

## Microbiology

# Unlocking a new way to fight against antibiotic resistance: Viruses are the key

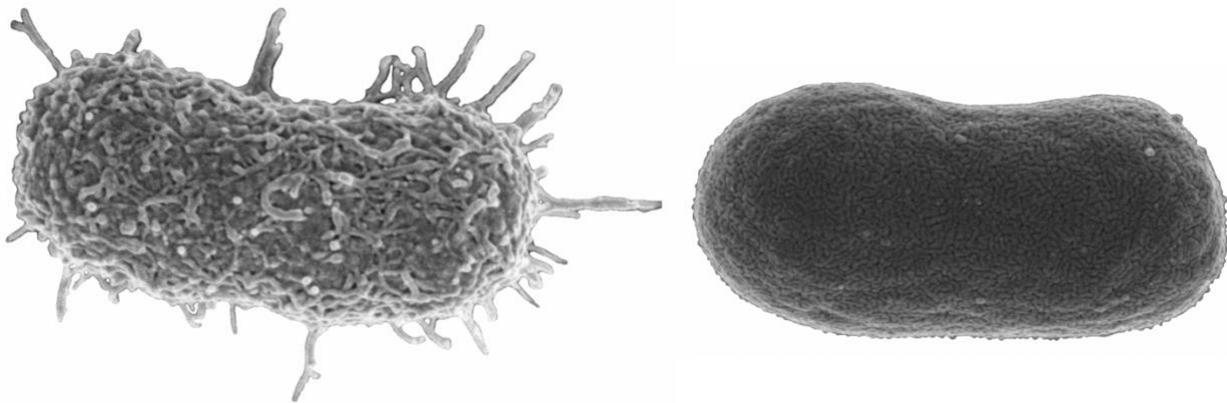
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### ABSTRACT

*We discovered viruses, called phages, that are capable of killing an antibiotic-resistant superbug lurking in intensive care units (ICUs). When the superbug tried to escape from phages it lost the protective layer that made it antibiotic-resistant. We forced the superbug into the dilemma of death by phages or death by antibiotics.*



Scanning electron micrographs of *Acinetobacter baumannii*. Credit: Dr Denis Korneev.

Most of us have suffered a bacterial infection at some point in our lives. Fortunately, a prompt prescription of the right antibiotic from our doctors puts us on the path to recovery. But in recent years, for an increasing number of patients, antibiotic treatments are failing. This is especially true if the place where the infections are acquired is a hospital.

Think about the amount of disinfectants, antibiotics, and cleaning procedures that are used in hospitals. Sure enough, they kill most of the microbes living there. But the ones that survive are ‘superbugs’, that is, they are bacteria that have evolved to resist all of those threats. Superbugs prey on the already vulnerable hospitalized patients, who frequently have underlying

conditions and weakened immune systems. It’s the perfect storm.

The specific superbug our research tries to fight is *Acinetobacter baumannii* (or *A. baumannii*, for short). It is responsible for up to 20% of infections in ICUs, affecting the lungs, wounds, and even bloodstreams, and carries a high mortality rate. In recent years, *A. baumannii* has become incredibly resistant to antibiotics, prompting the World Health Organization to call it a ‘critical threat’.

Let us take a detour here and recognize how the COVID-19 pandemic, caused by a virus, has turned our lives upside down. It might lead you to think all viruses are dangerous, and hardly anyone could blame you. However, referring back to our

novel research, you might be surprised to know that we work with viruses that can be our allies.

Bacteriophages (or phages) are viruses that—instead of infecting and killing human cells—only infect and kill bacteria. Phages are everywhere, from the soil outside our houses, to oceans, to even our guts and skin. They are quite picky: a certain phage will only kill a specific type of bacteria. This is because the proteins on the tail end of a phage need to match and attach to receptors on the surface of the bacterial cell in a lock-and-key fashion to initiate infection. Our project began hunting for phages that had the key to kill *A. baumannii*.

We found the phages we were looking for in raw sewage (untreated waste water) which is incredibly rich in all sorts of microbes. We cleaned and characterized them. When we added them to cultures of *A. baumannii*, we were pleased to see they annihilated the bacterial population, or so we thought.

Through the process of evolution, many bacteria can outsmart life threatening agents, including antibiotics and phages. In our experiments, after merely 8 hours we observed the emergence of a bacterial population capable of resisting the phages' attack. They were phage-resistant mutants.

Our research took a turn, and we sought to discover the method through which *A. baumannii* had become phage-resistant. To do this, we first compared the genetic makeups of the original bacteria and the phage-resistant mutants to find the differences between them. We found that the phage-resistant mutants had errors in the genes that would normally contain the

instructions to produce a bacterial structure called 'capsule'.

The bacterial capsule is an outer layer made up of sugars. It covers and protects bacteria; because it is sticky, it helps bacteria attach to medical devices and human tissues; and because it is thick and viscous, it stops the entry of antibiotics.

Our genetic analysis suggested that the phage-resistant population lacked these capsules, however, we looked for further confirmation. We used high power microscopy to explore the surface of the bacteria. The picture atop this article shows our results. To the left, the original *A. baumannii* has its beautiful sticky capsule intact; to the right, the surface of phage-resistant *A. baumannii* looks flat and dull. The capsule is gone.

Next, we questioned why the lack of capsule was protecting *A. baumannii* from our phages. Utilizing an 'adsorption assay', where we test if phages can bind to bacteria, we discovered that our phages could not perform the lock-and-key recognition of capsule-deficient bacteria. Our phages had the key, but the lock was nowhere to be found.

However, because we knew that capsules prevent the entry of antibiotics, we tested if *A. baumannii* had lost some of its resistance to antibiotics. Out of nine tested antibiotics, we observed this 'resensitization' effect with seven of them. In trying to escape from phages, *A. baumannii* had let its guard down against antibiotics.

Our results show that we can take advantage of bacterial evolution and use phages and antibiotics in combination to

treat this dangerous superbug. We are currently working on animal trials of our therapeutic one-two-punch approach. Our end goal is to have a proven weapon against *A. baumannii* infections and, hopefully, to make ICUs safer.