

Why can resistance persist after we stop using an antibiotic?

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Removing an antibiotic removes one selective pressure. It does not reset the bacterial population to the state it occupied before resistance spread. The resistant organisms still exist, their genetic backgrounds may have changed, and other conditions may continue to favor the resistance-bearing lineage or the DNA carrying it. Evolution has no command that restores the earlier state when one environmental condition is reversed.

Here, persistence means continued presence of inherited resistance in a population. It does not mean the distinct phenomenon of antibiotic-tolerant persister cells surviving exposure without necessarily carrying inherited resistance. The question is about changes across generations and populations, not an instruction about when anyone should start or stop treatment.

1. What would have to make resistance decline?

Imagine resistant and susceptible variants competing without the antibiotic. If resistance imposes a reproductive disadvantage, and otherwise comparable susceptible competitors are present, selection can reduce the resistant fraction. The important word is “if.” Fitness costs vary with the resistance mechanism, genetic background and environment. Reviews of resistance reversibility identify those costs, compensation and genetic linkage as major determinants of the outcome. [1]

Absence of the drug is not itself a force that deletes a resistance gene. It changes the consequences of carrying that gene. Loss then depends on reproduction, mutation, segregation, migration or other processes actually producing and amplifying alternatives. A population cannot be assumed to contain a successful susceptible replacement merely because an observer would prefer one.

2. Separate compensation from reversion

Reversion restores a susceptible state through a genetic change that removes or reverses the relevant resistance mechanism. Compensation can instead improve the performance of a resistant organism while leaving its resistance intact. The distinction is central to population-genetic treatments of the problem. A compensatory change alleviates a cost; it need not be another mutation that directly increases resistance. [2]

Consider a machine carrying a useful but inefficient modification. Removing that modification and improving the rest of the machine are different responses to its inefficiency. The analogy captures two alternatives without implying that bacteria plan repairs. Variants arise, and their reproductive consequences influence which become common.

Because the background can change, restoring one earlier DNA state may also fail to restore the earlier organism's performance. A useful experiment compares reconstructed combinations of resistance and compensatory changes in both drug-free and drug-containing conditions. Measuring only the final resistant strain leaves the contribution of each change unresolved. [2]

3. How a small residual cost changes the timetable

An intentionally simple model makes the consequence visible. Let the resistant fraction be p , let susceptible reproductive output be 1, and let resistant output be $1 - c$ per generation. Assume a large, closed population, constant conditions, no new mutation, no transfer and no other differences. The next resistant fraction is $p_{\text{next}} = p(1 - c)/(1 - cp)$.

Writing the resistant-to-susceptible odds as $O = p/(1 - p)$ makes the same relation easier to follow: after n generations, $O_n = O_0(1 - c)^n$. This is a deduction from the stated model, not a prediction for a patient or community.

Start with $p = 0.90$, so the odds are 9. With an assumed cost $c = 0.02$, after 100 generations the odds are approximately $9 \times 0.98^{100} = 1.19$, corresponding to a resistant fraction of about 0.544. With a cost reduced to 0.002, the corresponding fraction is about 0.880. A tenfold reduction in cost makes disappearance much slower in this model, even though both costs are positive.

Neither result tells us how many calendar days are involved. Generations in a homogeneous model are not interchangeable with time in a structured infection or environmental reservoir. The model's value is to identify which parameter controls the conditional prediction and why assuming a substantial cost without measuring it can mislead.

4. The gene may travel with something else

Resistance can be genetically linked to traits favored by other conditions. Selection on the linked package can then maintain a resistance determinant even when its own antibiotic is absent. Andersson and Hughes discuss this co-selection alongside compensation and low-cost resistance. [1] Removing one pressure does not necessarily remove every advantage associated with the carrier.

This is especially relevant when resistance determinants occur on mobile genetic elements such as plasmids. Their fate cannot be inferred solely from the growth rate of one isolated host strain: inheritance, loss, transfer and selection on other carried traits all belong in the accounting. The general existence of horizontal transfer does not, by itself, establish which of these processes dominates a particular persistence case.

A decline in a gene's frequency and a decline in the absolute number of resistant organisms also differ. If the total bacterial population increases while the resistant fraction decreases, the absolute count can still rise. Reports need to say which quantity was measured and where the sampling boundary was drawn.

5. What evidence would distinguish the explanations?

Competition measurements can estimate a cost under specified conditions. Genome comparisons can locate candidate changes. Genetic reconstruction can test whether those changes alter resistance or compensate for a disadvantage. Longitudinal sampling can show whether the same lineage persists or is repeatedly replaced by resistant arrivals. Each observation resolves a different part of the question.

A sequence change found in a successful lineage is not automatically a compensatory mutation. It may be neutral, linked to a causal change, or beneficial for a different reason. Likewise, observing persistence after an intervention does not prove that the intervention had no effect. The relevant comparison is with an appropriate alternative history, not simply with immediate elimination.

The remaining uncertainty is usually conditional and quantitative: which costs matter in the actual environment, which competitors are available, how much immigration or

transfer occurs, and which linked traits remain selected. A broad evolutionary mechanism does not supply those measurements for every organism and setting.

6. Reversal is a hypothesis, not a reset button

Resistance can persist because its cost is small, its cost has been compensated, or other selective and ecological processes maintain it. Withdrawal can favor decline in some circumstances without guaranteeing that outcome. [1,2] The correct question is therefore what changed in the relative success and transmission of the relevant variants, not why evolution failed to run backward.

Related reading

Article 028, “Why does sexual reproduction persist?”, asks how the transmission and recombination of inherited variants affect evolutionary outcomes. The link is optional and reciprocal.

References

- [1] D. I. Andersson and D. Hughes. Antibiotic resistance and its cost: is it possible to reverse resistance? *Nature Reviews Microbiology* 8, 260–271 (2010). <https://doi.org/10.1038/nrmicro2319>
- [2] P. Schulz zur Wiesch, J. Engelstädter and S. Bonhoeffer. Compensation of Fitness Costs and Reversibility of Antibiotic Resistance Mutations. *Antimicrobial Agents and Chemotherapy* 54, 2085–2095 (2010). <https://pmc.ncbi.nlm.nih.gov/articles/PMC2863634/>