

TITLE: COLISTIN-RESISTANT *Enterobacter kobei* HARBORYING *mcr* AND *bla*_{KPC-2} ARE ISOLATED FROM BRAZILIAN COASTAL WATER

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ABSTRACT:

Polymyxins are the last resort for the treatment of infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE). For this reason, the worldwide spread of horizontally transferred *mcr* genes responsible for colistin resistance is a global public health concern. As far as we know, the few reports of co-occurrence of *mcr* and carbapenemase-encoding genes are restricted to clinical settings in Brazil. This study focused on the characterization of two *Enterobacter kobei* isolates (CB-221 and CB-722) recovered from recreational coastal waters in Brazil that carried both *mcr* and *bla*_{KPC-2} genes. CB-221 and CB-722 were identified as *Enterobacter cloacae* complex by MALDI-TOF and found to produce carbapenemase by Carba-NP. Both isolates showed a multidrug-resistant phenotype with high colistin MICs (32 and >512 ug/mL for CB-221 and CB-722, respectively). Whole-genome sequencing (WGS) confirmed both strains as *E. kobei*. Resistome analysis identified acquired resistance determinants to β -lactams, aminoglycosides, colistin, macrolides, and fluoroquinolones; as well as to fosfomicin and trimetoprim in CB-722. CB-221 harbored only the *mcr-9* variant, while CB-722 carried *mcr-9*, *mcr-5* and the truncated *mcr-10* (90.49% of coverage). Regarding beta-lactamases-encoding genes, both isolates carried *bla*_{KPC-2} and the intrinsic *bla*_{ACT-6}, while CB-722 also carried *bla*_{TEM-1A}, *bla*_{OXA-9}, and *bla*_{GES-16}. The plasmid markers Col(pHAD28), Col440II, and IncU were found in CB-221, while CB-722 showed Col440I, IncU, IncP6, ColE10, and IncQ1 groups in addition to these. Complementary analysis using long-reads WGS of CB-722 revealed the occurrence of *mcr-5*, and the carbapenemase-encoding genes *bla*_{KPC-2} and *bla*_{GES16} in a hybrid IncU/IncP6-type and 41 Kb-long plasmid. The *mcr-9* was detected on the chromosome, and the truncated *mcr-10* in a non-typeable and 156 Kb-long plasmid. Also, a second copy of *bla*_{KPC-2} was detected in a small IncQ1 plasmid (8 Kb), with high coverage to other *bla*_{KPC-2}-carrying IncQ-plasmids found in Brazilian clinical isolates. Considering that *Enterobacter cloacae* complex species are part of human and animal microbiota, as well they are commonly found in environmental sources, their presence in recreational coastal waters carrying *mcr* and carbapenemase-encoding genes may highlight a possible route for community dissemination of clinically relevant antimicrobial resistance determinants.

Keywords: *mcr*; *bla*_{KPC-2}; *mcr* and *bla*_{KPC-2} co-occurrence; *Enterobacter kobei*, recreational coastal water

Development Agency: CNPq, FAPERJ