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Entitled

*THE ROLE OF PLASMIDS AND CLONES IN THE EMERGENCE OF CARBAPENEM RESISTANT
ENTEROBACTERIACEAE IN THE UNITED ARAB EMIRATES*

by

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Abstract

Resistance to carbapenems, the ultimate beta-lactam antibiotics used to treat life-threatening Gram-negative infections associates with very high mortality. Consequently, carbapenem resistant *Enterobacteriaceae* (CRE), which are usually multi- or extremely drug resistant, are considered a critical pathogen. To help controlling their spread, we investigated the molecular epidemiology of CRE in the United Arab Emirates (UAE) and its neighboring countries. CRE isolated in the UAE were screened for IncX3 incompatibility type plasmids carrying carbapenemases. The complete sequence of the IncX3 plasmids identified was established. Thirty CRE carried blaNDM-1, blaNDM-4, blaNDM-5, blaNDM-7, blaOXA-181 and blaKPC-2 on IncX3 plasmids. These CRE belonged to 16 sequence types of five different species. Phylogenetic analysis of the conserved regions of local IncX3 plasmids and of those described globally clustered them according to the carbapenemase genes carried, suggesting that they do not evolve locally, rather, are imported from other regions. Furthermore, we investigated members of the *Klebsiella pneumoniae* ST14 clone, which was found to be significantly associated with NDM- and OXA-48-like double carbapenemase production, with extreme drug resistance, and with being isolated from Emirati patients in Dubai. To gain a deeper insight into the molecular features of this clone, 39 CRKP-ST14 selected from five cities of the UAE, from Bahrain and from Saudi Arabia were subjected to whole genome sequencing, and their resistome, virulome and core genome MLST was assessed. cgMLST revealed three clusters of 16 isolates from five UAE cities (C1), 11 isolates from three UAE cities and Bahrain (C2) and the 5 isolates from Saudi Arabia (C3), respectively, and seven singletons. Resistance gene profile and carbapenemase carrying plasmid types were variable in both C1 and C2 clusters. Cluster 2 exhibited a capsular switch from K2 to K64. The successful dissemination of the CRKP-14 clone could be explained by the genetic flexibility demonstrated. Our data show that the emergence of CRE in the United Arab Emirates is a complex phenomenon of likely international transfer of successful plasmids, and also of countrywide clonal transmission of a genetically flexible high-risk *Klebsiella pneumoniae* clone.

Keywords: Enterobacteriaceae, carbapenem resistance, horizontal gene transfer, IncX3 plasmid, *Klebsiella pneumoniae* ST14 clone