trying to get line numbers working

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Seems that the header-includes bit above does work to add line numbers and double space (although it does generate a few warning messages)

##### Background

Insecticide resistance threatens the control of vectors and particularly malaria. New insecticides are being developed to address this. Potential strategies for using new insecticides include mixtures, sequences and rotations and there are recommendations for how best to implement these to manage resistance. There is, however, limited recent, accessible modelling work addressing the evolution of resistance under different operational strategies. Previous work concludes that preferred strategies will be situation specific. There is potential to improve the level of mechanistic understanding within the operational community of how insecticide resistance can be expected to evolve in response to different strategies.

This paper develops an accessible, mechanistic picture of how the evolution of insecticide resistance is likely to respond to potential intervention strategies to help guide both management and policy. The aim is to reach an audience unlikely to read a more detailed modelling paper. We use our model to develop a mechanistic understanding of how insecticide resistance is expected to increase with the use of insecticides in isolation, sequence and mixtures. The model flexibly represents two independent genes coding for resistance to two insecticides. We look principally at the ability of the insecticides to kill susceptible mosquitoes, how much resistance counteracts this, the proportion of mosquitoes that are exposed to insecticides and costs of resistance.

##### Results

We use the model to demonstrate the evolution of resistance under different inputs and how this fits with intuitive reasoning about the selection pressure exerted by insecticides. We show that an insecticide used in a mixture, relative to alone, always prompts slower evolution of resistance, but resistance to the two insecticides may evolve more slowly when used in sequence. We show that the ability of insecticides to kill susceptible mosquitoes (effectiveness), has the most influence on whether resistance to two insecticides is likely to arise faster in a mixture or sequence.

##### Conclusions

Our model makes more open the process of insecticide resistance evolution and how it is likely to respond to insecticide use. We provide a simple user-interface allowing further exploration (<https://andysouth.shinyapps.io/MixSeqResist1>). These tools can contribute to operational decisions in insecticide resistance management.

## Keywords

insecticide resistance; public health; mosquitoes; vector-borne diseases; infectious diseases; malaria; population genetics

## Background

Insecticide resistance is a problem for malaria [1][2][3] other vector borne diseases [4] and agriculture [5]. Malaria alone still results in hundreds of thousands of deaths per year. Recent malaria control efforts have centred on treated bed nets and indoor residual spraying, both reliant on insecticides. Treated nets were recently estimated to contribute 68% and indoor residual spraying 13% to averting more than 500 million falciparum malaria cases between 2000 and 2015 [6]. A recent malaria transmission model [7] predicts that even low pyrethroid resistance is likely to increase malaria incidence in Africa by reducing the performance of bed nets.

The WHO produced a Global Plan for Insecticide Resistance Management in malaria vectors (GPIRM)[1] which includes recommendations on operational strategies for managing resistance including the use of insecticide mixtures when they become available. Efforts are under way to develop new insecticides that will be effective in the light of existing resistance and allow additional options within insecticide resistance management. The Innovative Vector Control Consortium (IVCC) was set up in 2005 to develop new vector control tools and particularly new insecticides to address insecticide resistance in malaria transmitting mosquitoes [8][9]. Three new insecticides are now in development [9] and likely to be available around 2020 [2]. It is important that decisions about how best to use the new insecticides to delay the onset of resistance are made before insecticides are released [3].

Modelling studies have investigated the evolution of insecticide resistance in insecticide mixtures including in a public health context e.g. [10][11][12] but much of the work was done more than 20 years ago and there remained some confusion about the results [13]. In an earlier paper [13] we described the technical details of a flexible model used to investigate the relative benefits of mixtures and sequences. Here we provide an accessible summary of the model and use selected parameter values to describe mechanistically how the evolution of resistance is influenced by different inputs. This mechanistic understanding can contribute to the debate on the relative merits of different insecticide strategies extending existing frameworks [12][4][5][1].

My working plot.

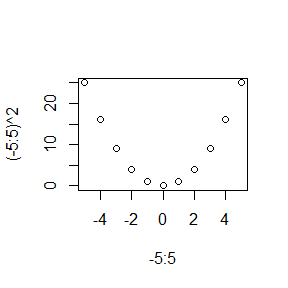


Figure 1: A smiley face because I work.

**Table 2. Effect of inputs on resistance when insecticides used singly or in sequence**

|  |  |  |
| --- | --- | --- |
| Parameter to increase | effect on resistance evolution | Mechanism |
| 1. Effectiveness | faster | reduced fitness of SS in presence of insecticide |
| 2. Exposure | faster | reduced fitness of SS overall |
| 3. Dominance of restoration | faster | increased fitness of SR in presence of insecticide |
| 4. Resistance restoration | faster | increased fitness of RR in presence of insecticide |
| 5. Frequency | faster | less change needed to reach resistance threshold |
| 6. Cost of resistance | slower | reduced fitness of RR in absence of insecticide |

**Table 3. Effect of inputs on resistance when insecticides used in a mixture**

|  |  |  |
| --- | --- | --- |
| Parameter to increase | effect on resistance evolution | Mechanism |
| 1. Effectiveness | **slower** | one insecticide reduces the fitness of individuals resistant to the other thereby reducing selection pressure from the other |
| 2. Exposure | faster (but less than for single) | reduced fitness of individuals susceptible to one insecticide increases selection pressure for that resistance. However at the same time selection pressure is reduced by reduced fitness of resistant individuals caused by the other insecticide |
| 3. Dominance of restoration | faster | increased fitness of heterozygotes |
| 4. Resistance restoration | faster | increased fitness of resistants |
| 5. Frequency | faster | less change needed to reach resistance threshold |
| 6. Cost of resistance | slower | reduced fitness of resistants in absence of insecticide |

**Table 4. Effect of inputs on the difference between mixture and sequential use**

|  |  |  |
| --- | --- | --- |
| Parameter to increase | increase favours mix or sequence | Mechanism |
| 1. Effectiveness | mixture | Higher effectiveness gives faster resistance for sequence and slower resistance in mixture |
| 2. Exposure | sequence | Higher exposure gives faster resistance for sequence and mixture but the greater effect on mixture favours sequence. |
| 3. Dominance of restoration | neither | Higher dominance gives faster resistance in both sequences and mixtures such that the difference between them is not changed. |
| 4. Resistance restoration | neither | As for dominance of restoration. Higher resistance restoration gives faster resistance in both sequences and mixtures such that the difference between them is not changed. |
| 5. Frequency | neither | As for dominance and resistance restoration. Higher starting frequencies give faster resistance in both sequences and mixtures such that the difference between them is not changed. |
| 6. Cost of resistance | mixture | Higher costs slow the evolution of resistance more in a mixture than when used in sequence (but with higher costs in a sequence there is a greater chance for resistance levels to decline for the insecticide not being used). |

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