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RICAI

Emergent aztreonam-avibactam resistance among NDM and OXA-48-producing *Escherichia coli* clinical isolates from Germany and Switzerland

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NARA
Nationales Referenzlaboratorium zur Früherkennung neuer Antibiotikaresistenzen und Resistenzmechanismen

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Carbapenemase-producing Enterobacterales

At the top of the most difficult-to-treat bacterial infections

Metallo-β-lactamases (MBL)

- Nosocomial and community-acquired infections worldwide
- Extremely limited therapeutical options

Penicillins
Broad-spectrum cephalosporins
Carbapenems
non-β-lactams

Clavulanate
Tazobactam

NDM
VIM, IMP

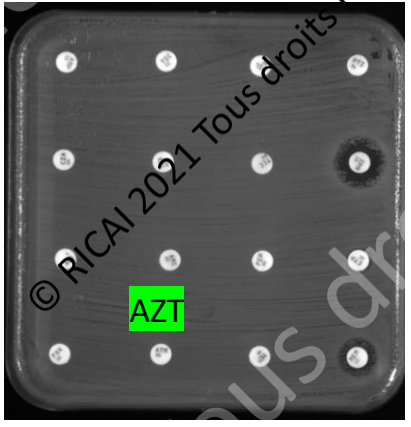
Avibactam
Relebactam
Vaborbactam

Aztreonam

Therapeutic option

NDM-5 *E. coli*

NDM-5 + CTX-M-15 *E. coli*



The ATM-AVI combination

Avibactam

an excellent inhibitor of many β-lactamases (ESBL and AmpC enzymes, OXA-48-like and KPC)

The ATM-AVI combination therapy
among the last resort options against MBL-producing *E. coli*

Jayol A, Nordmann P, Poirel L, Dubois V. JAC 2018

In this study

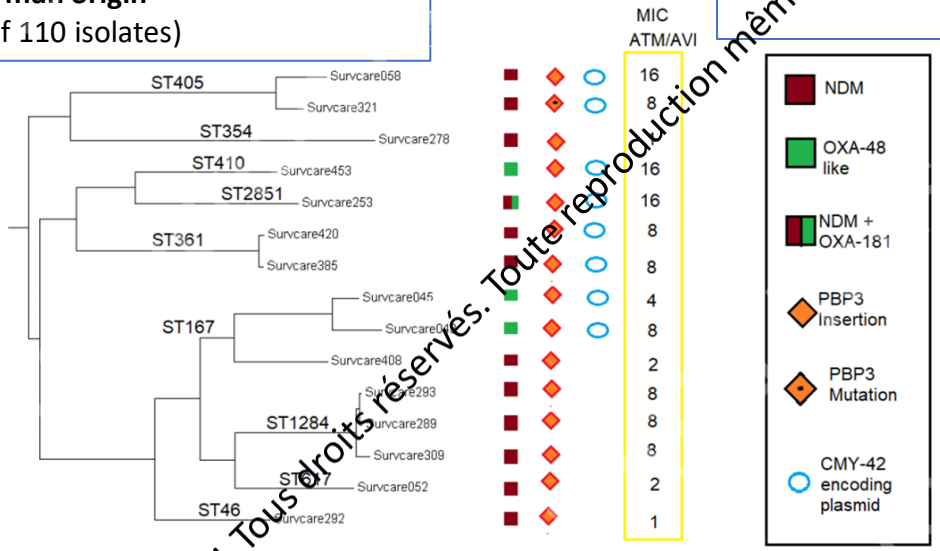
Here, we characterize the ATM-AVI resistance in a series of carbapenem-resistant NDM- and OXA-producing *Escherichia coli* clinical isolates from Germany and Switzerland (n=113)

RESULTS AND DISCUSSION

ATM-AVI R or I strains

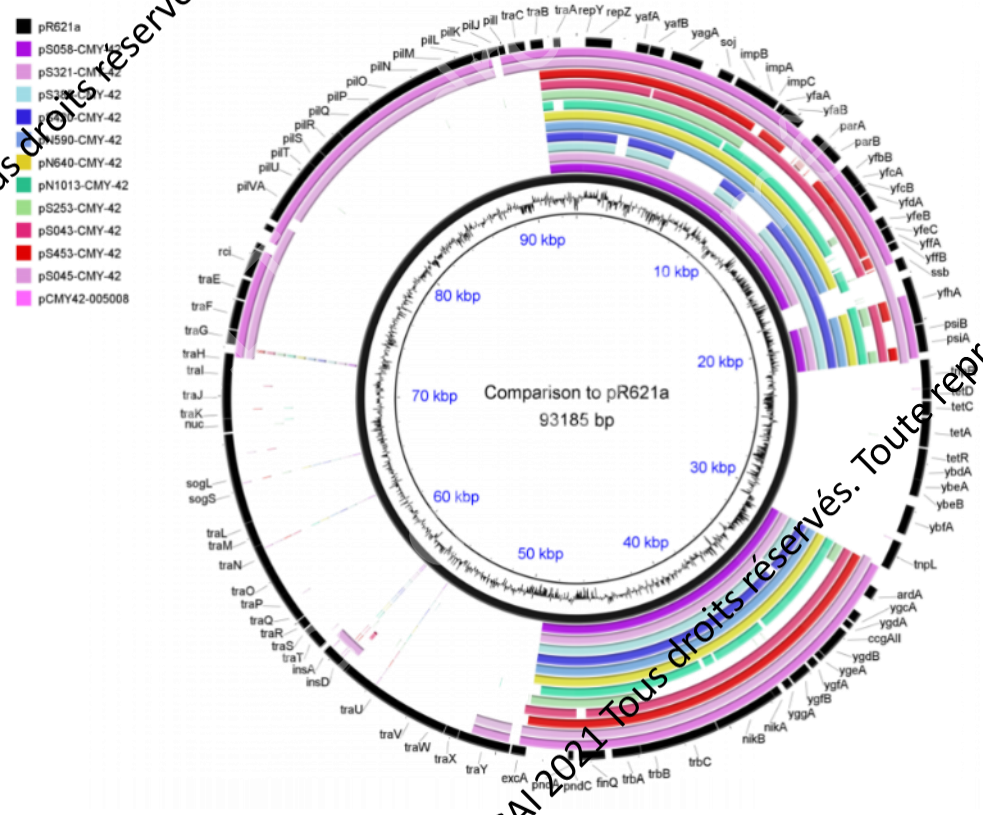
15 NDM- and OXA-48/OXA-181 producing *E. coli* of German origin
(out of 110 isolates)

3 NDM-producing *E. coli* of Swiss origin



The variability of resistance level to ATM-AVI is related to presence of amino acid insertion in PBP-3, expression and probably to the level of expression of CMY-42/Ma, a specific plasmid-mediated cephalosporinase that compromises in part, the activity of aztreonam.

CMY-42 plasmids

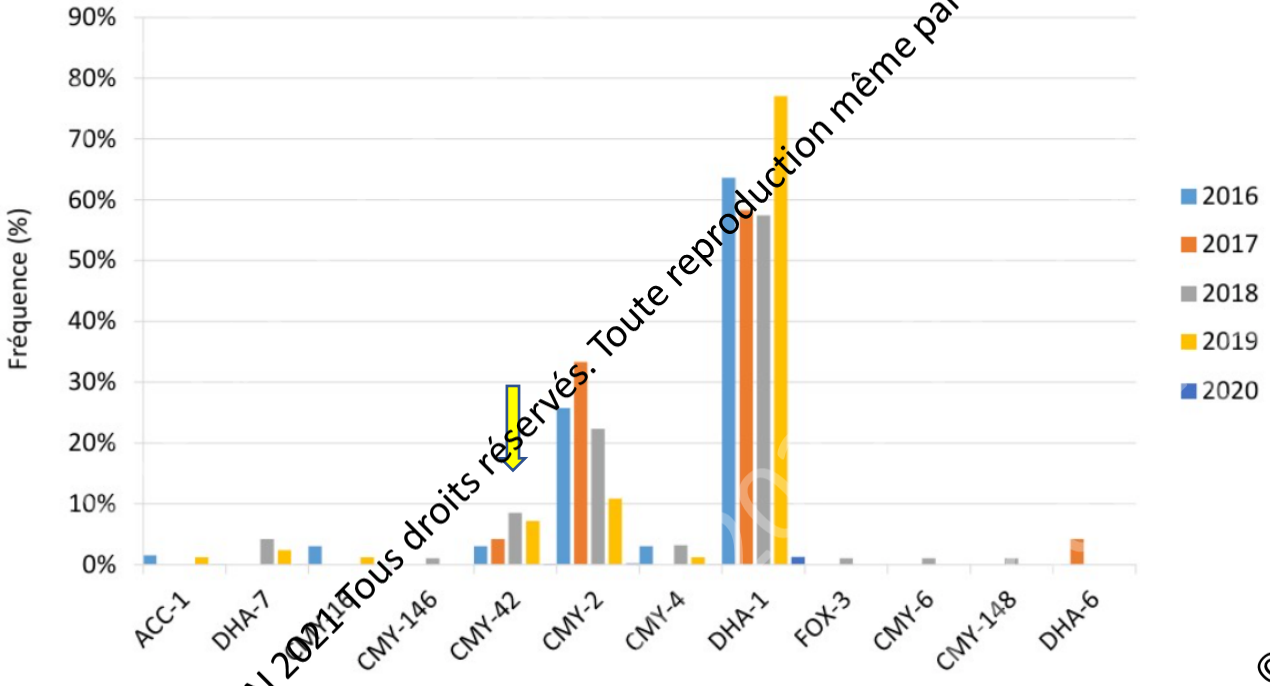


Comparison of the CMY-42 encoding IncIγ plasmids included the pCMY152 42_005008 with the pR621a as reference.

- The CMY-42 alleles are present at an identical location on IncIγ plasmids of 27 – 53 kb.
- Many plasmids carry deletions of transfer genes (***traB-Y***) and the conjugative pilus (pilI-V) (Figure) as previously also reported.
- It is unlikely that these truncated plasmids can directly promote transfer of CMY-42 (horizontal transfer)
- Plasmids were highly stable across a 7-day serial passage in the absence of antibiotics.
- Nevertheless, they all carry the Type I partition machinery 3 (ParAB) and a toxin-antitoxin PndBA post-segregational killing system, that can ensure stable presence and inheritance (vertical transfer) even without antibiotic selection.

CNR
RÉSISTANCE AUX ANTIBIOTIQUES

Diversité des céphalosporinases plasmidiques identifiées chez les entérobactéries (2016-2020).



Courtesy K. Jeannot: P. Plesiat

Conclusion

- Elevated MICs of ATM-AVI resulted from combination of different resistance mechanisms, including modification of PBP3 protein sequence through specific amino acid insertions, and production of a CMY-type enzyme, CMY-42.

- Emergent aztreonam-avibactam resistance may be identified with MBL producing strains but also with carbapenem-hydrolyzing class D β-lactamases (OXA-48 and OXA-181), even if this combination is not yet in clinical use.

- Their occurrence in carbapenem-resistant *E. coli*, that are associated with community spread, could limit use of ATM-AVI combination as a first line therapy