Taking malaria transmission out of the bottle: implications of mosquito dispersal for vector-control interventions

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Most malaria transmission models assume enclosed systems of people, parasites, and vectors in which neither emigration nor immigration of mosquitoes is considered. This simplification has facilitated insightful analyses but has substantial limitations for evaluating control measures in the field. Here we show that mosquito dispersal can confound conventional approaches to evaluating malaria vector-control interventions, and explore this association with a model of two villages between which mosquito subpopulation exchange occurs. Exchange of mosquitoes between such subpopulations can readily explain the discrepancy between experimental efficacy measurements for insecticide-treated nets and their much lower apparent effectiveness when in use. Our results indicate that current approaches to assessing malaria interventions that confer community-level protection may be severely compromised by mosquito dispersal in many endemic settings. The true effectiveness of many vector-control methods may be much greater than previously appreciated and the application of such interventions should be consolidated into larger contiguous spatial units so that more effective local suppression of malaria can be achieved. Spatially explicit modelling formats that consider vector dispersal as a determinant of malaria transmission and control are needed urgently for rational planning and evaluation of efforts to roll back malaria.

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The proven efficacy of insecticide-treated nets,[1] most recently in operational settings,[2–5] has rejuvenated confidence in vector control as a viable means to tackle malaria in Africa. Historically established approaches such as indoor residual spraying of insecticides and mosquito abatement through targeted larvicide application and environmental management are therefore receiving renewed consideration as tools with which to "roll back" malaria.[6–8] Although a drastic reduction in human exposure to infectious mosquito bites is needed to substantially relieve malaria burden in most parts of tropical Africa,[9,10] it is clear that such goals can be achieved even in areas of extremely high transmission intensity.[2–8,11–16]

In addition to conferring individual protection to users, insecticide-treated nets can also suppress local transmission rates by reducing longevity of vectors and diverting them to non-human hosts.[17] Although individual-level protection is relatively easy to quantify using standard randomised controlled trials or demographic surveillance methodology,[1–3] several studies indicate that these approaches may underestimate community-level protection because it is shared by both users and non-users in the surrounding area.[11,13–16,18,19] Indeed, it was recently shown in east Africa that the community-level effects of bednets can be more important than the more readily assessed individual effects.[14,16] Adult mosquitoes are capable of flying distances of several kilometres, which means that their mobility and behavioural adaptability can profoundly affect local malaria-transmission intensity and intervention effectiveness.[20–23] Given the predominantly communal effects of many vector-control approaches (larval control in particular)[7,8,24] and mounting evidence that the equivalent effects of insecticide-treated nets may have been underestimated,[11,13–16,18] there is an urgent need to quantify the effect of vector dispersal on malaria-control measures and the accuracy of efforts to assess them.

Malaria in a bottle

Although the importance of spatial correlation in surveying malaria risk has been highlighted,[25] almost all models of malaria transmission assume enclosed systems of people, parasites, and mosquito vectors in which neither emigration nor immigration is considered.[26–31] This "malaria in a bottle" concept has proven a valuable simplifying assumption for analyses of malaria-transmission processes and their sensitivity to various forms of control. Nevertheless, field-based researchers often view this take on malaria transmission as unrealistic and there is a growing need to develop spatially explicit frameworks for modelling the movements of vectors, as well as the genes and parasites they carry.[21,32–34] We have explored the possible effect of parasite influx into areas where active infection control is operational and concluded that even low rates of immigration by infected people can seriously undermine such efforts.[35] The effect of vector dispersal on mosquito population structure, human exposure to transmission, and our ability to control transmission has long been appreciated[21–23] but its underlying determinants and

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quantitative importance remain poorly understood. Specifically, the failure of some bednet trials to show community-level suppression of malaria transmission has been directly attributed to vigorous long-range dispersal of the vector, although a quantitative mechanistic basis for this hypothesis has never been elucidated.[22,36]

Opening the bottle

Here we explore the relation between vector dispersal and malaria transmision in quantitative terms to consider the interactions between two adjacent foci of human settlement, between which vectors exchange at varying rates but which are otherwise isolated. Our objective is not to explicitly model mosquito dispersal and its consequences in completely realistic detail since this is a complex undertaking beyond the scope of this article. Instead, we aim to use the simplest possible extensions of existing enclosed-system models, combined with currently available field measurements from a well-studied part of The Gambia, to show the clear shortcomings of existing study designs and the pressing need for theoretical advances. By varying the level of coverage in a village targeted with a bednet programme and the amount of vector subpopulation exchange between villages, we show that vector dispersal can spread the effects of malaria control over wide areas, potentially compromising local suppression as well as accurate measurement and assessment of these benefits.

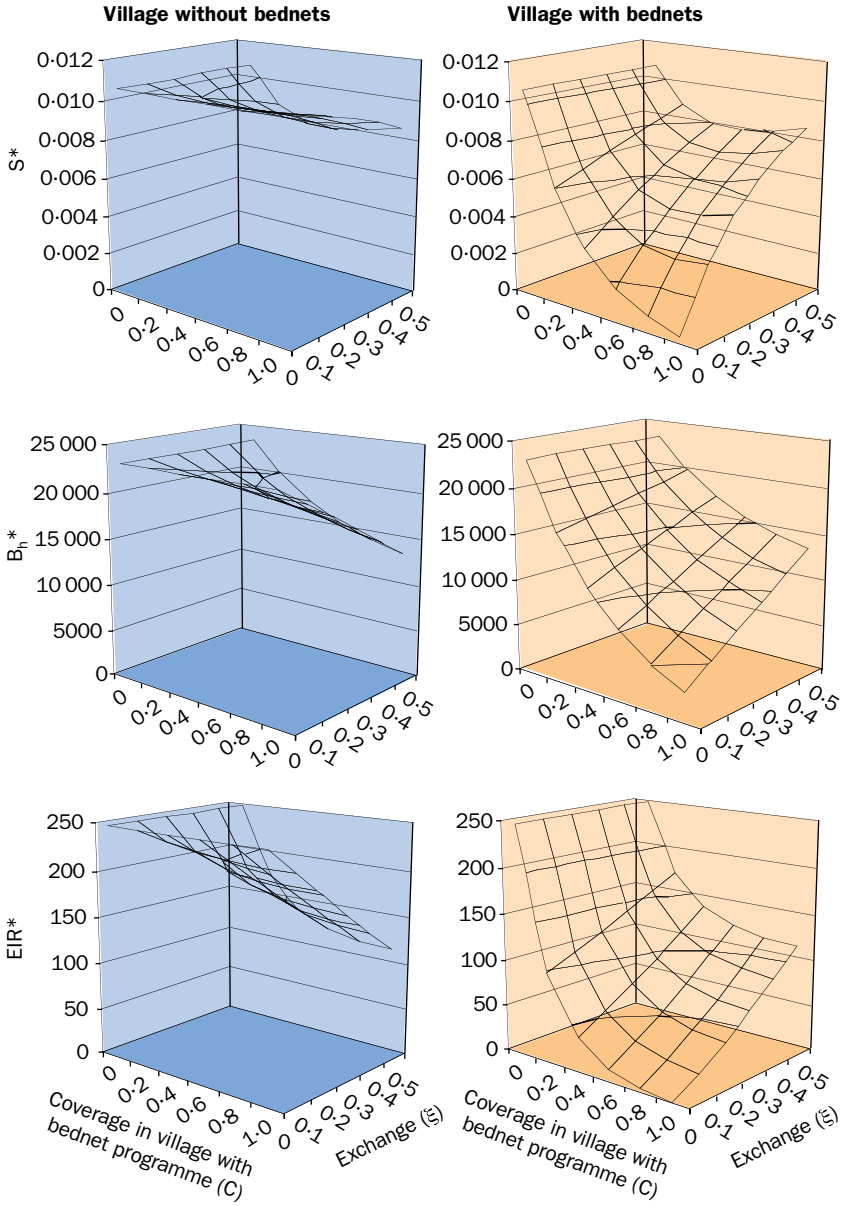

Figure 1. The predicted effects of bednets on sporozoite prevalence (S; infectious bites per bite), human biting rate (B_h*; bites per person per year), and entomological inoculation rate (EIR*; infectious bites per person per year) in two adjacent villages where one has an ongoing bednet programme and the other does not. Each response-surface plot indicates the influence of bednet coverage in the intervention village (C) and vector exchange with its neighbour (ξ) on transmission.*

Modelling the effects of mosquito dispersal between villages

We extend a conventional enclosed transmission-system model[20,28] by considering two adjacent villages between which varying rates of vector exchange occur as a result of mosquito dispersal. We model the effects of an insecticide-treated bednet programme in one of the villages and explore the effects of vector exchange on malaria transmission characteristics of both villages at varying rates of coverage in the village with bednets. Note that here we are only considering community-level protection—or the "mass effect" as it is often called—that results in a lowering of overall transmission and equitable protection of users and non-users alike. The additional effect of protecting individual users is well established and has been expertly discussed elsewhere,[1–3] although recent studies suggest such individual effects can be less important than those at the communal level.[14,16] Similarly, we focus our discussion on effects of control measures on transmission intensity only, and refer interested readers to a more detailed review of the important association between transmission intensity and clinical disease burden.[9]

Instead of the conventional model of single human, vector, and parasite populations, we simply assume that there are two identical villages adjacent to each other with two overlapping mosquito subpopulations that are connected

via dispersal. We also assume that one village has an active control programme achieving varying rates of effective coverage, C, with bednets, whereas no control measures are implemented in the other village. We do not model mosquito exchange in terms of migration rates per unit time or per feeding cycle because we are only aware of one direct field estimate for daily migration of an African malaria vector, and this is from a setting where there have been no bednet trials.[37] Furthermore, modelling such detailed processes explicitly is, by necessity, very complex and would confound our primary objective: to quantitatively outline the epidemiological importance of vector dispersal in the simplest possible terms for a broad audience, including non-modellers. We therefore model the dispersal of mosquitoes in terms of their exchange between villages over their entire lifetimes, because this is a parameter for which a direct estimate is available[22] from an area where bednets have been extensively studied and are seen to have no community-level effects on the vector population.[36,38]

The extent of overall exchange between the two mosquito subpopulations is denoted by ξ, indicating all possibilities for exchange at any stage during the vector's lifetime and can thus be directly translated into an average distribution between two sites. Average distribution reflects the results of mark-release-recapture estimates of exchange, which compare the probability of recapturing a mosquito in a different village to that where it was originally collected with the probability that it will be recaptured in the same place, assuming constant sampling efficiency.[22,39] It is, therefore, important to note that this definition can be measured directly as the recapture distribution between the two villages, and simply indicates the net effect of subpopulation mixing across all mosquito age groups rather than explicit subcomponents of this process such as emigration or immigration rate. Thus, values for ξ vary between 0 and 0·5, indicating complete separation ranging through to complete exchange, and, effectively, a single mosquito subpopulation shared by the two villages.

We vary degree of exchange between the two villages but otherwise model them with an adapted form of a previously described cyclical model using field-measured parameters for Namawala in Tanzania, a well-characterised holoendemic site where intense transmission is facilitated by abundant *Anopheles arabiensis*.[28] We initially consider a single isolated and enclosed village and model the effects of bednets as previously described.[20] The effects of full bednet coverage in the village with a control programme are modelled, based on detailed experimental hut trials, on the assumption that at full coverage bednets halve both the probability of mosquito vectors surviving each feeding cycle (P_f) and the probability that they will obtain a bloodmeal from people rather than other vertebrates (Q_h).[20] This assumed efficacy is equivalent to 75% personal protection of individual bednet users and therefore represents a conservative median of results from several experimental assessments of insecticide-treated nets.[40–42] Note that this simulation of 75% personal protection does not include additional protection that may be accrued from community-level effects achieved at high coverage rates. At any given rate of coverage (C), the effects of bednets on the lifetime transmission potential of vectors[17] are indicated as local effective survival per feeding cycle (P_f^*) and local effective human blood index (Q_h^*), calculated by weighting as previously described:[20]

(1) $P_f^* = P_f (1-C) + 0{\cdot}5\, P_f C$

(2) $Q_h^* = Q_h (1-C) + 0{\cdot}5\, Q_h C$

An essential component of this model is an estimate of the total biting rate of all emerging mosquitoes on all hosts (Z), which is calculated as the product of the emergence rate (E) and the total number of bites taken from all hosts by an average mosquito in its lifetime (b). The total number of bites per lifetime is in turn calculated as the sum of the effective probabilities of surviving all possible numbers of feeding cycles (i) so, for an enclosed system, Z is readily estimated based on emergence rate and survival alone:

(3) $Z = E\, b = E \sum_{i=1}^{\infty} (P_f^*)^i$

Here, we extend the model by considering two villages, one of which has an ongoing treated bednet programme and another village that does not. The exchange-mediated effects of bednets in the malaria-controlled village on vector population density in the village with uncontrolled malaria, and vice versa, are based on the comparative subpopulation sizes of inward net influx and net local retention. For example, the effective total number of bites taken by all mosquitoes from all hosts in the village with vector control (Z^{c*}) can be estimated as the sum of the products of net locally retained mosquitoes ($Z^c (1-\xi)$) and net influx from its neighbour with uncontrolled malaria ($Z^u \xi$):

(4) $Z^{c*} = Z^c (1-\xi) + Z^u \xi$

Conversely, the effective total number of mosquito bites occurring in the village with uncontrolled malaria (Z^{u*}) can be similarly calculated:

(5) $Z^{u*} = Z^u (1-\xi) + Z^c \xi$

The sporozoite prevalence (S) for either village under baseline conditions was estimated as previously described, based on field estimates of the mean infectiousness of the human population, vector survival per feeding cycle, vector human-blood index, vector feeding-cycle length, and mean temperature for Namawala village.[28] The effective sporozoite prevalence (S*) for each village under given rates of bednet coverage was calculated as the average of the value expected in that village if no dispersal took place and that of the neighbouring village, weighted according to the relative contribution of net retention and influx, respectively:

(6) $S^{c*} = (S^c Z^c [1-\xi] + S^u Z^u \xi) / (Z^c [1-\xi] + Z^u \xi)$

(7) $S^{u*} = (S^u Z^u [1-\xi] + S^c Z^c \xi) / (Z^u [1-\xi] + Z^c \xi)$

We then estimate the effective biting rate experienced by people (B_h^*) in either village by dividing the total number of effective bites taken from people ($Q_h^* Z^*$) by the number of people present (N_h):

(8) $B_h^{c*} = Q_h^{c*}\, Z^{c*} / N_h^c$

(9) $B_h^{u*} = Q_h^{u*}\, Z^{u*} / N_h^u$

Effective entomological inoculation rate (EIR*) for each village is then calculated as the product of S* and B_h^*.[43] Under varying rates of bednet coverage in the intervention village, the exchange of vector subpopulations between it

and its uncovered neighbouring village was varied, from 0 to 0·5, indicating completely separate villages ranging all the way through to completely free exchange in two villages sharing essentially one and the same vector subpopulation.

The effect of mosquito dispersal on malaria vector control

As previously reported,[20] simple models that ignore dispersal and exchange predict far greater bednet effects on community-level transmission than those typically reported,[16,19,36,38,44–47] even at quite low rates of effective coverage (figure 1). Although these results should be interpreted cautiously, bearing in mind the potential limitations of the model and its input parameters, the sheer magnitude of this discrepancy merits careful consideration. This theoretical extrapolation of measurements from single experimental huts[40–42] to widespread community application contrasts starkly with the measured effects of bednets on transmission in real African villages, which typically are much less marked[16,19,44–46] or even undetectable.[19,36,38,47] Figure 1 shows that emigration of mosquitoes from areas covered with control measures such as bednets and their continual replacement by immigrants from nearby uncontrolled areas can result in substantial attenuation of local impact in the control site. These results also confirm that such exchange processes can mediate substantial suppression of malaria beyond the control site because vector efflux from the intervention village is curtailed and the infectiousness of those vectors is reduced.[11,13–16,18]

It is also worth noting that vector subpopulation exchange reduces the effects of the control programme in the covered village much more than it suppresses transmission in the neighbouring uncovered village. This is because the control programme limits its own contribution to the total number of mosquitoes by increasing mosquito mortality (figure 2) and, hence, becomes more sensitive to immigration from external sources as it becomes more effective locally. The effects of vector exchange on the distribution of intervention impact are predicted to be very large indeed at exchange rates that have been documented in pairs of Gambian villages 1 km or more apart (ξ=0·12–0·25).[22] The spread and dilution of vector control impact across landscapes may be greater than suggested in figure 1 in situations where the controlled area is smaller than the area with which it shares vectors. In practical terms, the local benefits of village-scale control programmes may be particularly compromised where, for example, there is more than one village nearby, where the neighbouring village has a larger local mosquito subpopulation, or where there are many homesteads on nearby farms that are not covered by the programme. At the transmission intensity experienced across much of tropical Africa, radical reductions of EIR are needed to detectably alleviate disease burden,[9,43] so the attenuation of local impacts by bednets on clinical indicators of malaria may even more seriously undermine the ability of conventional epidemiological study designs to show and quantify intervention efficacy.

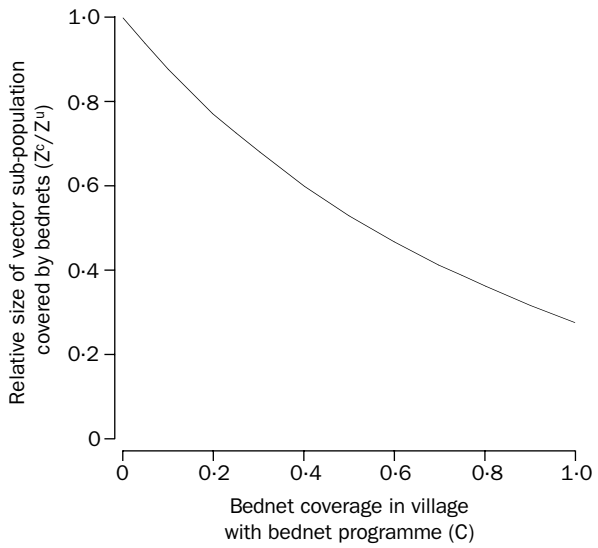

Figure 2. The predicted effects of increasing bednet coverage (C) on the relative size of the vector subpopulations in villages with (Z^c; bites per year) and without (Z^u; bites per year) bednets, assuming no vector exchange (ξ=0).

Implications of mosquito dispersal for assessment of vector-control measures

In addition to spreading the effects of bednets on malaria transmission over large areas, dispersal and exchange also compromise our ability to measure these effects using conventional experimental designs. Field trials of malaria-control measures that can affect community-level transmission are often done using matched pairs of villages for intervention and non-intervention groups.[1] These villages are often quite close to each other and quite similar to the simplified scenario we have modelled here. Where vector exchange between intervention and non-intervention villages is significant, the measured efficacy of the intervention becomes attenuated because the effects of control are shared between both villages, resulting in an equilibration between the two (figure 3) even though transmission is suppressed overall (figure 1). Thus, our results support the view that the lack of apparent effects of bednets on transmission at community level in some African settings, including The Gambia,[36,38,47] may be at least partly explained by exchange between mosquito subpopulations in intervention villages and the non-intervention villages with which they are compared.[22] Mosquitoes commonly disperse over distances in excess of 1 km[21] and high exchange rates have been reported for Gambian villages separated by such distances[22] where detailed bednet trials have shown no apparent community-level suppression of malaria transmission.[36,38]

The lack of reported community-level effects on the vector population in The Gambia contrasts starkly with other trials of insecticide-treated nets and residual sprays across Africa.[12,13,44–46] This apparent inefficacy seems even more at odds with experimental hut trials in the same setting that indicate treated nets kill most vectors that encounter them[41,42] and should readily suppress local transmission at high rates of coverage, as predicted here under conditions of

little or no vector exchange (figure 1). Our analysis confirms and quantitatively elucidates the suggestion that frequent failure to observe effects on community-level transmission does not necessarily mean that these effects are not occurring.[18,22] We conclude that many assessments of malaria vector-control methods may have systematically underestimated their efficacy and effectiveness.

Re-examining the right-hand side of figure 1 outlines just how much could be achieved by contiguous coverage with bednets over areas wide enough to negate the effects of dispersal. These predicted community-level effects (figures 1 and 3) are much greater than the simulated levels of personal protection to individual users (relative risk, compared with non users=0·25) on which the former are based. Our results therefore support recent field studies emphasising the importance of high coverage for maximising the effectiveness of such powerful malaria-control tools[13–16] and achieving the drastic reductions of EIR needed to alleviate disease burden in highly endemic areas.[9]

Efficacious mosquitocidal measures such as treated nets[40–42] have the potential to radically suppress malaria transmission where high coverage can be achieved at district rather than village level. Much greater effects may become apparent than have yet been shown by randomised controlled trials using small spatial units[1] or with existing demographic surveillance approaches.[2,3] Future trials of vector-control interventions should consider larger geographic units for assignment to test and control treatments so that the confounding effects of vector dispersal can be negated. This recommendation particularly applies to approaches that confer protection at community level only. Potentially powerful interventions such as larval control[7,8,24,48] will need to be applied at high coverage over large contiguous areas so that immigration from uncovered areas is kept to a minimum and local impact is maximised.

Several observations point towards the need to consider much larger geographic units for malaria vector-control trials: (1) substantial vector exchange can occur over distances well in excess of 1 km,[22] with considerable potential to undermine local effectiveness (figures 1 and 3); (2) by direct measurement migration rates are in excess of 300 m per day in a rural African setting;[37] (3) most transmission in holoendemic settings is via mosquitoes that are 2–3 weeks old and may have travelled several kilometres since emergence;[28] (4) and marked reductions of EIR are needed to achieve disease burden alleviation in much of tropical Africa.[9,43] Taken together, these observations suggest that trials in many settings could necessitate the use of geographic units 10 km or more in diameter to prevent underestimation of efficacy. This suggested figure is an upper limit that can probably be contracted in settings where high host and larval habitat availability limit dispersal. We therefore propose this surprisingly large figure as an educated guess for reconsidering the minimum size requirement for "malaria-control zones" in African settings. As such it is meant to stimulate further debate and investigation, rather than to be accepted as an absolute recommendation and adopted immediately. Recent field studies have shown precisely these kinds of effects on malaria transmission and burden, over distances of up to 2·5 km,[11,13–15,18] but even larger effects over longer distances may well become apparent as study designs and analytical methods are adapted accordingly.

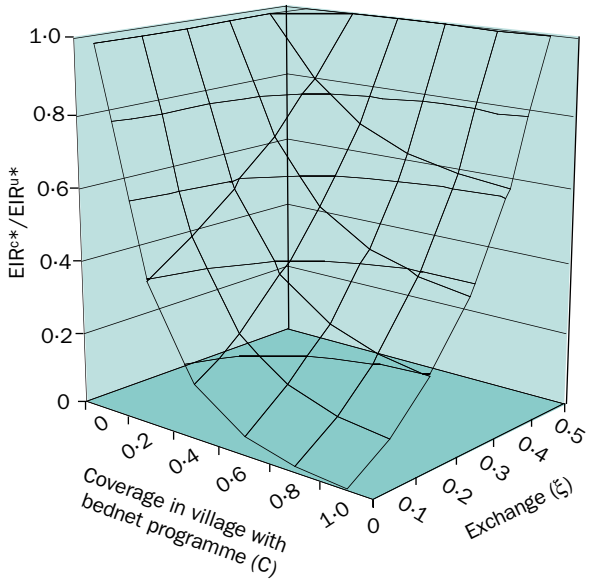

Figure 3. The predicted effects of bednets on the apparent impact of a bednet programme in terms of the transmission intensity in the village covered with bednets ($EIR^{c}*$) compared with the non-intervention village which is not ($EIR^{u}*$). The response-surface plot reflects the influence of bednet coverage in the intervention village (C) and vector exchange with its neighbour (ξ) on transmission.

Limitations of enclosed-system malaria transmission models

Our analysis clearly shows that inherent limitations of models assuming isolated malaria transmission systems may seriously limit their utility. This finding is in agreement with direct field studies highlighting the likely underestimation of total impact by bednets in previous trials.[11,13–16,18] The model we have presented here illustrates the importance of dispersal but cannot be considered fully representative of important subtleties that exist in real-life malaria transmission settings. For example, real mosquitoes are not restricted to pairs of villages and will tend to disperse further across landscapes as they become older and more likely to be infectious. Thus, if this process was modelled in terms of mosquito migration as a rate of movement per day or per feeding cycle, over two-dimensional landscapes, even more dramatic dispersion of impacts on sporozoite prevalence might become apparent. We therefore suggest that the effect of mosquito dispersal may be even greater than we have outlined here and needs to be addressed explicitly through the further development of malaria-transmission models and their parameterisation in the field. Emerging evidence that mosquitoes can learn and acquire fidelity to feeding or oviposition sites may require careful consideration.[49] Furthermore, dispersal is an anisotropic event with dispersal between pairs of sites often occurring more often in one direction than another.[37,50–52] Although host and larval habitat availability, as well as wind direction, are proven

determinants of mosquito flight direction and distance,[21,32,49–54] current understanding of ecological variation of vector dispersal range remains qualitative. The role of mosquito mobility needs to be quantitatively elucidated if malaria-transmission models are to become practically useful for designing and assessing malaria-control intervention packages at fine geographic scales. Thus, models are needed that not only analyse the effects of dispersal on vector population dynamics, gene flow, and malaria-transmission potential but also consider its underlying ecological determinants such as landscape structure, meteorology, and the distribution of bloodmeal host and larval habitat resources.[21,32–34]

Conclusions

Here we have shown that vector dispersal at rates often encountered in the field can confound conventional evaluation methods when applied to malaria-control interventions that confer community-level protection. We conclude that the true effectiveness of insecticide-treated nets may have been grossly underestimated and that even greater cost-effectiveness may be shown by appropriately tailored assessment methodology. Future assessments of malaria-control tools will either require improved analytical approaches that explicitly consider vector dispersal or will have to be implemented over geographic scales that negate its confounding effects. Conventional models of malaria transmission can be extremely misleading in terms of their quantitative output values and have limited use for planning or assessing malaria-control interventions. We therefore suggest that, as efforts to roll back malaria from the tropics continue, both field-based researchers and their theoretical counterparts have important parts to play by developing new spatially explicit modelling formats that consider vector dispersal a critically important determinant of malaria transmission and control. In the meantime, continuing trials and operational programmes should reconsider the geographic scales on which they implement and assess interventions. We recommend that such control efforts should be consolidated into larger contiguous spatial units so that more effective local suppression of malaria transmission can be shown by researchers and delivered to heavily burdened target populations. We suggest that geographic units 10 km or more in diameter may be needed for trials of vector-control interventions, although we caution that this surprisingly large figure is merely an educated guess. Nevertheless, the possibility that this figure may be realistic and that the efficacy of currently available vector-control tools may have been seriously underestimated highlight the need for reexamination of this important link between ecology and epidemiology by modellers, public-health specialists, and field biologists alike.

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Conflicts of interest

None declared.

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