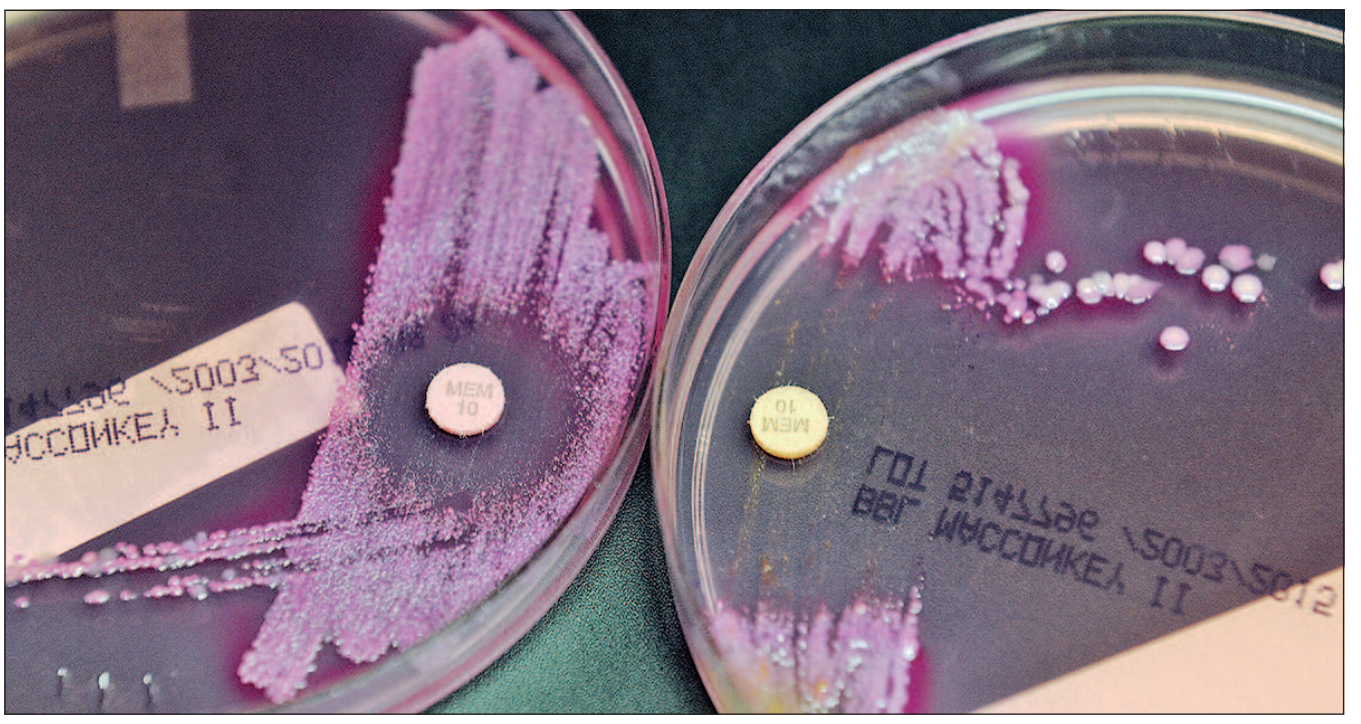
RESEARCHERS DISCOVER WAYS BACTERIA WITHSTAND ANTIBIOTICS



Wally Skalij / Los Angeles Times

A bacterial sample at left contains carbapenem-resistant Enterobacteriaceae, able to grow despite the presence of an antibiotic.

Scientists Spying on 'Superbugs'

By Emily Baumgaertner
Los Angeles Times

Scientists have discovered another way that single-celled organisms have outsmarted us.

The tiny bacteria that live inside our guts have an ingenious way of withstanding the onslaught of antibiotics we throw at them, according to a report published recently in the journal Science. The two-part system allows bacterial cells to stay alive until another bacterium can deliver a lifeline, packaged in a snippet of DNA.

Microbes 1, Humans 0.

"I'm afraid our findings are great news for bacterial cells — not so good for us," said study leader Christian Lesterlin, a researcher in the Molecular Microbiology and Structural Biochemistry program at Université Lyon in France.

Lesterlin and his colleagues knew that superbugs could repel even our most modern medicines. What they didn't know was how they managed to pull it off.

"These are amazing abilities they have, to be able to adapt and survive in harsh environments with antibiotics," he said. "But the more we understand about it, the more we can do for human health."

For most of human history, bacteria have had their way with us. Though some of them are helpful, others cause dangerous diseases like pneumonia, cholera and meningitis. The bacterium Yersinia pestis wiped out roughly 20% of the world's population in the mid-1300s during the pandemic known as the Black Death.

When scientists developed antibiotics in the early 1900s, humans enjoyed the upper hand — for a while. Some of the drugs target the machinery that maintains a bacterium's all-important cell wall. Others rob bacteria of the proteins they need to carry out essential functions or damage the DNA needed to reproduce.

It took just a few decades for the first drug-resistant strains to appear. Since, the invention of each new antibiotic invited a jeering reply.

Doctors responded by prescribing another antibiotic drug, and another. Then two drugs together. Then three. But the arsenal is all but depleted, and there are strains of Escherichia coli, Klebsiella pneumoniae, acinetobacter and enterococcus that have evolved to overcome almost every medicine thrown at them.

So scientists are racing to understand superbugs' tactics. Among the most urgent questions is this: How does antibiotic resistance spread between bacteria cells, even — or especially — in the presence of antibiotics that are designed to knock them back?

Bacteria know better than to wait around for a random mutation in their DNA that will protect them from antibiotics. Those mutations will come but not often: For some drugs, only about 1 in 10,000 bacteria will develop resistance that way. For other drugs, only about one in a billion will do so. Either way, that's not very efficient.

Luckily for bacteria, they have plasmids at their disposal. These are circular snippets of DNA, and they can include genes that carry instructions for repelling specific antibiotics. Bacteria can swap useful plasmids with one another while socializing together in the human gut.

Lesterlin's team wanted to visualize how the exchange worked. They put a regular strain of Escherichia coli bacteria in one petri dish and a strain that is resistant to the antibiotic tetracycline in another dish. Then they saturated both plates with tetracycline and watched closely.

Logic suggested the bacteria cells lacking the ability to resist the drug would die. Instead, they simply went to sleep. After several hours, the researchers combined the contents of the two dishes and used a technique called live-cell microscopy to watch in real time as plasmids were transferred in two minutes from tetracycline-resistant bacteria cells to tetracycline-sensitive ones.

Less than two hours later, the plasmid produced a protein called TetA resistance factor, which makes bacteria impervious to tetracycline. That was "shockingly counter-intuitive," Lesterlin said, since tetracycline blocks the production of proteins by binding to the machinery required to make them.

The next question was this: How could bacteria get away with producing drug-resistance proteins right there in the presence of a protein-inhibiting drug?

As the hosts on QVC might say, one can never have too many accessories.

That's especially true for something called the AcrAB-TolC multidrug efflux pump, which sits on the cell's outer membrane and ejects various toxic antibiotics that have invaded the cell's interior.

Despite the pump's fancy-sounding name, it's not sufficient to keep the cell thriving amid a surge of antibiotics. But it buys vital time for the groggy cell to acquire a plasmid with an all-important resistance gene.

In the team's experiments, the pump kept tetracycline levels low enough to give the cell a chance to translate the resistance gene into a version of the TetA protein that was immune to the antibiotic.

Then that TetA protein took the reins in sustaining the newly drug-resistant cell, which went on to grow and multiply.

"Thanks to the multidrug efflux pump, bacteria have the ability to remain dormant — not quite dead but not quite alive — just waiting for a little help from a neighbor," Lesterlin said.

Rudimentary microbiology discoveries like this one might seem far removed from the front lines of the war on superbugs. But military analysts and athletes alike will tell you that the key to victory is to study your enemy. Understanding basic cell functions could reveal gaping holes in our strategy to combat antibiotic resistance — and weaknesses of their own that we might exploit.

For now, scientists remain locked in a race that could mean life or death for all organisms involved. Antibiotic-resistant bacteria kill at least 23,000 people in the United States per year, according to the Centers for Disease Control and Prevention — an estimate that most experts consider conservative.

The United Nations warns that, without action, drug-resistant infections could kill 10 million people annually by 2050. That's a public health nightmare, but hardly a surprise.

Study: Medical marijuana laws not curbing opioid deaths

BY Carla K. Johnson
AP Medical Writer

A new study shoots down the notion that medical marijuana laws can prevent opioid overdose deaths, challenging a favorite talking point of legal pot advocates.

Researchers repeated an analysis that sparked excitement years ago. The previous work linked medical marijuana laws to slower than expected increases in state prescription opioid death rates from 1999 to 2010. The original authors speculated patients might be substituting marijuana for painkillers, but they warned against drawing conclusions.

Still, states ravaged by painkiller overdose deaths began to rethink marijuana, leading several to legalize pot for medical use.

When the new researchers included data through 2017, they found the reverse: States passing medical marijuana laws saw a 23% higher than expected rate of deaths involving prescription opioids.

Legalizing medical marijuana "is not going to be a solution to the opioid overdose crisis," said Chelsea Shover of Stanford University School of Medicine. "It would be wonderful if that were true, but the evidence doesn't suggest that it is."

"We weren't happy when a billboard went up saying marijuana laws reduce overdose deaths."

— Brendan Saloner, Johns Hopkins Bloomberg School of Public Health

Shover and colleagues reported the findings Monday in Proceedings of the National Academy of Sciences. It's unlikely, they said, that medical marijuana laws caused first one big effect and then the opposite. Any beneficial link was likely coincidental all along.

"We don't think it's reasonable to say it was saving lives before but it's killing people now," Shover said.

In the opioid crisis, dozens of forces are playing out across the nation in different ways. How widely available is the overdose antidote naloxone? Who has insurance? How broadly does insurance cover addiction treatment?

What's more, prescription pills once were involved in the largest share of overdose deaths, but that changed as heroin and then fentanyl surged. The studies on marijuana laws and opioid deaths don't account for that.

The new study undermines recent policy changes in some states. Last week, New Mexico joined New York, New Jersey and Pennsylvania in approving marijuana for patients with opioid addiction.

"I was told my paper helped change the law in New York. I was appalled," said Rosalie Liccardo Pacula of the Rand Drug Policy Research Center. She co-authored a 2018 study on marijuana laws and overdose deaths.

Experts agree evidence doesn't support marijuana as a treatment for opioid addiction. Drugs like buprenorphine, morphine and naltrexone should be used instead, Pacula said.

Authors of the original research welcomed the new analysis.

"We weren't happy when a billboard went up saying marijuana laws reduce overdose deaths," said Brendan Saloner of Johns Hopkins Bloomberg School of Public Health. "That was very hard for us to rein in."

Marijuana has been shown to help ease chronic pain, and other studies have suggested medical marijuana laws may reduce opioid prescribing. So there's still reason to believe that for some people, marijuana can substitute for opioids as a pain reliever.

As for addiction and the overdose crisis, "we should focus our research and policies on other questions that might make a difference," Shover said.

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