Defining DNA differences to track and tackle typhoid

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For the first time, next-generation DNA sequencing technologies have been turned on typhoid fever - a disease that kills 600,000 people each year. The results will help to improve diagnosis, tracking of disease spread and could help to design new strategies for vaccination.

The study sets a new standard for analysing the evolution and spread of a disease-causing bacterium: it is the first study of multiple samples of any bacterial pathogen at this level of detail. It uncovers previously hidden genetic signatures of the evolution of individual lineages of *Salmonella Typhi*.

The team developed methods that are being used to type outbreaks, allowing researchers to identify individual organisms that are spreading in the population: using Google Earth, the outbreaks can be easily visualized. The team hope that these mapping data can be used to target vaccination campaigns more successfully with the aim of eradicating typhoid fever.

Unlike most related *Salmonella* species, and in contrast to many other bacteria, *Typhi* is found only in humans and the genomes of all isolates are superficially extremely similar, hampering attempts to track infections or to type more prevalent variants. The detail of the new study transforms the ability of researchers to tackle *Typhi*.

"Modern genomic methods can be used to develop answers to diseases that have plagued humans for many years," explains Professor Gordon

Dougan from the Wellcome Trust Sanger Institute and senior author on the study. "Genomes are a legacy of an organism's existence, indicating the paths it has taken and the route it is on. This analysis suggests we may have found *Typhi*'s Achilles' heel: in adapting to an exclusively human lifestyle, it has become complacent, its genome is undergoing genetic decay and it's heading up an evolutionary dead end in humans.

"We believe that concerted vaccination programmes, combined with epidemiological studies aiming to track down and treat carriers, could be used to eradicate typhoid as a disease."

There are 17 million cases of Typhoid fever each year - although the World Health Organization cautions that this is a 'very conservative' estimate. Young people are most at risk: in Indonesia, nine out of ten cases occur in 3-19-year-olds.

"A key to survival of *Salmonella Typhi* is its ability to lie dormant in carriers, who show no symptoms but remain able to infect others," says Kathryn Holt, a PhD student at the Wellcome Trust Sanger Institute and first author on the study. "Our new tools will assist us in tracing the source of typhoid outbreaks, potentially even to infected carriers, allowing those individuals to be treated to prevent further spread of the disease.

"Using the genomic biology of this study, we can now type *Typhi*, identify the strain that is causing infection, identify carriers and direct vaccination programmes most efficiently. It is a remarkable step forward."

The study is a collaboration between researchers at the Wellcome Trust Sanger Institute, University College, Cork, Institut Pasteur in Paris and Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam. The team studied 19 isolates of *Typhi* from ten countries, using new

sequencing methods that meant they could capture the rare signals of genetic variation in this stubborn genome. They produced more than 1.7 billion letters of genetic sequence and found evidence of fewer than 2000 mutation events, suggesting very little evolution since the emergence of *Typhi* at least 15,000 years ago.

Their analysis shows that the *Typhi* genome is decaying - as it becomes more closely allied to us, its human host, it is losing genes that are superfluous to life in the human body. More importantly, genes that contain instructions for the proteins on the surface of the bacterium - those most often attacked by our immune system defences - vary much less than do the equivalent genes in most other bacteria, suggesting that *Typhi* has a strategy to circumvent the selective pressures of our immune system.

"Both the genome and the proteins that make up the surface of *Typhi* - the targets for vaccines - show amazingly little variation," says Professor Julian Parkhill, Head of Pathogen Genomics. "We have been able to use novel technologies, developed for the analysis of human genome variation, to identify this variation: this would have been impossible a year ago. The technologies we have developed here could also be used in the battles against other disease-causing bacteria."

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