Key genetic clue missing in fight against superbugs

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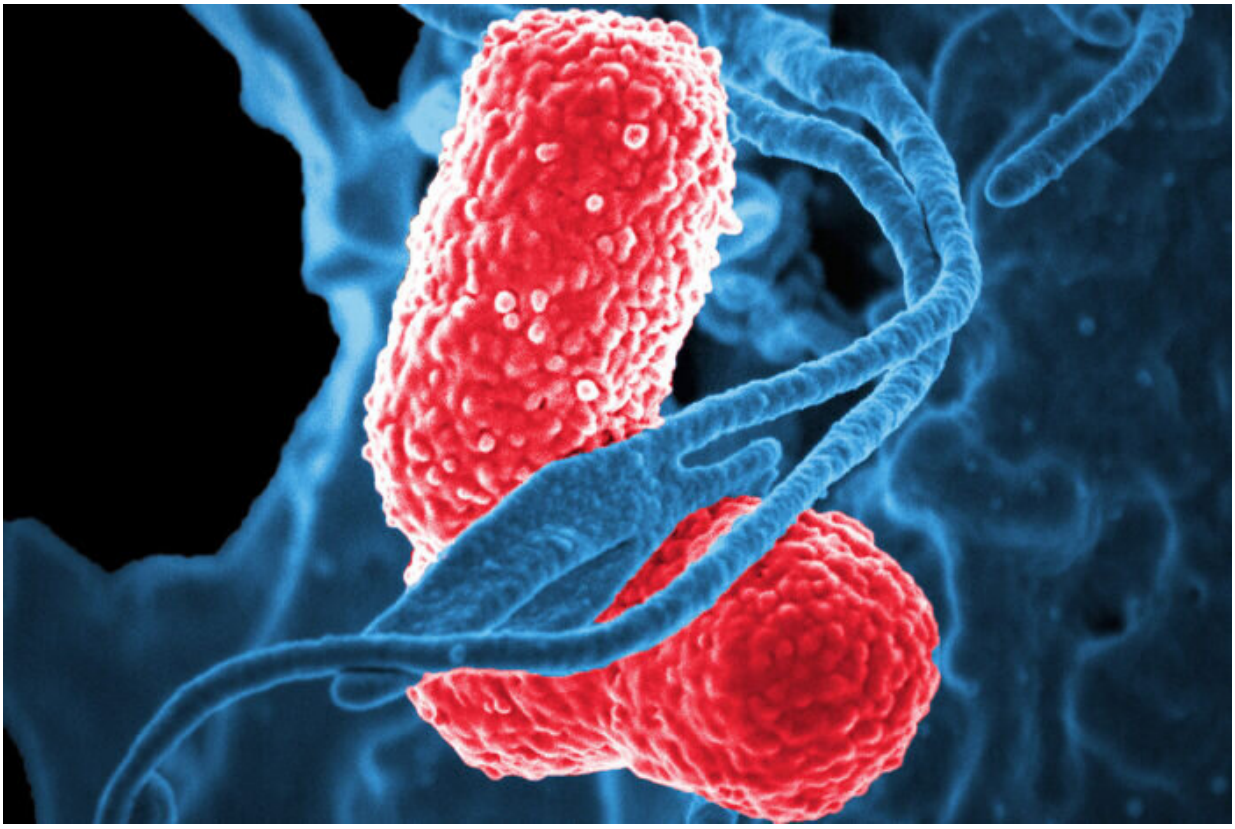

White blood cells (blue) attack two Klebsiella bacteria (pink) in this colorized scanning electron microscopic image. Credit: David Dorward/NIAID

For the first time, researchers have discovered how antibiotic resistance genes are spreading, at a continental scale, via bacterial plasmids in the

hospital superbug, Klebsiella pneumoniae.

Researchers from the Center for Genomic Pathogen Surveillance, based jointly at the Wellcome Sanger Institute and the Big Data Institute, University of Oxford, together with their collaborators used genome sequencing technology to analyze plasmids—genetic structures in bacteria that can carry antibiotic resistance genes—as well as bacterial chromosomes from K. pneumoniae samples taken from European hospital patients.

The findings, published today (24th September) in *Proceedings of the National Academy of Sciences*, reveal three different pathways by which antibiotic resistance genes spread via plasmids through bacterial populations. Researchers say it is critical that plasmids are included when tracking antibiotic resistance in order to have the best chance of stopping superbugs.

Members of the Enterobacteriaceae family of bacteria can become resistant to last-line antibiotics called carbapenems, and are listed as a critical threat in the World Health Organization's list of priority pathogens. Within this family, Klebsiella pneumoniae is an opportunistic pathogen that causes serious diseases, including pneumonia and meningitis.

K. pneumoniae becomes resistant to carbapenems by acquiring antibiotic resistance genes, known as carbapenemase genes, which code for an enzyme that chews up the antibiotic.

In K. pneumoniae, these carbapenemase genes are usually found on plasmids—smaller circular pieces of DNA that are additional to the bacterial chromosome. Plasmids can jump between different strains and species of bacteria, meaning antibiotic resistance genes can quickly spread and drive the rapid rise in antibiotic resistant bacterial infections

worldwide.

Therefore, researchers must include plasmids when tracking the evolution and spread of bacteria to get a true picture of how antibiotic resistance genes are spreading. However it has previously been difficult to use genome sequencing to reliably track plasmid evolution, due to the variability in size and structure of their genetic sequences.

Now with long-read sequencing technology researchers are able to read and reconstruct complete sequences for plasmids.

In a new study, researchers from the Center for Genomic Pathogen Surveillance and their collaborators conducted long-read genome sequencing on 79 K. pneumoniae samples from patients, taken from a Europe-wide survey.

The team generated complete plasmid sequences from these samples, and studied them along with more than 1700 previously short-read sequenced K. pneumoniae samples from the same survey to understand how antibiotic resistance genes are spreading through the bacterial population in European hospitals.

Dr. Sophia David, first author from the Center for Genomic Pathogen Surveillance said: "To fully understand how antibiotic resistance is spreading, we need to consider the role of plasmids. In this study, which is the first to analyze the genetic sequences of plasmids at a continental scale, we discovered three primary routes by which antibiotic resistance genes are spreading via plasmids through the K. pneumoniae population."

The three pathways of transmission involve one plasmid jumping between multiple strains, multiple plasmids spreading among multiple strains, and multiple plasmids spreading within one strain of K.

pneumoniae.

Professor Hajo Grundmann, co-lead author from the University of Freiburg in Germany, said: "These new insights into the three routes of spread of antibiotic resistance genes in K. pneumoniae are critical for controlling outbreaks of antibiotic resistant infections. Knowing these transmission strategies enables tailoring of interventions, either to control the dominant plasmid, control the dominant strain, or in complicated situations, control both. For example, if there was a hospital outbreak and the strain carried a high-risk plasmid, there's a chance this plasmid might jump into other bacterial strains or species, which would need to be monitored."

The team also found that plasmids encoding carbapenemase genes were most successful in spreading when acquired by a high-risk strain. This reinforces the importance of preventing transmission of high-risk strains through early detection and rigorous infection control in healthcare environments.

Professor David Aanensen, co-lead author and Director of the Center for Genomic Pathogen Surveillance said: "When tracking certain antibiotic resistant bacteria, plasmids are one of the missing parts of the puzzle. Analyzing the genetic sequences of both bacterial chromosomes and plasmids can give us a more detailed picture of how antibiotic resistance genes and mechanisms spread in a population. Genomic surveillance of bacteria should include plasmids and other mobile elements in order to tackle the rise in antibiotic resistant infections."

More information: Sophia David et al. Integrated chromosomal and plasmid sequence analyses reveal diverse modes of carbapenemase gene spread among Klebsiella pneumoniae, *Proceedings of the National Academy of Sciences* (2020). DOI: 10.1073/pnas.2003407117

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