Medical Xpress

Tracking MRSA evolution and transmission

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For the first time, researchers have shown how transmission of MRSA from one person to another can be precisely tracked in a hospital setting. The team have developed a remarkable new method that can 'zoom' from large-scale inter-continental transmission events to the much finer detail of person-to-person infection of MRSA within a single hospital.

The ability to track strains in this way will enable researchers to understand how strains can spread so rapidly, and should lead to novel infection control strategies, not only for MRSA but also for other emerging superbugs.

The team used new very high-throughput DNA sequencing technologies to compare individual MRSA isolates from patients to precisely show their genetic relatedness. Very quickly they were able to spot single-letter changes in the genetic code and to identify differences between even the most closely related of MRSA isolates.

"We looked at two very different sets of samples," explains Dr Simon Harris, from the Wellcome Trust Sanger Institute and co-lead author on the study. "We have 42 samples taken from people across the globe, who became infected with MRSA between 1982 and 2003. The second set is from a single hospital in northeast Thailand, and consists of 20 samples from patients who developed MRSA infection within 7 months of each other, all possibly linked by a chain of person-to-person transmission"

"We wanted to test whether our method could successfully zoom in and out to allow us to track infection on a global scale - from continent-to-

continent, and also on the smallest scale - from person-to-person."

The team sequenced the whole genomes of all the samples using a next-generation DNA sequencing technology. This technique reveals the minutiae of single-letter genetic changes in the hospital samples, and showed that no two infections were caused by entirely identical bacteria. Based on these subtle genetic differences, the researchers divided the Thai hospital samples into two groups. In the larger group of 13 bacteria they found five which were extremely similar and differed altogether by just 14 single-letter changes.

"This group of five related MRSA strains caused infections in patients who were resident in intensive care units in adjacent blocks of the hospital," explains Dr Ed Feil, from the Department of Biology and Biochemistry at the University of Bath and co-lead author on the study, "and all were isolated within a few weeks of each other. By contrast, bacteria from patients housed in other parts of the hospital were much less similar."

"This cemented our theory - based on the sequence comparison - that there were two different groups of isolates that had had been introduced to the hospital separately."

Importantly, the team was also able to determine the rate at which DNA sequence typically mutated, providing an unprecedented insight into the rate of evolution in vivo. The particular MRSA strain studied acquired about one single-letter change every six weeks.

To understand better the evolution and global spread of MRSA over several decades and large geographic distances, the team looked at samples from hospitals in North and South America, Europe, Australia and Asia collected over a period of more than twenty years by the CEM/NET Initiative, an international project in molecular epidemiology

organized by Instituto de Tecnologia Química e Biológica (ITQB) and The Rockefeller University - and headed by Dr Herminia de Lencastre.

By identifying single letter changes in the individual genomes and making calculations based on the dates at which the samples were taken, the team derived a mutation rate and developed an evolutionary tree of MRSA. One major interest from these studies is to suggest where and when this type of MRSA might have emerged.

The European isolates were concentrated around the base of the evolutionary tree and their calculated mutation rate suggested that this MRSA emerged in the 1960s in Europe, bolstering established theories that the origins of MRSA correlate with the introduction of widespread antibiotic use in Europe in the 1960s.

The team also found that clusters of isolates that were genetically very similar were typically also highly consistent in their geographic source.

"Telling the difference between isolates within one species is fundamentally important in the development of public health strategies," says Dr Stephen Bentley, from the Wellcome Trust Sanger Institute and senior author on the study. "It allows researchers and public health officials to see how infections are spread: from person to person; from hospital to hospital; from country to country."

For many years, scientists have been searching for improved methods to allow them to distinguish, reliably and within the same species, one bacterial isolate from another. Until now, even the best methods for identifying the differences between bacterial genomes have been unable to differentiate between all isolates - leaving gaps and uncertainties in pathways of transmission.

The success of the new method relies on comparing whole genomes,

whereas previous methods have relied on looking at either single loci or limited numbers of regions in the genome.

"This new method has allowed us to gain insights into fundamental processes of evolution in S. aureus, one of the most important bacterial pathogens in healthcare in the world," explains Dr Sharon Peacock, from the Department of Medicine at the University of Cambridge University and the Faculty of Tropical Medicine at Mahidol University, Bangkok, Thailand and an author on the study. "We are now able to discriminate between one strain and another, even where they are very closely related. Our research should inform global surveillance strategies to track the spread of MRSA.

"The implications for public health are clear: this technology represents the potential to trace transmission pathways of MRSA more definitively so that interventions or treatments can be targeted with precision and according to need.'

It is not only applicable to MRSA: the research reaches further into public health. The team suggest that the new approach could underpin future studies into the transmission and evolution of other bacteria that are a significant health burden.

More information: Harris S, Feil EJ et al. (2010) Evolution of MRSA during hospital transmission and intercontinental spread. *Science*. Available online at doi: 10.1126/science.1182395

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