple analytical models to allow visualization and quantification of where and when human exposure actually occurs as a behavioural interaction [6, 47, 61, 62].

majority of human populations, most people sleep indoors at night for security reasons, so very little of the biting activity measured outdoors is relevant to normal human exposure patterns [60]. Taking the major African malaria vector *An. gambiae* as an example, the traditional narrative describing it as *endophilic* is inaccurate, because their biting rates indoors and outdoors are usually similar and they have no strong or consistent preference for attacking people in either location [50]. It is the timing of biting activity that caused most historical exposure to occur indoors. This human-specialized mosquito species usually exhibits biting activity peaks that occur in the middle of the night when most people are asleep indoors (**Figure 5A**), and therefore vulnerable to attack unless protected with an LLIN. It is therefore more accurate to say that these vectors are highly *nocturnal*, feeding mostly at times when humans exhibit strong *endophilic* tendencies [35], and that is why most human exposure occurred indoors at night before the scale up of LLIN use (**Figure 5C**).

Contrasting with vector populations like those of *Anopheles farauti* in the Solomon Islands, where humans are mostly exposed to outdoors, the most important feature of this behavioural interaction is again the timing of host-seeking activity. By feeding predominantly in the evening, this species can readily attack humans indoors or outdoors while they are still awake and active so bed net use is impractical (**Figure 5B and D**). Again, biting densities are similar indoors and outdoors (**Figure 5B**), so it is inaccurate to describe this vector as *exophagic* in the strict sense, and much more important to emphasize that so much exposure occurs outdoors because it is *crepuscular*, with feeding activity that peaks at dusk when people are awake, active and cannot use bed nets.

The overall exposure distribution estimates represented by the areas under the curves in **Figure 5C and D**, can then be combined with direct field estimates for the proportion of bloodmeals obtained from humans to visualize the maximum limit of *biological coverage* [63] achievable with human-targeted measures like LLINs as simple box graphs (**Figure 6**).

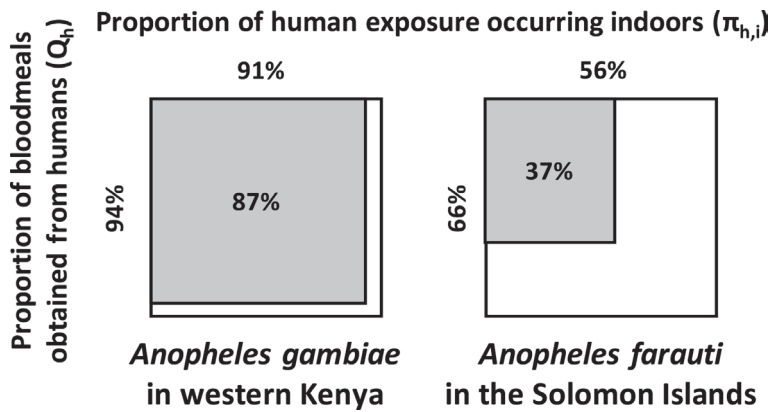


Figure 6. Box diagrams illustrating how the two different vectors described in **Figure 5** differ in terms of their overall behavioural vulnerability to population suppression with long-lasting insecticidal nets, expressed as the maximum achievable *biological coverage* of blood resources used by the mosquitoes [6].

Presenting measured behavioural interactions between mosquitoes and humans in such intuitive graphical formats is important for enabling accurate interpretation, and can be facilitated with user-friendly spreadsheet templates or automated visualization options in surveillance data dashboards.

6. Life history analyses to identify otherwise non-obvious vector control challenges and opportunities

The use of models to look at entire life histories of mosquitoes was central to the very earliest work of Ross [64], and to the ethos of *epidemiological entomology* defined by Garrett-Jones half a century ago [65]. While direct interpretation of simple indicators should provide the essential core of evidence used to inform programmatic decisions, astute application of analytical models to examine the life histories of mosquito populations can also yield important insights that would not otherwise be obvious.

For example, the slow-acting toxicity of pyrethroids to mosquitoes that are clearly resistant to this insecticide class was only recently identified as being central to the sustained impacts of LLINs [59]. While most African *Anopheles* populations are now sufficiently resistant against pyrethroids to survive immediately after exposure, they do suffer increased mortality over the longer term, essentially all of which occurs within the 10 days required for the parasite to complete sporogonic development [59]. As a result, while pyrethroid resistance clearly does compromise the impacts of LLINs [66], it falls far short of abrogating them entirely, so they remain an invaluable tool for malaria vector control [59].

Also, fitting process-explicit models of mosquito population dynamics to vector density trends may yield some insights that cannot be obtained by direct interpretation. Such mechanistic modelling analyses have been successfully applied to field data to identify negative density-dependence of mosquito reproduction, which make vector populations more robust to control than would otherwise be expected [67]. Similar models have been fitted to the population trajectories of self-propagating populations in large cages, which were experimentally exposed to different vector control measures and combinations thereof. These biologically-informative analyses quantified impacts on specific target parameters like survival and fecundity, helped confirm that near-extinction of these small populations was achieved, and revealed a surprising mode of action for one of these emerging technologies (Ng'habi et al., Unpublished). Such approaches could be readily extended to data from routine population dynamics monitoring, allowing the complementarities, synergies and redundancies achieved by combinations of vector control measures to be understood at an unprecedented level of detail.

Relatively simple deterministic models have also been used to illustrate how insecticide resistance traits and intervention avoidance behaviours can interact synergistically, allowing resilient mosquito populations to persist despite widespread LLIN use without necessitating any major adaptations of their preferred feeding times [68]. By foraging cautiously and repeatedly inside houses, to maximize their feeding opportunities while minimizing

their contact with LLINs, even nocturnal species like *An. arabiensis* can continually search around from one house to the next until an unprotected non-user is located [68]. By combining endophagy with exophily in this way, *An. arabiensis* can achieve feeding success rates despite high LLIN coverage that are only a quarter lower than in the absence of nets [68]. Furthermore, the resilience of such nocturnal but behaviourally plastic species may be further enhanced by physiological resistance to insecticides and opportunistically feeding upon animals, resulting in redistribution of feeding activity onto a combination of livestock and humans who either lack nets or are encountered outdoors at times when they are unprotected [68, 69].

However, life history analyses of how resilient mosquito species survive despite high LLIN coverage also identifies some exciting intervention opportunities that would not otherwise be obvious. For example, the most direct corollary of the observation that mosquitoes forage cautiously through several houses to find an unprotected human is that this creates enhanced opportunities to kill them if more effective indoor control methods can be deployed [7, 68, 69]. Emerging options for doing just that range from insecticidal eave tubes [70] and eave baffles [71] to untreated entry traps [72] and three-dimensional window screening [73].

More detailed consideration of life history distributions for the same vector population also reveals an even more counter-intuitive opportunity for such housing modifications to have an impact upon residual transmission. By the time a female *An. arabiensis* is old enough to have incubated malaria parasites through to infectious sporozoites, she will usually have completed at least 4 gonotrophic cycles, during which time she will most probably have been inside a house at least once [69]. So even though approximately half of all transmission events occur outdoors, they are all preceded by at least one house-entry event during which the guilty mosquito may be killed [69]. It is therefore possible to reduce levels of malaria transmission occurring outdoors using interventions that target mosquitoes when they enter or attempt to enter houses [69].

More strategically, this particular simulation analysis [69] also suggests a thematic perspective that may be useful to apply more broadly to life history analyses. It may often be more valuable to look for opportunities to intervene early in the life cycle of mosquitoes rather than targeting transmission events occurring when they are far older. The life histories of adult mosquitoes are cyclical so targeting mosquitoes when they engage in frequently repeated behaviours, in this case house entry, can have far greater impact than would be obvious from face-value interpretation of the fraction of single feeding events that occur indoors.

7. Global inequities of data handling and analytical capacity

So why are most reported entomological data not linked to explicit species identification data, and why are insightful analytical approaches so underutilized by control programmes? The simple answer is that most of the existing global capacity for advanced analysis of malaria-related data is in the wrong places, predominantly located at centres of excellence in high income countries with no local malaria transmission (**Figure 7**).

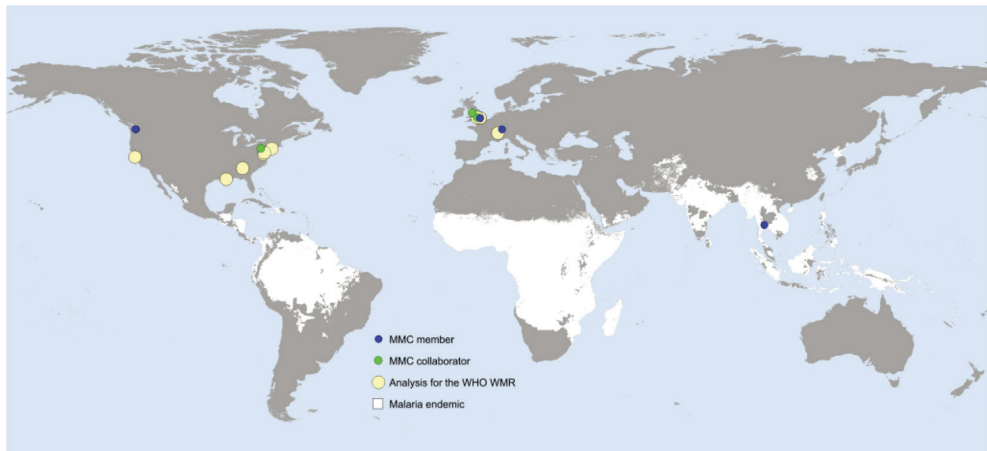


Figure 7. The global geographic distribution of current members and collaborators in the Malaria Modelling Consortium (MMC), as well as analytical contributors to the World Health Organization 2015–2017 World Malaria Report (WHO-WMR), overlaid upon a map with contemporary malaria endemicity (white).

To a large extent, these geographic inequities of data analysis capacity are an understandable consequence of pre-existing global poverty, education and opportunity patterns. However, accepting the *status quo* illustrated in **Figure 7** is not consistent with the ‘think global, act local’ ethos of successful malaria elimination programmes, and these global capacity inequities need to be addressed urgently if malaria is ever to be eradicated.

If the strategic vision presented by the global modelling community in **Figure 8** continues to be implemented in the context of the world map in **Figure 7**, several consequences are inevitable:

1. Malaria-related data will be collected in low-income countries but largely analyzed in high-income countries with no malaria problem to speak of.
2. Collectors of malaria-related data will have insufficient opportunity and training support to analyze their own data, develop their analytical skills and influence policy and practice. The data interrogation processes essential to timely use and effective quality control of surveillance data will remain underdeveloped where they are needed most.
3. Analysts of malaria data will continue to live far away from the point of data collection and the programme staff who collect it in the field, so their ability to critically analyze and interpret it will remain limited by lack of hands-on field experience and direct access to those who have it.
4. These two communities will remain separated by thousands of kilometers, as well as their very different roles and perspectives (**Figure 9A**). The synergistic interface required between human beings to achieve optimal data collection processes, critical analyses and appropriate programmatic responses (**Figure 9B**) will not be realized.

5. Ongoing geographic separation of data collection and analysis functions will continue to exacerbate recent trends towards overspecialization and excessive compartmentalization of entomologists, epidemiologists and mathematical modellers. Generalist but nevertheless expert *malaria*ologists, as exemplified by the working competence in entomology, epidemiology and process-explicit modelling of Ross or Garrett-Jones (**Figure 9B**), will remain a rare breed.

A particularly worrisome issue, which we doubt will spontaneously self-resolve, is the inability of programmes in malaria endemic countries to critically appraise the reliability and relevance of advanced modelling studies carried out at a distance. Some of the greatest mistakes in the history of global malaria policy and practice have arisen from over-confident interpretation of models that were very useful but nevertheless imperfect [75]. In the vast majority of endemic countries today, neither the national malaria control programmes nor the national universities and research institutes they should be able look to for locally-available expert

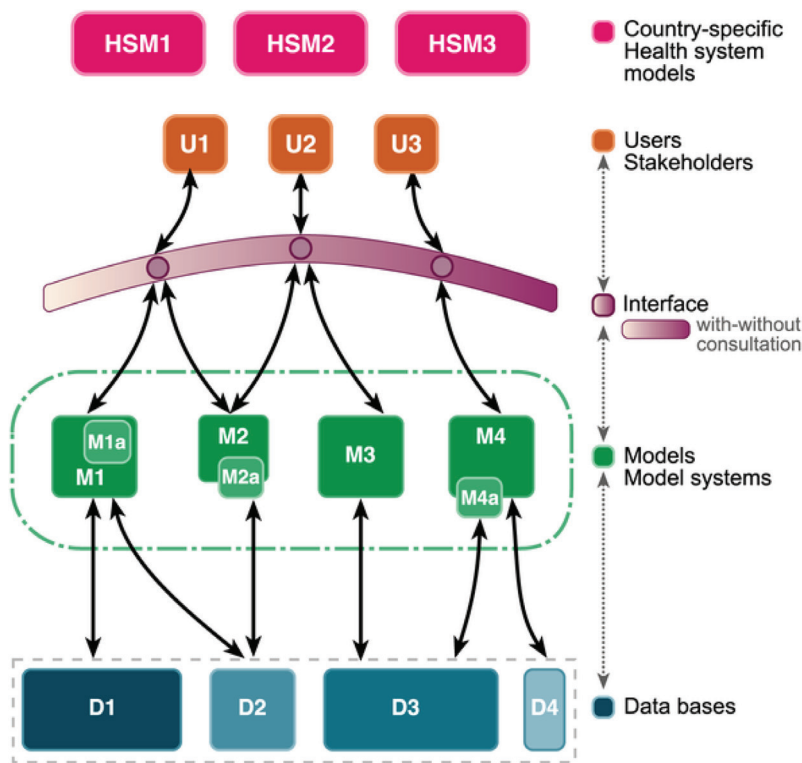


Figure 8. The schematic illustration of the comprehensive framework for malaria modelling presented by the malERA Consultative Group on Malaria Modelling in 2011 [74]. Consultations will allow policy makers, research scientists, and other stakeholders (U, users/stakeholders) from different country-specific health systems (HSM, country-specific health system models) to draw advice and analysis from multiple, independently derived models (M) grounded on data collected (D, data bases) from research on vector ecology, malaria epidemiology, and control through an interface that emphasizes direct engagement between modellers or modelling groups and end users.

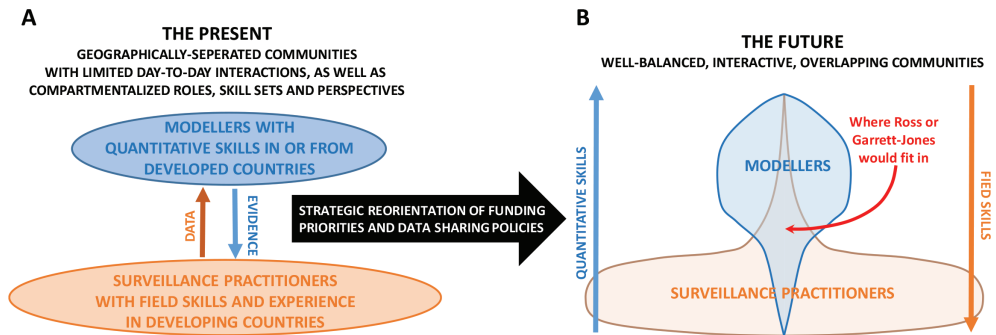


Figure 9. A schematic illustration of how data collection and analysis roles are currently distributed (A), and how they should be actively reformed going forward (B).

advice, currently have sufficient capacity to appraise the merits and limitations of state-of-the-art modelling analyses.

While analytical and predictive models can add considerable value to any data interpretation exercise, they also have some fundamental limitations that need to be considered. Even the most complex mathematical model is a deliberately simplified conceptual representation of reality. It is therefore important to critically understand what the limitations of both the models and the data themselves are, and how those uncertainties limit confidence in their interpretation:

... fitting complex models to multiple types of data is challenging, and model predictions are always likely to be unreliable at very high spatial resolution. The twin objectives of understanding the dynamics and making quantitative predictions can also be in conflict, because the push to include all relevant factors in a locally calibrated predictive model rapidly leads to complex behaviour that can no longer be explained [23].

One of the most important reasons to develop a cadre of expert modellers in endemic countries is so they can advise their national programmes based on a full understanding of the uncertainties and inaccuracies of model-generated evidence. Expert modellers working at locally-owned and governed institutions in malaria-endemic countries have a vital role to play in guiding critical appraisal by their non-specialist colleagues who might otherwise be tempted to either disregard the results of modelling analyses they do not understand, or accept them at face value based on a level of trust that may not be warranted:

'... it is challenging for a non-specialist to distinguish modelling that is useful from poor quality modelling that may support misguided policies' [23].

8. Epidemiological implications of the *Portfolio Effect*: Malaria transmission systematically tends to be more stable than it appears

Mosquito dispersal, human movement, heterogeneities in the intensity of transmission, and over-dispersed distributions of parasite infection durations have all been recognized as factors

that stabilize malaria transmission and frustrate efforts to eliminate it [23]. Indeed, the importance of all these phenomena has been illustrated with a range of different mathematical models. However, all models are systematically biased to underestimate the stability of complex biological systems simply because they are models [23, 76, 77]. Conservation biologists have recently adopted the *portfolio effect* concept from economics, to guide their thinking in relation to ecosystem management. Diversification stabilizes investment portfolios, thereby reducing risks of catastrophic losses [78]. The same is true of complex, biologically and environmentally diverse ecosystems, which are always more stable than any of their component species, habitats or subsets thereof [79]. Mathematical models are deliberately designed to be simpler than the biological system they are intended to mimic [23, 76, 77], so they systematically underestimate their complexity, stability and resilience. Malaria transmission therefore tends to be more stable and less vulnerable to control than face-value interpretation of predictive mathematical models suggest (Killeen & Reed, Unpublished).

The extent to which portfolio effects make malaria transmission resilient against vector control is probably impossible to quantify. Nevertheless, simply being mindful of the overall principle can help moderate expectations of intervention impacts upon guilds of multiple vectors distributed across highly heterogeneous environments. The diversity of overlapping transmission dynamics these complex biological and environmental interactions generate result in malaria transmission that is far more resilient to programmatic-scale control than any single characterized species or location. In many tropical settings, elimination of malaria will probably necessitate elimination of its most efficient vectors [80], possibly including key vectors of residual transmission which readily, flexibly and opportunistically feed upon either humans or animals [1]. Malaria parasite populations that spread their reproductive bets across two or more vectors with different behaviours, ecological niches, seasonal dynamics and vulnerability to specific control measures will always be more difficult to eliminate, and will usually require more diverse intervention packages, than in settings with a single vector species. Furthermore, where individual vector species spread their own reproductive bets across multiple aquatic habitat types, resting sites or blood sources, this creates refugia that limit the impact of any given vector control measure applied in any given time and place. No matter how much detail we try to capture in our mathematical models of vector biology and malaria transmission, they will always under-represent the full complexity and diversity of those interactions, so they are biased towards under-estimating the resilience of malaria transmission against vector control. Whatever vector population response trajectory is expected following introduction of a new vector control measure, the portfolio effect will tend to flatten it out to some unknown extent. The only sensible way to integrate the implications of the portfolio effect into our efforts is to interpret entomological surveillance data and simulation models with considerable restraint (Killeen & Reed, Unpublished).

9. A healthier future for malaria surveillance data collection, ownership and utilization

Global inequities of capacity and opportunity are a difficult but massively important issue to discuss [81]. We have no wish to offend any of our colleagues based at prestigious institutes

in wealthier, cooler, malaria-free countries, nor do we suggest that the capacities they bring to the table are anything less than invaluable. However, the existing *status quo* is neither effective nor fair, and will persist until it is deliberately addressed with far more south-centred funding schemes and productive data sharing mechanisms (**Figure 9**). The time has come for the systematic redistribution of funding investment, to unambiguously prioritize locally-owned and governed institutions in the low-income countries struggling with malaria on an ongoing basis.

And data governance structures that incentivize productive *south–south* and *south–north* (as distinct from *north–south*) collaborations are equally important. For many surveillance staff, investigators and institutions in developing countries, ownership of their data and the analytical opportunities it provides constitute their most important means leverage when negotiating fair conditions in collaborations through which they can develop their data handling and analytical capacities. South-centred platforms for archiving and sharing data, that empower data collectors and incentivize development-friendly collaborations with expert partners from high-income countries, are urgently needed. Looking beyond entomological surveillance, invaluable lessons may be learned from the encouraging experiences of regional and global networks for monitoring anti-malarial drug resistance [82].

The funding and data sharing policies that have shaped the global capacity distribution illustrated in **Figure 7** need to be progressively and aggressively reformed. Vocal advocacy for such strategic changes are a job for everyone in the malaria surveillance community. Each of us are, in our own way, responsible for the landscape as it stands today, and have no-one to blame but ourselves if such inequities and inefficiencies are allowed to persist. Unless we all play our part in actively finding solutions, we must accept that we are passively perpetuating the problem.

10. Conclusions

Considerable progress towards development and deployment of a much broader diversity of vector control tools can be achieved through far more widespread adaptation of established entomological field methods to programmatic surveillance platforms. However, ensuring such data are effectively collected, analyzed, interpreted and acted upon will require that current geographic inequities of analytical capacity are decisively addressed. Specifically, funding and data sharing systems need to be re-oriented to prioritize south-centred collaborations that enable low-income malaria-endemic countries to develop and institutionalize their own expertise base.

Acknowledgements

We thank numerous colleagues for invaluable discussions over the years that have contributed to this perspective, particularly Tom Smith, Samson Kiware and John Gimnig for sharing their experiences with entomological informatics, as well as Mafalda Viana, Jason Matthiopoulos and Heather Ferguson for their insights on life history modelling.

Conflict of interest

The authors declare no competing interests.

Acronyms

LLIN: long lasting insecticidal nets

IRS: indoor residual spraying

MMC: Malaria Modelling Consortium

malERA: Malaria Eradication Consultative Group on Malaria Modelling

WHO: World Health Organization

WHO-WMR: World Health Organization-World Malaria Report

Author details

Gerry F. Killeen^{1,2*}, Prosper P. Chaki¹, Thomas E. Reed³, Catherine L. Moyes⁴ and Nicodem J. Govella¹

*Address all correspondence to: gkilleen@ihi.or.tz

1 Department of Environmental Health and Ecological Sciences, Ifakara Health Institute, Ifakara and Dar es Salaam, United Republic of Tanzania

2 Department of Vector Biology, Liverpool School of Tropical Medicine, Liverpool, United Kingdom

3 School of Biological, Earth and Environmental Sciences, University College Cork, Cork, Republic of Ireland

4 Big Data Institute, Li Ka Shing Centre for Health Information and Discovery, University of Oxford, Oxford, United Kingdom

References

- [1] Killeen GF, Kiware SS, Okumu FO, Sinka ME, Moyes CL, Massey NC, Gething PW, Marshall JM, Chaccour CJ, Tusting LS. Going beyond personal protection against mosquito bites to eliminate malaria transmission: Population suppression of malaria vectors that exploit both human and animal blood. *BMJ Global Health*. 2017;**2**:e000198. DOI: 10.1136/bmjgh-2016-000198

- [2] Killeen GF, Tatarsky A, Diabate A, Chaccour C, Marshall J, Okumu FO, Brunner S, Newby G, Williams Y, Malone D, Tusting L, Gosling R. Developing an expanded vector control toolbox for malaria elimination. *BMJ Global Health*. 2017;**2**:e000211
- [3] Barreaux P, Barreaux AMG, Sternberg ED, Suh E, Waite JL, Whitehead SA, Thomas MB. Priorities for broadening the malaria vector control tool kit. *Trends in Parasitology*. 2017; **33**:763-774. DOI: 10.1016/j.pt.2017.06.003
- [4] Kiware SS, Chitnis N, Tatarsky A, Wu S, Castellanos HMS, Gosling R, Smith D, Marshall JM. Attacking the mosquito on multiple fronts: Insights from the vector control optimization model (VCOM) for malaria elimination. *PLoS One*. 2017;**12**:e0187680. DOI: 10.1371/journal.pone.0187680
- [5] Sinka ME, Bangs MJ, Manguin S, Rubio-Palis Y, Chareonviriyaphap T, Coetzee M, Mbogo CM, Hemingway J, Patil AP, Temperley WH, Gething PW, Kabaria CW, Burkot TR, Harbach RE, Hay SI. A global map of dominant malaria vectors. *Parasites & Vectors*. 2012;**5**:69. DOI: 10.1186/1756-3305-5-69
- [6] Killeen GF. Characterizing, controlling and eliminating residual malaria transmission. *Malaria Journal*. 2014;**13**:330. DOI: 10.1186/1475-2875-13-330
- [7] Killeen GF, Marshall JM, Kiware SS, South AB, Tusting LS, Chaki PP, Govella NJ. Measuring, manipulating and exploiting behaviours of adult mosquitoes to optimize malaria vector control impact. *BMJ Global Health*. 2017;**2**:e000212
- [8] Killeen GF, Seyoum A, Gimnig JE, Stevenson JC, Drakeley CJ, Chitnis N. Made-to-measure malaria vector control strategies: Rational design based on insecticide properties and coverage of blood resources for mosquitoes. *Malaria Journal*. 2014;**13**:146
- [9] The malERA refresh consultative panel on combination interventions and modelling: An updated research agenda for combination interventions and modelling in malaria elimination and eradication. *PLoS Medicine*. 2017;**14**:e1002453. DOI: 10.1371/journal.pmed.1002453
- [10] Gatton ML, Chitnis N, Churcher T, Donnelly MJ, Ghani AC, Godfray HC, Gould F, Hastings I, Marshall J, Ranson H, Rowland M, Shaman J, Lindsay SW. The importance of mosquito behavioural adaptations to malaria control in Africa. *Evolution*. 2013;**67**:1218-1230. DOI: 10.1111/evo.12063
- [11] Govella NJ, Chaki PP, Killeen GF. Entomological surveillance of behavioural resilience and resistance in residual malaria vector populations. *Malaria Journal*. 2013;**12**:124. DOI: 10.1186/1475-2875-12-124
- [12] Hemingway J, Beaty BJ, Rowland M, Scott TW, Sharp BL. The innovative vector control consortium: Improved control of mosquito-borne diseases. *Trends in Parasitology*. 2006;**22**:308-312. DOI: 10.1016/j.pt.2006.05.003
- [13] Hemingway J, Ranson H, Magill A, Kolaczinski J, Fornadel C, Gimnig J, Coetzee M, Simard F, Roch DK, Hinzoumbe CK, Pickett J, Schellenberg D, Gething P, Hoppe M,

- Hamon N. Averting a malaria disaster: Will insecticide resistance derail malaria control? *Lancet*. 2016;**387**:1785-1788. DOI: 10.1016/S0140-6736(15)00417-1
- [14] Ranson H, Lissenden N. Insecticide resistance in African *Anopheles* mosquitoes: A worsening situation that needs urgent action to maintain malaria control. *Trends in Parasitology*. 2016;**32**:187-196. DOI: 10.1016/j.pt.2015.11.010
- [15] Smith T, Ross A, Maire N, Chitnis N, Studer A, Hardy D, Brooks A, Penny M, Tanner M. Ensemble modeling of the likely public health impact of a pre-erythrocytic malaria vaccine. *PLoS Medicine*. 2012;**9**:e1001157. DOI: 10.1371/journal.pmed.1001157
- [16] Galactionova K, Tediosi F, Camponovo F, Smith TA, Gething PW, Penny MA. Country specific predictions of the cost-effectiveness of malaria vaccine RTS,S/AS01 in endemic Africa. *Vaccine*. 2017;**35**:53-60. DOI: 10.1016/j.vaccine.2016.11.042
- [17] Penny MA, Pemberton-Ross P, Smith TA. The time-course of protection of the RTS,S vaccine against malaria infections and clinical disease. *Malaria Journal*. 2015;**14**:437. DOI: 10.1186/s12936-015-0969-8
- [18] Cameron E, Battle KE, Bhatt S, Weiss DJ, Bisanzio D, Mappin B, Dalrymple U, Hay SI, Smith DL, Griffin JT, Wenger EA, Eckhoff PA, Smith TA, Penny MA, Gething PW. Defining the relationship between infection prevalence and clinical incidence of *Plasmodium falciparum* malaria. *Nature Communications*. 2015;**6**:8170. DOI: 10.1038/ncomms9170
- [19] Penny MA, Galactionova K, Tarantino M, Tanner M, Smith TA. The public health impact of malaria vaccine RTS,S in malaria endemic Africa: Country-specific predictions using 18 month follow-up phase III data and simulation models. *BMC Medicine*. 2015;**13**:170. DOI: 10.1186/s12916-015-0408-2
- [20] Pemberton-Ross P, Smith TA, Hodel EM, Kay K, Penny MA. Age-shifting in malaria incidence as a result of induced immunological deficit: A simulation study. *Malaria Journal*. 2015;**14**:287. DOI: 10.1186/s12936-015-0805-1
- [21] Brady OJ, Slater HC, Pemberton-Ross P, Wenger E, Maude RJ, Ghani AC, Penny MA, Gerardin J, White LJ, Chitnis N, Aguas R, Hay SI, Smith DL, Stuckey EM, Okiro EA, Smith TA, Okell LC. Role of mass drug administration in elimination of *Plasmodium falciparum* malaria: A consensus modelling study. *Lancet Global Health*. 2017;**5**: e680-e6e7. DOI: 10.1016/S2214-109X(17)30220-6
- [22] Okell L, Slater H, Ghani A, Pemberton-Ross P, Smith TA, Chitnis N, Penny M, Wenger E, Gerardin J, Maude R, Aguas R, White LJ, Brady OJ, Hay SI, Okiro E, Kern S: Consensus Modelling Evidence to Support the Design of Mass Drug Administration Programmes. Geneva: World Health Organization; 2015. 20p. Available from: <http://www.who.int/malaria/mpac/mpac-sept2015-consensus-modelling-mda.pdf> [Accessed: 2018-04-16]
- [23] Smith TA, Chitnis N, Penny M, Tanner M. Malaria modeling in the era of eradication. *Cold Spring Harbor Perspectives in Medicine*. 2017;**7**:313-332. DOI: 10.1101/cshperspect.a025460
- [24] Brady OJ, Godfray HC, Tatem AJ, Gething PW, Cohen JM, McKenzie FE, Perkins TA, Reiner RC Jr, Tusting LS, Sinka ME, Moyes CL, Eckhoff PA, Scott TW, Lindsay SW,

- Hay SI, Smith DL. Vectorial capacity and vector control: Reconsidering sensitivity to parameters for malaria elimination. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 2016;**110**:107-117. DOI: 10.1093/trstmh/trv113
- [25] Clements AN, Paterson GD. The analysis of mortality and survival rates in wild populations of mosquitoes. *Journal of Applied Ecology*. 1981;**18**:373-399
- [26] Killeen GF, McKenzie FE, Foy BD, Schieffelin C, Billingsley PF, Beier JC. A simplified model for predicting malaria entomologic inoculation rates based on entomologic and parasitologic parameters relevant to control. *American Journal of Tropical Medicine and Hygiene*. 2000;**62**:535-544
- [27] Killeen GF, Okumu FO, N'Guessan R, Coosemans M, Adeogun A, Awolola S, Etang J, Dabiré RK, Corbel V. The importance of considering community-level effects when selecting insecticidal malaria vector products. *Parasites & Vectors*. 2011;**4**:160. DOI: 10.1186/1756-3305-4-160
- [28] Eckhoff PA. Mathematical models of within-host and transmission dynamics to determine effects of malaria interventions in a variety of transmission settings. *American Journal of Tropical Medicine and Hygiene*. 2013;**88**:817-827. DOI: 10.4269/ajtmh.12-0007
- [29] Charlwood JD, Smith T, Billingsley PF, Takken W, Lyimo EOL, Meuwissen JHET. Survival and infection probabilities of anthropophagic anophelines from an area of high prevalence of *Plasmodium falciparum* in humans. *Bulletin of Entomological Research*. 1997;**87**:445-453
- [30] Moore SJ, Davies CR, Hill N, Cameron MM. Are mosquitoes diverted from repellent-using individuals to non-users? Results of a field study in Bolivia. *Tropical Medicine & International Health*. 2007;**12**:532-539. DOI: 10.1111/j.1365-3156.2006.01811.x
- [31] Sangoro O, Turner E, Simfukwe E, Miller JE, Moore SJ. A cluster-randomized controlled trial to assess the effectiveness of using 15% DEET topical repellent with long-lasting insecticidal nets (LLINs) compared to a placebo lotion on malaria transmission. *Malaria Journal*. 2014;**13**:324. DOI: 10.1186/1475-2875-13-324
- [32] Ogoma SB, Mmando A, Kyeba JS, Horstmann S, Malone D, Killeen GF. A low technology emanator treated with the volatile pyrethroid Transfluthrin confers long term protection against outdoor-biting vectors of lymphatic filariasis, arboviruses and malaria. *PLoS Neglected Tropical Diseases*. 2017;**11**:e0005455
- [33] Trape JF, Tall A, Sokhna C, Ly AB, Diagne N, Ndiath O, Mazonot C, Richard V, Badiane A, Dieye-Ba F, Faye J, Ndiaye G, Diene Sarr F, Roucher C, Bouganali C, Bassene H, Toure-Balde A, Roussilhon C, Perraut R, Spiegel A, Sarthou JL, da Silva LP, Mercereau-Puijalon O, Druilhe P, Rogier C. The rise and fall of malaria in a West African rural community, Dielmo, Senegal, from 1990 to 2012: A 22 year longitudinal study. *Lancet Infectious Diseases*. 2014;**14**:476-488. DOI: 10.1016/S1473-3099(14)70712-1
- [34] Sougoufara S, Thiaw O, Cailleau A, Diagne N, Harry M, Bouganali C, Sembène PM, Doucoure S, Sokhna C. The impact of periodic distribution campaigns of long-lasting

- insecticide-treated bed nets on malaria vector dynamics and human exposure in Dielmo, Senegal. *American Journal of Tropical Medicine and Hygiene*. In press, 2018;**98**:1343-1352. DOI: 10.4269/ajtmh.17-0009
- [35] Killeen GF. A revival of epidemiological entomology in Senegal. *American Journal of Tropical Medicine and Hygiene*. In press, 2018;**98**:1216-1217. DOI: 10.4269/ajtmh.18-0162
- [36] Garrett-Jones C, Boreham P, Pant CP. Feeding habits of anophelines (Diptera: Culicidae) in 1971-1978, with reference to the human blood index: A review. *Bulletin of Entomological Research*. 1980;**70**:165-185
- [37] Silver JB. Blood feeding and its epidemiological significance. *Mosquito Ecology: Field Sampling Methods*. Dordrecht, the Netherlands: Springer; 2008. pp. 677-769
- [38] Garrett-Jones C. The human blood index of malarial vectors in relationship to epidemiological assessment. *Bulletin of the World Health Organization*. 1964;**30**:241-261
- [39] Kiswewski AE, Mellinger A, Spielman A, Malaney P, Sachs SE, Sachs J. A global index representing the stability of malaria transmission. *American Journal of Tropical Medicine and Hygiene*. 2004;**70**:486-498
- [40] Garrett-Jones C. A method for estimating the man-biting rate. Geneva: World Health Organization; 1964. Document No.: WHO/Mal/450
- [41] Kawada H, Dida GO, Ohashi K, Komagata O, Kasai S, Tomita T, Sonye G, Maekawa Y, Mwatele C, Njenga SM, Mwandawiro C, Minakawa N, Takagi M. Multimodal pyrethroid resistance in malaria vectors, *Anopheles gambiae* s.s., *Anopheles arabiensis*, and *Anopheles funestus* s.s. In western Kenya. *PLoS One*. 2011;**6**:e22574. DOI: 10.1371/journal.pone.0022574
- [42] Reimer L, Fondjo E, Patchoke S, Diallo B, Lee Y, Ng A, Ndjemai HM, Atangana J, Traore SF, Lanzaro G, Cornel AJ. Relationship between kdr mutation and resistance to pyrethroid and DDT insecticides in natural populations of *Anopheles gambiae*. *Journal of Medical Entomology*. 2008;**45**:260-266
- [43] Nkya TE, Akhouayri I, Poupardin R, Batengana B, Mosha F, Magesa S, Kisinza W, David JP. Insecticide resistance mechanisms associated with different environments in the malaria vector *Anopheles gambiae*: A case study in Tanzania. *Malaria Journal*. 2014;**13**:28. DOI: 10.1186/1475-2875-13-28
- [44] Ondeto BM, Nyundo C, Kamau L, Muriu SM, Mwangangi JM, Njagi K, Mathenge EM, Ochanda H, Mbogo CM. Current status of insecticide resistance among malaria vectors in Kenya. *Parasites & Vectors*. 2017;**10**:429. DOI: 10.1186/s13071-017-2361-8
- [45] Coleman M, Hemingway J, Gleave KA, Wiebe A, Gething PW, Moyes CL. Developing global maps of insecticide resistance risk to improve vector control. *Malaria Journal*. 2017;**16**:86. DOI: 10.1186/s12936-017-1733-z
- [46] Govella NJ, Okumu FO, Killeen GF. Insecticide-treated nets can reduce malaria transmission by mosquitoes which feed outdoors. *American Journal of Tropical Medicine and Hygiene*. 2010;**82**:415-419. DOI: 10.4269/ajtmh.2010.09-0579

- [47] Bugoro H, Cooper RD, Butafa C, Iro'ofa C, Mackenzie DO, Chen CC, Russell TL. Bionomics of the malaria vector *Anopheles farauti* in Temotu Province, Solomon Islands: Issues for malaria elimination. *Malaria Journal*. 2011;**10**:133. DOI: 10.1186/1475-2875-10-133
- [48] Moiroux N, Damien GB, Egrot M, Djenontin A, Chandre F, Corbel V, Killeen GF, Pennetier C. Human exposure to early morning *Anopheles funestus* biting behavior and personal protection provided by long-lasting insecticidal nets. *PLoS One*. 2014;**9**:e104967. DOI: 10.1371/journal.pone.0104967
- [49] Massey NC, Garrod G, Wiebe A, Henry AJ, Huang Z, Moyes CL, Sinka ME. A global bionomic database for the dominant vectors of human malaria. *Scientific Data*. 2016;**3**: 160014. DOI: 10.1038/sdata.2016.14
- [50] Huho BJ, Briët O, Seyoum A, Sikaala CH, Bayoh N, Gimnig JE, Okumu FO, Diallo D, Abdulla S, Smith TA, Killeen GF. Consistently high estimates for the proportion of human exposure to malaria vector populations occurring indoors in rural Africa. *International Journal of Epidemiology*. 2013;**42**:235-247. DOI: 10.1093/ije/dys214
- [51] Gryseels C, Durnez L, Gerrets R, Uk S, Suon S, Set S, Phoeuk P, Sluydts V, Heng S, Sochantha T, Coosemans M, Peeters Grietens K. Re-imagining malaria: Heterogeneity of human and mosquito behaviour in relation to residual malaria transmission in Cambodia. *Malaria Journal*. 2015;**14**:165. DOI: 10.1186/s12936-015-0689-0
- [52] Killeen GF, McKenzie FE, Foy BD, Schieffelin C, Billingsley PF, Beier JC. The potential impacts of integrated malaria transmission control on entomologic inoculation rate in highly endemic areas. *American Journal of Tropical Medicine and Hygiene*. 2000;**62**:545-551
- [53] WHO. Malaria Surveillance, Monitoring and Evaluation: A Reference Manual. Geneva: World Health Organization; 2018. 105 p. Available from: <http://apps.who.int/iris/bitstream/handle/10665/272284/9789241565578-eng.pdf?sequence=1&isAllowed=y> [Accessed: 2018-04-16]
- [54] Silver JB. Mosquito Ecology: Field Sampling Methods. 3rd ed. Dordrecht, the Netherlands: Springer; 2008. 1494 p
- [55] Chaki PP, Dongus S, Kannady K, Fillinger U, Kelly A, Killeen GF. Community-owned resource persons for malaria vector control: Enabling factors and challenges in an operational programme in Dar es Salaam, Tanzania. *Human Resources for Health*. 2011;**9**:21
- [56] Chaki PP, Govella NJ, Shoo B, Hemed A, Tanner M, Fillinger U, Killeen GF. Achieving high coverage of larval-stage mosquito surveillance: Challenges for a community-based mosquito control programme in urban Dar es Salaam, Tanzania. *Malaria Journal*. 2009;**8**:311. DOI: 1475-2875-8-311 [pii] 10.1186/1475-2875-8-311
- [57] Dengela D, Seyoum A, Lucas B, Johns B, George K, Belemvire A, Caranci A, Norris LC, Fornadel CM. Multi-country assessment of residual bio-efficacy of insecticides used for indoor residual spraying in malaria control on different surface types: Results from program monitoring in 17 PMI/USAID-supported IRS countries. *Parasites & Vectors*. 2018;**11**:71. DOI: 10.1186/s13071-017-2608-4

- [58] Massue DJ, Moore SJ, Mageni ZD, Moore JD, Bradley J, Pigeon O, Maziba EJ, Mandike R, Kramer K, Kisinza WN, Overgaard HJ, Lorenz LM. Durability of Olyset campaign nets distributed between 2009 and 2011 in eight districts of Tanzania. *Malaria Journal*. 2016;**15**:176. DOI: 10.1186/s12936-016-1225-6
- [59] Viana M, Hughes A, Matthiopoulos J, Ranson H, Ferguson HM. Delayed mortality effects cut the malaria transmission potential of insecticide-resistant mosquitoes. *Proceedings of the National Academy of Sciences of the United States of America*. 2016;**113**:8975-8980. DOI: 10.1073/pnas.1603431113
- [60] Lindblade KA. Does a mosquito bite when no-one is around to hear it? *International Journal of Epidemiology*. 2013;**42**:247-249. DOI: 10.1093/ije/dyt004
- [61] Bayoh MN, Walker ED, Kosgei J, Ombok M, Olang GB, Githeko AK, Killeen GF, Otieno P, Desai M, Lobo NF, Vulule JM, Hamel MJ, Kariuki S, Gimnig JE. Persistently high estimates of late night, indoor exposure to malaria vectors despite high coverage of insecticide treated nets. *Parasites & Vectors*. 2014;**7**:380
- [62] Killeen GF. A second chance to tackle African malaria vector mosquitoes that avoid houses and don't take drugs. *American Journal of Tropical Medicine and Hygiene*. 2013;**88**:809-816. DOI: 10.4269/ajtmh.13-0065
- [63] Kiware SS, Chitnis N, Devine GJ, Moore SJ, Majambere S, Killeen GF. Biologically meaningful coverage indicators for eliminating malaria transmission. *Biology Letters*. 2012;**8**:874-877. DOI: 10.1098/rsbl.2012.0352
- [64] Ross R. *The Prevention of Malaria*. London: Murray; 1911. 669 p
- [65] Garrett-Jones C, Shidrawi GR. Malaria vectorial capacity of a population of *Anopheles gambiae*: An exercise in epidemiological entomology. *Bulletin of the World Health Organization*. 1969;**40**:531-545
- [66] Protopopoff N, Mosha JF, Lukole E, Charlwood JD, Wright A, Mwalimu CD, Manjurano AFWM, Kisinza W, Kleinschmidt I, Rowland M. Effectiveness of a long-lasting piperonyl butoxide-treated insecticidal net and indoor residual spray interventions, separately and together, against malaria transmitted by pyrethroid-resistant mosquitoes: A cluster, randomised controlled, two-by-two factorial design trial. *Lancet*. 2018;**391**:1577-1588. DOI: 10.1016/S0140-6736(18)30427-6
- [67] Russell TL, Lwetiojera D, Knols BGJ, Takken W, Killeen GF, Ferguson HM. Linking individual phenotype to density-dependent population growth: The influence of body size on the population dynamics of malaria vectors. *Proceedings of the Royal Society B*. 2011;**278**:3142-3151
- [68] Killeen GF, Chitnis N. Potential causes and consequences of behavioural resilience and resistance in malaria vector populations: A mathematical modelling analysis. *Malaria Journal*. 2014;**13**:97

- [69] Killeen GF, Govella NJ, Lwetoijera DW, Okumu FO. Most outdoor malaria transmission by behaviourally-resistant *Anopheles arabiensis* is mediated by mosquitoes that have previously been inside houses. *Malaria Journal*. 2016;**15**:225. DOI: 10.1186/s12936-016-1280-z
- [70] Sternberg ED, Ng'habi KR, Lyimo IN, Kessy ST, Farenhorst M, Thomas MB, Knols BG, Mnyone LL. Eave tubes for malaria control in Africa: Initial development and semi-field evaluations in Tanzania. *Malaria Journal*. 2016;**15**:447. DOI: 10.1186/s12936-016-1499-8
- [71] Killeen GF, Masalu JP, Chinula D, Fotakis EA, Kavishe DR, Malone D, Okumu F. Control of malaria vector mosquitoes by insecticide-treated combinations of window screens and eave baffles. *Emerging Infectious Diseases*. 2017;**23**:782-789. DOI: 10.3201/eid2305.160662
- [72] Diabate A, Bilgo E, Dabire RK, Tripet F. Environmentally friendly tool to control mosquito populations without risk of insecticide resistance: The Lehmann's funnel entry trap. *Malaria Journal*. 2013;**12**:196. DOI: 10.1186/1475-2875-12-196
- [73] Khattab A, Jylha K, Hakala T, Aalto M, Malima R, Kisinza W, Honkala M, Nousiainen P, Meri S. 3D mosquito screens to create window double screen traps for mosquito control. *Parasites & Vectors*. 2017;**10**:400. DOI: 10.1186/s13071-017-2322-2
- [74] MalERA Consultative Group on Modeling. A research agenda for malaria eradication: Modeling. *PLoS Medicine*. 2011;**8**:e1000403. DOI: 10.1371/journal.pmed.1000403
- [75] Garrett-Jones C. Prognosis for interruption of malaria transmission through assessment of the mosquito's vectorial capacity. *Nature*. 1964;**204**:1173-1175
- [76] McKenzie FE. Why model malaria? *Parasitology Today*. 2000;**16**:511-516
- [77] McKenzie FE, Samba EM. The role of mathematical modeling in evidence-based malaria control. *American Journal of Tropical Medicine and Hygiene*. 2004;**71**:94-96
- [78] Markowitz H. Portfolio selection. *Journal of Finance*. 1952;**7**:77-91
- [79] Schindler DE, Reed TE, Armstrong J. The portfolio concept in ecology and evolution. *Frontiers in Ecology and Evolution*. 2013;**13**:257-263. DOI: 10.1890/140275
- [80] Killeen GF, Seyoum A, Sikaala CH, Zomboko AS, Gimnig JE, Govella NJ, White MT. Eliminating malaria vectors. *Parasites & Vectors*. 2013;**6**:172. DOI: 10.1186/1756-3305-6-172
- [81] Geissler PW, Okwaro F. Discuss inequality. *Nature*. 2014;**513**:303. DOI: 10.1038/513303a
- [82] Merson L, Gaye O, Guerin PJ. Avoiding data dumpsters-toward equitable and useful data sharing. *New England Journal of Medicine*. 2016;**374**:2414-2415. DOI: 10.1056/NEJMp1605148

