A novel age-structured mosquito model for assessing the mechanisms behind vector control success

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RESEARCH

A novel age-structured mosquito model for assessing the mechanisms behind vector control success

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Abstract

Background: Vector control is a vital tool utilised by malaria control and elimination programmes worldwide, and as such it is important that we can accurately quantify the expected public health impact of a range of vector control methods. There are very few previous models that consider vector control induced changes in the age-structure of the vector population and the resulting impact this will have on transmission.

Methods: The steady-state solution of a novel age-structured deterministic compartmental model describing the mosquito gonotrophic cycle is analytically derived, with the age of each mosquito measured in the number of gonotrophic cycles (or successful blood meals) completed. From this model we derive analytical expressions for key transmission measures, such as the effective reproductive ratio under control, R_c, and investigate the impact of combinations of commonly used vector control methods on the age-structure of the vector population.

Results: Our model output is an explicit solution that can be used to directly quantify key transmission statistics and investigate the age-structured impact of vector control. Application of this model confirms current knowledge that adult-acting interventions, such as IRS or LLINs, can be highly effective at reducing transmission, due to the dual effects of repelling and killing mosquitoes. However, we demonstrate how larval measures can be implemented in addition to adult-acting measures to reduce R_c and mitigate the impact of waning insecticidal efficacy. We also find that mid-ranges of LLIN coverage see the largest effect of reduced net integrity on transmission.

Conclusions: Whilst well-maintain adult-acting vector control measures are substantially more effective than larval-based interventions, incorporating larval control in existing LLIN or IRS programmes could substantially reduce transmission. This would most benefit areas with low coverage or poor maintenance of interventions.

Keywords: modelling; mosquito; malaria; vector control; age-structure

Background

In 2018 there were approximately 228 million cases of malaria worldwide and 405 000 deaths, with children under age 5 accounting for 67% of all fatalities [1]. Since 2004 2 billion nets have been distributed to populations at risk of malaria and their usage has been attributed to 68% of prevented cases in Africa since 2000 [2, 3], particularly in pregnant women and children, in whom bednet usage has more

than doubled (26% to 61%) since 2010. The majority of these nets are long lasting insecticide treated nets (LLINs) and by 2018 between 40% and 80% coverage of the population at risk had been achieved in all 11 high burden to high impact (HBHI) countries, although actual usage may be substantially lower.

However, from 2014 to 2018 there has been little change in the incidence rate of malaria, with bednet coverage remaining constant since 2016 [1]. In addition, the use of indoor residual spraying (IRS) has declined, with coverage dropping from 5% in 2010 to 2% in 2018 [4]. This may, in part, be linked to reports from 81 countries describing the development of insecticide resistance [5]. In addition, there are requirements to maintain LLIN efficacy through regular distribution, with each net typically lasting for up to 3 years, or 20 washes, which can prove difficult to achieve in many countries. Larvicidal methods of control are not currently widely used, but empirical studies have shown using larvicides to reduce mosquito densities can have a positive impact on incidence and parasite prevalence [6]. In particular, potentially due to the similar mechanisms employed by LLINs and IRS, combining adult-acting methods has been shown to have limited additional effect [7], but larval control has been recommended by the World Health Organization (WHO) as an appropriate supplementary measure to adult vector control.

The existing wide-spread and successful usage of vector control to combat malaria demonstrates the vital role of the mosquito in sustaining transmission. The importance of a deep understanding of how the mechanisms by which these interventions work, as well as the underlying mosquito ecology, has been previously noted [8, 9].

Vector control interventions target the mosquito, impacting the feeding cycle and population characteristics. This means that to understand the mechanism through which vector-based interventions reduce transmission, it is first necessary to understand how vector control measures and coverage affect the vector dynamics. The challenges associated with maintaining vector control interventions also mean that it would be useful to understand how transmission changes with the waning efficacy of these interventions over time. Greater characterisation of the changing dynamics of the mosquito population under vector control would also be vital to any future vector-based surveillance (xeno-monitoring) strategy.

A number of widely used models focusing on transmission dynamics have tended to simplify vector dynamics [10, 11], whereas models that focus on vector dynamics often do not include transmission [9, 12]. Although the historical literature does include good characterisation of the dynamical differences between larval and adult control [13, 14, 15, 16, 17], few previous modelling efforts have combined changes in a full range of vector population measures, including abundance and age-structure, with the resulting impact on transmission [18].

By constructing an age-structured mosquito population model of the gonotrophic cycle that also includes mosquito infection status, we aim to further investigate these dynamics. In particular, we consider the effect of different vector control measures on the age- and infection-structure of the vector population and calculate the impact on the reproductive number under control, R_c, a key transmission measure that can be used to predict long-term elimination or resurgence [16].

Early models of malaria incorporated the mosquito population size, highlighting the importance of the vector to host ratio in determining transmission dynamics

[19]. These were extended to derive a formula for the basic reproduction number, R_0, based on this ratio and a number of other variables, including mosquito feeding and survival rates [13]. Recent models have expanded this further to consider the stages of the feeding cycle [20, 21], including vector control interventions at the larval or adult stages but with no age-structure within the adult vector population, with many more models including vector control in some form [22, 23, 24, 25, 26, 27, 28, 29, 30]. However, an independent review of 388 mosquito-borne pathogen models found only 5 models that considered any two-intervention combination of LLINs, IRS and larvicides and only one that considered all three [18].

One study used an updated version of Macdonald's theory of vectorial capacity to consider combinations of larval and adult vector control measures, demonstrating that combined measures could provide an improved ratio of effect size to effort and potentially bring R_c below 1 [15]. However, combining interventions may not always provide additional benefit, with a recent review reporting no detectable changes where pyrethroid-based IRS was implemented in communities using LLINs [7], and relative outcomes could be impacted by the waning efficacy of insecticides over time.

Age-structure has also been modelled explicitly in a number of ways, including splitting the mosquito population into life-cycle stages (egg, larvae, pupae, adult) [31] and focusing on the age-structure of the host population [32, 33]. Partial differential equations (PDEs) have been used to consider adult mosquito age-structure within a transmission model, allowing continuous aging of the mosquito population [34], but this has not been used to compare different vector control measures and their impact on the population structure.

Although vector control methods have long been recognised as important in malaria control and elimination [35], the increasing risk of insecticide resistance and questions around sustainability of interventions have prompted discussions on the best strategy [14, 15, 36, 37]. LLINs are the most commonly used measure, but there is also wide-spread usage of IRS and other insecticidal spraying methods. Larvicidal methods are often seen as practically more challenging to implement [38], but it has previously been suggested that it may be easier to target spatially-confined larval stages than their highly mobile adult counterparts [39] and that using multiple interventions at different stages of the life-cycle could give improved results [9, 17, 17]. As such, there is need to broader analysis of the relative benefits of different vector control methods and their combinations, including whether larvicidal options could be used to mitigate the waning effects of insecticide-based adult acting interventions.

Methods

The analytical solution of a simple age-structured deterministic compartmental model is used to describe the mosquito gonotrophic cycle. The age-structure of the population is measured in the number of gonotrophic cycles, or number of successful blood meals, completed by each individual mosquito. The steady-state of this model is used to investigate the impact of common vector control methods (LLINs, IRS and larvicides) on the age-structure and transmission potential of the vector population.

Gonotrophic cycle model with vector control

Considering the gonotrophic cycle of an adult mosquito, we divide the stages into four categories: blood-seeking (B), fed (F), gestating (G) and ovipositing (O) [20]. In the absence of intervention new adult mosquitoes are considered to be born into the emerged class at rate β and obey a constant natural death rate g. Dynamics can then be described using the following system of ordinary differential equations (ODEs):

$$\begin{aligned}
\frac{dB}{dt} &= \beta(1-\theta) + \pi_1 O - \pi_2(q_1+q_2)B - gB && (1)\\
\frac{dF}{dt} &= \pi_2 q_1 B - \pi_3 F - gF && (2)\\
\frac{dG}{dt} &= \pi_3(1-q_3)F - \pi_4 G - gG && (3)\\
\frac{dO}{dt} &= \pi_4 G - \pi_1 O - gO\,, && (4)
\end{aligned}$$

where π_2 represents the baseline rate of feeding and moving from blood-seeking to fed; π_i, $i = 1, 3, 4$, denote the movement between the other states. The parameters π_i for $i = 1, ..., 4$ are chosen to give a 3 day feeding cycle length with 0.68 day mean blood-seeking duration [40]. Lardeux et al. observed a minimum 2 day period for gestation, matching up to an approximate 3 day gonotrophic cycle [41], hence the blood-seeking and gestating stages are assumed to take up the majority of the cycle duration (full details are specified Additional File 1). The magnitude of β is used to control the baseline transmission conditions.

Common notation uses d, s and r to represent the death, success and repelling ratios respectively, but here were use slightly different notation to facilitate ease of mathematical analysis in the results. q_1 and q_2 represent the probabilities of vector success or death, respectively, during a feeding attempt and q_3 is the probability a vector dies after feeding (due to IRS). When no vector control is in use $q_1 = 1$ and $q_2 = q_3 = 0$. We consider a successful feed to have occurred in any of three potential scenarios: biting indoors despite LLIN or IRS presence; biting indoors in the absence of LLINs or IRS; biting outdoors (taken to occur in proportion $1 - Q$, where Q is the probability of a blood meal being taken indoors) – including cattle. Death due to IRS is considered as an additional probability of not surviving between the fed and gestating classes, post feeding and potential transmission. The birth rate is multiplied by a scaling factor $(1 - \theta)$, where $\theta = \theta_0\hat{\theta}$ is a proportional population reduction due to larvicides; θ_0 is the coverage (i.e. proportion of larval sites treated) and $\hat{\theta}$ is the efficacy of the intervention, or proportional reduction in adult mosquitoes emerging from a treated larval site.

The values of q_i, $i = 1, ..., 3$ are given by the following equations, calculated using the feeding dynamics described by Figure 1,

$$\begin{aligned}
q_1 &= (1-Q) + Q\big(1-\gamma+\gamma\sigma_I\big)\big(1-\omega+\omega\sigma_L\big)\,, && (5)\\
q_2 &= Q\omega\nu_L\big(1-\gamma(1-\sigma_I)\big)\,, && (6)\\
q_3 &= Q\gamma\nu_I\,, && (7)
\end{aligned}$$

with ω and γ representing the coverage of LLINs and IRS respectively. σ_L and ν_L are the success and death probabilities of feeding in the presence of an LLIN, where $1-\sigma_L-\nu_L$ is the probability of repeating. σ_I is the probability of successfully feeding in the presence of IRS, where $1-\sigma_I$ is the probability of repeating, and ν_I is the probability of death during the Fed class immediately after exposure to IRS. Values of all parameters are given in Additional File 1: Section 1, Tables S2 and S3.

Age structure

To gain insight into the age-structure of the vector population we consider a generational formulation of the gonotrophic cycle model, where a subscript i denotes the number of times mosquitoes in a given class have completed the cycle, giving an infinite series of ODEs:

$$\frac{dB_i}{dt} = \begin{cases} \beta(1-\theta) - \pi_2(q_1+q_2)B_i - gB_i & \text{if } i=0 \\ \pi_1 O_{i-1} - \pi_2(q_1+q_2)B_i - gB_i & \text{if } i \geq 1 \end{cases} \tag{8}$$

$$\frac{dF_i}{dt} = \pi_2 q_1 B_i - \pi_3 F_i - gF_i \tag{9}$$

$$\frac{dG_i}{dt} = \pi_3(1-q_3)F_i - \pi_4 G_i - gG_i \tag{10}$$

$$\frac{dO_i}{dt} = \pi_4 G_i - \pi_1 O_i - gO_i\,. \tag{11}$$

Births can only occur into generation $i=0$ and vectors are assumed to survive up to a maximum of 10 gonotrophic cycles [42]. Using this model it is possible to calculate the parity of the population.

A frequently used assumption in modelling vector borne diseases is that the vector population is at equilibrium if vector control in a given setting is fixed, as the vector dynamics are faster than the human dynamics. We can hence derive the following relationship between sequential blood-seeking classes:

$$B_i^* = KB_{i-1}^*\,, \tag{12}$$

where

$$K = \frac{\pi_1\pi_2\pi_3\pi_4 q_1(1-q_3)}{(\pi_2(q_1+q_2)+g)(\pi_3+g)(\pi_4+g)(\pi_1+g)} \tag{13}$$

is a constant and $K<1$ as at equilibrium each generation will be smaller than the previous younger generation, with the newly emerged generation being the largest. This quantity, K, can also be interpreted as the gonotrophic cycle survival probability, or the proportion of the vectors that are gravid (have had at least one bloodmeal). As the constant term is less than unity, the difference equation can be solved to get an explicit formula, $B_i^* = K^i B_0^*$, which can be used to calculate the number of vectors in each feeding generation for initial conditions

$$B_0 = \frac{\beta(1-\theta)}{\pi_2(q_1+q_2)+g}\,. \tag{14}$$

The proportion of the population that have completed at least one feeding cycle (are parous) is given by

$$1 - \frac{B_0}{\sum_i B_i}\,. \tag{15}$$

Vector infection model

We consider a standard SEI model for the vector population with three disease states: susceptible (S), exposed (Y) and infectious (Z). Extending the ODE model (as in Eqns 1-4) to include disease requires sub-dividing each stage of the cycle into these three states, giving a new system of twelve ODEs for each generation, i. We assume births only occur in the susceptible population and in generation $i = 0$. Assuming a prevalence x in the human population and a probability c that a vector becomes infected after biting an infectious human, then a proportion xc of susceptible vectors moving from blood-seeking to fed become exposed to disease; all exposed mosquitoes can become infected, this occurs at rate $1/v$ where v is the average vector incubation period. Due to timescales of infection and vector lifespan we do not consider recovery from infection. See Fig. 2 for a diagram of the full model dynamics and Additional File 1: Section 2, Table S3, for the disease parameter values used.

As the host dynamics are slow in comparison to the vector dynamics, we assume that for any change in host prevalence the vector population reaches equilibrium in negligible time. Hence we can use the equilibrium state of the model as an approximation for the age and disease distributions for any given human prevalence and use these to calculate transmission measures commonly used in vector-borne disease epidemiology, such as the entomological incoluation rate (EIR), which can be estimated using field data [43, 44].

Entomological innoculation rate (EIR)

The entomological inoculation rate (EIR), E, is the expected number of infectious bites received by a single host across a defined time period, described by

$$E = maz\,, \tag{16}$$

where m is the ratio of mosquitoes to humans, a is the blood feeding rate on humans, and z is the fractional prevalence of infectious vectors.

Vectorial capacity

Vectorial capacity, V, denotes the total number of infectious bites that would eventually arise from all the mosquitoes that bite a single infectious human on a single day [45].

$$V = \frac{ma^2p^v}{-\ln(p)} = \frac{ma^2}{g}e^{-gv}\,, \tag{17}$$

where p is the vector daily survival probability and v is the extrinsic incubation period in the vector. Alternatively, g is the instantaneous vector death rate.

Basic reproductive number

From the vectorial capacity we can derive the basic reproductive number, R_0, for vector borne diseases. This differs from the usual interpretation of R_0 for non-vector diseases by focusing on the vector dynamics, describing the number of new infectious mosquitoes that would arise from a single infectious mosquito after one parasite generation [45].

$$R_0 = \frac{ma^2bc}{gr}e^{-gv} = \frac{ma^2bc}{-\ln(p)r}p^v = \frac{Vbc}{r}\,, \tag{18}$$

where b is the probability a bite from an infectious vector infects a human, c is the probability a bite on an infectious human infects a vector, and r is the human disease recovery rate. Under the assumption that these three parameters are approximately constant, R_0 is hence linearly proportional to vectorial capacity.

Vector control

Vector control interventions impact the vector population size, and hence the mosquito to human ratio, they also affect vector prevalence, feeding cycle length and death rate. Using our model to characterise these relationships for a range of coverages, we can directly calculate the aforementioned transmission measures in the presence of LLINs, IRS or larvicides, as well as any combination of the three (see Additional File 1: Section 3 for analytical derivations and functional forms).

Data describing the efficacy of different vector control interventions were taken from a range of sources, including a systematic review of IRS efficacy in Africa [46, 47, 48]. In this study we also vary the condition of LLINs, both in structural integrity [46] and insecticide waning effects (assuming a 2 year half-life [49]). We will consider IRS with pyrethroids in the primary instance, but also present some results for organophosphates as a comparison [48].

Results

The model derivation and analyses outlined above are the major focus of this paper, in particular the explicit quasi-equilibrium solution. We briefly present the impact of interventions and changes in vector dynamics on the age-structure of the vector population and the transmission of disease using these expressions. The model is presented here in the context of malaria, but could easily be extended to consider other mosquito-borne diseases by adjusting the disease-specific parameters.

As has been noted previously, both LLIN and IRS usage have a two-pronged effect on the vector population. Repelling vectors from feeding extends the blood-seeking phase, decreasing the frequency of blood meals per vector. In addition, the insecticidal effects also reduce the total population size by killing vectors either before (LLIN) or after (IRS) feeding. These effects both act to decrease the number of average blood meals per vector per lifetime, hence reducing the likelihood of successful contraction, incubation and transmission of disease. Considering the vector population structure, this manifests as a smaller total population with the age-distribution shifted towards the younger generations (Figure 3).

Conversely, larvicides work by targeting larval stages and hence reducing the adult emergence rate. This results in a reduction in overall population size, but doesn't impact the behaviour or habits of the vectors once they have developed to adulthood, or their individual transmission potential. Our model therefore predicts a linear impact on population size and vector prevalence and doesn't impact the shape of the generational distribution (also Figure 3).

LLINs mostly act by repelling or killing vectors pre-feeding, meaning the effect on R_c scales up faster with coverage than that of IRS, which mostly kills vectors post-feeding (Figure 4). The addition of larvicides to either of these measures reduces the coverage required to bring R_c below 1 (see Table). In particular, perfect (100%) coverage of pyrethroid-based IRS doesn't bring R_c below 1 unless implemented in combination with high coverage larvicidal usage.

Mid-ranges of LLIN coverage see the largest effect of reduced integrity on the effective reproductive ratio, R_c, a key measure of transmission (Figure 5: top). However, the difference between vector population size grows wider as coverage increases. Using larvicides at 50% coverage in combination with LLINs can mitigate most of these effects, with combined usage of poor condition (80 hole) LLINs and larvicides performing better than good condition (6 hole) LLINs used in isolation for low coverages of up to almost 30%.

Using larvicides with LLINs can also help to slow the effect of waning insecticidal efficacy on transmission over time by helping to keep the vector population size down (Figure 5: bottom). However, even at high coverages these reductions in efficacy may still undermine program outcomes if new LLINs are not distributed sufficiently frequently.

Discussion

The model developed here provides an easy-to-use analytical framework for investigating the complex interactions between vector control interventions, age-structured vector population dynamics and disease transmission. It could be extended in a number of ways, including further analysis of the impact of waning interventions, as demonstrated in Figure 5, or the increase of insecticidal resistance.

Our results demonstrate that LLINs and IRS are more effective than larvicidal interventions, and that the gap in utility increases with increasing coverage, but that larval control can still play an important role in maximising programme impact. The effect of LLINs and IRS is closely comparable at low coverage, but as coverage increases LLINs have an progressively larger impact than IRS on transmission. Additionally, in medium to high transmission settings the slower decrease in R_c with increasing IRS coverage is insufficient to break transmission, even for an unrealistic 100% coverage, if not acting in combination with other measures. Although our results suggest high levels of LLIN usage ($\geq$74%) could bring R_c below one in the scenario considered, heterogeneous biting patterns may undermine this effect [50]. Larvicides may therefore be able to play a role in sustaining, or even advancing, existing gains [51, 52], particularly in low transmission settings where incidence has been brought down artificially through other interventions.

The definitions of coverage used (percentage of individuals sleeping under LLINs, houses sprayed, or larval breeding sites treated) are difficult to compare across

interventions, particularly in terms of the associated costs and feasibility. It has been suggested that LLINs may require less effort to scale up coverage in the 40-80% coverage region [15], but coverage measures often exclude considerations of adherence. Additionally, we have only considered night biting mosquitoes in our analysis and in a setting with high proportions of day biting mosquitoes we would expect LLINs and IRS to have a reduced effect, whilst larvicidal impact should be mostly unchanged.

For larvicidal coverage it would be impossible to find and treat every breeding site if the area considered wasn't very small, and would require regular maintenance [47], meaning that achieving high coverage in the terms described here is likely to be difficult in practice, although there has been some progress in developing slow-release larvicides, with the potential for effects lasting closer to 6 months to a year [53]. Even if regular maintenance is required, larvicidal use can be instilled locally without reliance on large funders and the impact doesn't depend on population adherence or mosquito feeding behaviours, making it an attractive option for programmes looking for supplementary control measures.

We have made a number of additional assumptions about the mosquito biology, including that infection has no impact on vector fitness and that mortality remains constant with age (up to a maximum life span). This second assumption is consistent with current understanding of wild mosquito populations; although senescence is observed in laboratory mosquitoes, wild mosquitoes are expected to die long before they can exhibit any substantial deterioration with age [54]. Our current understanding of the first assumption is broadly inconclusive, with conflicting views and results across the literature [55].

Our model doesn't presently take account of seasonal changes in vector population sizes and behaviours, which is known to have a substantial effect on malaria transmission [56]. At lower temperatures both the extrinsic incubation period and gonotrophic cycle are expected to take longer, with our parameters reflecting temperatures of approximately 28°C or higher [41, 57]. For regions where temperatures drop below this level for a sustained period of time the extended incubation and cycle lengths should lead to reduced transmission, meaning our results are more reflective of high season transmission.

It is also important to remember that scale-ups in use of insecticides to combat transmission can result in wide-spread insecticide resistance and behavioral changes in sleeping conditions can lead to changes in biting behavior [58, 59, 37]. These factors have the potential to undermine progress made using vector control measures, and in particular evidence of this has been seen in a number of malaria control programs [60, 61, 62]. This is less of a problem for larvicidal interventions, which are less widely used and have a wider range of chemical and biological agents [63]. Settings where resistance has been observed or is feared may benefit from a combination of interventions, in particular larvicides could be used to accelerate gains and delay resistance by slowing the vector birth rate [52].

Conclusions

Whilst well-maintained adult-acting vector control measures are substantially more effective than larval-based interventions if used in isolation, incorporating larval control in existing LLIN or IRS programmes could substantially reduce transmission.

This would most benefit areas with low coverage or poor maintenance of interventions, or where insecticide resistance means that LLINs and IRS have reduced efficacy.

Additionally, the model framework developed here is adaptable to different species of mosquito and would be easily extended to consider a number of other mosquito-borne infections through a change of parameterisation. The utility of explicitly describing the impact of different interventions on the vector population size and structure could therefore assist with developing a greater understanding of vector ecology and epidemiology, which could be beneficial in developing future control measures and planning for the impact of insecticide resistance.

Abbreviations

Declarations

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Availability of data and materials
All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests
The authors declare that they have no competing interests.

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Authors' contributions
MJK and TDH devised the project and main conceptual ideas. MJK over saw the development of the model framework. ELD implemented the model and wrote the manuscript. All authors provided critical feedback and helped shape the research and analysis. All authors read and approved the final manuscript.

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References

1. Organization, W.H., et al.: World malaria report 2019 (2019)
2. RBM Partnership to End Malaria: 2 billion mosquito nets delivered worldwide since 2004. https://endmalaria.org/news/2-billion-mosquito-nets-delivered-worldwide-2004
3. Drakeley, C., Lines, J.: In for the long haul: 20 years of malaria surveillance. The Lancet infectious diseases **14**(6), 445–6 (2014)
4. Chen, I., Cooney, R., Feachem, R.G., Lal, A., Mpanju-Shumbusho, W.: The lancet commission on malaria eradication. The Lancet **391**(10130), 1556–1558 (2018)
5. Rosenthal, P.J., John, C.C., Rabinovich, N.R.: Malaria: How are we doing and how can we do better? The American journal of tropical medicine and hygiene **100**(2), 239 (2019)
6. Choi, L., Majambere, S., Wilson, A.L.: Larviciding to prevent malaria transmission. Cochrane Database of Systematic Reviews (8) (2019)
7. Choi, L., Pryce, J., Garner, P.: Indoor residual spraying for preventing malaria in communities using insecticide-treated nets. Cochrane Database of Systematic Reviews (5) (2019)
8. Ferguson, H.M., Dornhaus, A., Beeche, A., Borgemeister, C., Gottlieb, M., Mulla, M.S., Gimnig, J.E., Fish, D., Killeen, G.F.: Ecology: a prerequisite for malaria elimination and eradication. PLoS medicine **7**(8) (2010)
9. White, M.T., Griffin, J.T., Churcher, T.S., Ferguson, N.M., Basáñez, M.-G., Ghani, A.C.: Modelling the impact of vector control interventions on anopheles gambiae population dynamics. Parasites & vectors **4**(1), 153 (2011)

10. Sequeira, J., Louçã, J., Mendes, A.M., Lind, P.G.: Transition from endemic behavior to eradication of malaria due to combined drug therapies: An agent-model approach. Journal of Theoretical Biology **484**, 110030 (2020)
11. Bai, Z., Peng, R., Zhao, X.-Q.: A reaction–diffusion malaria model with seasonality and incubation period. Journal of mathematical biology **77**(1), 201–228 (2018)
12. Eckhoff, P.A.: A malaria transmission-directed model of mosquito life cycle and ecology. Malaria journal **10**(1), 303 (2011)
13. Macdonald, G., et al.: The epidemiology and control of malaria. The Epidemiology and Control of Malaria. (1957)
14. Killeen, G.F., Chitnis, N., Moore, S.J., Okumu, F.O.: Target product profile choices for intra-domiciliary malaria vector control pesticide products: repel or kill? Malaria journal **10**(1), 207 (2011)
15. Brady, O.J., Godfray, H.C.J., Tatem, A.J., Gething, P.W., Cohen, J.M., McKenzie, F.E., Perkins, T.A., Reiner, R.C., Tusting, L.S., Sinka, M.E., *et al.*: Vectorial capacity and vector control: reconsidering sensitivity to parameters for malaria elimination. Transactions of the Royal Society of Tropical Medicine and Hygiene **110**(2), 107–117 (2016)
16. Smith, D.L., Battle, K.E., Hay, S.I., Barker, C.M., Scott, T.W., McKenzie, F.E.: Ross, macdonald, and a theory for the dynamics and control of mosquito-transmitted pathogens. PLoS pathogens **8**(4) (2012)
17. Brady, O.J., Godfray, H.C.J., Tatem, A.J., Gething, P.W., Cohen, J.M., McKenzie, F.E., Alex Perkins, T., Reiner Jr, R.C., Tusting, L.S., Scott, T.W., *et al.*: Adult vector control, mosquito ecology and malaria transmission. International health **7**(2), 121–129 (2015)
18. Reiner Jr, R.C., Perkins, T.A., Barker, C.M., Niu, T., Chaves, L.F., Ellis, A.M., George, D.B., Le Menach, A., Pulliam, J.R., Bisanzio, D., *et al.*: A systematic review of mathematical models of mosquito-borne pathogen transmission: 1970–2010. Journal of The Royal Society Interface **10**(81), 20120921 (2013)
19. Ross, R.: Report on the Prevention of Malaria in Mauritius. Waterlow, ??? (1908)
20. Killeen, G.F., Govella, N.J., Lwetoijera, D.W., Okumu, F.O.: Most outdoor malaria transmission by behaviourally-resistant anopheles arabiensis is mediated by mosquitoes that have previously been inside houses. Malaria journal **15**(1), 225 (2016)
21. Le Menach, A., Takala, S., McKenzie, F.E., Perisse, A., Harris, A., Flahault, A., Smith, D.L.: An elaborated feeding cycle model for reductions in vectorial capacity of night-biting mosquitoes by insecticide-treated nets. Malaria journal **6**(1), 10 (2007)
22. Gu, W., Novak, R.J.: Predicting the impact of insecticide-treated bed nets on malaria transmission: the devil is in the detail. Malaria Journal **8**(1), 256 (2009)
23. Gu, W., Novak, R.J.: Habitat-based modeling of impacts of mosquito larval interventions on entomological inoculation rates, incidence, and prevalence of malaria. The American journal of tropical medicine and hygiene **73**(3), 546–552 (2005)
24. Smith, D.L., Hay, S.I., Noor, A.M., Snow, R.W.: Predicting changing malaria risk after expanded insecticide-treated net coverage in africa. Trends in parasitology **25**(11), 511–516 (2009)
25. Chitnis, N., Schapira, A., Smith, T., Steketee, R.: Comparing the effectiveness of malaria vector-control interventions through a mathematical model. The American journal of tropical medicine and hygiene **83**(2), 230–240 (2010)
26. Yakob, L., Yan, G.: Modeling the effects of integrating larval habitat source reduction and insecticide treated nets for malaria control. PloS one **4**(9) (2009)
27. Killeen, G.F., Knols, B.G., Gu, W.: Taking malaria transmission out of the bottle: implications of mosquito dispersal for vector-control interventions. The Lancet infectious diseases **3**(5), 297–303 (2003)
28. Smith, D.L., Dushoff, J., McKenzie, F.E.: The risk of a mosquito-borne infection in a heterogeneous environment. PLoS biology **2**(11), 368–368 (2004)
29. Worrall, E., Connor, S., Thomson, M.: A model to simulate the impact of timing, coverage and transmission intensity on the effectiveness of indoor residual spraying (irs) for malaria control. Tropical Medicine & International Health **12**(1), 75–88 (2007)
30. Griffin, J.T., Bhatt, S., Sinka, M.E., Gething, P.W., Lynch, M., Patouillard, E., Shutes, E., Newman, R.D., Alonso, P., Cibulskis, R.E., *et al.*: Potential for reduction of burden and local elimination of malaria by reducing Plasmodium falciparum malaria transmission: a mathematical modelling study. The Lancet Infectious Diseases **16**(4), 465–472 (2016)
31. Hancock, P.A., Godfray, H.C.J.: Application of the lumped age-class technique to studying the dynamics of malaria-mosquito-human interactions. Malaria journal **6**(1), 98 (2007)
32. Hethcote, H.W., Thieme, H.R.: Stability of the endemic equilibrium in epidemic models with subpopulations. Mathematical Biosciences **75**(2), 205–227 (1985)
33. Geisse, K.V., Butler, E.J.M., Cordovez, J.M.: Effects of natural acquired immunity in an age-structured malaria model. Technical report, Technical report, July (2012)
34. Rock, K., Wood, D., Keeling, M.: Age-and bite-structured models for vector-borne diseases. Epidemics **12**, 20–29 (2015)
35. Killeen, G.F., Smith, T.A., Ferguson, H.M., Mshinda, H., Abdulla, S., Lengeler, C., Kachur, S.P.: Preventing childhood malaria in africa by protecting adults from mosquitoes with insecticide-treated nets. PLoS medicine **4**(7) (2007)
36. Griffin, J.T., Hollingsworth, T.D., Okell, L.C., Churcher, T.S., White, M., Hinsley, W., Bousema, T., Drakeley, C.J., Ferguson, N.M., Basáñez, M.-G., et al.: Reducing plasmodium falciparum malaria transmission in africa: a model-based evaluation of intervention strategies. PLoS medicine **7**(8) (2010)
37. Churcher, T.S., Lissenden, N., Griffin, J.T., Worrall, E., Ranson, H.: The impact of pyrethroid resistance on the efficacy and effectiveness of bednets for malaria control in africa. Elife **5**, 16090 (2016)
38. Utzinger, J., Tozan, Y., Singer, B.H.: Efficacy and cost-effectiveness of environmental management for malaria control. Tropical Medicine & International Health **6**(9), 677–687 (2001)
39. Killeen, G.F., Fillinger, U., Knols, B.G.: Advantages of larval control for african malaria vectors: low mobility and behavioural responsiveness of immature mosquito stages allow high effective coverage. Malaria Journal

1(1), 8 (2002)
40. Killeen, G., McKenzie, F., Foy, B., Schieffelin, C., Billingsley, P., Beier, J.: 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 **62**(5), 535–544 (2000). doi:10.4269/ajtmh.2000.62.535
41. Lardeux, F.J., Tejerina, R.H., Quispe, V., Chavez, T.K.: A physiological time analysis of the duration of the gonotrophic cycle of Anopheles pseudopunctipennis and its implications for malaria transmission in Bolivia. Malaria journal **7**(1), 141 (2008)
42. Hughes, A., Lissenden, N., Viana, M., Toé, K.H., Ranson, H.: Anopheles gambiae populations from Burkina Faso show minimal delayed mortality after exposure to insecticide-treated nets. Parasites & vectors **13**(1), 17 (2020)
43. Kilama, M., Smith, D., Hutchinson, R., Kigozi, R., Yeka, A., Lavoy, G., Kamya, M., Staedke, S., Donnelly, M., Drakeley, C., *et al.*: Estimating the annual entomological inoculation rate for plasmodium falciparum transmitted by anopheles gambiae sl using three sampling methods in three sites in uganda. Malaria Journal **13**(1), 111 (2014)
44. Smith, D.L., Perkins, T.A., Reiner Jr, R.C., Barker, C.M., Niu, T., Chaves, L.F., Ellis, A.M., George, D.B., Le Menach, A., Pulliam, J.R., *et al.*: Recasting the theory of mosquito-borne pathogen transmission dynamics and control. Transactions of the Royal Society of Tropical Medicine and Hygiene **108**(4), 185–197 (2014)
45. Smith, D., Drakeley, C., Chiyaka, C., Hay, S.: A quantitative analysis of transmission efficiency versus intensity for malaria. Nature Communications **1**, 108 (2010)
46. Ngufor, C., N'Guessan, R., Boko, P., Odjo, A., Vigninou, E., Asidi, A., Akogbeto, M., Rowland, M.: Combining indoor residual spraying with chlorfenapyr and long-lasting insecticidal bed nets for improved control of pyrethroid-resistant anopheles gambiae: an experimental hut trial in benin. Malaria Journal **10**(1), 343 (2011)
47. Kroeger, A., Horstick, O., Riedl, C., Kaiser, A., Becker, N.: The potential for malaria control with the biological larvicide bacillus thuringiensis israelensis (bti) in peru and ecuador. Acta Tropica **60**(1), 47–57 (1995)
48. Sherrard-Smith, E., Griffin, J.T., Winskill, P., Corbel, V., Pennetier, C., Djénontin, A., Moore, S., Richardson, J.H., Müller, P., Edi, C., *et al.*: Systematic review of indoor residual spray efficacy and effectiveness against Plasmodium falciparum in Africa. Nature Communications **9**(1), 1–13 (2018)
49. Wanjala, C.L., Zhou, G., Mbugi, J., Simbauni, J., Afrane, Y.A., Ototo, E., Gesuge, M., Atieli, H., Githeko, A.K., Yan, G.: Insecticidal decay effects of long-lasting insecticide nets and indoor residual spraying on Anopheles gambiae and Anopheles arabiensis in Western Kenya. Parasites & Vectors **8**(1), 1–10 (2015)
50. Smith, D.L., McKenzie, F.E., Snow, R.W., Hay, S.I.: Revisiting the basic reproductive number for malaria and its implications for malaria control. PLoS Biol **5**(3), 42 (2007)
51. Derua, Y., Kahindi, S., Mosha, F., Kweka, E., Atieli, H., Zhou, G., Lee, M.-C., Githeko, A., Yan, G.: Susceptibility of anopheles gambiae complex mosquitoes to microbial larvicides in diverse ecological settings in western kenya. Medical and veterinary entomology **33**(2), 220–227 (2019)
52. Derua, Y.A., Kweka, E.J., Kisinza, W.N., Githeko, A.K., Mosha, F.W.: Bacterial larvicides used for malaria vector control in sub-saharan africa: review of their effectiveness and operational feasibility. Parasites & vectors **12**(1), 426 (2019)
53. Afrane, Y.A., Mweresa, N.G., Wanjala, C.L., Gilbreath III, T.M., Zhou, G., Lee, M.-C., Githeko, A.K., Yan, G.: Evaluation of long-lasting microbial larvicide for malaria vector control in kenya. Malaria journal **15**(1), 577 (2016)
54. Ryan, S., Ben-Horin, T., Johnson, L.: Malaria control and senescence: the importance of accounting for the pace and shape of aging in wild mosquitoes. Ecosphere **6**(9), 1–13 (2015)
55. Ferguson, H.M., Read, A.F.: Why is the effect of malaria parasites on mosquito survival still unresolved? Trends in parasitology **18**(6), 256–261 (2002)
56. Epopa, P.S., Collins, C.M., North, A., Millogo, A.A., Benedict, M.Q., Tripet, F., Diabate, A.: Seasonal malaria vector and transmission dynamics in western burkina faso. Malaria journal **18**(1), 113 (2019)
57. Ohm, J.R., Baldini, F., Barreaux, P., Lefevre, T., Lynch, P.A., Suh, E., Whitehead, S.A., Thomas, M.B.: Rethinking the extrinsic incubation period of malaria parasites. Parasites & vectors **11**(1), 1–9 (2018)
58. Fornadel, C., Norris, L., Glass, G., Norris, D.: Analysis of anopheles arabiensis blood feeding behavior in southern zambia during the two years after introduction of insecticide-treated bed nets. The American Journal of Tropical Medicine and Hygiene **83**(4), 848–853 (2010)
59. Weill, M., Lutfalla, G., Mogensen, K., Chandre, F., Berthomieu, A., Berticat, C., Pasteur, N., Philips, A., Fort, P., Raymond, M.: Comparative genomics: Insecticide resistance in mosquito vectors. Nature **423**(6936), 136 (2003)
60. Ranson, H., Lissenden, N.: Insecticide resistance in african anopheles mosquitoes: a worsening situation that needs urgent action to maintain malaria control. Trends in Parasitology **32**(3), 187–196 (2016)
61. Hemingway, J., Ranson, H., Magill, A., Kolaczinski, J., Fornadel, C., Gimnig, J., Coetzee, M., Simard, F., Roch, D., Hinzoumbe, C., *et al.*: Averting a malaria disaster: Will insecticide resistance derail malaria control? The Lancet **387**(10029), 1785–1788 (2016)
62. Toé, K., Jones, C., N'Fale, S., Ismail, H., Dabiré, R., Ranson, H.: Increased pyrethroid resistance in malaria vectors and decreased bed net effectiveness, burkina faso. Emerging Infectious Diseases **20**(10), 1691 (2014)
63. Dusfour, I., Vontas, J., David, J.-P., Weetman, D., Fonseca, D.M., Corbel, V., Raghavendra, K., Coulibaly, M.B., Martins, A.J., Kasai, S., et al.: Management of insecticide resistance in the major aedes vectors of arboviruses: Advances and challenges. PLoS neglected tropical diseases **13**(10) (2019)

Figures
Tables
Additional Files
Additional file 1
Additional file 1 contains further details on the parameterisation of the model and derivation of functional forms for the key transmission measures considered. Section 1 describes the data used to parameterise the gonotrophic cycle

Figure 1 Gonotrophic cycle with vector control. A schematic depicting the mosquito gonotrophic cycle model. In the model mosquitoes move from Blood-seeking (B), to Fed (F), to Gestating (G), to Ovipositing (O) and back to Blood-seeking. Larvicide usage impacts the emergence, or birth, rate of adult mosquitoes and LLIN and IRS interactions take place between Blood-seeking and Fed.

Figure 2 SEI disease model in mosquitoes. A schematic depicting the SEI (susceptible, exposed, infectious) formulation of the disease model used. Upon successful feeding, mosquitoes become infected with probability p and enter the exposed class. Mosquitoes transition from exposed to infectious at rate $1/\nu$, where ν is the extrinsic incubation period of malaria.

Figure 3 Population age-distribution with disease. Bar plots showing the age-distribution of a vector population at equilibrium (total count, indexed by number of gonotrophic cycles completed) with a variety of vector control interventions (top row) and combinations (bottom). All interventions are assumed to have 50% coverage. Bars are coloured by the proportion of vectors in each cycle generation that are susceptible (green), exposed (yellow) and infectious (red) for malaria at 40% host prevalence. Vertical lines represent the mean (dashed) and median (dot-dashed) number of gonotrophic cycles a mosquito passes through before dying.

Figure 4 Reproductive ratio, R_c, by vector control method and coverage. Graphs showing the relationship between R_0 and coverage for the two adult-acting vector control interventions, with or without additional 50% coverage of larvicides: LLINs (solid, blue); LLINs and larvicides (dashed, yellow); IRS (dotted, red); IRS and larvicides (dot-dashed, purple). Left: linear y-axis; Right: logarithmic y-axis. All results for a mid-to-high transmission setting ($R_0 = 60$).

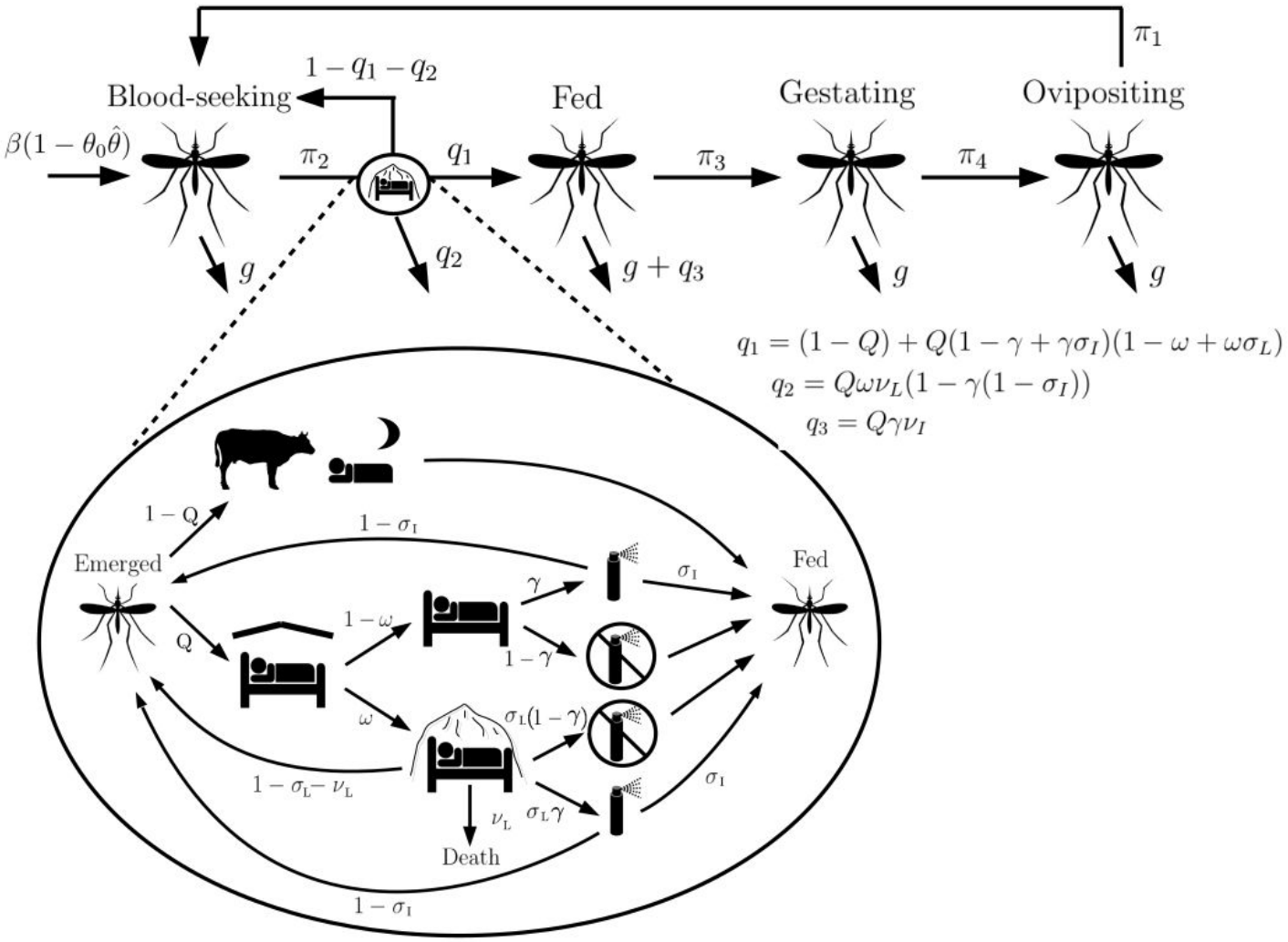
Figure 5 LLIN integrity and waning insecticidal effects. Top row: Graphs showing the relationship between R_c (left) and vector population size (right) and LLIN coverage for good condition nets (6 holes: solid, blue; 6 holes plus 50% larvicides: dashed, yellow) and poor condition nets (80 holes: dot-dashed, blue; 80 holes plus 50% larvicides: dotted, yellow). Bottom row: Graphs showing changes in R_c and vector population size over time due to waning insecticidal efficacy with an assumed half life of 2 years, for LLINs only (solid, blue) and LLINs with 50% larvicides (dashed, yellow). All results for a mid-to-high transmission setting ($R_0 = 60$).

Table 1 Vector control coverage combinations required to bring $R_c < 1$, for a setting where $R_0 = 60$. Larvicidal percentages reflect proportion of larval sites treated.

Larvicides	LLINs (6 holes)	LLINs (80 holes)	IRS (pyrethroids)	IRS (organophosphates)
None	74%	96%	NA	56%
50%	69%	91%	100%	51%
100%	61%	80%	84%	43%

model and vector control interventions. Section 2 describes the malaria-specific disease parameters used. Section 3 contains details on the derivation of the transmission measures (EIR, R_c, and vectorial capacity) under vector control interventions.

Figures



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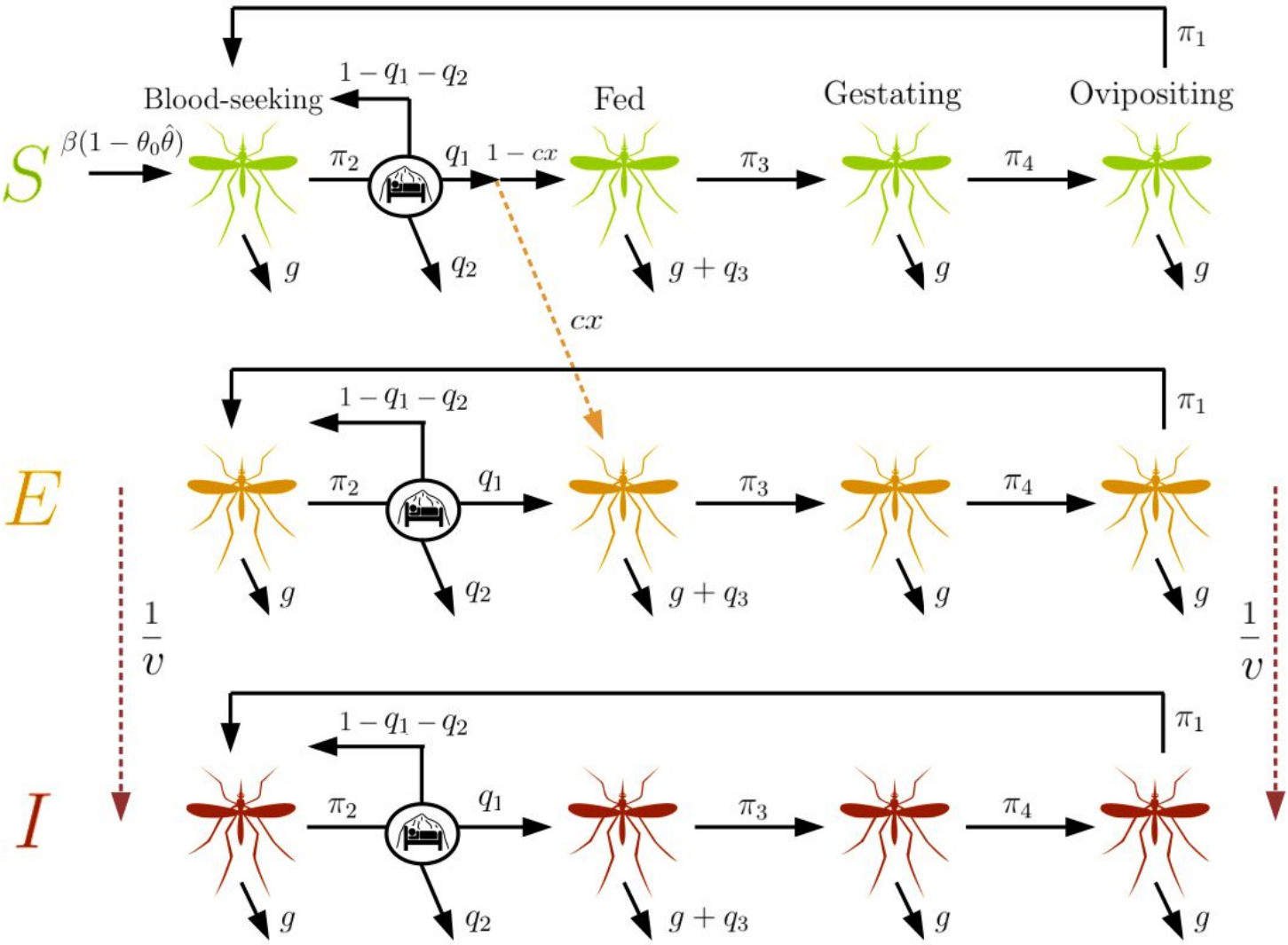

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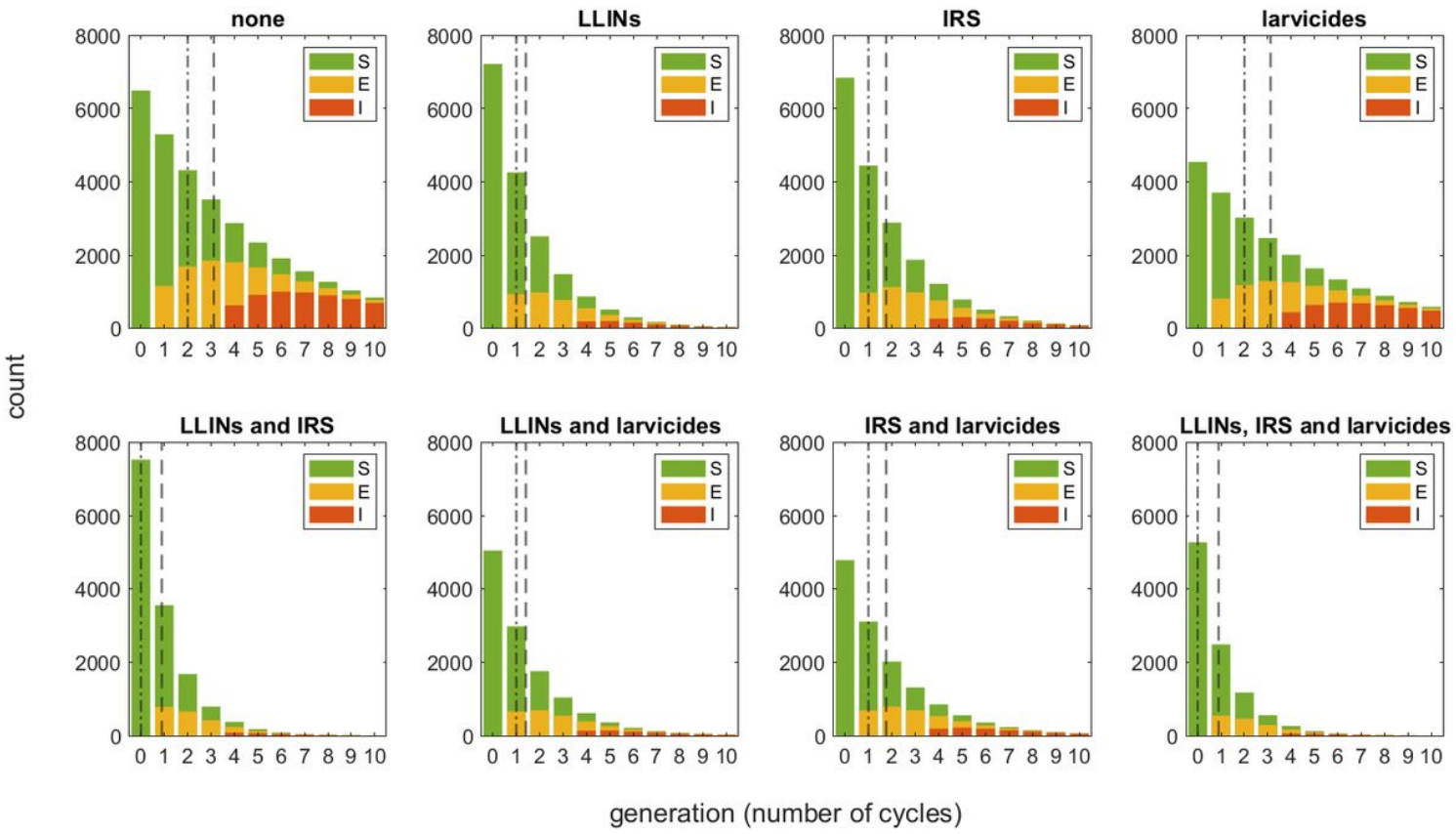

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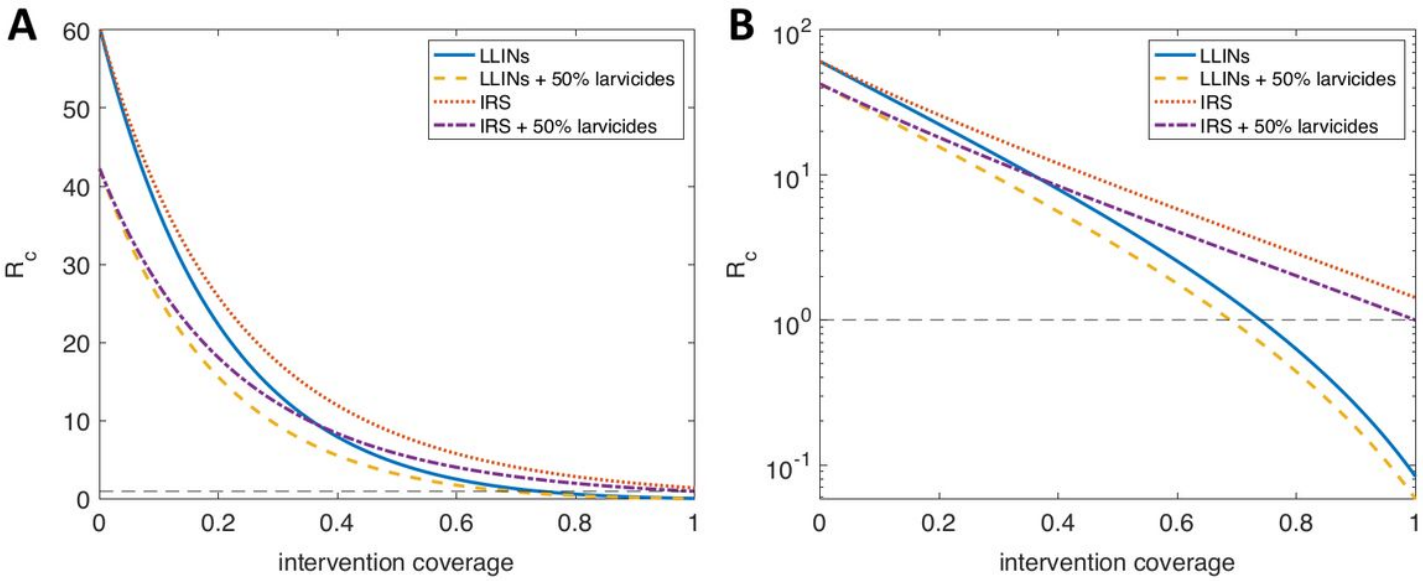

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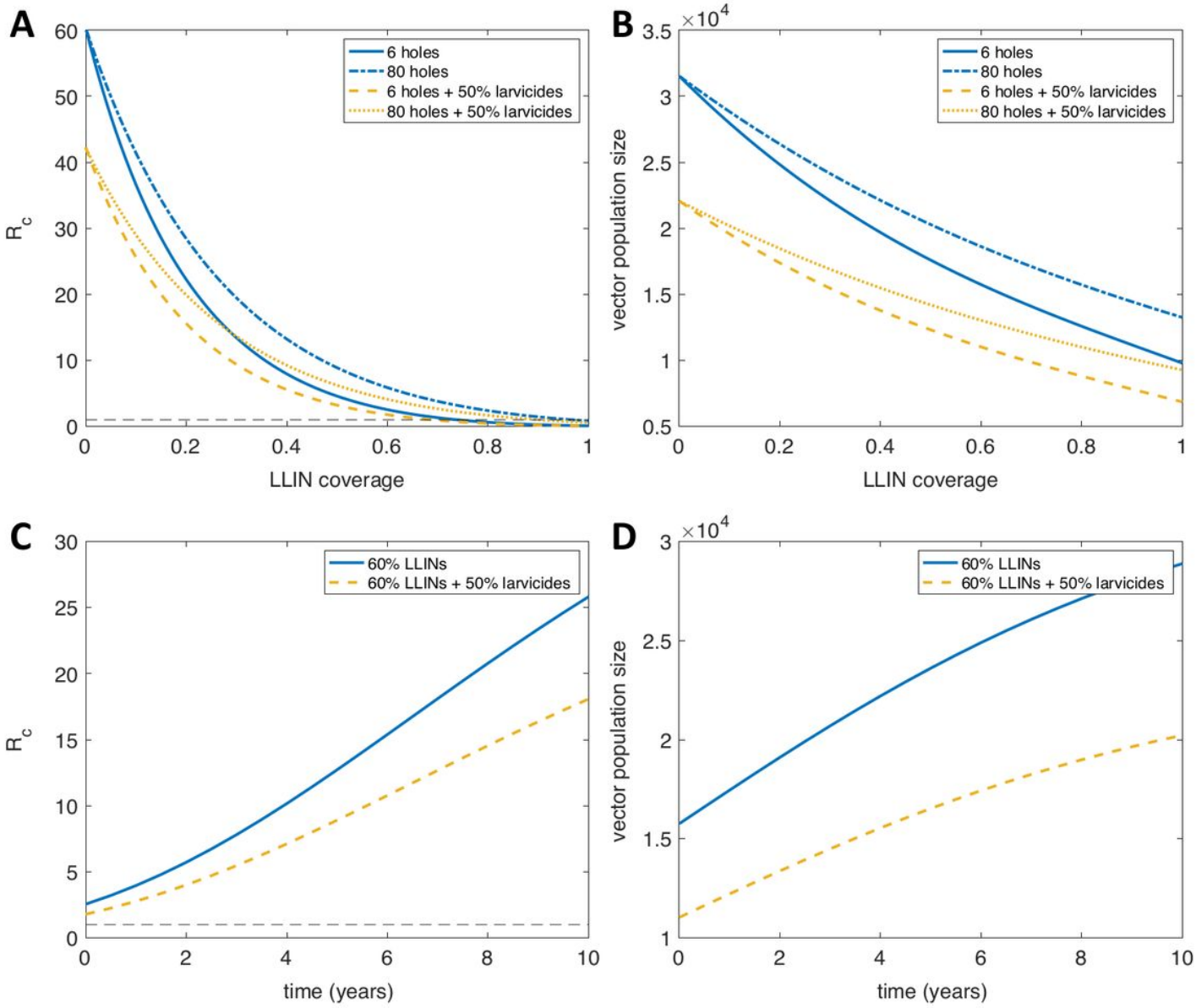

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Supplementary Files

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