Comparing evolution of insecticide resistance under insecticide rotations and sequential use.

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Here a few paragraphs and plots from an in-preparation manuscript comparing rotations and sequences in terms of the evolution of resistance predicted by a population genetics model. In the majority of cases across a wide parameter space the results predict similar outcomes for rotations and sequences. We did find rare model scenarios where there was a substantial benefit of rotations over sequences but this depended on one aspect of the model that we now think may not be realistic (it concerned what happened when resistance frequencies declined below starting levels due to costs of resistance). We are continuing to test the model to develop final scenarios to appear in the manuscript.

## Results

#### Results1. form of resistance evolution with and without costs and dispersal.

Example model runs are shown with no costs or dispersal (Fig 2), with just resistance costs (Fig 3) and with just dispersal from untreated refugia (Fig 4).

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 (Fig 2). 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. If the rotation interval is short enough then the insecticide can be used a few times before the resistance thresholds are reached.

When resistance costs are included (Fig 3), resistance allele frequencies decline in periods when the corresponding insecticide is not in use. Thus for sequences the decline can allow insectides to be returned to use later on because resistance has declined below threshold levels in contrast with the situation in Figure 2.

Adding representation of an untreated refugia and dispersal between it and the treated area also allows resistance allele frequencies to decline when an insecticide is not in use (Fig 4). 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.

#### Results2 : comparing rotations and sequences across model runs.

In all the example runs shown the resistance threshold (allele frequency of 0.5) was reached for all insecticides within the course 500 generations which was the maximum limit imposed in the model. There were many model runs [*quantify later when run finalised*] in which resistance frequencies for at least some insecticides were below thresholds at the end of 500 generations. Such a run could be considered a successful strategy given the conditions of the scenario because insecticides below the resistance threshold are still available to be used.

Thus to aid the comparison of rotations and sequences model runs can be broadly classified into four groups :

1. both strategies succeeded : for both rotations and sequences resistance thresholds for all insecticides not reached within 500 generations.
2. neither strategy succeeded
3. rotation only succeeded
4. sequence only succeeded

The number of model runs in each of these groups for the different scenarios are shown in Fig 5. In the base scenario with no costs or dispersal (Fig 5A) the majority of runs do not succeed, a small proportion succeed for both strategies and none succeed for either strategy alone. When costs of reistance are added (Fig 5B) more runs succeed for both strategies, up to about half of those that succeed for neither, and a small proportion (< 4%) succeed for rotations alone. Adding both costs and dispersal results in more runs succeeding for both than neither (Fig 5C) and the proportion of runs where rotations only succeed is similar to the scenario with costs alone.

Figure 2. 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 of 10 generations and the lower plot a sequence in which the insecticide is changed when a resistance threshold of 0.5 is reached. In this example the rotation and the sequence reach the endpoint, with all insecticides having a resistance frequency above 0.5, 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. All other inputs are kept constant between the rotation and the sequence. Effectiveness=0.7, exposure=0.7, male exposure proportion=0.5, resistance restoration=0.5, dominance of resistance=1.

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Figure 3. 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. Effectiveness=0.7, exposure=0.7, male exposure proportion=0.5, resistance restoration=0.5, dominance of resistance=1, cost=0.05, dominance of cost=1.

Figure 3. 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 and sequence last a similar amount of time. 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. Effectiveness=0.7, exposure=0.7, male exposure proportion=0.5, resistance restoration=0.5, dominance of resistance=1, cost=0.05, dominance of cost=1.

Figure 4. 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. Effectiveness=0.7, exposure=0.7, male exposure proportion=0.5, resistance restoration=0.5, dominance of resistance=1, cost=0, coverage=0.5, dispersal=0.1.

Figure 4. 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. Effectiveness=0.7, exposure=0.7, male exposure proportion=0.5, resistance restoration=0.5, dominance of resistance=1, cost=0, coverage=0.5, dispersal=0.1.

Figure 5. Success of model runs under different scenarios and strategies. Model runs classed as a success if there are still insecticides for which resistance is below the threshold of 0.5 after 500 generations (circa 50 years for Anopheles). With no costs or dispersal both strategies succeeded in around 5% of runs and neither did in 95%. When costs alone were included the proportion of runs in which both, neither and rotation succeeded was 38%, 60% and 2%. When dispersal alone was included both strategies succeeded in 20% or runs and neither did in 80%, in only 0.1% of runs did rotation alone succeed.

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