Study shows antibiotic resistance genes persist in E. coli through 'genetic capitalism'

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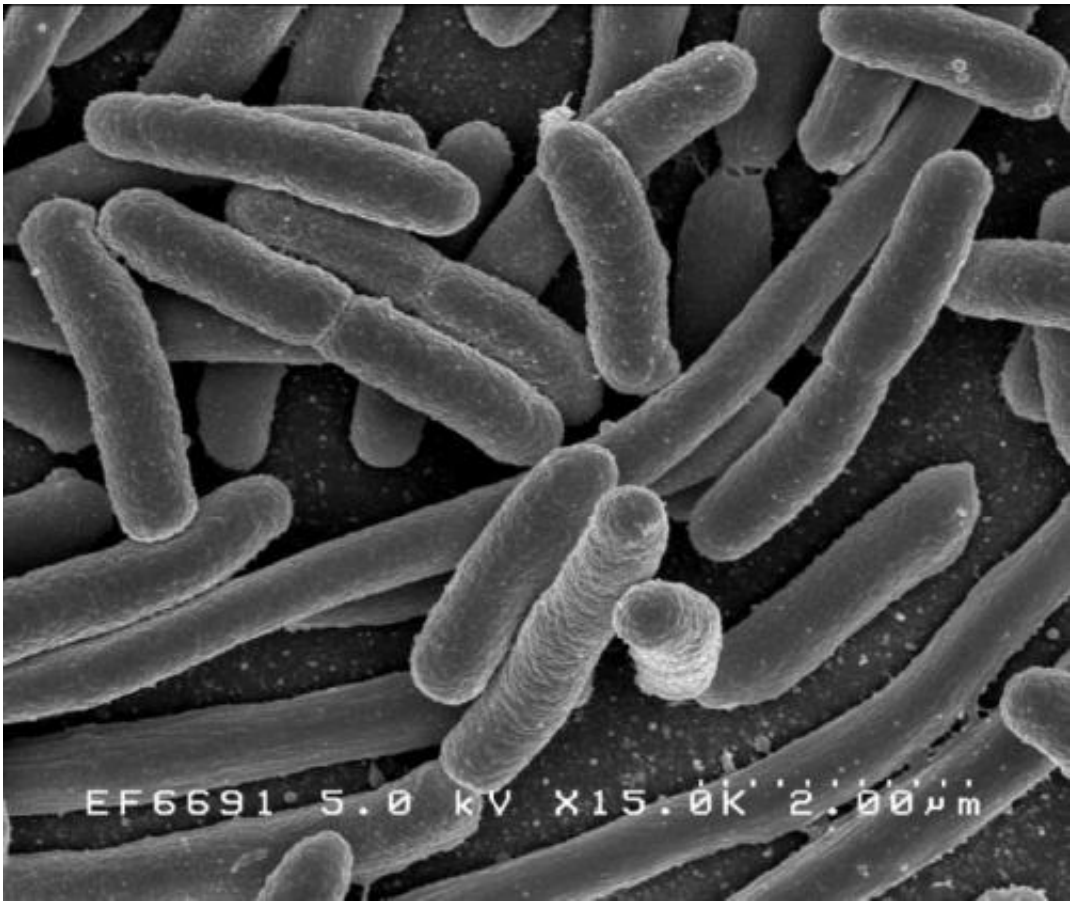

Escherichia coli. Credit: Rocky Mountain Laboratories, NIAID, NIH

We have known for some time that over-use of antibiotics is causing a frightening increase in antibiotic resistance in bacteria, through the rapid spread of antibiotic resistance genes. What may be behind this is not just

the spread of these genes, but a fundamental change in the way evolution is driving the economy of gene content among microbes.

Normally, according to evolutionary theory, genes that become prevalent in a population are chosen through natural selection, where survival of organisms carrying a specific gene is determined by an economic no-nonsense cost-benefit analysis. Now, however, it appears that excessive human interference is turning bacteria into rapacious gene-hoarding "genetic capitalists," driving a more unexpected evolutionary process.

A new study, published in the current issue of the journal *Cladistics*, analyzes a massive genetic data set involving genomes of 29,255 strains of the bacterium *Escherichia coli* (*E. coli*) collected between 1884 and 2018 to examine the evolution of 409 different genes that enable various strains of bacteria to resist various antibiotics. The researchers examined whether the genes that confer antibiotic resistance, once acquired, tended to persist massively in the bacterial lineage—a phenomenon known as 'genetic capitalism'—or disappear once they are no longer required for survival, through a normal evolutionary process known as 'stabilizing selection.'

In a normal, non-disrupted world, the processes of evolution course corrects changes to bacterial genomes to account for "cost." In adding an extra gene that introduces an extra cost by adding to the bacterium's processes, natural selection balances the change with larger or more long-term survival parameters, such as more rapid growth and more reproduction—and a "stabilizing selection" process should theoretically dominate by favoring the elimination of genes whose costs unnecessarily interfere.

A wide variety of genes that help bacteria resist antibiotic compounds (antibiotics released by other microorganisms and now co-opted in human medicine and agriculture) have probably been around for more

than a billion years, but were never so necessary to bacterial survival as to be widespread in bacterial genomes. The expectation, following evolutionary theory, was that these genes, like bulky, high-maintenance tools being carried in a bacterial toolkit, would tend to disappear when they were no longer needed.

The study found that "stabilizing selection" is no longer the evolutionary rule for antibiotic resistance genes.

"Bacteria are under constant competitive pressure from other microorganisms, battling for resources and space or defending against attack," noted Daniel Janies, the Carol Grotnes Belk Distinguished Professor of Bioinformatics and Genomics at the University of North Carolina at Charlotte, and the study's corresponding author. "The energy budget of *E. coli* is pretty tight—it's been said that even adding an extra base to a gene will make the bacterial lineage less fit.

"In the absence of selective forces of antibiotics, the bacterial lineage would evolve to lose genes that confer antibiotic resistance—anything that's unnecessary. That's stabilizing selection—the bacterial lineages should come back to the wild type through selective forces or be outcompeted," he said.

And yet instead, in the evolutionary history of *E. coli* over the past 134 years, the study found that preserving genetic changes that conferred antibiotic resistance was more likely to occur than losing them through long-term selection.

"Most of the genes we examined show gains in a bacterial lineage, but rarely show losses," Janies said. "Imagine how carrying all these genes—sometimes up to 30 of them—should impact the evolutionary fitness of a bacterium."

While increasing antibiotic resistance in bacteria is hardly a new discovery, Janies notes that the scope of its occurrence shows that massive human interference is causing the advent of a widespread hoarding of genes that confer antibiotic resistance that was unlikely to have happened under normal evolutionary pressure.

"Since the industrialization of antibiotics we've seen that the cost of thriving or just surviving for *E. coli* requires one or more—or upwards of thirty of antibiotic resistance genes, " Janies said. "The forces that we are applying through industrialization of antibiotics are very strong."

However, the study also shows that not all genes that confer antibiotic resistance for *E. coli* are effected to the same extent by the new evolutionary pressures. The study tracks five different ways that genes can confer resistance to antibiotics and measures differences between these broad antibiotic classes in whether they are pushed from stabilizing selection to genetic capitalism or not.

"What we wanted to do is to look at the history of these processes through the lens of a very large data set collected over 134 years and see if there were qualitative differences and functional differences in the genes that behave by the principles of stabilizing selection and those that exhibit genetic capitalism."

The study did find that antibiotic resistance genes that work through mechanisms of "replacement" (replacing bacterial cell molecules that are targets of antibiotic compounds with different molecules) or "efflux" (causing the transport of antibiotic compounds out of the cell) are still more likely to be subject to being eliminated through stabilizing selection than to participate as currency in genetic capitalism—probably because these two mechanisms are extremely costly to the routine functioning of the bacterial cell.

Nevertheless, all the other antibiotic resistance mechanisms behave as if they are under the principle of "genetic capitalism," favoring the persistence of genes, showing that, overall, the tendency to retain these costly resistance genes has become the new rule for bacterial lineages.

"This study really helps to stratify the severity or risk of different types of resistance," noted UNC Charlotte bioinformatician Colby Ford, the paper's first author. "In other words, we can better pinpoint antibiotics that are at a higher risk of bacteria developing a more permanent form of resistance to, which should be avoided."

The researchers note that some antibiotic resistance genes (the types of that still show strong effects of stabilizing selection) may still be reduced in bacterial populations by "antibiotic cycling"—taking certain antibiotics out of use for a while until stabilizing selection reduces the presence of the resistance gene in bacterial populations.

"It's an alarming finding, but I didn't want to write the 'doom and gloom paper' - I think there is some hope for managing some kinds of antibiotic resistance," Janes said. "If there is a take-home message that can be used for antibiotic stewardship it's that some classes of antibiotics, those that work via target replacement and efflux, are subject to stabilizing selection, if we have the will and organization to invoke antibiotic cycling."

More information: Colby T. Ford et al, Genetic capitalism and stabilizing selection of antimicrobial resistance genotypes in Escherichia coli, *Cladistics* (2020). DOI: 10.1111/cla.12421

Provided by University of North Carolina at Charlotte

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