Insecticide rotations delay evolution of resistance in a minority of model runs when compared to sequential use.

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## Abstract

Insecticide resistance threatens the control of the vectors of dangerous diseases including malaria, dengue and zika. Recent increases in insecticide resistance in public health are an evolutionary process caused by sustained exposure of insect populations to a small number of available insecticides. Resistance is a particular problem in public health as compared to agriculture because insecticides need to be longer lasting to provide affordable protection and there are fewer available active ingredients. Efforts to limit the development of insecticide resistance are grouped under the term Insecticide Resistance Management (IRM). The main strategies advocated to reduce the development of resistance are 1) rotations, 2) sequences, 3) mixtures and 4) mosaics. Rotations regularly switch between the use of different insecticides with a short time step (one or a few years) irrespective of resistance levels. Sequences, in contrast, switch from one insecticide to another only when resistance levels have reached a critical, defined threshold usually over a longer timescale.

Rotations are often advocated as one of the best options for limiting the development of resistance.

Testing different IRM strategies in the field is difficult and there has been little recent modelling work on insecticide rotations.

In this paper a model is described allowing rotations and sequences to be compared in terms of their effect on the evolution of insecticide resistance. The model is used to develop a mechanistic understanding of when and why insecticide resistance is likely to evolve faster with rotations or sequences.

The results suggest that under more likely circumstances than not the evolution of insecticide resistance will reach resistance thresholds at very similar times for rotations and sequences.

However under a less common, but still plausible, set of circumstances there are predicted to be large adavnatages to using a rotations as compared to a sequence.

The advantages to a rotation only occur when there are costs of resistance or dispersal from untreated areas, and there is high dominance of cost and low dominance of selection.

The mechanisms for these results are explained.

Other operational factors will favour rotations or sequences aside from the implications for the evolution of resistance. Developing an understanding of the evolutionary implications allows a more explicit consideration of these other factors on their own merits.

## Introduction

Despite much field and modelling work on the evolution of resistance under different insecticide or drug strategies [1] there is a small evidence base to support decisions about the use of insecticides in public health [2].

Rotations are advocated as one of the most favoured approaches for Insecticide Resistance Management (IRM)[3].

Here a modern modelling approach is described to allow an assessment of the potential benefits, in terms of the evolution of resistance, of rotations over sequences.

## Methods

A population genetic model was developed simulating changes over time in the frequencies of resistant and susceptible alleles in response to fitness differences. The model uses a similar approach to that described in [4] to compare insecticide mixtures and sequences. The implementation is simpler here because for rotations and sequences there is only a need to follow one insecticide at a time. The simpler implementation allows the model to be run for an unlimited number of insecticides. The algebra behind the model is described in the supplementary information.

Sequences : one insecticide is used until resistance threshold frequency (0.5 in this case) is reached, then switch to new insecticide. Rotations : use insecticide for set time, switch to other.

In both cases continue until no more insecticides below the resistance threshold remain.

Within the model inputs effect fitness as shown in Figure 1, differences in fitness lead to the changes in allele frequencies over time.

The model was run under four main scenarios : 1. no resistance fitness costs or dispersal link to untreated areas 2. fitness costs of resistance added 3. dispersal link to untreated areas (no costs) 4. costs and dispersal

To generate a decline in resistance over time when an insecticide is not being used either fitness costs or a dispersal link to an untreated area are required.

#### Assessing relative performance of insecticide use strategies

It is necessary to choose a measure to quantify the performance of an insecticide-use strategy and enable comparison with an alternative. For this we summed the number of generations when an insecticide was deployed and the resistance allele frequency for that insecticide was below 0.5. This allowed comparison between strategies using a variable number of insecticides. Previously time-to-resistance, namely the number of generations it takes to reach a defined resistance threshold (usually a resistance allele frequency of 0.5), was used. Using time-to-resistance worked when considering just two insecticides, but when the number of insecticides is a variable it is not sufficient.

## Results

#### Results1. no resistance fitness costs or dispersal from untreated refugia

When there are no resistance fitness costs or dispersal links to untreated refugia resistance frequencies do not decline when an insecticide is not in use. Thus for sequences once resistance thresholds are reached the resistance frequencies remain at that level and the insecticide cannot be re-used. For rotations resistance frequencies step upwards when insecticides are in use and remain at a plateau when they are not.

When there were no costs or dispersal there was no difference between rotations and sequences in the number of generations below the resistance threshold.

#### Results2. fitness costs of resistance added

With fitness costs included 67% of model runs, similar to those in the previous section, gave no difference between rotations and sequences in the number of generations below the resistance threshold.

In contrast to the previous section 7% of model runs generated an advantage of greater than 20% for rotations over sequences.

#### Results3. dispersal from untreated refugia added

## Discussion

Comparing time below resistance thresholds for rotations and sequences, the model shows :

1. rotations and sequences the same when no costs or dispersal
2. with resistance costs, 67% of runs still the same for rotations and sequences, but 7% of runs have > 20% advantage for rotations
3. with dispersal, ...

In very rare circumstances rotations can lead to the resistance frequencies for a group of insecticides being kept below resistance thresholds for a very long period of time (and substantially longer than for sequential use). Is it possible that these rare circumstances where parameter values are 'just-right' could be implemented operationally ?

### Caveats

The model does not (although it could) include the potential effects of modifier genes ameliorating the costs of resistance alleles. It has been suggested that rotations could be favoured as a strategy because they keep resistance frequences lower and restrict selection pressure for modifier genes [3]. However, there is little evidence to support the existence of such modifier genes in insectide resistance []. Even with the existence of modifier genes it is unlikely that they would provide much of an advantage to rotations in the scenarios we describe. In the modelled scenarios the use of an insecticide is stopped when the resistance frequency for that insecticide reaches 0.5. Thus in all scenarios resistance frequencies do not remain at high levels for long. In this situation it seems unlikely that modifiers would be selected for.

### Conclusions

In their effect on the evolution of insecticide resistance, rotations and sequences are most often the same. Infrequently, in less than 10% of model runs set between plausible limits, there are substantial benefits to the rotation strategy over a sequence. There was naver a substantial benefit of a sequence over a rotation. Whether or not insecticide rotations are predicted to offer sizeable benefits over sequences is dependent on coarse and fine scale issues about the nature of insecticide resistance that are yet to be agreed upon. The model shows that resistance costs and/or dispersal from untreated refugia are necessary to provide an evolutionary advantage to rotations. However even when these requirements are satisfied particular combinations of inputs are required to generate the advantage of rotations.

The model only compares rotations and sequences in terms of their effect on the evolution of resistance. There are other operational reasons for why a sequence or a rotation may be favoured.

## TODO

*try to come up with brief name for model output to make it easier to refer to it later*

## Figures

Figure 1. Comparing the increase in resistance frequencies over time for a rotation and a sequence when there no resistance fitness costs or dispersal from untreated refugia. The upper plot shows a rotation with a regular interval and the lower plot a sequence when the insecticide is changed when a resistance threshold of 0.5 is reached. In this example the rotation and the sequence are stopped at the same time. For the sequence the resistance frequency for each insecticide increases to reach the threshold in one step and that insecticide cannot be used again. For the rotation the resistance frequency for each insecticide increases in shorter steps while it is in use and remains at the constant level while not. There are three insecticides, the resistance frequency for each is shown in the sub-plots, and the shaded boxes within each sub-plot show when that insecticide was in use. The simulation is stopped when there are no remaining insecticides for which the resistance frequency is below the threshold. All other inputs are kept constant between the rotation and the sequence.

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Figure 2. Comparing the increase in resistance frequencies over time for a rotation and a sequence when there are resistance fitness costs. The upper plot shows a rotation with a regular interval and the lower plot a sequence when the insecticide is changed when a resistance threshold of 0.5 is reached. In this example the rotation lasts longer than the sequence. For the sequence the resistance frequency for each insecticide increases to reach the threshold in one step but in contrast to the previous figure resistance frequencies decline when the insecticide is not in use allowing it to be used again. For the rotation the resistance frequency for each insecticide increases in shorter steps while it is in use and similarly declines while not. There are three insecticides, the resistance frequency for each is shown in the sub-plots, and the shaded boxes within each sub-plot show when that insecticide was in use. The simulation is stopped when there are no remaining insecticides for which the resistance frequency is below the threshold. All other inputs are kept constant between the rotation and the sequence.

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Figure 3. Comparing the increase in resistance frequencies over time for a rotation and a sequence with dispersal from untreated refugia. The upper plot shows a rotation with a regular interval and the lower plot a sequence when the insecticide is changed when a resistance threshold of 0.5 is reached. In this example the rotation and the sequence last the same time. In both cases the resistance frequencies in the treated areas (red lines) increase when an insecticide is in use. Resistance frequencies in the untreated areas (blue lines) increase after those in the treated areas as a result of dispersal from the treated areas. When an insecticide stops being used the resistance frequency in the treated area declines due to dispersal from the untreated area. For the sequence the resistance frequency for each insecticide increases to reach the threshold in one step and consistent with the previous figure resistance frequencies decline when the insecticide is not in use allowing it to be used again. For the rotation the resistance frequency for each insecticide increases in shorter steps while it is in use and similarly declines while not. There are three insecticides, the resistance frequency for each is shown in the sub-plots, and the shaded boxes within each sub-plot show when that insecticide was in use. The simulation is stopped when there are no remaining insecticides for which the resistance frequency is below the threshold. All other inputs are kept constant between the rotation and the sequence.

Figure 3. Comparing the increase in resistance frequencies over time for a rotation and a sequence with dispersal from untreated refugia. The upper plot shows a rotation with a regular interval and the lower plot a sequence when the insecticide is changed when a resistance threshold of 0.5 is reached. In this example the rotation and the sequence last the same time. In both cases the resistance frequencies in the treated areas (red lines) increase when an insecticide is in use. Resistance frequencies in the untreated areas (blue lines) increase after those in the treated areas as a result of dispersal from the treated areas. When an insecticide stops being used the resistance frequency in the treated area declines due to dispersal from the untreated area. For the sequence the resistance frequency for each insecticide increases to reach the threshold in one step and consistent with the previous figure resistance frequencies decline when the insecticide is not in use allowing it to be used again. For the rotation the resistance frequency for each insecticide increases in shorter steps while it is in use and similarly declines while not. There are three insecticides, the resistance frequency for each is shown in the sub-plots, and the shaded boxes within each sub-plot show when that insecticide was in use. The simulation is stopped when there are no remaining insecticides for which the resistance frequency is below the threshold. All other inputs are kept constant between the rotation and the sequence.

Figure 4. Effect of cost and dispersal on the difference between rotations and sequences

Figure 4. Effect of cost and dispersal on the difference between rotations and sequences

Figure X. [todo need to modify caption from MJ paper, start by saying that only in left panel during application of the insecticide] The effect of model inputs on the fitness of genotypes for a single insecticide. Fitness is shown on the y-axis and the different genotypes (SS, SR, RR) on the x axis. Firstly the exposure input determines the proportion of the population in the left and right panels (exposed and not exposed). For those that are exposed (left panel) insecticide effectiveness sets the fitness for SS, resistance restoration 'restores' a portion of the fitness for RR and dominance of resistance determines how the fitness for SR lies between that of SS and RR. For those that are not exposed, fitness of SS is set to 1 by definition, resistance cost determines the fitness of RR and again dominance of cost determines how the fitness for SR sits between that of SS and RR. In this example effectiveness=0.8, resistance restoration=0.5 which 'restores' half of the fitness lost due to the insecticide, dominance of resistance=0.7 which sets the fitness of the SR closer to RR than SS. Resistance cost=0.3 which reduces fitness in the absence of the insecticide from 1 to 0.7, and dominance of cost=0.8 which sets fitness of SR close to RR.

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