To fight drug-resistant bugs, slowing their evolution may be best strategy

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Public health officials constantly fret about microbes developing resistance to drugs. It's a serious problem. Antibiotics and other infection-fighting agents don't always kill all of their microbial targets. Those that survive presumably have a tendency to resist the drug. When they reproduce, their offspring may inherit that resistance to the drug, some perhaps with novel genetic features that make them even more resistant. Eventually a fully resistant strain can evolve. It's a horror film on a microscopic screen, and there's nothing good about it — except perhaps to illustrate that germs understand evolution better than some school boards do.

Of course, modern medicine isn't powerless. Microbes that evolve to resist one drug might easily to succumb to another weapon from the medical arsenal. So it makes sense that biomedical researchers should be pursuing the discovery of new drugs like the New York Jets draft quarterbacks — if you collect enough of them, maybe one will work. It's an obvious strategy: in any arms race, the best plan is always to stockpile more weapons than the other team.

Or at least that what naïve amateur logicians typically claim. It's possible, though, that weapons escalation isn't always the best approach. And with drug resistance there is, in fact, an alternative strategy. Rather than speeding up drug discovery, it might be a better idea to slow down microbial evolution.

Naturally, it would be nice to do both. But resources are always limited, and in this case it seems like most of them flow to the discovering-new-drugs option rather than managing the evolution of resistance.

"Although precise estimates are difficult to come by, it would appear that the research effort devoted to drug discovery currently far exceeds that devoted to resistance management," Nathan McClure and Troy Day of Queen's University in Kingston, Canada, write in a recent paper (arxiv.org/abs/1304.7715) .

McClure, a biologist, and Day, a mathematician, decided to apply some math to the situation and discovered that today's dominant strategy might not actually be too bright.

"Our results illustrate that slowing the evolution of drug resistance has a greater effect on the performance of the drug supply system than does speeding up drug development," they write.

They created a rather simplistic model to do their analysis, assuming one drug works for a while until resistance makes it useless. Doctors would then opt for another choice from the portfolio of available drugs. As long as the drug discovery rate outpaces the speed of microbial evolution, drugs will be available to fight the disease. But if evolution outruns drug discovery, resistance wins.

Simple calculations show that slowing down the pace of resistance evolution lengthens the length of time ("time to failure") that drugs will remain useful lifetime of drugs. Of course, so does speeding up drug discovery. But for all the scenarios examined, McClure and Day, slowing evolution did a better job of extending the time to failure than decreasing the time it takes to discover new

drugs. Adding complications to the analysis, such as allowing more than one drug to be used at once, didn't change the basic mathematical result.

"The results show that slowing evolution increases the expected time to failure and drug availability more than decreasing the time between drug arrivals," McClure and Day write.

They emphasize that their results do not suggest that pharmaceutical companies shutter their research departments. But from a policy standpoint, shifting some of the emphasis from drug discovery to "resistance management" seems advisable. That might mean adopting more sophisticated measures for making sure antibiotics are prescribed and used correctly. Research into optimum dose levels and timing of drug delivery might also help slow down resistance evolution. And perhaps there are other strategies that haven't been thought of yet because nobody has been thinking very much about it.

It's possible that drug development will someday succeed in baffling microbes so completely that resistance will no longer nee managing. But for now, that's about as likely as Tim Tebow playing quarterback in the Super Bowl.

"Evolution management is not only a significant component of the solution to the problem of drug resistance," McClure and Day write, "but may in fact be the most important component."

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