New research traces evolutionary path of multidrug-resistant strep bacteria

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Despite penicillin and the dozens of antibiotics that followed it, streptococcus bacteria have remained a major threat to health throughout the world. The reason: the superb evolutionary skills of this pathogen to rapidly alter its genetic makeup. In a landmark paper published this week in *Science*, scientists from Rockefeller University and the Sanger Institute have used full genome sequencing to identify the precise steps in the molecular evolution of *Streptococcus pneumoniae*. Their research shows the changes the genome of this bacterium has undergone in time and during its massive geographic spread over the globe.

According to the World Health Organization, fatal pneumococcal disease — mostly among children from underdeveloped countries — claims an estimated 4 million casualties per year. Humans are not only the primary targets of pneumococcal disease but also represent the major and possibly the only ecological reservoir on our planet for this bacterial species, which colonizes the nasopharynx of preschool age children.

The researchers, led by the Sanger Institute's Stephen D. Bentley, used high resolution genome sequencing on clinical isolates of *S. pneumoniae* provided by a number of collaborating laboratories, including the Laboratory of Microbiology and Infectious Diseases at Rockefeller University, headed by Alexander Tomasz. With data available for the date, geographic site and infection site of these isolates, Bentley and colleagues were able to produce a roadmap for the evolution of a major multidrug resistant clones of pneumococci known as the PMEN clone 1, sequence type 81.

The scientists pinpointed the probable date of birth, 1970, and the likely birthplace, Europe, of this extremely successful multidrug resistant clone. The clone then spread to South and North America, South Africa and Asia. The presence of this clone in 12 New York City hospitals was demonstrated by Tomasz's group in 2001. Perhaps more importantly, the findings provide evidence that the mechanism of genetic change in *S. pneumoniae* is primarily not through acquisition of point mutations but more often — 88 percent of the time — through genetic recombination.

"The phenomenon of genetic transformation, which led Oswald Avery and his Rockefeller colleagues in 1944 to identify DNA as the genetic material, is the very process that Streptococcus pneumoniae uses during evolution in its real in vivo environment," says Tomasz.

Other phenomena first identified in the laboratory also appear in stages of pneumococcal evolution in vivo. For instance, at least some of the recombination changes observed among the clinical isolates seem to use the "competence" system, a DNA uptake mechanism induced by a specific bacterial quorum sensing agent first detected by Tomasz and colleagues in laboratory experiments. Also, the mechanism of penicillin resistance, first identified by Tomasz and colleagues in the 1980s as changes in the affinity of penicillin target proteins known as penicillin binding proteins, or PBPs, is shown to involve the borrowing of genes from other bacteria, a finding previously documented in studies of individual penicillin resistant isolates.

"Perhaps the most fascinating part of the research is the description of how rapidly this clone has responded to massive in vivo interventions in the clinical environment, such as the introduction of penicillin and other antibiotics and — more recently — the introduction of conjugate anti-pneumococcal vaccines," says Tomasz. "These vaccines are directed against the most abundant serotypes of this bacterium, which are carried in the nasopharynx of children and which cause invasive disease."

"This research also demonstrates the importance of close collaborations between groups like the Sanger Laboratory, with expertise in high resolution genomic analysis, and laboratories that can provide carefully characterized collections of bacterial isolates, such as ours. This type of collaboration fits well with the Rockefeller University's tradition of engaging in studies that combine clinical with translational science," says Tomasz. "Such an alliance between molecular biology and epidemiology promises further interesting insights into the mechanism of bacterial evolution in vivo. It may ultimately allow us to understand PMEN-1's secret of success – to learn why this clone was able to spread so widely while others died off."

Provided by Rockefeller University