COURS D'AUTOMNE EN INFECTIOLOGIE

LES PENSIÈRES, VEYRIER-DU-LAC, 13-15 novembre 2023

ÉPIDÉMIOLOGIE DE LA RÉSISTANCE DES BACILLES À GRAM- ET NOUVEAUX MÉCANISMES DE RÉSISTANCE

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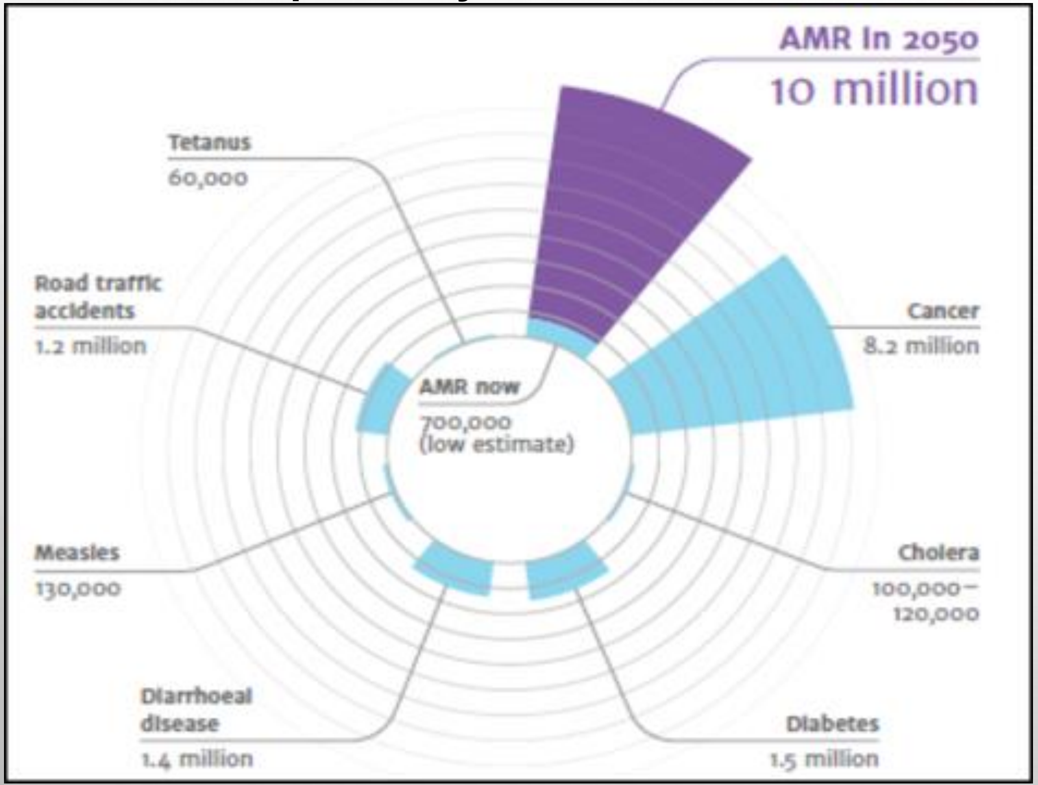
CNR associé Résistance aux antibiotiques
Faculté de Médicine, Université Paris-Saclay
Unité EERA, Institut Pasteur

CONFLITS D'INTÉRÊTS

- CONTRATS DE RECHERCHE DE MERCK, PFIZER, ASTRAZENECA, SHIONOGI, MENARINI,
- CONTRATS DE RECHERCHE DE CEPHEID, MAST, BD, HOLOGIC, NG BIOTECH, QIAGEN, BIOMÉRIEUX

LE FARDEAU DES BACTÉRIES MULTI-RÉSISTANTES (BMR)

“Si rien n’est fait, le fardeau lié aux BMR pourrait représenter **10 millions de morts /an d’ici 2050 & un coût de 100 mille millards de dollars US”**
Jim O’Neill report, May 2016



THE LANCET

January 2022

Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis

*Antimicrobial Resistance Collaborators**

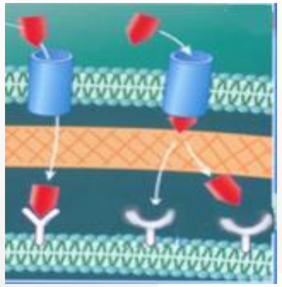
Summary
Background Antimicrobial resistance (AMR) poses a major threat to human health around the world. Previous publications have estimated the effect of AMR on incidence, deaths, hospital length of stay, and health-care costs for specific pathogen–drug combinations in select locations. To our knowledge, this study presents the most comprehensive estimates of AMR burden to date.

4.95 million deaths associated with bacterial AMR, 1.27 million deaths attributable to bacterial AMR

E. coli, S. aureus, K. pneumoniae, S. pneumoniae, A. baumannii, P. aeruginosa: 929 000 deaths deaths attributable to bacterial AMR

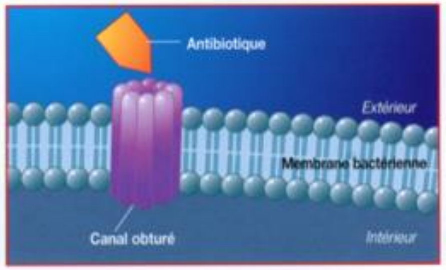
MRSA, ESBL- *E. coli*, Fluoroquinolone R, *E. coli*, CR *A. baumannii*, CR *K. pneumoniae*, and ESBL- *K. pneumoniae*

RÉSISTANCE AUX ß-LACTAMINES, BACILLES GRAM NÉGATIF

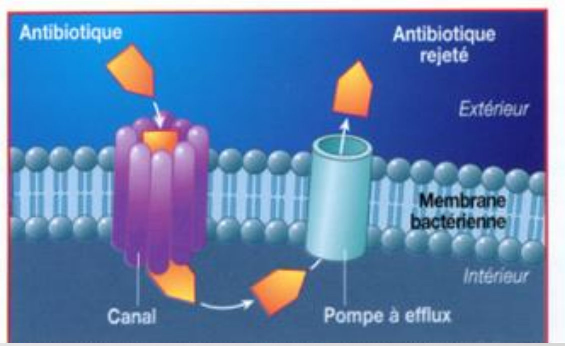


Modification des PLPs

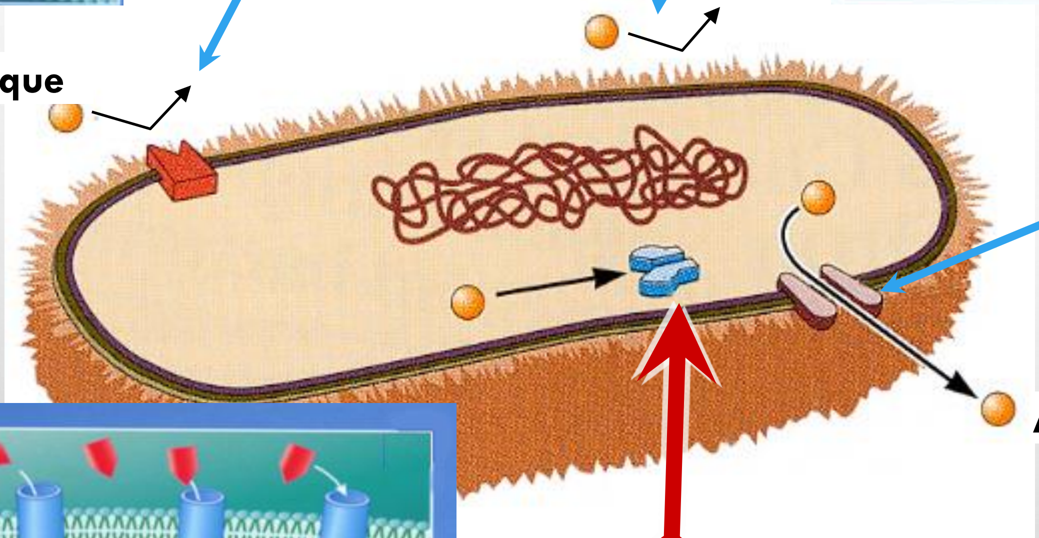
Diminution de la perméabilité



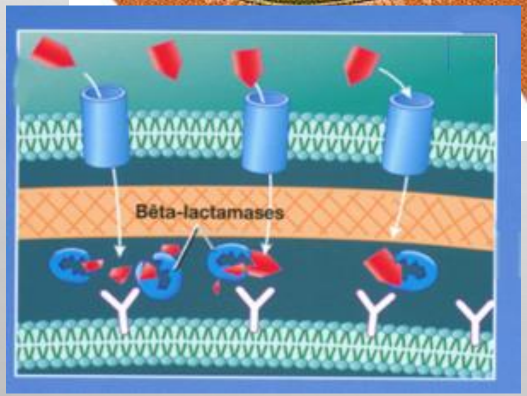
Sur expression Pompes à efflux



Antibiotique



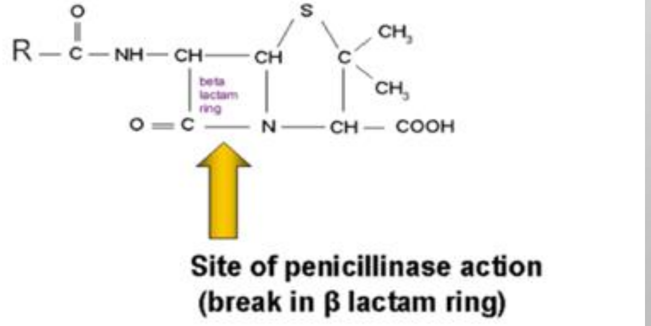
Antibiotic



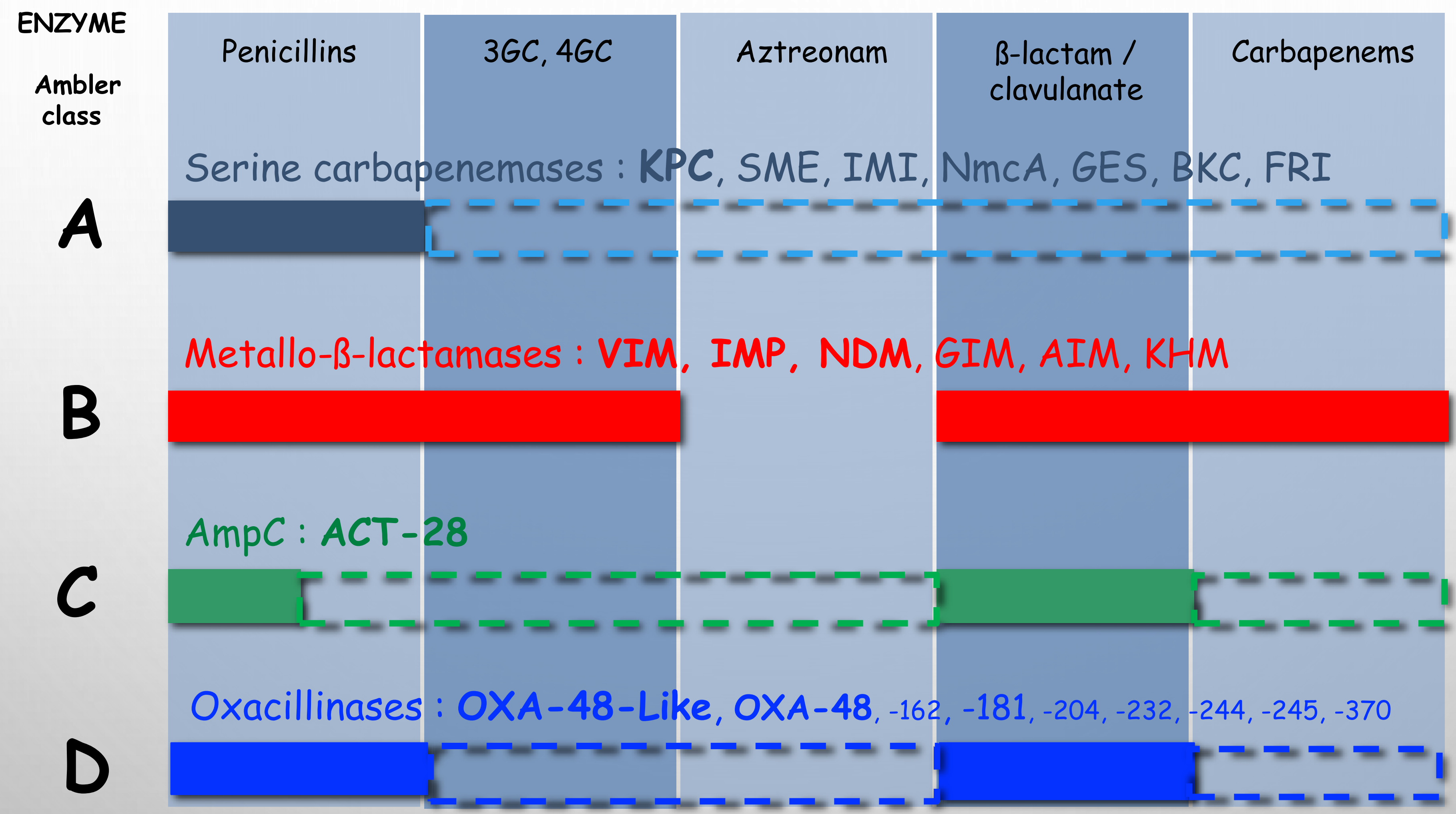
ß-Lactamases

- Sérine active (A, C, D)
- MBLs (B)

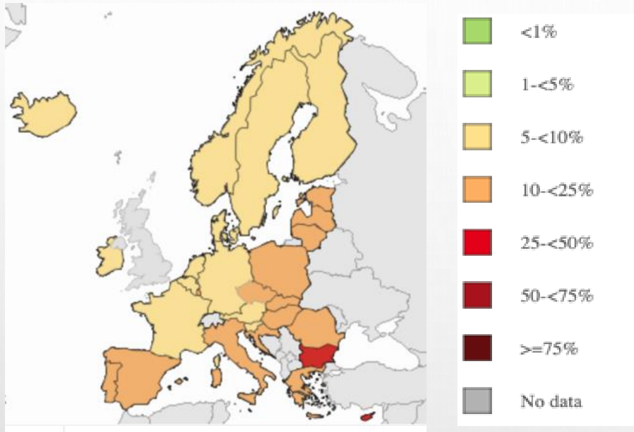
>7900 ß-lactamases
(BLDB database: http://www.bldb.eu/)



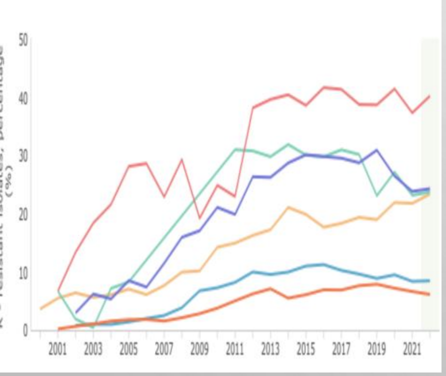
Profiles d'hydrolyses



ENTÉROBACTÉRIES RÉSISTANTES AUX C3G

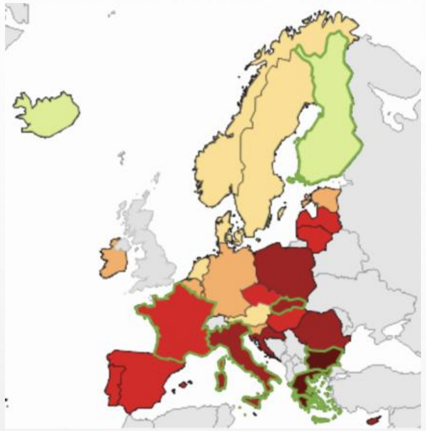


E. coli
- **0.8%** in 2002
- **8.3%** in 2022

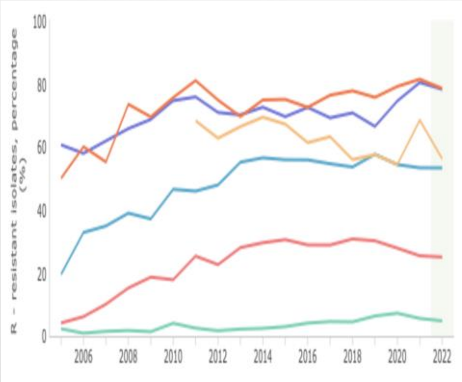


Bulgaria, 40.2 %

Italy, 24.2%
Slovakia 23.7 %
Greece, 23.3 %
France, 8.4%
Finland, 6.1 %



K. pneumoniae
- **6.1%** in 2006
- **25 %** in 2022



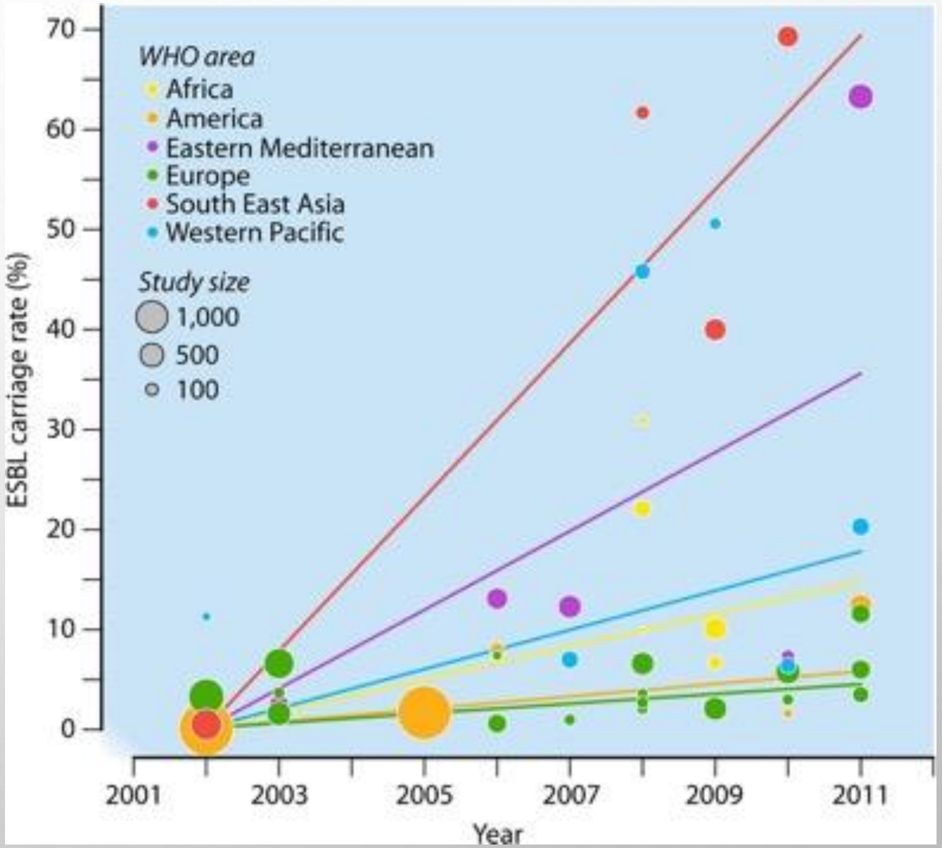
Bulgaria, 78.5 %
Greece, 78.2 %

Slovakia 56,1%
Italy, 53.3%

France, 25 %

Finland, 4,8 %

Portage sain d'Enterobacterales-BLSE



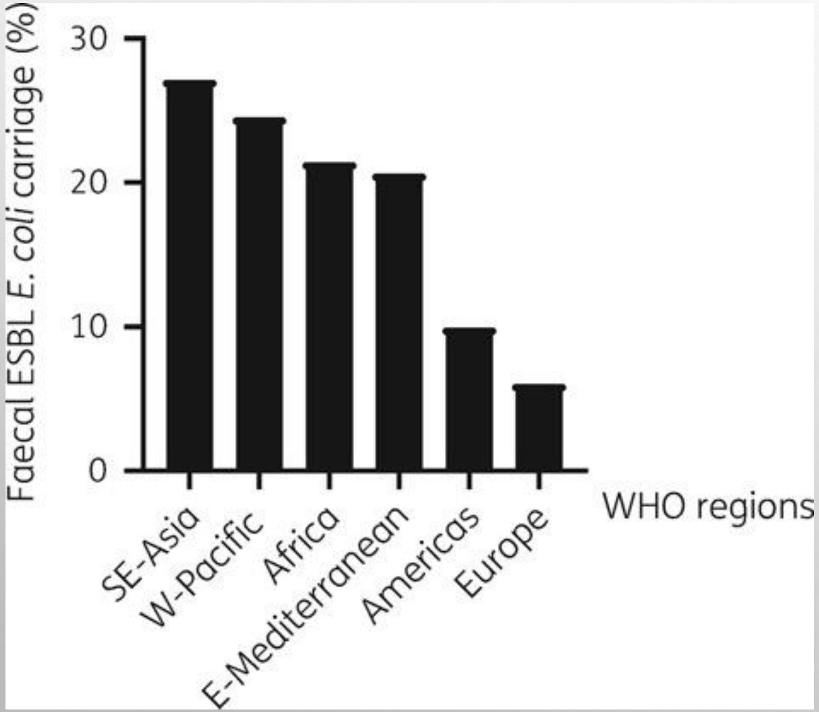
Dissémination des BLSEs de type CTX-M

Woerther, et al. *Clin Microbiol Rev* 2013;26:744–58

The global prevalence and trend of human intestinal carriage of ESBL-producing *Escherichia coli* in the community

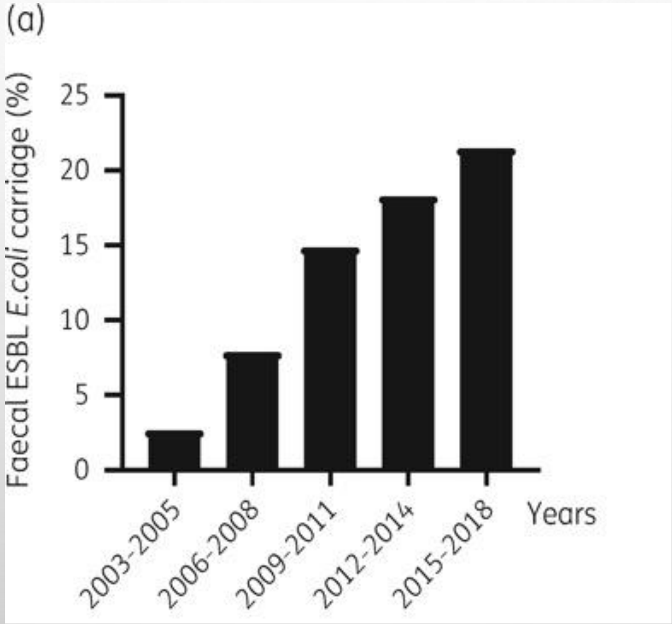
Yihienew M. Bezabih[1*], Wilber Sabiiti[2], Endalkachew Alamneh[3], Alamneh Bezabih[4], Gregory M. Peterson[3], Woldesellassie M. Bezabhe[3] and Anna Roujeinikova[5]

POOLED PREVALENCE OF INTESTINAL ESBL *E. COLI* CARRIAGE AMONG HEALTHY INDIVIDUALS IN SIX WHO REGIONS

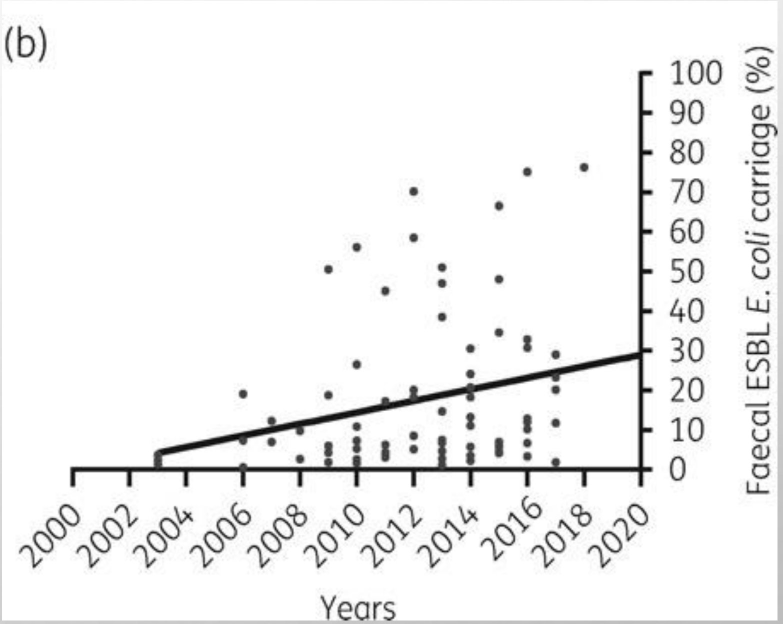


Global trend in faecal ESBL *E. coli* carriage among healthy individuals.

Pooled prevalence showing a clear increase from one 3 year interval to another.



A simple linear regression plot depicting the trend of carriage (1.5% rise per year, P=0.021).



2000-2020

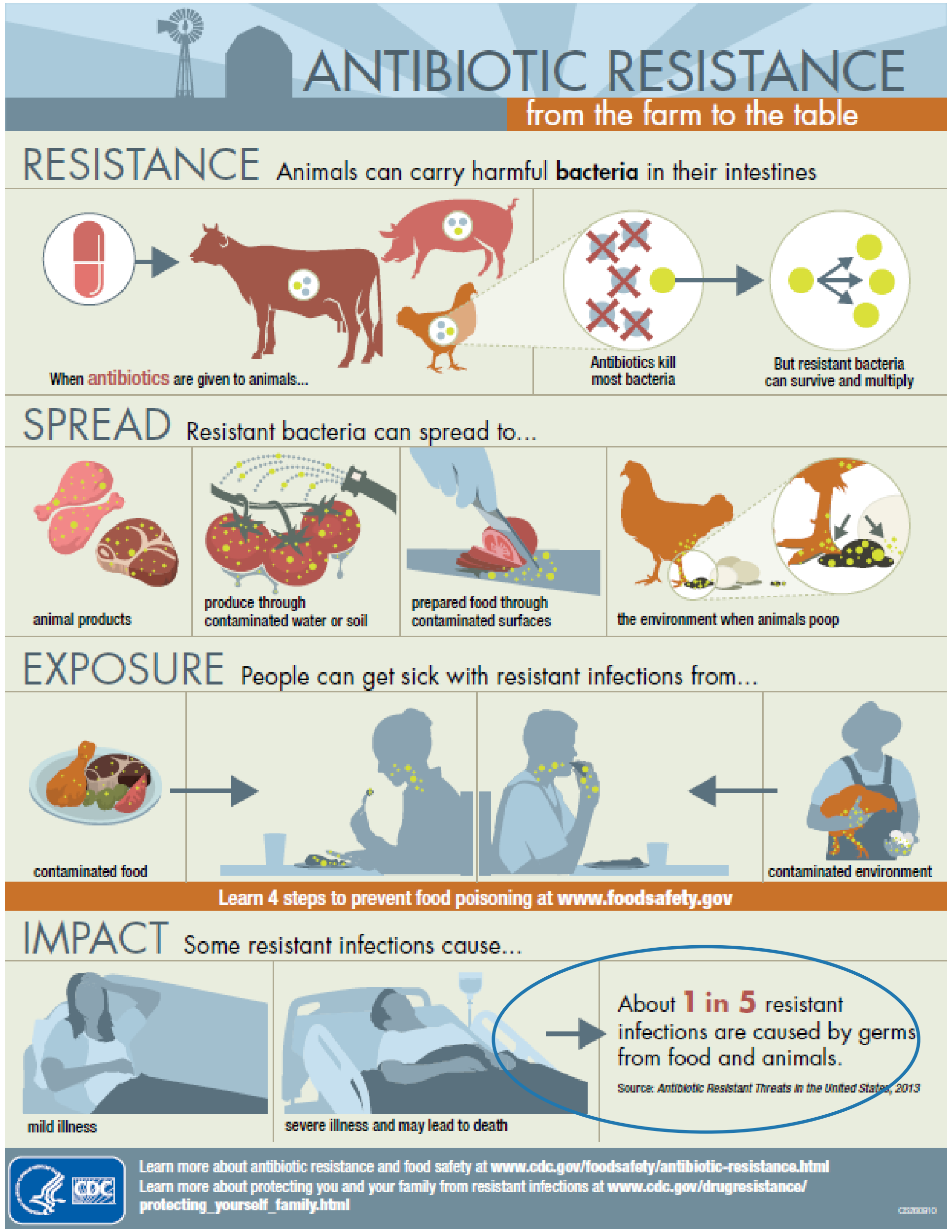
J Antimicrob Chemother, Volume 76, Issue 1, January 2021, Pages 22–29,

E. COLI- PRODUCTEURS DE BLSE*:* OU ÊTES VOUS?

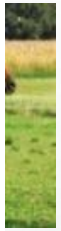
Animaux d'élevages







…imaux de compagnie

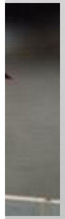


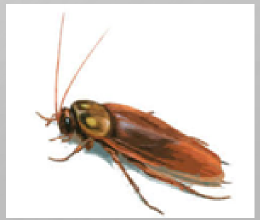
…LSE:

…n"

Environne…


Animaux sauvages

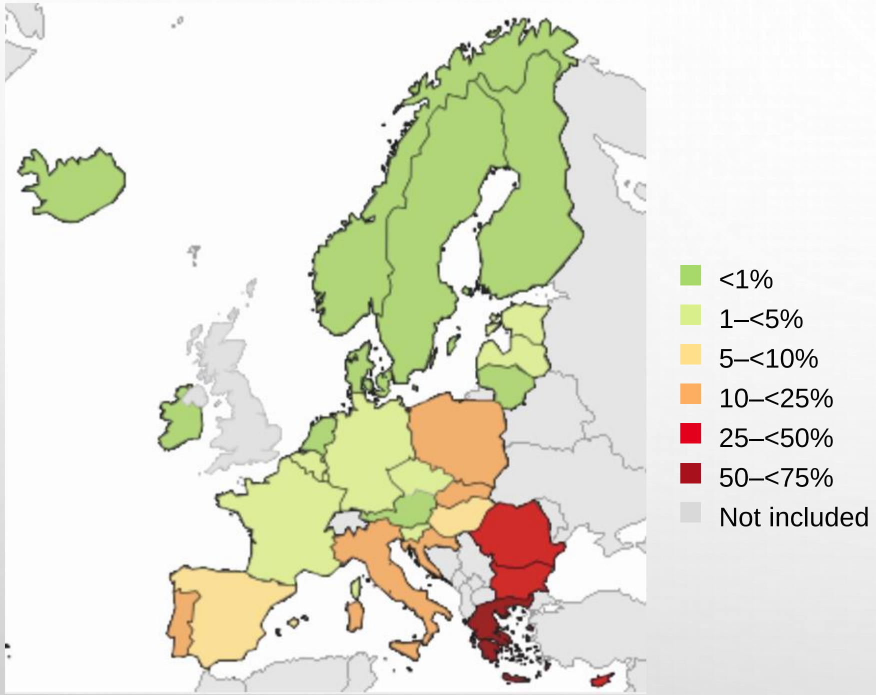




RÉSISTANCE AUX CARBAPÉNÈMES EN EUROPE

Bactériémie à *K. pneumoniae* résistantes aux carbapénèmes en Europe 2021 (ECDC)

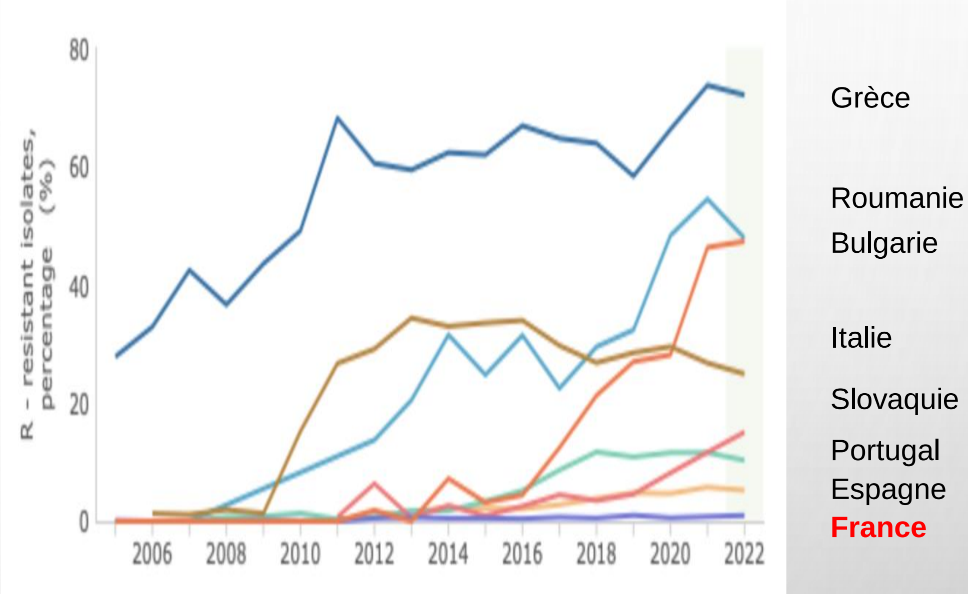
E. coli
France: 0.1%
Greece: 1.5 %

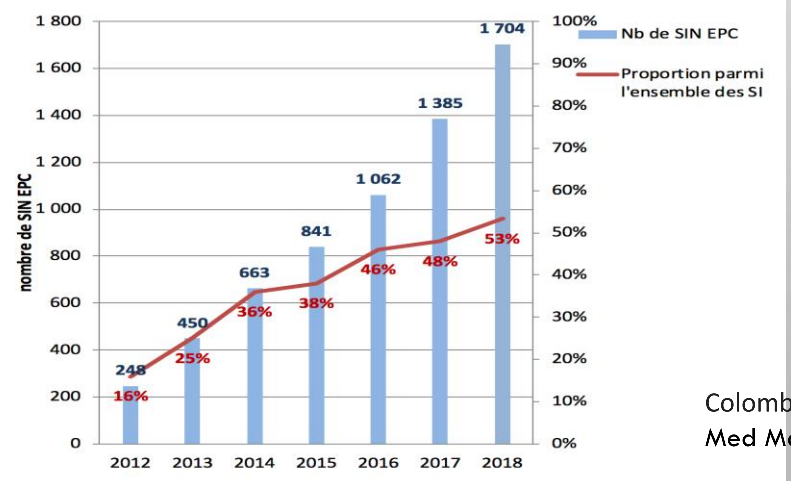


1 %	**5.2 %**	**10.3 %**	**15.0 %**	**24.9 %**	**47.3 %**	**47.8%**	**72.0 %**
France	Espagne	Portugal	Slovaquie	Italie	Bulgarie	Roumanie	Grèce

CRE restent sensibles à peu d'ATB (colistine, + qques nouvelles molécules)
Mais résistance décrites en Italie et Grèce (15 à 25 %)
=> pan-résistance, impasses thérapeutiques
=> Taux de mortalité élevés (30-70%)

Evolution des Kp CRE, Bactériémies

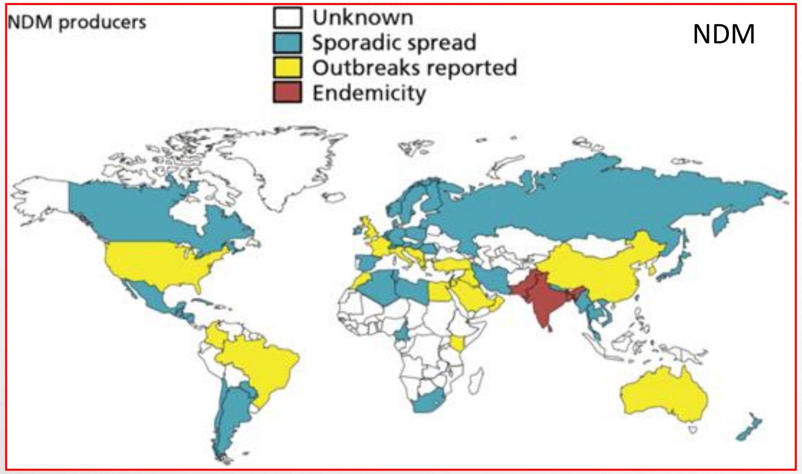


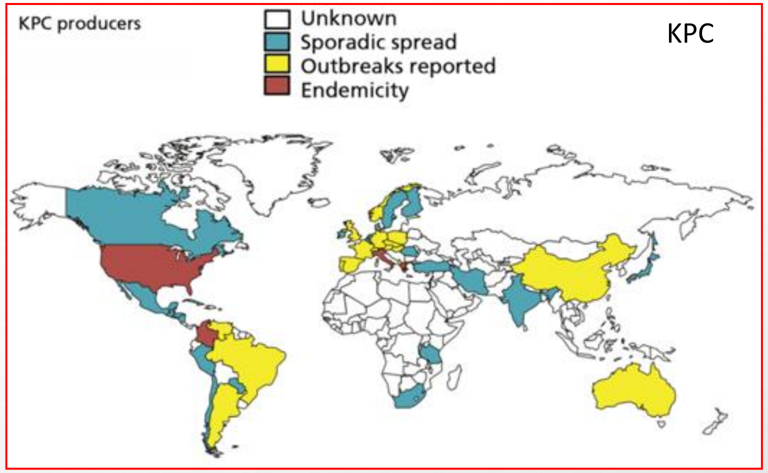


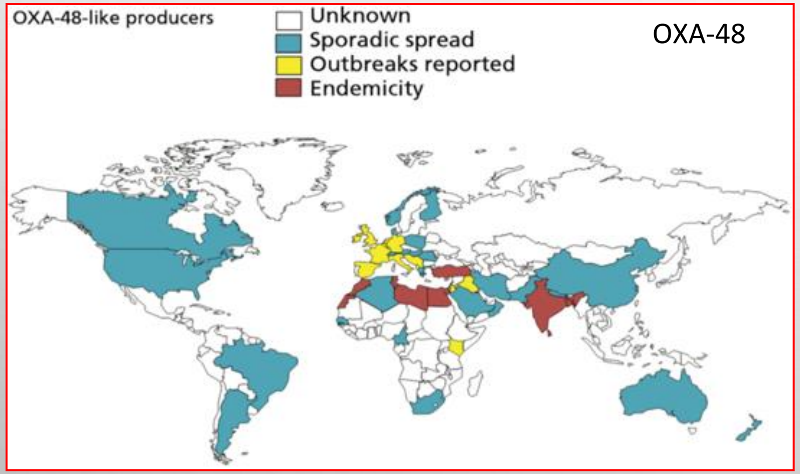
CPE Notification, France

Colomb-Cotinat M, Med Mal Infect. 2020

LES EPCS DANS LE MONDE



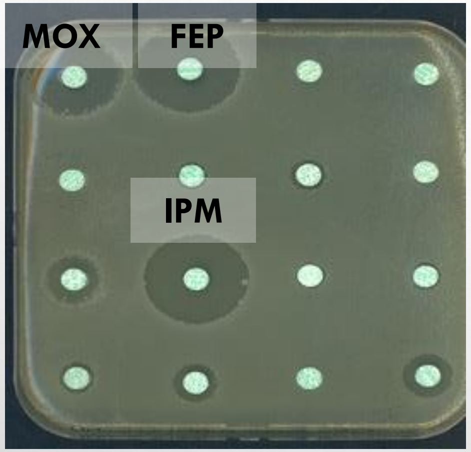




CRE: RÉSISTANCE AUX CARBAPÉNÈMES CHEZ LES ENTÉROBACTÉRIES

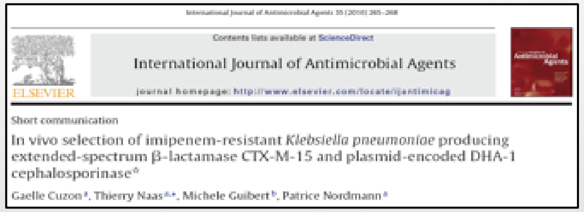
1) Diminution de la perméabilité de la membrane externe + β-lactamase avec faible niveau d'hydrolyse des carbapénèmes

Résistance aux C3G
BUT
Sensibilité aux carbapénèmes



Lee EH, Nicolas MH, Kitzis MD, Pialoux G, Collatz E, Gutmann L. AAC 1991, 35:1093-8

après
21 jours: imipénème en monothérapie


International Journal of Antimicrobial Agents 35 (2010) 285–288

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

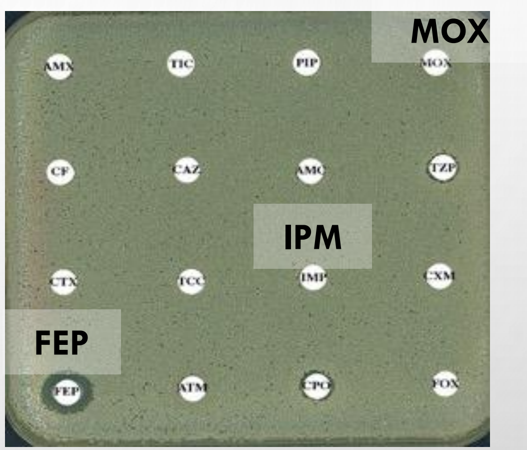
ELSEVIER

Short communication

In vivo selection of imipenem-resistant *Klebsiella pneumoniae* producing extended-spectrum β-lactamase CTX-M-15 and plasmid-encoded DHA-1 cephalosporinase*

Gaelle Cuzon[a], Thierry Naas[a,*], Michele Guibert[b], Patrice Nordmann[a]

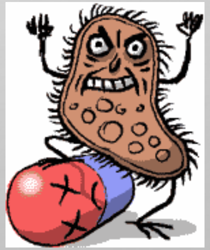
Résistance aux carbapénèmes
par
Diminution de perméabilité



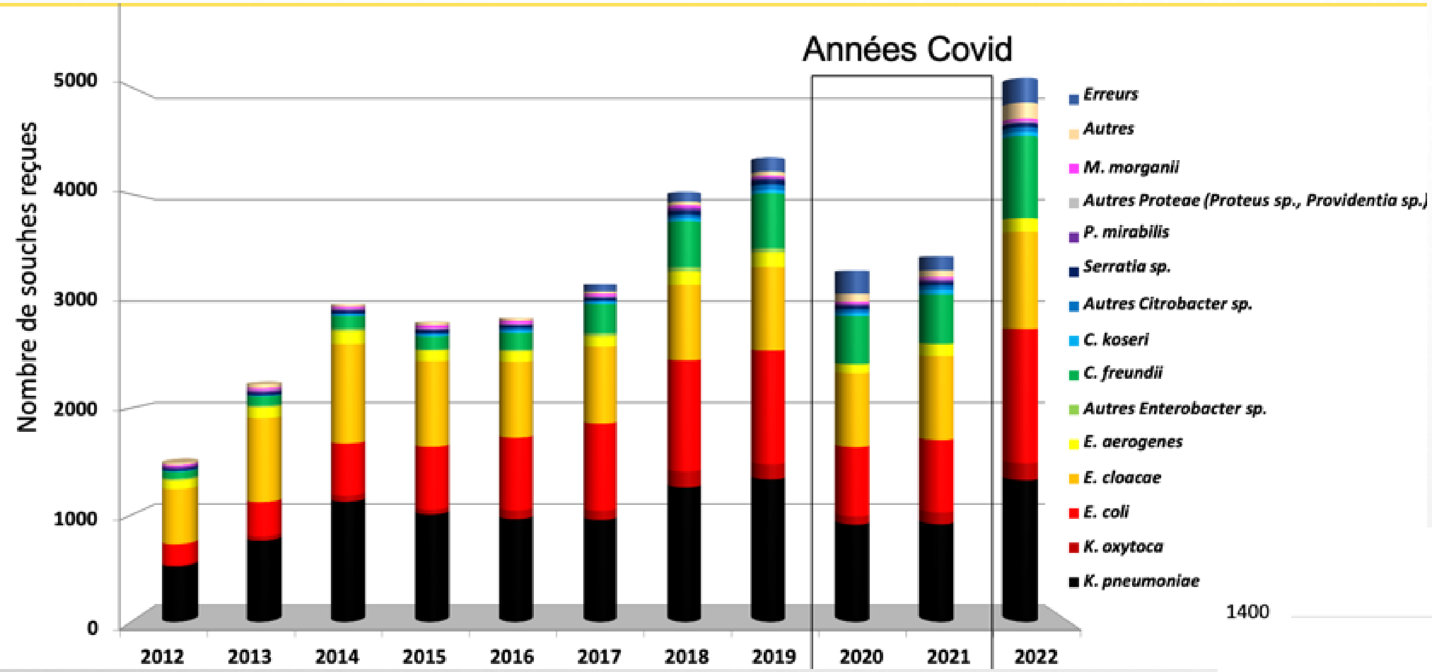
Important pour le traitement, **MAIS pas de** dissémination épidémique,
=> coût en terme de fitness des mutations chromosomiques

2) Carbapénèmases (Entérobactéries productrices de Carbapénèmases)

- Hautement épidémique => clones à hauts risques
- Plasmidique
- Difficile à détecter (PAS toujours BMR ou résistante aux carbapénèmes)



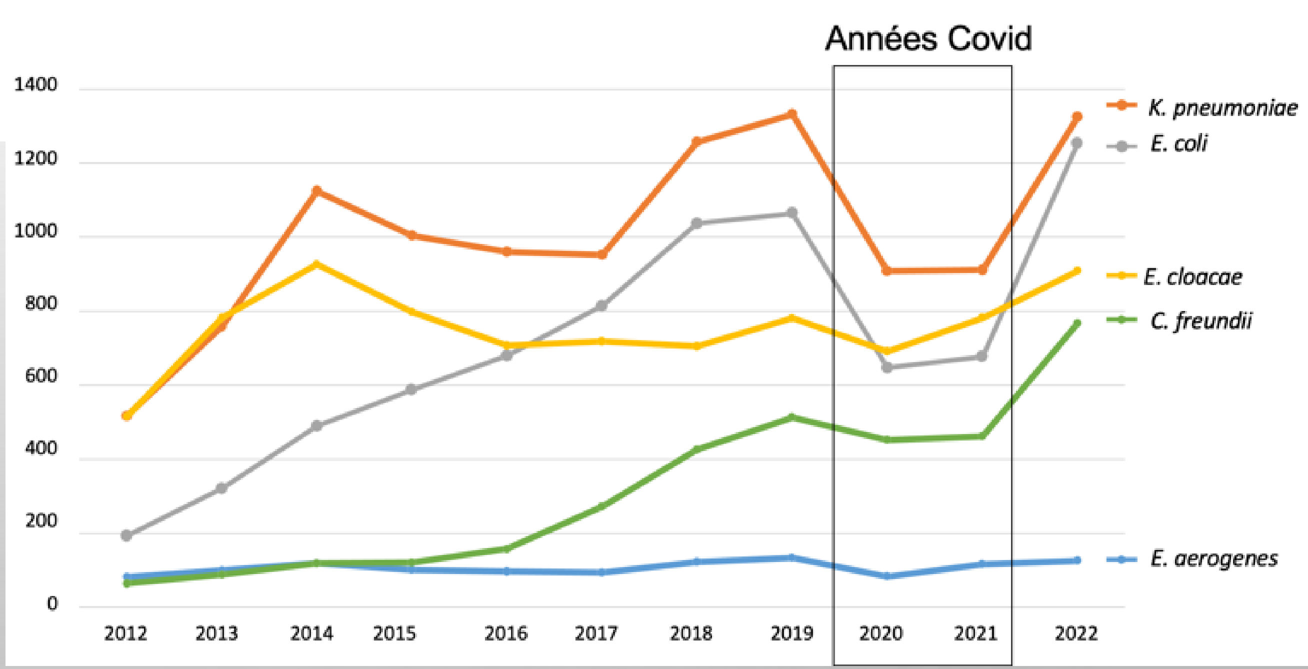
NOMBRE DE SOUCHES ADRESSÉES AU CNR PAR ANNÉE ET PAR ESPÈCES



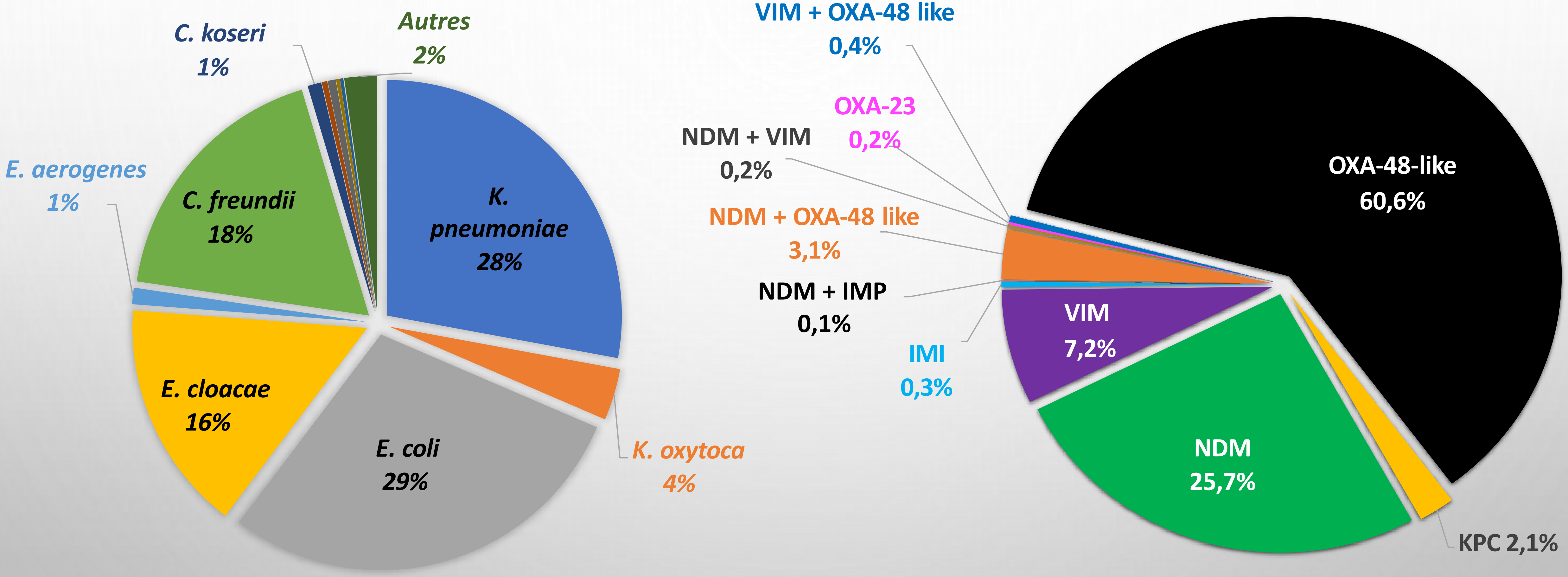
Evolution des principales espèces reçues/ année

Bonne nouvelle:
Positivité de 81%, grâce aux LFIA

Mauvaise nouvelle:
Augmentation de *E. coli*

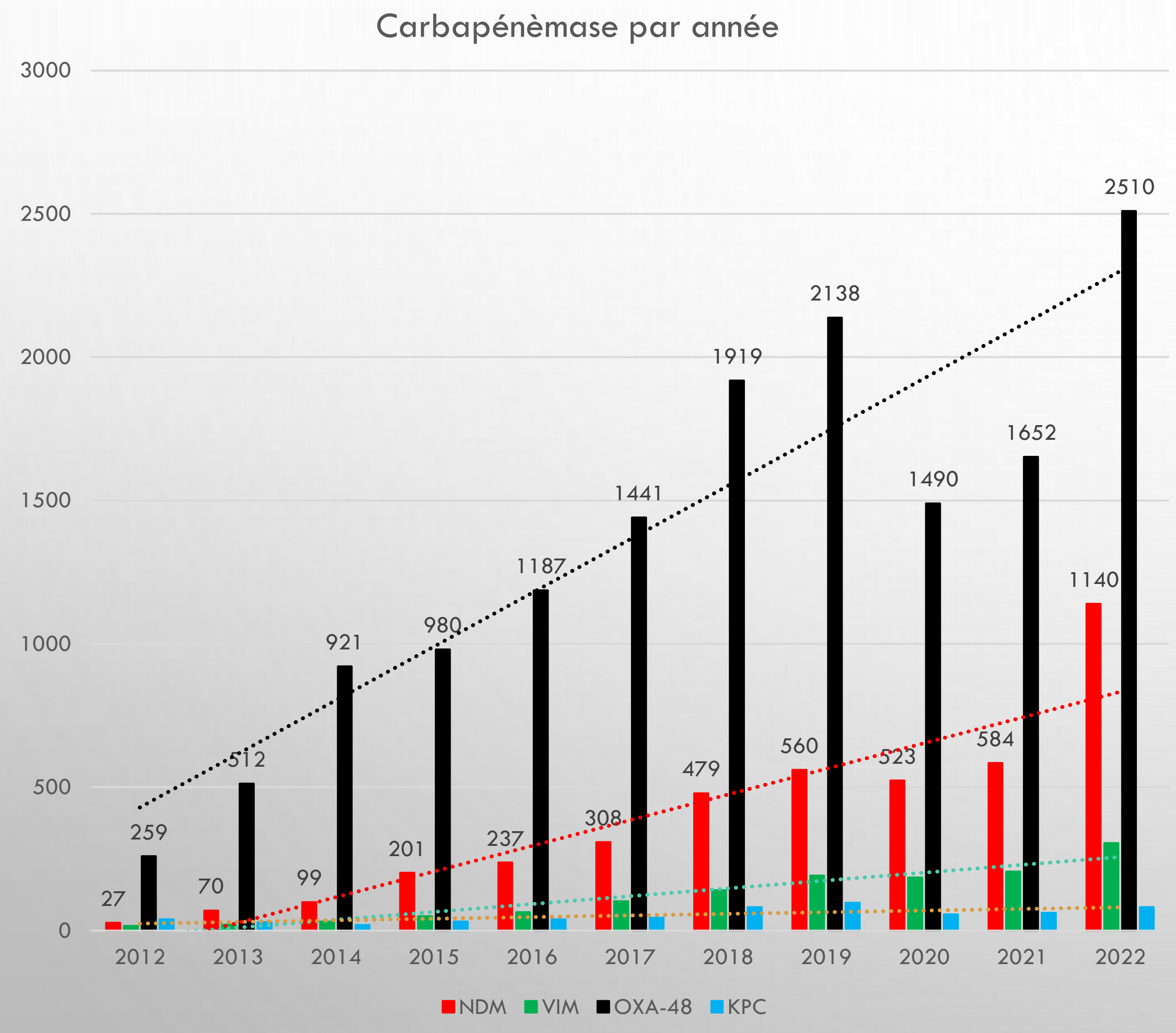


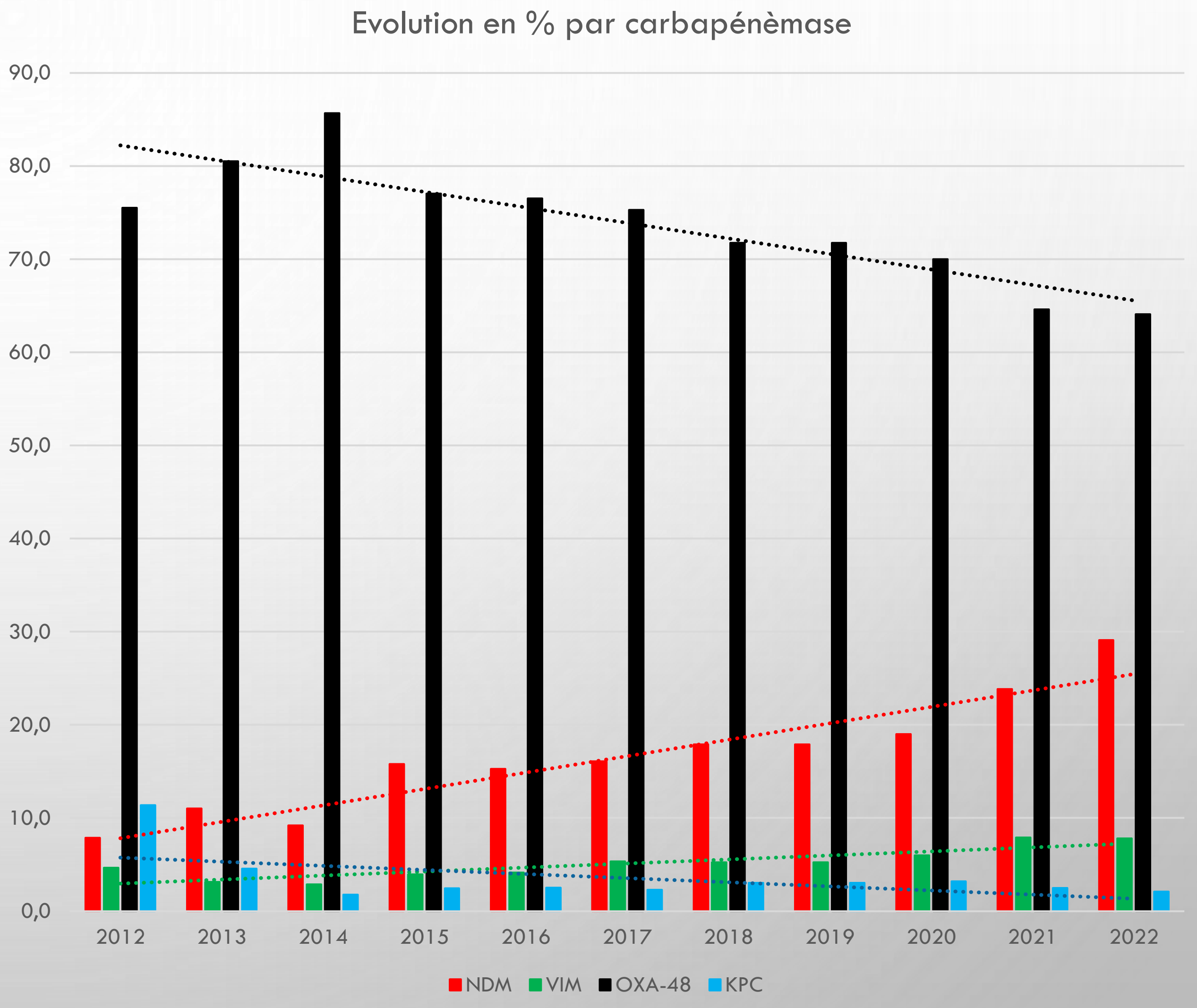
DISTRIBUTION DES SOUCHES REÇUES EN 2022 PAR ESPÈCES ET PAR CARBAPÉNÈMASE



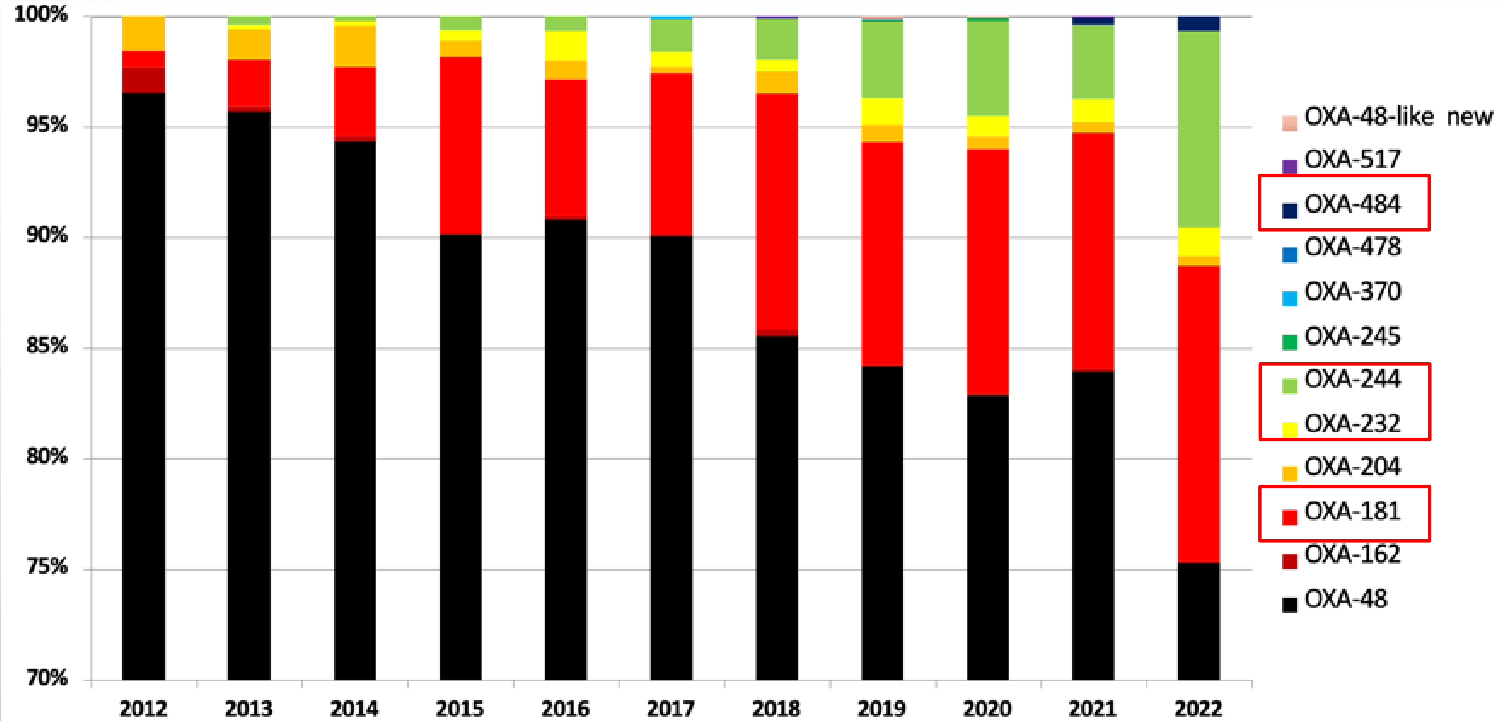
36,7% de MBLs

EVOLUTION DE L'ÉPIDÉMIOLOGIE DES EPC (FRANCE 2012–2022)



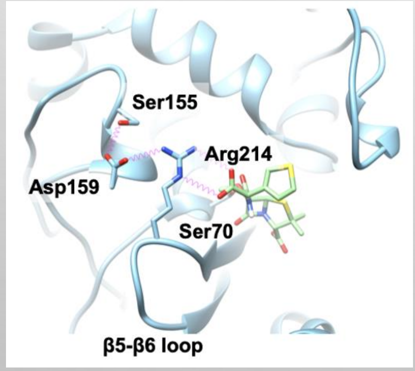


DIVERSIFICATION DES OXA-48-LIKE



OXA-484	**95% *E. coli* (ST410++)**
OXA-244 (n=210)	**97,6% *E. coli* (ST38++)**
OXA-232 (n=25)	***K. pneumoniae***
OXA-181 (n=316)	**39,8% *E. coli* (ST410>ST940)** **26,6% *K. pneumoniae* (ST11)** **21,9% *C. freundii***

R214G, OXA-244
R214S, OXA-232



AMERICAN SOCIETY FOR MICROBIOLOGY Antimicrobial Agents and Chemotherapy®

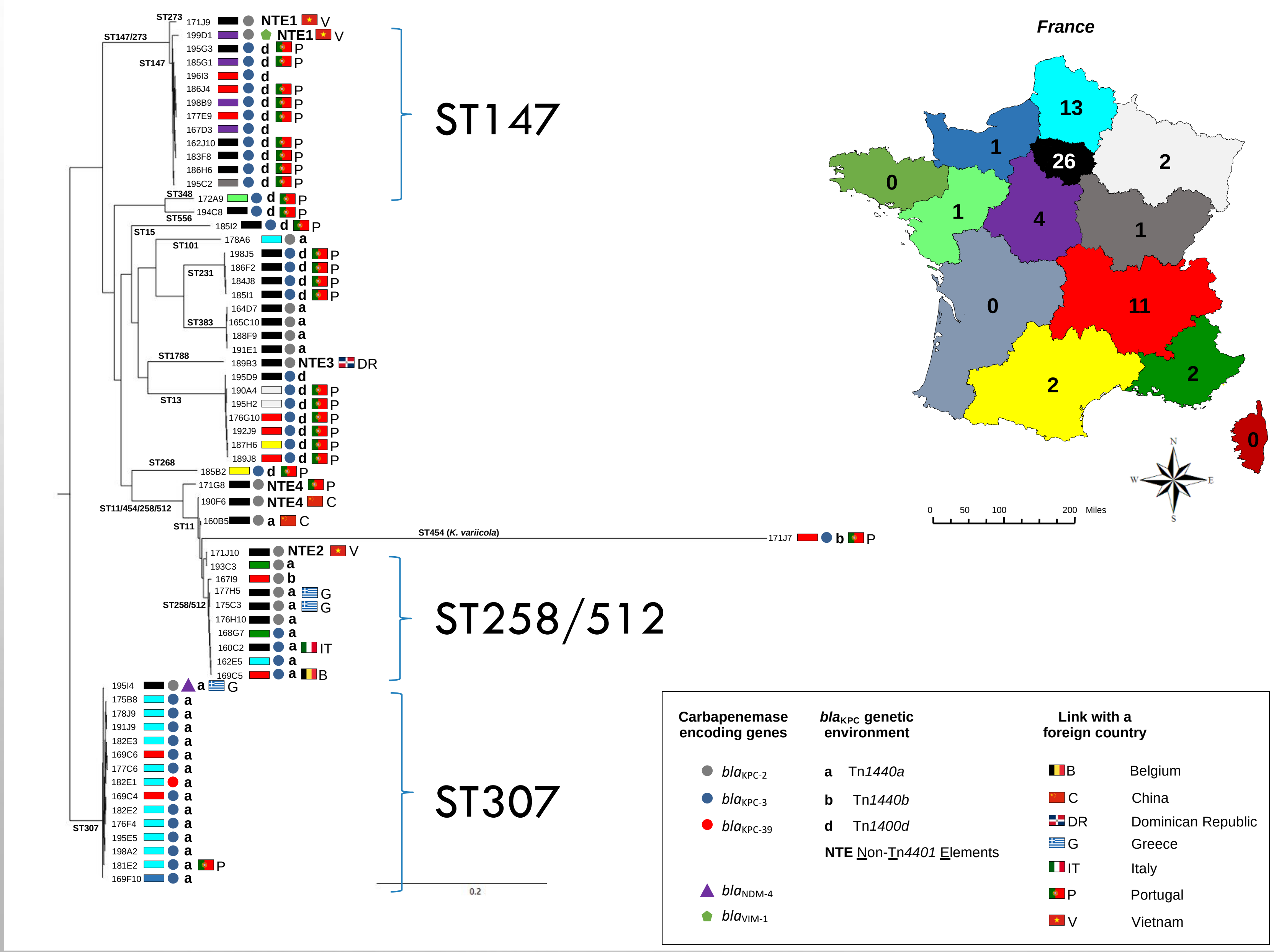
July 2017

OXA-244-Producing *Escherichia coli* Isolates, a Challenge for Clinical Microbiology Laboratories

Yannick Hoyos-Mallecot, Thierry Naas, Rémy A. Bonnin, Rafael Patino, Philippe Glaser, Nicolas Fortineau, Laurent Dortet

	ChromID Carba Smart	Carba NP	Maldi-Tof MS	Xpert Carba-R
% of detection	14,3%	57,1%	71,4%	100%

K. pneumoniae KPC (2018)



RESEARCH

Emergence of New Non–Clonal Group 258 High-Risk Clones among *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae* Isolates, France

Rémy A. Bonnin, Agnès B. Jousset, Adriana Chiarelli, Cécile Emeraud, Philippe Glaser, Thierry Naas, Laurent Dortet

Emerging Infectious Diseases
www.cdc.gov/eid • Vol. 26, No. 6, June 2020

ST307 et ST147:
=> clones à haut risque

RÉSISTANCE À L'ASSOCIATION CEFTAZIDIME/AVIBACTAM

KPC-39-Mediated Resistance to Ceftazidime-Avibactam in a *Klebsiella pneumoniae* ST307 Clinical Isolate AAC, 2021, 65: e01160-21

Agnès B. Jousset,[a,b,c,d] Saoussen Oueslati,[a,c] Cécile Emeraud,[a,b,c,d] Rémy A. Bonnin,[a,b,c] Laurent Dortet,[a,b,c,d] Bogdan I. Iorga,[e] Thierry Naas[a,b,c,d]

Different phenotypic expression of KPC β-lactamase variants and challenges in their detection

Saoussen Oueslati[1], Linda Tlili[1], Cynthia Exilie[1], Sandrine Bernabeu[1,2], Bogdan Iorga[3], Rémy A. Bonnin[1,4], Laurent Dortet[1,2,4] and Thierry Naas[1,2,4]*

J Antimicrob Chemother 2020; 75: 769–771

Unravelling ceftazidime/avibactam resistance of KPC-28, a KPC-2 variant lacking carbapenemase activity

Saoussen Oueslati[1], Bogdan I. Iorga[2], Linda Tlili[1], Cynthia Exilie[1], Agustin Zavala[2], Laurent Dortet[1,3,4], Agnès B. Jousset[1,3,4], Sandrine Bernabeu[1,3], Rémy A. Bonnin[1,4] and Thierry Naas[1,3,4]*

J Antimicrob Chemother 2019; 74: 2239–2246

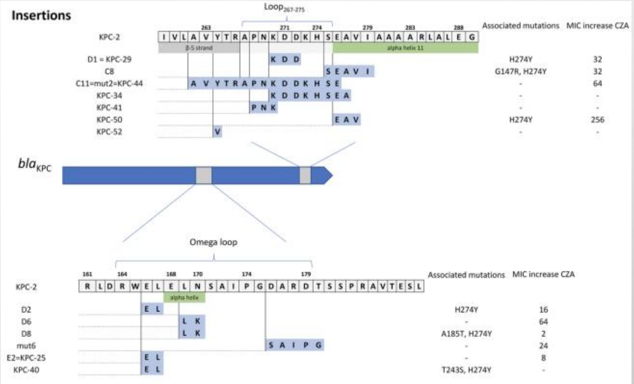
AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

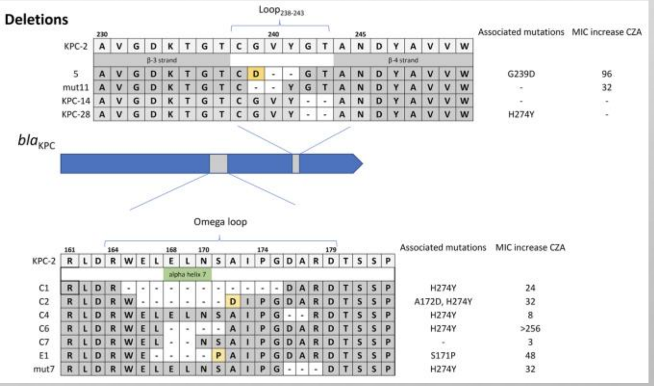
MECHANISMS OF RESISTANCE

KPC Beta-Lactamases Are Permissive to Insertions and Deletions Conferring Substrate Spectrum Modifications and Resistance to Ceftazidime-Avibactam

Claire Amaris Hobson,[a] Stéphane Bonacorsi,[a,b] Hervé Jacquier,[a,c] Alaksh Choudhury,[a] Mélanie Magnan,[a] Aurélie Cointe,[a,b] Béatrice Bercot,[a,c] Olivier Tenaillon,[a] André Birgy[a,b]

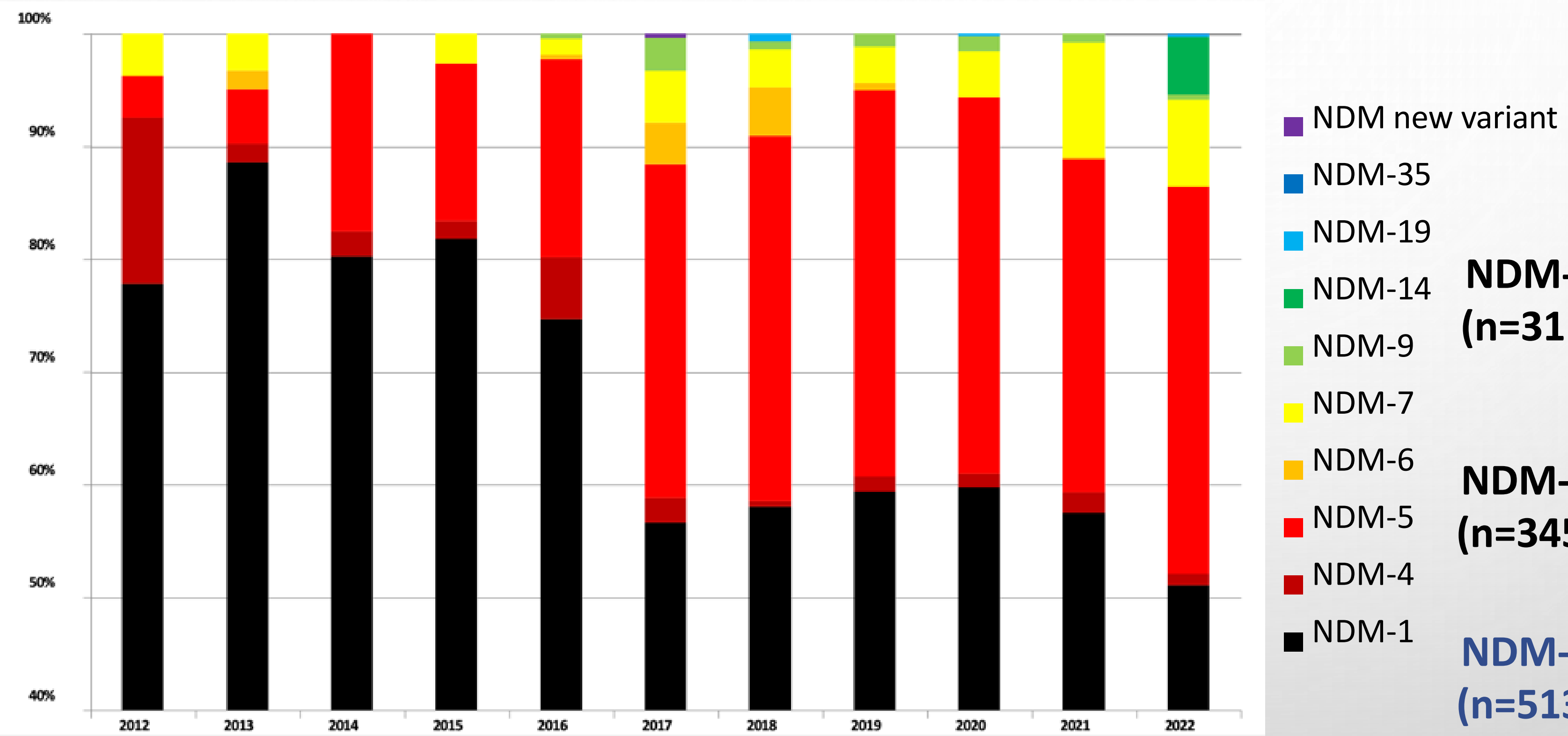
Boucle 267-275





Boucle Oméga
164-179

DIVERSIFICATION DES NDM



NDM-14 ***K. pneumoniae*** **ST-147 (Maroc)**
(n=31 (Juin)

NDM-5 (n=345)
77,3% *E. coli* (ST167, 405, 410, 361)
13,0% *K. pneumoniae*

NDM-1 (n=513)
49,3% *K. pneumoniae* (ST147)
21,8% *E. cloacae*
12,7% *C. freundii*
9,7% *E. coli*

BETA-LACTAMASE DATABASE (BLDB)

http://www.bldb.eu/

Naas T, et al. Beta-lactamase database (BLDB) – structure and function *J Enz Inh Med Chem* 2017;32:917–9

Beta-Lactamase DataBase - Structure and Function

Home | Enzymes | Structures | Mutants | Kinetics | BLAST

Class A | Sub-class B1 | Sub-class B2 | Sub-class B3 | Class C | Class D

Sub-class B1		Sub-class B2		Sub-class B3	
AFM	ANA	CphA	CVI	AIM	ALG6
BcII	BIM	PFM	SFH	ALG11	AM1
BlaB	CAM	YEM		BJP	BLEG
CfiA	CGB			CAR	CAU
CEMC19	CrxA			CHI	CPS
CX1	DIM			CRD3	CSR
EBR	ECV			DHT2	EAM
ElBla2	FIA			ECM	EFM
FIM	GIM			ELM	ESP
GMB	GRD23			EVM	FEZ
HBA	HMB			GOB	L1
IMP	IND			LMB	LRA2
JOHN	KHM			LRA3	LRA7
MOC	MUS			LRA8	LRA12
MYO	MYX			LRA17	LRA19
NDM	ORR			MEMA1	MIM
PAN	PEDO			MSI	NWM
PKB	PST			PAM	PEDO
SFB	SHD			PJM	PLN
SHN	SIM			POM	PNGM
SLB	SPM			RM3	SAM
SPN79	SPS			SER	SIE
STA	SZM			SIQ	SMB
TTU	TMB			SPG	SPR
TUS	VAM			SSE	B3SU1
VIM	VMB			B3SU2	THIN
VMH	WUS				
ZHO	ZOG				

2023

Class	# ß-lactamase	depuis 2016
A	1938	X 1.5
B1	**605**	X 2.7
B2	**24**	X 1.3
B3	**309**	X 3.8
C	3808	X 5.8
D	1273	X 2.1
Total	**7949**	**X 2.8**

B1 Acquises Entérobactéries

IMP (102)

NDM (61)

VIM (86)

GIM (3) Allemagne, Japon

KHM (1) Japon

TMB (2) France, Magreb (pyo et ab)

P. aeruginosa

AFM (4) Chine

BIM (1) Brésil

CAM (1) Canada,

DIM (1) Europe

FIM (1) Italie Pyo

HMB (1) Allemagne

SPM (1) Brésil

A. baumannii

SIM (2) Corée, Japon

Vibrio alginolyticus

VMB (2) Chine

B3 Acquises Entérobactéries

LMB-1 Autriche, Argentine

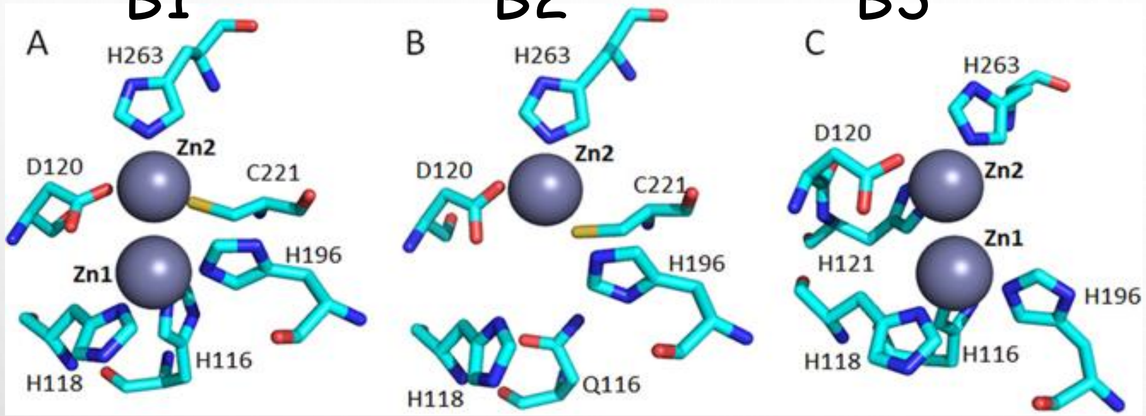
SMB (1) Japon

P. aeruginosa

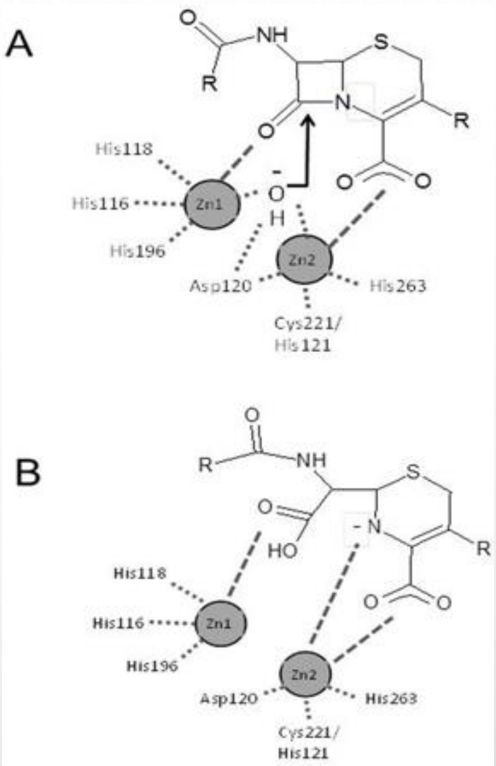
AIM (2)

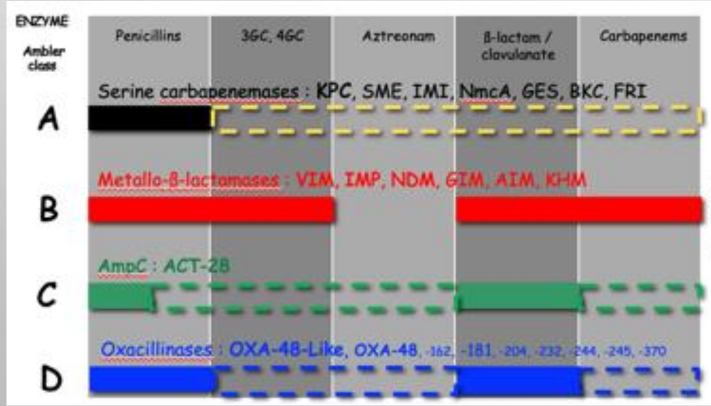
Mécanisme d'action : MBLs

B1 B2 B3

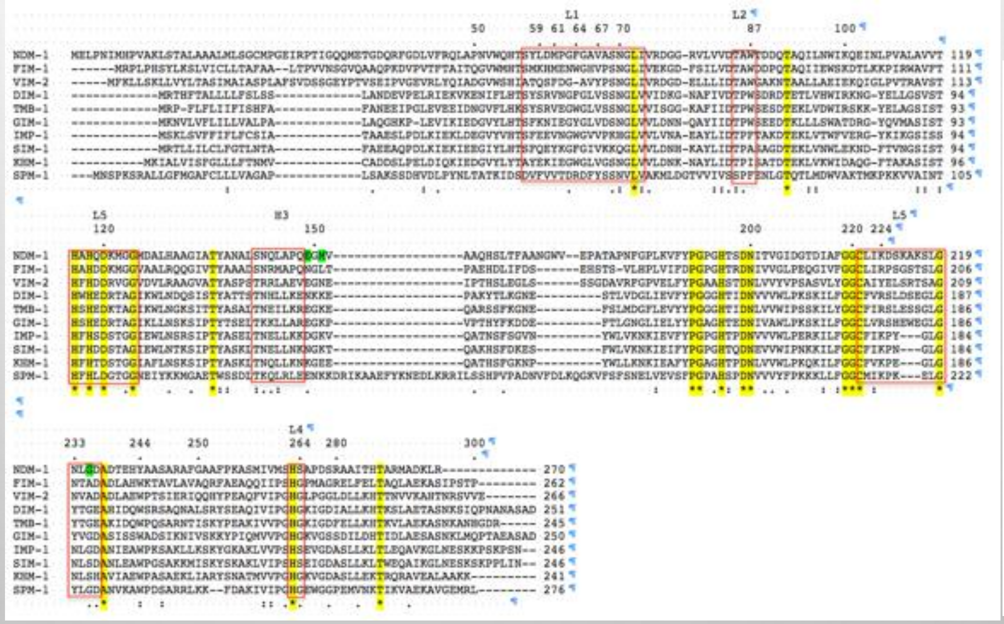


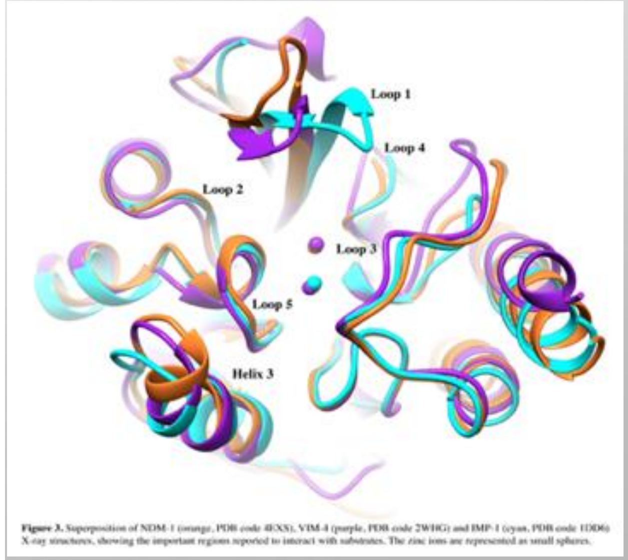
- A divalent transition metal ion, most often zinc, linked to a histidine or cysteine residue or both, reacts with the carbonyl group of the amide bond.





B1 et B3
B2 carbapénème uniquement





Colistin ?

Cefiderocol ?

(isolats 2018-2019)

antibiotics MDPI

Article

In vitro activity of cefiderocol and comparators against Carbapenem-resistant Gram-negative pathogens from France and Belgium

Saoussen Oueslati,[1,2,3] Pierre Bogaerts,[4] Laurent Dortet,[1,2,3] Sandrine Bernabeu,[1,2] Hend Ben Lakhal,[5] Chris Longshaw[6],

Mechanism	# of isolates	No. isolates per MIC (µg/ml) ≤0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	>64	% Susceptibility at breakpoint of 2 µg/ml	4 µg/ml
Enterobacterales	222	6	5	13	18	31	67	39	27	5	5	1	2	3	81	93
Non CPE	67	2	1	2	10	10	17	15	8	0	0	1	1	0	85	97
KPC	24	0	0	1	0	5	11	5	1	1	0	0	0	0	92	96
other class A GES,IMI,SME,fri…	9	0	0	2	1	2	2	0	1	1	0	0	0	0	78	89
MBLs	54	1	1	3	3	3	15	11	11	1	3	1	0	1	69	89
NDM	21	0	0	0	0	2	4	4	7	1	2	0	0	1	48	81
VIM	17	0	0	0	1	0	6	6	2	0	1	1	0	0	76	88
IMP	13	1	1	3	2	0	4	0	2	0	0	0	0	0	85	100
other Mbls (LMB, GIM, TMB)	3	0	0	0	0	1	1	1	0	0	0	0	0	0	100	100
OXA-48	51	3	2	5	4	11	16	5	3	2	0	0	0	0	90	96
Multi-Carbas	17	0	1	0	0	0	6	3	3	0	1	0	1	2	59	76

81% S

MBL 69 % S

NDM 48 % S

Species	Resistance mechanism (# of isolates)	Antimicrobial agent	MIC (µg/ml) Range	MIC50	MIC90	S/I/R S (%)	I (%)	R (%)
Enterobacterales								
	Total (222)	Cefiderocol	≤0.03->64	1	4	**81**	/	19
		Ceftolozane-tazobactam	≤0.03->64	64	>64	19	/	81
		Cefepime	≤0.5->16	>16	>16	14	10	76
		Ceftazidime	0.12->64	>64	>64	9	8	83
		Ceftazidime-avibactam	0.06->64	4	>64	63	/	37
		Aztreonam	≤0.5->32	>32	>32	14	4	82
		Meropenem	0.06->64	8	>64	36	20	44
		Amikacin	≤4->64	≤4	>64	70	/	30
		Ciprofloxacin	≤0.25->4	>4	>4	30	5	65
		Colistin	≤0.5->8	≤0.5	>8	84	/	16
		Tigecycline	≤0.25->4	≤0.25	2	73	/	27

Frozen BMD, IHMA

84 % S

Aztreonam/ceftazdime-avibactam

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SUSCEPTIBILITY

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Aztreonam plus Clavulanate, Tazobactam, or Avibactam for Treatment of Infections Caused by Metallo-β-Lactamase-Producing Gram-Negative Bacteria

Cécile Emeraud,[a,b,c,d] Lelia Escaut,[e] Athénaïs Boucly,[d,f,g] Nicolas Fortineau,[a,b,c] Rémy A. Bonnin,[b,c,d] Thierry Naas,[a,b,c,d] Laurent Dortet[a,b,c,d]

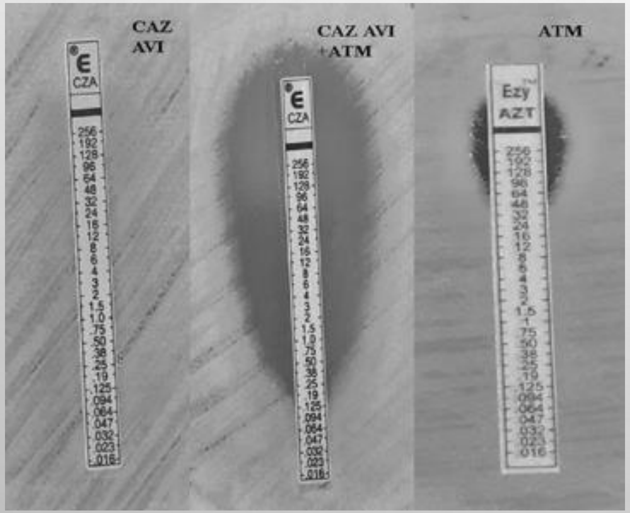


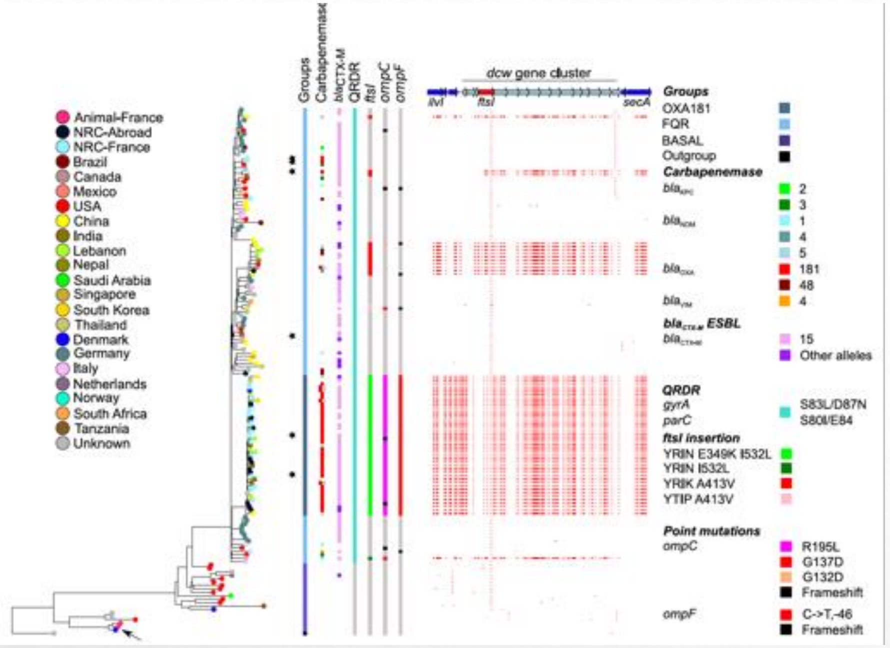
TABLE 2 MICs and categorization according to CLSI breakpoints for antimicrobials on MBL-producing *Enterobacteriaceae*, MBL-producing *P. aeruginosa*, and *S. maltophilia*

		MICs (mg/liter) by treatment[a]						
Enterobacteriaceae sp.	β-Lactamases	ATM	CZA	C/T	AMC	ATM+ CZA	ATM+ C/T	ATM+ AMC
E. coli	NDM-1 + OXA-1 + OXA-10 + CMY-16 + TEM-1	32	>256	>256	16	0.125	24	8
E. coli	NDM-1 + CTX-M-15 + TEM-1	>256	>256	>256	12	1	>256	2
E. coli	NDM-1 + OXA-1 + OXA-2 + CTX-M-15 + TEM-1	>256	>256	>256	24	2	>256	8
E. coli	NDM-1 + CTX-M-15 + TEM-1	>256	>256	>256	32	6	>256	8
E. coli	NDM-4 + CTX-M-15 + OXA-1	>256	>256	>256	96	6	>256	4
E. coli	NDM-4 + CTX-M-15 + CMY-6	>256	>256	>256	>256	6	>256	24
E. coli	NDM-5 + TEM-1 + CTX-M-15	>256	>256	>256	96	8	>256	64
E. coli	NDM-6 + CTX-M-15 + OXA-1	>256	>256	>256	16	1	>256	2
E. coli	NDM-7 + ESBL	>256	>256	>256	96	4	>256	32
K. pneumoniae	NDM-1 + CTX-M-15 + SHV-11 + OXA-1	>256	>256	>256	12	0.125	24	0.38
K. pneumoniae	NDM-1 + CTX-M-15 + CMY-4 + OXA-1	>256	>256	>256	32	0.75	>256	16
K. pneumoniae	NDM-1 + CTX-M-15 + OXA-1 + OXA-9 + TEM-1 + SHV-28 + SHV-11	>256	>256	>256	32	0.25	>256	3
K. pneumoniae	NDM-1 + OXA-1 + SHV-11	>256	>256	>256	12	0.047	0.094	0.094
K. pneumoniae	NDM-1 + OXA-1 + CTX-M-15 + TEM-1 + SHV-28 + OXA-9 + CMY-6	>256	>256	>256	16	0.047	3	0.25
K. pneumoniae	NDM-1 + TEM-1 + CTX-M-15 + SHV-12 + OXA-9	>256	>256	>256	12	0.125	96	1
K. pneumoniae	NDM-1 + TEM-1 + CTX-M-15 + SHV-12 + OXA-9	>256	>256	>256	12	0.125	96	0.5
K. pneumoniae	NDM-1 + TEM-1 + CTX-M-15 + SHV-11 + OXA-1	>256	>256	>256	12	0.064	8	0.38
Salmonella enterica	NDM-1 + CTX-M-15 + TEM-1 + OXA-1 + OXA-9 + OXA-10	>256	>256	>256	16	0.125	16	0.5
E. coli	VIM-1 + CTX-M-3	>256	>256	>256	16	0.125	24	0.5
E. coli	VIM-4 + ESBL	16	>256	>256	24	1.5	24	16
K. pneumoniae	VIM-1 + SHV-5	>256	>256	>256	>256	0.25	192	1.5
K. pneumoniae	VIM-1 + SHV-12	>256	>256	>256	16	0.125	4	0.25
K. pneumoniae	VIM-1 + ESBL	>256	>256	>256	>256	12	16	12
K. pneumoniae	VIM-1 + SHV-5	16	>256	>256	>256	6	12	32
K. pneumoniae	VIM-1 + TEM-1 + SHV-5	96	>256	>256	>256	96	64	48
K. pneumoniae	VIM-1 + SHV-5	>256	>256	>256	24	0.25	8	0.75
K. pneumoniae	VIM-1 + SHV-5	>256	>256	>256	12	0.125	2	0.38
K. pneumoniae	VIM-19 + CTX-M-3 + TEM-1 + SHV-1	6	32	>256	16	0.047	2	1.5
Enterobacter cloacae	VIM-1 + SHV-70	256	128	>256	48	0.094	0.25	0.19
E. cloacae	VIM-4 + CTX-M-15 + TEM-1 + SHV-31	64	>256	>256	64	1	64	32
Citrobacter freundii	VIM-2 + TEM-1 + ESBL	16	16	>256	32	0.25	2	24
C. freundii	VIM-2 + TEM-1 + OXA-9 + OXA-10	32	24	>256	32	1.5	16	24
E. coli	IMP-8 + SHV-12	128	>256	>256	24	0.19	2	0.38
K. pneumoniae	IMP-8 + SHV-12	>256	48	>256	12	0.094	32	0.25
E. cloacae	IMP-8 + SHV-12	12	>256	>256	24	0.032	0.064	0.094
E. cloacae	GIM-1 + ESBL	12	>256	48	24	0.5	8	16
Enterobacter hormaechei	TMB-1 + overexpressed Case[b]	64	64	32	32	0.5	12	12
C. freundii	TMB-1 + overexpressed Case	64	96	32	12	0.125	12	12
K. pneumoniae	NDM-1 + OXA-181 + SHV-11 + TEM-1 + CTX-M-15 + OXA-1	64	>256	>256	48	0.094	8	2
K. pneumoniae	NDM-1 + OXA-181 + SHV-27 + CTX-M-15 + TEM-1 + OXA-1	128	>256	>256	96	0.25	16	3
K. pneumoniae	NDM-1 + OXA-181 + SHV-11 + CTX-M-15 + OXA-1	256	>256	>256	>256	0.19	32	3
K. pneumoniae	NDM-1 + OXA-181 + SHV-11 + TEM-1 + CTX-M-15 + OXA-9	>256	>256	>256	>256	0.19	>256	12
K. pneumoniae	NDM-1 + OXA-181 + SHV-2 + CTX-M-15 + OXA-1	>256	>256	>256	32	0.125	32	1.5
C. freundii	NDM-1 + OXA-181 + OXA-1 + OXA-9 + OXA-10 + CTX-M-15 + TEM-1	>256	>256	>256	64	0.75	>256	12
E. coli	NDM-1 + OXA-48 + ESBL	32	>256	>256	48	0.094	12	8
E. coli	NDM-1 + OXA-48 + ESBL	>256	>256	>256	>256	0.75	>256	4
E. coli	NDM-1 + OXA-48 + ESBL	>256	>256	>256	>256	1	>256	4
K. pneumoniae	NDM-1 + OXA-232 + ESBL	64	>256	>256	>256	0.094	24	3
E. coli	NDM-1 + OXA-232 + ESBL	>256	>256	>256	>256	1	>256	8
E. coli	NDM-5 + OXA-232 + ESBL	>256	>256	>256	96	1	>256	64
S. maltophilia		>256	>256	>256	32	2	128	2
S. maltophilia		>256	>256	6	96	1.5	6	2
S. maltophilia		>256	>256	>256	>256	4	>256	4
S. maltophilia		>256	16	72	16	1	8	2
S. maltophilia		>256	>256	>256	>256	0.75	24	0.75
P. aeruginosa	VIM-2 + overexpressed cephalosporinase	16	24	>256	>256	8	12	16
P. aeruginosa	IMP-2 + overexpressed cephalosporinase	12	>256	>256	>256	6	12	24
P. aeruginosa	IMP-1 + overexpressed cephalosporinase	128	>256	>256	>256	96	48	64

[a]Black, gray, and white colored MICs correspond to resistant, intermediate, and susceptible categorization, respectively, according to CLSI breakpoints, as updated in 2018. *Pseudomonas* sp. breakpoints were used for *Stenotrophomonas maltophilia*. ATM, aztreonam; CZA, ceftazidime-avibactam; C/T, ceftolozane-tazobactam; AMC, amoxicillin-clavulanate.

[b]Case, chromosome-encoded cephalosporinase.

E. coli ST410



Patiño-Navarrete *et al. Genome Medicine* (2020) 12:10
https://doi.org/10.1186/s13073-019-0699-6

Genome Medicine

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Stepwise evolution and convergent recombination underlie the global dissemination of carbapenemase-producing *Escherichia coli*

Rafael Patiño-Navarrete[1,2], Isabelle Rosinski-Chupin[1,2†], Nicolas Cabanel[1,2], Lauraine Gauthier[1,3,4,5], Julie Takissian[1,5], Jean-Yves Madec[6], Monzer Hamze[7], Remy A. Bonnin[1,4,5], Thierry Naas[1,3,4,5†] and Philippe Glaser[1,2*†]

a

```
CTCAATACCATTCCT------------CGAATTAACGGCCACGAA
L  N  T  I  P              Y  R  I  N  G  H
L  N  T  I  P  Y  T  I  P  Y  R  I  N  G  H  A413V
L  N  T  I  P  Y  R  I  P  Y  R  I  N  G  H  A413V
L  N  T  I  P  Y  R  I  N  Y  R  I  N  G  H  E349K+I532L
L  N  T  I  P  Y  R  I  K  Y  R  I  N  G  H  A413V
       333
```

FtsI – PBP3

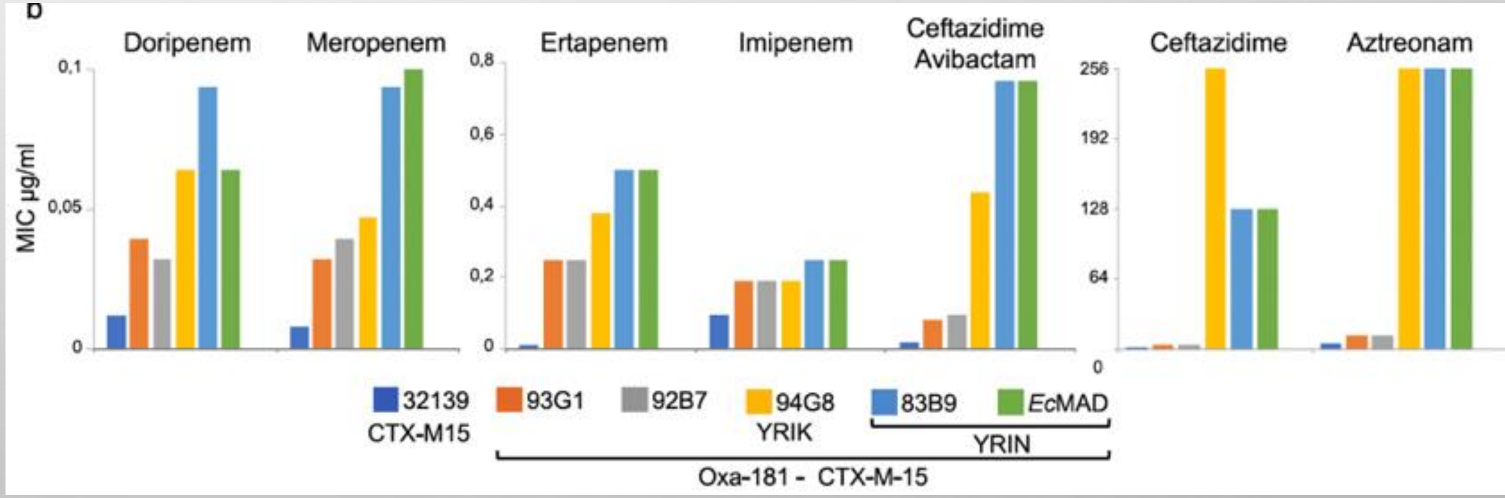
b

	Control	YRIN	E349K	I532L	YRIN E349K	E349K I532L	YRIN E349K I532L
ATM	0.032	0.19	0.032	0.047	0.125	0.38	0.5
AMX	5	2	5	10	16	32	28
PIP	1	1.5	1	1.5	4	7	14
CTX	0.023	0.094	0.032	0.064	0.19	0.38	0.75
MER	0.012	0.012	0.008	0.014	0.008	0.016	0.014
ERT	0.002	0.004	0.004	0.004	0.005	0.008	0.008
IMI	0.19	0.19	0.19	0.19	0.125	0.19	0.19
CHL	4	4	4	4	4	4	4

2 4 8 16 32

c

d



E. coli ST410 et ST167

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RESEARCH ARTICLE

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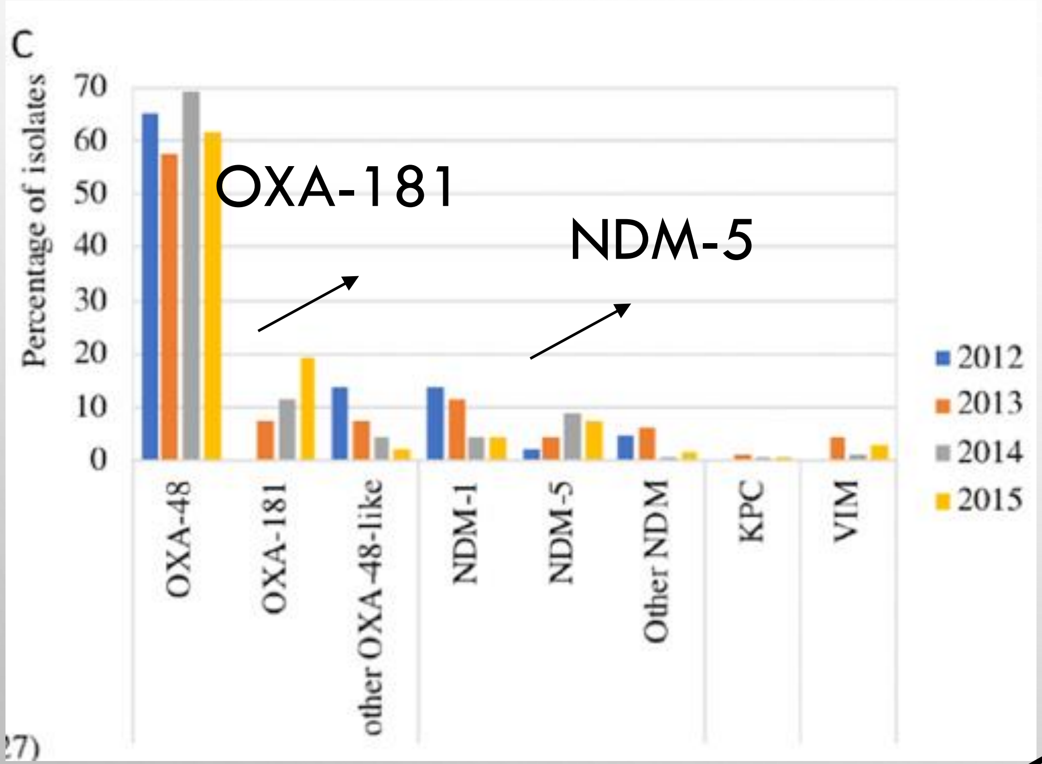
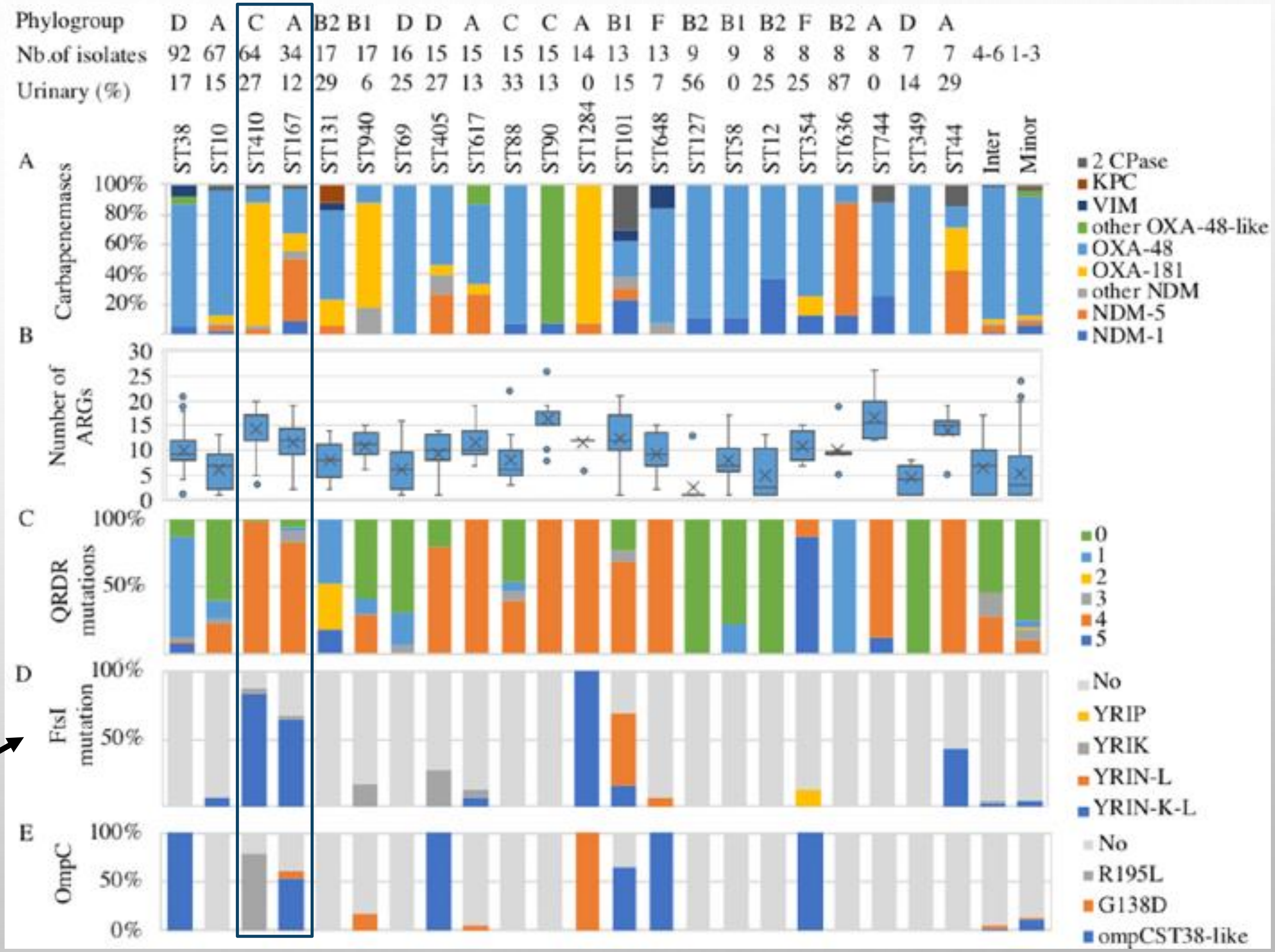
Specificities and Commonalities of Carbapenemase-Producing *Escherichia coli* Isolated in France from 2012 to 2015

Rafael Patiño-Navarrete,[a,b] Isabelle Rosinski-Chupin,[a,b] Nicolas Cabanel,[a,b] Pengdbamba Dieudonné Zongo,[a,b,c] Mélanie Héry,[a,d] Saoussen Oueslati,[a,d] Delphine Girlich,[a,d] Laurent Dortet,[a,d,e,f] Rémy A. Bonnin,[a,d,f] Thierry Naas,[a,d,e,f] Philippe Glaser[a,b]

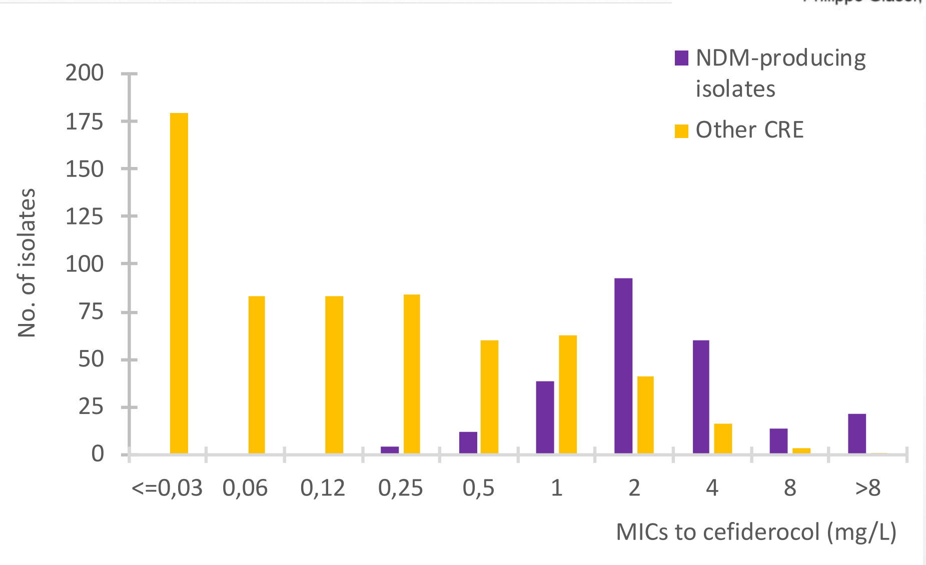


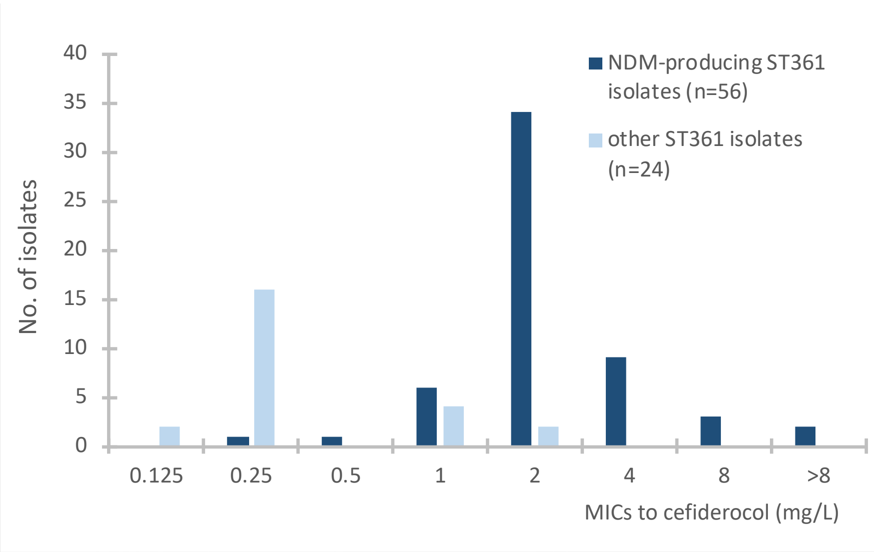


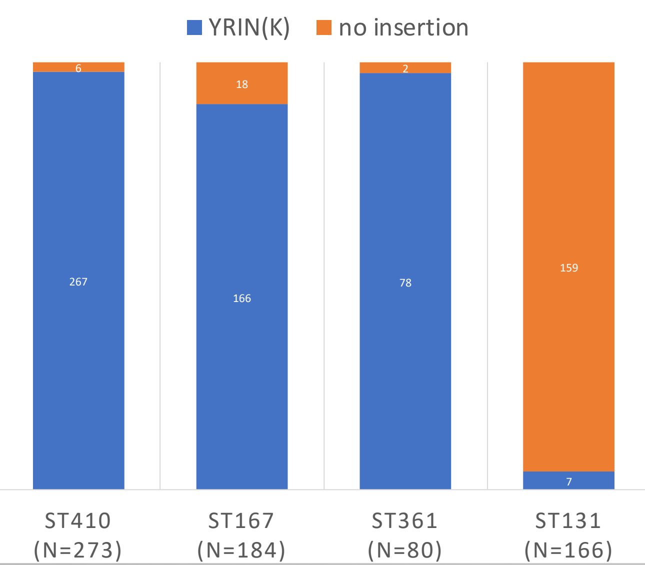
Population Analysis of *Escherichia coli* Sequence Type 361 and Reduced Cefiderocol Susceptibility, France

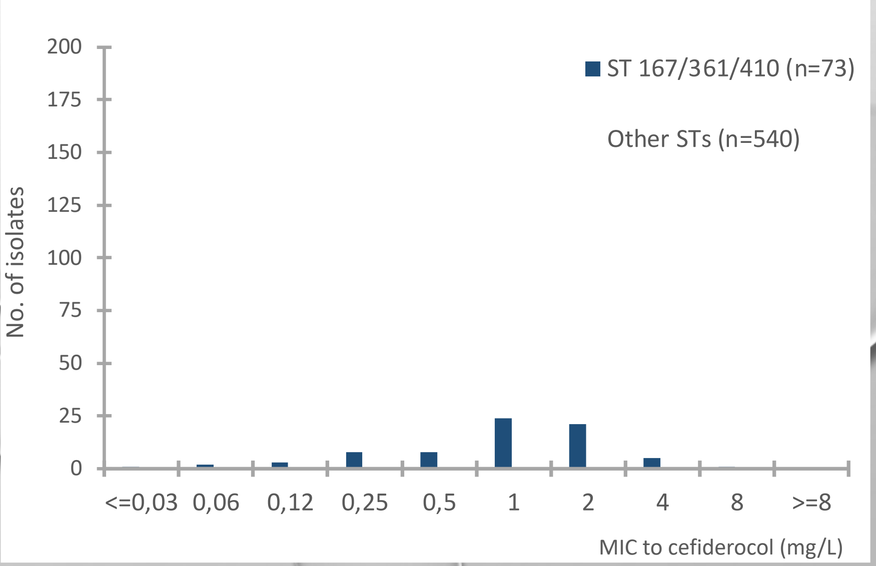
Agnès B. Jousset, Laura Bouabdallah, Aurélien Birer, Isabelle Rosinski-Chupin, Jean-François Mariet, Saoussen Oueslati, Cécile Emeraud, Delphine Girlich, Philippe Glaser, Thierry Naas, Rémy A. Bonnin, Laurent Dortet

EID, 2023









International Journal of Antimicrobial Agents 61 (2023) 106776

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journal homepage: www.elsevier.com/locate/ijantimicag

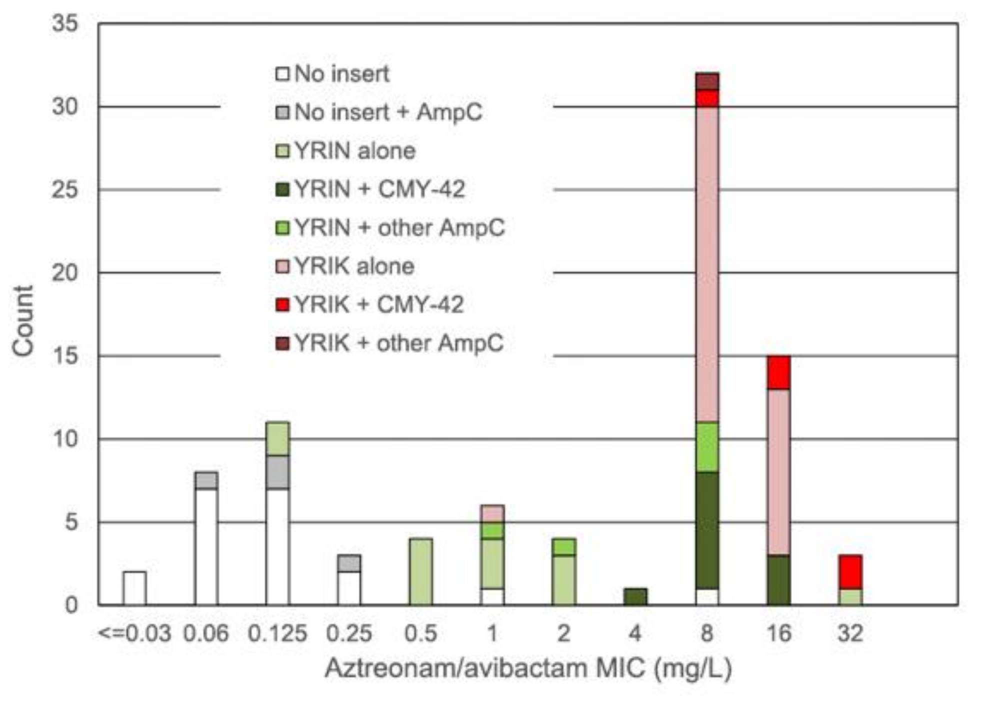
Activity of aztreonam/avibactam against metallo-*β*-lactamase-producing Enterobacterales from the UK: Impact of penicillin-binding protein-3 inserts and CMY-42 *β*-lactamase in *Escherichia coli*

David M. Livermore[a,*], Shazad Mushtaq[b], Anna Vickers[b], Neil Woodford[b]

Table 1
Susceptibility and resistance in the test panel.

Agents and EUCAST 2022 breakpoints	*Escherichia coli* NDM (*n*=122)		*Klebsiella* spp. NDM (*n*=121)		*Klebsiella* spp. IMP/VIM (*n*=70)		*Enterobacter* spp. NDM (*n*=91)		*Enterobacter* spp. IMP/VIM (*n*=62)	
	%S	% S+I	%S	% S+I	%S	% S+I	%S	% S+I	%S	% S+I
Aztreonam ≤1/>4	10.7	14.8	16.5	17.4	38.6	38.6	23.1	36.3	24.2	37.1
Aztreonam/avibactam ≤8+4/>8+4	**85.2**	**85.2**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**
Meropenem ≤2/>8	1.6	9.0	3.3	15.7	17.1	51.4	4.4	22.0	24.2	71.0
Ceftazidime ≤1/>4	0.0	0.0	0.0	0.0	0.0	1.4	0.0	0.0	0.0	0.0
Ceftazidime/avibactam ≤8+4/>8+4	1.6	1.6	0.0	0.0	4.3	4.3	0.0	0.0	0.0	0.0
Amikacin ≤8/>8	45.9	45.9	18.2	18.2	**81.4**	**81.4**	56.0	56.0	**85.5**	**85.5**
Ciprofloxacin ≤0.25/>0.5	6.6	9.0	10.7	12.4	14.3	21.4	17.6	23.1	22.6	40.3
Colistin ≤2/>2	**100.0**	**100.0**	**91.7**	**91.7**	**91.4**	**91.4**	**94.5**	**94.5**	**93.5**	**93.5**
Tigecycline ≤0.5/0.5 (*Escherichia coli* only)	93.4	**93.4**	No bpt	No bpt	No bpt	No bpt	No bpt	No bpt	No bpt	No bpt

S, susceptible; I, high-dose susceptible; R, resistant; bpt, breakpoint; EUCAST, European Committee on Antimicrobial Susceptibility Testing
Agents achieving >80% activity are shown in **bold** type.



- YRIK seul, et YRIN plus AmpC acquise (surtout CMY-42) sont associés à des CMIs plus élevés à l'aztreonam/avibactam (8–16 mg/L , versus 0.03–0.25 mg/L pour *E. coli* NDM sans insertion. => valeurs critiques pour aztreonam/avibactam?, Résistance clinique?
- Insertions plus mutations supplémentaires dans *ftsI* (PBP3), => CMIs 128 mg/L au cefiderocol et 256 mg/L au cefepime/taniborbactam, deux autres anti-MBLs.

Mutant selection
In vivo / in vitro

J Antimicrob Chemother 2023; **78**: 1125–1127
https://doi.org/10.1093/jac/dkad004
Advance Access publication 2 March 2023

Rapid selection of a cefiderocol-resistant *Escherichia coli* producing NDM-5 associated with a single amino acid substitution in the CirA siderophore receptor

Agnès B. Jousset[1,2,3], Corentin Poignon[1], Seher Yilmaz[4], Alexandre Bleibtreu [5,6], Cécile Emeraud[1,2,3], Delphine Girlich[1], Thierry Naas [1,2,3], Jérôme Robert[4,5], Rémy A. Bonnin [1,2] and Laurent Dortet [1,2,3]*

J Antimicrob Chemother 2022; **77**: 98–111
doi:10.1093/jac/dkab346 Advance Access publication 26 September 2021

Journal of Antimicrobial Chemotherapy

Selection and characterization of mutational resistance to aztreonam/avibactam in β-lactamase-producing Enterobacterales

Shazad Mushtaq[1], Anna Vickers[1], Nicholas Ellaby[1], Neil Woodford[1] and David M. Livermore[2]*

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Received 3 April 2021; accepted 23 August 2021

Background: Aztreonam/avibactam is being developed for its broad activity against carbapenemase-producing Enterobacterales, including those with metallo-β-lactamases (MBLs). Its potential to select resistance in target pathogens was explored. Findings are compared with previous data for ceftazidime/avibactam and ceftaroline/avibactam.

Methods: Single-step mutants were sought from 52 Enterobacterales with AmpC, ESBL, KPC, MBL and OXA-48-like enzymes. Mutation frequencies were calculated. MICs were determined by CLSI agar dilution. Genomes were sequenced using Illumina methodology.

Results: Irrespective of β-lactamase type and of whether avibactam was used at 1 or 4 mg/L, mutants could rarely be obtained at >4× the starting MIC, and most MIC rises were correspondingly small. Putative resistance (MIC >8 + 4 mg/L) associated with changes to β-lactamases was seen only for mutants of AmpC, where it was

avibactam, where Asp179Tyr arises readily in KPC enzymes, conferring frank resistance. Asn346 substitutions in AmpC enzymes may remain a risk, having been repeatedly selected with multiple avibactam combinations *in vitro*.

The risk of mutational resistance to aztreonam/avibactam appears smaller than for ceftazidime/avibactam, where Asp179Tyr arises readily in KPC enzymes, conferring frank resistance. Asn346 substitutions in AmpC enzymes may remain a risk, having been repeatedly selected with multiple avibactam combinations in vitro.

Résistance haut niveau aux aminoglycosides16S rRNA méthylation

Plasmid-Mediated High-Level Resistance to Aminoglycosides in *Enterobacteriaceae* Due to 16S rRNA Methylation

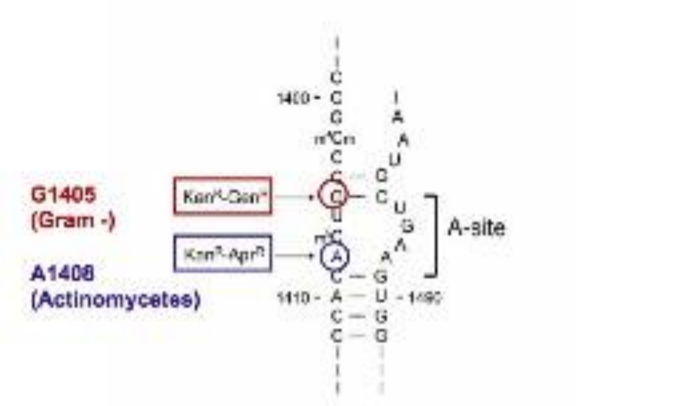
Marc Galimand,[1*] Patrice Courvalin,[1] and Thierry Lambert[1,2]

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2003, p. 2565–2571 Vol. 47, No. 8

- **2003 :** Description of *ARM A* a 16S rRNA methylase in a *K. pneumoniae* BM4336 (Paris, 2000) conjugative plasmid 80 kb ($bla_{\text{ctx-m-3}}$)
- **2003:** *Rmta* (*P. Aeruginosa* AR-2, 1997, japan) Yokoyama et al., Lancet, 2003,362;1888-93
- 2004: *Rmtb* (*S marcescens* S-95, 2002, japan) Doi et al., AAC, 2004, 48 (2) 491-6
- 2006: *Rmtc* (*P mirabilis* ARS68, 2003, japan) Wachino et al, AAC, 2006, 50(1), 178-84
- 2007: *Rmtd* (*P. aeruginosa* PA0905, 2005, Brazil) Doi et al., AAC, 2007,51, 852-6
- Rmte,f,g….
- 2007: *Npma* (*E. coli*, 2003, japon) Wachino, AAC, 2007, 51, 4401-09

Données CNR
3 % des CPEs in 2018
6 % des CPEs in 2020

- 183 isolats (90.15%) avec une seule 16S-RMTase,
- 20 isolats (9.85%) avec 2 (surtout *rmtB* + *rmtF*).
- **160 isolats associés à NDM**



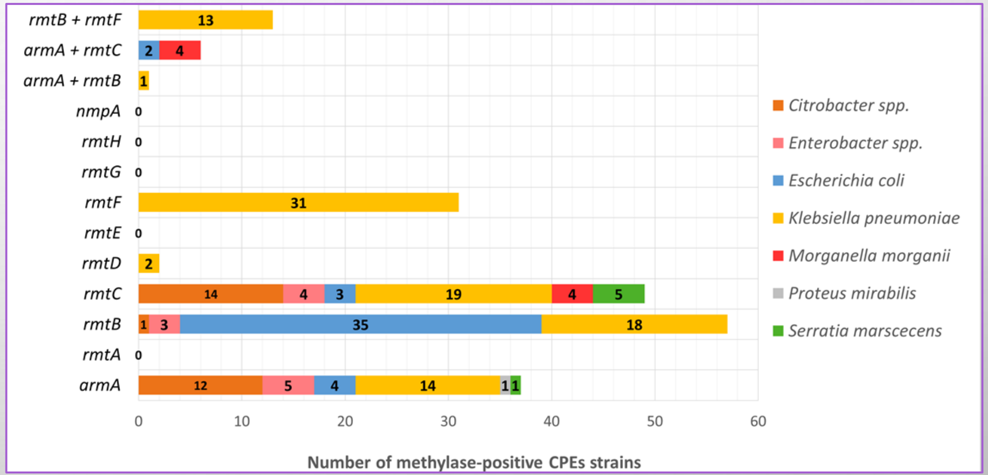
(Doi et al. CID 2007; 45:88-94)

Résistance haut niveau

Gentamicin, Tobramycin, Amikacin, Isepamicin, Kanamycin, Netilmicin, arbekacin, **plazomycin**

Epargne:

Neomycin, **Apramycin**, streptomycin



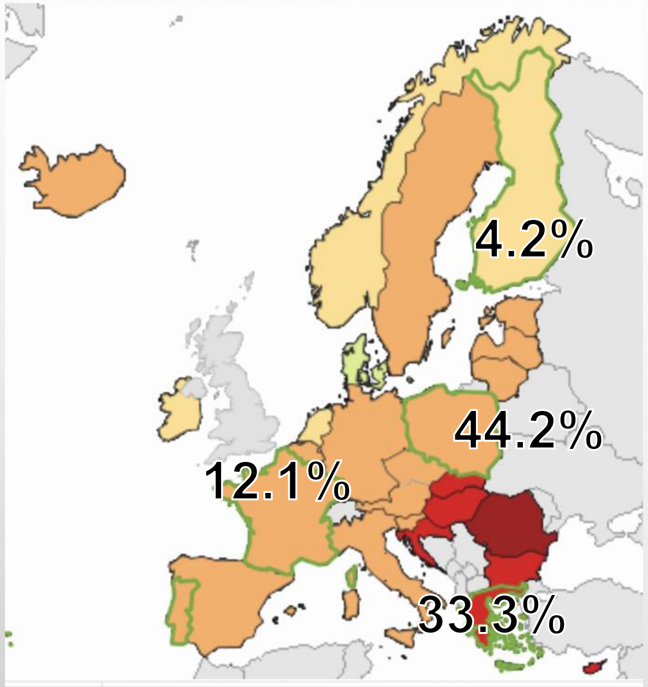
AMERICAN SOCIETY FOR MICROBIOLOGY mBio RESEARCH ARTICLE Therapeutics and Prevention

ApmA Is a Unique Aminoglycoside Antibiotic Acetyltransferase That Inactivates Apramycin

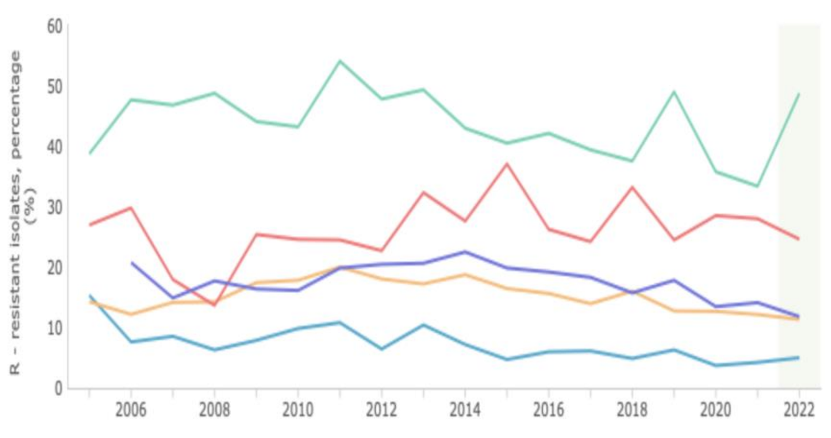
Emily Bordeleau,[a] Peter J. Stogios,[b,c] Elena Evdokimova,[b,c] Kalinka Koteva,[a] Alexei Savchenko,[b,c,d] Gerard D. Wright[a]

RESISTANCE AUX CARBAPENEMES ET *P. AERUGINOSA*

Carbapenem resistance *P. aeruginosa* bacteriemia in 2021 (ECDC)



- <1%
- 1–<5%
- 5–<10%
- 10–<25%
- 25–<50%
- 50–<75%
- Not included



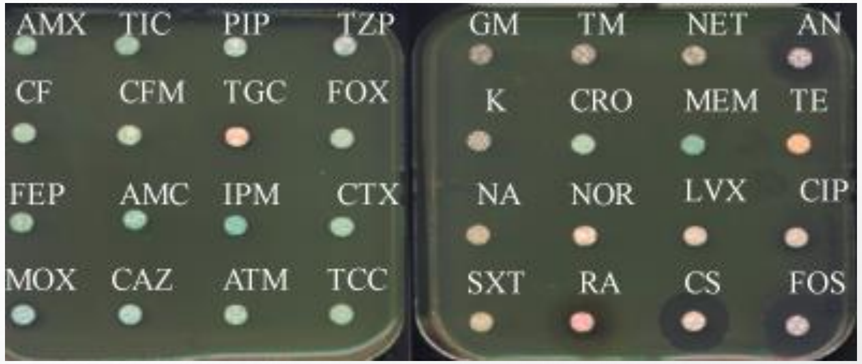
48.7% (887 tested) Grece

24.6 % (469 tested) Pologne

11.8 % (1129 tested) Portugal
11.3 % (3498 tested) France

5.0 % (422 tested) Finlande

P. aeruginosa et KPC

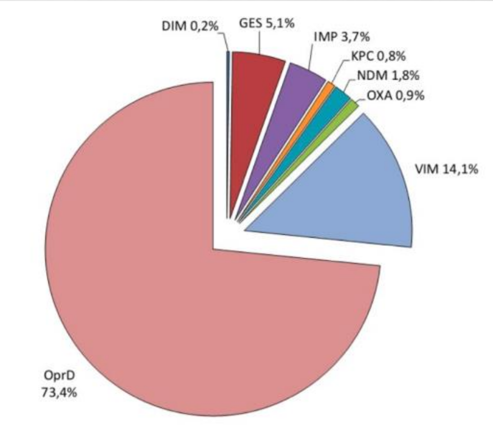


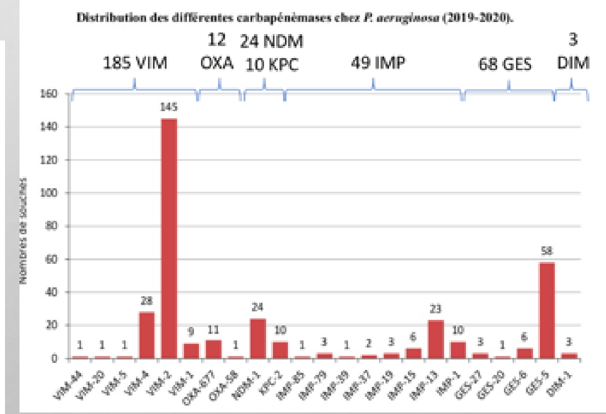
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2011, p. 3929–3931 Vol. 55, No. 8
0066-4804/11/$12.00 doi:10.1128/AAC.00226-11

Emergence of NDM-1 Metallo-β-Lactamase in *Pseudomonas aeruginosa* Clinical Isolates from Serbia∇

Branko Jovcic,[1]# Zorica Lepsanovic,[2]# Vesna Suljagic,[2] Gorjana Rackov,[2] Jelena Begovic,[1] Ljubisa Topisirovic,[1] and Milan Kojic[1]*

In France 26,6% of IMPR received at CNR are CPs

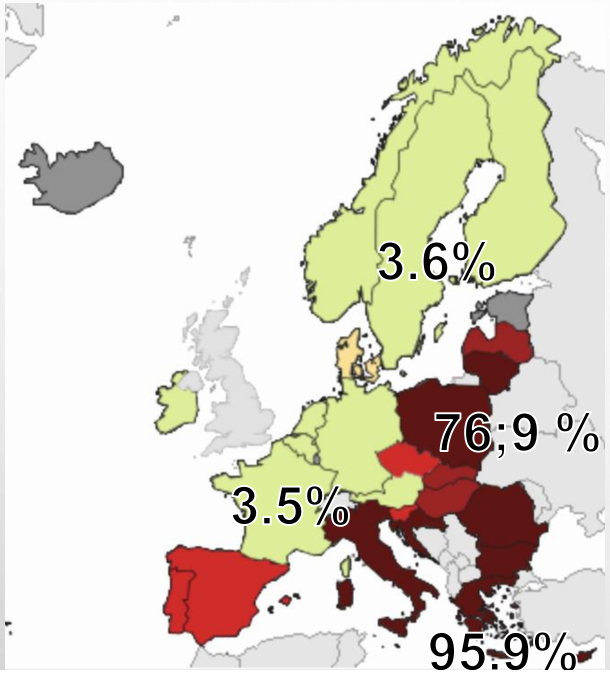




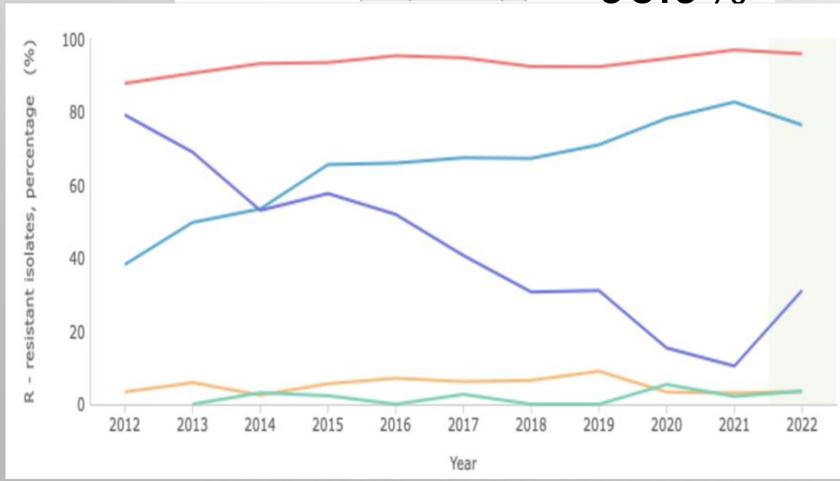
15% de GES

RESISTANCE AUX CARBAPENEMES ET *A. BAUMANNII*

Carbapenem resistance *A. baumannii* bacteriemia in 2021 (ECDC)



- <1%
- 1–<5%
- 5–<10%
- 10–<25%
- 25–<50%
- 50–<75%
- ≥75%
- Not included
- No data



96.9 % Grèce (1531 tested)

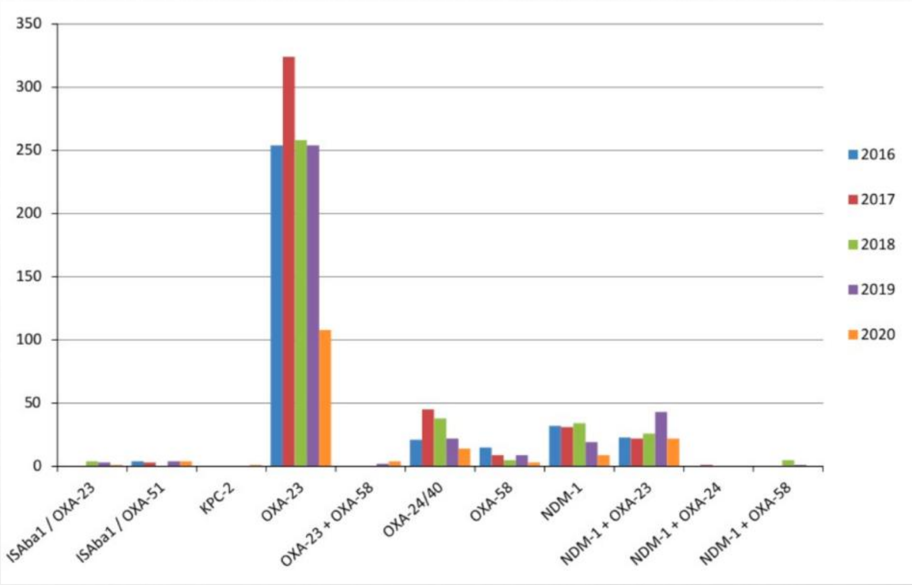
76.9 % Pologne (466 tested)

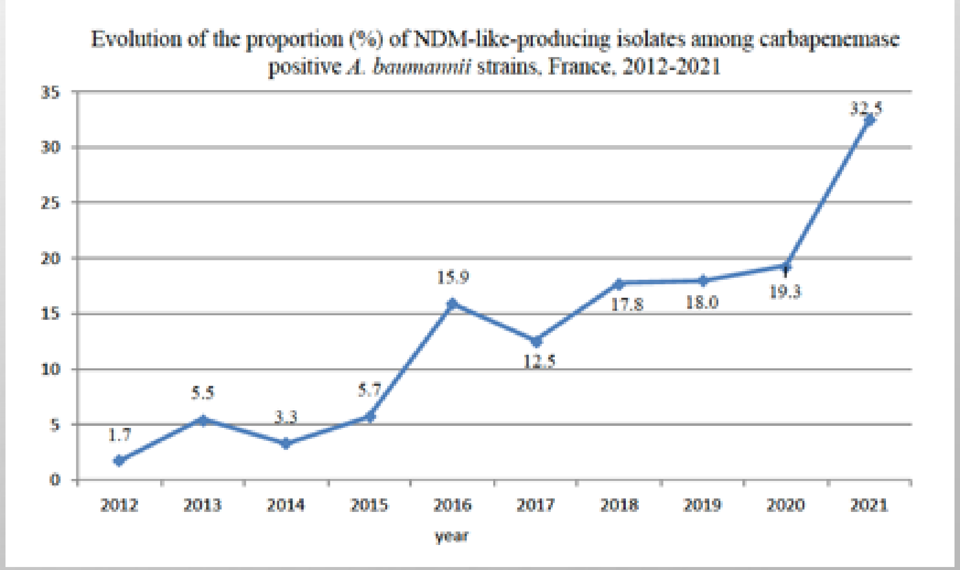
31.1 % Portugal (122 tested)

3.6 % Finlande (28 tested)

3.5 % France (857 tested)

Carbapenemase-producing *A. baumannii* France 2016–2020, F-NRC





Et le Cefiderocol?

frontiers | Frontiers in Microbiology

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Gaillot S, Oueslati S, Vuillemenot J-B, Bour M,
Iorga BI, Triponney P, Plésiat P, Bonnin RA,

Genomic characterization of an NDM-9-producing *Acinetobacter baumannii* clinical isolate and role of Glu152Lys substitution in the enhanced cefiderocol hydrolysis of NDM-9

Susie Gaillot[1], Saoussen Oueslati[2], Jean-Baptiste Vuillemenot[1,3], Maxime Bour[3], Bogdan I. Iorga[4], Pauline Triponney[3], Patrick Plésiat[1,3], Rémy A. Bonnin[2,5], Thierry Naas[2,5], Katy Jeannot[1,3] and Anaïs Potron[1,3]*

In vitro Activity of Cefiderocol and Comparators against Carbapenem-Resistant Gram-Negative Pathogens from France and Belgium

by Saoussen Oueslati [1,2,3], Pierre Bogaerts [4], Laurent Dortet [1,2,3], Sandrine Bernabeu [1,2], Hend Ben Lakhal [5], Christopher Longshaw [6], Youri Glupczynski [4] and Thierry Naas [1,2,3,*]

Mechanism	Total # of Isolates	# of Isolates per MIC (mg/L)													% Susceptible Isolates at Breakpoints of (mg/L)	
		≤0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	>64	≤2 [1]	≤4 [2]
P. aeruginosa	120	2	10	22	29	30	17	9	1	0	0	0	0	0	99	100
Non-CP, ESBLs	31	0	1	7	8	7	4	3	1	0	0	0	0	0	97	100
MBLS	77	2	8	13	19	18	12	5	0	0	0	0	0	0	100	100
VIM	56	1	7	12	14	11	8	3	0	0	0	0	0	0	100	100
IMP	11	0	0	1	4	5	1	0	0	0	0	0	0	0	100	100
NDM, GIM, DIM, SPM, AIM	10	1	1	0	1	2	3	2	0	0	0	0	0	0	100	100
OXA-198, GES, KPC	12	0	1	2	2	5	1	1	0	0	0	0	0	0	100	100
A. baumannii	82	1	7	11	6	15	16	13	3	3	1	0	0	6	84	88
ESBL, Non CP	26	0	0	4	1	6	5	7	0	0	1	0	0	2	88	88
OXA-23, 40, 58, 143	40	1	7	7	5	5	10	2	1	1	0	0	0	1	93	95
NDM-like	10	0	0	0	0	0	0	3	2	2	0	0	0	3	30	50
VIM, IMP	6	0	0	0	0	4	1	1	0	0	0	0	0	0	100	100
S. maltophilia	25	22	2	1	0	0	0	0	0	0	0	0	0	0	100	100
B. cepacia	13	10	0	1	0	1	0	0	0	1	0	0	0	0	92.3	92.3
A. xylosoxidans	12	0	0	1	4	4	2	1	0	0	0	0	0	0	100	100
Elizabethkingia sp	2	0	0	1	0	0	1	0	0	0	0	0	0	0	100	100

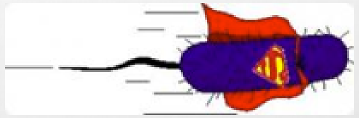
99% S

84% S

30% NDM

Conclusions: Epidémiologie des EPCs

- Dissémination des BLSEs => consommation accrue de carbapénèmes
- Il est impossible de prévenir l'émergence de la résistance et donc des EPCs. Même dissémination que les BLSEs?
- L'épidémiologie change: Emergence
  - De nouvelles carbapénèmases dans des fonds génétiques particuliers
  - De nouveaux variants avec des extensions de spectre (KPC resistant Avi)
  - Concentration des mécanismes. Plusieurs carbapénèmases (3 différentes)



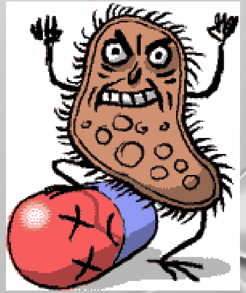
- **Que peut on faire?**

  -> On peut retarder leur diffusion (à l'hôpital) par la mise en place de mesures d'hygiènes renforcées

  -> identification rapide des porteurs

  -> identification du mécanisme de résistance pour utiliser les nouvelles molécules au mieux

  -> Besoin ++++ **de nouveaux antibiotiques surtout anti MBLs**



- Quelle sera la situation d'ici 5 ans: ? => de la résistance va apparaitre avec l'utilisation des nouvelles molécules

REMERCIEMENTS

- **Dr Laurent Dortet**
- Dr Rémy Bonnin
- Dr Delphine Girlich
- Dr Agnes Jousset
- Dr Cécile Emeraud

Besoins de CMIs +++ avec les MBLs

Clinical Microbiology and Infection 28 (2022) 1156.e1–1156.e5

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journal homepage: www.clinicalmicrobiologyandinfection.com

Research note

Comparison of disk diffusion, MIC test strip and broth microdilution methods for cefiderocol susceptibility testing on carbapenem-resistant enterobacterales

Rémy A. Bonnin [1, 2], Cécile Emeraud [1, 2, 3], Agnès B. Jousset [1, 2, 3], Thierry Naas [1, 2, 3], Laurent Dortet [1, 2, 3, *]

E-tests et disques sous-estiment CMIs

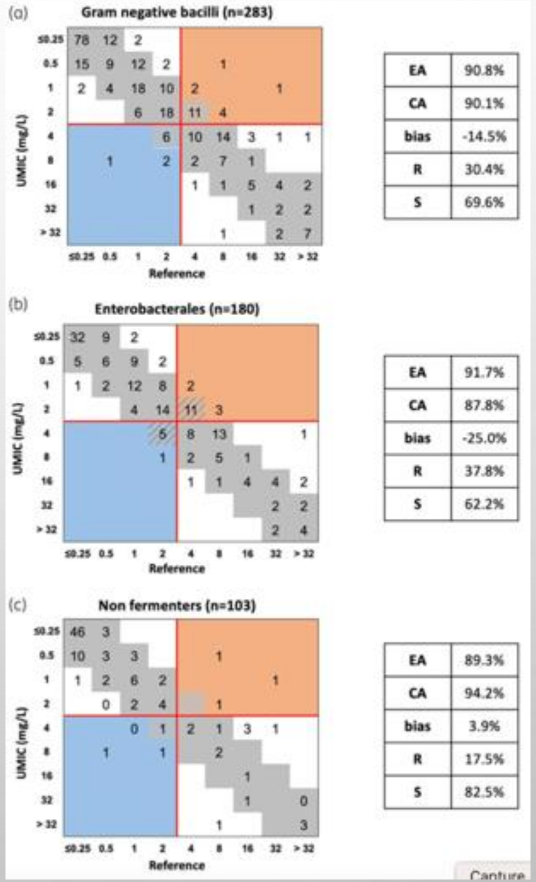
=> BMD +++

J Antimicrob Chemother
https://doi.org/10.1093/jac/dkad149

Journal of Antimicrobial Chemotherapy

Performance evaluation of the UMIC® Cefiderocol to determine MIC in Gram-negative bacteria

Laurent Dortet [1,2,3]†, Claudia Niccolai[4,5]†, Niels Pfennigwerth [6]†, Stefanie Frisch[7], Camille Gonzalez[1,2], Alberto Antonelli[4,5], Tommaso Giani[4,5], Robert Hoenings[7], Soeren Gatermann[6]†, Gian Maria Rossolini[4,5]† and Thierry Naas [1,2,3*]†

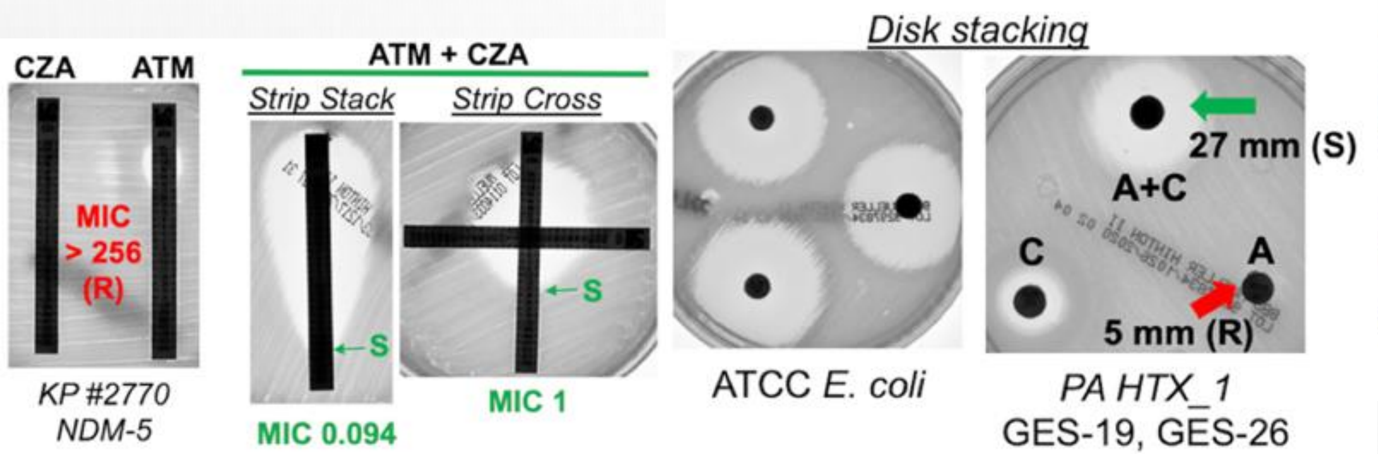


American Society for Microbiology | Antimicrobial Agents and Chemotherapy®

SUSCEPTIBILITY

Evaluation of Susceptibility Testing Methods for Aztreonam and Ceftazidime-Avibactam Combination Therapy on Extensively Drug-Resistant Gram-Negative Organisms

Ayesha Khan,[a] Samuel G. Erickson,[a] Cedric Pettaway,[a] Cesar A. Arias,[a,b] William R. Miller,[a] Micah M. Bhatti[c]



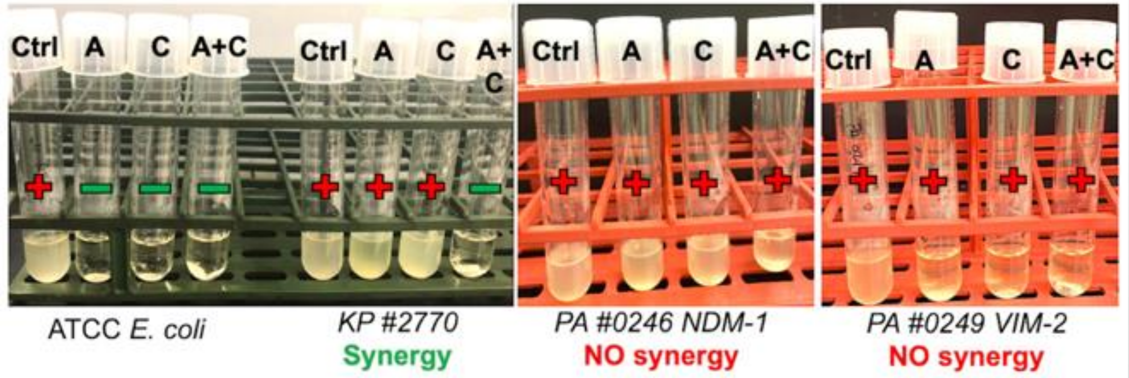


TABLE 4 Evaluation of overall qualitative and quantitative performance of combination testing methods compared to mBMD[a]

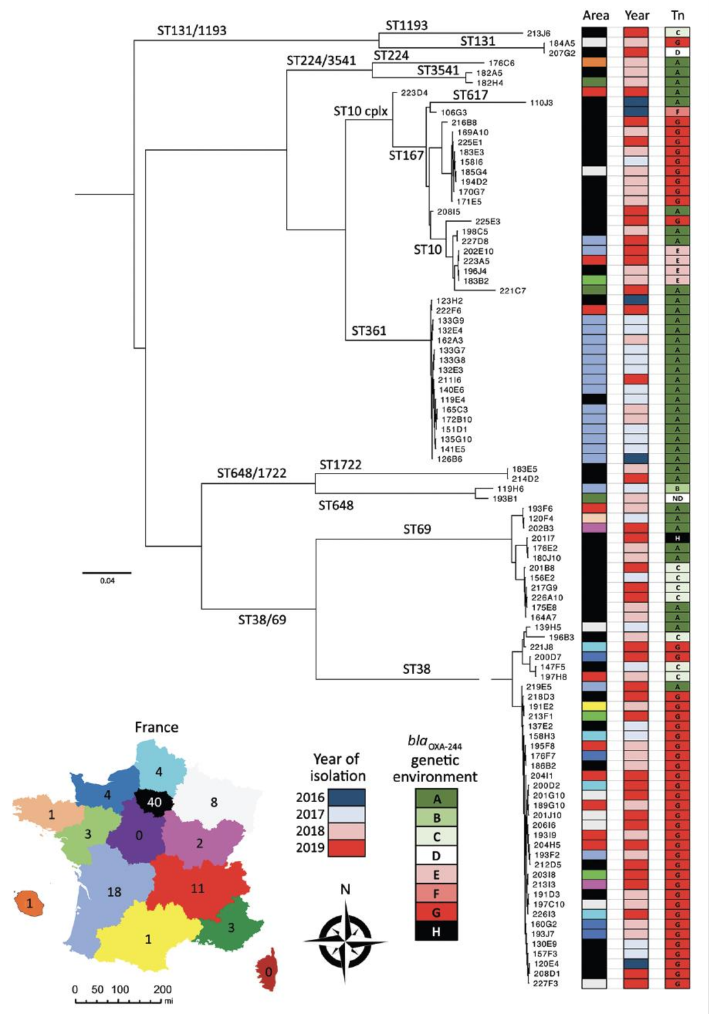
	Results by assay					
			Strip stacking		Strip crossing	
Parameter	Disk elution	Disk stacking	E-test	MTS	E-test	MTS
Sensitivity	100	42.67	87.5	100	95.83	100
Specificity	100	100	100	100	100	100
EA			38/45 (84)	38/45 (84)	42/45 (93)	42/45 (93)
CA	51/51 (100)	22/51 (43)	42/51 (82)	43/51 (84)	46/51 (90)	48/51 (94)
VME		0/7	0/7	0/7	0/7	0/7
ME		16/37 (43)	2/37 (5)	1/37 (3)	2/37 (5)	0/37
MI		13/51 (25)	7/51 (14)	7/51 (14)	3/51 (6)	3/51 (6)

[a]Sensitivity and specificity were calculated with a 95% confidence interval (CI); values are %. All other values are *n* (%): EA, evaluable essential agreement; CA, categorical agreement; VME, very major error; ME, major error; MI, minor error.

Liofilchem® Aztreonam-avibactam MTS™

Emergence and Polyclonal Dissemination of OXA-244–Producing *Escherichia coli*, France

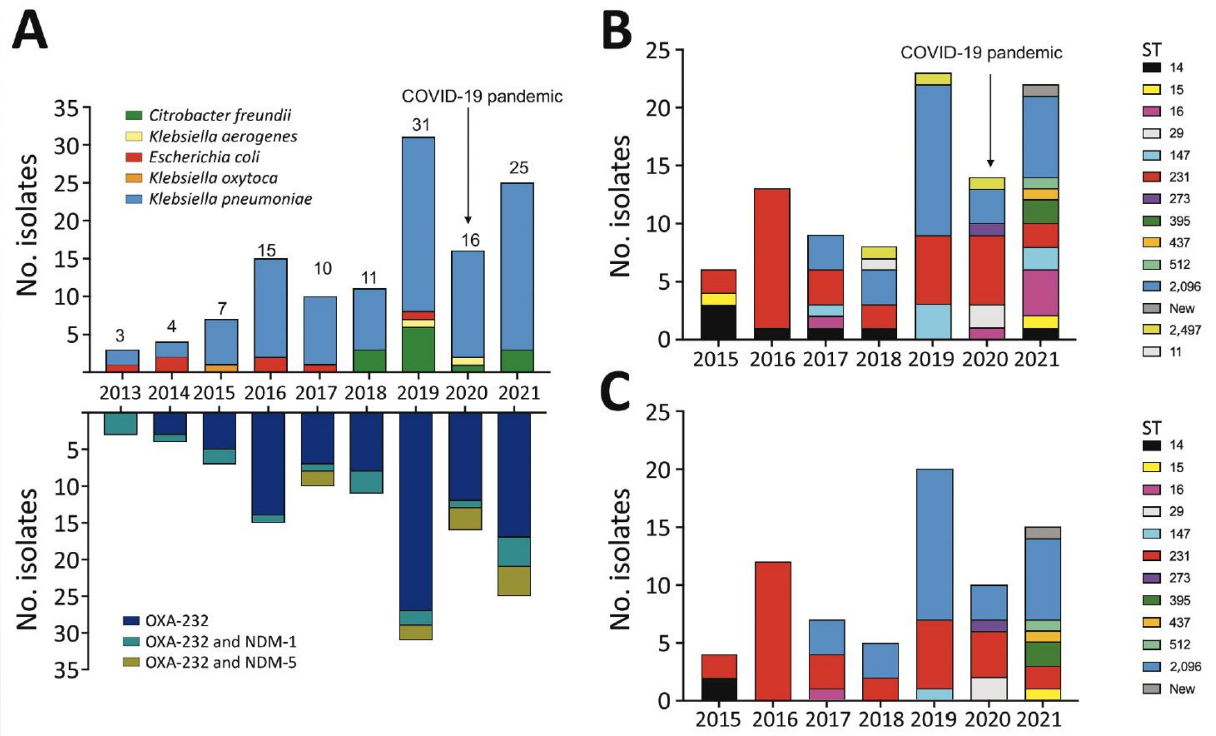
Cecile Emeraud, Delphine Girlich, Rémy A. Bonnin, Agnès B. Jousset, Thierry Naas, Laurent Dortet



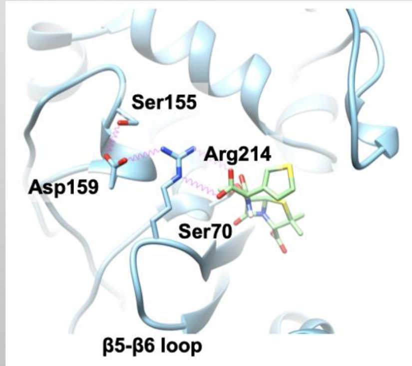
Emerging Infectious Diseases **27**, 2021

Polyclonal Dissemination of OXA-232 Carbapenemase–Producing *Klebsiella pneumoniae*, France, 2013–2021

Cecile Emeraud, Aurélien Birer, Delphine Girlich, Agnès B. Jousset, Elodie Creton, Thierry Naas, Rémy A. Bonnin, Laurent Dortet



R214G, OXA-244
R214S, OXA-232



AMERICAN SOCIETY FOR MICROBIOLOGY Antimicrobial Agents and Chemotherapy®

OXA-244-Producing *Escherichia coli* Isolates, a Challenge for Clinical Microbiology Laboratories

Yannick Hoyos-Mallecot, Thierry Naas, Rémy A. Bonnin, Rafael Patino, Philippe Glaser, Nicolas Fortineau, Laurent Dortet

July 2017

	ChromID Carba Smart	Carba NP	Maldi-Tof MS	Xpert Carba-R
% of detection	14,3%	57,1%	71,4%	100%