Antibiotics don't promote swapping of resistance genes

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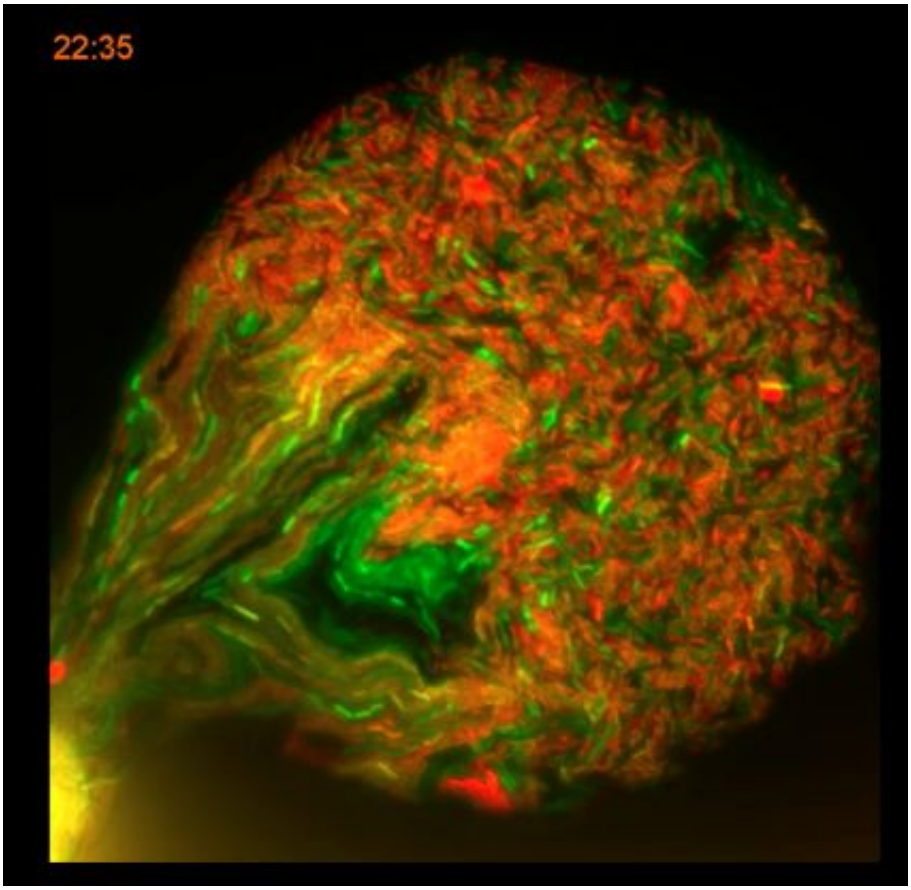

Researchers have shown that, outside of a few specific examples, antibiotics do not promote the spread of bacterial antibiotic resistance through genetic swapping, as previously assumed.

While the overuse of antibiotics is undeniably at the heart of the growing global crisis, new research published online April 11 in *Nature Microbiology* suggests differential birth and death rates and not DNA donation are to blame. The results have implications for designing antibiotic protocols to avoid the spread of antibacterial resistance.

"The entire field knows there's a huge problem of overusing antibiotics," said Lingchong You, the Paul Ruffin Scarborough Associate Professor of Engineering at Duke University and lead author on the paper. "It is incredibly tempting to assume that antibiotics are promoting the spread of resistance by increasing the rate at which bacteria share resistant genes with each other, but our research shows they often aren't."

It's long been known that bacteria can swap DNA through a process called conjugation, which allows helpful genes to spread quickly between individuals and even between species.

Because the number of resistant bacteria rises when antibiotics fail to kill them, researchers assumed that the drugs increased the amount of genetic swapping taking place. But You thought maybe the drugs were killing off the two "parent" lineages and allowing a newly resistant strain to thrive instead.

"Previous studies haven't been able to tease these two ideas apart, but our work decoupled them," said Allison Lopatkin, a doctoral student in You's laboratory and the lead author of the study. "We showed at the single-cell level that the exchange of resistant genes is not influenced by antibiotics at all, which is in contrast to the literature."

In her experiments, Lopatkin put bacterial cells under a sort of suspended animation where they could neither die nor reproduce but they could still swap genes. With the birth and death rates no longer a variable, the researchers could see how the rate of gene exchanges

responded to antibiotics.

They tested nine clinical pathogens commonly associated with the rapid spread of resistance and exposed them to ten common drugs representing each major class of antibiotics.The rates of gene exchange in each test remained flat and, in a few cases, actually decreased slightly as the concentration of antibiotics grew.

"It would seem that when antibiotics are applied, the DNA swapping has already occurred and continues to do so," You said. "Depending on their doses, the drugs can let the newly resistant bacteria emerge as the winners. When this occurs, the new strain is much more prevalent than before if tests are run after some growth of the new strain."

You points out that there are a few proven examples of antibiotics directly inducing the expression of the genes responsible for donating resistance, but they are very specific. For example, the antibiotic tetracycline induces the expression of genes that only transfer tetracycline resistance.

The new study shows that despite these outliers, antibiotics don't promote resistance spread by inducing global changes at the cellular level. The researchers hope further research will soon help clinicians design better antibacterial protocols.

"This has direct implications in terms of how we design doses and protocols," said You. "Some antibacterial combinations can drastically promote the overall transfer dynamics. Other combinations, on the other hand, can suppress the pathogens equally well without promoting genetic transfers. These are the issues we're hoping to address in follow-up research. We're trying to learn how to design the antibiotic treatment protocols in such a way that they will be effective but won't promote the spread of antibiotic resistance."

More information: "Antibiotics as a selective driver for conjugation dynamics," Allison J. Lopatkin, Shuqiang Huang, Robert P. Smith, Jaydeep K. Srimani, Tatyana A. Sysoeva, Sharon Bewick, David Karig, Lingchong You. *Nature Microbiology*, April 11, 2016. DOI: 10.1038/NMICROBIOL.2016.44

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