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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 commonly used vector control methods on the age-structure of the vector population.

Results: We derive and analyse a novel model with 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, are highly effective at reducing transmission, particularly in comparison to larvicide usage at the same coverage. We also find that scaling up coverage results in a wider gap in transmission reduction between adult-active and larval-based interventions. For LLINs and IRS the effective reproductive ratio under control, R_c , decreases exponentially with coverage, whereas for larvicides the relationship is linear. We also find that mid-ranges of LLIN coverage see the largest effect of reduced net integrity on transmission.

Conclusions: Well-maintained, adult-acting vector control measures are substantially more effective than larval-based action at reducing the transmission potential of the mosquito population, particularly at medium to high coverage levels.

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.

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.

The 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 [6, 7].

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 [8, 9], whereas models that focus on vector dynamics often do not include transmission [7, 10]. Few previous modelling efforts have combined changes in vector population measures, such as abundance and age-structure, with the resulting impact on transmission [11].

By constructing an age-structured mosquito population model that also includes mosquito infection status, we aim to address this knowledge gap. In particular, we investigate 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 [12].

Early models of malaria incorporated the mosquito population size, highlighting the importance of the vector to host ratio in determining transmission dynamics [13]. 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 [14]. Recent models have expanded this further to consider the stages of the feeding cycle [15, 16], 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 [17, 18, 19, 20, 21, 22, 23, 24]. 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 [11].

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) [25] and focusing on the age-structure of the host population [26, 27]. Partial differential equations (PDEs) have been used to consider adult mosquito age-structure within a transmission model, allowing continuous aging of the mosquito population [28], 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 [29], the increasing risk of insecticide resistance and questions around sustainability of interventions have prompted discussions on the best strategy [30, 31]. LLINs are the most commonly used measure, but there is also wide-spread usage of IRS and other insecticidal spraying method. Larvicidal methods are often seen as practically more challenging to implement [32], but it has previously been suggested that it may be easier to target spatially-confined larval stages than their highly mobile adult counterparts [30] and that using multiple interventions at different stages of the life-cycle could give improved results [7]. As such, there is a need for detailed analysis of the relative benefits of different vector control methods to inform future decision, in particular modelling can provide insights into whether it is worth exploring larvicidal options further through exhaustive and expensive field-based studies.

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) [15]. 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):

$$\frac{dB}{dt} = \beta(1 - \theta) + \pi_1 O - \pi_2(q_1 + q_2)E - gE \quad (1)$$

$$\frac{dF}{dt} = \pi_2 q_1 B - \pi_3 F - gF \quad (2)$$

$$\frac{dG}{dt} = \pi_3(1 - q_3)F - \pi_4 G - gG \quad (3)$$

$$\frac{dO}{dt} = \pi_4 G - \pi_1 O - gO, \quad (4)$$

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 magnitude

of β has little bearing on most results as we will generally focus on vector infection prevalence and relative population changes, but it could be chosen to fit a required population size. Similarly π_i , $i = 1, \dots, 4$ are chosen such that feeding (moving from blood-seeking to fed) is faster than the other transitions; relative values are dependent on the choice of cycle length.

Common notation uses d , s and r to represent the death, success and repelling ratios respectively, but here we 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 , $i = 1, \dots, 3$ are given by the following equations, calculated using the feeding dynamics described by Figure 1,

$$q_1 = (1 - Q) + Q(1 - \gamma + \gamma\sigma_I)(1 - \omega + \omega\sigma_L), \quad (5)$$

$$q_2 = Q\omega\nu_L(1 - \gamma(1 - \sigma_I)), \quad (6)$$

$$q_3 = Q\gamma\nu_I, \quad (7)$$

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:

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

$$\frac{dF_i}{dt} = \pi_2 p_1 B_i - \pi_3 F_i - (g + \gamma)F_i \quad (9)$$

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

$$\frac{dO_i}{dt} = \pi_4 G_i - \pi_1 O_i - gO_i. \quad (11)$$

Births can only occur into generation $i = 0$. Using this model it is possible to calculate the parity of the population.

A frequently used assumption in modelling vector borne diseases to assume 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:

$$B_n^* = K B_{n-1}^*, \quad (12)$$

where

$$K = \frac{\pi_1 \pi_2 \pi_3 \pi_4 q_1}{(\pi_2(q_1 + q_2) + g)(\pi_3 + g + \gamma)(\pi_4 + g)(\pi_1 + g)} \quad (13)$$

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, $B_n^* = K^n B_0^*$, which can be used to calculate the number of vectors in each feeding generation for initial conditions

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

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

$$1 - \frac{B_0}{\sum_i B_i}. \quad (15)$$

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 inoculation rate (EIR), which can be estimated using field data [33, 34].

Entomological inoculation 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

$$E = maz, \quad (16)$$

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 [35].

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

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 [35].

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

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.

Under 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).

Results

The model derivation and analyses outlined above is 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 predicts a linear impact on population size and vector prevalence and doesn't impact the shape of the generational distribution (also Figure 3).

The dual effect of killing and transmission prevention caused by adult-acting interventions, such as IRS or LLINs, scales up with coverage much faster than the population reduction method of larvicides. This translates to an exponential, rather than linear, decrease in the effective reproductive ratio under control with increasing coverage (Figure 4). This pattern is consistent across all transmission intensity settings considered ($R_0 = 3.2, 32, 96$) and it is possible to bring R_c below 1 using either IRS or LLINs in all scenarios (see Table). Perfect (100%) coverage of larvicides doesn't bring R_c below 1, even for the low intensity setting.

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). However, the difference between vector population size grows wider as coverage increases. Even at high coverages this type of reduction in efficacy may still undermine program outcomes if R_c is close to 1 and 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 predicting 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 dramatically with increasing coverage. Analysis of the population age-distribution under the various control measures showed that this is due to the dual effect of population reduction and biting

prevention, resulting in far fewer infectious mosquitoes in the population. The effect of LLINs and IRS is closely comparable at low to medium coverage, but as coverage increases above 70% LLINs have an progressively larger impact than IRS on transmission. Additionally, in medium to high transmission settings the linear decrease in R_c with increasing larvicidal coverage is insufficient to break transmission if not acting in combination with other measures. In low transmission settings, particularly those where transmission has been brought down artificially through other interventions, larvicides may still be able to play a role in sustaining gains [36, 37].

The definition of coverage used (percentage of individuals sleeping under bednets, houses sprayed, or larval breeding sites treated) is difficult to compare across interventions, particularly in terms of the associated costs and feasibilities, as well as adherence measures for LLINs. 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 throughout a year [38], meaning that achieving high coverage in the terms described here is unrealistic. As coverage of LLINs and IRS is easier to quantify, achieve and maintain, this exacerbates the comparably poor utility of larvicidal methods. However, 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 less effect. There have also recently been some progress in developing slow-release larvicides, with the potential for effects lasting closer to 6 months to a year [39].

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. 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 [40]. Our current understanding the first assumption is broadly inconclusive, with conflicting views and results across the literature [41].

Our current model doesn't take account of seasonal changes in vector population sizes and behaviours, which is known to have a substantial effect on malaria transmission [42]. However, as the relative benefit of the three measures is independent of vector population size, our comparisons remain valid. Potentially a low transmission season may mean that intervention efficacy and adherence would be less important during that period, meaning resources could be focused on periods of high 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 [43, 44]. 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 [45, 46, 47]. This is less of a problem for larvicidal interventions, which are less widely used and have a wider range of chemical and biological agents [48]. 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 [37].

Conclusions

If well-maintained, adult-acting vector control measures are substantially more effective than larval-based action at reducing the transmission potential of the mosquito population, particularly at medium to high coverage. However, the increasing emergence of insecticide resistance means that it is important to continue investigating new interventions. Larvicides could still be useful as a supplement to other control measures, or in areas where insecticide resistance means that LLINs and IRS have reduced efficacy, but would be insufficient to control transmission if used in isolation in the majority of settings.

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
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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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Figures

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 combinations of vector control interventions. 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.

Figure 4 Reproductive ratio, R_0 , by vector control method and coverage. Graphs showing the relationship between R_0 and coverage for the three main vector control interventions: LLINs (solid), IRS (dashed) and larvicides (dot-dashed). Low (green), medium (blue) and high (red) transmission scenarios are presented. Left: linear y-axis; Right: logarithmic y-axis.

Figure 5 LLIN integrity comparisons. Graphs showing the relationship between R_c (left) and population size (right) and LLIN coverage. Lines represent good condition (6 holes, solid) and poor condition (80 holes, dashed) for a mid-to-high estimate of $R_0 = 65$.

Table 1 Vector control coverage required to bring $R_c < 1$, by transmission intensity

	High ($R_0 = 96$)	Medium ($R_0 = 32$)	Low ($R_0 = 3.2$)
LLINs	88%	63%	21%
IRS	90%	67%	20%

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 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.