

Staying 1 step ahead: Research shows how bacteria keep ahead of vaccines and antibiotics

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New research provides the first detailed genetic picture of an evolutionary war between *Streptococcus pneumoniae* bacteria and the vaccines and antibiotics used against it over recent decades. Large-scale genome sequencing reveals patterns of adaptation and the spread of a drug-resistant lineage of the *S. pneumoniae* bacteria.

The study unmask the genetic events by which bacteria such as *S. pneumoniae* respond rapidly to new antibiotics and vaccines. The team suggest that knowing the enemy better could improve [infection control](#) measures.

S. pneumoniae is responsible for a broad range of human diseases, including [pneumonia](#), [ear infection](#) and [bacterial meningitis](#). Since the 1970s, some forms of the bacteria have gained resistance to many of the antibiotics traditionally used to treat the disease. In 2000 *S. pneumoniae* was responsible for 15 million cases of invasive disease across the globe. A new vaccine was introduced to the US in 2000 in an attempt to control disease resulting from the most common and drug resistant forms of the bacteria.

The new research uses DNA sequencing to precisely describe the recent evolution and success of a drug-resistant lineage of the bacteria called PMEN1 that has spread successfully to all continents.

"Drug resistant forms of *S. pneumoniae* first came onto the radar in the 1970s," says Dr Stephen Bentley, from the Wellcome Trust Sanger Institute and senior author on the study. "We sequenced 240 samples collected over the course of 24 years from the PMEN1 lineage of *S. pneumoniae*. By comparing the sequences, we can begin to understand how this [bacterium](#) evolves and reinvents itself genetically in response to human interventions."

The power of next-generation sequencing exposes *S. pneumoniae* as a pathogen that evolves and reinvents itself with remarkable speed. The degree of diversity was a real surprise in such seemingly closely related organisms.

First, the team had to distinguish between single letter mutations that are passed down 'vertically' when cells divide in two, and so-called 'horizontal' changes – called recombinations – where chunks of DNA letters are passed across from one bacterium to another and swapped over, changing the structure of their genomes.

"Separating these two kinds of change was the critical first step in unlocking the evolutionary history of the PMEN1 lineage," says Professor Julian Parkhill, Head of Pathogen Genomics at the Wellcome Trust Sanger Institute. "By looking only at the DNA mutations that are passed down through direct ancestry, we constructed an evolutionary tree. When we looked at our tree, we could see that the drug-resistant PMEN1 lineage originated around 1970 – about the time that saw the introduction of the widespread use of antibiotics to fight pneumococcal disease."

The team also use their tree to trace the origin of PMEN1 to Europe, and suggest that the lineage may have been introduced to the Americas and Asia on multiple occasions.

The 'vertical' mutations, however, could not fully account for the evolution and adaptability of this pathogen.

The team found that the 'horizontal' transfer of DNA had affected three-quarters of the *S. pneumoniae* genome. The team also found hotspots – areas of the genome that are particularly affected by horizontal transmission.

"We found that genes for antigens – the molecules that trigger our immune response – were particularly prone to this kind of change," says Dr William Hanage, Associate Professor of Epidemiology at Harvard School of Public Health, and a Visiting Reader at Imperial College London, where he devised the study with scientists at the Wellcome Trust Sanger Institute. "The remarkable amount of variation at these hotspots hints at ways *S. pneumoniae* can evade vaccines against these antigens.

"If the immune system targets these antigens, then the bacteria can simply change them, like a criminal changing their appearance to evade detection."

The authors also identify differences in the patterns of adaptation in response to antibiotics and vaccines.

"With antibiotics, different strains quite often adapt in the same way to become resistant," says Nicholas Croucher, from the Wellcome Trust Sanger Institute and first author on the paper. "With vaccines, it is quite different. What we see is a decline in the prevalence of bacteria that are susceptible to the vaccine. This, in turn, opens the door for bacteria that can evade the vaccine to fill the niche and become the dominant strain."

While the latest vaccination measures in the USA have almost completely removed the target pneumococcal strains from the

population, the pathogen has deep resources to draw on in response. The research suggests that variants that allowed some bacteria to escape the new vaccine were present before the vaccine was introduced. These variants then flourished, expanding to fill a 'gap in the market' as the grip of the dominant strain was weakened through vaccination.

The researchers suggest that the study provides important new clues into the genetic adaptability of bacteria like *S. pneumoniae*. They suggest that further focused sequencing programs may prove crucial to the future control of this, and other, bacterial [pathogens](#) that use similar mechanisms to outsmart human control measures.

More information: Croucher, NJ et al. (2010) Rapid pneumococcal evolution in response to clinical interventions. *Science*.

Provided by Wellcome Trust Sanger Institute

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