The antibiotic arms race moves at high speed

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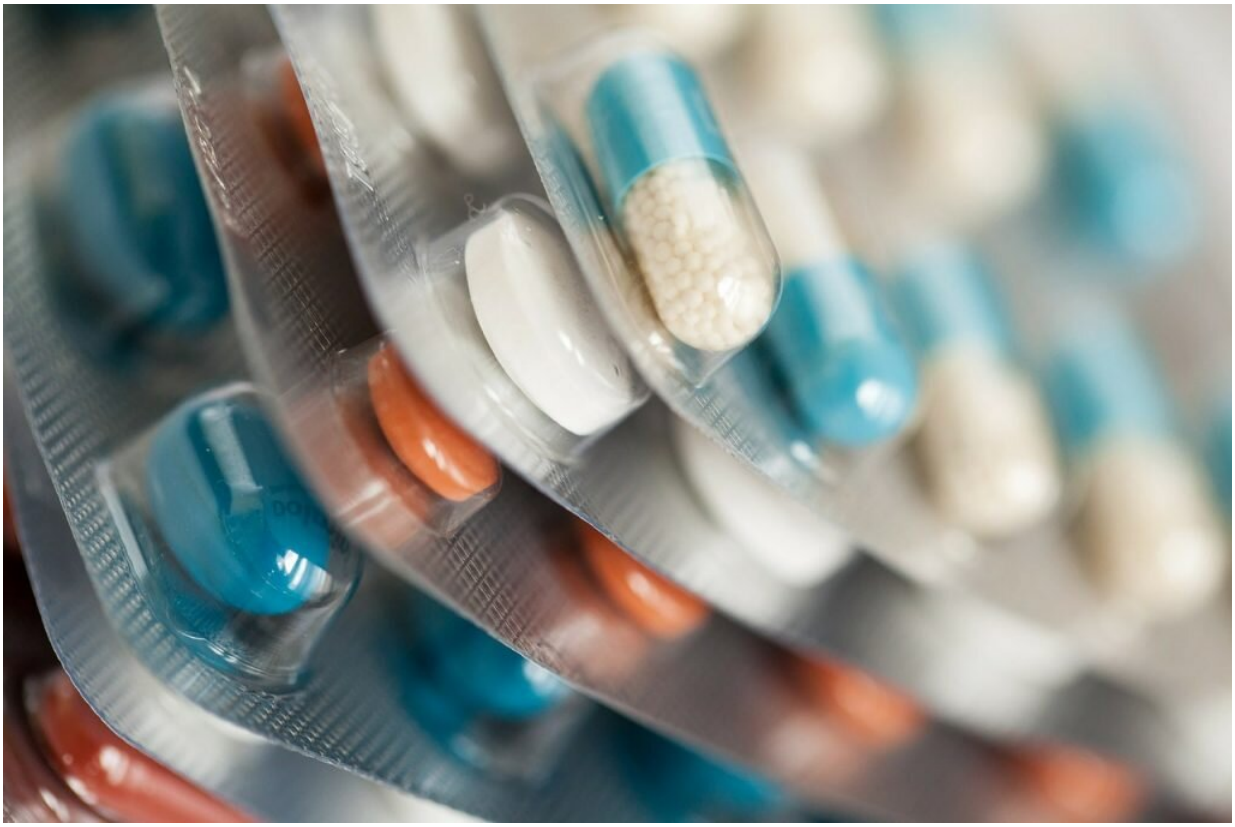

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Acinetobacter baumannii is a pathogen that creates serious problems in hospitals throughout the world. It causes opportunistic infections in the bloodstream, urinary tract, and other soft tissues, accounting for as much as 20 percent of infections spread in Intensive Care Units. As one of the pathogens involved in many multidrug-resistant infections caught in

hospitals, it was top of the highest priority "Critical" group of antibiotic-resistant pathogens the World Health Organization rated in 2017 as needing further research.

Unfortunately, Acinetobacter baumannii is one of the great survivors. It has an arsenal of tools to defend against antimicrobials, including the classical mechanisms of antibiotic resistance, along with an even more fundamental property—it forms biofilms. Acinetobacter baumannii biofilms can grow on a range of surfaces, including medical devices, making them persistent sources of contamination and infection. The National Institutes of Health estimates that biofilms are responsible for around four fifths of microbial infections in the body.

In a paper just published in *npj Biofilms and Microbiomes*, Macquarie University's Anahit Penesyan and her colleagues have looked at the evolution of Acinetobacter baumannii's defence mechanisms in its biofilm state, when exposed to low levels of antibiotics. They are alarmingly impressive.

The majority of bacteria don't just float around by themselves. They attach to each other, and to surfaces, forming so called biofilms, and becoming stronger as a whole than the sum of their parts. This added strength became even more sinister when the group exposed biofilms of Acinetobacter baumannii to low levels of two antibiotics—ciprofloxacin and tetracycline—for three days. These were chosen because the bacteria have only a low level of resistance to them, unlike some other antibiotics.

By the end of three days, the bacteria were already demonstrating consistent increases in antibiotic resistance. Of random biofilm isolates exposed to ciprofloxacin, 93 percent showed at least two-fold increased resistance towards this antibiotic, with 76 percent of those having at least a four-fold increase in resistance. Some 80 percent of ciprofloxacin-

exposed isolates also showed increased resistance to tetracycline, with one-third of them showing at least a four-fold increase. That means that these isolates would require double, quadruple, or even higher concentration of antibiotics for their effective control. This is often impossible and unsafe.

Much the same thing happened with the biofilms exposed to tetracycline. More than half (53 percent) at least doubled their resistance to tetracycline, with eight showing four -fold increases. Nine of the tetracycline-exposed isolates also gained increased resistance to ciprofloxacin, again as much as four times greater.

The team then tested the isolates for susceptibility to erythromycin—an antibiotic with a different structure and function from the antibiotics the biofilms had been exposed to. Many of the isolates that showed increased resistance towards ciprofloxacin and/or tetracycline were also resistant towards erythromycin. In other words, cells are becoming resistant to multiple antibiotics (multidrug resistant) when exposed to low levels of antibiotics in their natural, biofilm, state.

The majority of biofilm derived cells also gained an increased capacity to form biofilms, thus further strengthening their resilience.

These findings are a disturbing indication of what could be occurring in biofilms within infections, when they are exposed to antibiotics. They also have ramifications for antibiotic waste management. Low levels of antibiotics released into the environment may cause similar effects in biofilms growing in natural waterways, which may then spread antibiotic resistance still further.

We need to think how we use antibiotics in the future, so we don't make superbugs an even greater threat.

More information: Anahit Penesyan et al. Rapid microevolution of biofilm cells in response to antibiotics, *npj Biofilms and Microbiomes* (2019). DOI: 10.1038/s41522-019-0108-3

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