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# Mosquito resistance to insecticides

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# Contents

# Introduction

Natural selection acts on **phenotypes** that vary in survival and reproductive success, and the response to selection is a change in allele frequency resulting in evolution. In this free course, *Mosquito resistance to insecticides*, you will see how allele frequency can change rapidly in a population in response to selective pressure.

You will consider how **alleles** that arise and spread through a population because they confer resistance in that environment can have negative fitness consequences in other environments (a situation known as a trade-off). These principles can be illustrated by considering the example of the spread of mutant alleles of a gene called *ester* in populations of mosquitoes exposed to insecticides.

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# Learning Outcomes

After studying this course, you should be able to:

- describe how natural selection drives changes in allele frequencies, using mosquito resistance to insecticides as an example.

# 1 The *ester*[1] allele

In the 1960s, the French government attempted to rid its Mediterranean coast of mosquitoes (*Culex pipiens*) in order to attract tourists. It did this by regularly spraying the mosquito breeding sites located along the coast (Figure 1) with organophosphate insecticides that kill the mosquitoes by inhibiting an enzyme called acetylcholinesterase in the nervous system. The treatment was successful initially but, by 1972, the mosquito populations had begun to recover (Raymond et al., 1998).

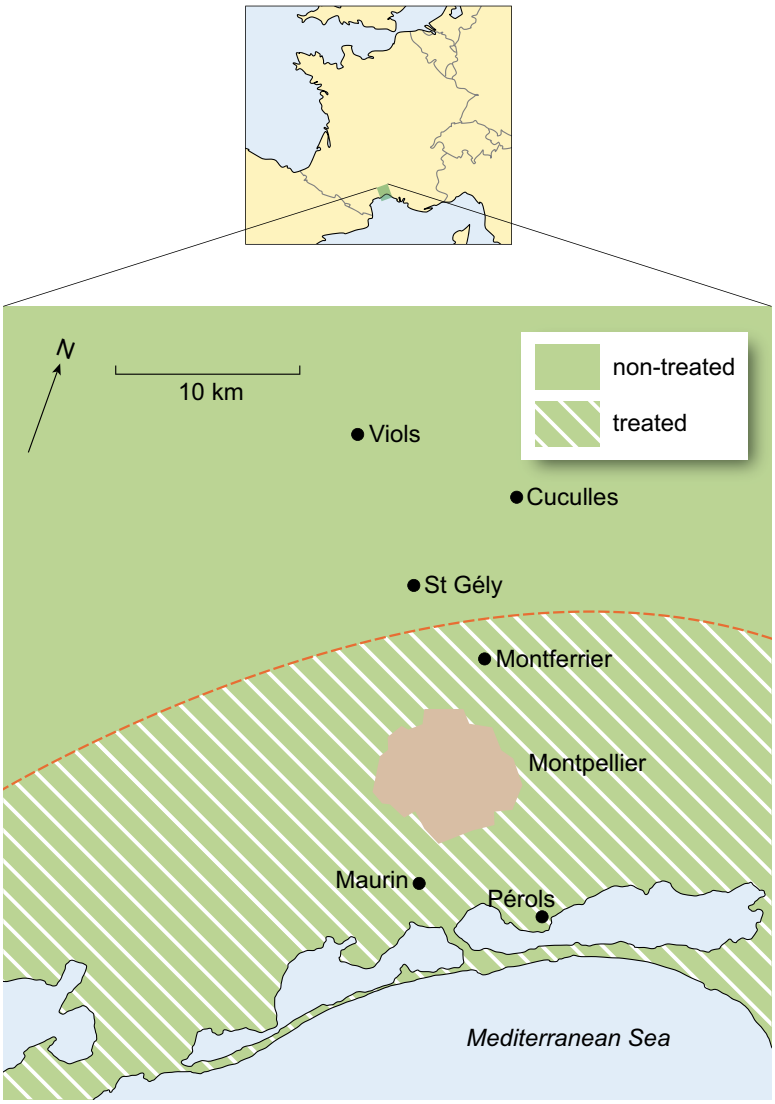


**Figure 1** Map indicating the location where mosquitoes were sprayed (hatched area), consisting of a 20–25 km-wide belt along the Mediterranean coast.

To understand the reason for this recovery, the responses of different mosquito populations to exposure to the insecticide were examined. Researchers collected mosquito larvae from populations near the coast, where they had been sprayed with insecticide, and from populations north of the spray area, which had never been exposed to insecticide. They exposed both samples to the insecticide. In populations near the coast, which were sprayed regularly, mosquitoes were able to withstand and survive quite

strong doses of the insecticide, but individuals taken from populations just north of the spraying area died when exposed to only weak doses.

Further research showed that the reason for the resistance in the coastal populations was a mutation at a locus called *ester* that encodes an esterase enzyme (called A1). The A1 esterase breaks down a wide range of toxins, including organophosphates. Mosquitoes that are vulnerable to the insecticide (and do not have the mutation) do not produce enough esterase to hydrolyse and thus inactivate the toxin. However, in resistant mosquitoes the mutated allele (called *ester*[1]) alters the expression of *ester* by gene amplification (i.e. several copies of the same gene are found in the same genome). This causes increased production of the A1 esterase and, as a consequence, resistance to the toxin.

Scientists monitored the frequency of the *ester*[1] allele in populations at and near the coast for several years.

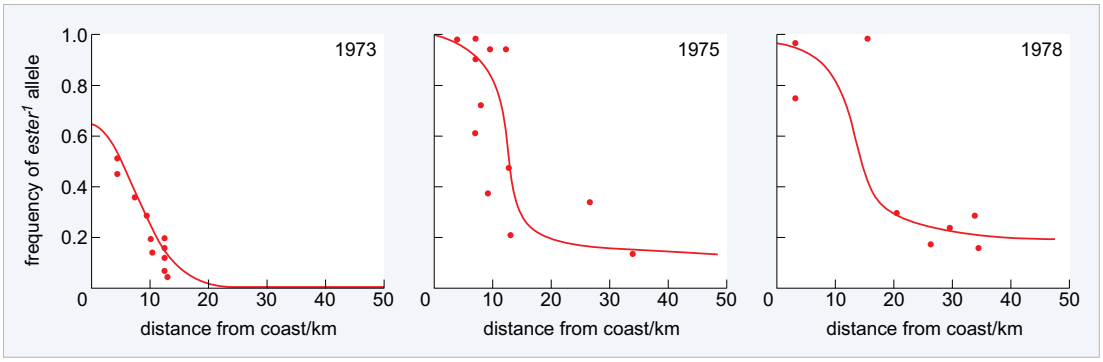


**Figure 2** Distance from the Mediterranean coast plotted against frequency of the *ester*[1] allele in mosquito populations in the south of France in the 1970s.

## Activity 1

In which populations was the *ester*[1] allele most common in each of the years shown?

### Answer

In all three years, the *ester*[1] allele frequency was highest in the populations closest to the coast.

## Activity 2

Describe how the *ester*[1] allele frequency changes with distance from the coast.

### Answer

In all three years, the *ester*[1] allele frequency declined sharply with distance inland. In 1973 the allele was not present in the mosquito populations that were furthest inland, but by 1975 and in 1978 it was detected in all populations, albeit at a much lower level in the inland populations.

## Activity 3

What was the *ester*[1] allele frequency in populations at the coast in 1973?

Answer

In 1973 the frequency of the *ester*[1] allele was over 0.6 in populations at the coast.

### Activity 4

Did the *ester*[1] allele reach fixation in any of the populations?

Answer

Yes, it reached fixation in the populations at the coast by 1975 (an allele frequency of 1.0 indicates fixation).

### Activity 5

What was the frequency of the *ester*[1] allele in the furthest inland mosquito populations by 1978?

Answer

Approximately 0.2.

In areas where mosquitoes were sprayed, *ester*[1] conferred a higher fitness on individuals carrying it, and these individuals passed the mutation on to their offspring. This resistance also spread to areas away from the coast (probably carried by mosquitoes migrating inland); however, as seen in Figure 2, it never reached a high frequency in inland populations. The reason for this is that the *ester*[1] mutation carries a fitness cost to mosquitoes carrying it. The overproduction of the A1 esterase has a side effect of interfering with cholinergic synapses of the central nervous system (those in which the neurotransmitter is acetylcholine). As a result, mosquitoes carrying the allele have a high susceptibility to predation and males have low reproductive success.

A mutation that has more than one effect on an organism – such as that which gave rise to the *ester*[1] allele – is said to exert a **pleiotropic** effect on the organism. In the case of the *ester*[1] allele, where the allele has opposing effects on fitness depending on the context, the effect is known as **antagonistic pleiotropy**.

So why did the *ester*[1] allele increase in coastal populations despite it increasing the likelihood of predation and lowering reproductive success? The reason is that the selection coefficient of a particular allele depends on the net effect of that allele on an organism's fitness. In the case of the mosquitoes, the fitness gains of resistance were greater than the losses due to predation (or other fitness deficits), but only in coastal regions where the mosquitoes were sprayed. Further inland, the *ester*[1] allele conferred no benefit because mosquitoes were not sprayed there. In these populations the *ester*[1] allele was disadvantageous because it raised the probability of predation and/or decreased reproductive success.

# 2 The *ester*$^4$ allele

Although *ester*$^1$ was the prevalent allele in the 1970s and early 1980s, a second mutation at the ester locus, *ester*$^4$, emerged in 1984 and replaced *ester*$^1$ in the 1990s. The replacement of *ester*$^1$ with *ester*$^4$ over the period 1986 to 1996 is depicted in Figure 3.

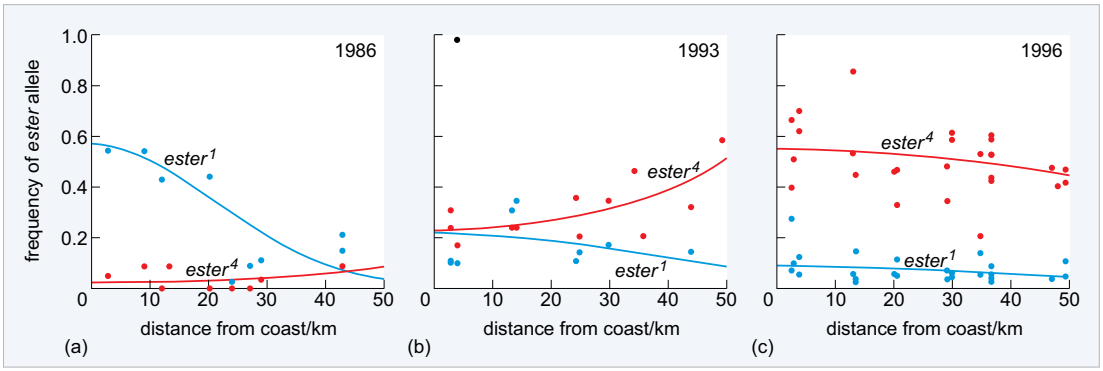


**Figure 3** Distance from the Mediterranean coast plotted against the frequency of the *ester*$^1$ (blue) and *ester*$^4$ (red) alleles in (a) 1986, (b) 1993 and (c) 1996.

## Activity 6

Describe the change in frequency with distance from the coast of both alleles over the three years.

### Answer

In 1986, the frequency of the *ester*$^1$ allele was nearly 0.6 at the coast and dropped to near zero at 50 km from the coast. *Ester*$^4$ occurred at a low frequency at the coast and increased very slightly with distance from the coast. In 1993 and 1996 the frequency of the *ester*$^1$ allele had declined in coastal regions while the *ester*$^4$ allele had increased in frequency at the coast and also away from the coast.

Laboratory experiments indicate that the reason for these changes in the frequency of the two alleles is that although *ester*$^4$ confers slightly less resistance to insecticides than *ester*$^1$, its negative effects on fitness are also less dramatic than those of *ester*$^1$. This is reflected in the slope of the curves shown in Figure 3 – there is no dramatic drop-off in the frequency of the *ester*$^4$ allele with increasing distance from the coast. This suggests that the allele is favoured at the coast but selection against it is less strong than was found for *ester*$^1$ further inland; that is, mosquitoes that migrate inland do not pay the price of carrying the *ester*$^4$ allele to the same extent as those carrying *ester*$^1$.

# Conclusion

As in the case of the mosquitos on the Mediterranean coast, many instances of insecticide resistance in insects are due to a single allele that is partially or fully dominant over the allele that determines susceptibility. In this free course, *Mosquito resistance to insecticides*, you have learned that these resistance alleles increase in frequency very rapidly when insecticide is applied because susceptible genotypes suffer very high mortality. However, in the absence of insecticides, resistant genotypes are 5% to 10% less fit than susceptible ones and so decline in frequency. Resistance to insecticides therefore illustrates a trade-off – traits that are advantageous in one environment can have effects that are disadvantageous in other environments.

# Glossary

alleles

Variants of a gene that may be followed genetically, usually through their phenotypic effect, but also using a molecular assay, such as PCR.

antagonistic pleiotropy

Refers to a situation in which a single gene creates multiple opposing effects, such that beneficial effects of a trait created by the gene are offset by 'losses' in other traits.

phenotypes

The observable traits or characteristics of an organism, such as its biochemical, morphological, physiological or behavioural characteristics.

pleiotropic

Describes a cellular process, signal or gene that has more than one effect, or more than one phenotypic outcome. At the genetic level, describes a situation where a single mutation affects two or more apparently unrelated phenotypic traits.

# References

Raymond, M., Chevillon, C., Guillemaud, T., Lenormand, T. and Pasteur, N. (1998) 'An overview of the evolution of overproduced esterases in the mosquito *Culex pipiens*', *Philosophical Transactions of The Royal Society B*, vol. 353, no. 1376, pp. 1707–11.

# Acknowledgements

This free course was written by Mandy Dyson.

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**Figures**

Figure 1: Lenormand, T. et al. (1999) 'Tracking the evolution of insecticide resistance in the mosquito Culex pipiens', *Nature*, vol. 400, pp. 861–4, Nature Publishing Group.

Figures 2 and 3: Raymond, M. et al. (1998) 'An overview of the evolution of overproduced esterases in the mosquito *Culex pipiens*', *Philosophical Transactions of The Royal Society B*, vol. 353, no. 1376, pp. 1707–11.

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