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From heteroresistance to resistance: a single nucleotide polymorphism (SNP) homogenizes population plasticity of gene amplification based heteroresistance

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Introduction
Heteroresistance (HR) describes the ability of a subpopulation to grow in the presence of inhibitory antibiotic concentrations. We found HR to ceftazidime (CAZ) in a clinical *Enterobacter cloacae* complex (ECC) strain (IMT49658).

Material & Methods
We performed extensive phenotypic (population analysis profiles, stability analysis of resistance, ScanLag) and molecular microbiological techniques (qRT-PCR, whole genome sequencing, raw read analysis) in order to show the plasticity and mechanism of HR in this ECC strain. We re-investigated the genome and phenotype of IMT 49658 after long-term evolution in 32 g/ml CAZ.

Results
WGS detected a plasmidal gene amplification with β-lactamase ampC *bla*DHA-1. qRT-PCR showed a high genomic copy number of *bla*DHA 1 in resistant subpopulations, decreasing when they reverted to susceptibility. Gene amplifications varied in single cells of one colony (raw read analysis). Resistant subpopulations showed heterogeneous lag times in ScanLag. After evolving ECC for 21 days in CAZ, we discovered a SNP in *dacB*, encoding for a stop codon. This mutant displayed low amplification levels but resistance in disk diffusion and homogenous lag times.

Conclusion
Long-term evolution in antibiotic niches drives the emergence of new resistant mutants, balancing the fitness costs of e.g., gene amplifications. Comprehension of the transition from HR to resistance is inevitable for successful treatment of infections from zoonotic bacteria.

Keywords

heteroresistance, plasticity, ceftazidime, Enterobacter spp.

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Professional Status of the Speaker

PhD Student

Junior Scientist Status

Yes, I am a Junior Scientist.

Primary author: Mr KUPKE, Johannes (Institute of Microbiology and Epizootics, FU-Berlin)

Co-authors: Mr BROMBACH, Julian (Institute of Microbiology and Epizootics Freie Universität Berlin); Mr WOLF, Silver Anthony (3Robert Koch Institute (RKI), MF2-Genome Sequencing and Genomic Epidemiology); Mrs THRUKONDA, Lakshmipriya (3Robert Koch Institute (RKI), MF2-Genome Sequencing and Genomic Epidemiology); Dr GHAZISAEEDHI, Fereshteh (Institute of Microbiology and Epizootics, Centre for Infection Medicine, Department of Veterinary Medicine, Freie Universität Berlin); Dr HANKE, Dennis (Institute of Microbiology and

Epizootics, Centre for Infection Medicine, Department of Veterinary Medicine, Freie Universität Berlin); Dr SEMMLER, Torsten (Robert Koch Institute (RKI), MF2-Genome Sequencing and Genomic Epidemiology, Berlin); Dr TEDIN, Karsten (Institute of Microbiology and Epizootics, Centre for Infection Medicine, Department of Veterinary Medicine, Freie Universität Berlin); Dr NORDHOLT, Niclas (Federal Institute for Materials Research and Testing (BAM), Department of Materials and the Environment (Dpt. 4), Berlin); Dr SCHREIBER, Frank (Federal Institute for Materials Research and Testing (BAM), Department of Materials and the Environment (Dpt. 4), Berlin); Dr LÜBKE-BECKER, Antina (1.)Institute of Microbiology and Epizootics, Centre for Infection Medicine, Department of Veterinary Medicine, Freie Universität Berlin, 2.) Veterinary Centre for Resistance Research (TZR), Department of Veterinary Medicine, Freie Universität Berlin); Prof. FULDE, Marcus (1.) Institute of Microbiology and Epizootics, Centre for Infection Medicine, Department of Veterinary Medicine, Freie Universität Berlin, 2.) Veterinary Centre for Resistance Research (TZR), Department of Veterinary Medicine, Freie Universität Berlin)

Presenter: Mr KUPKE, Johannes (Institute of Microbiology and Epizootics, FU-Berlin)

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