



## Let's move beyond costs of resistance!

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**A recommendation – based on reviews by Danna Gifford, Helen Alexander and 1 anonymous referee – of**

Lenormand T, Harmand N, Gallet R. 2018. Cost of resistance: an unreasonably expensive concept. bioRxiv 276675, ver. 3 peer-reviewed by Peer Community In Evolutionary Biology doi: [10.1101/276675](https://doi.org/10.1101/276675)

The increase in the prevalence of (antibiotic) resistance has become a major global health concern and is an excellent example of the impact of real-time evolution on human society. This has led to a boom of studies that investigate the mechanisms and factors involved in the evolution of resistance, and to the spread of the concept of "costs of resistance". This concept refers to the relative fitness disadvantage of a drug-resistant genotype compared to a non-resistant reference genotype in the ancestral (untreated) environment.

In their paper, Lenormand et al. [1] discuss the history of this concept and highlight its caveats and limitations. The authors address both practical and theoretical problems that arise from the simplistic view of "costly resistance" and argue that they can be prejudicial for antibiotic resistance studies. For a better understanding, they visualize their points of critique by means of Fisher's Geometric model.

The authors give an interesting historical overview of how the concept arose and speculate that it emerged (during the 1980s) in an attempt by ecologists to spread awareness that fitness can be environment-dependent, and because of the concept's parallels to trade-offs in life-history evolution. They then identify several problems that arise from the concept, which, besides the conceptual misunderstandings that they can cause, are important to keep in mind when designing experimental studies.

The authors highlight and explain the following points:

1. Costs of resistance do not necessarily imply pleiotropic effects of a resistance mutation, and pleiotropy is not necessarily the cause of fitness trade-offs.
2. Any non-treated environment and any treatment dose can result in a different cost.
3. Different reference genotypes may result in different costs. Specifically, the reference genotype has to be "optimally" adapted to the reference environment to provide an accurate measurement of costs.

Lenormand et al.'s paper [1] is a timely perspective piece in light of the ever-increasing efforts to understand and tackle resistance evolution [2]. Although some readers may shy away from the rather theoretical presentation of the different points of concern, it will be useful for both theoretical and empirical readers by illustrating the misconceptions that can arise from the concept of the cost of resistance. Ultimately, the main lesson to be learned from this paper may not be to ban the term "cost of resistance" from one's vocabulary, but rather to realize that the successful fight against drug resistance requires more differential information than the measurement of fitness effects in a drug-treated vs. non-treated environment in the lab [3-4]. Specifically, a better integration of the ecological aspects of drug resistance evolution and maintenance is needed [5], and we are far from a general understanding of how environmental factors interact and influence an organism's (absolute and relative) fitness and the effect of resistance mutations.

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## Appendix

Reviews by Danna Gifford, Helen Alexander and 1 anonymous referee: <https://doi.org/10.24072/pci.evolbiol.100052>