The emergence of *tet*(X) variants highlight challenges for the global genomic surveillance of tigecycline resistance

Tigecycline is one of the last-line antimicrobials against infections caused by multidrug-resistant bacteria. Recent articles published in *The Lancet Microbe* have highlighted the spread of tigecycline resistance mediated by the RND efflux pump gene cluster *tmexCD-toprJ*, in clinically important pathogens.[1–3] Conversely, plasmid-borne *tet*(X) genes encoding tigecycline-inactivating enzymes have been quietly emerging.[4] Despite more than 20 *tet*(X) variants having already been described, their identification by large-scale genomic data is restricted. Herein, we analysed the global genomic distribution of *tet*(X) genes and addressed limitations and challenges in analysing their variants.

Based on genomic data available from the National Database of Antibiotic Resistant Organisms as of June 23, 2023, only *tet*(X2), *tet*(X3), *tet*(X4), and *tet*(X5) genes were identified. These genes totaled 954 sequences, which were present in medically important bacterial species obtained from humans, animals, foods, and the environment during 2007-22, from all continents except Antarctica (appendix p 2). Overall, Asian countries host the most bacterial genomes carrying *tet*(X) genes. Moreover, an early spread of *tet*(X) genes also appears to be occurring in low-income and middle-income countries; however, the availability of whole-genome sequences of bacterial strains is still restricted. The *tet*(X4) gene was the most prevalent variant and its silent emergence and spread among bacterial pathogens might represent a serious clinical challenge. Worryingly, high-risk clones of *tet*(X4)-positive *Escherichia coli* strains co-harboring carbapenemase and *mcr* genes were recently described in Asian countries.[5] This problem might be related to the selective pressure of the widespread use of tetracyclines in the animal sector.

Furthermore, 130 *tet*(X)-like sequences were also detected, but their variants were not identified due to an outdated resistome database (appendix p 3). As a result, other clinically important *tet*(X) genes have not been detected and might be hidden among the unidentified *tet*(X) variants. Recently, a new system classifying *tet*(X) variants into groups was proposed.[6] These issues hinder the accurate identification and tracking of *tet*(X) genes, leading to an incomplete understanding of the tigecycline resistance landscape.

In summary, tigecycline resistance mediated by *tet*(X) genes has been increasing globally and the identification and genomic analysis of novel *tet*(X) variants requires closer attention. It is plausible that novel *tet*(X) variants will continue to emerge because of deep surveillance under the One Health initiative. Although whole-genome sequencing has revolutionised our understanding of microbial genomics, manual curation of variants remains laborious and is delaying the actual epidemiology of *tet*(X) genes. Therefore, the creation of a *tet*(X) gene curation working group, as previously performed for β-lactamases and *mcr* genes, would be imperative for solving the assignment of *tet*(X) variants in a publicly available database.

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*João Pedro Rueda Furlan, Danny Fuentes-Castillo, Eliana Guedes Stehling, Nilton Lincopan, and Fábio P Sellera
jpedro.rueda@usp.br

Department of Clinical Analyses, Toxicology and Food Science, School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, São Paulo 14040-903, Brazil (JPRF, EGS); Departamento de Patología y Medicina Preventiva, Facultad de Ciencias Veterinarias, Universidad de Concepción, Chillán, Chile (DF-C); Department of Microbiology, Instituto de Ciências Biomédicas, University of São Paulo, São Paulo, Brazil (NL); Department of Clinical Analysis, Faculty of Pharmacy, University of São Paulo, São Paulo, Brazil (NL); Department of Internal Medicine, School of Veterinary Medicine and Animal Science, University of São Paulo, São Paulo, Brazil (FPS); School of Veterinary Medicine, Metropolitan University of Santos, Santos, Brazil (FPS)

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