Battle royale: How bacteria fight antibiotics and up the ante in chemical warfare

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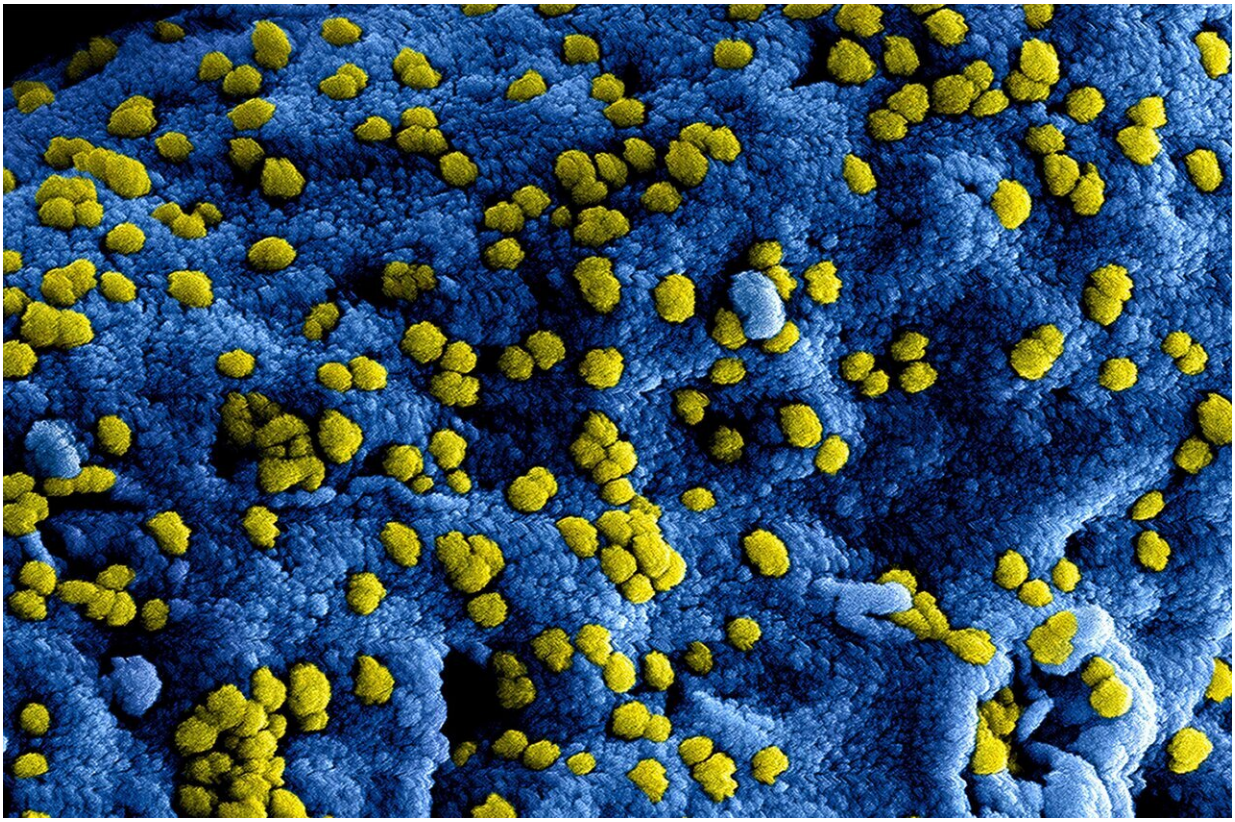

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Inadequate development of new antibiotics and rising rates of resistance by bacteria to existing antimicrobials are dual forces pushing the world ever closer to a post-antibiotic era.

It has been an 80-year war, the battle pitched by bacteria against the chemical warfare designed to knock out infections—and on multiple fronts, bacteria have gained the upper hand. Despite their microscopic size and lack of a brain, they know how to win the resistance war.

A team of researchers at Weill Cornell Medicine in New York and the MRC Centre for Molecular Bacteriology and Infection at Imperial College London has tackled how bacteria became resistant in the first place. They have deconstructed bacterial genetic strategies and other survival tactics, which they posit can pave the way to new types of antibiotics while saving many of the existing ones.

Writing in *Science Translational Medicine*, Drs. Sarah Schrader, Julien Vaubourgeix, and Carl Nathan painted a portrait that is dire—yet encouraging—as they demystified antibiotic resistance and defined how bacteria acquire the capacity to thwart what was previously lethal.

Key to their analysis is shedding light on the intricacies of antimicrobial resistance. They distinguished between heritable resistance—the acquisition of genes that confer resistance, and another type called phenotypic antimicrobial resistance. The latter refers to a reversible form of drug resistance not attributable to genes.

Drug resistance, the authors say, is one of several defenses against infectious disease that is on the rise. "In addition to our immune system, our major defenses against infectious disease are antibiotics, vaccines, sanitation, potable water, sound nutrition and public health infrastructure. All of these are failing in various parts of the world," they wrote.

"One key defense, the use of antibiotics, is beginning to fail worldwide because of the rise of antibiotic resistance, which is threatening to undermine the practice of medicine," they added.

Nowhere in infectious diseases has the fight against resistance been more persistent than in the ongoing battle against tuberculosis, which has become a multi-drug-resistant scourge in many parts of the world despite improvements in drug regimens and medication compliance programs. Phenotypic antimicrobial resistance has been a problem with TB.

Phenotypic antimicrobial resistance can arise under a variety of circumstances, and may sometimes be difficult to distinguish from genetically caused resistance. For example, phenotypic resistance can arise stochastically, which means it develops randomly and has a random distribution pattern.

Microbiologists also refer to this type of resistance as "spontaneous persistence" and "stochastic switching." But there are other causes of phenotypic resistance, which additionally can arise from bacterial exposure to conditions of altered environments, such as oxygen deprivation, acidification, oxidative stress, host immune responses and sub-lethal concentrations of antibiotics. As it turns out, phenotypic antibiotic resistance is more common than genetic resistance.

The new analysis by Schrader and her colleagues covers years of cumulative data about the nuances of drug resistance, a phenomenon that has proved lethal for countless patients around the world.

"Preventing deaths from antimicrobial resistance will require exploiting emerging knowledge not only about genetic antimicrobial resistance conferred by horizontal gene transfer or de novo mutations, but also about phenotypic antimicrobial resistance, which lacks a stably heritable basis," Schrader wrote.

Yet she and her colleagues aren't the first to sound an alarm about antibiotic resistance and they certainly won't be the last.

In 2018, the World Health Organization declared antibiotic resistance to be one of the biggest threats to global health, food security and development today. A growing number of infections, such as pneumonia, tuberculosis, gonorrhea and salmonellosis have become increasingly difficult to treat because resistant bugs have made antibiotics less effective, agency officials said.

Roughly a year after that report, the WHO released another. In 2019, the agency demanded "immediate, coordinated and ambitious action" to avert a potentially disastrous drug-resistance crisis. Unless the issue is addressed, drug resistant diseases could cause 10 million deaths each year by 2050, the agency predicted.

Currently, an estimated 700,000 people die each year because of drug resistance, according to WHO's estimates, which include 230,000 who die of multi-drug-resistant tuberculosis.

But in their lengthy analysis, Schrader and her team insist that emerging insights into the biology of drug resistance as well as technological advances that are under development can help the medical community "retake lost ground."

The key feature of antimicrobial resistance is the ability of a bacterial population to grow in the presence of an antibiotic. Being impervious to drugs has essentially flipped the script on humans who briefly thought 80 years ago that they had conquered bacteria through the use of chemical warfare. But the story of drug resistance is long—and perilous, some scientists say.

Phenotypic antimicrobial resistance, the major thrust of the Schrader report, isn't a new term, and is often seen in the scientific literature as a synonym for phenotypic tolerance, which Schrader and her team say was a term that predominated for many years after its introduction in 1986.

However, both of these terms were preceded by the word "persisters," which dates back to 1944, not long after penicillin emerged as a global wonder drug.

No one was more familiar with persisters—bacteria that didn't die despite high concentrations of antibiotic exposure—than British physician and microbiologist Alexander Fleming, discoverer of penicillin. "It's not difficult to make microbes resistant to penicillin in the laboratory, and the same thing has occasionally happened in the body," Fleming said in 1945 when he accepted the Nobel Prize that he shared with two other British penicillin researchers, Howard Florey and Ernst Chain. Although Fleming was aware that resistance was possible, he had no idea that it would become an enormous medical problem of its own.

"To cut off genetic antimicrobial resistance at its roots, we need to understand phenotypic antimicrobial resistance, which is more common than genetic," Schrader wrote. "The assertion that phenotypic antimicrobial resistance is more common than genetic is justified clinically by the prevalence of phenotypically resistant bacteria in biofilms and the presence of biofilms in many clinical settings."

A biofilm is a thick architectural assemblage of microbial cells that form a shell-like encasement with a layer of slime. The sole biological aim is to protect the bacterial colony inside, allowing it to thrive. Biofilms are most dangerous when they invade human cells shielding bacteria from antibiotics.

More information: Sarah M.Schrader et al. Biology of antimicrobial resistance and approaches to combat it, *Science Translational Medicine* (2020). DOI: 10.1126/scitranslmed.aaz6992