Strategic issues concerning vector-parasite interactions

10. Modelling the control of mosquito-borne diseases

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Abstract

We focus on strategies for controlling the epidemiology of mosquito-borne diseases that target the mosquito vector. In order to assess a particular strategy of mosquito population control, two broad issues require attention: the dynamics of the population, and the impact of the intervention on those dynamics. We describe two modelling approaches that are important tools in these respective tasks. Firstly, backwards modelling, the method of using models to interpret complex data, is a valuable means to understanding mosquito ecology. We exemplify backwards modelling with a brief review of research into how larval competition impacts on mosquito population dynamics, an important question to answer given that this density dependent process may significantly interact with some intervention strategies. Secondly, forwards modelling, whereby models are used to forecast the outcome of interacting ecological processes, allows ecological knowledge to be utilised so that the impacts of a particular strategy can be predicted. In particular, forward models allow investigation of how the performance of strategies may vary across different ecological settings. We exemplify forward modelling with an illustrative model of how climatic temperature may influence the effectiveness of a fungal biopesticide intervention. We end the chapter with a brief discussion on important future directions.

Keywords: mosquito-born disease, population dynamics, mathematical model, density-dependance, vector control, biopesticide

Introduction

While strategies to control most infectious diseases aim to target the pathogen, vector-borne diseases offer an alternative target: the vector. Mosquitoes are vectors of a number of major diseases, including malaria, dengue fever, and yellow fever (Gubler 1998).

At present chemical insecticides are the mainstay of mosquito control, delivered via insecticide treated nets (ITNs) and indoor residual spraying of insecticides (IRS). In the case of malaria, these technologies have successfully suppressed or eliminated transmission in some locations (Curtis and Mnzava 2000, Haworth 1988, Killeen *et al.* 2007), but they have been unable to eliminate malaria from the worst affected parts of tropical Africa, where control is difficult due to poverty and climatic conditions that are conducive to endemic transmission (Ferguson *et al.* 2010). A number of novel strategies are under intensive development, including biological control methods involving the introduction of bacterial and fungal infections into mosquito populations (Blanford *et al.* 2005, McMeniman *et al.* 2009, Moreira *et al.* 2009, Scholte *et al.* 2005), and the release of genetically modified mosquitoes to suppress the native population or initiate the spread of phenotypes that do not transmit disease (Burt 2003, Thomas *et al.* 2000, Ward *et al.* 2011).

As such, a various arsenal will, it is hoped, be available to future practitioners of mosquito control (Takken and Knols 2009). Clearly, in order to inform the design of control programmes in different areas to meet specific targets, there is a need to understand the impacts of each technology on the mosquito population and its capacity to transmit disease. This will require detailed knowledge of the ecology of the target mosquito population (Ferguson *et al.* 2010).

Models have an important role to play in both qualifying and quantifying the ecological consequences of the different control measures. Two types of modelling stand out in mosquito research, denoted in this chapter as `backward' and `forward' modelling (Figure 1). In the following Section 'Understanding mosquito ecology', we discuss how backward modelling, whereby models are sought to describe and explain observed population patterns, is becoming an important approach to understanding mosquito ecology. In order to illustrate the discussion, we focus on a particular aspect of mosquito ecology: the influence of larval competition on population-level dynamics. By contrast, forward modelling, whereby models are used to predict the outcome of interaction between ecological processes, has more often been used to asses the impacts of population control strategies (Section 'Models of strategies for controlling mosquito-borne diseases'). We note that the distinction between backward modelling as a tool to understand mosquito ecology, and forward modelling to understand mosquito control, is neither fundamental nor clear-cut, but rather a useful generalisation.

Understanding mosquito ecology

Despite the importance of mosquito ecology in determining patterns of disease transmission, our understanding of the basic ecology of relevant species is fragmented at best. For example, while a good deal is known about the habitat and blood-meal preferences of the important malaria vector *Anopheles gambiae* Giles, there are few data on the dry-season ecology or the mating behaviour of this species (Jawara *et al.* 2008, Lehmann *et al.* 2010, Takken and Boëte 2003). Amassing ecological data on a particular mosquito species is, clearly, a vital step towards building a general understanding of the ecology of said species. Data in itself, however, is only useful as far as it is understood: data interpretation is equally vital. In view of the large number of ecological processes and environmental factors that may impact on mosquito populations, it is often difficult to disentangle their interacting effects from observational data. If a researcher is focussed on elucidating the roles of particular processes, experimental studies may be designed so as to greatly reduce the number of confounding factors, yet even experimental data may be hard to interpret if the processes under study are complex. Mathematical models, however, are able to show how complex processes behave and interact for any given set of underlying assumptions (Kokko 2007, Turchin 2003). As such, models are increasingly being used to help interpret mosquito data.

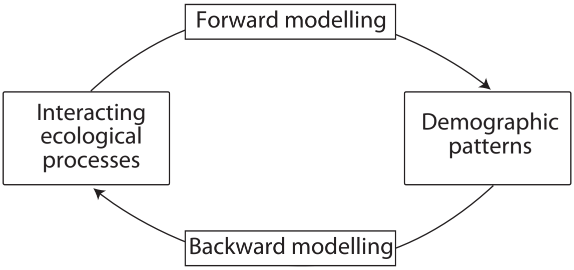

Figure 1. Two types of modelling approaches have been useful to the study of mosquito control. Forward modelling, whereby the interaction between a complex set of factors is predicted, has been particularly useful in the evaluation of mosquito control strategies. Backward modelling, on the other hand, is a method to interpret complex data and has been useful to the study of mosquito ecology.

In the remainder of this section, we exemplify how models have been used to aid the study of mosquito ecology by briefly reviewing research into a specific yet important question: what is the role of larval competition to mosquito population-level dynamics? (Dye and Hasibeder 1986, Legros *et al.* 2009, Russell *et al.* 2011b, Yang *et al.* 2008a,b). All the studies discussed employ a backward modelling approach (Figure 1), whereby data is used to parameterise one or more models. If there is more than one model, statistical tests are used to compare the performance of each model (Russell *et al.* 2011b, Yang *et al.* 2008a,b). In this way, the models act as alternative hypotheses, and the model comparison enables the hypotheses to be contested against one another, an increasingly popular approach in ecological research (Johnson and Omland 2004).

Larval competition

While it is widely acknowledged that exogenous factors, such as rainfall, play a major role in the regulation of mosquito populations (Edillo *et al.* 2004, Koenraadt *et al.* 2004), there is less certainty over the role of the density-dependent feedback that stems from larval competition (Legros *et al.* 2009). From the limited number of field studies that assess the process of population regulation in mosquito species, there is evidence that density-dependent feedback has an important influence on the population dynamics of *Aedes aegypti* L. (Dye 1984, Legros *et al.* 2009, Southwood *et al.* 1972), *Aedes vigilax* Skuse (Yang *et al.* 2008a,b) and *An. gambiae* (Russell *et al.* 2011b). Adult abundance may depend indirectly on juvenile density; for example higher larval density has been observed to prolong juvenile development time and reduce adult body size in *An. gambiae* (Gimnig *et al.* 2002, Russell *et al.* 2011b), which may reduce the population fitness (Russell *et al.* 2011b). The relative influence of larval competition and parasitism and predation of larvae on larval density is not well-quantified (Koenraadt *et al.* 2004, Service 1977).

There is strong motivation to redress this uncertainty: density dependent feedbacks may significantly impact on the success of population control measures, as discussed in the Section 'Models of strategies for controlling mosquito-borne diseases'. The studies reviewed below used very different data to asses the role of larval competition to population dynamics, broadly classed as 'Survivorship data' (Dye 1984, Legros *et al.* 2009) and 'Abundance time-series' (Dye 1984, Legros *et al.* 2009, Russell *et al.* 2011b, Yang *et al.* 2008a,b). We end this section with a brief perspective comparing the merits of the contrasting study designs.

Survivorship data

Dye (1984) fitted a model of *Ae. aegypti* population dynamics using data that measured the survivorship of cohorts during larval development, where the cohorts differed in initial density. Dye (1984) supposed that r_d, per capita density dependent mortality during the larval stage, may be described by the function:

$$r_d = aN^{\beta} \tag{1}$$

where N is the clutch size (density of eggs), and a and β are free parameters to describe the form of density dependence (Figure 2). In order to fit this model to the data, Dye (1984) was forced to ignore the possibility of concurrent density independent mortality occurring in the system: the data was not sufficient to fit a model allowing both causes of mortality. In doing so, Dye (1984) was able to estimate a and β using a non-linear regression analysis.

In turn, the parameter estimates obtained by Dye (1984) have been incorporated into more complex population models of *Ae. aegypti* (Phuc *et al.* 2007, Yakob *et al.* 2008a). This story, however, should perhaps act a cautionary tale on the importance of keeping the assumptions of a model in mind when assessing its conclusions. On relaxing the assumption that all larval mortality is due to density dependent factors, Legros *et al.* (2009) show that density dependence may have been significantly overestimated by Dye (1984), which casts doubt not only on Dye's conclusions (in defence, Dye is clear about the underlying assumptions), but also on the conclusions of the subsequent modelling studies. Legros *et al.* (2009) reason that the data set used by Dye is insufficient to reliably parameterise the function of Equation 1, and therefore to characterise the role of density dependence during larval growth. The moral: while overly complex models cannot be parameterised with limited data-sets (the hazards of overfitting), the assumptions of simpler models, that are parameterised with data, must be clear and remembered when those parameters are used subsequently.

Abundance time-series

If density dependent processes are sufficiently strong to impact on population dynamics, one may expect to detect the effects of density dependence in time-series data (Hanski 1990). In view of the number of (especially environmental) factors influencing population dynamics besides density dependence, this task will inevitably be a challenging one yet, if environmental data is collected concurrently, not necessarily a hopeless one. There has been debate over the most appropriate statistical test for density dependence in time-series (Hanski 1990), although the classical approach of employing a null model (density dependence is absent) has been prevalent in the past (Yang *et al.* 2008b). More recently, the approach of model selection (or 'multi-model inference', MMI) has become increasingly popular in many fields of ecology (Johnson and Omland 2004), and the evaluation of density dependence from time-series data is no exception (Brook

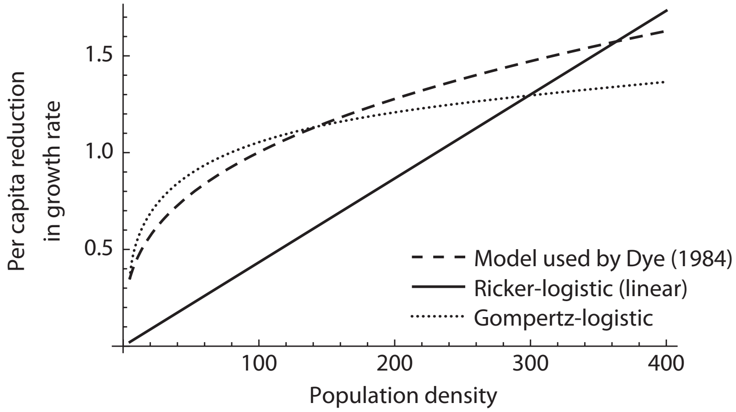

Figure 2. Different models of density dependence have been proposed for the effect of larval competition on population growth (see Equations 1-3). Empirical data have been used to compare these alternatives. The parameters are (α, β) = (0.23, 0.3) (Dye), and (r_m, K) = (1, 200) in both the Ricker-logistic and the Gompertz-logistic models: these parameters were chosen to illustrate the functional forms rather than derived from particular mosquito populations.

and Bradshaw 2006, Zeng *et al.* 1998). Unlike null model testing, model selection allows multiple hypotheses (models) to be compared simultaneously: each model is fitted from the available data, and the goodness-of-fit is compared across the models, often using selection criteria that penalise against model complexity (Johnson and Omland 2004).

Model selection has been employed to assess the relative roles of density dependent, density independent, and environmental processes in *An. gambiae s.l.* (Russell *et al.* 2011b), *Ae. vigilax* and across six tropical species (Yang *et al.* 2008a). To the best of our knowledge, these are the only published studies that have used time-series data to assess density dependence in mosquitoes. Each of the articles used maximum likelihood estimation to fit a suite of models to the respective data-sets, where the models differed in their representation of density dependent and environmental factors. The model performances were compared using Akaike's Information Criterion (AIC) (Russell *et al.* 2011b, Yang *et al.* 2008a,b) and, additionally, Bayesian Information criterion (BIC) and cross-validation (C-V) (Yang *et al.* 2008a,b).All three articles found significant evidence of density dependent feedbacks. Yang *et al.* (2008b) finds endogenous feedbacks to explain ~42% of the variation in growth rate of *Ae. vigilax*, with the remainder explained by exogenous environmental conditions, and the authors thus suggest a rule of thumb: 'negative density dependence is nearly as important as environmental conditions when predicting the abundance of mosquito populations over time'. Perhaps unsurprisingly, however, the details of how density dependence acts on the populations are much less consistent.

While Russell *et al.* (2011b) concur that density dependence is important to *An. gambiae s.l.*, the density dependent feedback component of the best model takes the Ricker-logistic form, whereby r_d, the per capita mortality rate due to density dependence during one time step (~ one generation) is linear:

$$r_d = \frac{r_m N_t}{K} \tag{2}$$

Where N_t is the population size at the start of the time step, r_m the maximal intrinsic growth rate, and K the carrying capacity. By contrast, Yang *et al.* (2008b) found the Gompertz-logistic model:

$$r_d = r_m \frac{\log N_t}{\log K} \tag{3}$$

to give an 'overwhelmingly better fit' for all six species in their study (both models were compared in both studies). This suggests density dependence acts at lower densities in the species studied by Yang *et al.* (2008b), yet the relative increase in density dependence as the population grows is less (Figure 2).

To investigate the interaction between environmental forces and density dependence, Yang *et al.* (2008a) compared (Gompertz-logistic) models for which the environmental factors impacted on, respectively, growth rate and carrying capacity. The data strongly supported the former model over the latter, suggesting that carrying capacity is relatively stable in their system while environmental variation alters the intrinsic growth rate. By contrast, the best model of *An. gambiae* linked the carrying capacity in Equation 2 to the most important environmental variable for this species (Russell *et al.* 2011b).

It is intriguing to seek the cause of these inter-specific differences, yet given that they are based on only two studies (Russell *et al.* 2011b, Yang *et al.* 2008a,b), which markedly differ in study design (for example, the time-series drastically differ in duration), it would be unwise to conclude, at this point, that the discrepancy is due to specific divergence. Further research on this issue would clearly be useful.

Perspective

Despite the shortcomings of Dye's (1984) analysis, the approach of quantifying density dependence through larval survivorship data, and more generally through experimental manipulation, may yet give valuable insights. The experimental set-up will need to be designed carefully, however, so that the data will be sufficient to fit the intended models (Legros *et al.* 2009). One key advantage of an experimental approach over a time-series approach is that the potentially confounding factors, such as environmental variation, can be largely controlled.

Larval survivorship data will not, unfortunately, reveal effects of larval competition other than alteration to the larval mortality rate. Survivorship data may, therefore, lead to an underestimation of density dependence in species for which larval competition has other fitness effects such as a reduction in emerging adult size. Time-series data, by contrast, will subsume all density dependent processes that impact on population dynamics. In order to determine the role of specific density dependent fitness effects from time-series, however, one has to know what to look for: time-series are more useful for testing than devising hypotheses. Observational studies, that measure the phenotypic effects of density dependence, have a valuable role to play in revealing potentially important fitness effects of density dependence (Gimnig *et al.* 2002). By keeping track of female wing-length through the study period, Russell *et al.* (2011b) were able to support the hypothesis that the effects of density dependence in *Anopheles gambiae* species is mediated by this larval plasticity in growth.

In summary, it is clear that our understanding of density dependence in mosquitoes has much room for improvement, yet it is encouraging to see recent publications on the issue: it is an active field. Density dependence is qualified using mathematical models that relate the effects of density dependence to population dynamics. These models have been quantified and evaluated from both survivorship data and from time-series. Both approaches have distinct strengths, and it is thus hoped that both are pursued in future studies.

Models of strategies for controlling mosquito-borne diseases

Many models that have been developed to analyse methods of controlling mosquito vectors of human diseases adopt a forward modelling approach, whereby population dynamic models, parameterised with data on mosquito ecology, are used to predict the outcome of an intervention. A difficulty is that models can become very complicated when they attempt to provide a detailed and realistic representation of mosquito ecology. Often models are developed to selectively include only the factors that have the most obvious relevance to a specific intervention, and the questions being asked of it. In this section, we discuss how such models are used to determine how the effects of intervention on a mosquito population, and its transmission of disease, are mediated by specific demographic processes, by ecological setting, and by details of how the intervention is applied. We exemplify this discussion with a case study in which a model is developed to predict how temperature affects the success of using fungal biopesticides to control *Anopheles* mosquitoes and, in turn, the malaria they vector (Box 1).

Box 1. Case study: modelling the effect of fungal biopesticides on malaria transmission at two different temperatures.

1. Modelling adult stage structure

Blood feeding behaviour in female adult *Anopheles* mosquitoes follows a gonotrophic cycle (Klowden 2007, Lardeux *et al.* 2008). The cycle consists of a host-seeking phase, during which mosquitoes actively search for a blood meal, and a non-host-seeking stage, during which blood from a recent blood meal is digested, oocytes are developed and eggs are oviposited, after which host-seeking activity begins again. The duration of the gonotrophic cycle varies depending on the temperature conditions the mosquito experiences, with faster metabolic rates occurring at higher temperatures (Lardeux *et al.* 2008). In warmer climates *Anopheles gambiae* typically take a blood meal every 2-3 days (Quinones *et al.* 1997) where as under cooler conditions there may be over 10 days between feeds (Paaijmans *et al.* 2010).

Hancock (2009) extended classical continuous time models of mosquito population dynamics (Hancock *et al.* 2009, MacDonald 1957, Ross 1911, Smith and McKenzie 2004) to incorporate gonotrophic structure. The model divides the adult mosquito population into two classes; those that are actively searching for a (human) blood meal and those that are not host-seeking, having not yet oviposited following their recent blood meal. Host-seeking mosquitoes are assumed to find blood meals at a continuous daily rate f, and mosquitoes spend a fixed period of time T_M in the non-host-seeking stage (Figure 3). Hancock (2009) showed that the equilibrium number of adult mosquitoes in the i^{th} host-seeking stage, S^*_{Hi}, is given by:

$$S^*_{Hi} = \frac{\varepsilon f^{-(i-1)\mu T_M}}{(\mu + f)^i} \qquad (4)$$

where ε is the daily rate at which adult mosquitoes are recruited and μ is the daily rate of adult mortality.

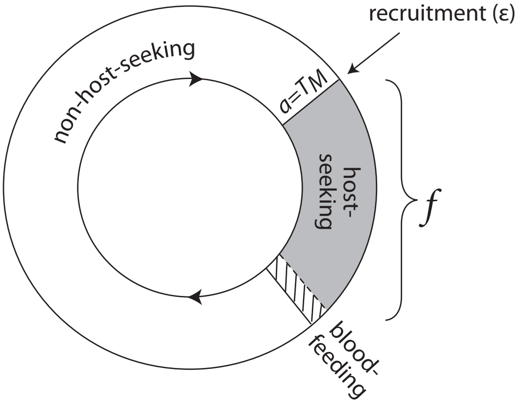

Figure 3. Diagram of the gonotrophic feeding processes represented in the model. Non-host-seeking mosquitoes resume host-seeking activity when the time since their last blood meal, a, reaches T_M days.

The model can be extended to incorporate a process of malaria transmission by the mosquito population by making assumptions about the proportion of humans that are infectious with malaria, the probability that malaria is transmitted during a bite by a mosquito on an infectious human, and the converse probability of a mosquito contracting malaria from biting an infected human. The malaria parasite is assumed to require a fixed period of incubation inside the mosquito of T_E days before it can be transmitted. With these assumptions the equilibrium number of host-seeking mosquitoes that have been infectious with malaria for i host-seeking periods, I^*_{Hi} can be calculated (Hancock 2009). This gives an expression for the equilibrium entomological inoculation rate (EIR), which is the number of infectious bites received per person per day (Hancock 2009):

$$EIR^* = f \sum_i I^*_{Hi} \tag{5}$$

The duration of the malaria parasite incubation period, T_E, is also strongly dependent on temperature. In warmer climates incubation can be completed in less than 10 days, whereas between 20-30 days can be required under cooler conditions (Paaijmans *et al.* 2009). As both this incubation period T_E and the time interval between blood feeds, $T_{M,}$ increase as temperature decreases, these two processes can act synergistically to reduce the rate of malaria transmission in cooler climates.

2. The impact of fungal biopesticides on malaria transmission

The stage-structure implemented in this model is relevant to mosquito control interventions which act differently on host-seeking and non-host-seeking stages of the mosquito lifecycle. For a fungal biopesticide intervention that involves spraying surfaces inside houses with spores of a fungal entomopathogen, mosquitoes that are host-seeking are more likely to contract the fungus than those that are not host-seeking and away from areas of human habitation. The model assumes that host-seeking mosquitoes contract the fungal pathogen at a daily rate F, and so the daily probability of infection is $P_f = 1\text{-}e^{-F}$. The conservative assumption that non-host-seeking mosquitoes have zero risk of fungal infection is adopted. Experimental studies show that fungal infection causes accelerated adult mortality, with the effect becoming more pronounced with increased age of infection (Blanford *et al.* 2005). Depending on the fungal strain that is used and the dose that is applied, a wide range of age-dependent mortality patterns have been observed (Blanford *et al.* 2005, Scholte *et al.* 2003, 2006). Here, we estimate the effect of fungal infection on adult mortality using data from recent field trials of the application of *Beauvaria bassiana* (Balsamo) Vuillemin in experimental huts in Tanzania (Mnyone, unpublished data). Weibull functions describing the rate of adult mortality as a function of the age of fungal infection were fitted to the experimental data (Hancock 2009; Figure 4). In the model, these functions describe the age-dependent effect of fungal infection on adult mortality (Hancock 2009).

We consider the effect of fungal biopesticide application on the rate of malaria transmission (the daily EIR, eqn 5) for two different temperature conditions. In the first case, the temperature is warm (a constant 30 °C), in which case we estimate that the duration of the non-host-seeking stage is T_M=2 days (Quinones *et al.* 1997) and the duration of malaria parasite incubation is T_E=8 days (Paaijmans *et al.* 2010). Secondly we consider a cool environment in which the temperature is a constant 20 °C, for which we estimate that T_M=6 days and T_E=20 days (Paaijmans *et al.* 2010). All other model parameters are the same as in Hancock (2009) unless otherwise specified.

Figure 5 shows the effect of the fungal biopesticide on the equilibrium daily EIR for different values of the daily probability of fungal infection experienced by host-seeking mosquitoes

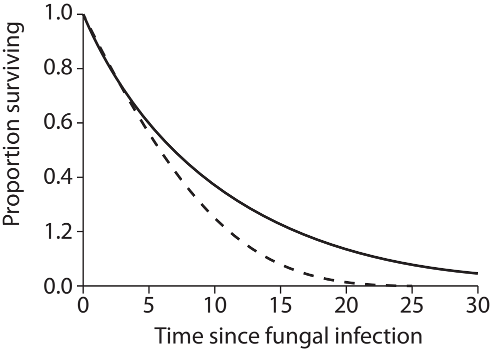

Figure 4. Model of the age-dependent effect of fungal infection on adult mortality. Mosquitoes uninfected with the fungal pathogen (solid line) and infected (dashed line) both experience natural mortality at a constant daily rate $\mu=0.1$. Mosquitoes that are fungus-infected experience additional mortality at a rate that depends on the time since fungal infection. The additional mortality rate $M_F(u)$ is modelled by a Weibull function of the fungal infection age u; $M_F(u) = \beta\mu_F(\mu_F u)^{\beta-1}$, where $\mu_F=0.068$ and $\beta=2.5$ are the Weibull rate and shape parameters respectively.

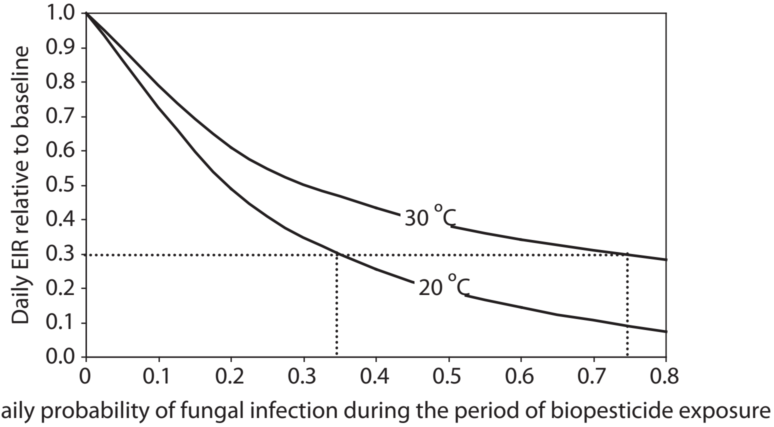

Figure 5. The equilibrium daily EIR as a proportion of the baseline EIR for different levels of the fungal biopesticide coverage. Solid lines show different values of constant temperature. Dotted lines indicate the coverage levels required to achieve a 70% reduction in the EIR for both temperatures.

(termed the 'coverage' of the biopestide). This shows that the fungal biopesticide is more efficient, having a greater proportional effect on the EIR, when the temperature is cooler. For example, if very high coverage can be achieved, the EIR is reduced by about 70% at the warmer temperature and by about 90% at the cooler temperature. It is perhaps more significant that a considerable reduction in the EIR, of about 70%, can be achieved with moderate to low biopesticide coverage (about 0.3-0.4) at 20 °C, but a similar proportional impact on the EIR would require a much higher coverage of about 0.7-0.8 at 30 °C.

The reason for the greater efficacy of the biopesticide at cooler temperatures is that there is more time for fungal infection to act when both the delay between blood feeds and the duration of malaria parasite incubation are longer. The experimental data shows that fungal infection is relatively slow to kill mosquitoes (Figure 4), and so is less effective in reducing malaria transmission when mosquitoes start taking malaria-infectious blood meals at a younger age. However, the intervention still produces a substantial decrease in the EIR at the warmer temperature, and Figure 5 indicates that the absolute reduction in the EIR will be greater at 30 °C because the baseline EIR is much higher when the temperature is warmer. An important caveat to these results is that the effect of fungal infection on mosquito mortality is also significantly affected by temperature. A study by Kikankie *et al.* (2010) measured the survival of fungus-infected mosquitoes at two different temperatures, and found that the fungus was significantly more virulent at warmer temperatures. Therefore, further investigation of how this intervention affects key aspects of mosquito demography across a range of different environmental conditions is needed to understand how malaria transmission can be impacted in different areas.

Demographic processes

The process of density-dependent larval competition, discussed in the previous section, is of central importance to certain novel strategies for controlling mosquito-borne diseases by releasing genetically modified mosquitoes. One such strategy developed to help control *Ae. aegypti* mosquitoes, which vector a number of important human diseases including dengue fever and yellow fever, involves the release of genetically modified male mosquitoes that carry a dominant genetic system that is lethal to their offspring. This strategy, known as RIDL (Phuc *et al.* 2007, Thomas *et al.* 2000), can be designed so that the offspring resulting from matings between wild females and the genetically modified males die either before starting or after completing larval development (Phuc *et al.* 2007). It is expected that the latter strategy (known as late-lethal) would be more effective that the first (known as early-lethal) in suppressing the wild mosquito population, because the doomed offspring would survive through the larval stage to compete for resources and so their death would not reduce the density-dependent competition experienced by the larval population. Models of the RIDL strategy address the question of how the suppression in adult abundance is affected by the higher density-dependent larval competition associated with the late-lethal strategy (Atkinson *et al.* 2007, Phuc *et al.* 2007). Atkinson *et al.* (2007) derive threshold conditions for the eradication of the dengue virus for the early-lethal and late-lethal strategies in terms of demographic parameters relevant to mosquito vectorial capacity. However, quantification of these thresholds requires detailed data on the relationship between the survival of larvae and their density, which is either very scarce or non-existant, as discussed previously.

Conversely, many vector control methods, both traditional and novel, target mosquitoes in the adult stage of their lifecycle, as it is the older-aged adult mosquitoes that transmit human diseases. Such strategies include IRS and ITNs. A number of novel strategies for adult mosquito control are currently being developed, motivated by the rising levels of resistance in mosquito populations to the commonly used insecticides (Ranson *et al.* 2009). In Box 1 we describe a model of a novel method of biological control of mosquito populations. Fungal biopesticides can be used to infect adult mosquitoes with a pathogenic fungus which interferes with their mobility and blood-feeding activity and reduces their lifespan (Blanford *et al.* 2005, Scholte *et al.* 2006, Scholte *et al.* 2005). The model focuses on the demography of adult *Anopheles* mosquitoes and aims to capture aspects of the adult mosquito's biology that are important to the effect of fungal biopesticides on the capacity of these mosquito populations to transmit malaria.

Ecological setting

An important purpose of models of mosquito control strategies is to investigate how the performance of strategies may vary across different ecological settings. Mosquito demographic rates can be strongly dependent on environmental conditions; for example temperature affects developmental processes in the mosquito, including the rate of development of the juvenile stages (Pascual *et al.* 2006), the rate of adult mortality, and the frequency of blood feeding (Paaijmans *et al.* 2010). The development rate of the parasites and viruses transmitted by mosquitoes is also sensitive to temperature (Paaijmans *et al.* 2009, Watts *et al.* 1987). Spatial analyses of malaria transmission intensity have used temperature and rainfall data to characterise the epidemiology of malaria throughout Africa in terms of whether the disease is likely to be absent, epidemic or endemic in different regions (Craig *et al.* 1999). The efficacy of vector-control interventions varies depending on the environmental conditions in the area where they are applied; for example IRS has been least effective in reducing malaria transmission in endemic tropical and lowland areas (Mabaso *et al.* 2004). In our case study we investigate how the ability of fungal biopesticide interventions to reduce the rate of malaria transmission may vary in areas with different temperature conditions (Box 1).

Seasonal fluctuations in mosquito abundance in response to rainfall patterns is also an important consideration for any mosquito control strategy. Accurate and effective early warning systems are valuable in allowing interventions to be implemented in time to contain seasonal outbreaks of disease (Thomson *et al.* 2006). Interventions such as the sterile insect technique (SIT), that involve releasing laboratory-reared mosquitoes to interfere with the reproduction of the wild population, may only be successful if they are well-timed. For example, the released mosquitoes may be overwhelmed if the natural population is rapidly expanding, but if the releases occur when conditions are too dry then the introduced mosquitoes may experience high mortality, particularly as they will need to locate relatively scarce suitable habitat to find mating partners. Given that mosquito abundance can increase over several orders of magnitude during the first 2-3 weeks of the rainy season (Laneri *et al.* 2010, Lehmann *et al.* 2010), seasonality represents a major practical challenge for these interventions in some areas.

Similar issues arise with newer technologies aiming to release genetically modified mosquitoes (Deredec *et al.* 2008, Gould *et al.* 2008, Marshall *et al.* 2011). These strategies can be used to spread genes through the population that have a detrimental effect on the mosquito or on the pathogen that it transmits, lowering the vectorial capacity of the population (a process known as 'population replacement'). Often it is necessary that the frequency of the gene exceeds a certain threshold level in the population in order for it to spread, and so the strategy requires the abundance of natural population to be sufficiently low that the insect releases can attain this frequency (Deredec *et al.* 2008, Marshall *et al.* 2011). This condition also applies to novel biological control methods involving the release of mosquitoes infected with *Wolbachia* bacteria, because *Wolbachia* also only spread once their infection frequency exceeds a threshold (Hancock *et al.* 2011a,b, Hoffmann *et al.* 2011, McMeniman *et al.* 2009, Moreira *et al.* 2009, Turelli 1994, Walker *et al.* 2011). Mosquito population dynamic models that explicitly represent seasonally varying demographic rates, and the mating frequency between released and wild mosquitoes, can be used to explore the effects of the timing of releases on the number of introduced insects required for spread to occur in a seasonal environment (Hancock *et al.* 2011a,b). The results emphasise that an ability to understand

and predict seasonal variation in mosquito population dynamics can be vital to the success of control strategies that involve deliberate mosquito releases.

Future directions

With growing attention being given to the control of mosquito vectors, it is clear that models will be increasingly called upon to build a theory of mosquito dynamics, and to investigate the impacts of specific control measures. Both the modelling approaches discussed in this chapter – backward modelling to interpret complex mosquito data, and forward modelling to predict the consequences of specific interventions – are currently being applied, yet this is a young field of research. We end this chapter with a brief comment on three important, yet under-studied, aspects of mosquito dynamics where modelling attention is required: evolution, spatial structure, and community effects.

Evolution

Both mosquito vectors, and the pathogens they transmit, have unfortunately proven themselves remarkably adaptable in the face of certain control measures. *An. gambiae s.l.*, for example, have evolved to become less susceptible to certain insecticides, both through physiological changes (John *et al.* 2008) and behavioural changes (Pates and Curtis 2005), in only a few decades at most. Genomic study is proving useful to resolving the molecular mechanisms of resistance evolution (Hemingway *et al.* 2004, Weill *et al.* 2003), yet genomic insight alone cannot reveal the spatio-temporal dynamics by which resistance spreads among populations. Population genetic models are increasingly being used to study how intervention strategies are affected by evolutionary feedbacks in pest control (Onstad and Guse 2008), yet fewer models have been specifically tailored to mosquitoes (but see Koella *et al.* 2009, Read *et al.* 2009). To predict the conditions necessary for novel intervention strategies to be successful, it is clearly necessary to account for the potentially disruptive process of resistance evolution.

Spatial structure

In recent decades, questions of population spatial structure have become increasingly central to ecological and evolutionary research (Borcard *et al.* 2004, Hanski 1999, Thomas and Kunin 1999). The spatio-temporal dynamics of mosquito populations will be critical to the success of high-tech control strategies (Knols and Scott 2003). For instance, transgenic technologies rely on gene-flow, and so in order to make robust predictions of the conditions necessary for transgenic technologies to succeed, it is imperative to use models that account for processes, such as dispersal, that mediate gene-flow (Yakob *et al.* 2008a,b). Thanks in part to improvements in mapping technology, field biologists are increasingly recording spatial as well as temporal details of mosquito populations (e.g. Eisen and Lozano-Fuentes 2009, Fillinger and Lindsay 2006, Majambere *et al.* 2010). Spatial realism is notorious for the extent to which it complicates population models, however, and so it is perhaps unsurprising that few attempts have been made to compare spatio-temporal data to spatially realistic population models (though see Xu *et al.* 2010). Somewhat more effort has been applied to developing spatially realistic forward models in order to ask how spatial complications might affect the operation of novel control measures (Yakob and Bonsall 2009, Yakob *et al.* 2008a,b), yet our understanding of the spatial dynamics of mosquitoes clearly still has a long way to go.

Wider ecological impacts

Predicting how mosquito control will impact upon interacting species is a difficult task, yet community effects are to be expected for those interventions which strongly impact on mosquito populations. To dismiss these effects invites the possibility of unexpected outcomes of intervention, including failure (e.g. in the control of pest mammals from New Zealand forests, Tompkins and Veltman 2006). It has been suggested that even the eradication of mosquito species would have few wider ecological impacts (Fang 2010), yet this view has been staunchly criticised (Smith 2010), and it is clear that more research is needed. Although empirical study (especially manipulative experimental study) will inevitably underpin this research, models are also required. Models will be essential to interpreting multi-species data, and predicting the consequences of inter-specific interactions. The framework of community modules may be particularly useful to the study of how particular interventions might influence species interactions (Gilman *et al*. 2010). The interaction between congeneric mosquito species, which share similar ecological niches yet may respond to control measures differently, deserves particularly close attention. For example, the congeneric *An. gambiae s.l.* and *An. funestus* Giles mosquitoes differ in the extent to which they have evolved resistance to insecticide-treated nets and indoor residual spraying (Russell *et al*. 2011a). Since the niches of these species overlap, it is to be expected that the responses of each species to intervention will influence one another.

References

Atkinson MP, Su Z, Alphey N, Alphey LS, Coleman PG and Wein LM (2007) Analyzing the control of mosquito-borne diseases by a dominant lethal genetic system. Proc Natl Acad Sci USA 104: 9540-9545.

Blanford S, Chan BHK, Jenkins N, Sim D, Turner RJ, Read AF and Thomas MB (2005) Fungal pathogen reduces potential for malaria transmission. Science 308: 1638-1641.

Borcard D, Legendre P, Avois-Jacquet C and Tuomisto H (2004) Dissecting the spatial structure of ecological data at multiple scales. Ecology 85: 1826-1832.

Brook BW and Bradshaw CJA (2006) Strength of evidence for density dependence in abundance time series of 1198 species. Ecology 87: 1445-1451.

Burt A (2003) Site-specific selfish genes as tools for the control and genetic engineering of natural populations. Proc R Soc Lond Ser B-Biol Sci 270: 921-928.

Craig MH, Snow RW and le Sueur D (1999) A climate-based distribution model of malaria transmission in sub-Saharan Africa. Parasitol Today 15: 105-111.

Curtis CF and Mnzava AEP (2000) Comparison of house spraying and insecticide-treated nets for malaria control. Bull WHO 78: 1389-1400.

Deredec A, Burt A and Godfray HCJ (2008) The population genetics of using homing endonuclease genes in vector and pest management. Genetics 179: 2013-2026.

Dye C (1984) Models for the population dynamics of the yellow fever mosquito, *Aedes aegypti*. J Anim Ecol 53: 247-268.

Dye C and Hasibeder G (1986) Population dynamics of mosquito-borne disease: effects of flies which bite some people more frequently than others. Trans R Soc Trop Med Hyg 80: 69-77.

Edillo FE, Toure YT, Lanzaro GC, Dolo G and Taylor CE (2004) Survivorship and distribution of immature *Anopheles gambiae s.l.* (Diptera: Culicidae) in Banambani village, Mali. J Med Entomol 41: 333-339.

Eisen L and Lozano-Fuentes S (2009) Use of mapping and spatial and space-time modeling approaches in operational control of *Aedes aegypti* and dengue. PLoS Negl Trop Dis 3: e411.

Fang J (2010) Ecology: a world without mosquitoes. Nature 466: 432.

Ferguson HM, Dornhaus A, Beeche A, Borgemeister C, Gottlieb M, Mulla MS, Gimnig JE, Fish D and Killeen GF (2010) Ecology: a prerequisite for malaria elimination and eradication. PLoS Med 7: e1000303.

Fillinger U and Lindsay SW (2006) Suppression of exposure to malaria vectors by an order of magnitude using microbial larvicides in rural Kenya. Trop Med Int Health 11: 1629-1642.

Gilman SE, Urban MC, Tewksbury J, Gilchrist GW and Holt RD (2010) A framework for community interactions under climate change. Trends Ecol Evol 25: 325-331.

Gimnig JE, Ombok M, Otieno S, Kaufman MG, Vulule JM and Walker ED (2002) Density-dependent development of *Anopheles gambiae* (Diptera: Culicidae) larvae in artificial habitats. J Med Entomol 39: 162-172.

Gould F, Huang YX, Legros M and Lloyd AL (2008) A Killer-Rescue system for self-limiting gene drive of anti-pathogen constructs. Proc R Soc Lond B Biol Sci 275: 2823-2829.

Gubler DJ (1998) Resurgent vector-borne diseases as a global health problem. Emerging Infect Dis 4: 442.

Hancock P, Thomas M and Godfray H (2009) An age-structured model to evaluate the potential of novel malaria-control interventions: a case study of fungal biopesticide sprays. Proc R Soc Lond Ser B-Biol Sci 276: 71.

Hancock PA (2009) Combining fungal biopesticides and insecticide-treated bednets to enhance malaria control. PLoS Comput Biol 5: e1000525.

Hancock PA, Sinkins SP and Godfray HCJ (2011a) Population dynamic models of the spread of *Wolbachia*. Am Nat 177.

Hancock PA, Sinkins SP and Godfray HCJ (2011b) Strategies for introducing *Wolbachia* to reduce transmission of mosquito-borne diseases. PLoS Negl Trop Dis, in press.

Hanski I (1990) Density dependence, regulation and variability in animal populations. Philos Trans R Soc Lond B Biol Sci 330: 141.

Hanski I (1999) Metapopulation ecology. Oxford University Press, New York, NY, USA.

Haworth J (1988) The global distribution of malaria and the present control efforts. In: Wernsdorfer WH and McGregor I (eds.) Malaria, Churchill Livingstone, Edinburgh, UK, pp. 1379-1420.

Hemingway J, Hawkes NJ, McCarroll L and Ranson H (2004) The molecular basis of insecticide resistance in mosquitoes. Insect Biochem Mol Biol 34: 653-665.

Hoffmann AA, Montgomery BL, Popovici J, Iturbe-Ormaetxe I, Johnson PH, Muzzi F, Greenfield M, Durkan M, Leong YS, Dong Y, Cook H, Axford J, Callahan AG, Kenny N, Omodei C, McGraw EA, Ryan PA, Ritchie SA, Turelli M and O'Neill SL (2011) Successful establishment of *Wolbachia* in *Aedes* populations to suppress dengue transmission. Nature 476: 454-457.

Jawara M, Pinder M, Drakeley CJ, Nwakanma DC, Jallow E, Bogh C, Lindsay SW and Conway DJ (2008) Dry season ecology of *Anopheles gambiae* complex mosquitoes in The Gambia. Malar J 7: 9.

John R, Ephraim T and Andrew A (2008) Reduced susceptibility to pyrethroid insecticide treated nets by the malaria vector *Anopheles gambiae s. l.* in western Uganda. Malar J 7: 92.

Johnson JB and Omland KS (2004) Model selection in ecology and evolution. Trends Ecol Evol 19: 101-108.

Kikankie CK, Brooke BD, Knols BGJ, Koekemoer LL, Farenhorst M, Hunt RH, Thomas MB and Coetzee M (2010) The infectivity of the entomopathogenic fungus *Beauveria bassiana* to insecticide-resistant and susceptible *Anopheles arabiensis* mosquitoes at two different temperatures. Malar J 9: (8 March 2010).

Killeen GF, Smith TA, Ferguson HM, Mshinda H, Abdulla S, Lengeler C and Kachur SP (2007) Preventing childhood malaria in Africa by protecting adults from mosquitoes with insecticide-treated nets. PLoS Med 4: 1246-1258.

Klowden MJ (2007) Making generalizations about vectors: is there a physiology of 'the mosquito'? Entomol Res 37: 1-13.

Knols BGJ and Scott TW (2003) Discussion-Ecological challenges concerning the use of genetically modified mosquitoes for disease control: synthesis and future perspectives. In: Takken W and Scott TW (eds.) Proceedings of the Frontis workshop on ecological challenges concerning the use of genetically modified mosquitoes for disease control Wageningen, the Netherlands 26-29 June 2002. Frontis, Wageningen, the Netherlands, pp. 235-242.

Koella JC, Lynch PA, Thomas MB and Read AF (2009) Towards evolution-proof malaria control with insecticides. Evol Appl 2: 469-480.

Koenraadt CJM, Githeko AK and Takken W (2004) The effects of rainfall and evapotranspiration on the temporal dynamics of *Anopheles gambiae* s.s. and *Anopheles arabiensis* in a Kenyan village. Acta Trop 90: 141-153.

Kokko H (2007) Modelling for field biologists and other interesting people. Cambridge University Press, Cambridge, UK.

Laneri K, Bhadra A, Ionides EL, Bouma M, Dhiman RC, Yadav RS and Pascual M (2010) Forcing versus feedback: epidemic malaria and monsoon rains in northwest India. PLoS Comput Biol 6: 13.

Lardeux F, Tejerina R, Quispe V and Chavez T (2008) A physiological time analysis of the duration of the gonotrophic cycle of *Anopheles pseudopunctipennis* and its implications for malaria transmission in Bolivia. Malar J 7.

Legros M, Lloyd AL, Huang YX and Gould F (2009) Density-dependent intraspecific competition in the larval stage of *Aedes aegypti* (Diptera: Culicidae): revisiting the current paradigm. J Med Entomol 46: 409-419.

Lehmann T, Dao A, Yaro AS, Adamou A, Kassogue Y, Diallo M, Sékou T and Coscaron-Arias C (2010) Aestivation of the African malaria mosquito, *Anopheles gambiae* in the Sahel. Am J Trop Med Hyg 83: 601-606.

Mabaso MLH, Sharp B and Lengeler C (2004) Historical review of malarial control in southern African with emphasis on the use of indoor residual house-spraying. Trop Med Int Health 9: 846-856.

MacDonald G (1957) The epidemiology and control of malaria. Oxford University Press, London, UK.

Majambere S, Pinder M, Fillinger U, Ameh D, Conway DJ, Green C, Jeffries D, Jawara M, Milligan PJ, Hutchinson R and others (2010) Is mosquito larval source management appropriate for reducing malaria in areas of extensive flooding in The Gambia? A Cross-over intervention trial. Am J Trop Med Hyg 82: 176.

Marshall JM, Pittman GW, Buchman AB and Hay BA (2011) Semele: a killer-male, rescue-female system for suppression and replacement of insect disease vector populations. Genetics 187: 535-U252.

McMeniman CJ, Lane RV, Cass BN, Fong AWC, Manpreet S, Wang Y and O'Neill SL (2009) Stable introduction of a life-shortening *Wolbachia* infection into the mosquito *Aedes aegypti*. Science 323: 141-144.

Moreira LA, Iturbe-Ormaetxe I, Jeffery JA, Lu GJ, Pyke AT, Hedges LM, Rocha BC, Hall-Mendelin S, Day A, Riegler M, Hugo LE, Johnson KN, Kay BH, McGraw EA, Van den Hurk AF, Ryan PA and O'Neill SL (2009) A *Wolbachia* symbiont in *Aedes aegypti* limits infection with Dengue, Chikungunya, and *Plasmodium*. Cell 139: 1268-1278.

Onstad DW and Guse CA (2008) Concepts and complexities of population genetics. In: Onstad DW (ed.) Insect resistance management. Biology, economics and predictions. Academic Press, New York, NY, USA, pp. 69-88.

Paaijmans KP, Blanford S, Bell AS, Blanford JI, Read AF and Thomas MB (2010) Influence of climate on malaria transmission depends on daily temperature variation. Proc Natl Acad Sci USA 107: 15135-15139.

Paaijmans KP, Read AF and Thomas MB (2009) Understanding the link between malaria risk and climate. Proc Natl Acad Sci USA 106: 13844-13849.

Pascual M, Ahumada JA, Chaves LF, Rodo X and Bouma M (2006) Malaria resurgence in the East African highlands: temperature trends revisited. Proc Natl Acad Sci USA 103: 5829-5834.

Pates H and Curtis C (2005) Mosquito behavior and vector control. Annu Rev Entomol 50: 53-70.

Phuc H, Andreasen MH, Burton RS, Vass C, Epton MJ, Pape G, Fu G, Condon KC, Scaife S, Donnelly CA, Coleman PG, White-Cooper H and Alphey L (2007) Late-acting dominant lethal genetic systems and mosquito control. BMC Biol 5: 11

Quinones ML, Lines JD, Thomson MC, Jawara M, Morris J and Greenwood BM (1997) *Anopheles gambiae* gonotrophic cycle duration, biting and exiting behaviour unaffected by permethrin-impregnated bednets in The Gambia. Med Vet Entomol 11: 71-78.

Ranson H, Abdallah H, Badolo A, Guelbeogo W, Kerah-Hinzoumbe C, Yangalbe-Kalnone E, Sagnon NF, Simard F and Coetzee M (2009) Insecticide resistance in *Anopheles gambiae*: data from the first year of a multi-country study highlight the extent of the problem. Malar J 8: 299.

Read AF, Lynch PA and Thomas MB (2009) How to make evolution-proof insecticides for malaria control. PLoS Biol 7: e1000058.

Ross R (1911) The prevention of malaria. Murray, London, UK.

Russell T, Govella N, Azizi S, Drakeley C, Kachur SP and Killeen G (2011a) Increased proportions of outdoor feeding among residual malaria vector populations following increased use of insecticide-treated nets in rural Tanzania. Malar J 10: 80.

Russell TL, Lwetoijera DW, Knols BG, Takken W, Killeen GF and Ferguson HM (2011b) Linking individual phenotype to density-dependent population growth: the influence of body size on the population dynamics of malaria vectors. Proc Biol Sci 278: 3142-3151.

Scholte E-J, Knols BGJ and Takken W (2006) Infection of the malaria mosquito *Anopheles gambiae* with the entomopathogenic fungus *Metarhizium anisopliae* reduces blood feeding and fecundity. J Invertebr Pathol 91: 43-49.

Scholte E-J, Ng'habi K, Kihonda J, Takken W, Paaijmans K, Abdulla S, Killeen GF and Knols BGJ (2005) An entomopathogenic fungus for control of adult African malaria mosquitoes. Science 308: 1641-1642.

Scholte E-J, Njiru BN, Smallegange RC, Takken W and Knols BGJ (2003) Infection of malaria (*Anopheles gambiae* s.s.) and filariasis (*Culex quinquefasciatus*) vectors with the entomopathogenic fungus *Metarhizium anisopliae*. Malar J 2.

Service MW (1977) Mortalities of immature stages of species-B of *Anopheles gambiae* complex in Kenya – comparison between rice fields and temporary pools, identification of predators, and effects of insecticidal spraying. J Med Entomol 13: 535-545.

Smith DL and McKenzie E (2004) Statics and dynamics of malaria infection in Anopheles mosquitoes. Malar J 3: 13.

Smith SM (2010) Mosquitoes: schemes to render them extinct are impracticable. Nature 466: 1041-1041.

Southwood TRE, Murdie G, Yasuno M, Tonn RJ and Reader PM (1972) Studies on the life budget of *Aedes aegypti* in Wat Samphaya Bankok Thailand. Bull WHO 46: 211-226.

Takken W and Boëte C (2003) An introduction to ecological challenges concerning the use of genetically-modified mosquitoes for disease control. In In: Takken W and Scott TW (eds.) Proceedings of the Frontis workshop on ecological challenges concerning the use of genetically modified mosquitoes for disease control Wageningen, the Netherlands 26-29 June 2002. Frontis, Wageningen, the Netherlands, pp. 9-14.

Takken W and Knols BGJ (2009) Malaria vector control: current and future strategies. Trends Parasitol 25: 101-104.

Thomas CD and Kunin WE (1999) The spatial structure of populations. J Anim Ecol 68: 647-657.

Thomas DD, Donnelly CA, Wood RJ and Alphey LS (2000) Insect population control using a dominant, repressible, lethal genetic system. Science 287: 2474-2476.

Thomson MC, Doblas-Reyes FJ, Mason SJ, Hagedorn R, Connor SJ, Phindela T, Morse AP and Palmer TN (2006) Malaria early warnings based on seasonal climate forecasts from multi-model ensembles. Nature 439: 576-579.

Tompkins DM and Veltman CJ (2006) Unexpected consequences of vertebrate pest control: predictions from a four-species community model. Ecol Appl 16: 1050-1061.

Turchin P (2003) Complex population dynamics. Princeton University Press, Princeton, NJ, USA.

Turelli M (1994) Evolution of incompatibility inducing microbes and their hosts. Evolution 48: 1500-1513.

Walker T, Johnson PH, Moreira LA, Iturbe-Ormaetxe I, Frentiu FD, McMeniman CJ, Leong YS, Dong Y, Axford J, Kriesner P, Lloyd AL, Ritchie SA, O/'Neill SL and Hoffmann AA (2011) The wMel *Wolbachia* strain blocks dengue and invades caged *Aedes aegypti* populations. Nature 476: 450-453.

Ward CM, Su JT, Huang Y, Lloyd AL, Gould F and Hay BA (2011) Medea selfish genetic elements as tools for altering traits of wild populations: a theoretical analysis. Evolution 65: 1149-1162.

Watts DM, Burke DS, Harrison BA, Whitmire RE and Nisalak A (1987) Effect of temperature on the vector efficiency of *Aedes aegypti* for dengue-2 virus. Am J Trop Med Hyg 36: 143-152.

Weill M, Lutfalla G, Mogensen K, Chandre F, Berthomieu A, Berticat C, Pasteur N, Philips A, Fort P and Raymond M (2003) Comparative genomics: insecticide resistance in mosquito vectors. Nature 423: 136-137.

Xu C, Legros M, Gould F and Lloyd AL (2010) understanding uncertainties in model-based predictions of *Aedes aegypti* population dynamics. PLoS Negl Trop Dis 4: e830.

Yakob L and Bonsall MB (2009) Importance of space and competition in optimizing genetic control strategies. J Econ Entomol 102: 50-57.

Yakob L, Alphey L and Bonsall MB (2008a) *Aedes aegypti* control: the concomitant role of competition, space and transgenic technologies. J Appl Ecol 45: 1258-1265.

Yakob L, Kiss IZ and Bonsall MB (2008b) A network approach to modeling population aggregation and genetic control of pest insects. Theor Popul Biol 74: 324-331.

Yang GJ, Bradshaw CJA, Whelan PI and Brook BW (2008a) Importance of endogenous feedback controlling the long-term abundance of tropical mosquito species. Popul Ecol 50: 293-305.

Yang GJ, Brook BW, Whelan PI, Cleland S and Bradshaw CJA (2008b) Endogenous and exogenous factors controlling temporal abundance patterns of tropical mosquitoes. Ecol Appl 18: 2028-2040.

Zeng Z, Nowierski RM, Taper ML, Dennis B and Kemp WP (1998) Complex population dynamics in the real world: modeling the influence of time-varying parameters and time lags. Ecology 79: 2193-2209.