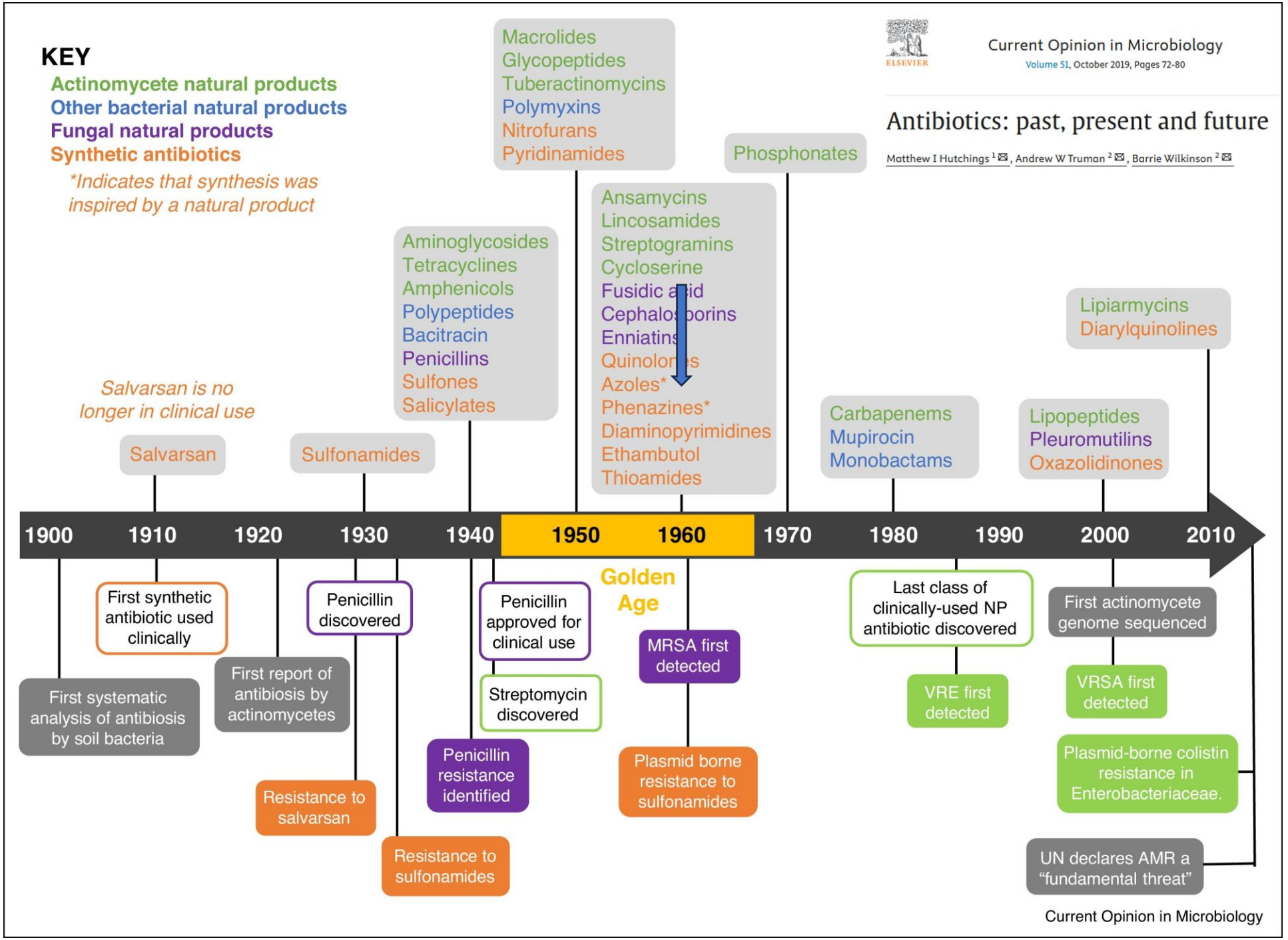
The Golden Age



β-Lactam antibiotics

The discovery of penicillin in 1929 is rightly recognized as a milestone in the history of medicine, and its introduction to the clinic in the 1940s revolutionized our ability to treat bacterial infections. Despite enormous progress in the field of antimicrobial chemo therapy in the more than 70 years after the first use of penicillin, as the centenary of Fleming's work approaches, the β-lactams remain the cornerstones of the antibacterial arsenal.

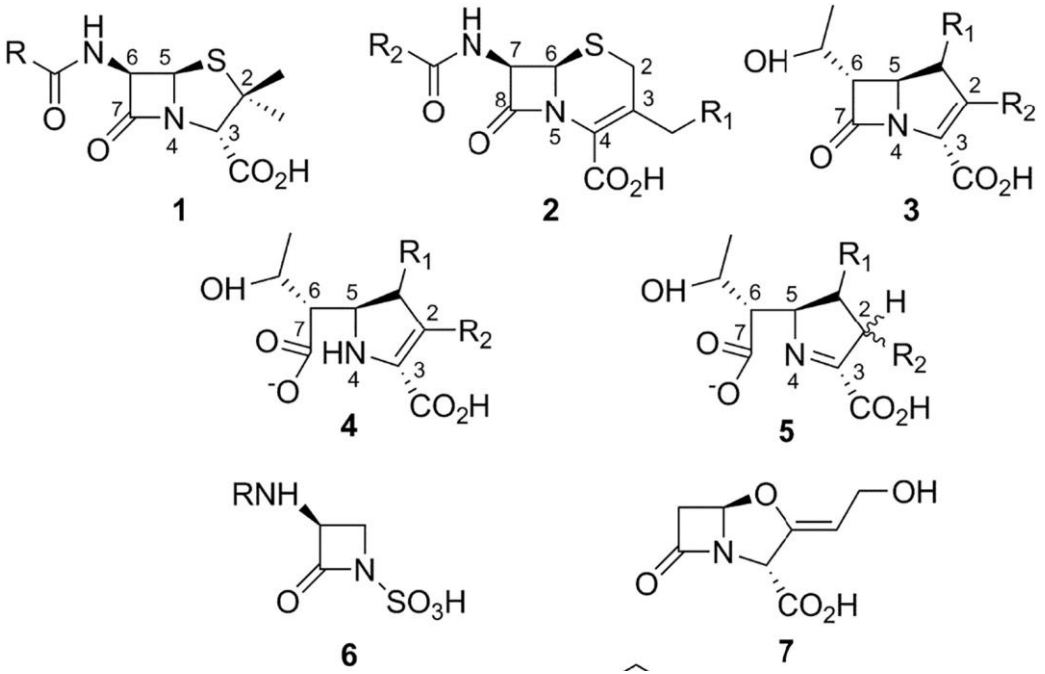
The fact that they remain both the single most prescribed antibiotic class and the most important in terms of sales attests to their continuing central role in the treatment of bacterial infections.

β-Lactams, like other antimicrobial classes, have undergone continuous development since their original introduction in order to improve properties such as potency, spectrum of activity, pharmacokinetic and safety profiles and to counter the emergence of resistance.

At present, four main classes of β-lactam antimicrobials are in clinical use (Fig. 1).

These comprise three types of bicyclic structure:

- **the penicillins** (**1**), in which the four-membered β-lactam in which the four-membered β-lactam ring is fused to a thiazolidine ring;
- **the cephalosporins** (**2**), where the fusion partner is a six-membered dihydrothiazine;
- **the carbapenems**, where the bicyclic system is completed by a five-membered pyrroline. **3**. (1-methyl) Carbapenem scaffold. **4**. Hydrolyzed carbapenem (Δ2-pyrroline form). **5**. Hydrolyzed carbapenem (Δ1-pyrroline form).
- **the monobactams** (**6**) are monocyclic systems. While each class was originally identified as a natural product (penicillin in 1929, cephalosporins by Newton and Abraham (building on the work of Brotzu) in 1954, olivanic acid (carbapenem) by Brown and co-workers in 1976 and monobactams by Sykes and Imada and their respective co-workers in 1981], each has since undergone extensive programs of modification to create arrays of semi-synthetic derivatives.
- **7**. **Clavulanic acid** an irreversible inhibitor of the most widely distributed class A enzymes



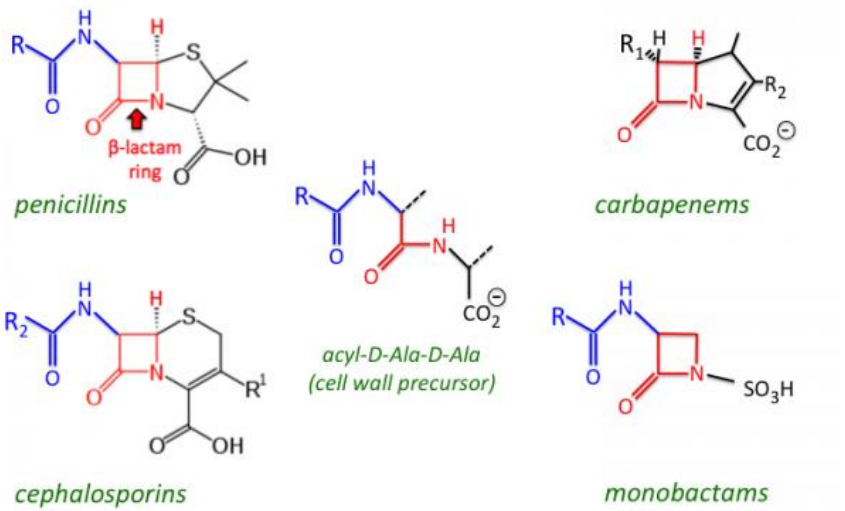
modification that allows for retention of antibacterial activity is possible at several positions on the β-lactam scaffold: C6 of penicillins, C7 and C3 of cephalosporins, C2 of carbapenems and C3 of monobactams.

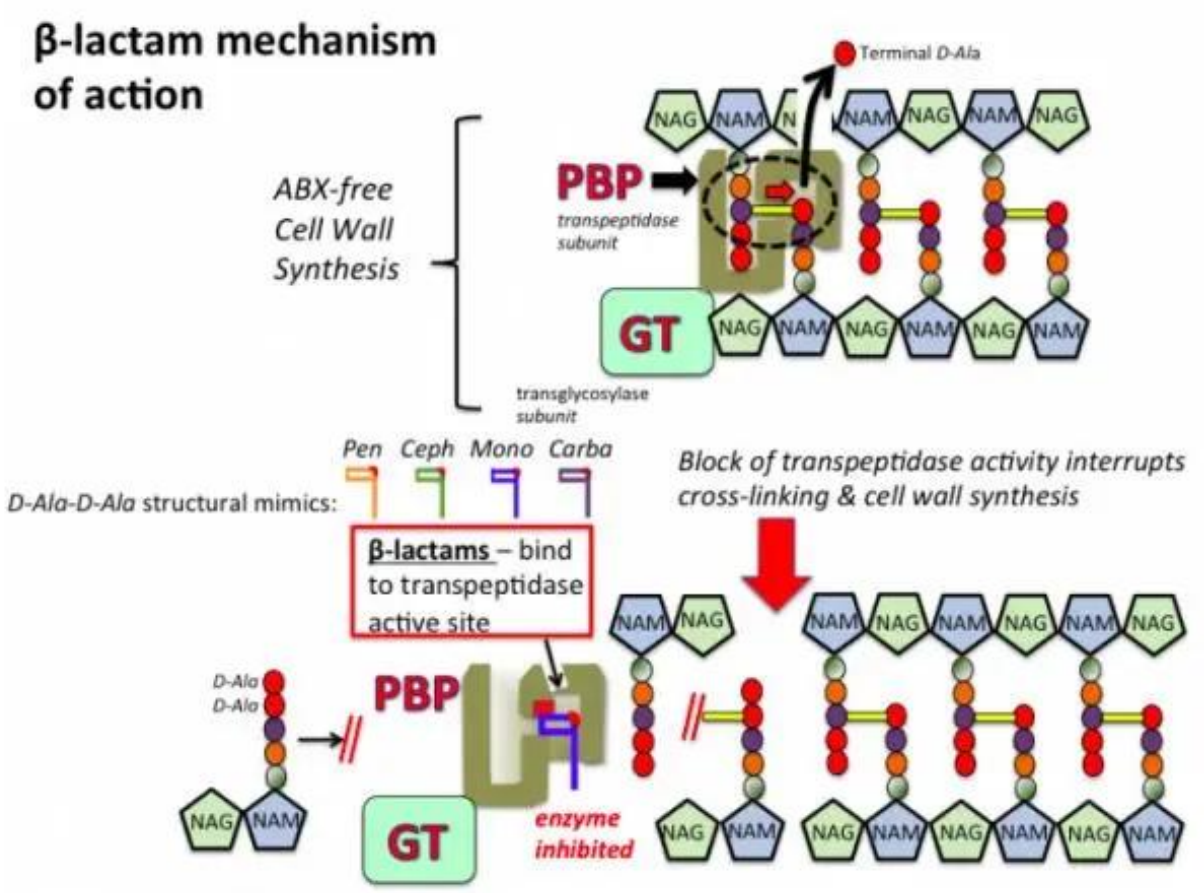
aminopenicillins (e.g., ampicillin)

methicillin to counter penicillin-resistant strains of Staphylococcus aureus ;

oxyiminocephalosporins (e.g., cefotaxime, ceftazidime)

The antibacterial activity of β-lactams was identified by Tipper and Strominger as based on their resemblance to the terminal D-Ala–D-Ala moiety of the peptidoglycan stem pentapeptide, with the β-lactam amide and adjoining carboxylate (or, in the case of monobactams, sulfonic acid) groups serving to mimic the peptide bond and terminal carboxylate of D-Ala–D-Ala. Activity then arises from reaction of the β-lactam ring with the nucleophilic serine of target penicillin-binding proteins (PBPs), leading to opening of the ring and irreversible PBP acylation that prevents formation of peptidoglycan transpeptide cross-links.

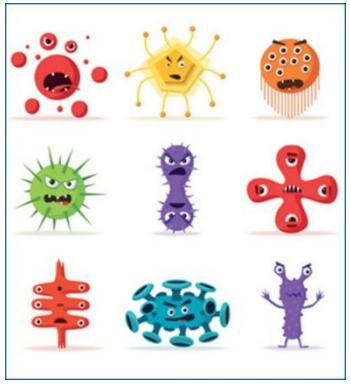




L'epidemiologia

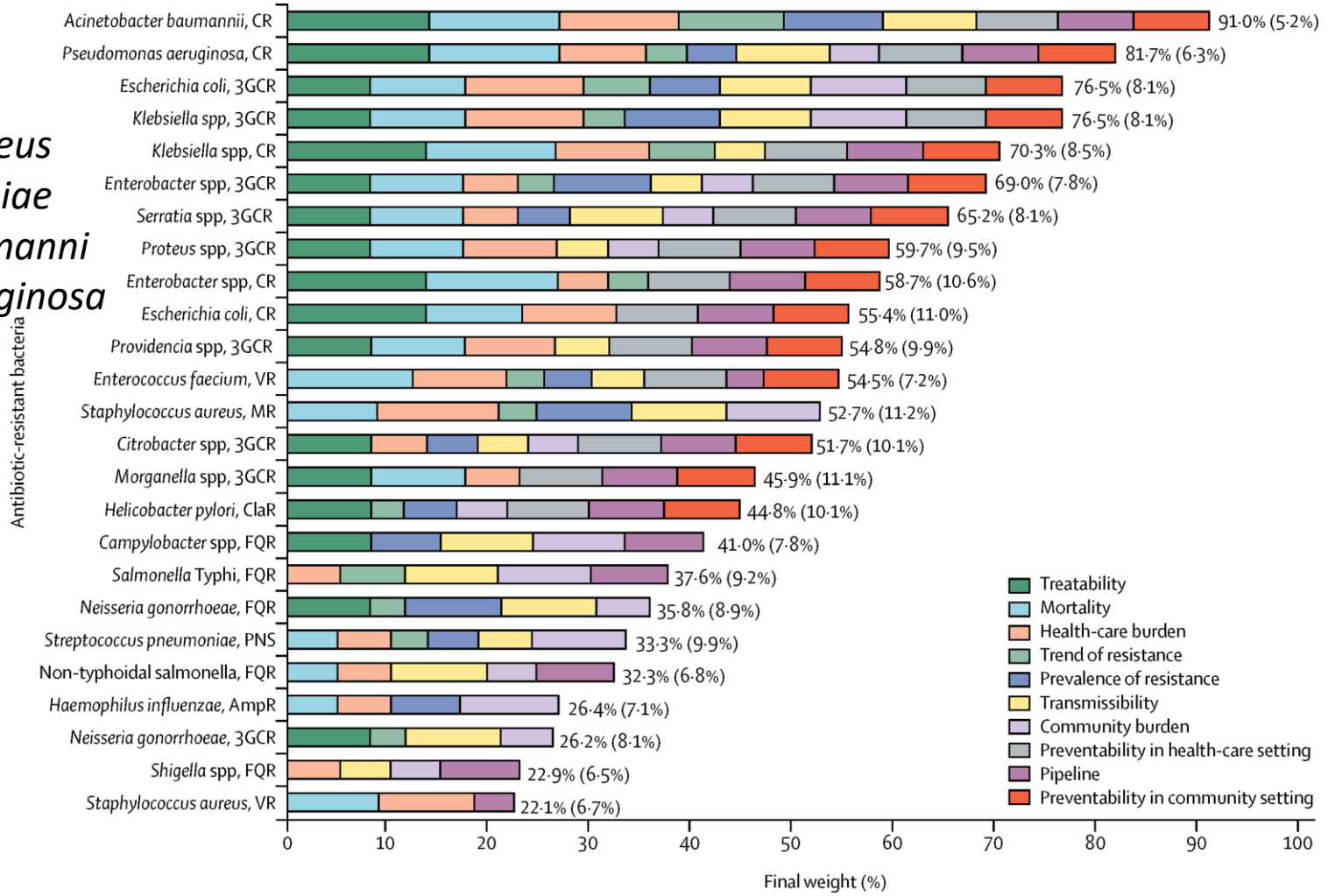
ESKAPE

E*scherichia coli*
S*taphylococcus aureus*
K*lebsiella pneumoniae*
A*cinetobacter baumanni*
P*seudomonas aeruginosa*
E*nterobacter* spp.



A crucial list of pathogens

G Tillotson,
The Lancet Infectious Diseases,18, 2018,234-236,



Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis

E Tacconelli et al., The Lancet Infectious Diseases, 18, March 2018, 318-327

Molti dei patogeni critici sono resistenti a beta-lattamici

Classification of β-lactamases

Identification of growing numbers of β-lactamases, coupled with availability of protein, and subsequently nucleotide, sequence information, established that these enzymes do not comprise a single homogeneous group but instead can be subdivided into multiple classes. Furthermore, as enzyme activity against different β-lactam substrates began to be reported, it became apparent that β-lactamases encompass a range of biochemical properties. With the explosion of sequence information, the number of identified β-lactamases has undergone a near-exponential increase; at the time of writing, the β-lactamase database (www.bldb.eu) contains over 4300 such enzymes that have undergone varying degrees of characterization.

Two systems of classifying this array of enzymes are in use:

- Bush–Jacoby–Medeiros activity-based system

- Ambler system based on sequence information. It divides β-lactamases into four distinct classes, termed A, B C and D (Fig. 2), identified on the basis of specific sequence motifs but also distinguished by fundamental differences in hydrolytic mechanism. A further fundamental division is between the three classes (A, C and D) of active-site serine enzymes (serine β-lactamases; SBLs) and class B that comprises a heterogeneous group of zinc metalloenzymes (metallo-β-lactamases, or MBLs). MBLs instead utilize a metal-activated water nucleophile to drive the hydrolytic reaction.

beta-lactamases

β-Lactamases and β-Lactamase Inhibitors in the 21st Century

Catherine L. Tooke[†], Philip Hinchliffe[†], Eilis C. Bragginton, Charlotte K. Colenso, Viivi H.A. Hirvonen, Yuiko Takebayashi and James Spencer

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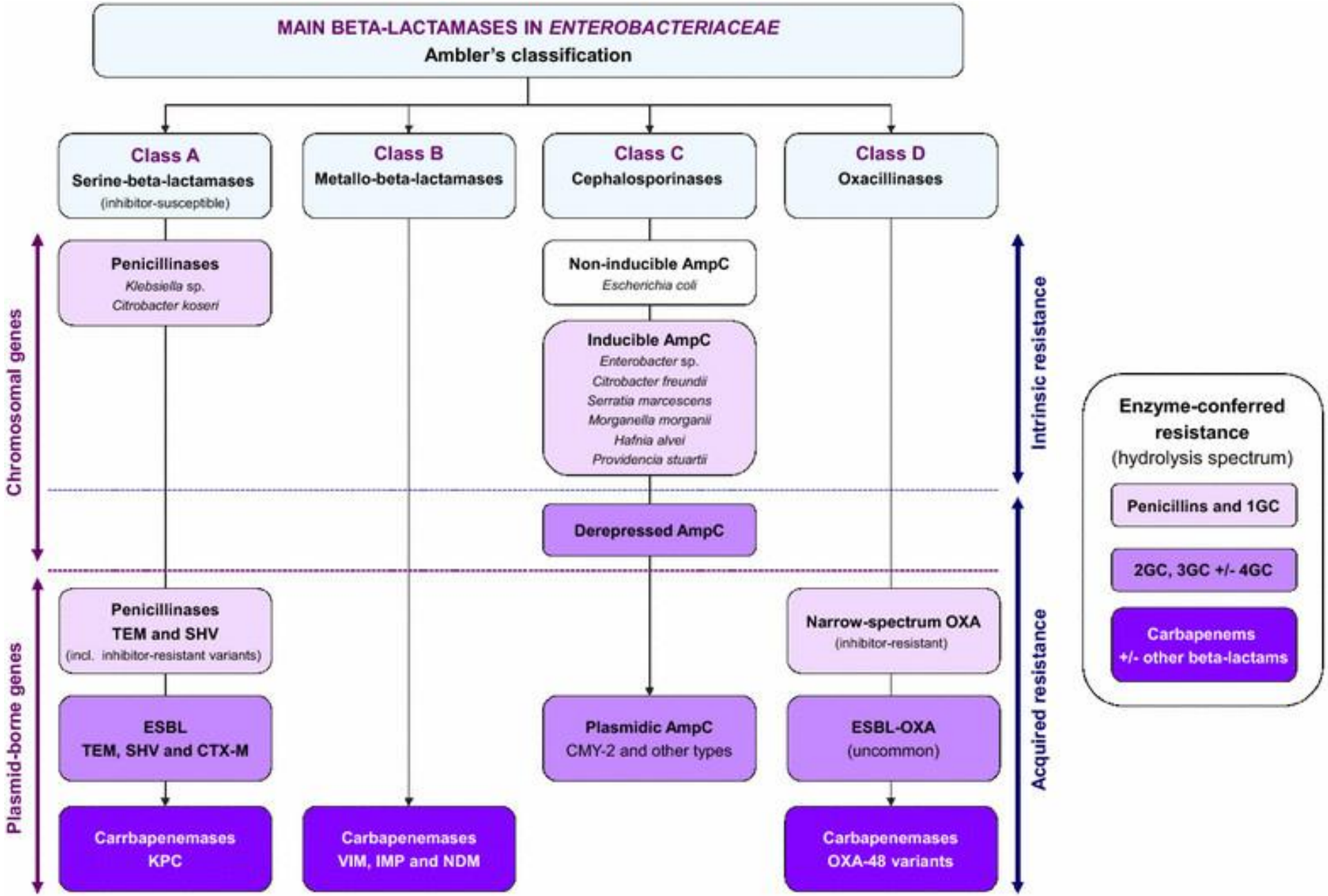
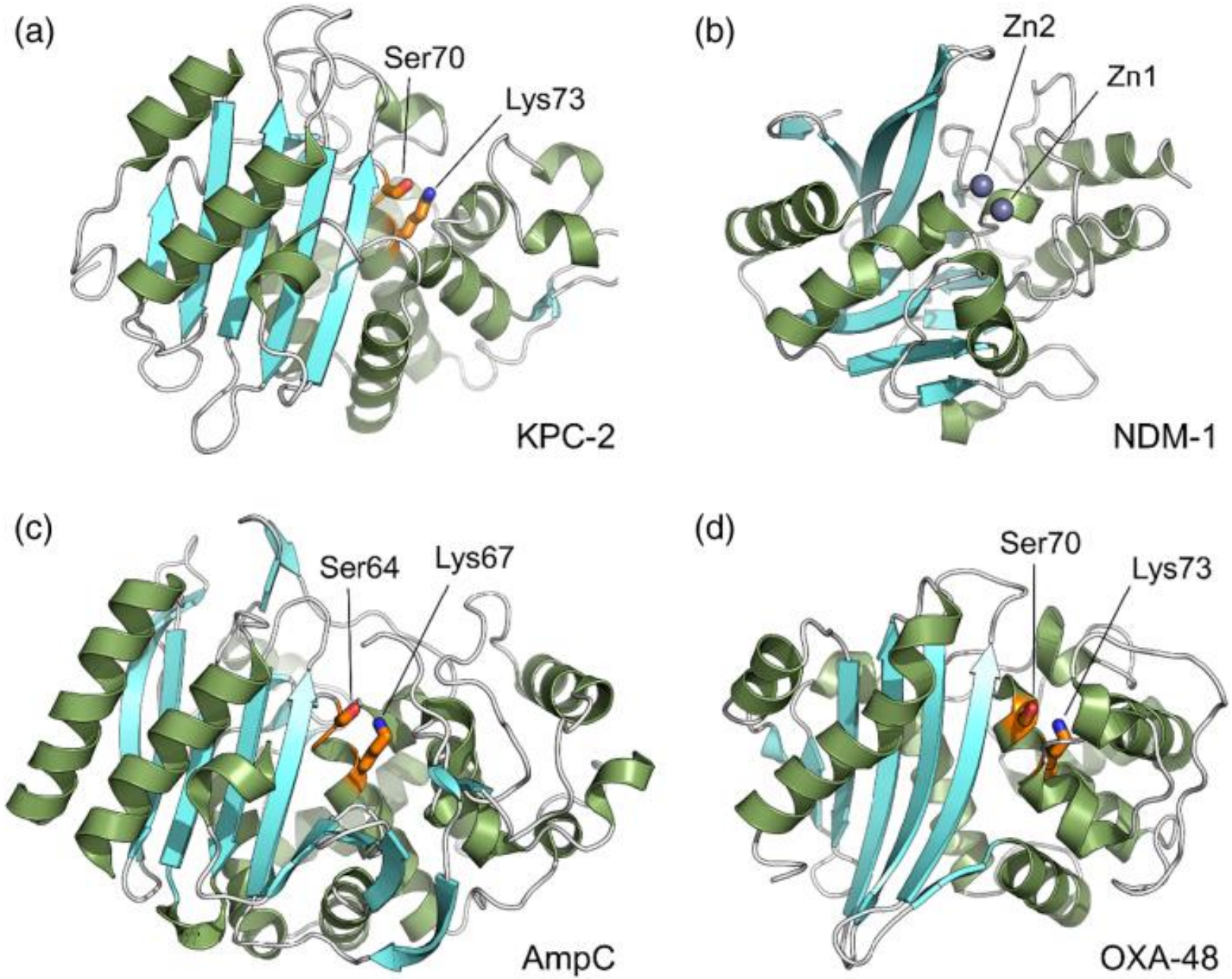
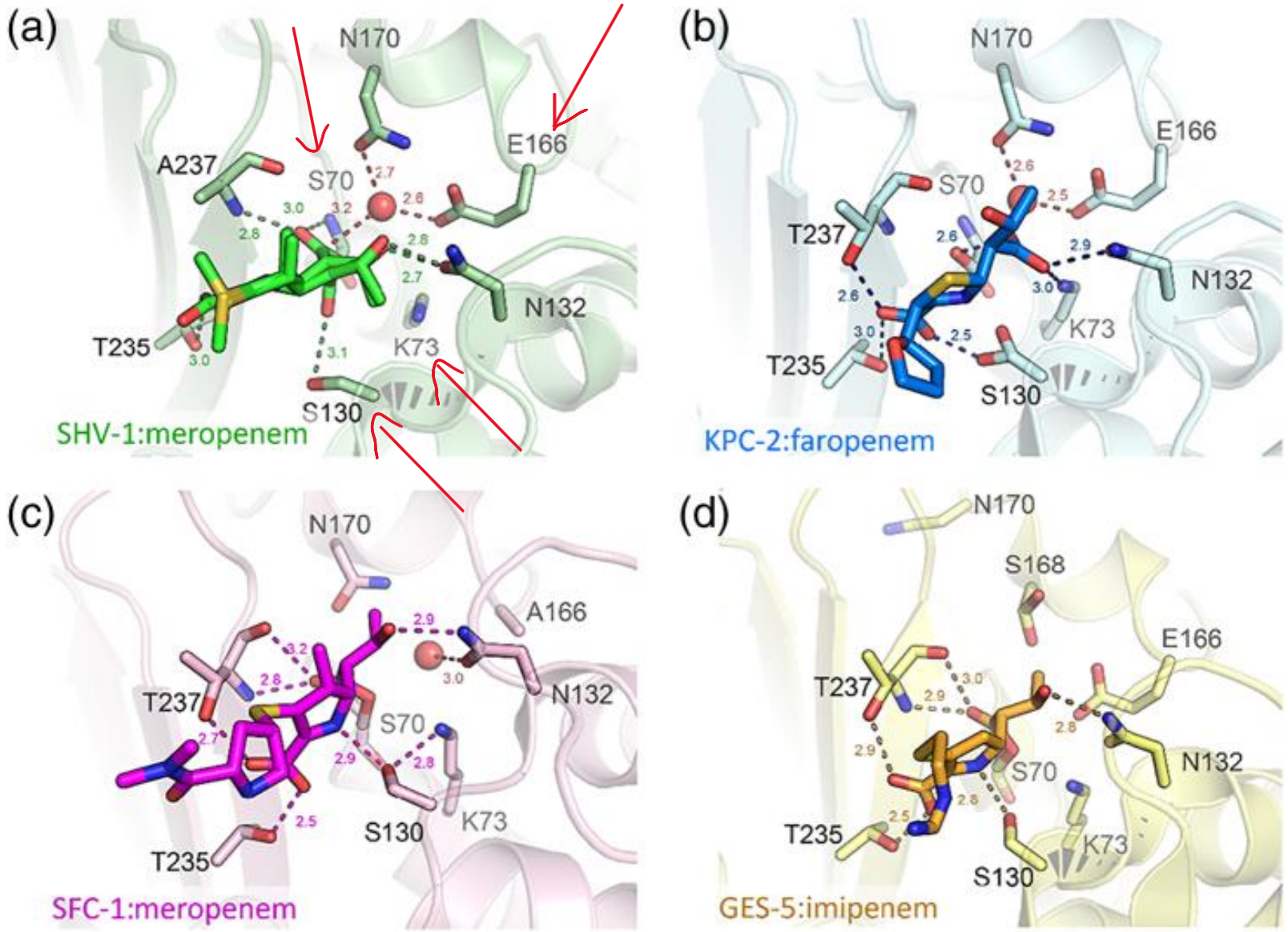
https://doi.org/10.1016/j.jmb.2019.04.002
Edited by C.G. Dowson


MAIN BETA-LACTAMASES IN ENTEROBACTERIACEAE
Ambler's classification
Class A
Serine-beta-lactamases
(inhibitor-susceptible)
Class B
Metallo-beta-lactamases
Class C
Cephalosporinases
Class D
Oxacillinases
Penicillinases
Klebsiella sp.
Citrobacter koseri
Non-inducible AmpC
Escherichia coli
Inducible AmpC
Enterobacter sp.
Citrobacter freundii
Serratia marcescens
Morganella morganii
Hafnia alvei
Providencia stuartii
Derepressed AmpC
Chromosomal genes
Intrinsic resistance
Penicillinases
TEM and SHV
(incl. inhibitor-resistant variants)
ESBL
TEM, SHV and CTX-M
Carrbapenemases
KPC
Carbapenemases
VIM, IMP and NDM
Plasmidic AmpC
CMY-2 and other types
Narrow-spectrum OXA
(inhibitor-resistant)
ESBL-OXA
(uncommon)
Carbapenemases
OXA-48 variants
Plasmid-borne genes
Acquired resistance
Enzyme-conferred resistance
(hydrolysis spectrum)
Penicillins and 1GC
2GC, 3GC +/- 4GC
Carbapenems
+/- other beta-lactams


(a)
Ser70
Lys73
KPC-2
(b)
Zn2
Zn1
NDM-1
(c)
Ser64
Lys67
AmpC
(d)
Ser70
Lys73
OXA-48

Class A serin-beta lactamases

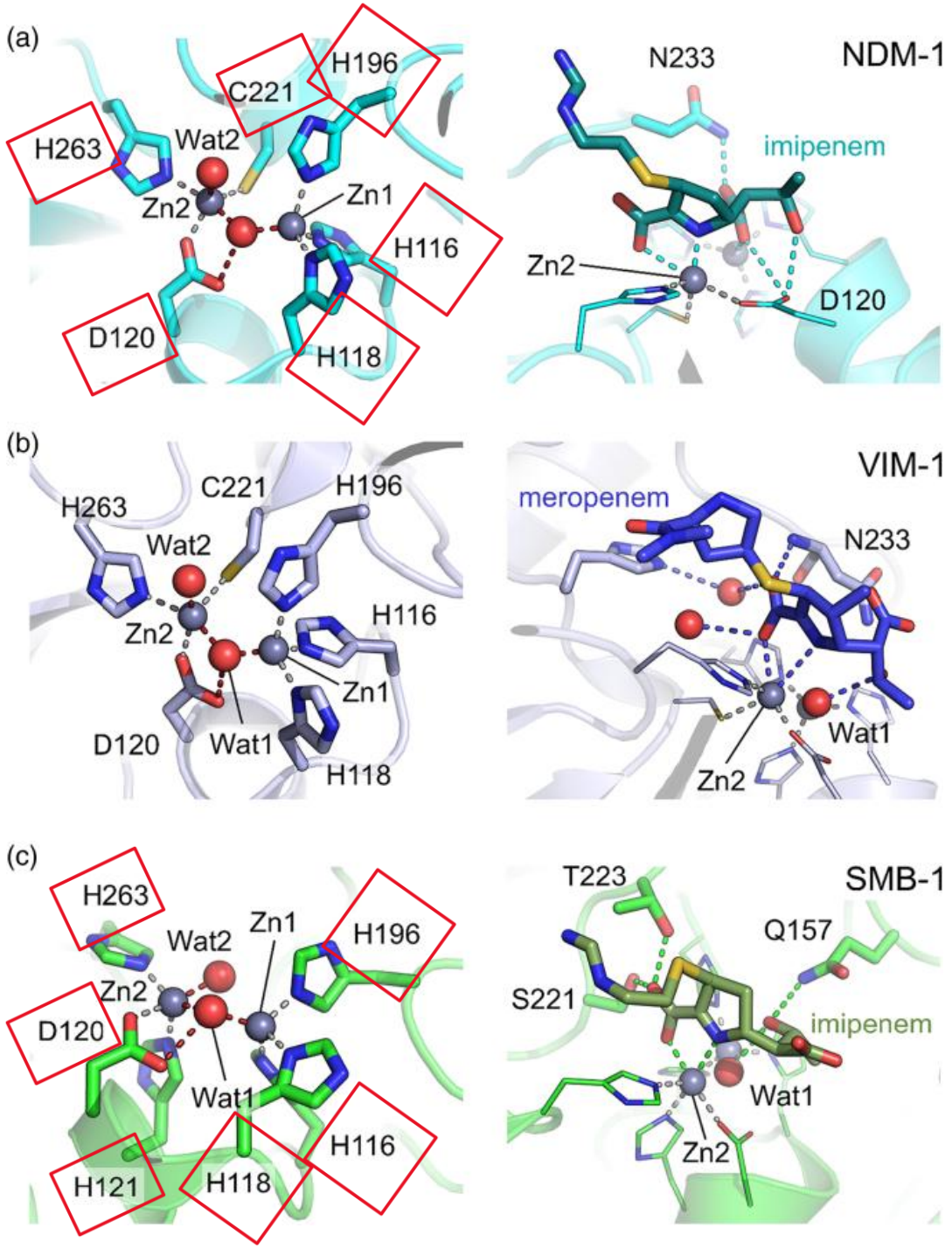
Ser70
Lys73
Ser130
Glu166

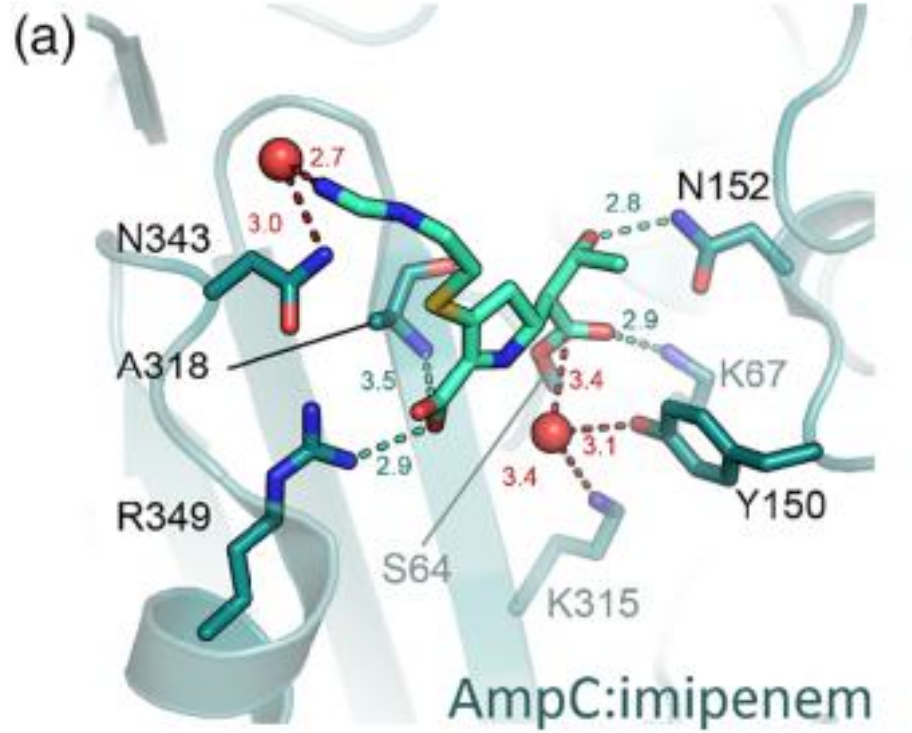


The class B, zinc-dependent, MBLs are unrelated to known PBPs and instead are members of a large, ancient and widely distributed metallohydrolase superfamily.

The identities of the residues that make up this center and its stoichiometry and architecture define three distinct MBL subfamilies (termed B1, B2 and B3).

- B1 enzymes (NDM-1, VIM-1), the most clinically important, possess a binuclear zinc center comprising tri-His (termed Zn1) and Cys-His-Asp (Zn2) metal sites;
- B3 enzymes (SMB-1), the Zn2-coordinating **Cys** is replaced by an additional His residue;
- B2 enzymes, the first His of the defining motif is replaced by **Asn**, resulting in a mononuclear enzyme in which only the Zn2 site is occupied

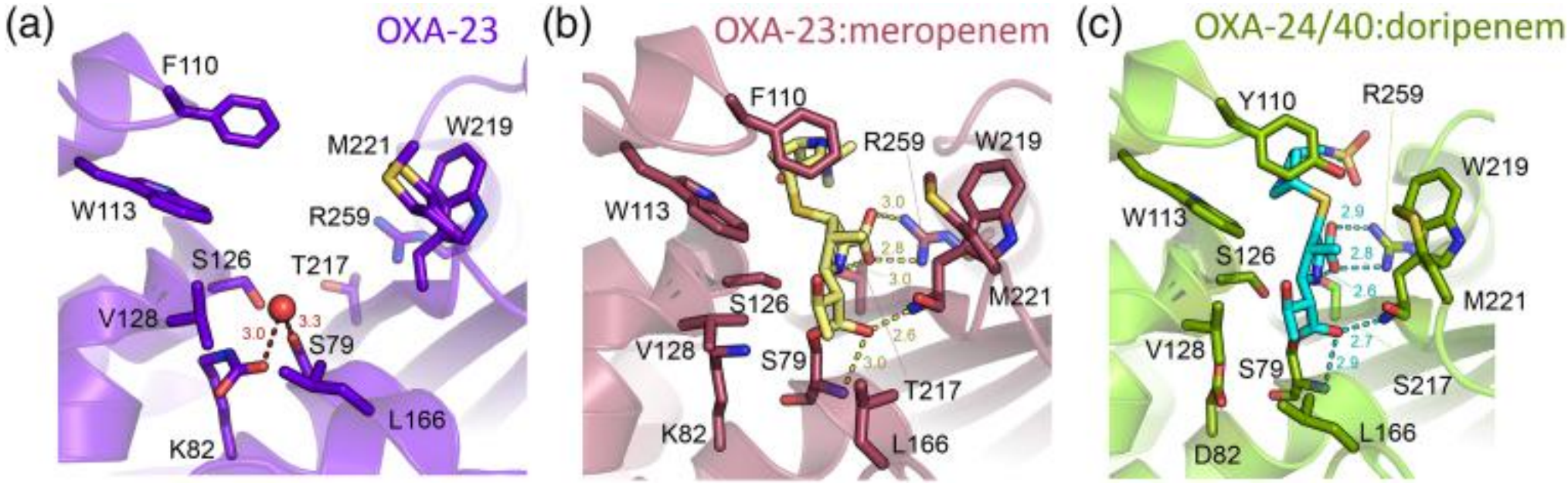




Class C β-lactamase active sites. (a) AmpC:imipenem complex (PDB:1LL5), imipenem acylenzyme covalently attached to Ser64 (note the presence of putative deacylating water adjacent to Tyr150) and (b) ADC-68 active site (note the residues 320 and 321 in the putative C-loop associated with carbapenem turnover). Distances (in Å) displayed as dashed lines. Important residues are represented as sticks (labeled), and waters are shown as spheres.

Class D serin-beta lactamases

The OXA enzymes of class D are the most diverse and in many respects the least well understood of all the β-lactamases. While the first enzymes identified had activity restricted to penicillins, the OXA class now encompasses enzymes active against cephalosporins and carbapenems and with widely differing sensitivities to inhibitors. Although many members are chromosomal, dissemination of plasmid-borne cephalosporinases in *P. aeruginosa*, and more recently the spread of carbapenem-hydrolyzing enzymes in *A. baumannii* and in Enterobacteriaceae (particularly *K. pneumoniae*), has increased the clinical significance of this class. The recent identification of OXA enzymes in a variety of Gram-positive species is further indication of the exceptionally wide distribution and diversity of these enzymes.



Active sites of class D β-lactamases and carbapenem acylenzymes. (a) Native OXA-23 (PDB 4KOX; note the hydrophobic bridge between **Phe110 and Met221 and carboxylated Lys82**; deacylating water is shown as a red sphere). (b) OXA-23:meropenem acylenzyme [PDB 4JF4; note the carbapenem acylenzyme (yellow) in Δ1-pyrroline form]. (c) OXA-24/40:doripenem acylenzyme [PDB 3PAE; note the carbapenem acylenzyme (cyan) in Δ2-pyrroline form]. **Carbapenem acylenzymes (b and c) shown as sticks covalently attached to Ser79.**

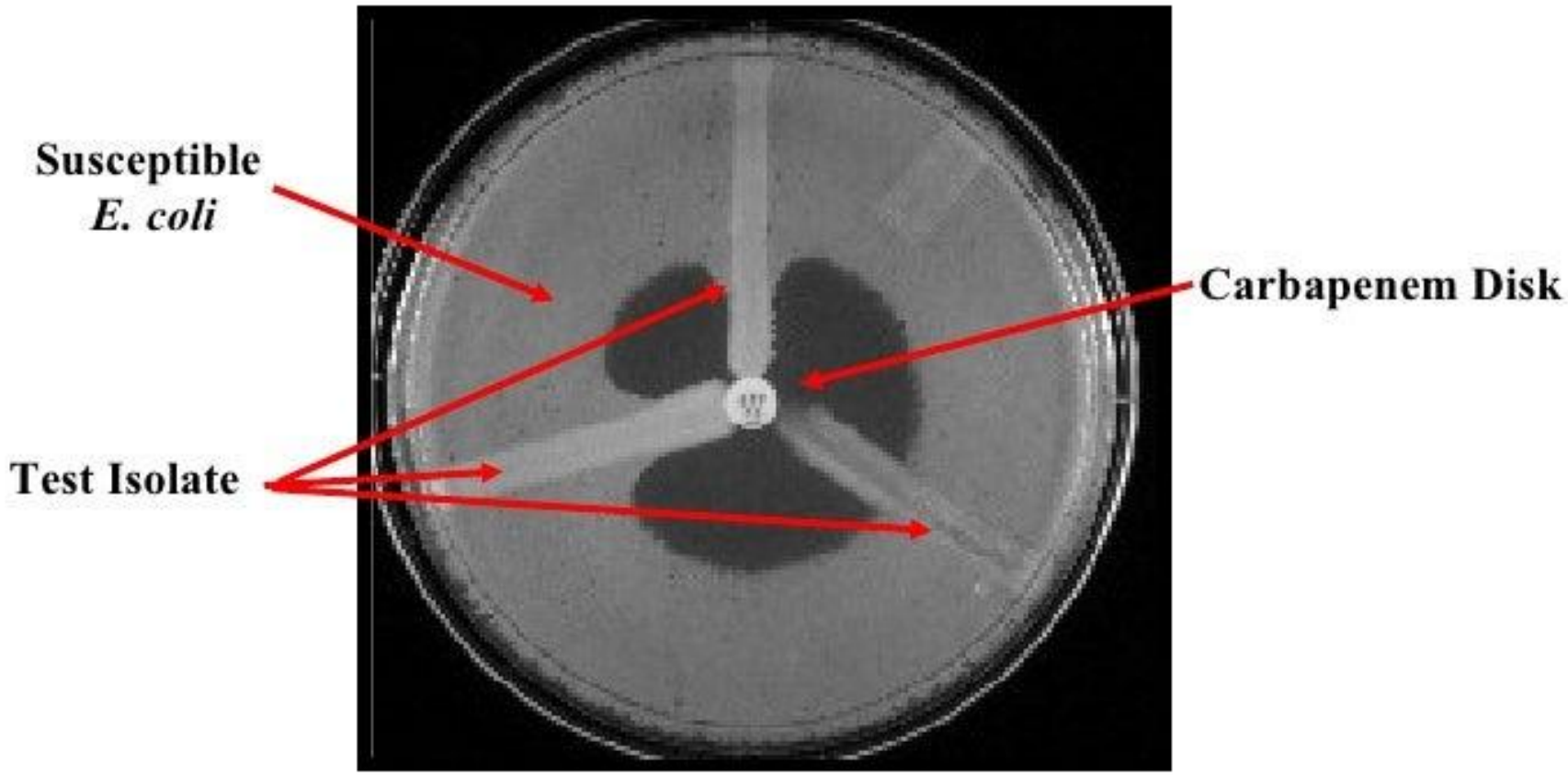
Detection of beta-lactamases

Test for Carbapenemase Detection

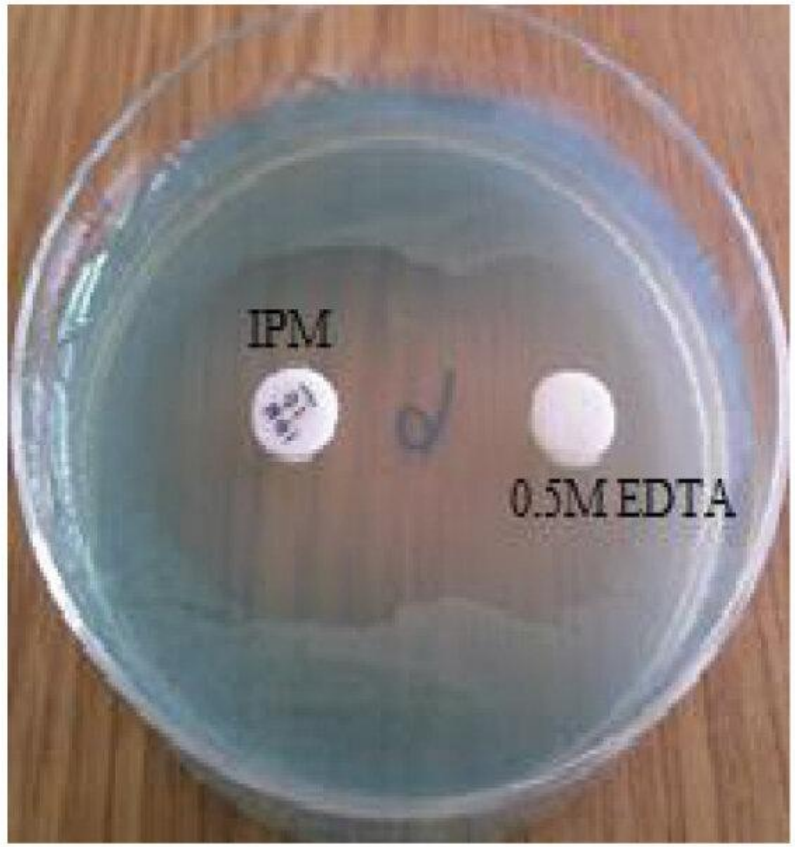
Anderson KF et al. Evaluation of methods to identify KPC in enterobacteriaceae. JCM 2007; 45: 2723 – 2725.

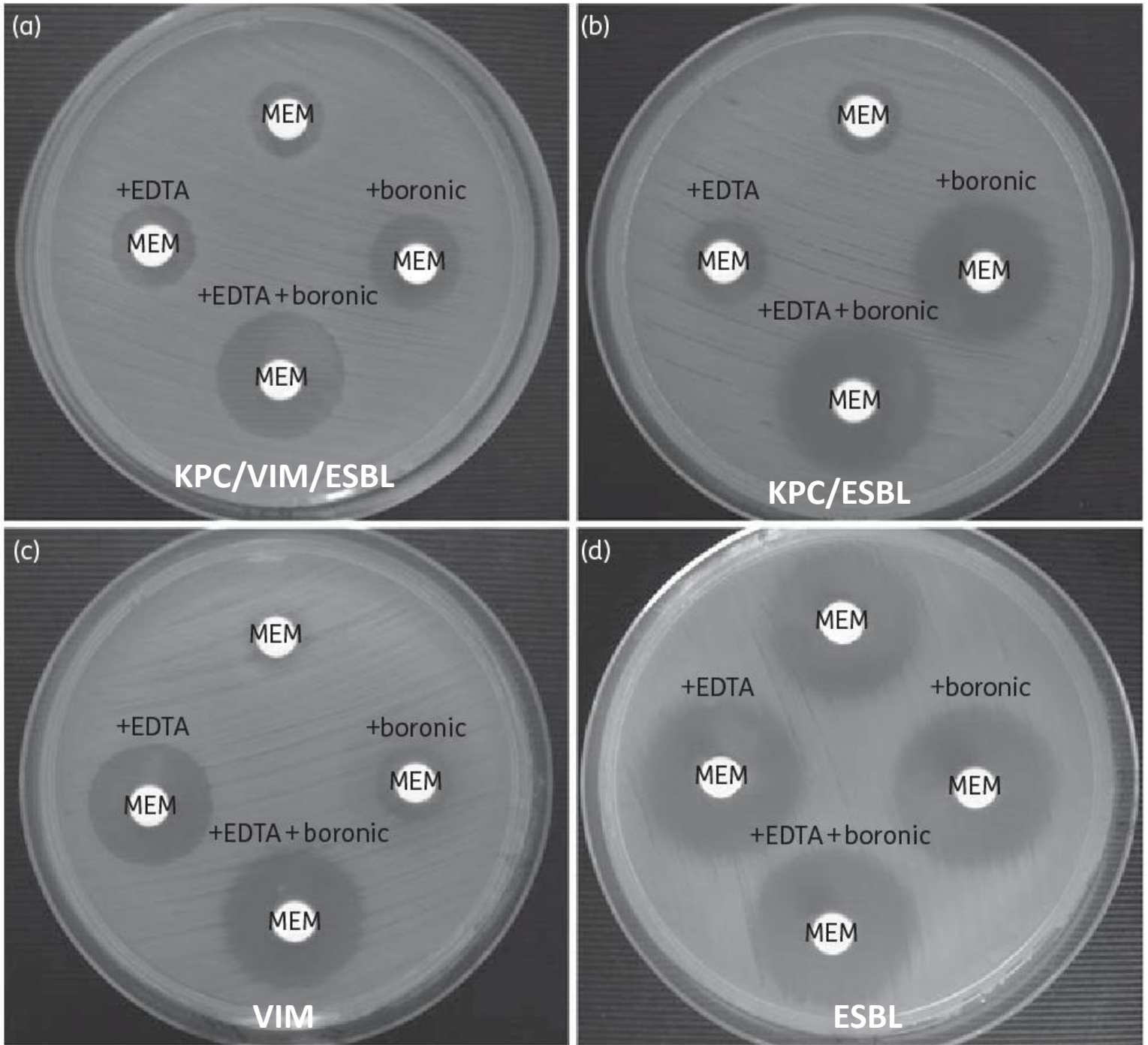
Modified Hodge Test (MHT)

Carbapenem Inactivation Assay



•Synergism with phenylboronic acid [PBA]: detect KPC (or other class A serine carbapenemases)
•Synergism with phenylboronic acid [PBA] and cloxacillin: detect AmpC carbapenemase
•Synergism with EDTA: for detection of Metallo beta-lactamases (MBLs)



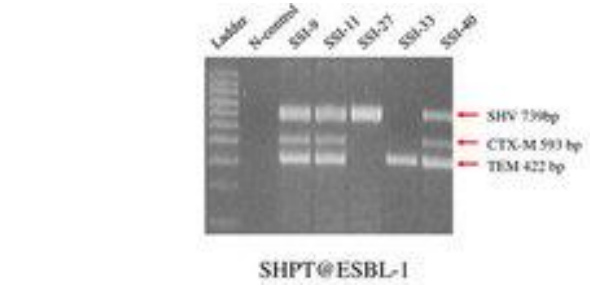


Representative results of the three combined-disc tests using discs of meropenem (MEM) alone and with EDTA, phenylboronic acid, or EDTA plus phenylboronic acid for

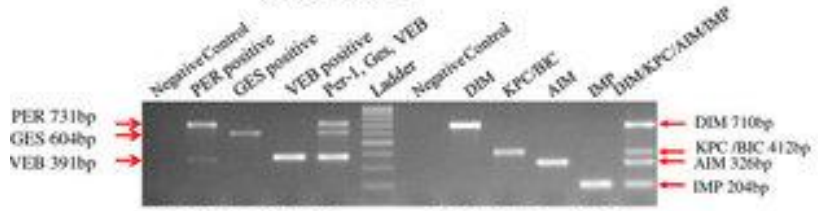
(a) a KPC/VIM/ESBL-possessing isolate
(b) a KPC/ESBL-possessing isolate
(c), a VIM-possessing isolate
(d) an AmpC/ESBL-possessing isolate

Carbapenemase detection on single colonies

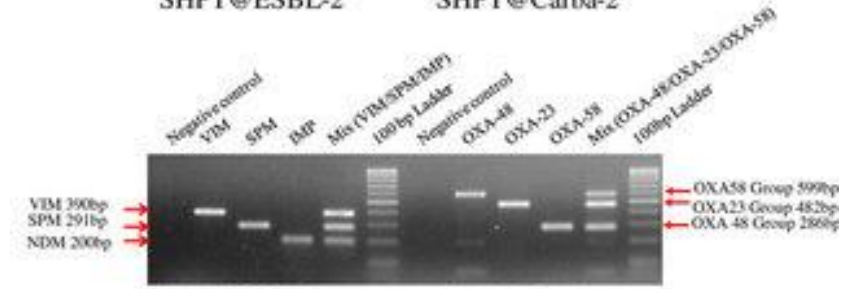
PCR MULTIPLEX



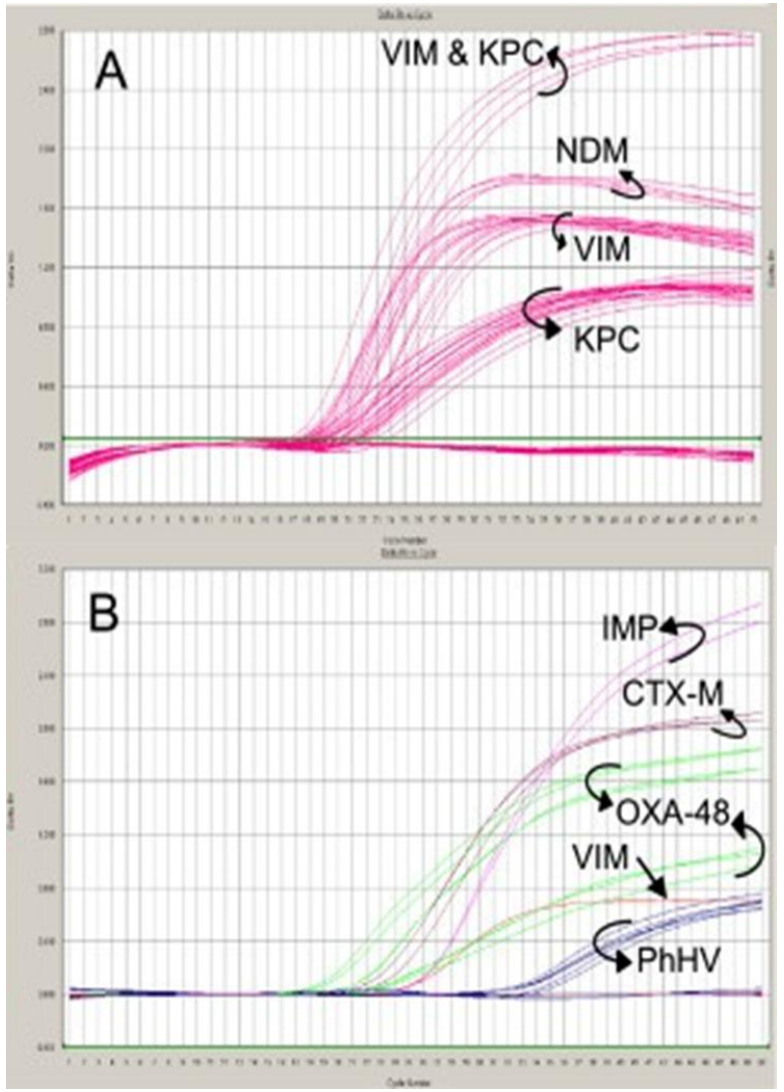
SHPT@ESBL-1



SHPT@ESBL-2 SHPT@Carba-2



SHPT@Carba-1 SHPT@Carba-3



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EPIDEMIOLOGY AND SURVEILLANCE

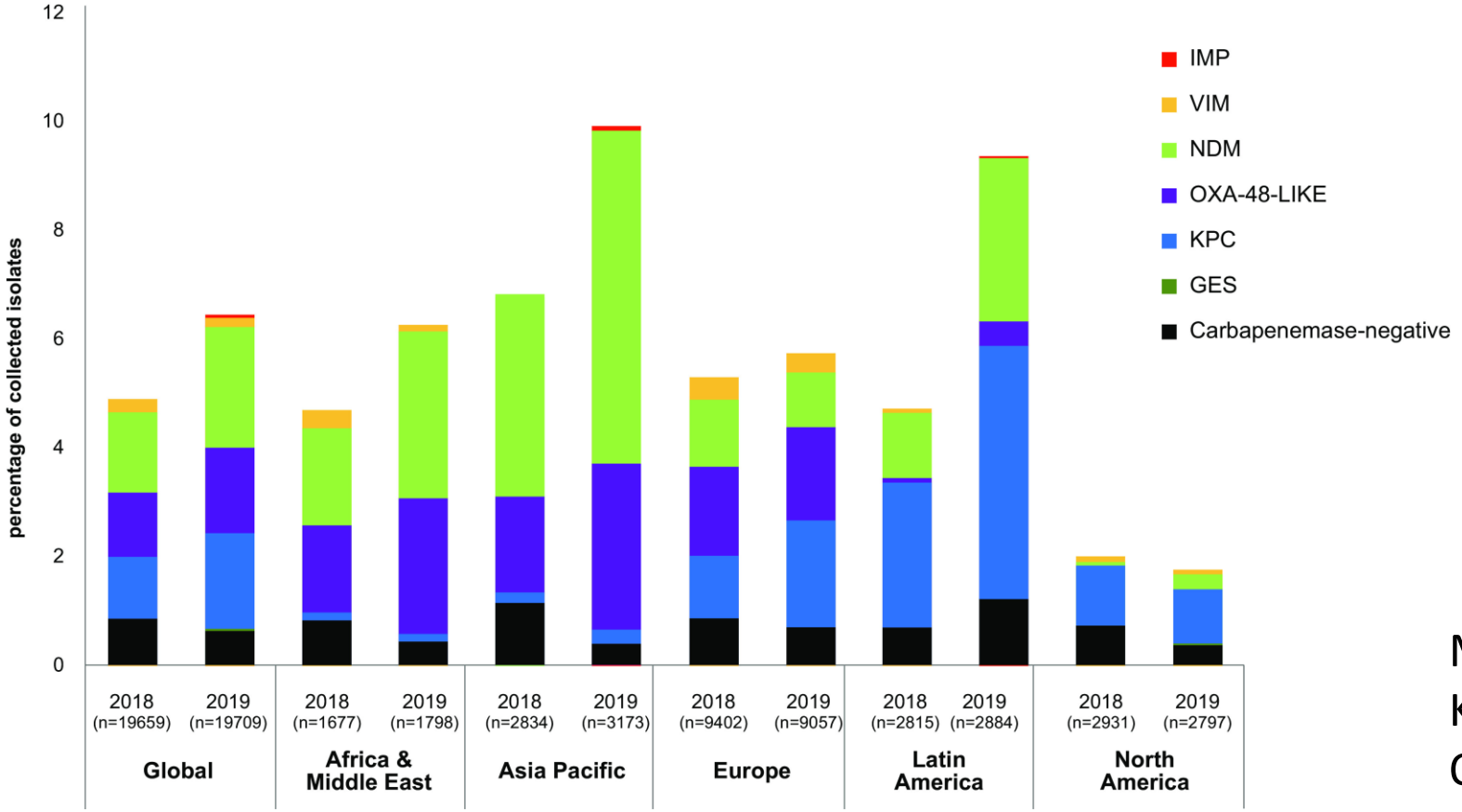
Epidemiology of Resistance Determinants Identified in Meropenem-Nonsusceptible *Enterobacterales* Collected as Part of a Global Surveillance Study, 2018 to 2019

Mark Estabrook,[a] Astrid Muyldermans,[b] Daniel Sahm,[a] Denis Pierard,[b] Gregory Stone,[c] Eric Utt[c]

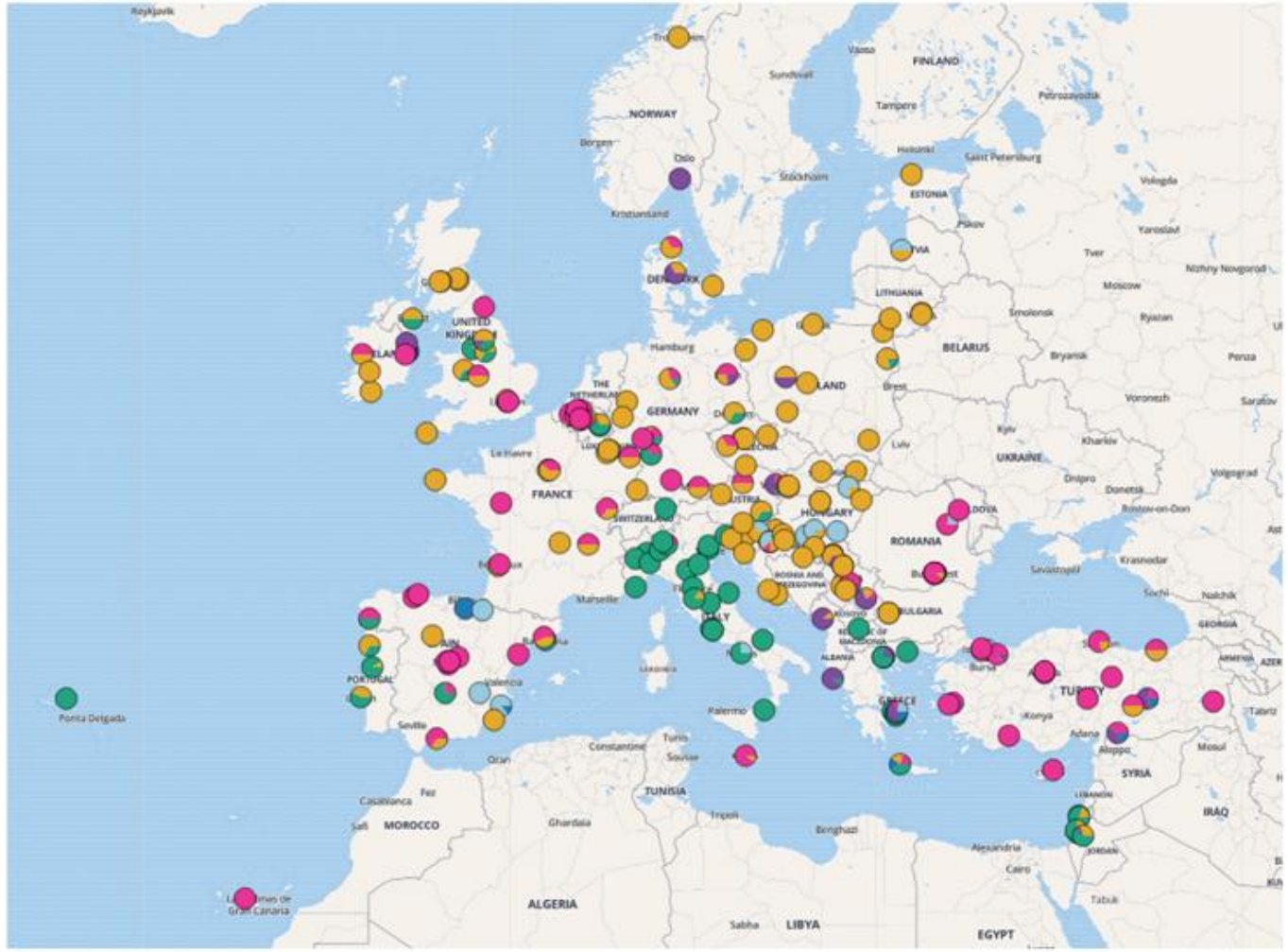
[a]IHMA, Schaumburg, Illinois, USA
[b]Department of Microbiology and Infection Control, Vrije Universiteit Brussel, Universitair Ziekenhuis Brussel, Brussels, Belgium
[c]Pfizer Inc., Gorton, Connecticut, USA

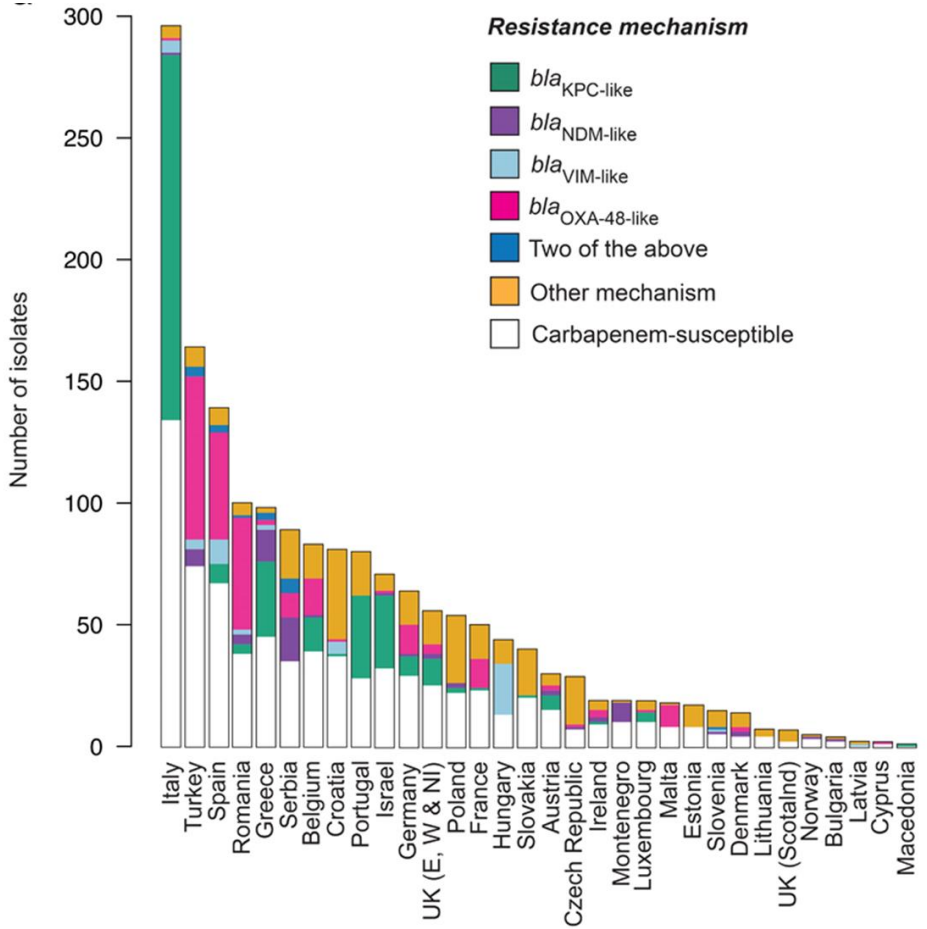
39,368 Enterobacterales da 55 paesi nel 2018 (n = 19,659) e nel 2019 (n = 19,709)

2,228 isolati (5.7%) MEM-NS



MBLs (36.7%, 818/2,228)
KPC (25.5%, 568/2,228)
OXA-48-like (24.1%, 538/2,228)





Epidemic of carbapenem-resistant *Klebsiella pneumoniae* in Europe is driven by nosocomial spread

Nat Microbiol. 2019 4:1919-1929

Sophia David[1], Sandra Reuter[2], Simon R Harris[3], Corinna Glasner[4], Theresa Feltwell[3], Silvia Argimon[1], Khalil Abudahab[1], Richard Goater[1], Tommaso Giani[5], Giulia Errico[6], Marianne Aspbury[7], Sara Sjunnebo[8], EuSCAPE Working Group; ESGEM Study Group; Edward J Feil[9], Gian Maria Rossolini[5,10], David M Aanensen[11,12], Hajo Grundmann[13,14]

nature communications

Article

https://doi.org/10.1038/s41467-024-49349-z

International and regional spread of carbapenem-resistant *Klebsiella pneumoniae* in Europe

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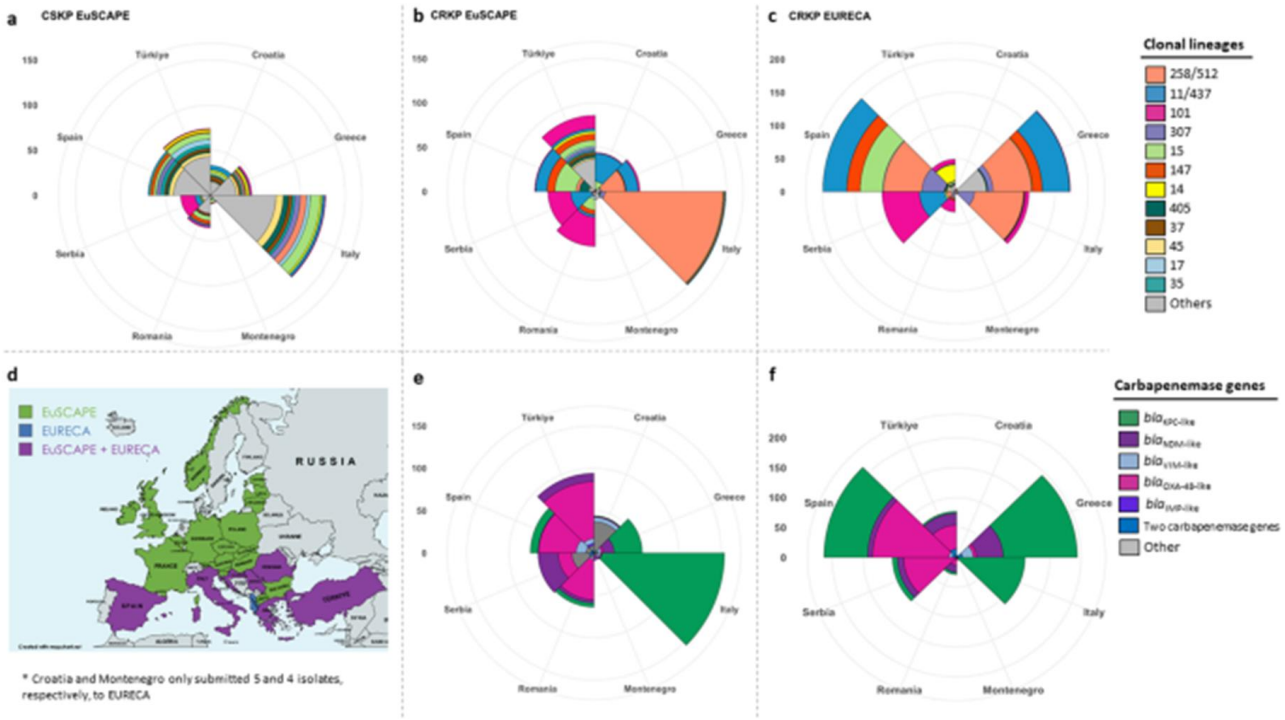
Mabel Budia-Silva[1], Tomislav Kostyanev[2,3], Stefany Ayala-Montaño[1], Jose Bravo-Ferrer Acosta[4], Maria Garcia-Castillo[5,6], Rafael Cantón[5,6], Herman Goossens[2], Jesus Rodriguez-Baño[4,6], Hajo Grundmann[1] & Sandra Reuter[1]

1Institute for Infection Prevention and Control, University of Freiburg– MedicalCenter, Freiburg, Germany.2Laboratory of Medical Microbiology, Universityof Antwerp, Antwerp,Belgium. 3Research GroupforGlobal CapacityBuilding, National FoodInstitute, Technical UniversityofDenmark, Kgs. Lyngby,Denmark. 4Unidad Clínica de Enfermedades Infecciosas y Microbiología, Instituto de Biomedicina de Sevilla (IBiS)/CSIC, Hospital Universitario Virgen Macarena; and DepartamentodeMedicina,UniversidaddeSevilla,Seville,Spain.5ServiciodeMicrobiología,HospitalUniversitarioRamónyCajalandInstitutoRamónyCaja de Investigación Sanitaria (IRYCIS), Madrid, Spain. 6CIBER de Enfermedades Infecciosas (CIBERINFEC), Institute de Salud Carlos III, Madrid, Spain.

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) studied at European level **in 2013-2014 - EuSCAPE collection**

Since in the EuSCAPE study most of the CRKP were from the South of Europe, the sequel project collected 687 CRKP recovered among clinical samples from 41 hospitals in nine Southern European countries in **2016-2018 - EURECA collection**



* Croatia and Montenegro only submitted 5 and 4 isolates, respectively, to EURECA

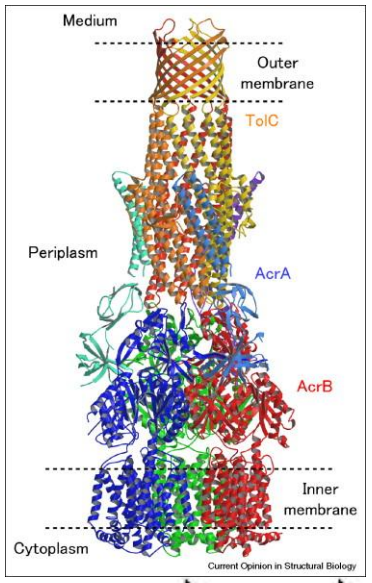
Identified 11 major clonal lineages, with most isolates belonging to the high-risk clones ST258/512, ST101, ST11, and ST307. ***bla*$_{KPC}$**-like was the most prevalent carbapenemase-encoding gene (46%) prevalent in Greece, Italy, and Spain; ***bla*$_{OXA-48-like}$** present in 39% of isolates, mostly by ST101 in Serbia and Romania and ST14 in Türkiye; ***bla*$_{NDM}$** in ST11 from Greece

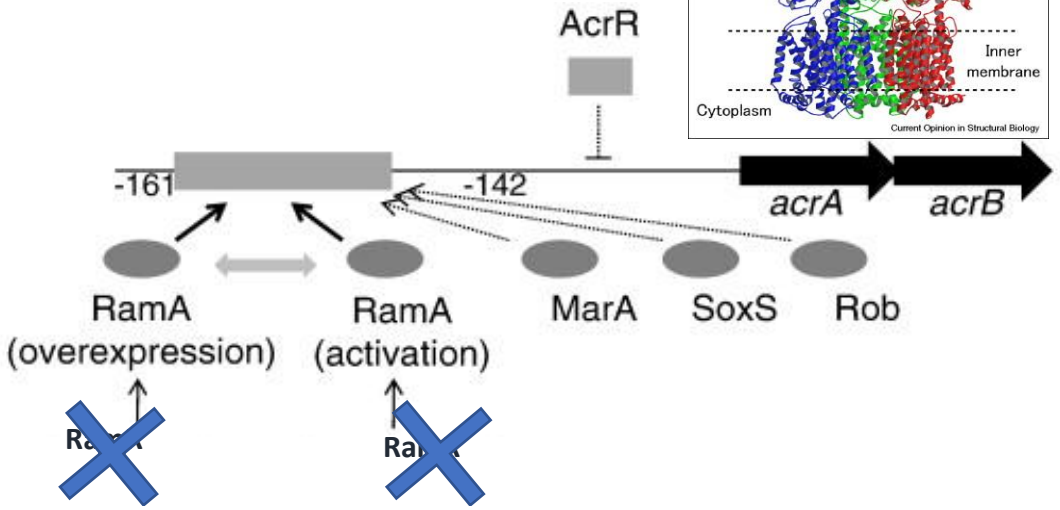
Se non abbiamo i carbapenemi cosa altro rimane? Domanda posta nel 2019

Antimicrobial agents	Recommended dose for CRE infections[a]	Comments
Meropenem	2 g every 8 h by prolonged infusion for isolates with MICs of 2–8 mg/L	May not be effective for isolates with MIC > 8 mg/L
Ertapenem	Consider 2 g every 24 h	Used in double-carbapenem therapy
Colistin	Loading dose of 9 MU, followed by 9 MU/day in 2–3 divided doses	
Polymyxin B	Loading dose of 2–2.5 mg/kg, followed by 5 mg/kg/day in 2 divided doses	
Tigecycline	Loading dose of 100 mg, followed by 50 mg every 12 h	Consider loading dose of 200 mg, followed by 100 mg every 12 h for severe infections
Eravacycline	1 mg/kg every 12 h	Approved by FDA in August 2018 for the treatment of cIAI. Activity against carbapenem-resistant *Enterobacteriaceae* has been demonstrated *In vitro*. Clinical data in CRE infections are still lacking
Gentamicin Tobramycin	5–7 mg/kg/day	Used in combination therapy. Consider a higher dose of 10–15 mg/kg/day for severe infections without other options. Risk of toxicity may increase. TDM is recommended
Amikacin	15–20 mg/kg/day	Used in combination therapy. Consider a higher dose of 25–30 mg/kg/day for severe infections without other options. Risk of toxicity may increase. TDM is recommended
Plazomicin	15 mg/kg/day	Approved by FDA in June 2018 for the treatment of cUTI including pyelonephritis. Activity against ESBL- and carbapenemase-producing *Enterobacteriaceae* has been demonstrated *In vitro*. Clinical data in CRE infections are still lacking
Fosfomycin	4 g every 6 h to 8 g every 8 h	Used in combination therapy

Sheu CC et al., **Infections Caused by Carbapenem-Resistant *Enterobacteriaceae*: An Update on Therapeutic Options.** Front. Microbiol., 30 January 2019 https://doi.org/10.3389/fmicb.2019.00080

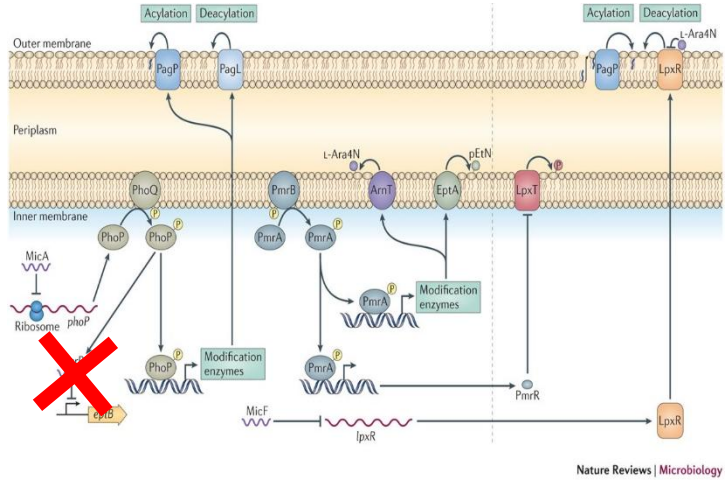
XDR ST147 *K. pneumoniae*





Colistin

ColR MgrB depletion

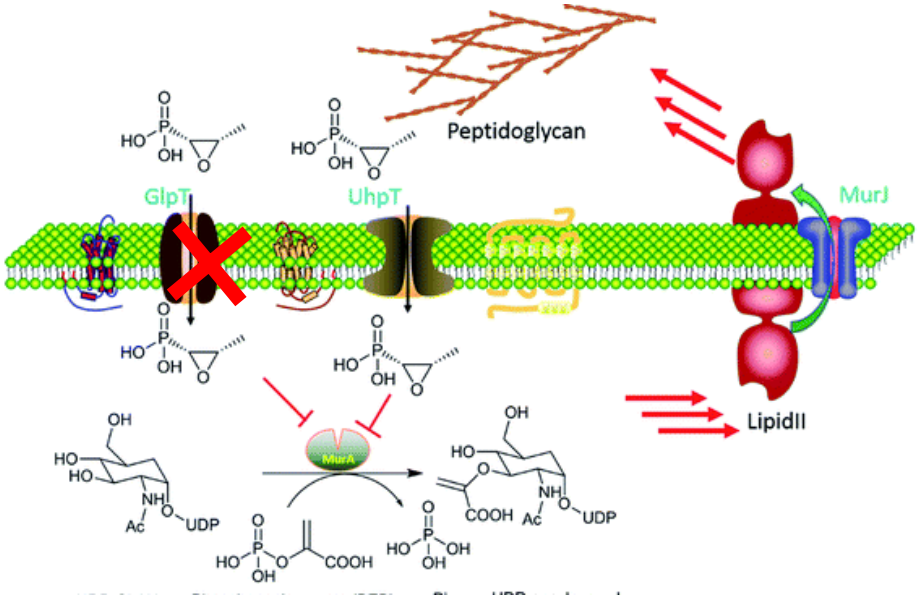


Tigecycline

TygR RamR depletion

Fosphomycin

FosR GlpT depletion



RAPID COMMUNICATION

Extremely drug-resistant NDM-9-producing ST147 *Klebsiella pneumoniae* causing infections in Italy, May 2020

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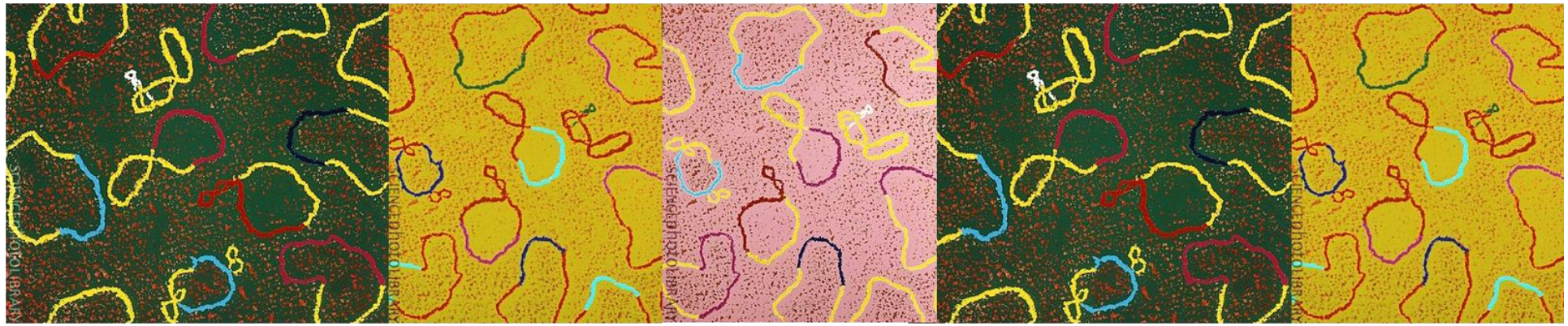
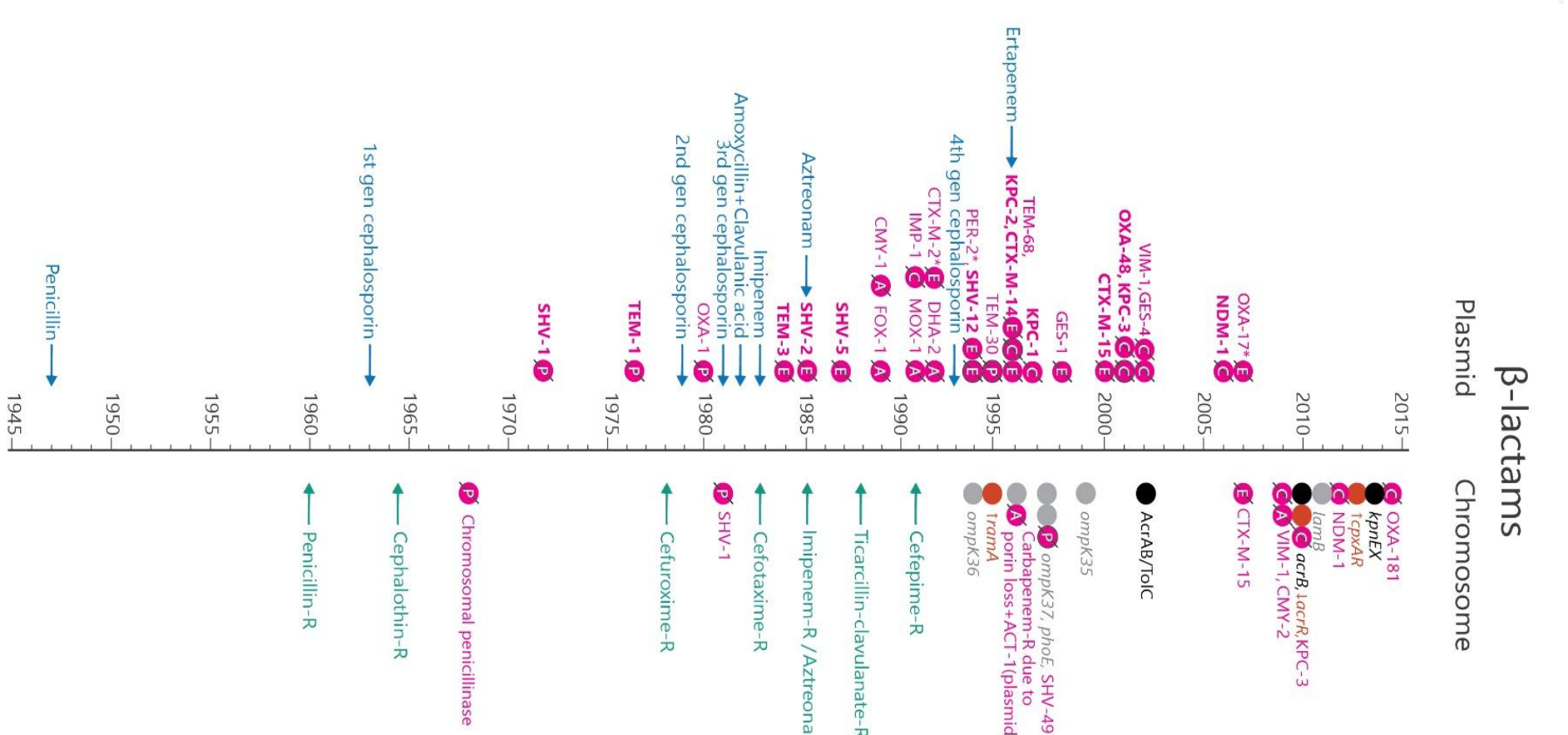
I plasmidi



Time-line describing the evolvement of *K. pneumoniae* resistome

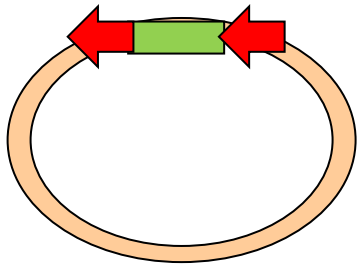


From: *Klebsiella pneumoniae*: a major worldwide source and shuttle for antibiotic resistance
Shiri Navon-Venezia, Kira Kondratyeva, Alessandra Carattoli
FEMS Microbiol Rev. 2017;41(3):252-275.

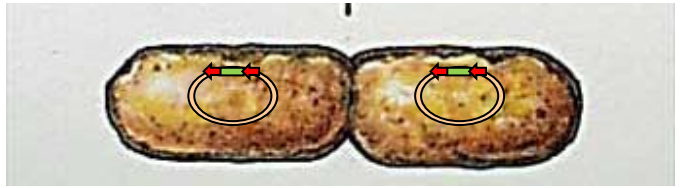
- Resistance gene

- Transposon

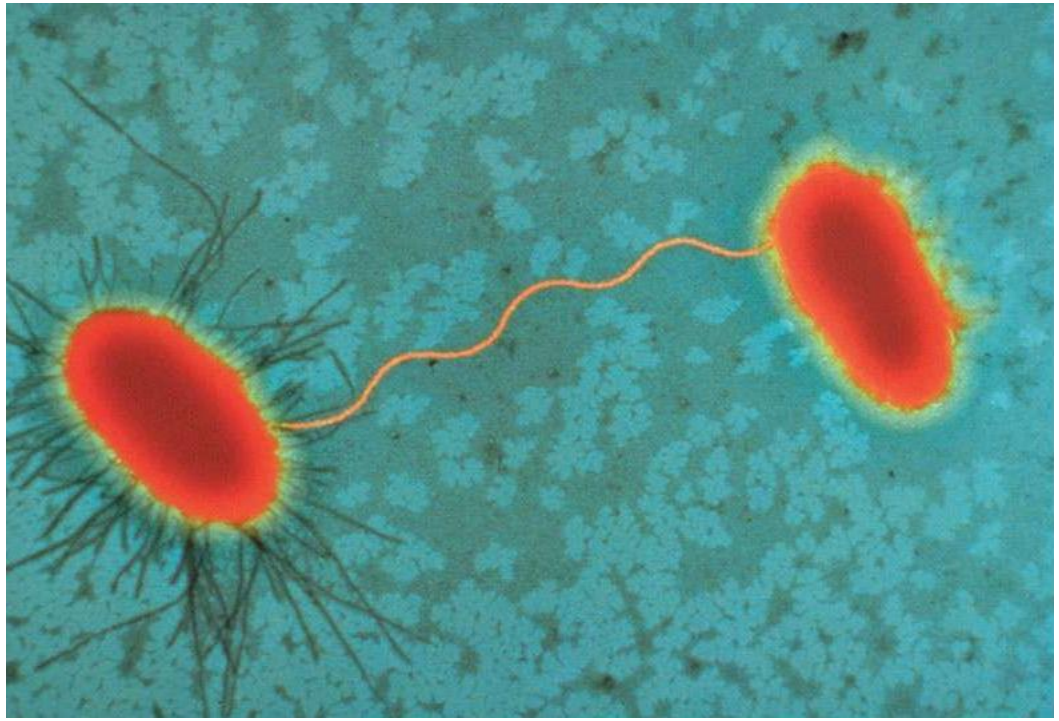
- Plasmids



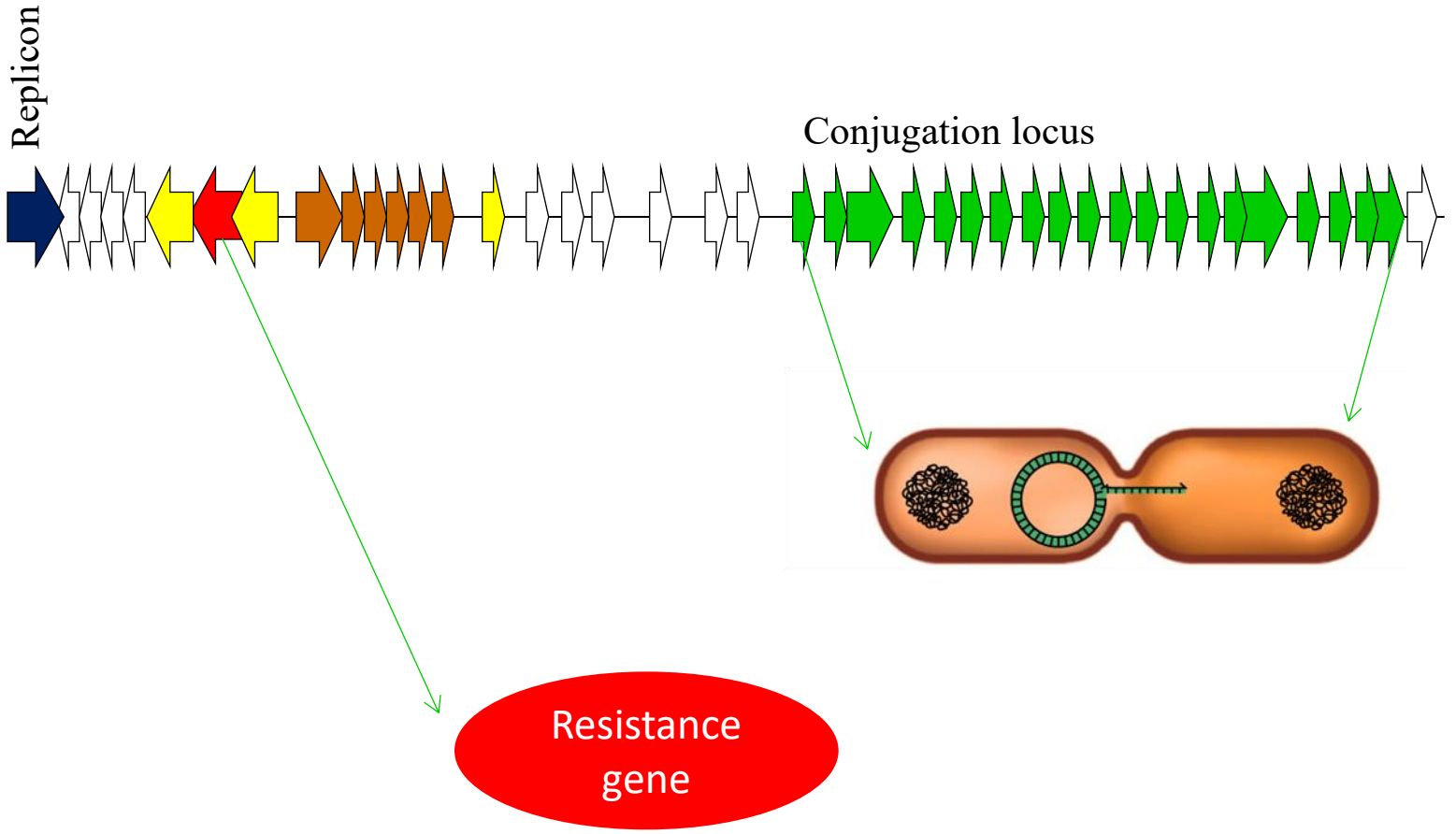
- Bacterial clones



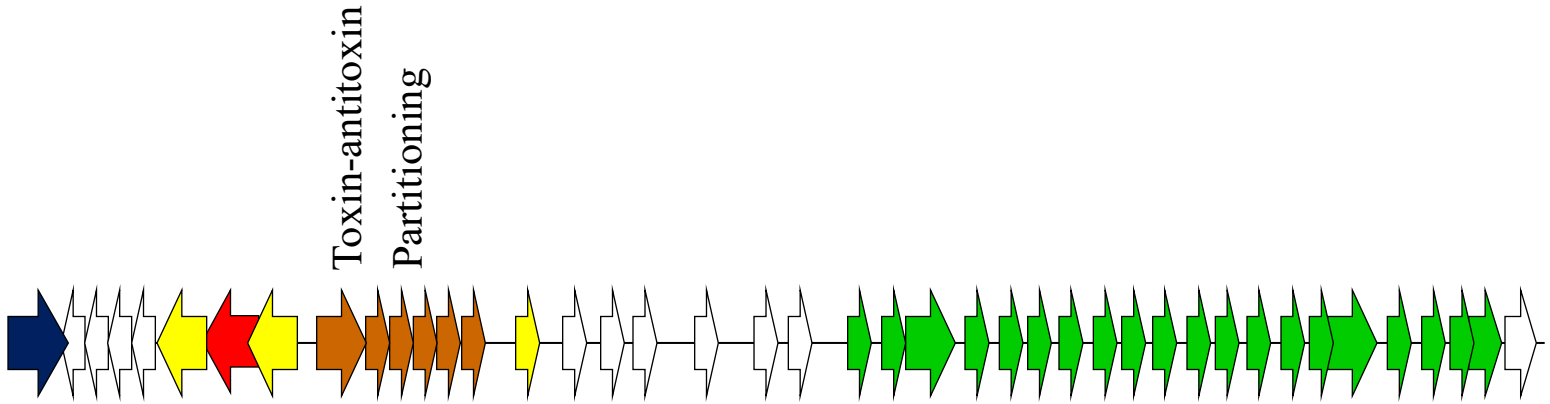
Bacterial sex

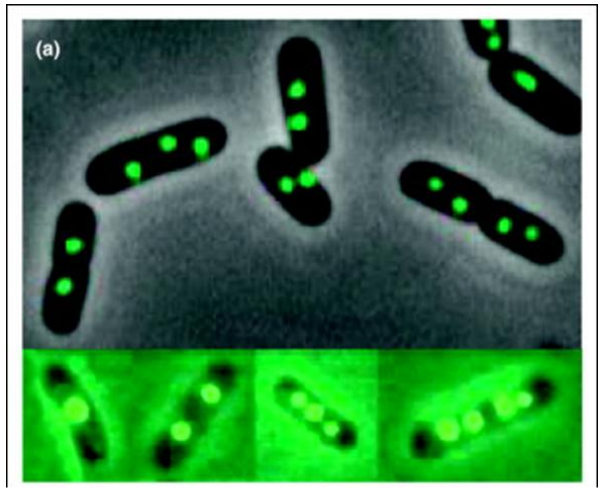


Self-conjugative plasmid (30-300 kb)

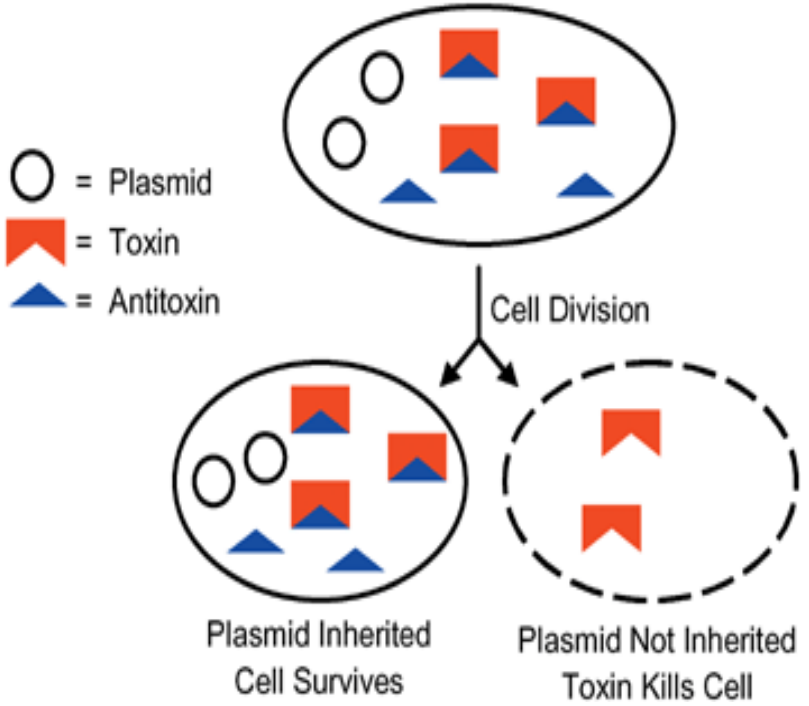


Stability and partitioning





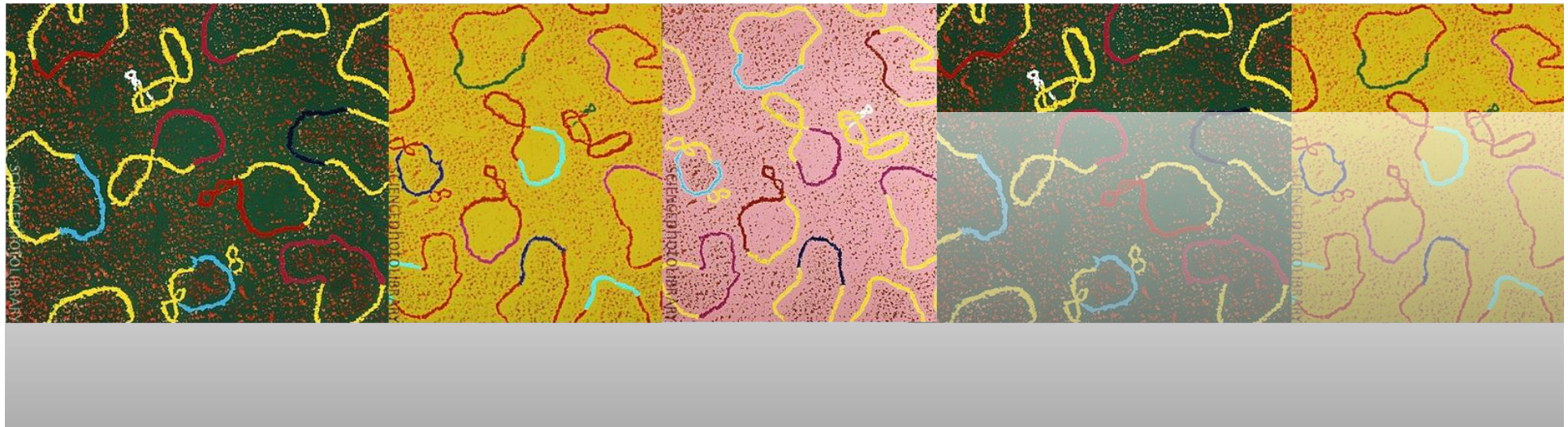
Szardenings F et al., 2011. Current Opinion in Microbiology 14 (6): 712-718



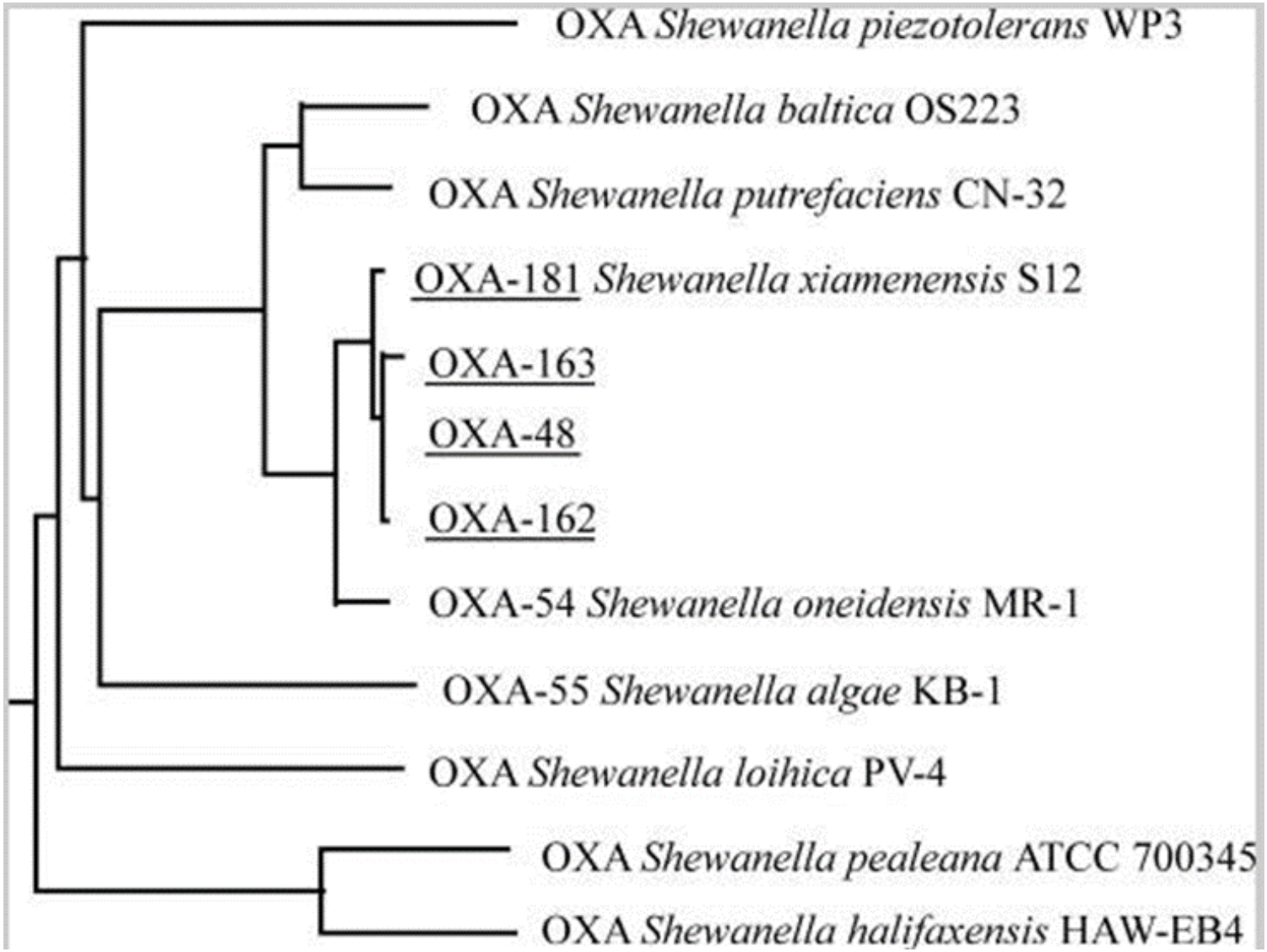
Una storia:

Un gene di carbapenemasi e la strategia di disseminazione *in*

Klebsiella pneumoniae e *Escherichia coli*

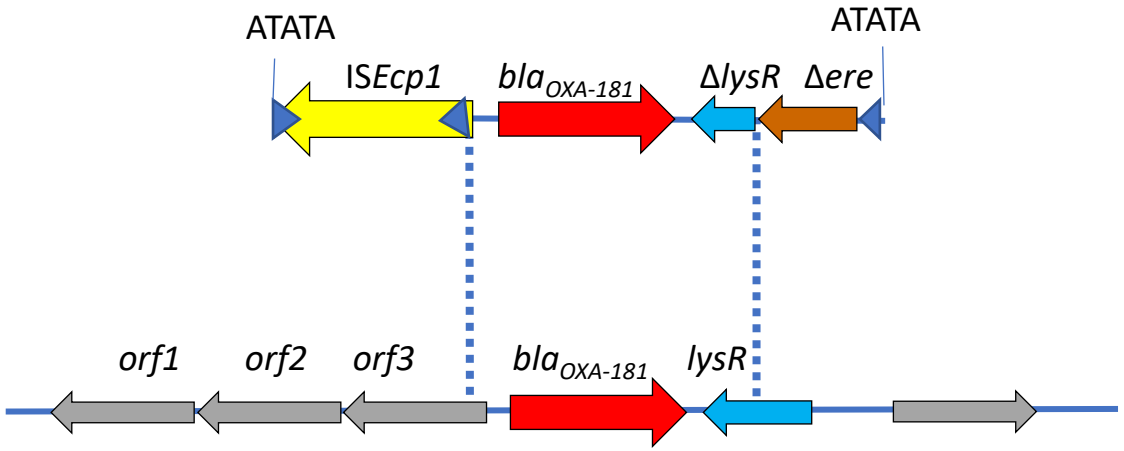


Carbapenemasi di Classe D : le origini



Potron *et al., AAC 2011, 55: 4405–4407*

L’origine di *bla*$_{\text{OXA-181}}$

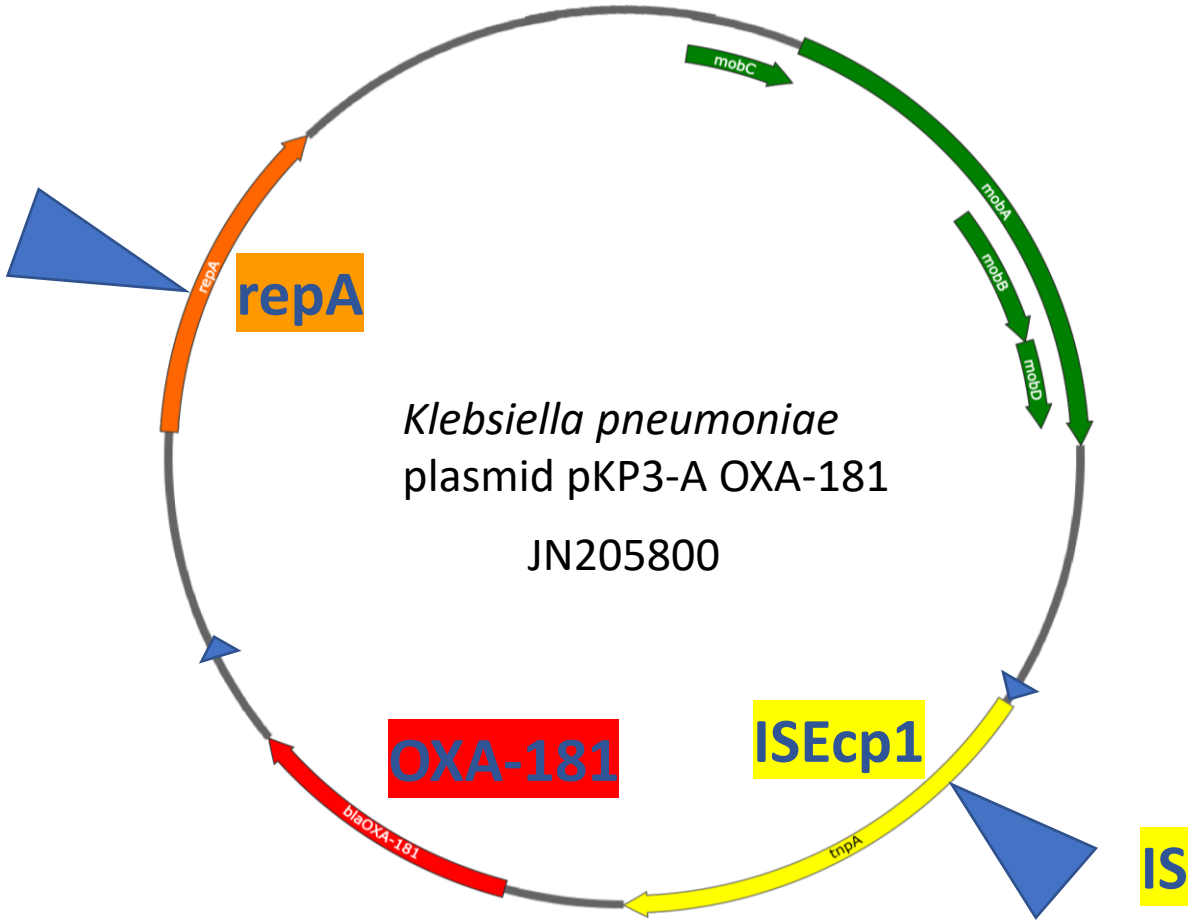


Klebsiella pneumoniae

Shewanella xiamenensis

Potron *et al., AAC 2011, 55: 4405–4407*

ColKP3 9 Kb


mobC
mobA
mobB
mobD
repA
repA
Klebsiella pneumoniae
plasmid pKP3-A OXA-181
JN205800
OXA-181
blaOXA-181
ISEcp1
tnpA
IS

Klebsiella pneumoniae pOXA-181_29144
KX523903 Czech Republic

Escherichia coli
pOXA181
KP400525 China

FDAARGOS_433
CP023897 Canada

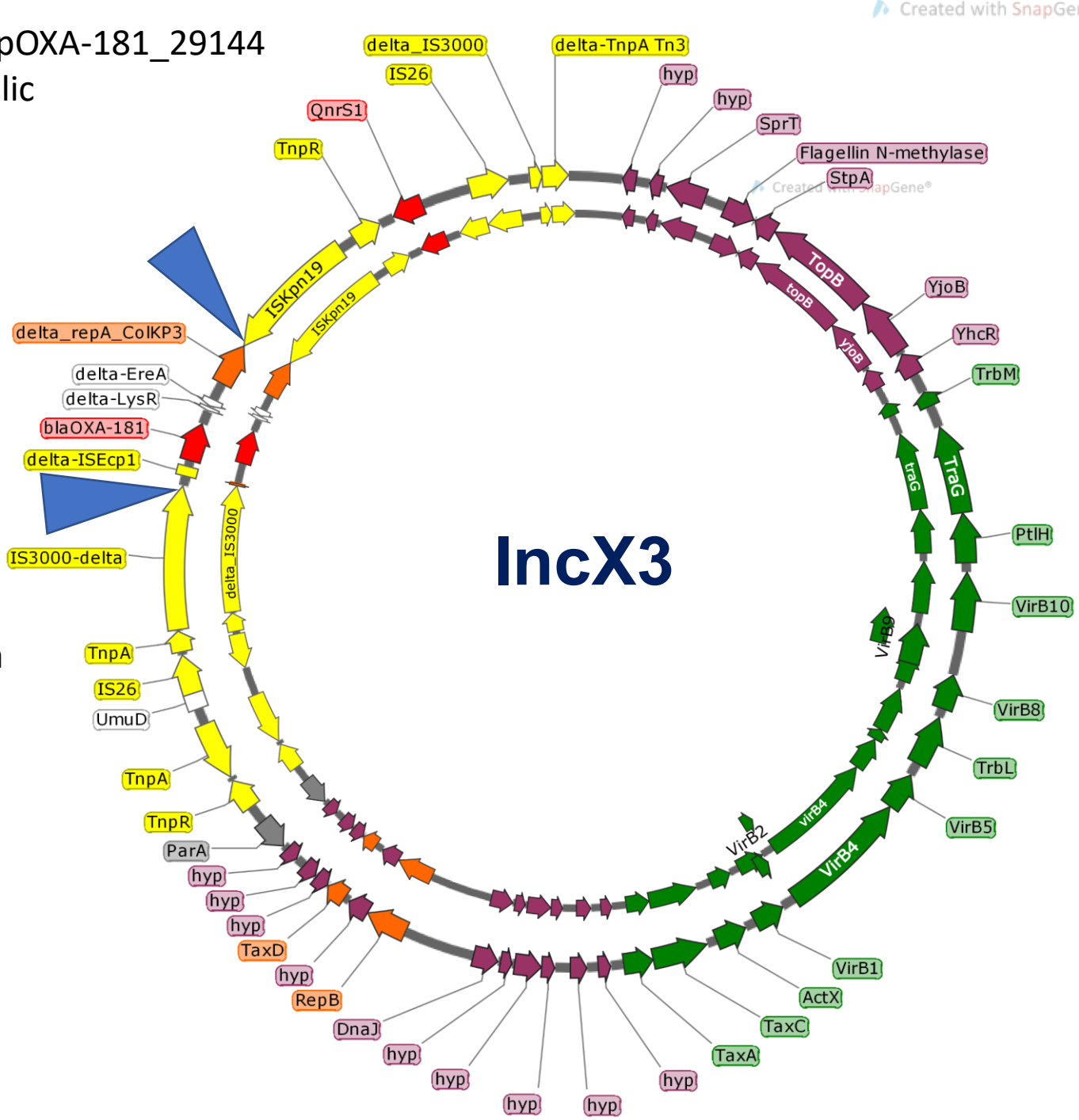
pAMA1167-OXA-181
CP024806, Denmark

pKBN10P04869C
CP026476, South Korea

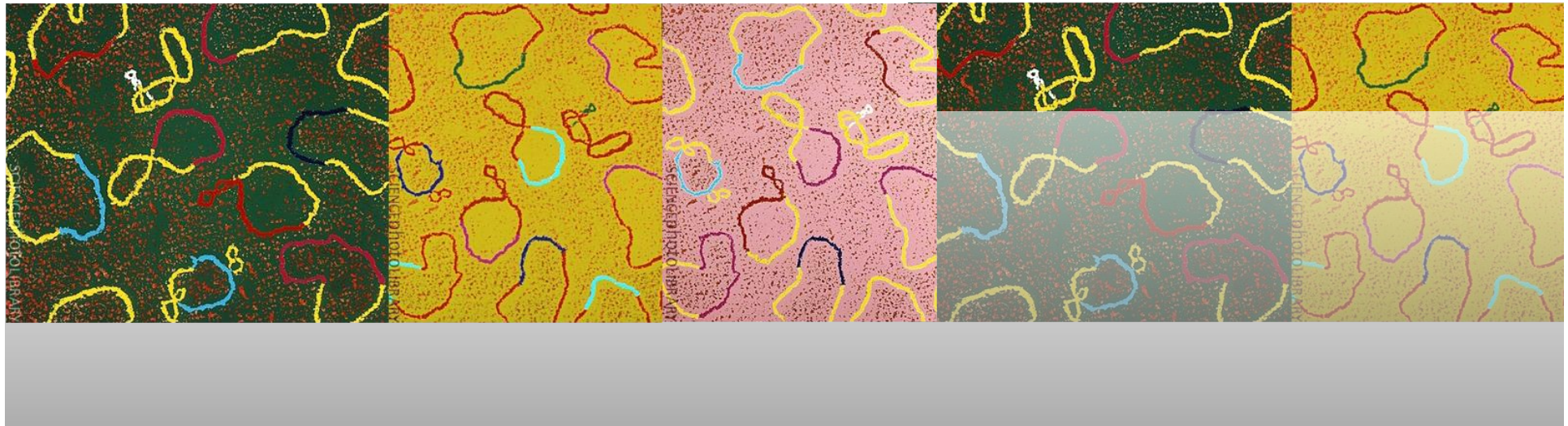
pOXA-181-IHIT35346
KX894452, Germany

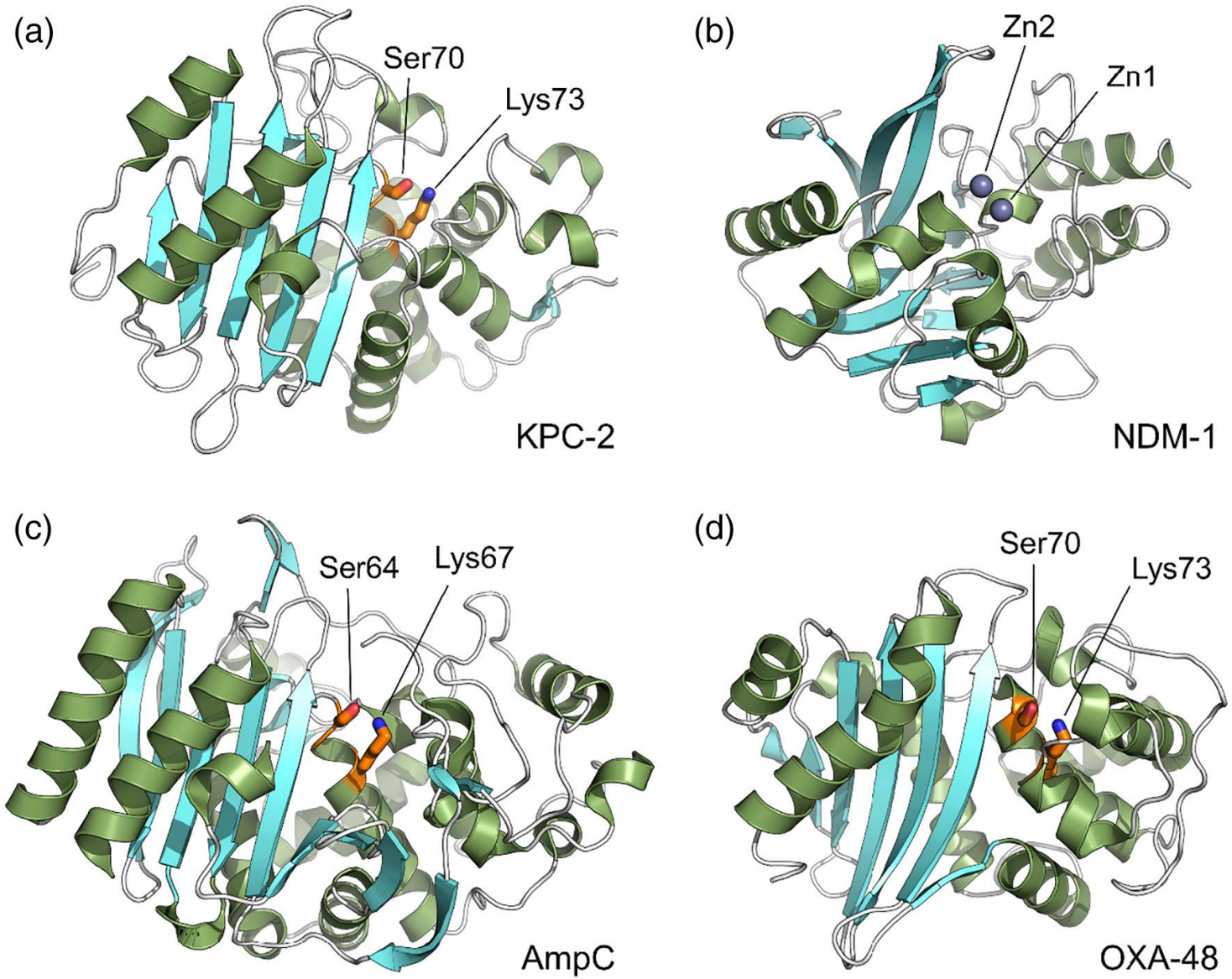
pKP_BO_OXA-181
MG228426, Italy

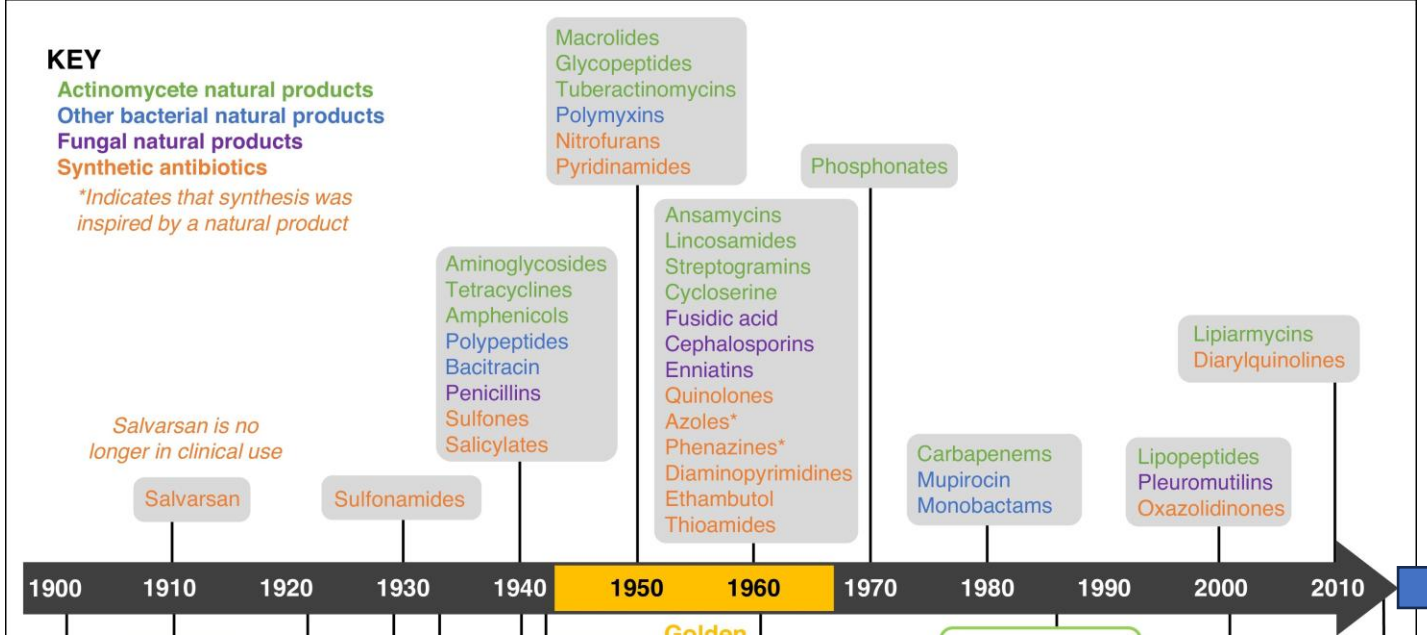
IncX3_OXA_181
MG570092, Lebanon

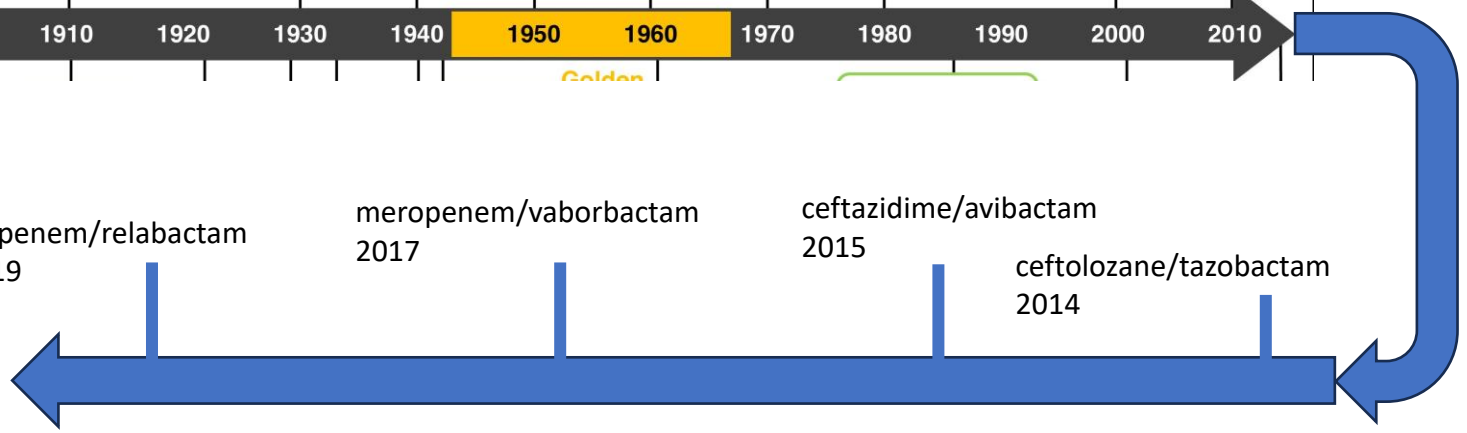


Cambio di approccio in farmacologia
La nuova golden age




(a)
Ser70
Lys73
KPC-2
(b)
Zn2
Zn1
NDM-1
(c)
Ser64
Lys67
AmpC
(d)
Ser70
Lys73
OXA-48





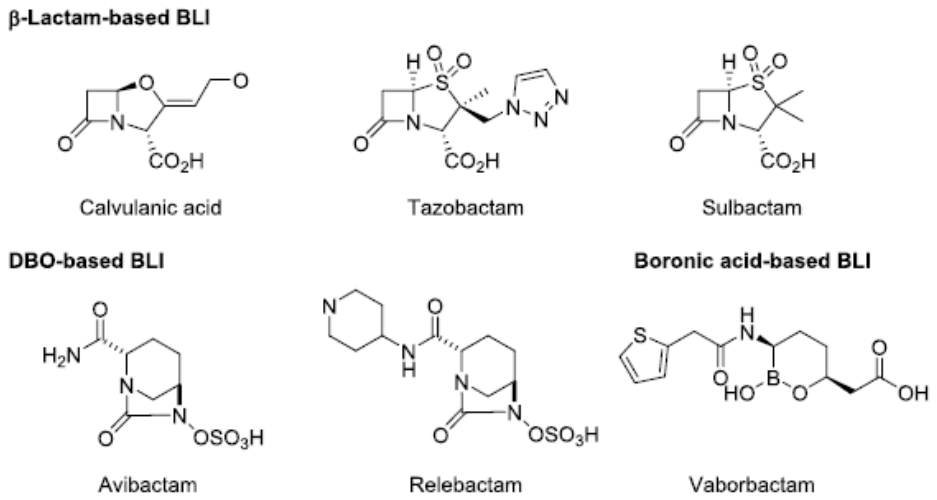
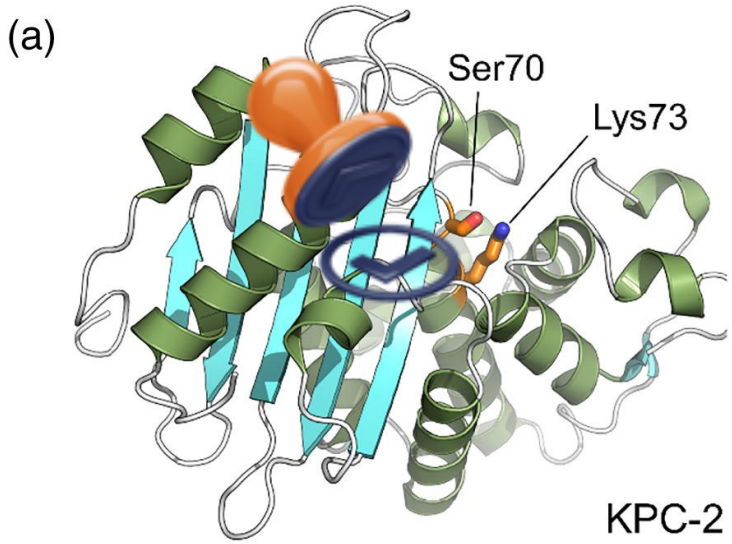
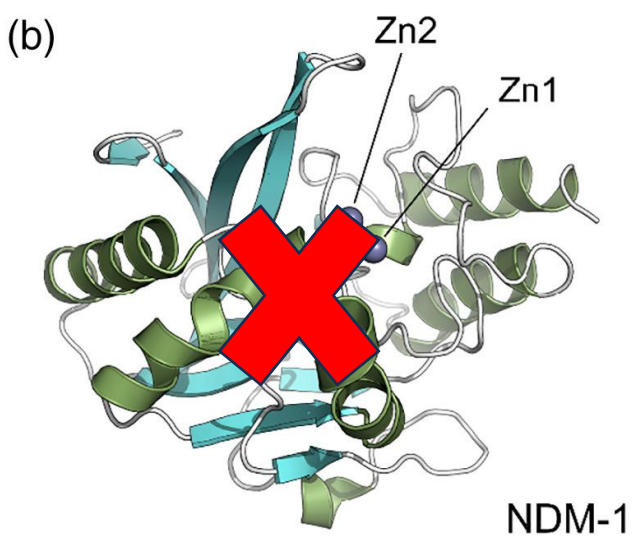
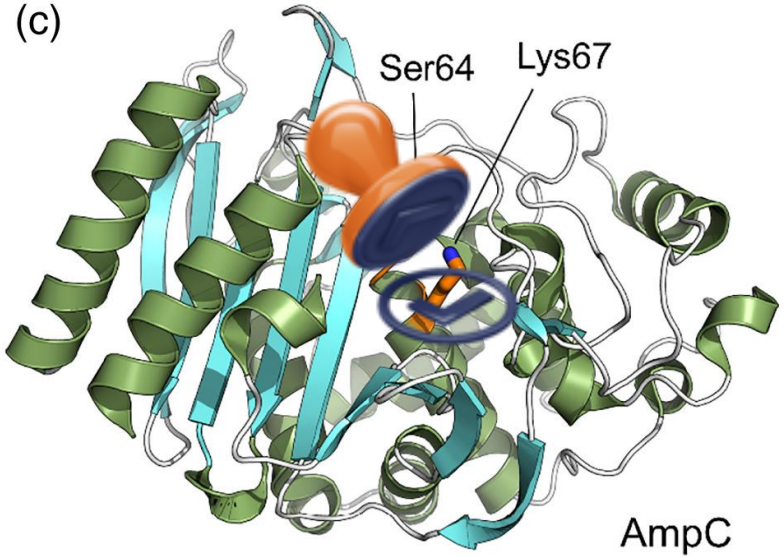


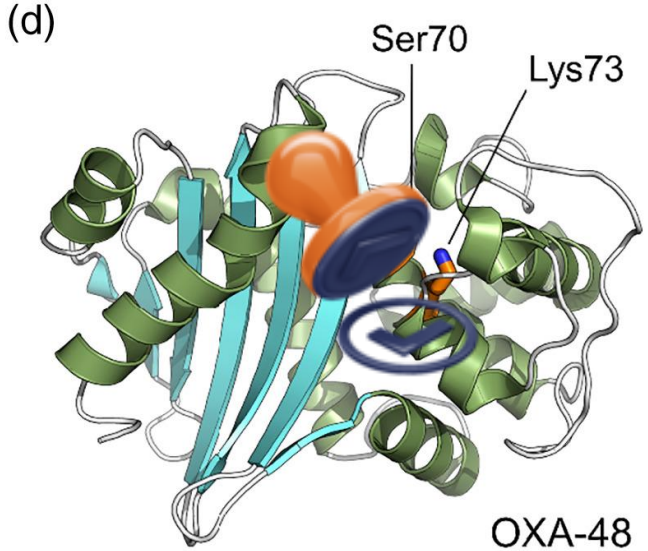
Figure 1. Structures of the approved BLIs.

Back to susceptibility

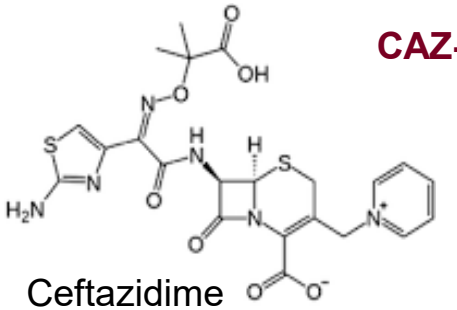

(a)
Ser70
Lys73
KPC-2

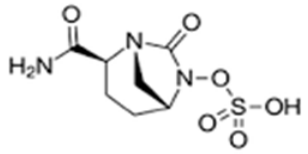

(b)
Zn2
Zn1
NDM-1


(c)
Ser64
Lys67
AmpC


(d)
Ser70
Lys73
OXA-48

CAZ-AVI

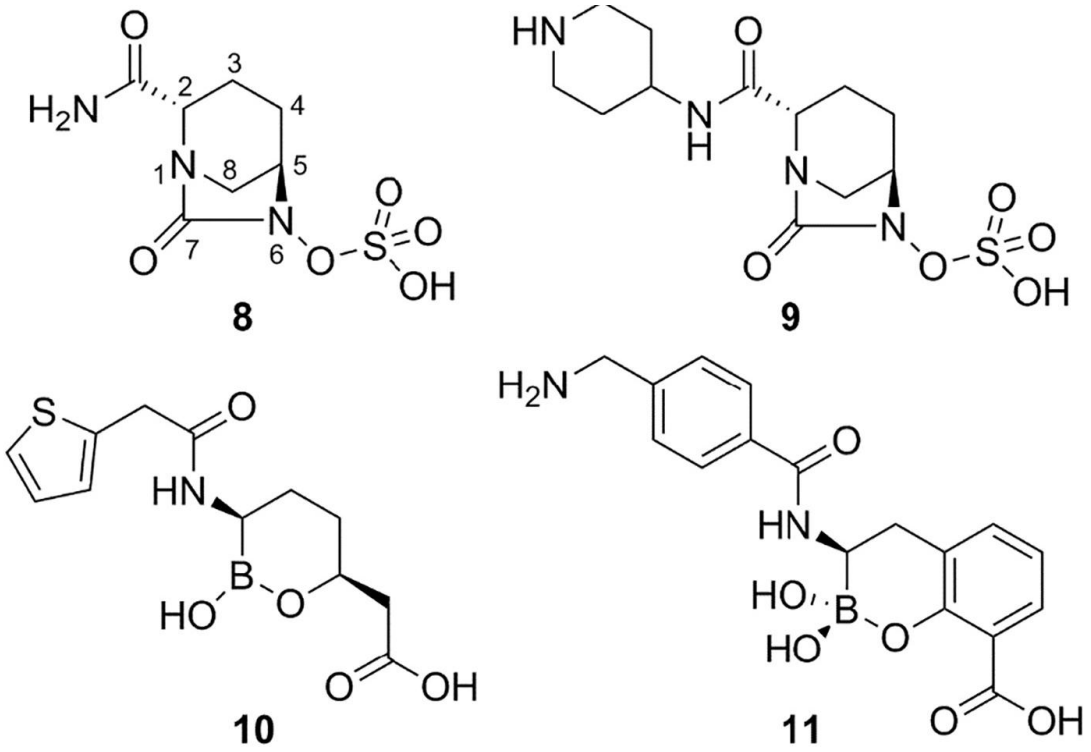

Ceftazidime


Avibactam

β-Lactamase inhibitors

Since the discovery and development of clavulanic acid as an irreversible inhibitor of the most widely distributed class A enzymes other penicillin-inhibitor combinations (amoxicillin–clavulanate, ampicillin–sulbactam, piperacillin–tazobactam) have found wide application as treatments for both community- and healthcare-associated infections by β-lactamase-producing organisms. However, their limited spectrum of activity, is confined to a subset of class A enzymes that, importantly, does not include KPC.

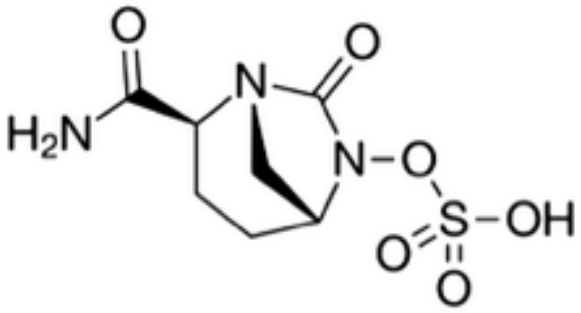
The search for more widely effective β-lactamase inhibitors is given added impetus by the continued weakness of the antibiotic discovery pipeline for Gram-negative bacteria.



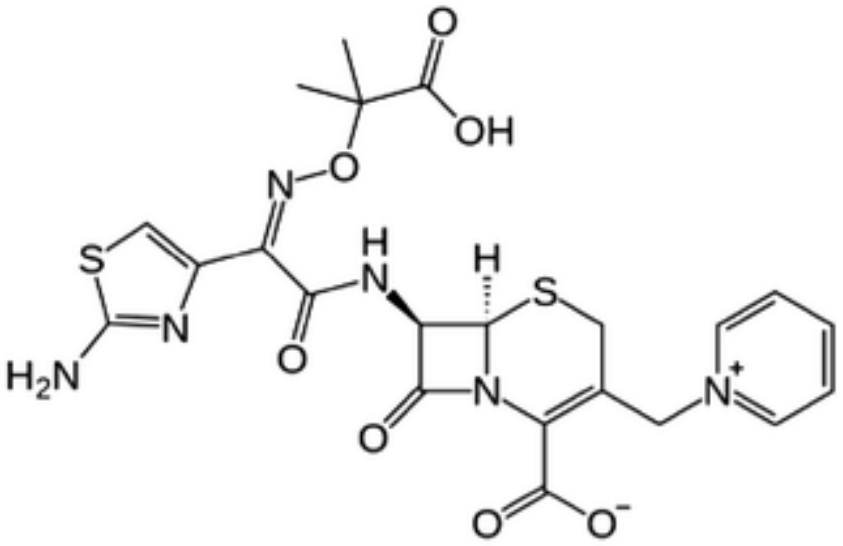
8. Avibactam. 9. Relebactam. 10. Vaborbactam. 11. Bicyclic boronate.

Chief among these is the introduction of the **diazabicyclooctanones (DBOs),** of which avibactam was the progenitor and first to reach the clinic as a combination with the oxyiminocephalosporin ceftazidime. Avibactam is a mechanism-based non-β-lactam β-lactamase inhibitor, based around a bicyclic core structure, that is able to acylate the active site of serine β-lactamases in a reversible manner

Ceftazidime/avibactam (CAZ/AVI) EMA authorized 2018

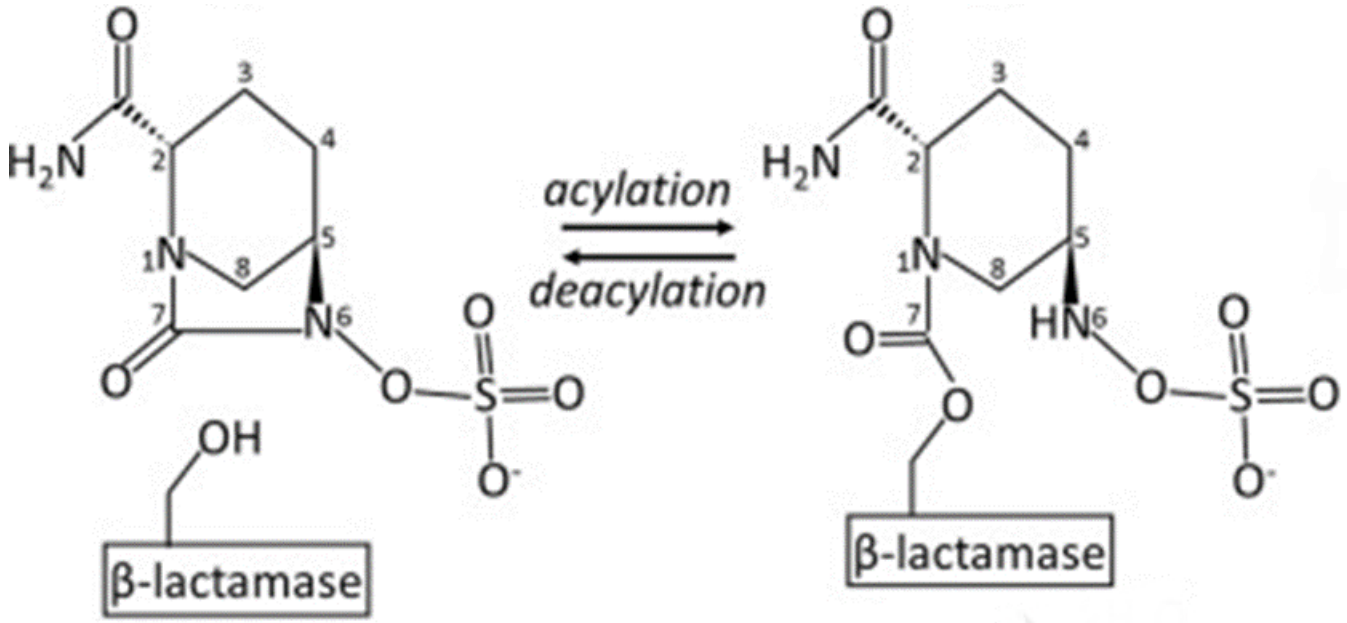


Avibactam

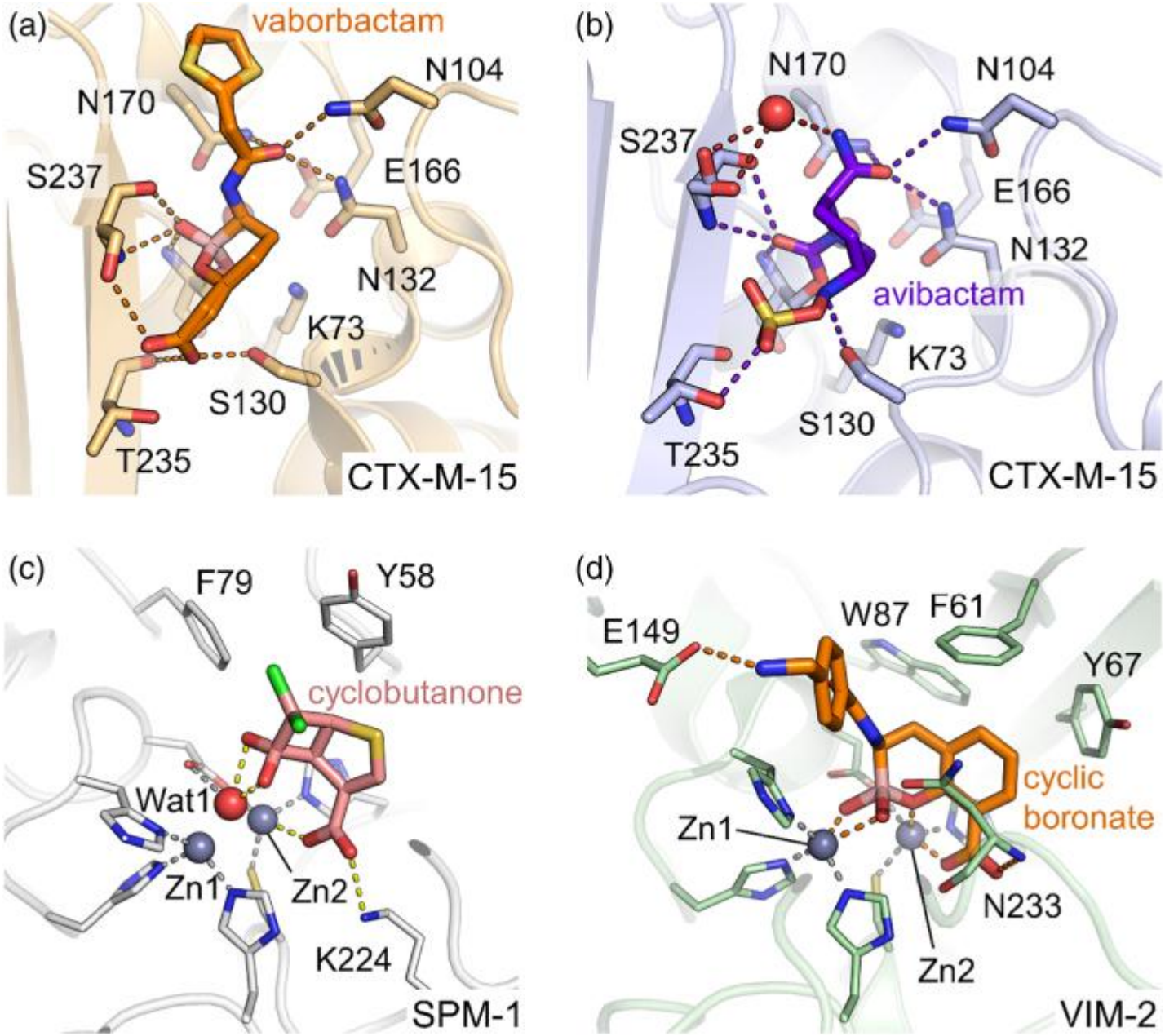


Ceftazidime

Avibactam is a structural class of inhibitor that does not contain a β-lactam core but maintains the capacity to covalently acylate its β-lactamase targets.



β-Lactamase inhibitors



CARBAPENEMASE TYPE MATTERS

Spectra of New and Anticipated β-Lactams and β-Lactamase Inhibitor Combinations, in Relation to Bacterial Group and Carbapenemase Type

	Enterobacterales			*Pseudomonas aeruginosa*	*Acinetobacter baumannii*	
Drug	**KPC**	**OXA-48**	**MBL**	**MBL**	**MBL**	**OXA**
Diazabicyclooctane-based inhibitor combinations						
Ceftazidime/avibactam	++	++	–	–	–	–
Imipenem/relebactam	++	–	–	–	–	–
Aztreonam/avibactam	++	++	++	+a	–	–
Boronate-based inhibitor combinations						
Meropenem/vaborbactam	++	–	–	–	–	–
Single agents						
Cefiderocol	++	++	+(+)b	++	+(+)b	++

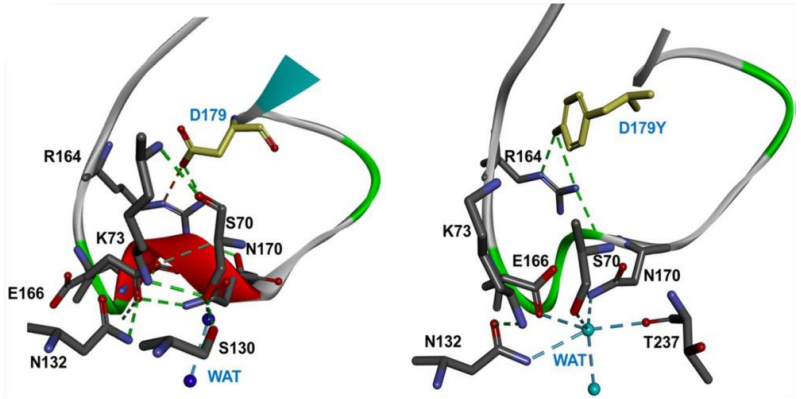
Abbreviations: -, not generally active; +, weak activity; ++, broadly active;
a:Aztreonam only has weak activity, in general, vs. *P. aeruginosa*.
b:MIC are raised for isolates with NDM MBLs, which are the commonest MBLs in Enterobacterales and *A. baumannii* (though not in *P. aeruginosa*).
Table adapted from Livermore et al., *Clinical Infectious Diseases*, Volume 71, Issue 7, 1 October 2020, Pages 1776–1782

CEFTAZIDIME/AVIBACTAM RESISTANCE

- **11 new KPC variants were identified in clinical isolates from 2020-2022**

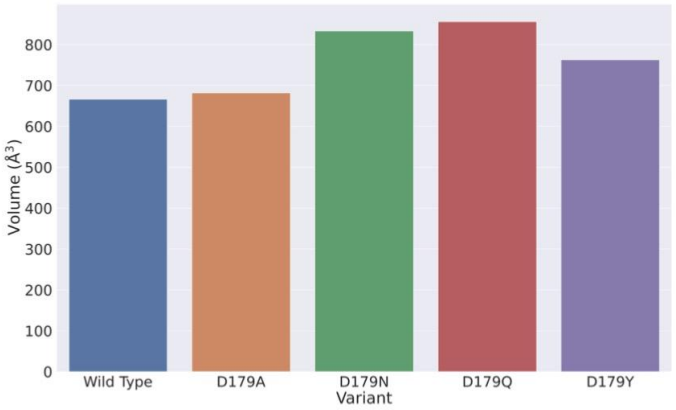
```
KPC-67   KLEQDFGGSI--//--FRLDRW----ELELNSAIPGDARDTSS---PRAVTESL~PTGRAPIVLAVYTRAPNKDDKDDKDD--------KYSEAVIAA
KPC-66   KLEQDFGGSI--//--FRLDRW----EL----NSAIPGDARDTSS---PRAVTESL~PTGRAPIVLAVYTRAPNKDD----------KYSEAVIAA
KPC-68   KLEQDFGGSI--//--FRLDRW----ELELNSAIPGDARDTSSSSPRAVTESL~PTGRAPIVLAVYTRAPNKDD----------KYSEAVIAA
KPC-69   KLEQDFGGSI--//--FRLDRWGLELELNSAIPGDARDTSS---PRAVTESL~PTGRAPIVLAVYTRAPNKDD----------KYSEAVIAA
KPC-70   KLEQDFGGSI--//--FRLDRW----ELELNSAIPGDARYTSS---PRAVTESL~PTGRAPIVLAVYARAPNKDD----------KYSEAVIAA
KPC-29   KLEQDFGGSI--//--FRLDRW----ELELNSAIPGDARDTSS---PRAVTESL~PTGRAPIVLAVYTRAPNKDDKDD--------KYSEAVIAA
KPC-31   KLEQDFGGSI--//--FRLDRW----ELELNSAIPGDARYTSS---PRAVTESL~PTGRAPIVLAVYTRAPNKDD----------KYSEAVIAA
KPC-49   KLEQDFGGSI--//--FRLDSW----ELELNSAIPGDARDTSS---PRAVTESL~PTGRAPIVLAVYTRAPNKDD----------KYSEAVIAA
KPC-39   KLEQDFGGSI--//--FRLDRW----ELELNSTIPGDARDTSS---PRAVTESL~PTGRAPIVLAVYTRAPNKDD----------KYSEAVIAA
KPC-3    KLEQDFGGSI--//--FRLDRW---ELELNSAIPGDARDTSS---PRAVTESL~PTGRAPIVLAVYTRAPNKDD----------KYSEAVIAA
KPC-110  KLEQDFGRSI--//--FRLDRW----ELELNSAIPGDARYTSS---PRAVTESL~PTGRAPIVLAVYTRAPNKDD----------KYSEAVIAA
KPC-154  KLEQDFGGSI--//--FRLDRW----ELELNSAIPGDARDTSS---PRAVTESL~PTGRAPIVLAVYTRAPNKDDKYSRAPNKDDKYSEAVIAA
KPC-111  KLEQDFGGSI--//--FRLDRW---ELELNSAILGDARYTSS---PRAVTESL~PTGRAPIVLAVYTRAPNKDD----------KYSEAVIAA
```

The dominant mechanism that lead to CAZ/AVI (CZA) resistance is conferred by KPC mutants

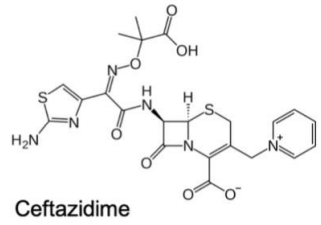


Replacing aspartic acid in tyrosine at position 179 changes the shape of the Ω-Loop, with a subsequent change in the phenotype.

KPC-2 CAZ/AVI-resistant variant substitutions increase volume of the active site



Increases access for bulky antibiotics such as ceftazidime

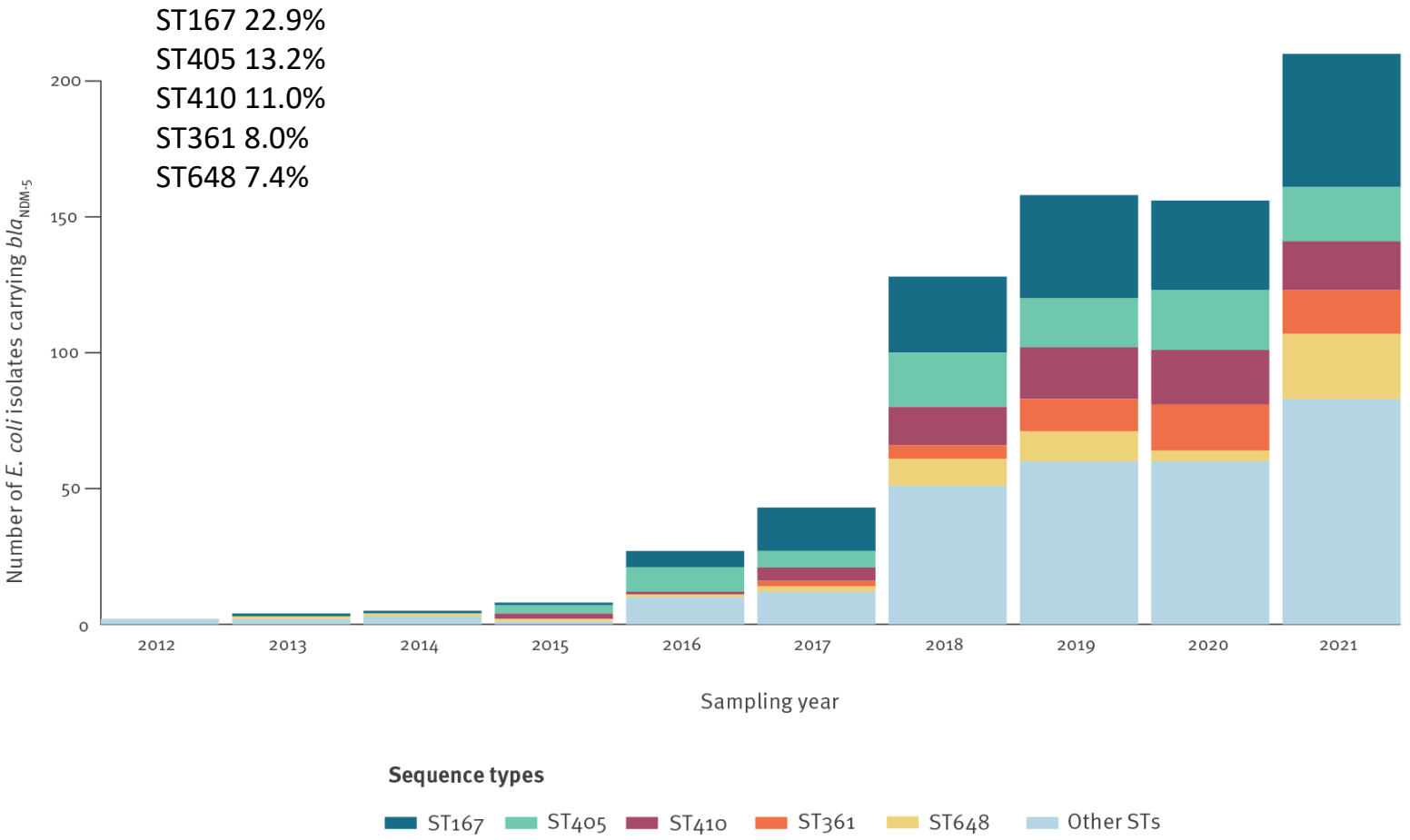


Ceftazidime

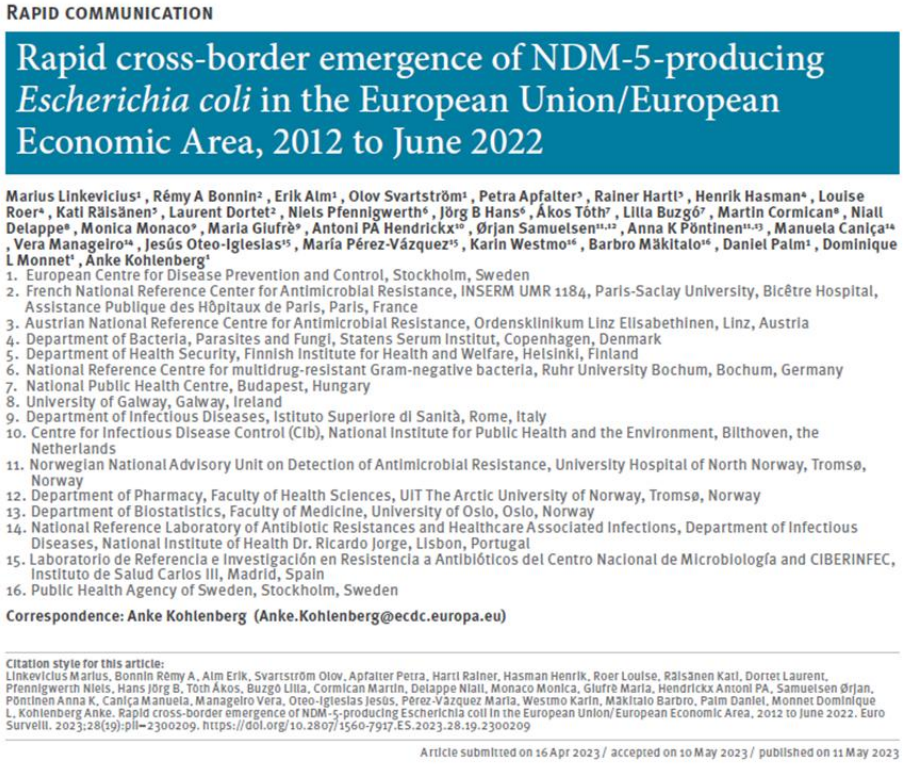
Figure S5 – Volumes of the expanded binding pockets in D179 variants.

Fig. S5. Parwana et al., Angew. Chem. Int. Ed. **2024**, *63*, e202317315

Frequency of sequence types of *Escherichia coli* isolates carrying bla_{NDM-5} over time by year of sampling (n = 741)



The European Centre for Disease Prevention and Control requested, via its EpiPulse platform, WGS and epidemiological data on *Escherichia coli* carrying $bla_{\text{NDM-5}}$ from European Union (EU)/European Economic Area (EEA) countries



RAPID COMMUNICATION

Rapid cross-border emergence of NDM-5-producing *Escherichia coli* in the European Union/European Economic Area, 2012 to June 2022

Marius Linkevicius[1], Rémy A Bonnin[2], Erik Alm[1], Olov Svartström[1], Petra Apfalter[3], Rainer Hartl[3], Henrik Hasman[4], Louise Roer[4], Kati Räisänen[5], Laurent Dortet[2], Niels Pfennigwerth[6], Jörg B Hans[6], Ákos Tóth[7], Lilla Buzgó[7], Martin Cormican[8], Niall Delappe[8], Monica Monaco[9], Maria Giufrè[9], Antoni PA Hendrickx[10], Ørjan Samuelsen[11,12], Anna K Pöntinen[11,13], Manuela Caniça[14], Vera Manageiro[14], Jesús Oteo-Iglesias[15], María Pérez-Vázquez[15], Karin Westmo[16], Barbro Mäkitalo[16], Daniel Palm[1], Dominique L Monnet[1], Anke Kohlenberg[1]

1. European Centre for Disease Prevention and Control, Stockholm, Sweden
2. French National Reference Center for Antimicrobial Resistance, INSERM UMR 1184, Paris-Saclay University, Bicêtre Hospital, Assistance Publique des Hôpitaux de Paris, Paris, France
3. Austrian National Reference Centre for Antimicrobial Resistance, Ordensklinikum Linz Elisabethinen, Linz, Austria
4. Department of Bacteria, Parasites and Fungi, Statens Serum Institut, Copenhagen, Denmark
5. Department of Health Security, Finnish Institute for Health and Welfare, Helsinki, Finland
6. National Reference Centre for multidrug-resistant Gram-negative bacteria, Ruhr University Bochum, Bochum, Germany
7. National Public Health Centre, Budapest, Hungary
8. University of Galway, Galway, Ireland
9. Department of Infectious Diseases, Istituto Superiore di Sanità, Rome, Italy
10. Centre for Infectious Disease Control (Cib), National Institute for Public Health and the Environment, Bilthoven, the Netherlands
11. Norwegian National Advisory Unit on Detection of Antimicrobial Resistance, University Hospital of North Norway, Tromsø, Norway
12. Department of Pharmacy, Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, Norway
13. Department of Biostatistics, Faculty of Medicine, University of Oslo, Oslo, Norway
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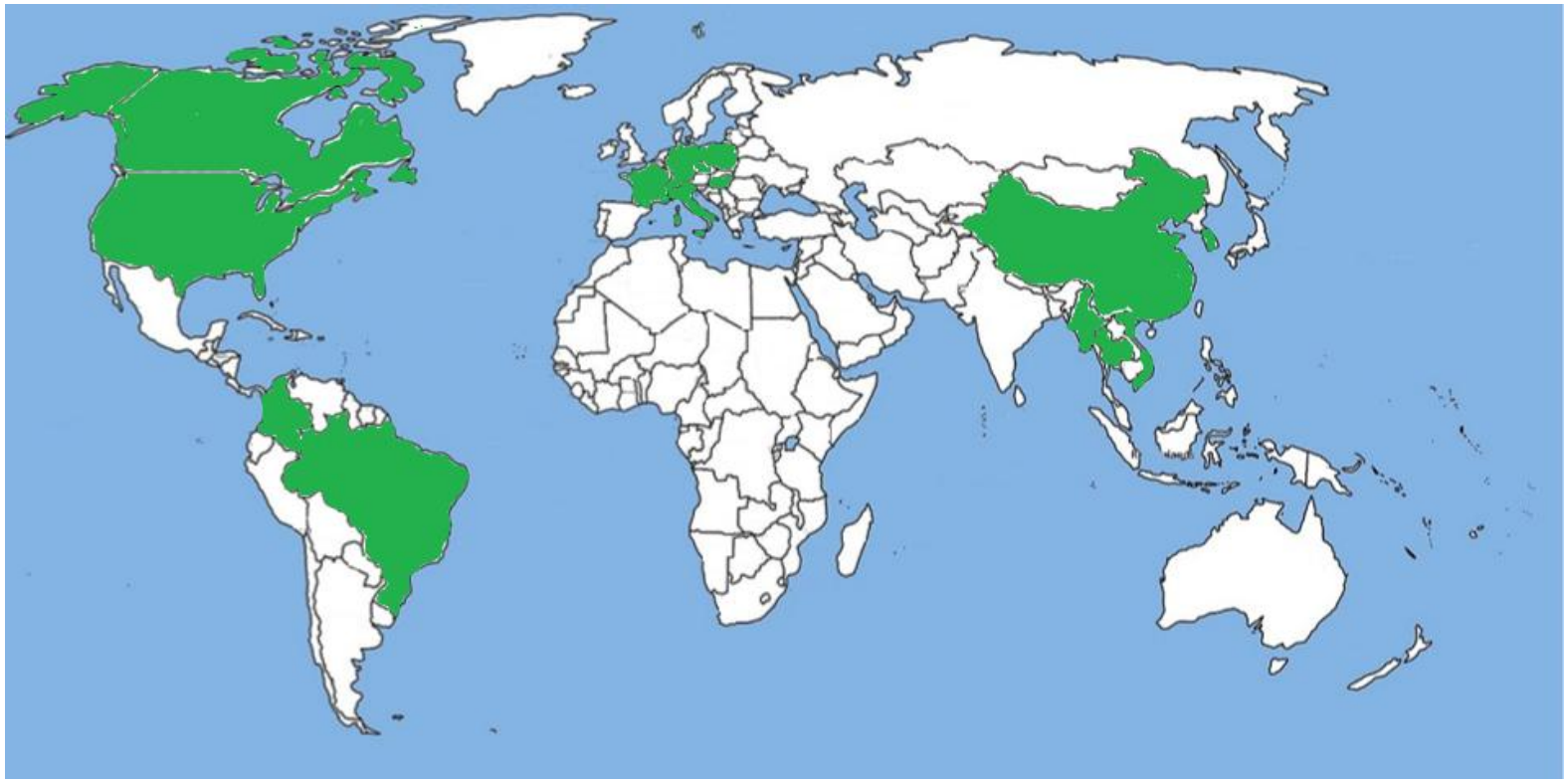
Article submitted on 16 Apr 2023 / accepted on 10 May 2023 / published on 11 May 2023

Eurosurveillance Volume 28, Issue 19, 11/May/2023

874 WGS *Escherichia coli* carrying $bla_{\text{NDM-5}}$
from 13 countries in 2012-2022
showed the predominance of
ST167, ST405, ST410, ST361 and **ST648**

IncF and NDM



Wu W, Feng Y, Tang G, Qiao F, McNally A, Zong Z. NDM Metallo-β-Lactamases and Their Bacterial Producers in Health Care Settings. Clin Microbiol Rev. 2019 Jan 30;32(2).

Int J Antimicrob Agents. 2018 Jul;52(1):76-81. doi: 10.1016/j.ijantimicag.2018.02.020. Epub 2018 Feb 28.

Emergence of NDM-5-producing Escherichia coli sequence type 167 clone in Italy

Maria Giufrè [1], Giulia Errico [1], Marisa Accogli [1], Monica Monaco [1], Laura Villa [1], Maria Antonietta Distasi [2], Tito Del Gaudio [2], Annalisa Pantosti [1], Alessandra Carattoli [1], Marina Cerquetti [3]

Affiliations + expand

PMID: 29501819 DOI: 10.1016/j.ijantimicag.2018.02.020

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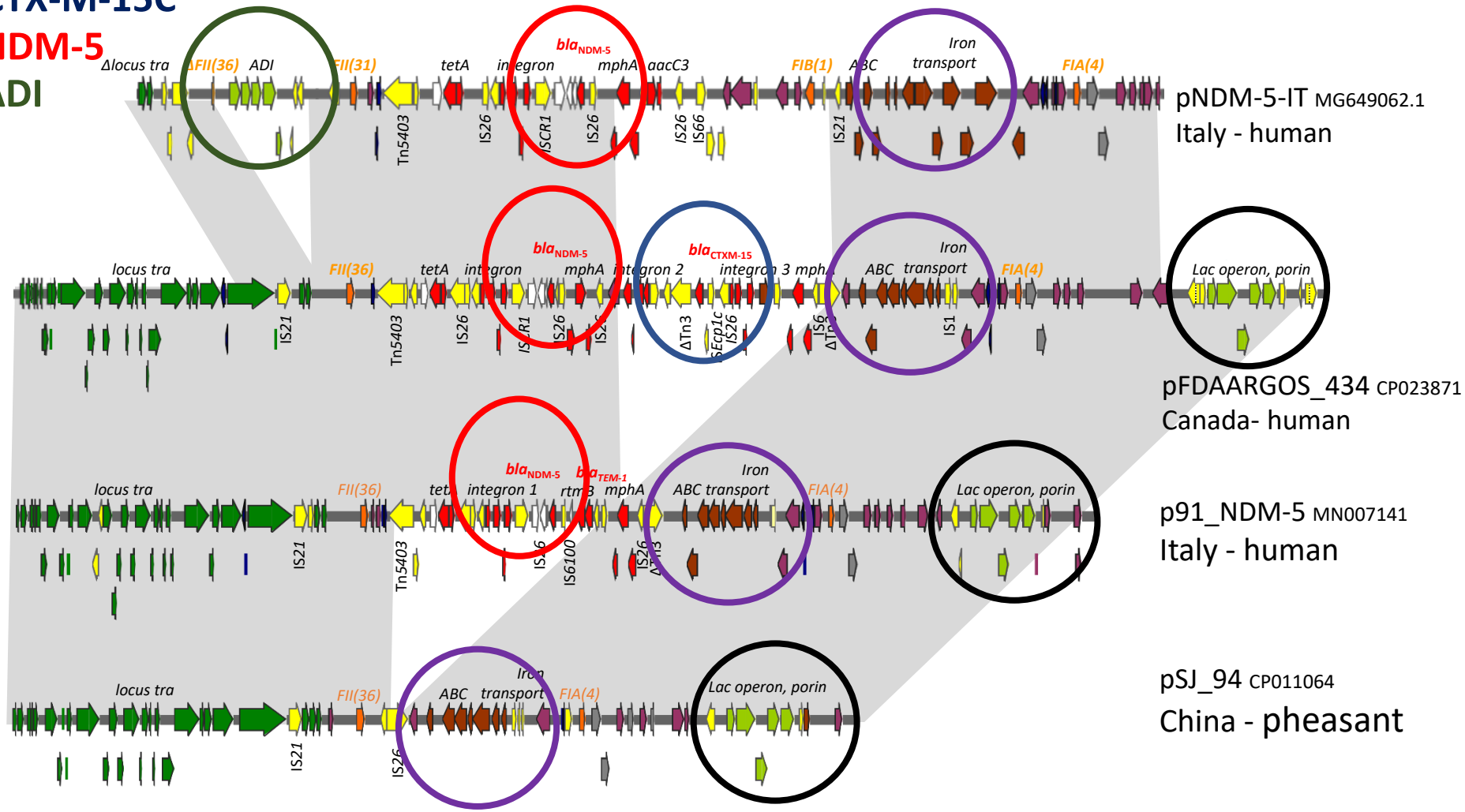
Abstract

The emergence of carbapenemase-producing Enterobacteriaceae (CPE) is a critical concern worldwide. In Italy, CPE isolates are very frequent, with the KPC enzyme types strongly predominant whereas the New Delhi metallo-β-lactamase (NDM) enzymes are extremely rare. Here we report the first detection of NDM-5-producing Escherichia coli sequence type 167 (ST167) isolates from two patients with urinary tract infection (Ec001 and Ec002 from urines), including one with colonisation (Ec003 from faeces) admitted to the same hospital 2 months apart in 2017. Minimum inhibitory concentrations (MICs) were determined by broth microdilution. The carbapenemase type was identified both by phenotypic and genotypic methods. Isolate genotypes were investigated by phylogenetic typing, multilocus sequence typing (MLST) and pulsed-field gel electrophoresis (PFGE). Next-generation sequencing (NGS) was used to obtain complete sequences of plasmids. The three E. coli isolates carried the bla_{NDM-5} gene, shared the same resistance phenotype and belonged to ST167. By PFGE, isolates showed the same profile, suggesting that they were the same strain. NGS revealed that the bla_{NDM-5} gene was located on a 99-kb multireplicon plasmid (designed pNDM-5-IT) with a peculiar scaffold constituted by four replicons of the IncF type (FIA, FIB and two copies of the FII

arginine deaminase (ADI) virulence factor. The ADI cluster carrying the arcA, arcB, arcC, and arcD genes and an additional FII31 replicon were acquired together in an IS66-IS1 module flanked by two inverted repeats

CTX-M-15C
NDM-5
ADI



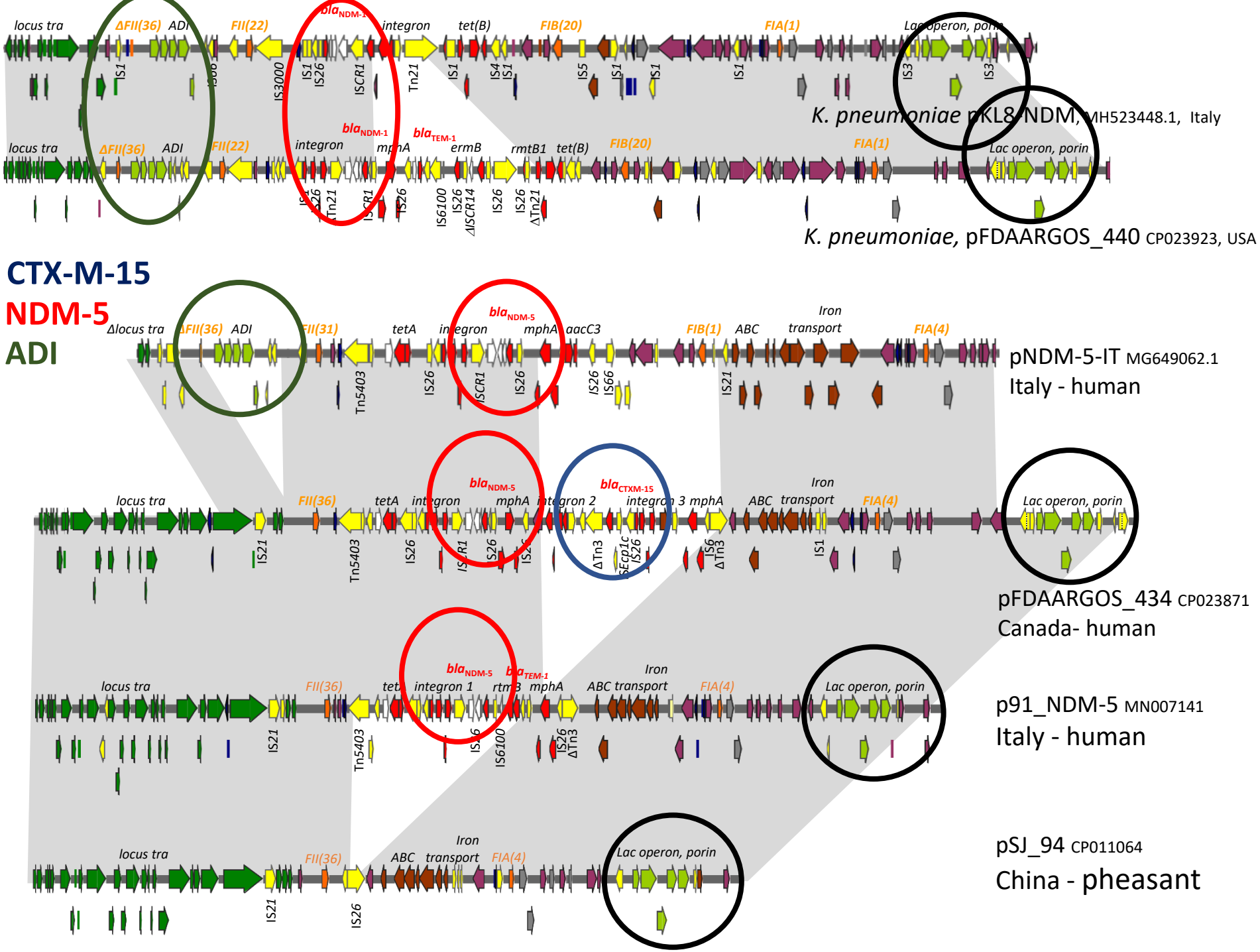
pNDM-5-IT MG649062.1
Italy - human

pFDAARGOS_434 CP023871
Canada- human

p91_NDM-5 MN007141
Italy - human

pSJ_94 CP011064
China - pheasant

E. coli ST167clone


CTX-M-15
NDM-5
ADI
locus tra
ΔFII(36)
ADI
FII(22)
integron
tet(B)
FIB(20)
FIA(1)
Lac operon, porin
mphA
ermB
rmtB1
K. pneumoniae pKL8-NDM, MH523448.1, Italy
K. pneumoniae, pFDAARGOS_440 CP023923, USA
Δlocus tra
FII(31)
tetA
aacC3
FIB(1)
ABC
Iron transport
FIA(4)
pNDM-5-IT MG649062.1
Italy - human
FII(36)
integron 2
integron 3
pFDAARGOS_434 CP023871
Canada- human
integron 1
ABC transport
p91_NDM-5 MN007141
Italy - human
pSJ_94 CP011064
China - pheasant

Emergence of *Escherichia coli* ST131 carrying carbapenemase genes, European Union/European Economic Area, August 2012 to May 2024

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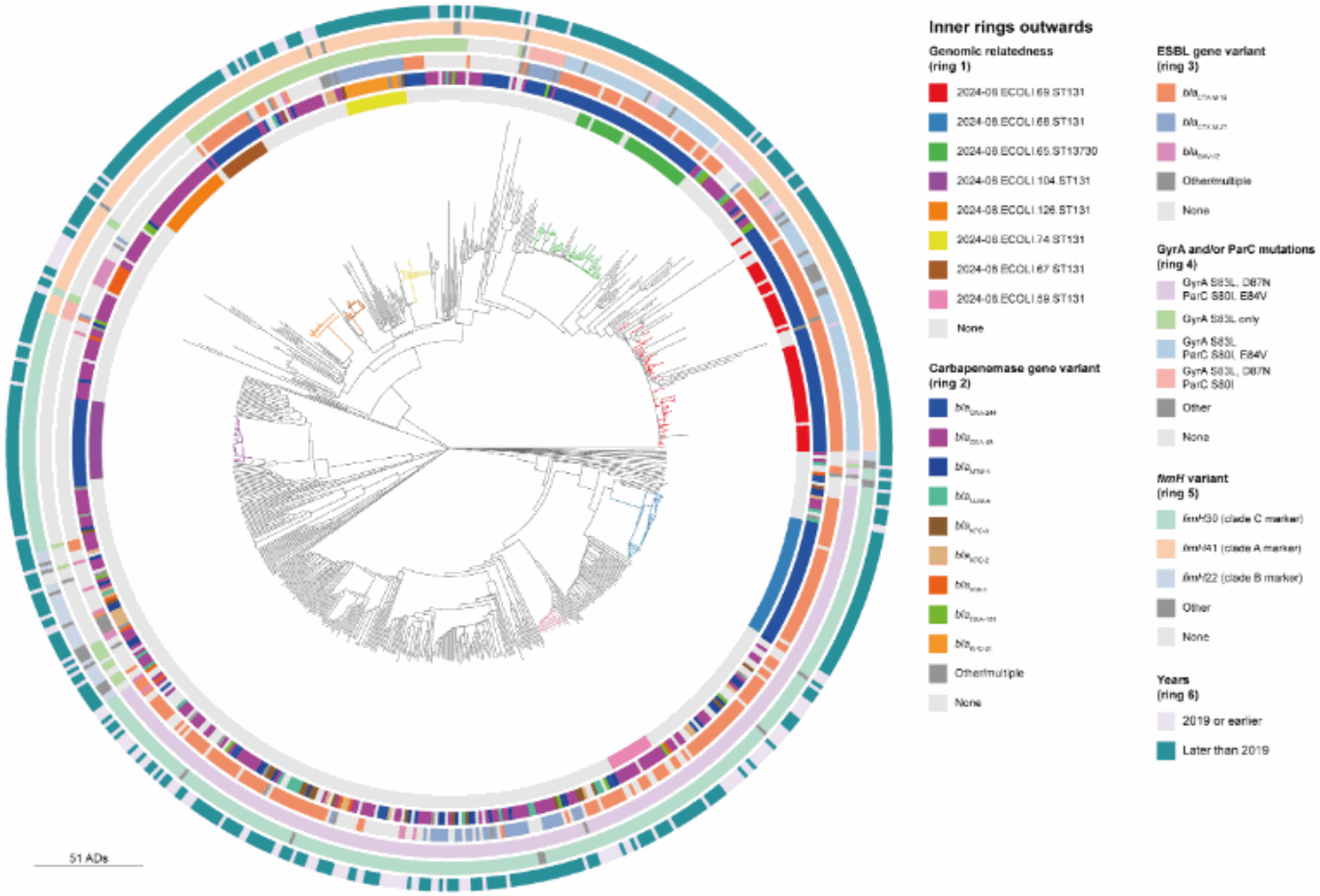
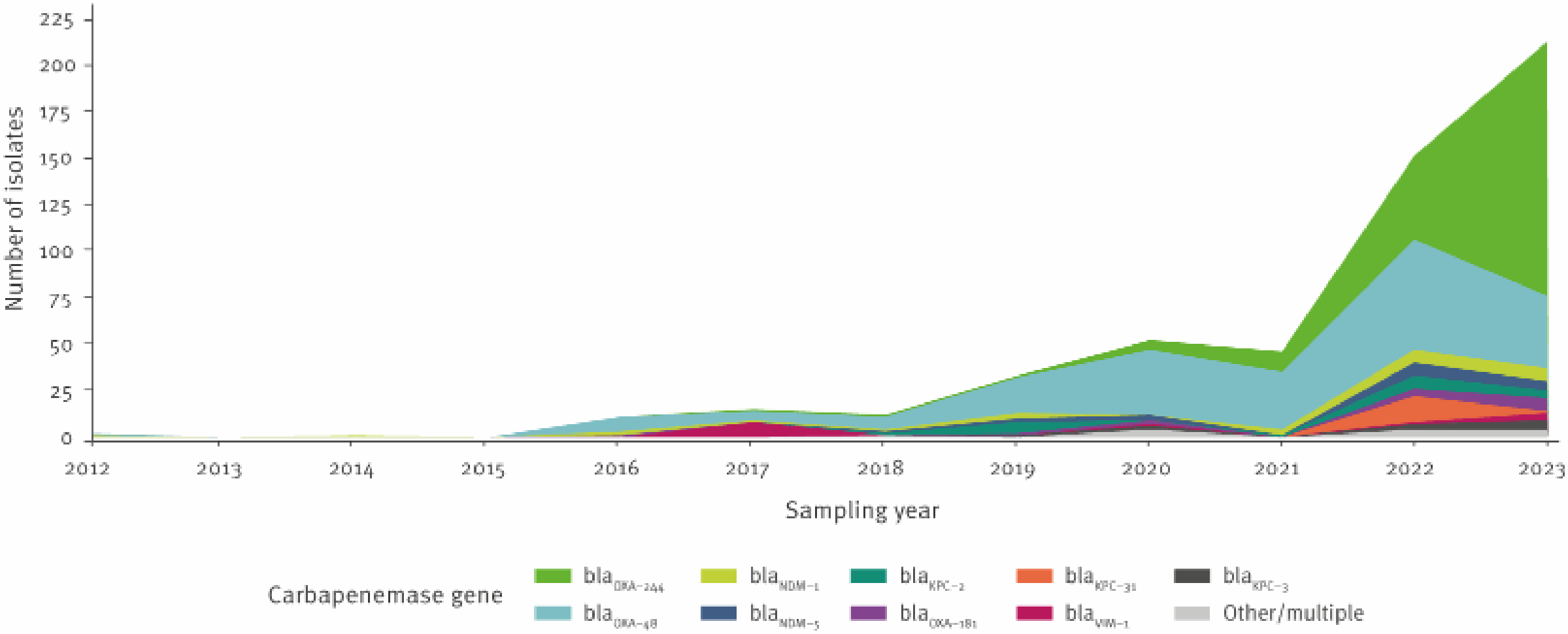
Published on 21 Nov 2024

***76%* were**
***bla*$_{OXA-244}$ n = 230**
and
***bla*$_{OXA-48}$ n = 224**

other n = 140

Worldwide, Sequence type (ST)131 is a high-risk lineage of global distribution.
12 April 2024, ECDC requested to NRLs the genomes of *Escherichia coli* sequence type (ST)131 and its single locus variants, carrying carbapenemase genes
660 sequences from 17 European Union/ European Economic Area countries





Detection of isolates carrying *bla*$_{\text{OXA-244}}$ increased sharply between 2021 and 2023.
Increasing diversity of carbapenemase (including metallo-beta-lactamase) genes over time

Characteristic	Group 1: *bla*$_{OXA-244}$ n = 230		Group 2: *bla*$_{OXA-48}$ n = 224		Group 3: other n = 140	
	n	%	n	%	n	%
Median age (years)	57		77		70	
Sex						
Male	69	30	81	36	51	36
Female	135	59	82	37	57	41
Not available	26	11	61	27	32	23
Type of sample						
Urine	115	50	58	26	57	41
Rectal/faeces	23	10	94	42	17	12
Blood	6	3	5	2	8	6
Other	28	12	11	5	15	11
Not available	58	25	56	25	43	31
Travel outside the EU/EEA in the past 12 months						
Yes	35	15	5	2	8	6

***bla*$_{OXA-244}$** with a high proportion of female patients, a relatively low median age, the frequent detection of isolates from urine samples, and slightly more frequent documentation of travel outside the EU/EEA within 12 months before detection. *bla* $_{OXA-244}$ formed multi-country clusters,

***bla* $_{OXA-48}$**-carrying isolates were predominantly detected within one country, e.g. France or Ireland.

bla $_{OXA-244}$ suggest a potential association with community-acquired urinary tract infections.

Of note, *E. coli* carrying *bla* $_{OXA-244}$ often do not grow on screening media for carbapenemase-producing Enterobacterales (CPE) and are most likely under-detected.

The apparent association of *E. coli* ST131 carrying *bla* $_{OXA-244}$ with community-acquired UTIs might therefore only represent the tip of the iceberg in terms of patient colonisation in the community.

Previous global surveys of carbapenemase-producing *E. coli* covering different geographical areas and time periods have identified only few *E. coli* ST131 isolates carrying *bla* $_{OXA-48}$ and none carrying *bla* $_{OXA-244}$

Published 03 April 2025

RAPID COMMUNICATION

Emergence of *Salmonella enterica* carrying *bla*$_{OXA-181}$ carbapenemase gene, Italy, 2021 to 2024

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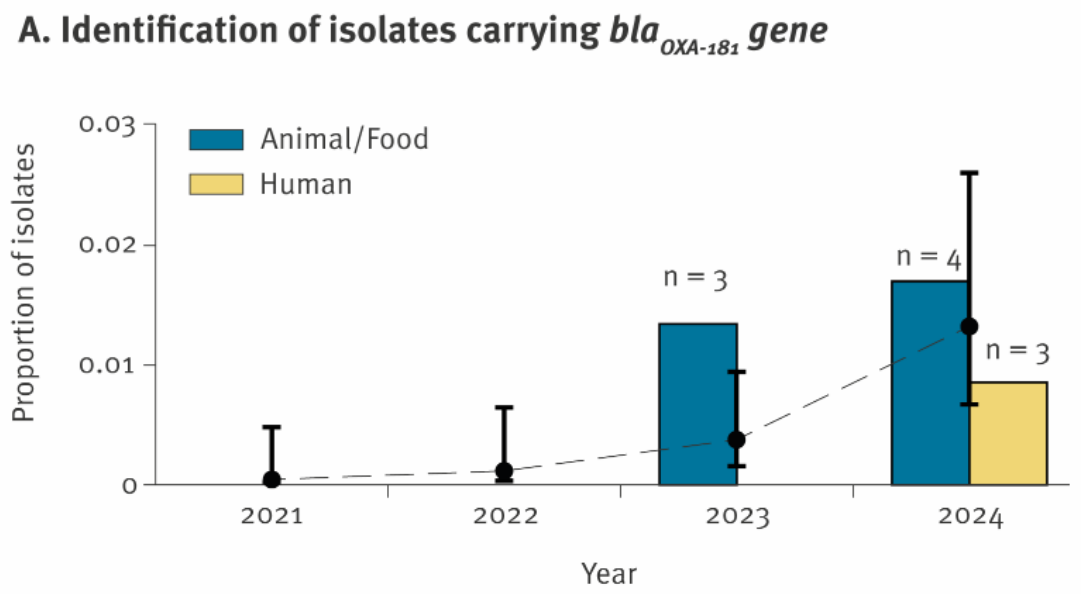
Salmonella isolates from humans (n = 2,824) and animals and food (n = 8,574) from Lombardia and Emilia-Romagna regions.
62% of all Italian pigs and 38% of cattle are resident in these 2 Italian regions.
***bla*$_{OXA\ 181}$** gene in 16 (0.14%) isolates, four from 2023 and 12 from 2024.
12 from pigs or pork, 3 from humans and 1 isolate was from a wild roe deer.
1,4,[5],12:I monophasic variant of *Salmonella* Typhimurium



Characterisation of *Salmonella enterica* isolates from humans, animals and food carrying the *bla*

Characteristics					
Isolate ID	Isolation date	Source	Serovar	ST	*bla*$_{OXA-181}$ localisation
2023-050284-001-01	Feb 2023	Pig	MVST	34	Plasmid IncX1
2023-257642-001-01	Aug 2023	Wild roe deer	SR	469	Chromosome
2023-307061-002-01	Oct 2023	Pig[b]	MVST	34	Plasmid IncX1
2023-403546-001-01	Dec 2023	Pig[b]	MVST	34	Plasmid IncX1
2024-005381-001-01	Jan 2024	Pig[b]	MVST	34	Plasmid IncX1
2024-005381-003-01	Jan 2024	Pig[b]	MVST	34	Plasmid IncX1
2024-005381-004-01	Jan 2024	Pig[b]	MVST	34	Plasmid IncX1
2024-132632-002-01	Apr 2024	Pork	SB	2640	Plasmid IncX3
2024-132632-004-01[c]	Apr 2024	Pork	SB	2640	Plasmid IncX3
2024-132632-005-01[c]	Apr 2024	Pork	SB	2640	Plasmid IncX3
2024-124985-001-01	Apr 2024	Human	MVST	34	Plasmid IncX1
2024-142809-005-01	May 2024	Human	MVST	34	Plasmid IncX1
2024-074445-001-01	Mar 2024	Human	MVST	34	Plasmid IncX3
2024-271534-004-01[c]	Sep 2024	Pig	SL	155	Plasmid IncX1
2024-271534-005-01	Sep 2024	Pig	SL	155	Plasmid IncX1

Journal of Medicinal Chemistry

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Drug Annotation

Cite This: J. Med. Chem. 2020, 63, 2789−2801

pubs.acs.org/jmc

Discovery of Taniborbactam (VNRX-5133): A Broad-Spectrum Serine- and Metallo-β-lactamase Inhibitor for Carbapenem-Resistant Bacterial Infections

Bin Liu,[⊗,†] Robert E. Lee Trout,[†] Guo-Hua Chu,[†] Daniel McGarry,[†] Randy W. Jackson,[†] Jodie C. Hamrick,[†] Denis M. Daigle,[†] Susan M. Cusick,[†] Cecilia Pozzi,[‡] Filomena De Luca,[§] Manuela Benvenuti,[‡] Stefano Mangani,[‡] Jean-Denis Docquier,[§] William J. Weiss,[∥] Daniel C. Pevear,[†] Luigi Xerri,[†] and Christopher J. Burns[⊗,†]

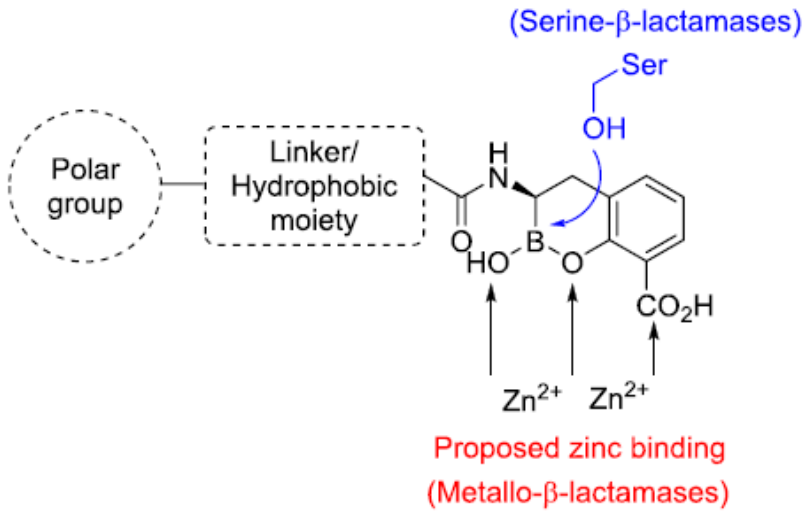


Figure 3. Strategy for designing a cyclic boronate-based pan-BLI showing putative active-site serine- or zinc-binding interactions.

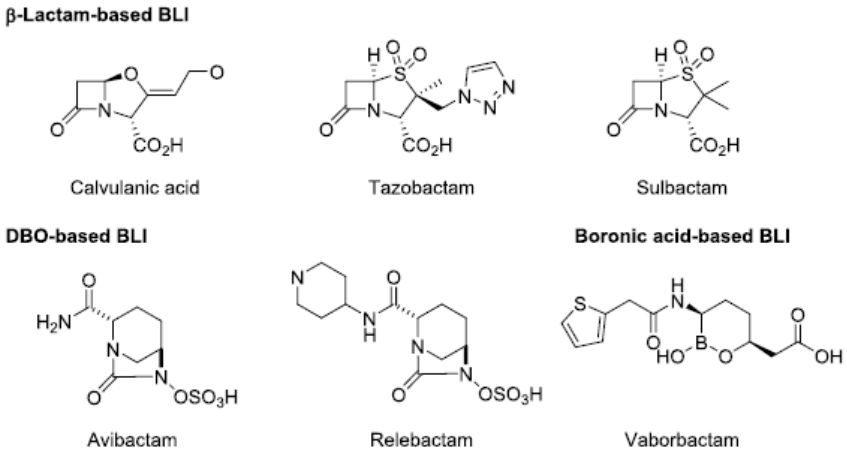
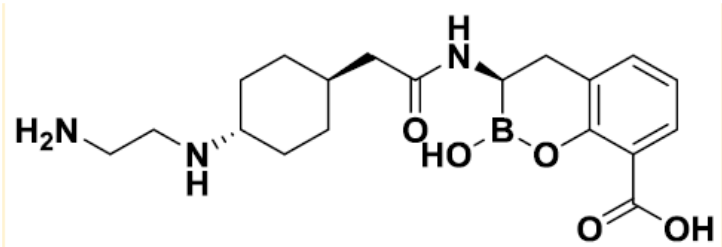
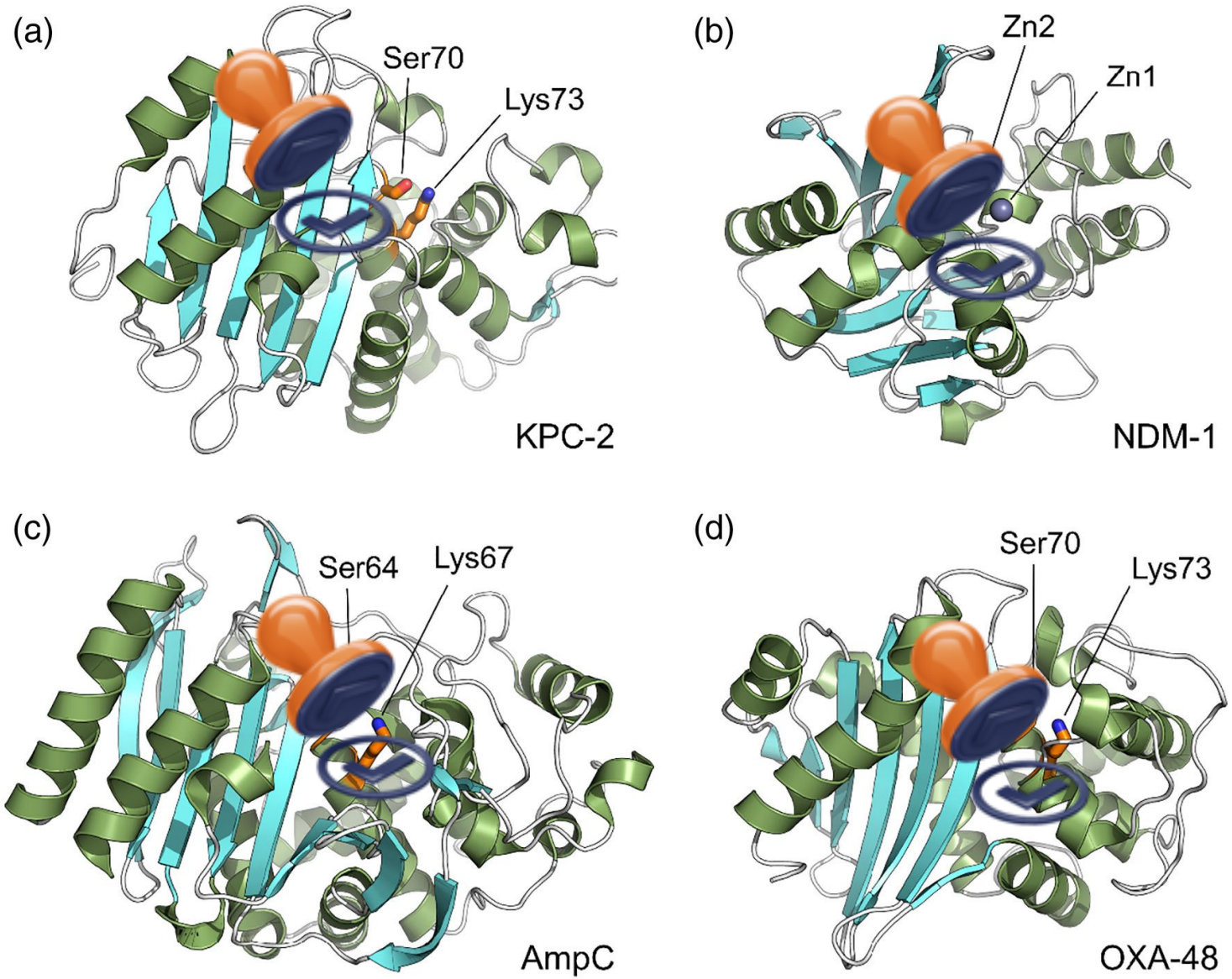
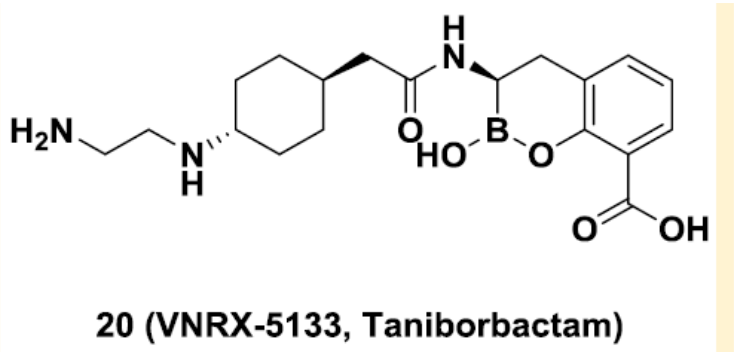


Figure 1. Structures of the approved BLIs.



20 (VNRX-5133, Taniborbactam)





20 (VNRX-5133, Taniborbactam)

NDM-like β-lactamases hydrolyse all β-lactams (BLs) except monobactams, and are not inactivated by most of the recently developed β-lactamase inhibitors (BLIs) (avibactam, relebactam, vaborbactam, nacubactam or zidebactam).

The newly developed cyclic boronate BLI, taniborbactam, alias VNRX-5313, is one of the few BLIs possessing significant inhibitory activity against MBLs, with the exception of IMP-like enzymes, and is currently in clinical development in combination with cefepime.

Table 1: Susceptibility of parent and clinically-evolved KPC variant producing *K. pneumoniae* isolates.

K. pneumoniae producing KPC-3 relative to clinically evolved KPC-variant producing isolates	Minimal Inhibitory Concentration (µg/mL)					
	ceftazidime	ceftazidime/ avibactam	ceftolozane	ceftolozane/ tazobactam	cefepime	cefepime/ VNRX-5133
Kp 47621 (WT parent)	>128	2	>64	>64	>128	1
Kp 47623 (D179D, T243M)	>128	64	>64	>64	8	0.5
Kp 47769 (WT parent)	>128	2	64	64	16	0.125
Kp 47771 V240G	>128	64	>64	>64	16	4
Kp 47772 D179Y	128	16	64	64	8	2
Kp 47953 (WT parent)	128	8	64	64	8	2
Kp 48152 (T243A)	128	16	64	32	8	2
Kp 48823 (WT parent)	128	2	64	64	8	2
Kp 48824 (A177E, D179Y)	>128	>128	>64	>64	4	1
Kp 48825 (L7P, A177E, D179Y)	>128	>128	>64	>64	1	0.5

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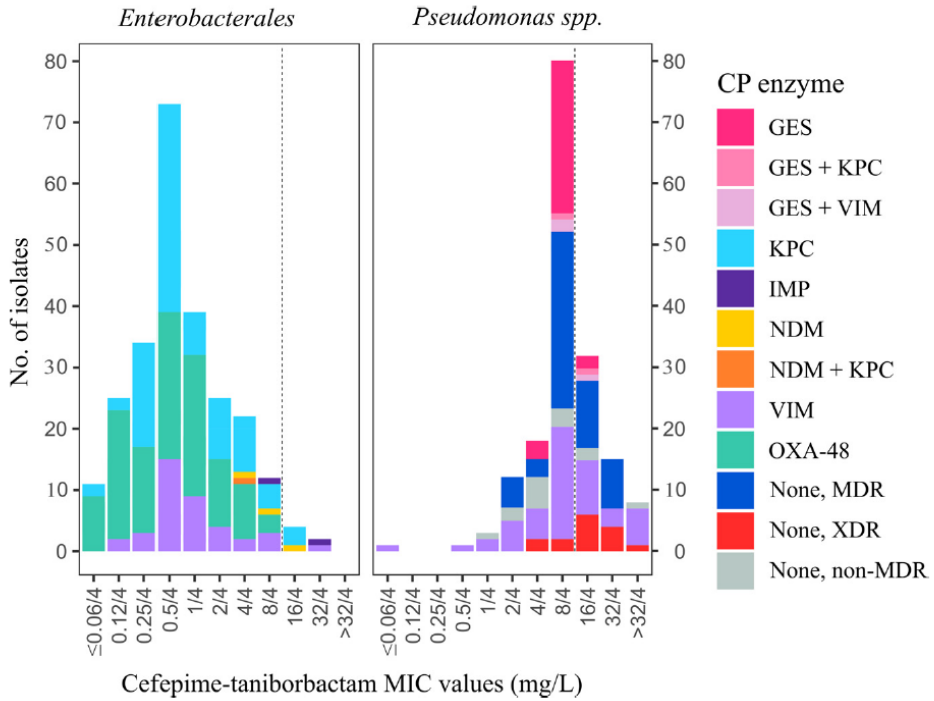
SUSCEPTIBILITY

In Vitro Activity of Cefepime-Taniborbactam against Carbapenemase-Producing *Enterobacterales* and *Pseudomonas aeruginosa* Isolates Recovered in Spain

Marta Hernández-García,[a,b] María García-Castillo,[a,b] Patricia Ruiz-Garbajosa,[a,b] Germán Bou,[b,c] María Siller-Ruiz,[d] Cristina Pitart,[e] Irene Gracia-Ahufinger,[f] Xavier Mulet,[b,g] Álvaro Pascual,[b,h,i,j] Nuria Tormo,[k] Rafael Cantón[a,b]



J Antimicrob Chemother. 2023 Sep 5;78(9):2382-2384. doi: 10.1093/jac/dkad210.

Wide dissemination of Gram-negative bacteria producing the taniborbactam-resistant NDM-9 variant: a One Health concern

Christophe Le Terrier [1 2], Patrice Nordmann [1 3 4], Chloé Buchs [1], Doris Yoong Wen Di [5], Gian Maria Rossolini [6 7], Roger Stephan [8], Mariana Castanheira [9], Laurent Poirel [1 3]

Here we report the *in vitro* activity of cefepime/taniborbactam in comparison with other recently developed BL/BLI combinations against a collection of NDM-9 producers.

Our collection included four different bacterial species: *E. coli*, *Klebsiella pneumoniae*, *Klebsiella variicola* and *Acinetobacter baumannii*, recovered either from human or water origins and from four different countries (France, Switzerland, South Korea, USA) located in three different continents.
In addition, some other worldwide reports indicated a large variety of bacterial species that includes *E. coli, Klebsiella aerogenes, K. pneumoniae, K. variicola, Cronobacter sakazakii* and *A. baumannii* as carriers of the bla_{NDM-9} gene. They have been recovered from humans but also from animals (chickens) and the environment (rivers), and in many different countries including China, French Polynesia, Italy, South Korea, Tunisia and Switzerland.

Table 1. Susceptibility testing of NDM-9-producing isolates for the different BL/BLI combinations tested

					MICs (mg/L)[a]								
Strain	ST	Country of isolation/ and year	Origin	BL(s)	CAZ	CZA	FEP	FEP-TAN	FEP-ZID	FEP-ZID 1:1	IMP	I/R	MEM
E. coli	167	USA 2015	Clinical	NDM-9, CTX-M-65	>256	>128	>256	>128	≤0.125	0.25	>256	>128	64
E. coli	167	USA 2015	Clinical	NDM-9, CTX-M-65, TEM-1	>256	>128	>256	>128	≤0.125	0.125	>256	>128	32
K. pneumoniae	147	Switzerland 2018	Water	NDM-9, SHV-11, CTX-M-15, OXA-9, TEM-1	>256	>128	256	128	4	4	128	128	16
K. pneumoniae	147	Italy 2020	Clinical	NDM-9, CTX-M-15, OXA-1, OXA-9, TEM-1A	>256	>128	>256	128	0.5	0.5	128	128	8
K. variicola GJ1	363	South Korea 2016	Water	NDM-9, LEN-13	>256	>128	128	128	8	8	256	>128	32
K. variicola GJ2	363	South Korea 2016	Water	NDM-9, LEN-13, TEM-1B	>256	>128	128	128	4	4	>256	>128	32
K. variicola GJ3	363	South Korea 2016	Water	NDM-9, LEN-13, CTX-M-65, TEM-1B	>256	>128	128	128	4	4	>256	>128	32
A. baumannii	52	Switzerland 2021	Clinical	NDM-9, OXA-58	>256	>128	>256	>128	>128	>32	>256	>128	128
K. pneumoniae	147	Switzerland 2022	Clinical	NDM-1, TEM-1, OXA-9, CTX-M-224, CTX-M-54	>256	>128	>256	1	0.25	0.25	8	8	8
E. coli ATCC 27922	NA	—	—	—	≤0.25	≤0.125	≤0.25	≤0.125	≤0.125	≤0.03	≤0.25	0.25	≤0.25

—, no BL; ZID, zidebactam; NAC, nacubactam, FEP-ZID 1:1, cefepime/zidebactam at 1:1 ratio; MEM-NAC 1:1, meropenem/nacubactam at 1:1 ratio.
[a]CAZ, ceftazidime; CZA, ceftazidime/avibactam; FEP, cefepime; FEP-ZID, cefepime/zidebactam; FEP-TAN, cefepime/taniborbactam; IMP, imipenem; I/R, imipenem/relebactam; MEM, meropenem; MVB, meropenem/vaborbactam; MEM-NAC, meropenem/nacubactam; ATM, aztreonam; AZA, aztreonam/avibactam; FDC, cefiderocol. In those BL/BLI combinations, zidebactam, nacubactam, relebactam, avibactam were used at fixed concentration of 4 μg/mL. Vaborbactam were used at fixed concentration of 8 μg/mL.

We show here that the future effectiveness of cefepime/taniborbactam, but also of any other BL/BLI combination supposed to include taniborbactam as BLI, might be compromised by the circulation of the NDM-9 enzyme. Worryingly, the potential of the NDM-9-encoding gene to successfully spread among many different species and many different environments is proven here, as a good example of a One Health critical issue.

Of particular concern is the report of an MDR NDM-9-producing ST147 *K. pneumoniae* that was clonally related to other NDM-1-producing *K. pneumoniae* isolates being part of a nosocomial outbreak involving patients hospitalized in the same region of Italy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Antimicrob Agents Chemother. 2024 Feb 7;68(2):e0151023. doi: 10.1128/aac.01510-23. Epub 2024 Jan 4.
The metallo-β-lactamases strike back: emergence of taniborbactam escape variants
Pranita D Tamma [1], Jose M Munita [2]
Affiliations + expand
PMID: 38174925 PMCID: PMC10848767 (available on 2024-07-04) DOI: 10.1128/aac.01510-23
Abstract
Metallo-β-lactamases (MBLs) have evolved relatively rapidly to become an international public health threat. There are no clinically available β-lactamase inhibitors with activity against MBLs. This may change with the introduction of cefepime-taniborbactam. Herein, we review three manuscripts (S. I. Drusin, C. Le Terrier, L. Poirel, R. A. Bonomo, et al., Antimicrob Agents Chemother 68:e01168-23, 2024, https://doi.org/10.1128/aac.01168-23; C. Le Terrier, C. Viguier, P. Nordmann, A. J. Vila, and L. Poirel, Antimicrob Agents Chemother 68:e00991-23, 2024, https://doi.org/10.1128/aac.00991-23; D. Ono, M. F. Mojica, C. R. Bethel, Y. Ishii, et al., Antimicrob Agents Chemother 68:e01332-23, 2024, https://doi.org/10.1128/aac.01332-23) in which investigators describe elegant experiments to explore MBL/taniborbactam interactions and modifications to MBLs, in response, to reduce the affinity of taniborbactam. Challenges with MBL inhibition will not disappear; rather, they will evolve commensurate with advancements in medicinal chemistry.
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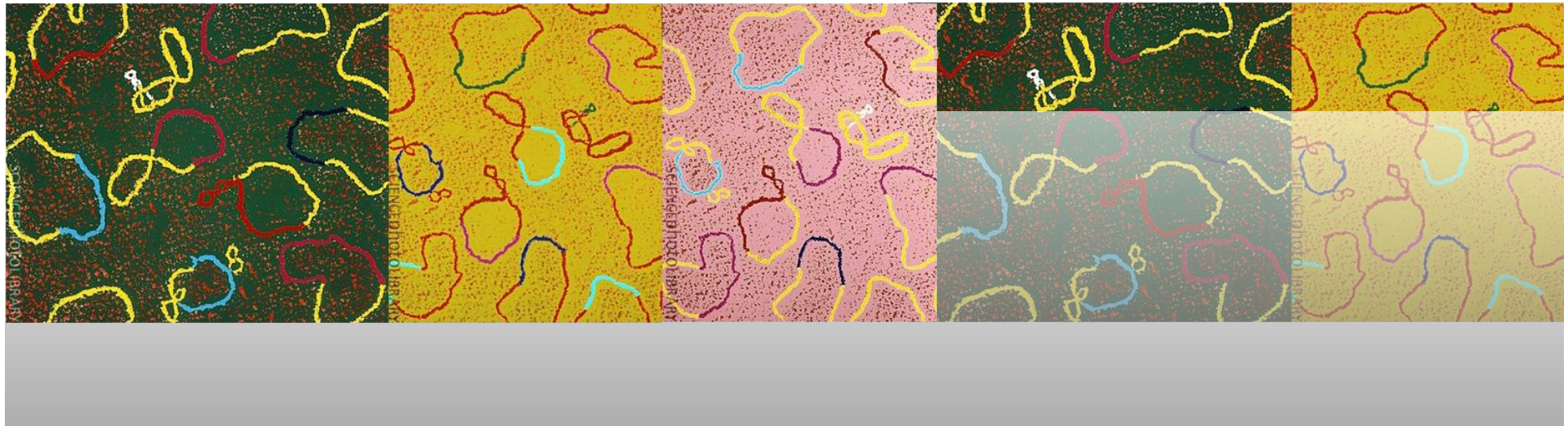
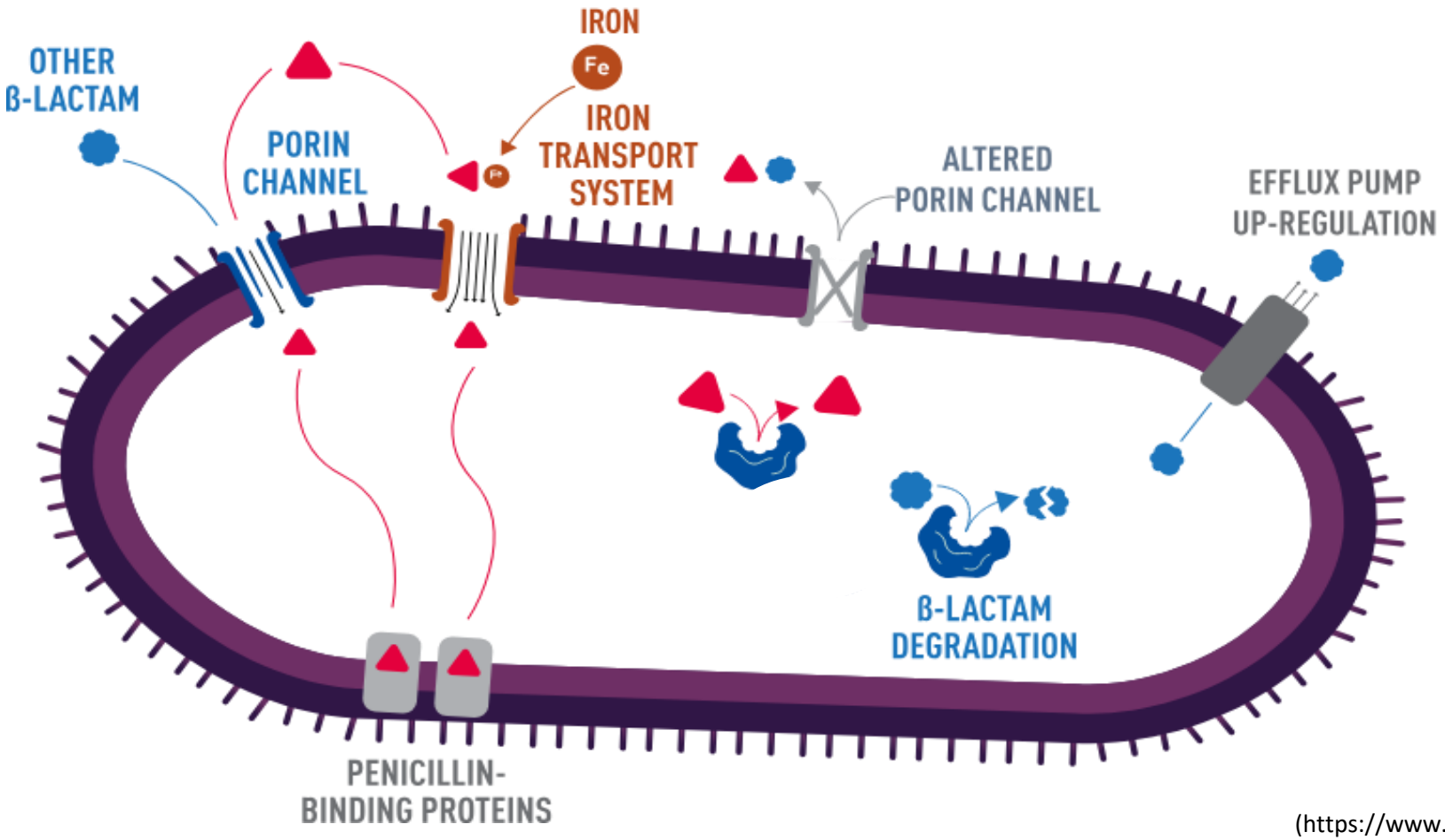
Cambio di approccio
Il cavallo di Troia



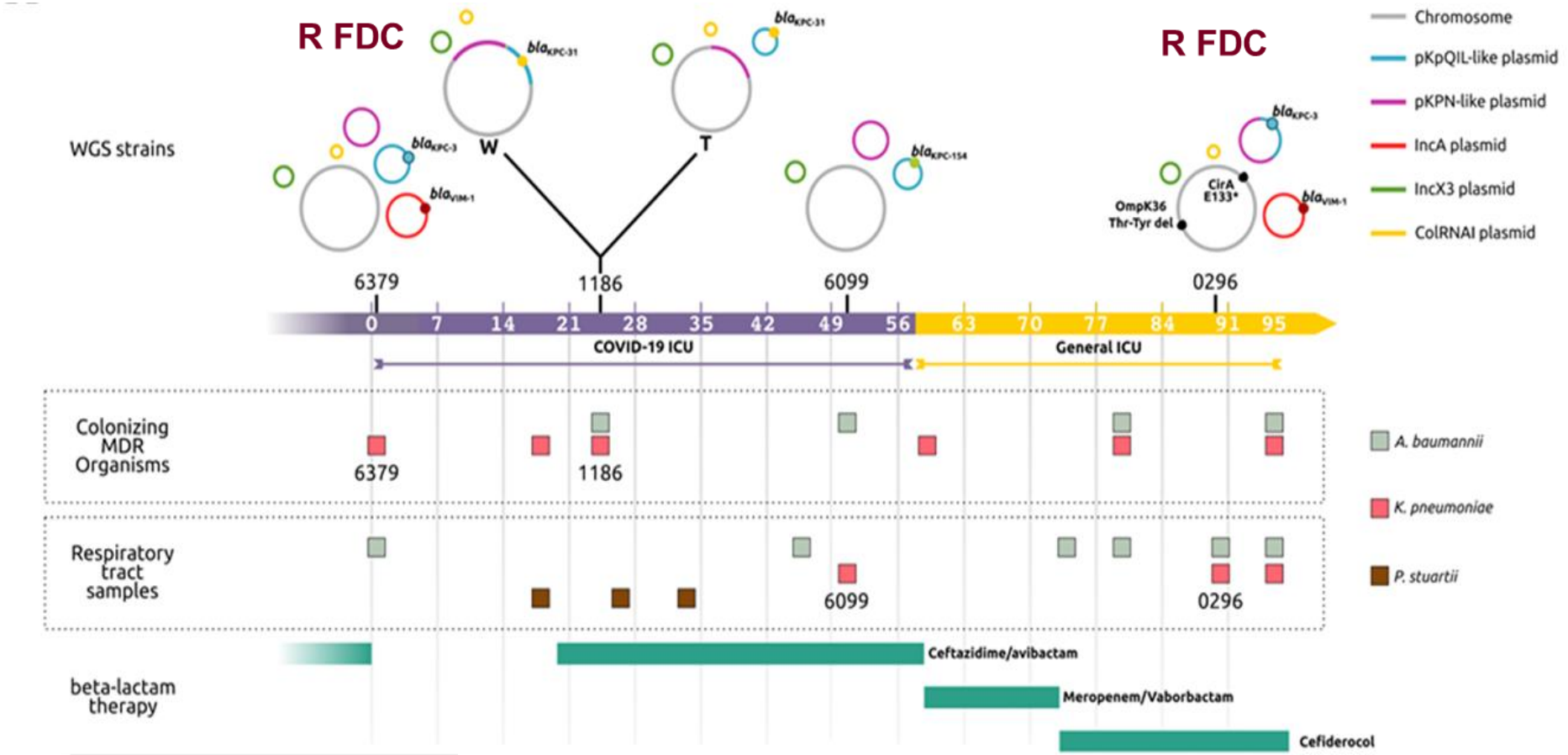
CEFIDEROCOL (FDC)

- Siderophore cephalosporin with activity against carbapenem-resistant gram-negative bacteria
- FDC is subject to active transport through the **iron transport system**, including TonB-dependent receptors as well as passive diffusion through porin channel



(https://www.fetroja.com/mechanism-of-action)

Genotypic Evolution of *Klebsiella pneumoniae* Sequence Type 512



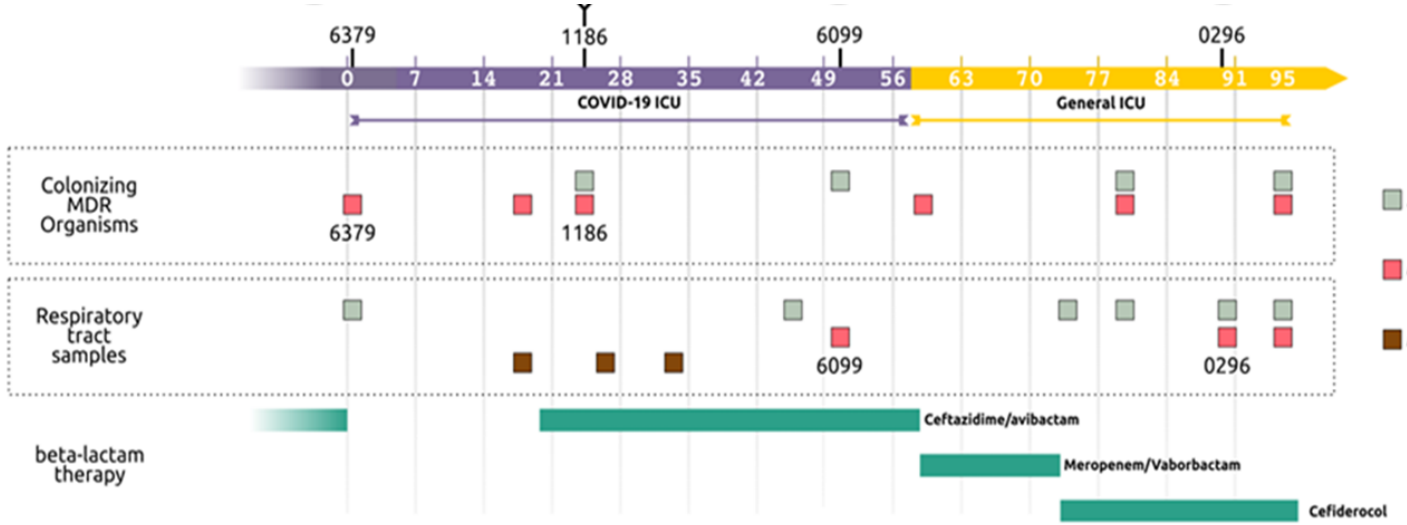
EMERGING INFECTIOUS DISEASES

Evolution of *Klebsiella pneumoniae* Sequence Type 512 during Ceftazidime/Avibactam, Meropenem/Vaborbactam, and Cefiderocol Treatment, Italy

Gabriele Arcari, Federico Cecilia, Alessandra Oliva, Riccardo Polani, Giammarco Raponi, Federica Sacco, Alice De Francesco, Francesco Pugliese, Alessandra Carattoli

In vivo evolution of *K. pneumoniae* sequence type 512 in a patient during hospitalization under the treatment with CZA, Meropenem/Vaborbactam, and FDC.

CASE 1: FDC RESISTANCE



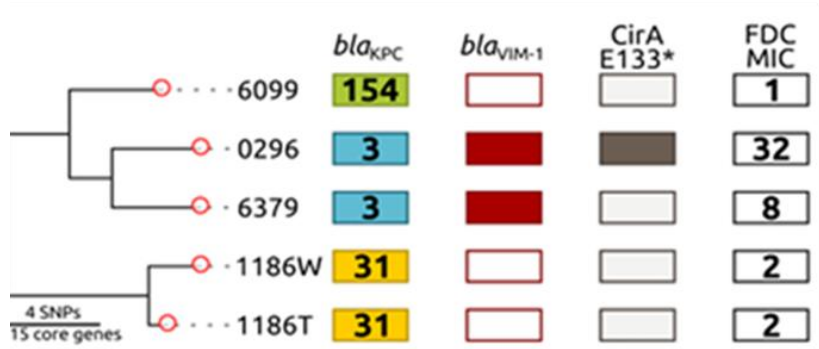


Table 1. Minimal inhibitory concentrations in ml/L of *Klebsiella pneumoniae* ST512 analyzed in this study

Strain	AZT	CZA*	FDC†	MEM	MVB*	IMI	COL	FOS	AMK	GTM	CIP	SXT	TGC
6379	>4	>256	8	32	1.5	>8	>4	>64	16	≤2	>1	>4/76	2
1186W	>4	32	2	2	0.25	≤1	>4	>64	>16	≤2	>1	≤2/38	≤1
1186T	>4	32	2	4	0.25	≤1	>4	>64	>16	≤2	>1	≤2/38	≤1
6099	>4	16	1	16	0.5	>8	>4	>64	≤8	≤2	>1	≤2/38	≤1
0296	>4	>256	32	32	0.047	>8	>4	>64	≤8	≤2	>1	>4/76	≤1
EUCAST Breakpoint	4	8	2	8	8	4	2	32	8	2	0.5	4	ND

AZT: Aztreonam, **CZA**: Ceftazidime/Avibactam, **FDC**: Cefiderocol, **MEM**: Meropenem, **MVB**: Meropenem/Vaborbactam, **IMI**: Imipenem. **COL**: Colistin, **FOS**: Fosfomycin, **AMK**: Amikacin, **GTM**: Gentamicin, **CIP**: Ciprofloxacin, **SXT**: Trimethoprim/Sulfametoxazole, **TGC**: Tigecycline

Numbers in bold indicate resistant strains according to EUCAST breakpoints

*: Tested using the gradient strip method (Liofilchem, Roseto degli Abruzzi, Italy)

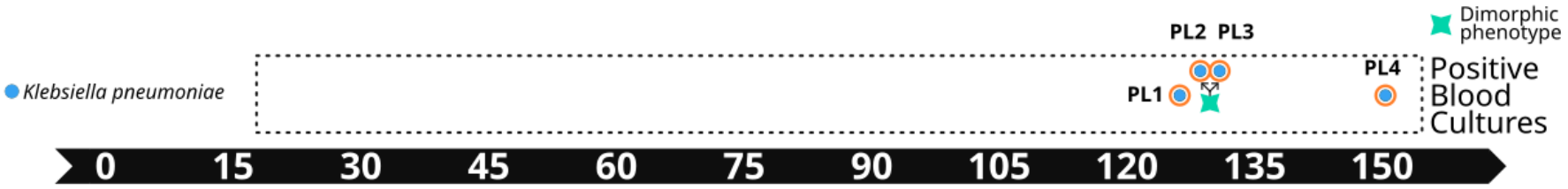
†: Tested using the Compact Antimicrobial Susceptibility Panel broth microdilution method (Liofilchem)

cirA mutation

Cefiderocol

R FDC

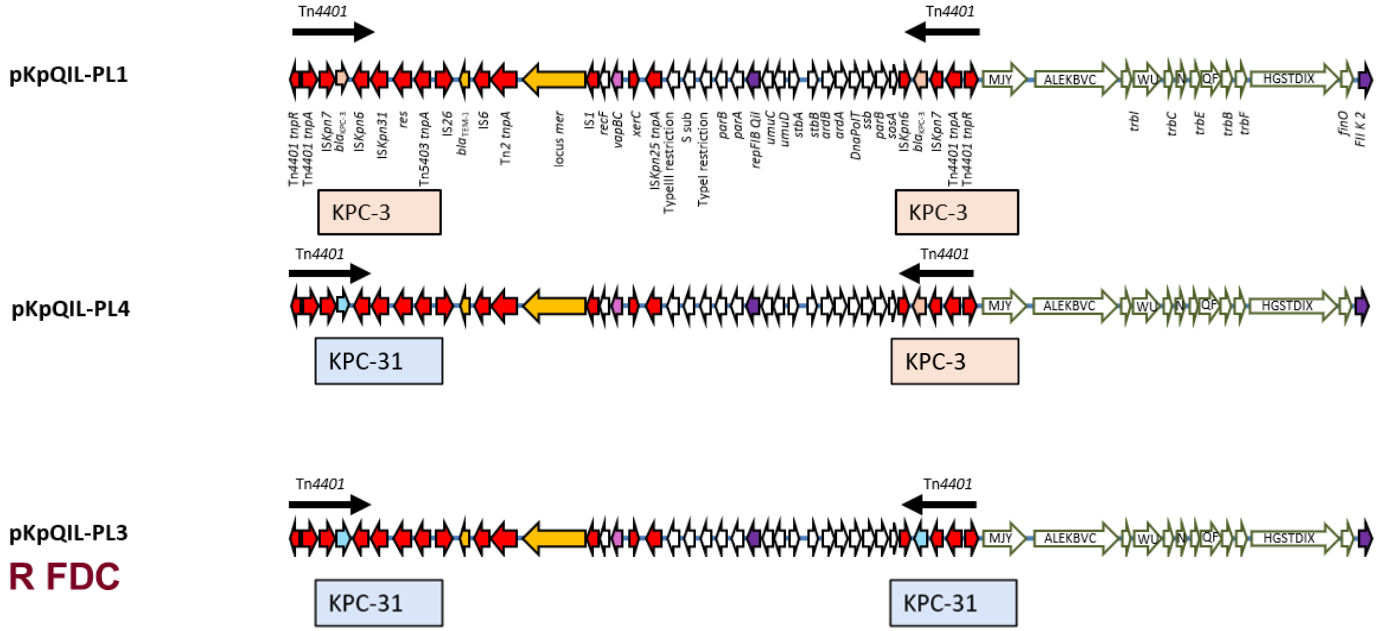
CASE 2: FDC RESISTANCE



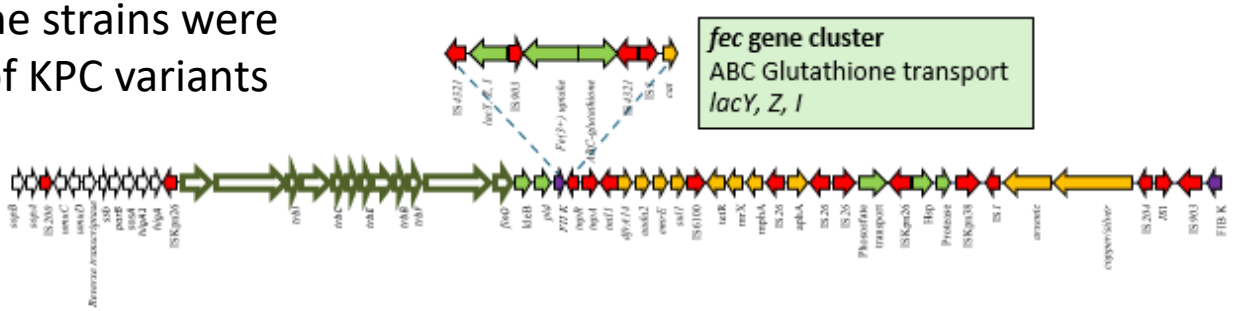
- **PL1**: CZA S
  wt *cirA*
  FDC MIC: 0,5 mg/L

- **PL2 = PL4:** CZA R
  wt *cirA*
  FDC MIC: 2 mg/L

- **PL3**: CZA R
  wt *cirA*
  FDC MIC: **4** mg/L



⇨ Differences between the strains were diverse combinations of KPC variants and a *fec* gene cluster



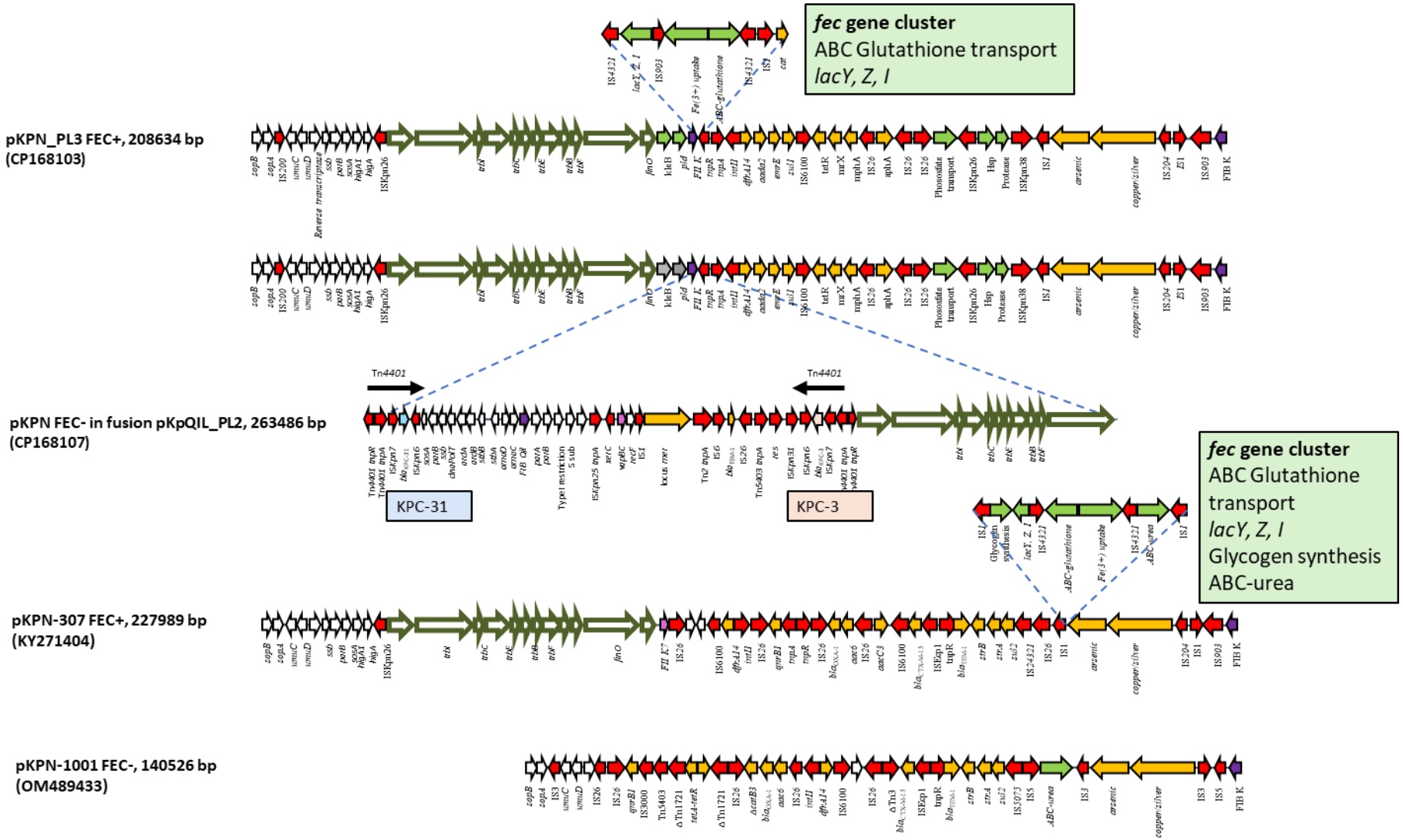
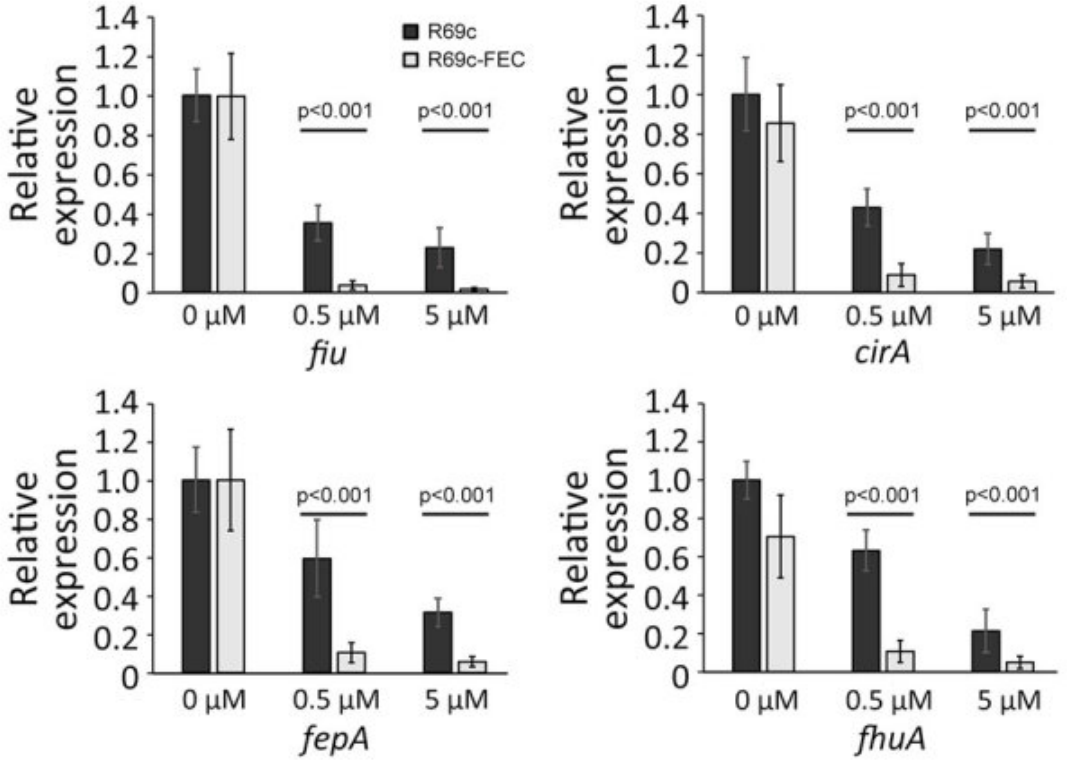


Figure S4. Maps of pKPN plasmids. Major structural features of pKPN-PL3, pKPN-PL2 identified in PL3 and PL2 *K. pneumoniae* isolates, respectively. pKPN-PL2 is fused with pKpQIL-PL2 plasmid (map and integration site are indicated below the pKPN-PL2 map by dot lines). Maps of the two reference pKPN-307 and pKPN-1001 plasmids representing the largest and smaller pKPN plasmid identified in our previous studies in ST307 and ST512 *K. pneumoniae* isolates, respectively are also included for comparison.

RESULTS

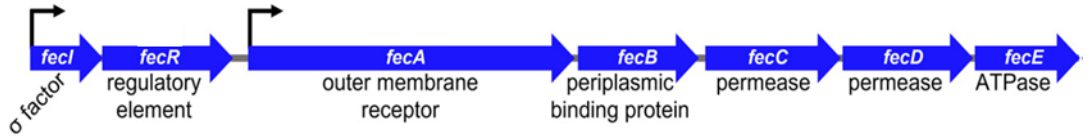
Expression of ferrisiderophore receptor genes in presence of ferric citrate



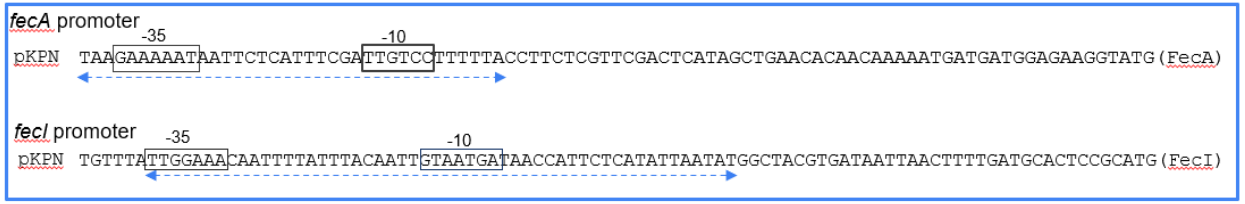
- The inhibition was almost complete (90%) in cells carrying the R69c-FEC plasmid and only partial in R69c-carrying cells

- The markedly reduced expression of ferrisiderophore receptor genes correlated with the higher FDC MICs

Ferric citrate uptake system

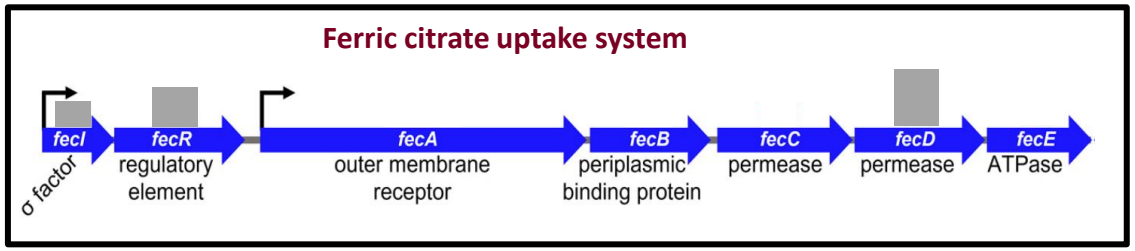


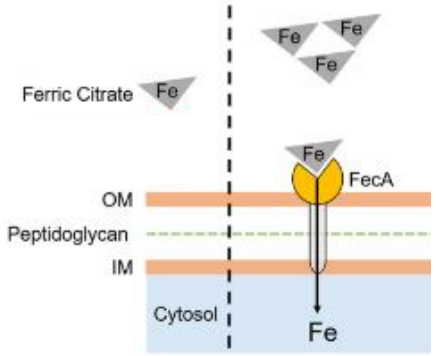
Fur binding region= dotted double arrows

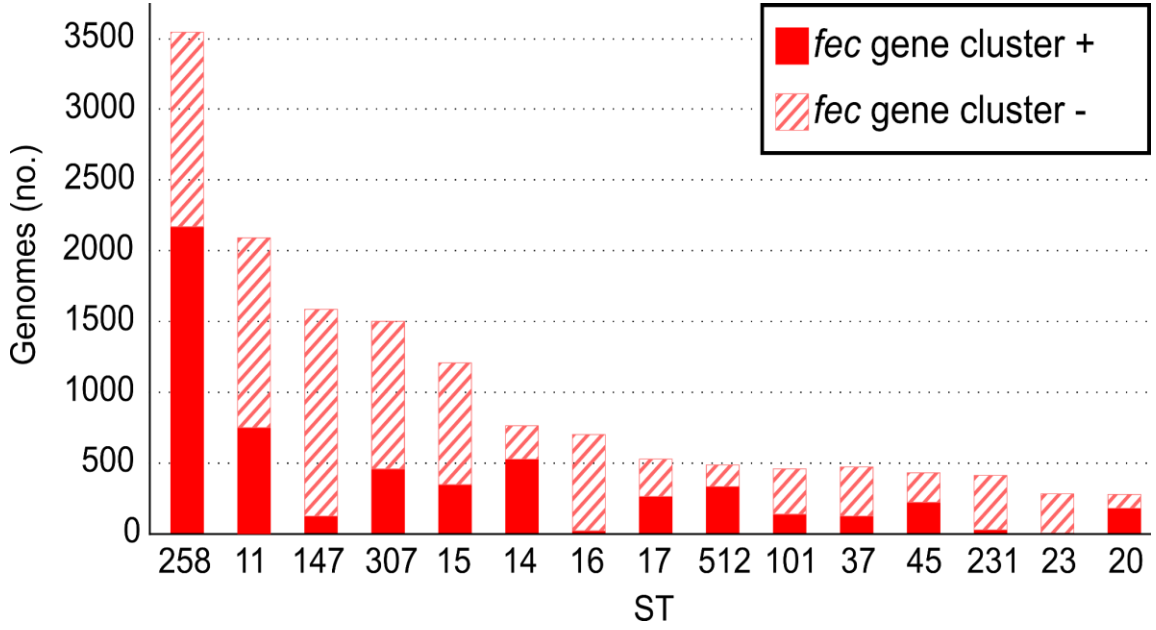


GLOBAL EPIDEMIOLOGY

- A global screening of 27,793 *K. pneumoniae* genomes identified the *fec* gene cluster in 38.4% of the samples.
- 24.0% carried a *fec* gene cluster identical to *K. pneumoniae* PL3
- The distribution of the *fec* gene cluster varied across the 15 most common STs
- ST512 showed high prevalence, with 68% of *fec*-carrying isolates







Emerg Infect Dis. 2025 Jan;31(1):123–124. doi: 10.3201/eid3101.241426

Cefiderocol Resistance Conferred by Plasmid-Located Ferric Citrate Transport System in KPC-Producing *Klebsiella pneumoniae*

Riccardo Polani [1], Alice De Francesco [1], Dario Tomolillo [1], Irene Artuso [1], Michele Equestre [1], Rita Trirocco [1], Gabriele Arcari [1], Guido Antonelli [1], Laura Villa [1], Gianni Prosseda [1], Paolo Visca [1], Alessandra Carattoli [1,✉]

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PMCID: PMC11682805 PMID: 39714320

Abstract

Cefiderocol (FDC), a siderophore-cephalosporin conjugate, is the newest option for treating infection with carbapenem-resistant gram-negative bacteria. We identified a novel mechanism contributing to decreased FDC susceptibility in *Klebsiella pneumoniae* clinical

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OXA β-lactamases from *Acinetobacter* spp. are membrane bound and secreted into outer membrane vesicles

Lucia Capodimonte,[1,2] Fernando Teixeira Pinto Meireles,[3] Guillermo Bahr,[1,2] Robert A. Bonomo,[4,5,6,7] Matteo Dal Peraro,[3] Carolina López,[1] Alejandro J. Vila[1,2,7]

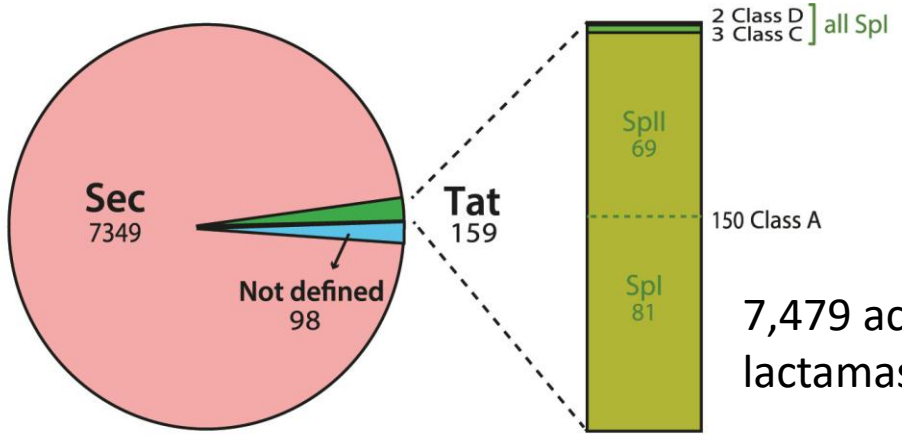
3 Institute of Bioengineering, School of Life Science, École Polytechnique Fédérale de Lausanne (EPFL), Switzerland 4Department of Molecular Biology and Microbiology, Case Western Reserve University Sch Medicine, Cleveland, Ohio, USA 5Research Service, Louis Stokes Cleveland Department of Veterans Affa Center, Cleveland, Ohio, USA 6Departments of Pharmacology, Biochemistry, Proteomics and Bioinform Western Reserve University School of Medicine, Cleveland, Ohio, USA 7CWRU-Cleveland VAMC Center Antimicrobial Resistance and Epidemiology (Case VA CARES), Cleveland, Ohio, US

β-lactamases from Gram-negative bacteria are generally regarded as soluble, periplasmic enzymes. N-terminal signal peptide directs β-lactamase precursor to one of the two main export pathways (Sec or Tat) responsible for protein translocation into the periplasmic space.

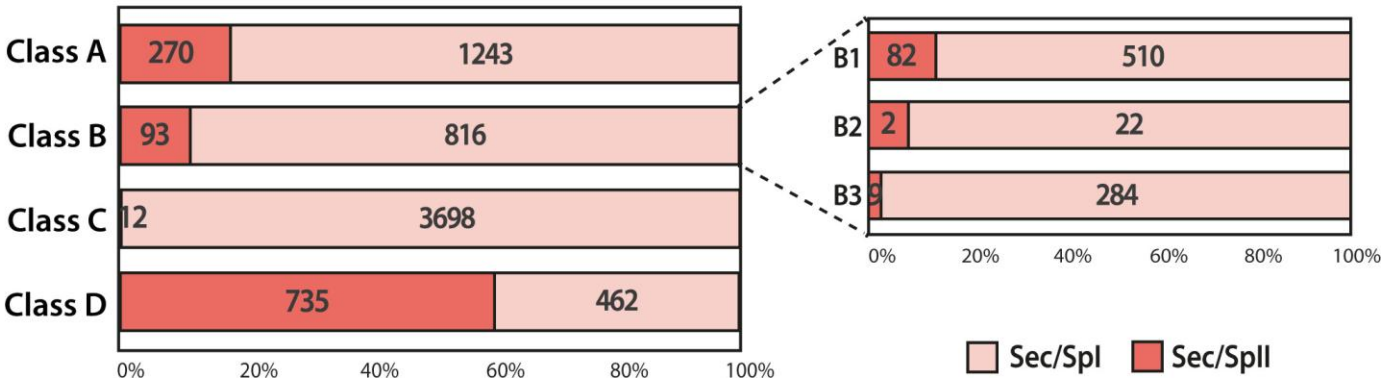
Predominance of putative lipidated enzymes in the Class D OXAs.

In the case of lipoproteins, the signal peptides are cleaved by the Type II signal peptidase (Sec/SpII) Namely, 60% of the OXA Class D enzymes contain a lipobox sequence in their signal peptide.

This contrasts with β-lactamases from other classes, which are predicted to be mostly soluble proteins (NDM-1 is lipidated)



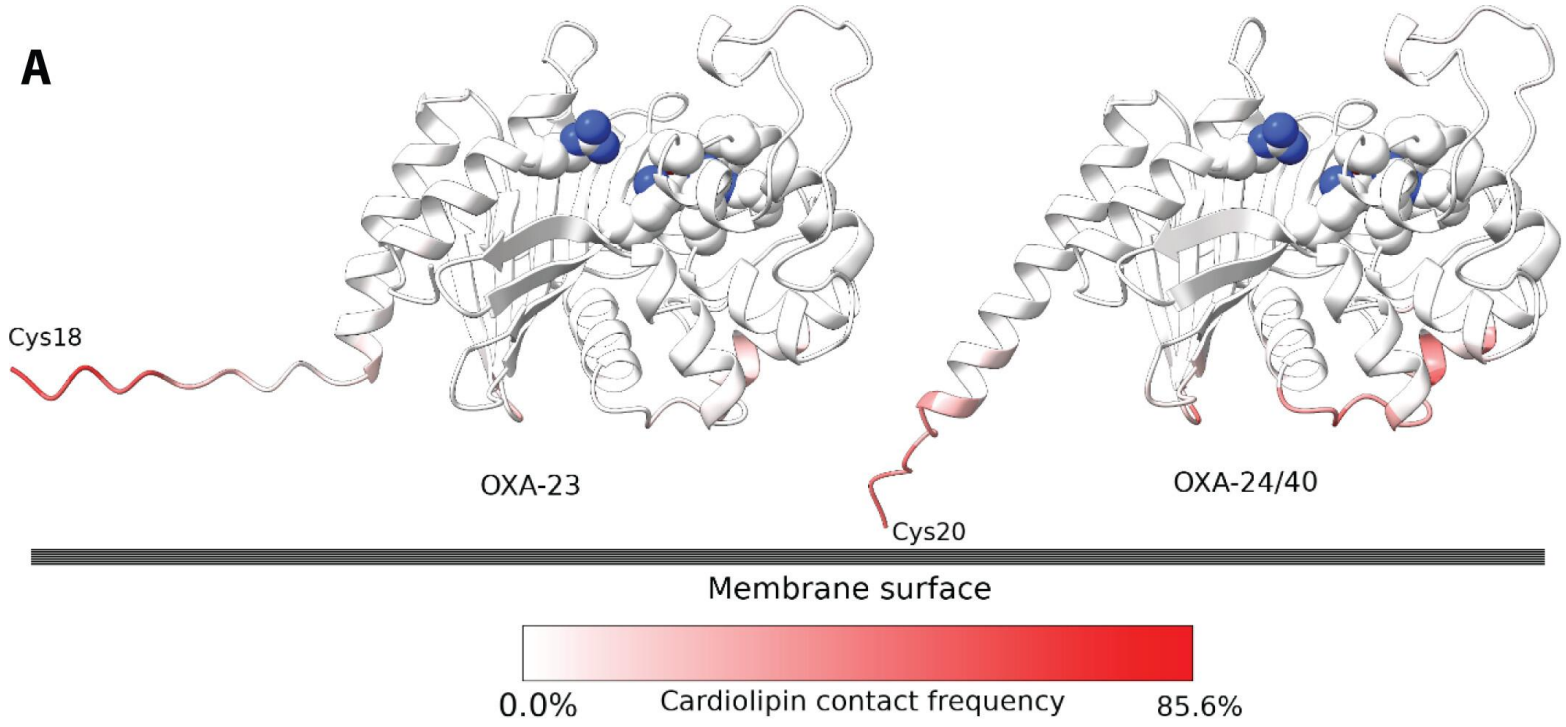
7,479 accessible β-lactamase sequences



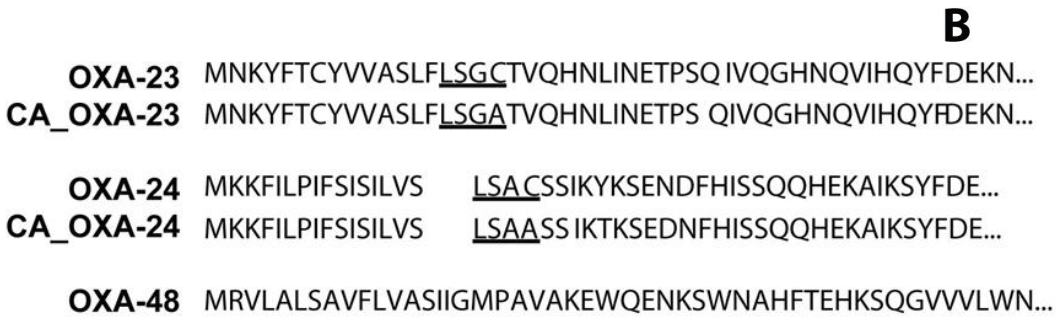
>99% lipidated OXAs are present in *Acinetobacter* spp.

OXA-23 and OXA-24/40 are lipidated, membrane-bound proteins in *Acinetobacter baumannii*.

In contrast, OXA-48 (commonly produced by Enterobacterales) lacks a lipobox and is a soluble protein.

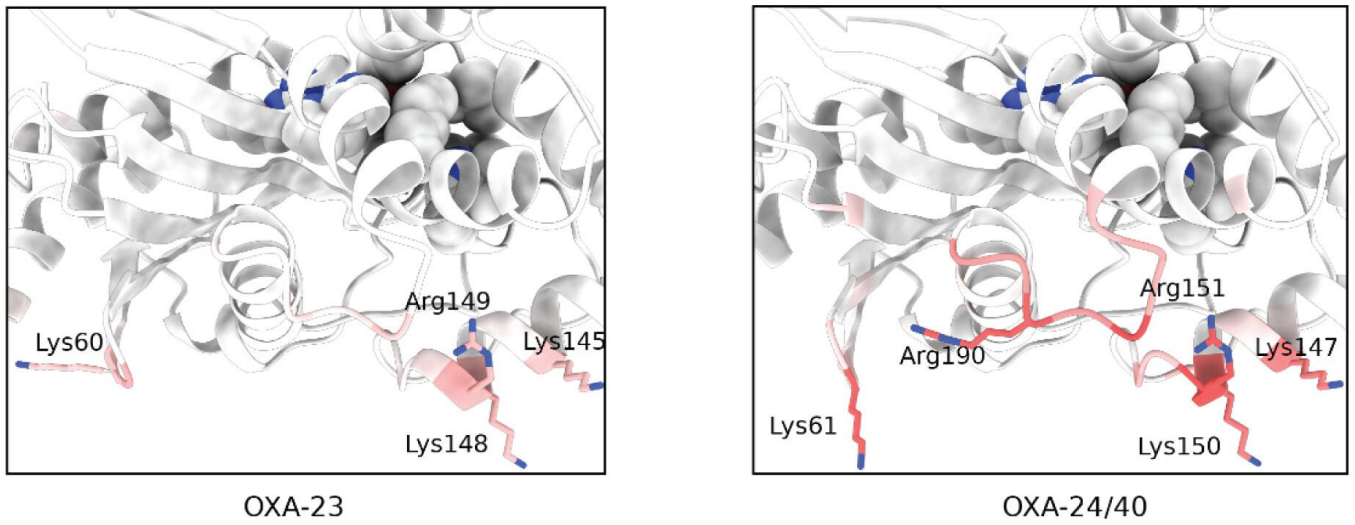


The cysteine residue located at C-terminus is the target of lipidation.



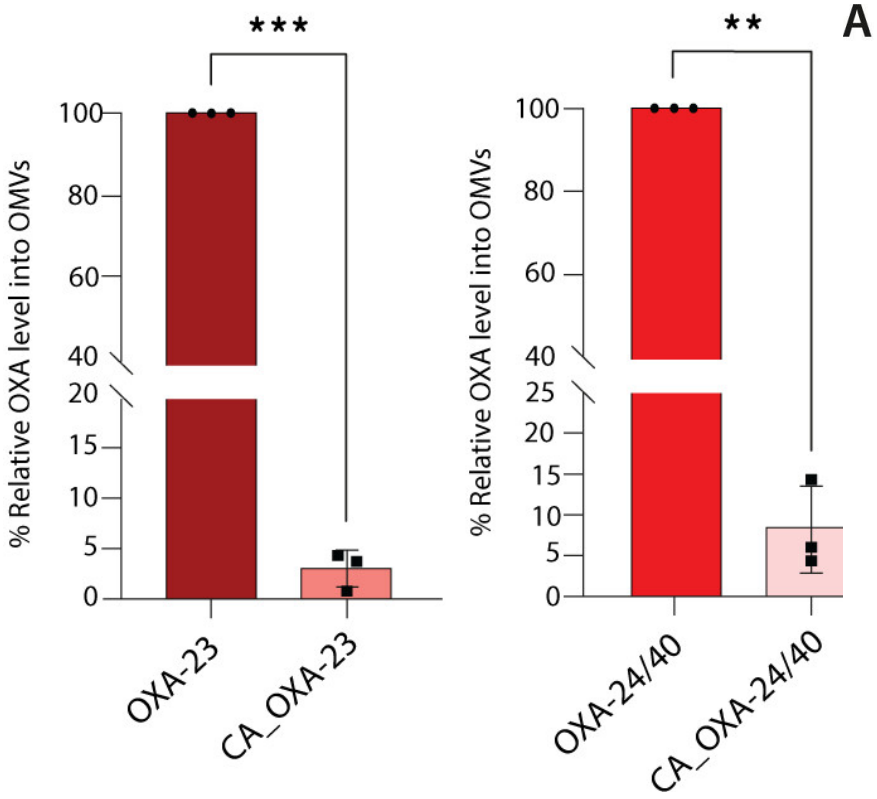
lipidated cysteines (Cys18 and Cys20)

Cys for Ala in both proteins (Cys18 in OXA-23 and Cys20 in OXA-24/40)

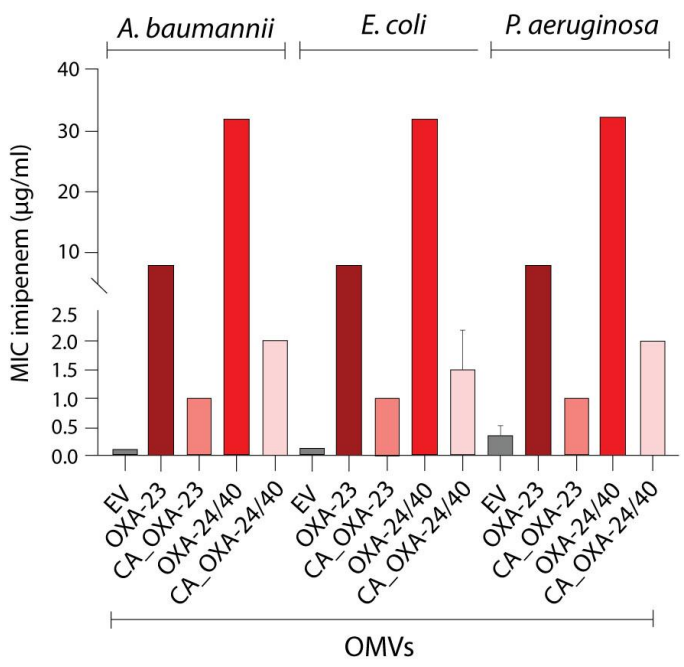


The membrane-bound β-lactamases are OMVs loaded with lipidated β-lactamases.
These are vehicles for antimicrobial resistance and its dissemination. This advantage could be crucial in polymicrobial infections, in which *Acinetobacter* spp. are usually involved

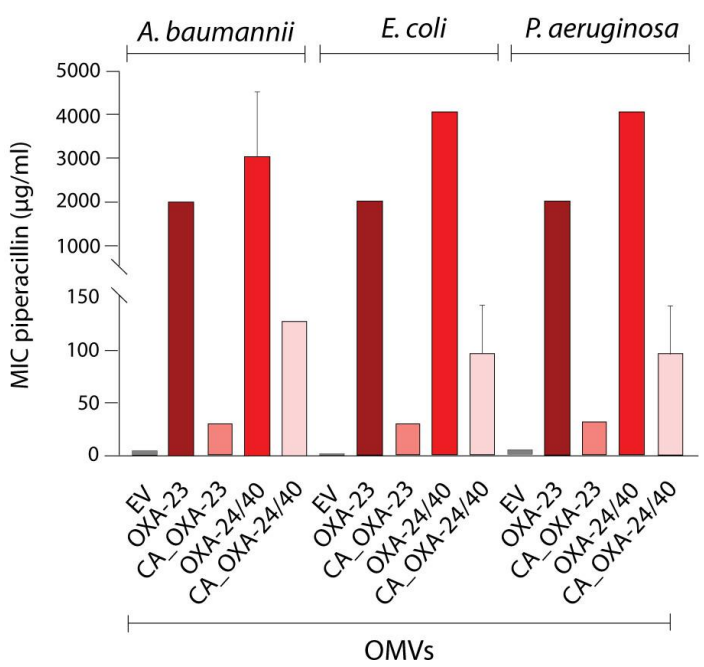
Lipidated OXAs are selectively secreted into OMVs



A



B



CA_OXA-23 and CA_OXA-24/40 variants in *A. baumannii* resulted in the accumulation of both proteins only in the periplasmic fractions as soluble proteins membrane anchoring of OXAs results in packaging into OMVs.

We tested this in β-lactam-susceptible *A. baumannii, E. coli, and Pseudomonas aeruginosa* cells treated with OMVs from *A. baumannii* carrying the empty vector (EV) or expressing OXAs in the presence of imipenem or piperacillin, and we determined the MICs