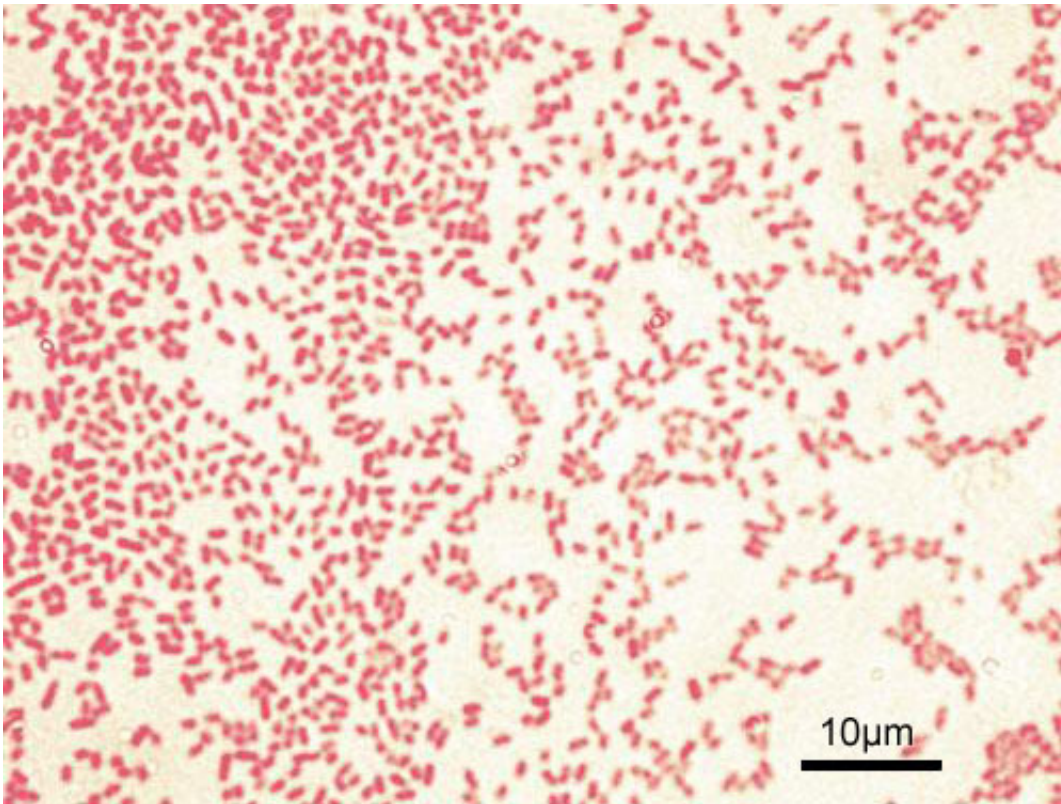


Peptide cocktails show promise in combating antibiotic resistance

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Gram-stained *P. aeruginosa* bacteria (pink-red rods) Credit: Wikipedia

Antibiotics are essential tools in modern medicine, regularly used to treat bacterial infections and prevent infections during surgery. However, the widespread use of antibiotics has led to many bacteria developing resistance, posing a significant threat to public health.

A recent study [published](#) in *PLOS Biology* highlights the urgent need for new strategies to control bacterial infections due to the growing threat of antibiotic-resistant pathogens. Proper antibiotic use, quick diagnostics, and careful development of new antimicrobial agents, ideally less likely to select for resistance than current antibiotics, are crucial.

Antibiotic resistance is emerging as a pressing global health challenge. While individuals themselves do not become resistant to antibiotics, the bacteria causing infections can develop this resistance, leading to more difficult-to-treat illnesses. Recent data from the World Health Organization highlights the severity of this issue, with some countries reporting resistance rates as high as 42% for certain common bacterial strains. In the United States, the Centers for Disease Control and Prevention estimates that over 2 million antibiotic-resistant infections occur annually, underscoring the urgency of addressing this crisis.

The study explored whether newly developed random antimicrobial peptide mixtures can significantly reduce the risk of resistance evolution compared to single sequence [antimicrobial peptides](#). The research team used the ESKAPE pathogen *Pseudomonas aeruginosa*, a model gram-negative bacterium, known for its challenging infections due to inherent resistance to many drug classes and its ability to form biofilms.

Pseudomonas aeruginosa was experimentally evolved in the presence of antimicrobial peptides or random antimicrobial peptide mixtures to assess resistance evolution and cross-resistance between treatments. The study also examined the fitness costs of resistance on bacterial growth and used whole-genome sequencing to identify mutations responsible for resistance. Additionally, changes in the pharmacodynamics of the evolved bacterial strains were analyzed.

The findings suggest that random antimicrobial peptide mixtures pose a much lower risk of resistance evolution compared to single antimicrobial

peptides and mostly prevent cross-resistance to other treatments while maintaining or improving drug sensitivity.

The study was led by Prof. Zvi Hayouka from the Institute of Biochemistry Food science and Nutrition at the Faculty of Agriculture, Food and Environment at the Hebrew University of Jerusalem, and Prof. Jens Rolff from the Freie Universität Berlin, along with postdoctoral fellow Dr. Bernardo Antunes, who was affiliated with both Hebrew University and Freie Universität Berlin.

Prof. Hayouka emphasized the significance of their work, stating, "The growing threat of antibiotic-resistant bacteria demands innovative solutions. Our research on random antimicrobial peptide mixtures presents a promising approach to outpace bacterial resistance, offering a viable alternative to traditional antibiotics and safeguarding public health."

This research suggests that *Pseudomonas aeruginosa* can detect these antimicrobial agents but cannot develop effective resistance within 4 weeks in vitro. Additionally, these antimicrobial peptide cocktails are affordable to synthesize and have proven to be non-toxic and non-hemolytic in a [mouse model](#) with strong efficacy profiles in several mouse models of the human pathogenic bacterial infection model.

The findings advocate for the use of random antimicrobial peptide cocktails over single peptides, as resistance developed in vitro against single peptides. Despite some antibiotics, like Teixobactin, initially being deemed "resistance-proof," this was later disproven, necessitating caution even with the promising results for the random peptide mixture.

Further research should explore the interaction of these random peptide mixtures with the host immune system. Employing peptides that synergize with the host response could diminish dosage requirements and

side effects. This approach could be a cost-effective method to reduce bacterial loads and prevent resistance.

"It will still be quite some time before we are ready for practical applications," says Prof. Jens Rolff. "Still, our current work demonstrates the potential that these combinations have when it comes to reducing antimicrobial resistance."

More information: Bernardo Antunes et al, The evolution of antimicrobial peptide resistance in *Pseudomonas aeruginosa* is severely constrained by random peptide mixtures, *PLOS Biology* (2024). [DOI: 10.1371/journal.pbio.3002692](https://doi.org/10.1371/journal.pbio.3002692)

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