Medical Xpress

Researchers first to predict when bacteria may become resistant to antibiotics

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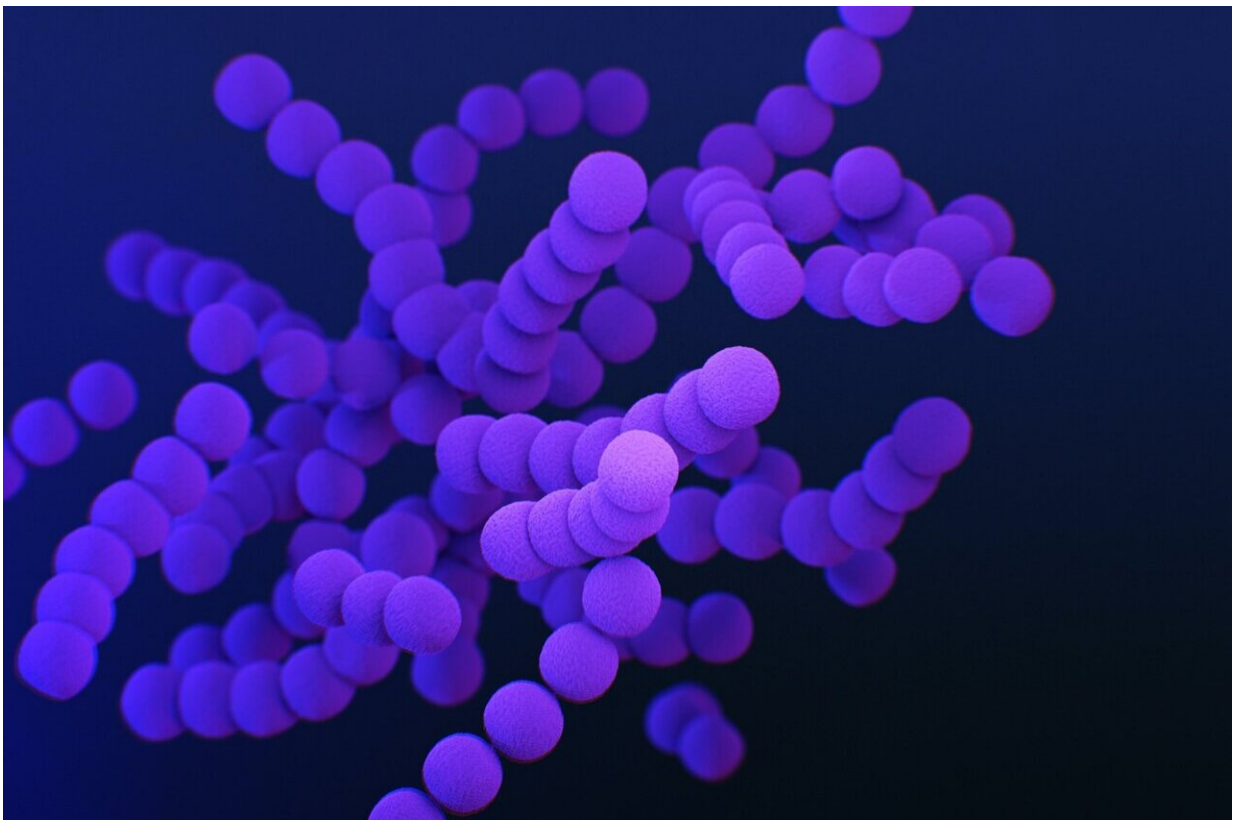

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Scientists have spotted signs of 'pre-resistance' in bacteria for the first time—signs that particular bacteria are likely to become resistant to antibiotics in the future—in a new study led by UCL and Great Ormond

Street Hospital researchers.

The findings, published in *Nature Communications*, will allow doctors in the future to select the best treatments for bacterial infections.

The team led by Great Ormond Street Hospital (GOSH) and the UCL Great Ormond Street Institute of Child Health, in collaboration with the Peruvian Tuberculosis program and funded by Wellcome and the National Institutes of Health (U.S.), sequenced the full genomes of over 3,000 tuberculosis (TB) samples, tracing TB infections back through patients over nearly two decades.

Mycobacterium tuberculosis (TB) is a bacterial infection that largely affects the lungs. It was the second leading infectious cause of death after COVID-19 in 2020, killing 1.5m people. It can be cured if treated with the right antibiotics, but treatment is lengthy and many people most at risk lack access to adequate healthcare. Drug-resistant TB can develop when people do not finish their full course of treatment, or when drugs are not available or are of poor quality.

Multi-drug resistant TB represents a huge, unsustainable burden and totally drug resistant strains have been detected in a handful of countries. As health systems struggle to cope with the pandemic, progress on TB treatment globally has slowed.

In order to develop a better understanding of, and ultimately better treatments for, TB, this new research has identified for the first time how to pre-empt drug resistance mutations before they have occurred. The researchers have termed this concept 'pre-resistance': when a disease-causing organism—such as a virus or bacteria—has a greater inherent risk of developing resistance to drugs in the future.

By analyzing thousands of bacterial genomes, the study has the potential

to be applied to other infectious diseases and paves the way towards personalized pathogen 'genomic therapy'—where drugs are selected based on the DNA of the specific pathogen causing the illness, preventing drug resistance from developing.

The work is the culmination of 17 years' research in the suburbs of Lima, Peru, where Dr. Louis Grandjean, Consultant in Infectious Diseases at GOSH and Associate Professor at UCL Great Ormond Street Institute of Child Health, leads a research group.

The international team compared tuberculosis samples from 3,135 different samples to reconstruct a TB bacterial 'family tree' – known as phylogeny. The team then used computational analysis to identify the ancestral genetic code of bacteria that then went on to develop drug resistance. The team identified the key changes associated with the development of resistance by looking through the 'branches' of the family tree to see which were the most likely to go on to develop drug resistance.

The authors described how variations in the TB genome predicted that a particular branch would likely become drug resistant, and then validated their findings in an independent global TB data set.

Dr. Grandjean, senior author of the international study, said: "We're running out of options in antibiotics and the options we have are often toxic—we have to get smarter at using what we have to prevent drug resistance.

"This is the first example of showing that we can get ahead of drug resistance. That will allow us in the future to use the pathogen genome to select the best treatments."

Ph.D. student Arturo Torres Ortiz (UCL Great Ormond Street Institute

of Child Health), first author of the paper, said: "We hope this discovery could provide a way of treating difficult conditions in the future by targeting specific pathogen genomes that are most likely to become drug resistant in the future."

More information: Genomic Signatures of Pre-Resistance in Mycobacterium tuberculosis, *Nature Communications* (2021). DOI: 10.1038/s41467-021-27616-7

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