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BRIEF REPORT

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Emergence and polyclonal dissemination of NDM-5/OXA-181 carbapenemase-producing *Escherichia coli* in the French Indian Ocean territories

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Abstract

Aim Located in the Southwest Indian Ocean area (SIOA), the two French overseas territories (FOTs) of Reunion and Mayotte islands are heavily impacted by antimicrobial resistance. The aim of this study was to investigate all cases of NDM-5 and OXA-181 carbapenemase-producing *Escherichia coli* (CP*Ec*) in these two FOTs between 2015 and 2020, to better understand the regional spread of these last-line treatment resistant bacteria.

Methods All *E. coli* isolates not susceptible to ertapenem from various public and private hospitals on Reunion and Mayotte islands were screened for carbapenemase production. Clinical and microbiological data were collected for each case. Genotypic analysis of the isolates was carried out using WGS to determine the clonality relationship between the isolates and the genetic support of the carbapenemase-encoding genes.

Results A total of 92 isolates of NDM-5 ($n=67$) and OXA-181 ($n=25$) CP*Ec* was collected from Reunion ($n=55$) and Mayotte ($n=37$) islands. Whole-genome sequencing identified 4 majors STs (ST58, ST167, ST405 and ST410). Genotypic analysis demonstrated numerous intra-ST possible cross transmission events, including strains isolated in both islands. Finally, all isolates (100%) carried the $bla_{\text{NDM-5}}$ or $bla_{\text{OXA-181}}$ genes on plasmids (IncF2, IncX3), most of which were conserved and identified in various STs.

Conclusion We highlighted the dual dissemination of successful plasmids and the worrying circulation of high-risk clones *via* patients transfer between these two FOTs. It is therefore essential to effectively screen these patients for CP*Ec* carriage on admission and to take these plasmids into account when investigating intra- or inter-hospital CP*Ec* outbreaks.

Keywords Emergence, Polyclonal dissemination, NDM-5, OXA-181, Carbapenemases, *Escherichia coli*, Southwest Indian Ocean, Plasmids, Outbreak

†Laurent Dortet and Guillaume Miltgen have contributed equally to this study.

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Introduction

The worldwide spread of carbapenemase-producing *Enterobacterales* (CPE) over the last two decades is now a major public health problem, leading to the lack of therapeutic alternatives to treat infections [1]. New Delhi metallo-β-lactamase (NDM) and carbapenem-hydrolyzing oxacillinases (OXA-48-like) are among the most prevalent carbapenemases enzymes reported in *Enterobacterales* [2, 3]. NDM-5 is a two-amino acid variant of NDM-1 (Val-88-Leu; Met-154-Leu) which is responsible for increased hydrolytic activity towards carbapenems and third-generation cephalosporins (3GCs) [4]. Unlike NDM-1, NDM-5 is mainly produced by *Escherichia coli*, with the dissemination of high-risk international clones such as ST167 or ST410 that are particularly reported in China and the Indian subcontinent [2, 5]. NDM-5-producing *E. coli* have also been reported in Europe [6, 7]. The OXA-181 carbapenemase is a variant of OXA-48 that differs in four amino acid substitutions (Thr-104-Ala; Asn-110-Asp; Glu-168-Gln; Ser-171-Ala). OXA-181 and OXA-48 possess a very similar hydrolytic profile, but with significantly lower hydrolytic activity than NDM carbapenemases [4, 8]. Like NDM-5, OXA-181 was reported almost exclusively in *Enterobacterales* and particularly in *E. coli*. Again, the Indian subcontinent is considered to be the main reservoir of those OXA-181-producing *E. coli* although these CPEs have also been reported in Europe [8–11].

The islands of Reunion and Mayotte (French overseas territories, FOTs) are located in the Southwest Indian Ocean Area (SIOA) and constitute two migratory crossroads between Southern Africa and the India (Fig. 1). These two territories are heavily impacted by the phenomenon of antimicrobial resistance, particularly among Gram-negative bacilli. Currently, there is very few data regarding the epidemiology of CPEs in this area, with the exception of Reunion Island [12, 13]. The first cases of NDM-5 or OXA-181-producing *E. coli* in this area were reported in 2021 (sampling: 2017–2019) in Madagascar, Mozambique and Tanzania [14–16]. In Reunion Island, a sharp increase of the incidence of CPEs has been observed since 2015, mostly linked to the increased prevalence of NDM-5 and OXA-181-producing *E. coli* (Fig. S1). In this study, we investigated cases of NDM-5 and OXA-181 carbapenemase-producing *E. coli* (CP*Ec*) in these two FOTs between 2015 and 2020, to identify the driving forces responsible for their dissemination in the SIOA.

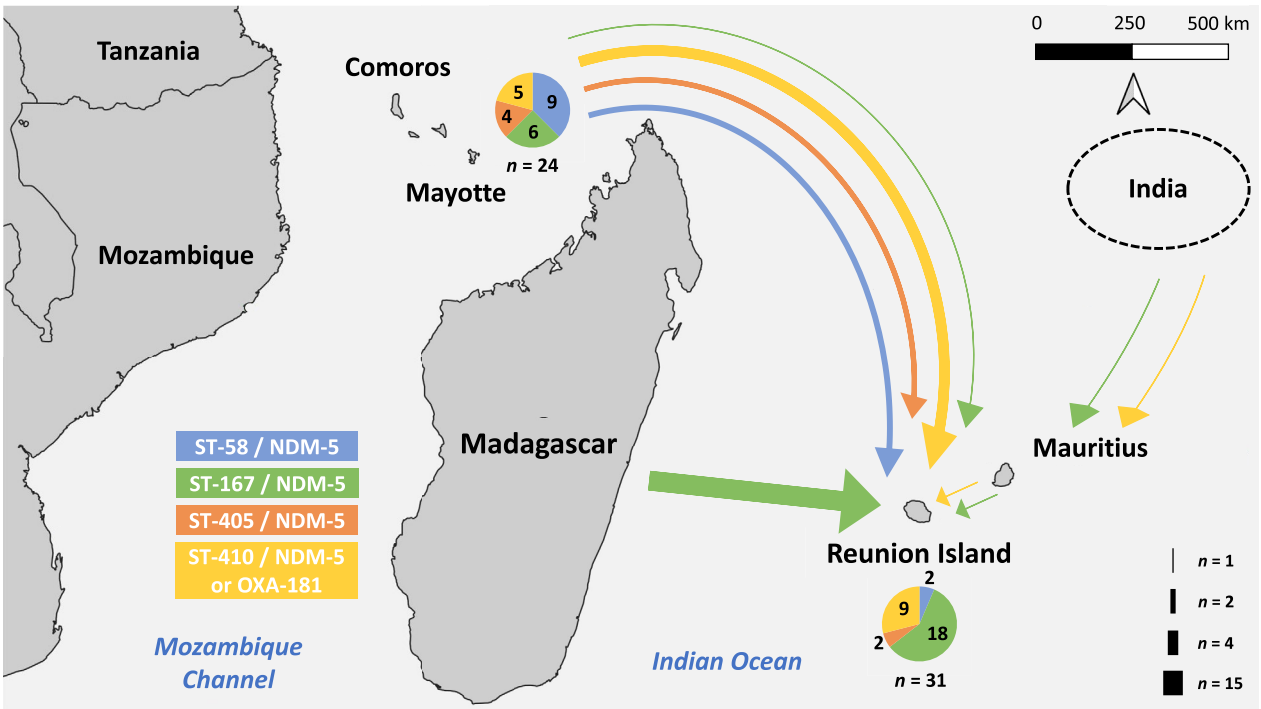

Fig. 1 Map summarizing the main sequence types (STs) of carbapenemase-producing *E. coli* circulating in the Southwest Indian Ocean area. The arrows represent the isolates detected on Reunion Island, belonging to the 4 main STs (ST58, ST167, ST405, ST410) in patients linked to another island in the region ($n = 28$). It should be noted that 3 other isolates belonging to these main STs had been found in Reunionese patients with no link with a foreign country

Material and methods

Bacterial isolates and clinical data

All *E. coli* isolates not susceptible to ertapenem, from various public and private hospitals on the islands of Reunion and Mayotte, and detected between March 2015 (first case of NDM-5-producing *E. coli* in Mayotte Island) and December 2020, were screened for carbapenemase production. For each patient, only one isolate was conserved, *i.e.* the first one detected. Non-susceptibility to ertapenem was defined as an inhibition zone diameter < 25 mm (disk diffusion method, I2a, Montpellier, France) or a MIC > 0.5 mg/L (gradient strips, E-test, bioMérieux, Marcy l'Étoile, France or broth microdilution, Sensititre, Thermofisher, East Grinstead, UK) according to 2021 European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations [17]. *Escherichia coli* isolates were identified by matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS; Bruker Daltonics, Bremen, Germany) and were confirmed by whole-genome sequencing (WGS). For each case, several clinical data were collected, including age, gender, place and institution of hospitalisation, site of bacterial isolation, infection or colonisation status, and any link with a foreign country.

Carbapenemase detection

Screening for carbapenemase-encoding genes (bla_{KPC}, bla_{IMP}, bla_{NDM}, $bla_{OXA\text{-}48\text{-}like}$ and bla_{VIM}) was performed by PCR using the GeneXpert system (Xpert® Carba-R, Cepheid, Sunnyvale, USA) or immunochromatographic assay (NG-Test CARBA-5, NG Biotech, Guipry, France) and confirmed by WGS.

Antimicrobial susceptibility testing

The susceptibility of each isolate to amikacin, aztreonam, ceftazidime, ceftazidime-avibactam, ceftolozane-tazobactam, ciprofloxacin, colistin, ertapenem, fosfomycin, gentamicin, imipenem, meropenem, tigecycline and trimethoprim-sulfamethoxazole was assessed by broth microdilution according to 2021 EUCAST recommendations [17]. MICs were determined using Sensititre™ FRAM1GN panels (Thermofisher, East Grinstead, UK). The aztreonam/clavulanate and aztreonam/avibactam combinations were evaluated by gradient strips superposition (E-test, bioMérieux, Marcy l'Étoile, France) as previously described [18].

Whole-genome sequencing and genotypic analysis

Whole genome sequencing was performed on all strains using Illumina technology (MiSeq, Illumina). Illumina reads were assembled using Shovill v1.1.0 and SPAdes v3.14.0. MLST and resistome/plasmidome analyses were performed using mlst v2.11 and Abricate v1.0.1 softwares (–db resfinder, plasmidfinder). For phylogenetic analysis, WGS sequence reads of the genomes of NDM-5 and OXA-181 CP*Ec* were aligned to genes sequences included in the *wg*MLST scheme of Enterobase (http://enterobase.warwick.ac.uk/schemes/Escherichia.wgMLST/wgMLST_ref.fasta). Metadata and phylogenetic trees were visualised using iTOL v6.5.2. Strains were considered to be clonally related (possibly by cross-transmission) if they differed by fewer than 20 SNPs in their common genome.

The genetic environment of the $bla_{NDM\text{-}5}$ and $bla_{OXA\text{-}181}$ resistance genes was analysed using additional long-read sequencing (R9.4.1 MinION, Oxford Nanopore; Fig. 2a

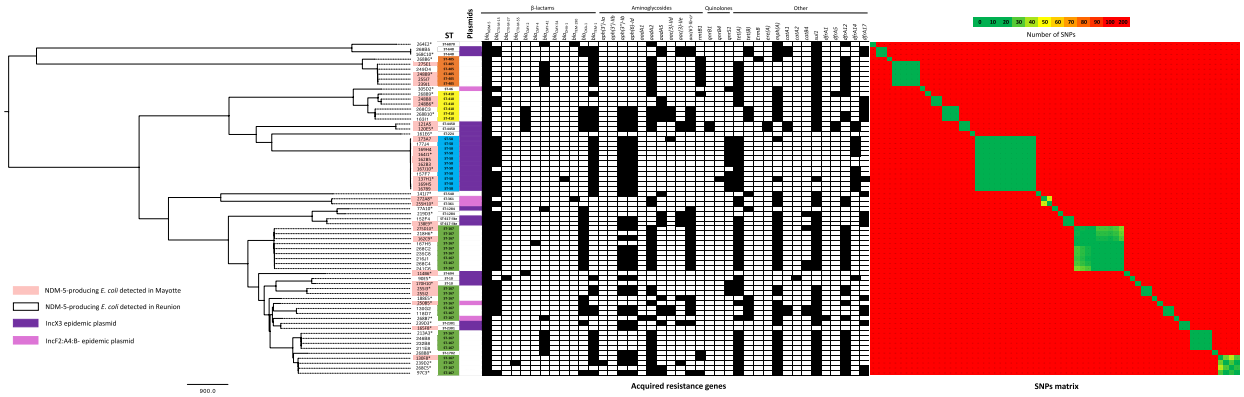

Fig. 2 **a**,**b** Phylogenetic analysis of the 92 NDM-5 or OXA-181 *E. coli* isolates using WGS. Dendrograms representing the phylogenetic analysis of the NDM-5 (2a) and OXA-181 (2b) carbapenemase-producing *E. coli* isolates ($n = 92$, Reunion and Mayotte islands, 2015–2020) with acquired resistance mechanisms and a heatmap for SNPs analysis on the whole genome. Isolate numbers with a star are those whose genomes have been sequenced in long reads (Oxford Nanopore technology, $n = 52$). The presence of acquired resistance genes is indicated by black boxes. Isolates considered clonally related are shown in green boxes in the heatmap. There is a grey zone between 20 and 80 SNPs, that does not allow to conclude that isolates are clonally related, and above 80 SNPs, isolates can be considered as not clonally related (represented as red boxes)

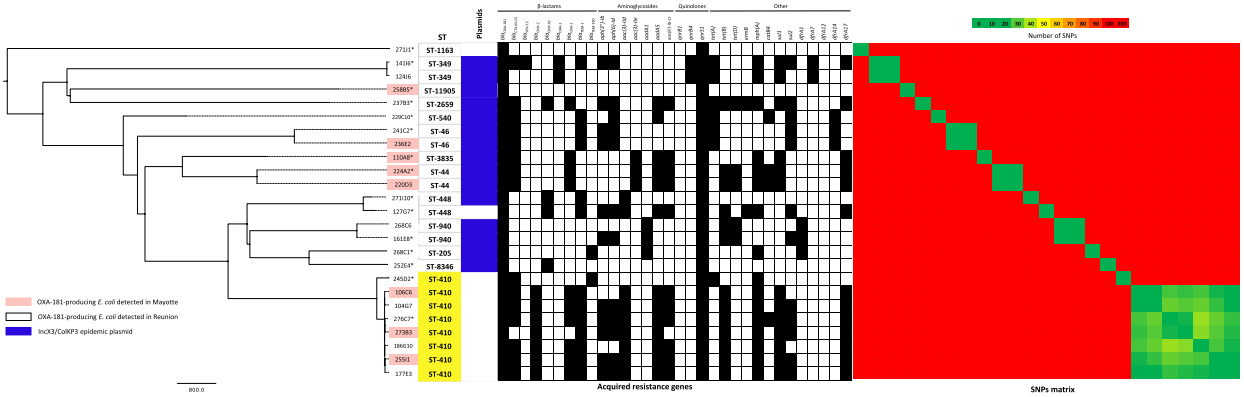

Fig. 2 continued

and b, $n=52$ star-marked isolates). The resulting *de novo* assemblies were generated using Flye v2.9.1 on filtered long reads (–nano-raw; –iterations 2). The initial quality filtering process involved applying Filtlong v0.2.1 with associated Illumina short-reads as a reference. Medaka v1.7.2 was then used for sequence correction (-m r941_min_sup_g507), followed by two rounds of short-read polishing using Polypolish v0.5.0 and Pypolca v0.3.0. A similarity analysis of resulting carbapenemase-encoding plasmids was performed using a mash-distance approach [19].

Results

From March 2015 to December 2020, a total of 92 non-redundant isolates of NDM-5 ($n=67$) and OXA-181 ($n=25$) producing *E. coli* were collected. These strains were isolated from samples collected in Reunion ($n=55$) and in Mayotte ($n=37$) islands. These clinical isolates were cultured from rectal swabs ($n=70$), urine samples ($n=20$), blood culture ($n=1$) and peritoneal fluid ($n=1$). Accordingly, 83% of patients were considered to be colonised ($n=76$) whereas 17% were infected ($n=16$). Most of the isolates recovered from Reunion Island were identified in patients originated from the Comoros archipelago (34.5%; $n=19$) and Madagascar (32.7%; $n=18$). Only 9.1% ($n=5$) were found in Reunionese patients having no link with foreign countries (Table S1).

The susceptibility rates to the main relevant antibiotics were 100% for colistin and tigecycline, 97.8% for fosfomycin and 89.1% for amikacin. All OXA-181 producers remained susceptible to ceftazidime-avibactam. On the opposite, all NDM-5 producers were highly resistant to ceftazidime-avibactam but 79.1% and 77.6% remained susceptible to the aztreonam-avibactam and aztreonam-clavulanate combinations, respectively (Table S2).

Whole-genome sequencing analysis was performed on the 92 genomes of NDM-5 or OXA-181 CP*Ec*. We identified 17 and 13 different STs among NDM-5 or OXA-181 producers, respectively. Among NDM-5 producers, the 4 most common STs were ST167 ($n=24$), ST58 ($n=11$), ST405 ($n=6$) and ST410 ($n=6$), while the ST410 was predominant among OXA-181 producers ($n=8$). Note that ST410 isolates carrying the $bla_{\text{NDM-5}}$ and $bla_{\text{OXA-181}}$ genes were not clonally related. Among the isolates recovered on Reunion Island ($n=55$), 31 strains belonged to one of these 4 major STs and 28 of these isolates were linked to an import from abroad (Fig. 1).

Regarding phylogenetic analysis, among NDM-5 producers, ST167 and ST410 were polyclonal including possible patient-to-patient transmission (Fig. 2a; Table S3). On the opposite, the ST58 (0–10 SNPs) and ST405 (0–12 SNPs) mostly corresponded to potential outbreaks occurring between the two islands likely resulting of patients transfer (Fig. 2a). For OXA-181 CP*Ec*, the most prevalent ST, ST410, included 8 isolates among which 7 belonged to the same potential outbreak (Fig. 2b), again including patients from the 2 islands.

The plasmid structures associated with the $bla_{\text{NDM-5}}$ and $bla_{\text{OXA-181}}$ resistance genes was analysed with a hybrid assembly on 52 non-clonally related isolates from different STs (Fig. 2a and b, star-marked isolates). In all isolates, the $bla_{\text{NDM-5}}$ and $bla_{\text{OXA-181}}$ genes were located on plasmids (100%). Finally, we identified three major conserved plasmids with >99.9% homology within different STs. The $bla_{\text{NDM-5}}$ gene was mainly carried on a IncX3 ($n=24$, 35.8%, mean length = 45,302 bp) and IncF[F2:A4:B-] ($n=5$, 7.5%, mean length = 118,780 bp) plasmids, while the $bla_{\text{OXA-181}}$ gene was most often located on an IncX3/ColKP3 plasmid ($n=15$, 60%, mean length = 50,589 bp; Fig. 3). The remaining plasmid structures, which code for carbapenem resistance, were associated with various Inc groups or IncRST and exhibited lower levels of homology (Table S3).

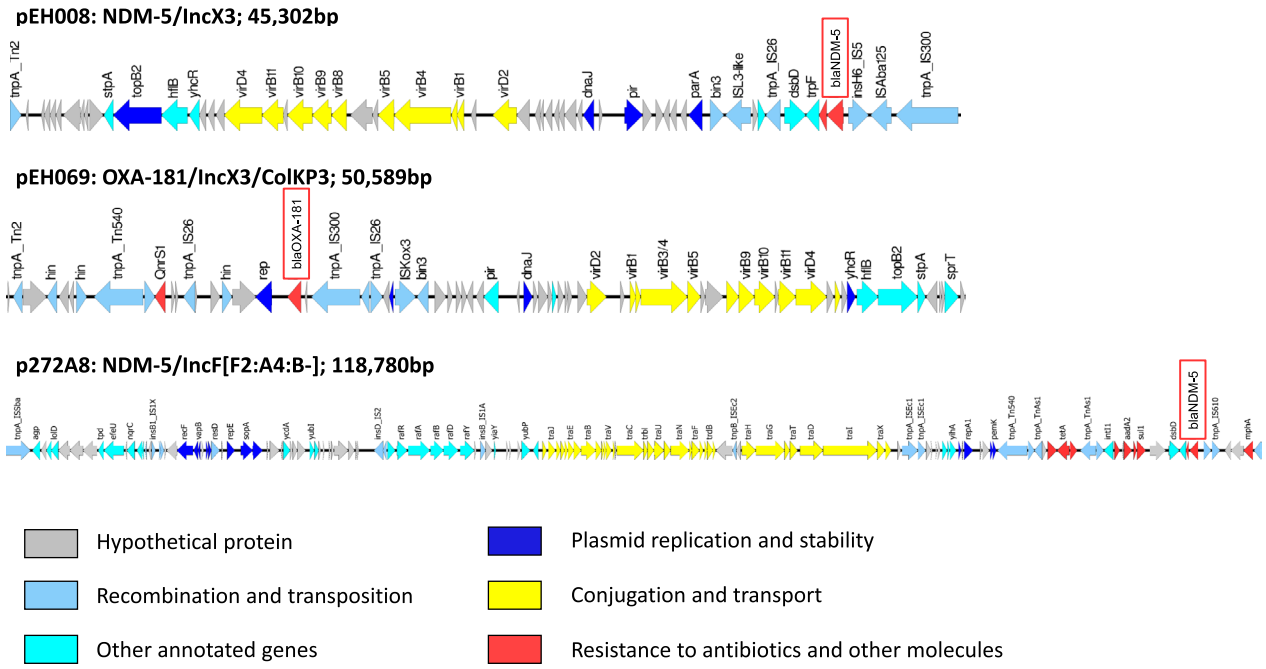

Fig. 3 Three major conserved plasmids (IncX3, IncX3/ColKP3, IncF[F2:A4:B-]) found in carbapenemase-producing *E. coli* isolates common to different STs. The figure was generated using Easyfig and annotated using RAST, then manually refined based on BLAST analyses against UniProtKB/Swiss-Prot

Discussion

On Reunion Island, NDM-5 and OXA-181-producing CP*Ec* isolates play a major role in the increase of reported CPE cases (1st position ahead of *K. pneumoniae* since 2018, data not shown) and are strongly linked to imported isolates (more than 90%). The vast majority of isolates detected on Reunion Island were identified in patients with links to a foreign country, mainly the Comoros archipelago. These epidemiological results highlight the fact that these regions of the Mozambique Channel are heavily affected by the spread of CPEs and suggest the existence of multiple hotspots or reservoirs in these territories with links to Southern Africa. This finding underlines the importance of effective screening policies for these at-risk patients for CPE carriage.

The main clades detected belonged to ST58, ST167, ST405 and ST410. Among these clades, we found very close links (≤20 SNPs) between isolates from Reunion and Mayotte islands, with possible outbreaks going unnoticed. In addition, we identified a strong correlation between sequence types and patients' geographical origin (ST58 and Mayotte; ST167 and Madagascar, Fig. 1). Very little epidemiological data currently exist in the SIOA, but isolated cases of NDM-5 or OXA-181 *E. coli* have nevertheless recently been reported [14–16]; they belonged to several of these STs. Some of which are recognised as high-risk endemic clones in India and China (ST167 and ST405), with potential resistance to the aztreonam/avibactam combination [20]. Finally, comparison of ST410 isolates with those from the French National Reference Centre did not reveal any link with strains from other countries (Fig. S3) [21].

Regarding the analysis of replicons associated with the $bla_{\text{NDM-5}}$ and $bla_{\text{OXA-181}}$ genes, we identified already known epidemic plasmids (IncF2, IncX3) acquired in several STs, suggesting a dual dissemination of these resistance genes (successful STs and plasmids) [22]. These results are in accordance with the current epidemiological data, that identified IncX3 plasmids [5, 23] as the main vector for the $bla_{\text{NDM-5}}$ gene, particularly in China and India. The $bla_{\text{OXA-181}}$ gene was mainly carried on the IncX3/ColKP3 hybrid plasmid, which is mainly distributed in *E. coli* and *K. pneumoniae*, particularly in China [24]. The important role that these epidemic plasmids can play justifies the new hospital hygiene recommendations aimed at targeting the carbapenem resistance gene and not just the bacterial species (carrying this gene) in the management of intra- or inter-hospital CPE outbreaks (25).

Conclusion

To conclude, this dual dissemination of successful plasmids and the worrying circulation of high-risk clones is very problematic since it strongly limits therapeutic alternatives (most often not available in these East African territories, apart from FOTs). Of note, some clonally-related strains are now being found in Reunionese patients who have never travelled abroad, suggesting that these CP*Ec* clones started to become endemic on this island. It is therefore essential to strengthen cooperation in the SIOA and enable molecular surveillance of CPEs, in order to better control the spread of these highly spreading *E. coli* clones.

Abbreviations

CPE	Carbapenemase-producing *Enterobacterales*
CP*Ec*	Carbapenemase-producing *Escherichia coli*
EUCAST	European committee on antimicrobial susceptibility testing
FOT	French overseas territory
Inc	(Plasmid) Incompatibility
MALDI-TOF MS	Matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry
MLST	Multi locus sequence typing
NDM	New Delhi metallo-β-lactamase
OXA	Oxacillinase
PCR	Polymerase chain reaction
SIOA	Southwest Indian ocean area
SNP	Single nucleotide polymorphism
ST	Sequence type
WGS	Whole genome sequencing

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12941-025-00778-8.

Additional file1 (DOCX 22 KB)

Additional file2 (PDF 153 KB)

Additional file3 (PPTX 84 KB)

Additional file4 (DOCX 40 KB)

Additional file5 (DOCX 48 KB)

Additional file6 (XLSX 164 KB)

Additional file7 (XLSX 24 KB)

Author contributions

GM, LD and PM designed the study. TV, TG, LS, MD collected and analysed the data. MP, LS and DW performed the genomic/bioinformatics analyses and data illustrations. TV and GM wrote the original manuscript. TBC, OB, PM, LD and GM revised the manuscript.

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Availability of data and materials

The 92 genomes of the isolates obtained by short-read sequencing and the 3 genomes (hybrid assemblies) including the 3 major plasmids in this article have been deposited on the Genbank platform under the BioProject PRJNA1116609 (references SAMN41537884, SAMN41537885 and SAMN41537886 and Table S4).

Declarations

Ethical approval and consent to participate

Not required.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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