

DIU stratégies thérapeutiques et préventives en pathologie infectieuse

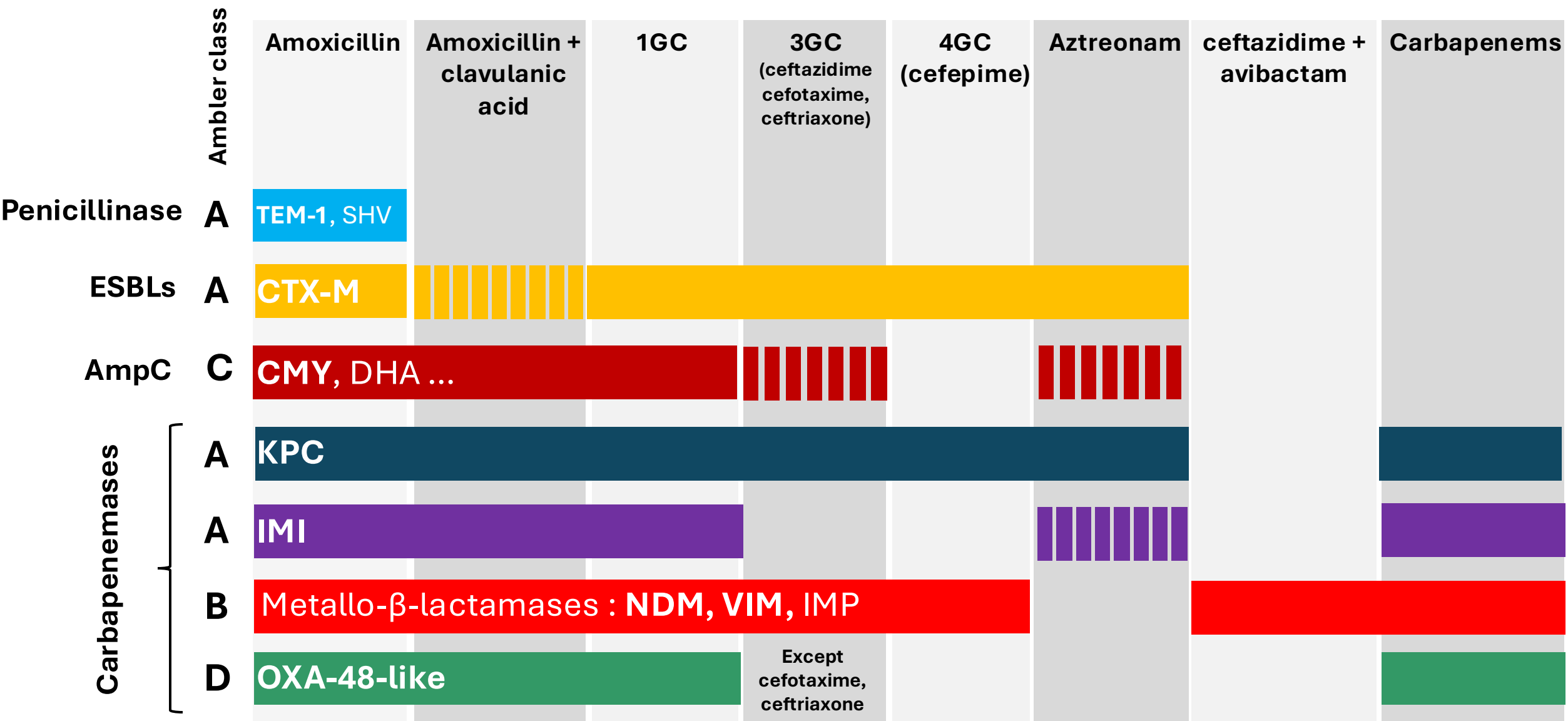
Mécanismes de résistance émergents chez les Enterobacterales,
Pseudomonas aeruginosa et *Acinetobacter baumannii*

Pr. Laurent DORTET

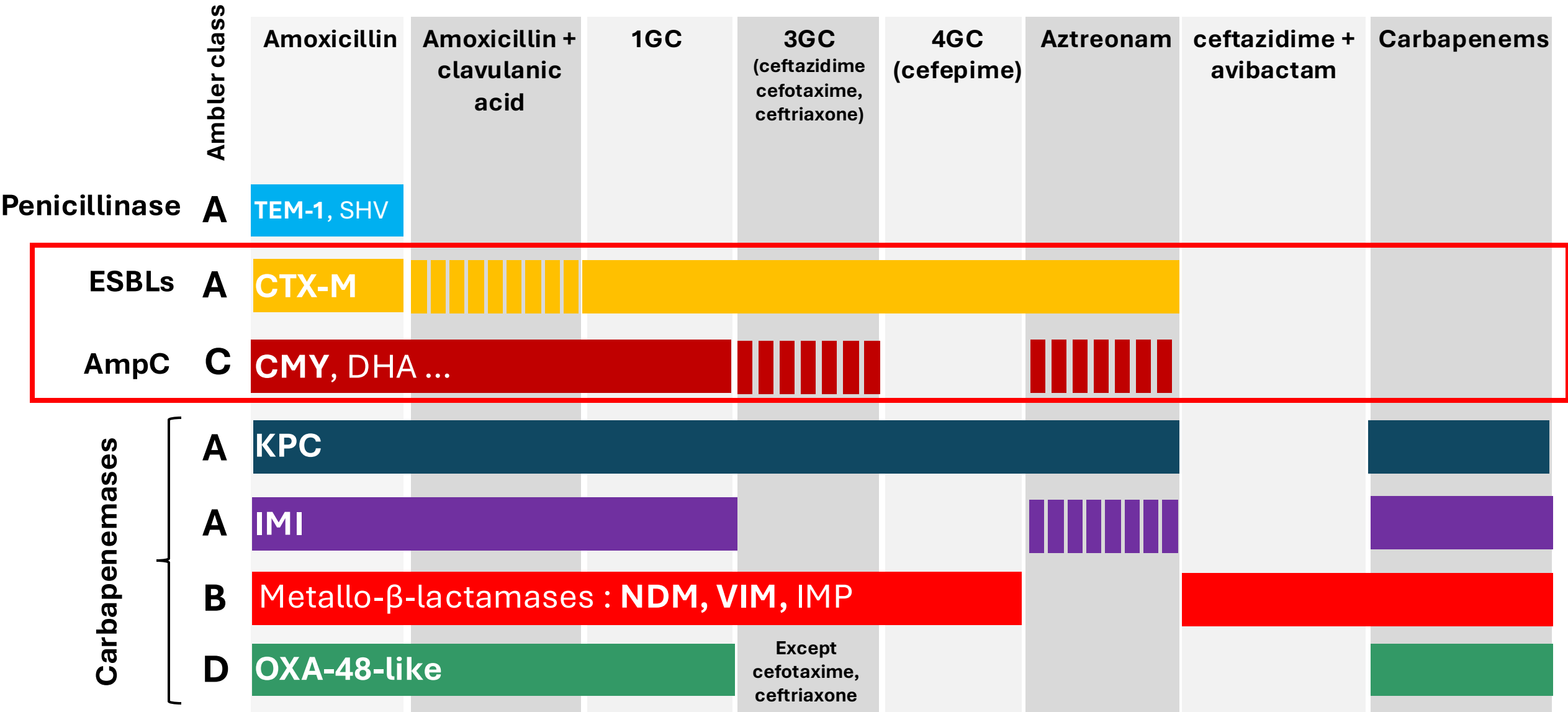
CNR Résistance aux Antibiotiques
CHU Bicêtre, service de Bactériologie-Hygiène

Résistances émergentes chez les Enterobacterales

Hydrolytic profile of β -lactamases in Enterobacteriales

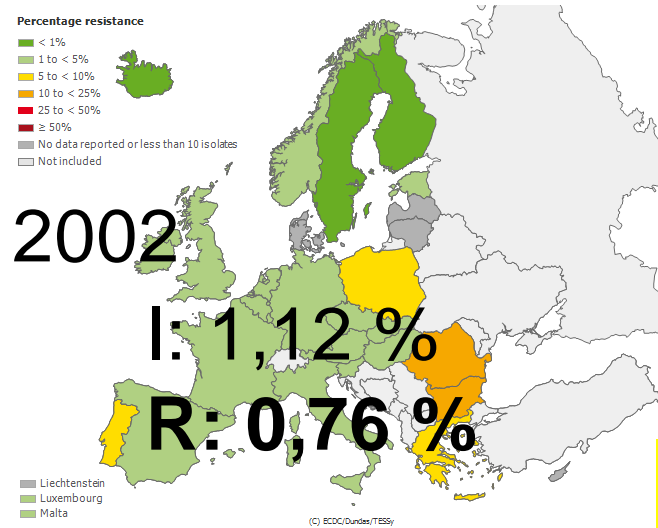


C3G resistance in *Enterobacteriales*

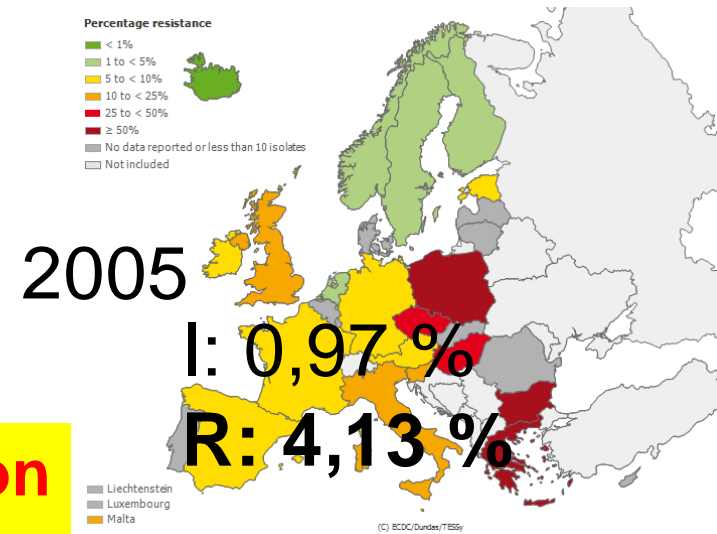


C3G resistance in *Enterobacteriales* in Europe

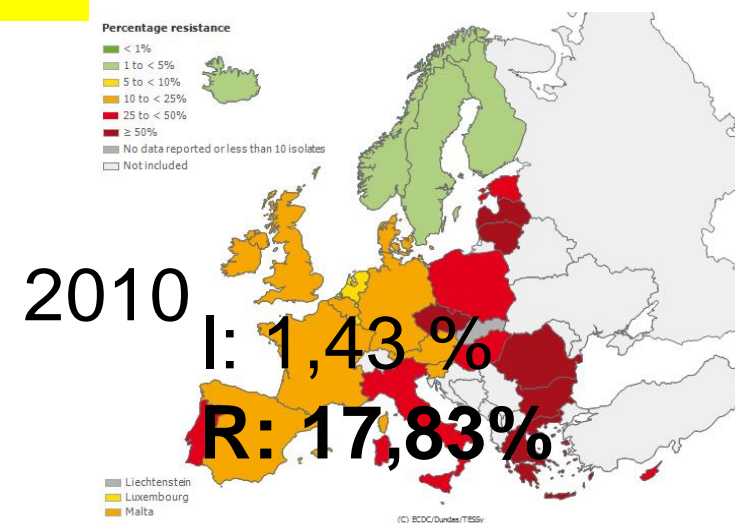
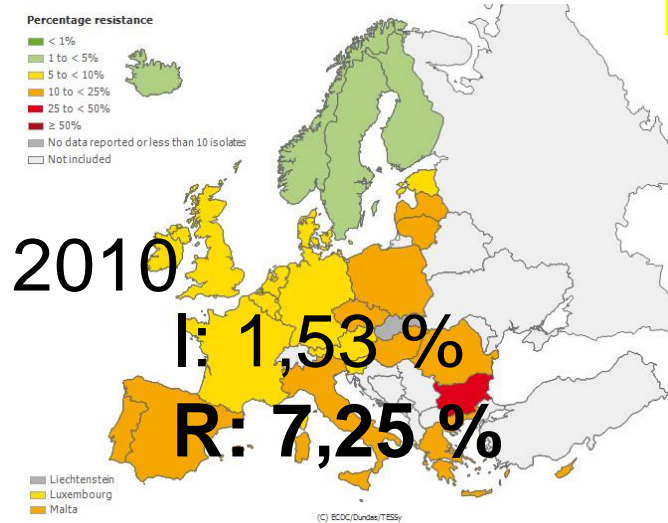
E. coli



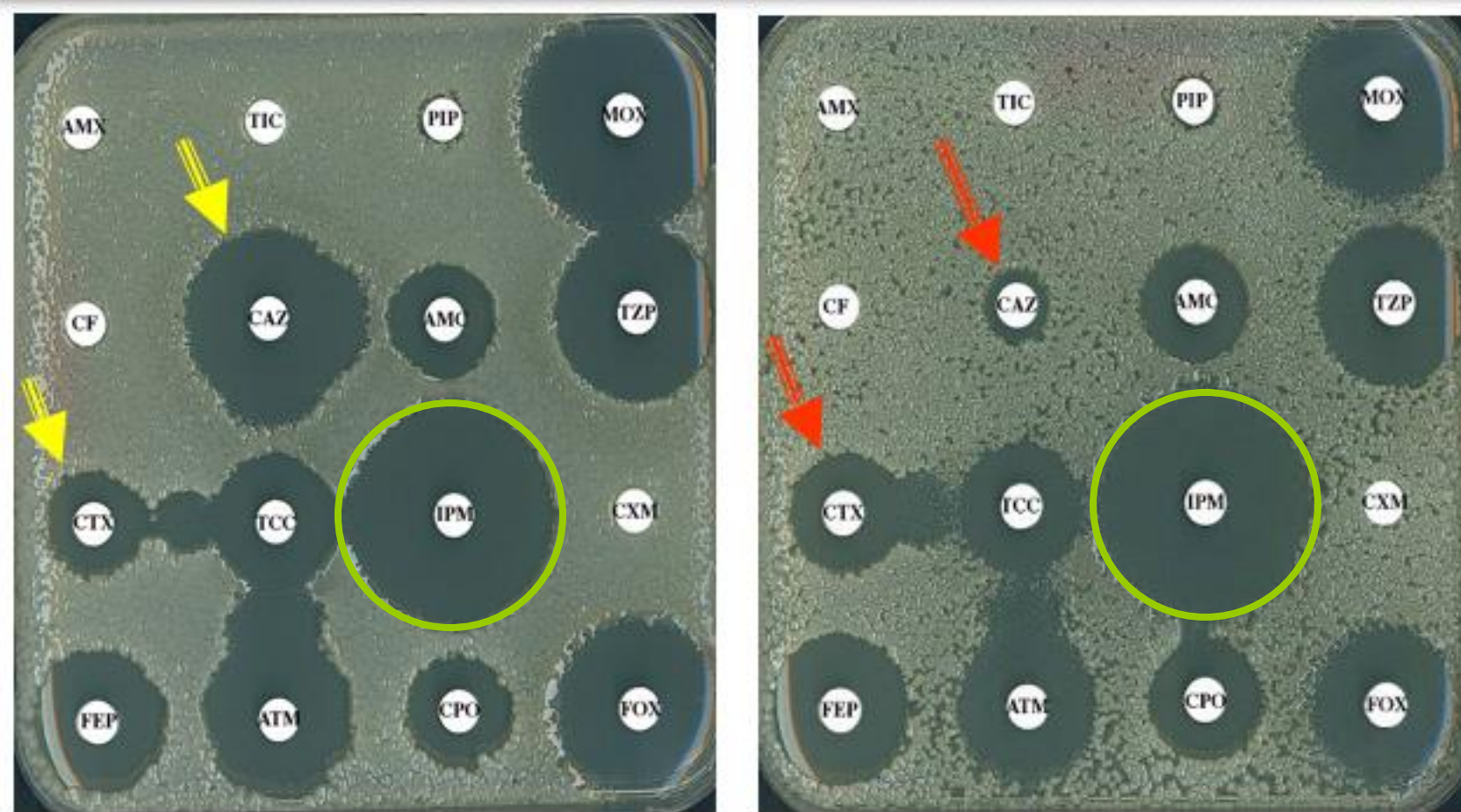
K. pneumoniae



**Explanation
ESBL**



CTX-Ms : Cefotaxime hydrolysis ... and all other 3CG

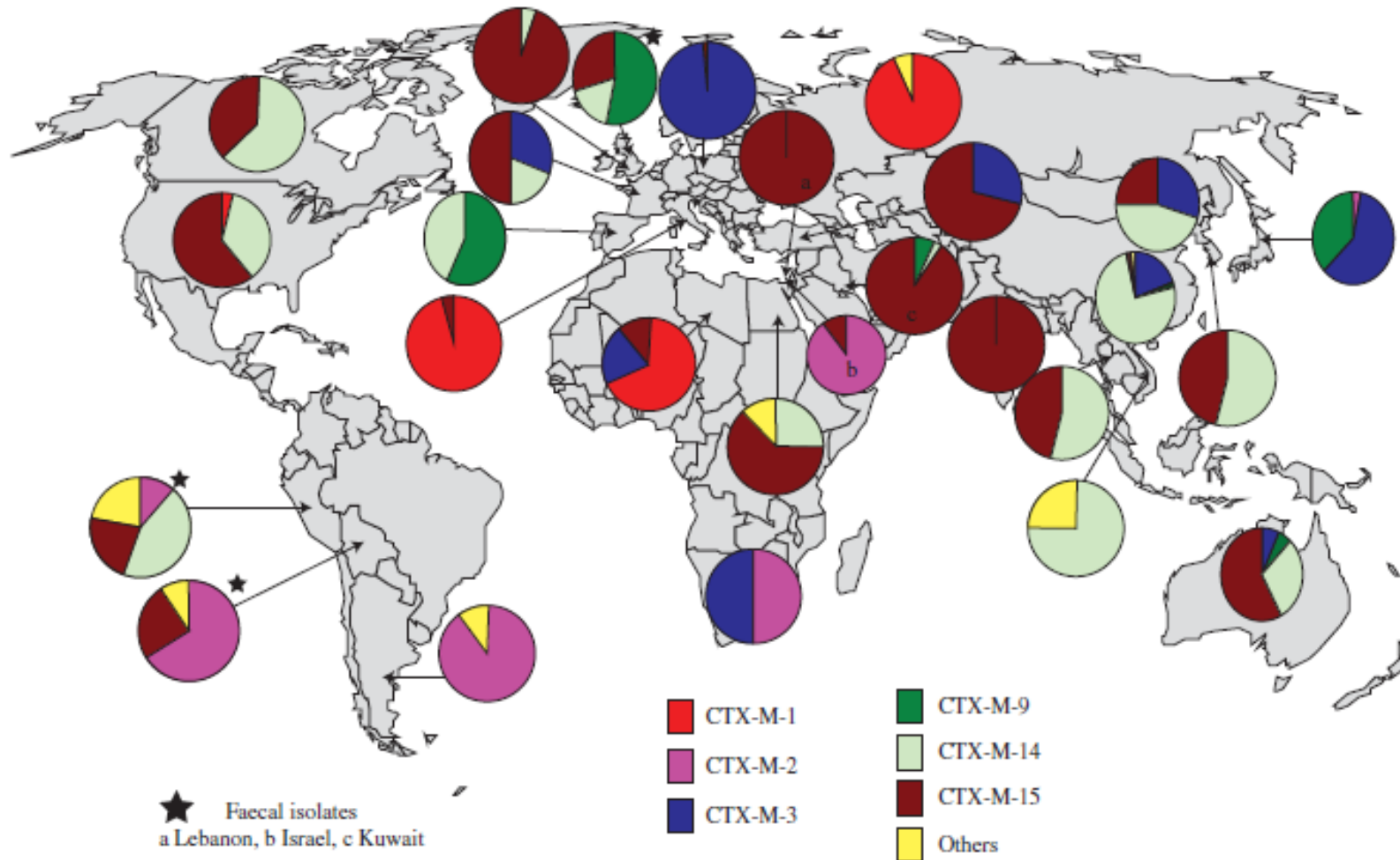


CTX-M-3

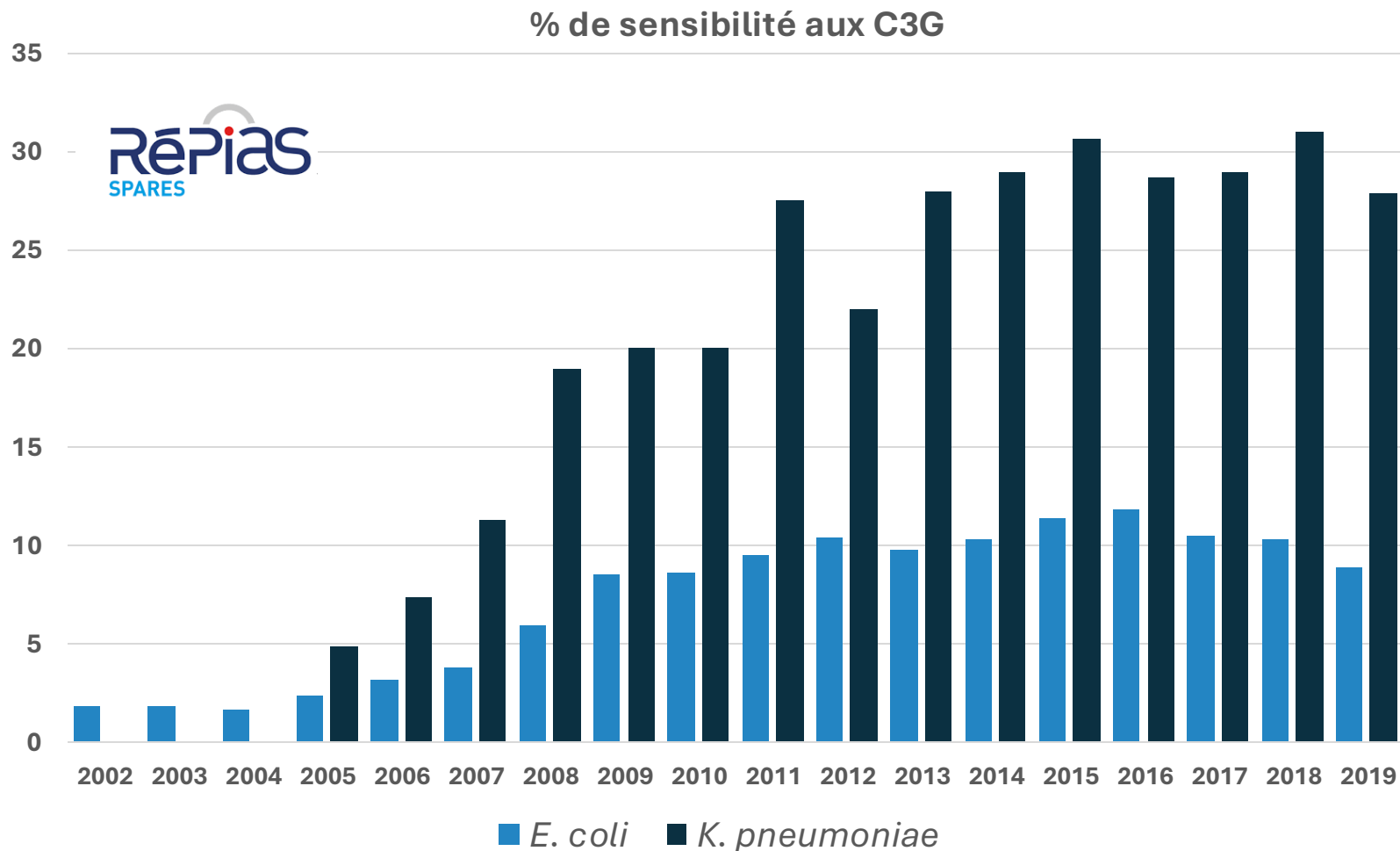
E. coli

CTX-M-15

Worldwide dissemination of CTX-M



Evolution of resistance at the hospital in France



Vers un plateau à 25-30% chez *K. pneumoniae*, amorce de diminution de la résistance aux C3G chez *E. coli* depuis 2016

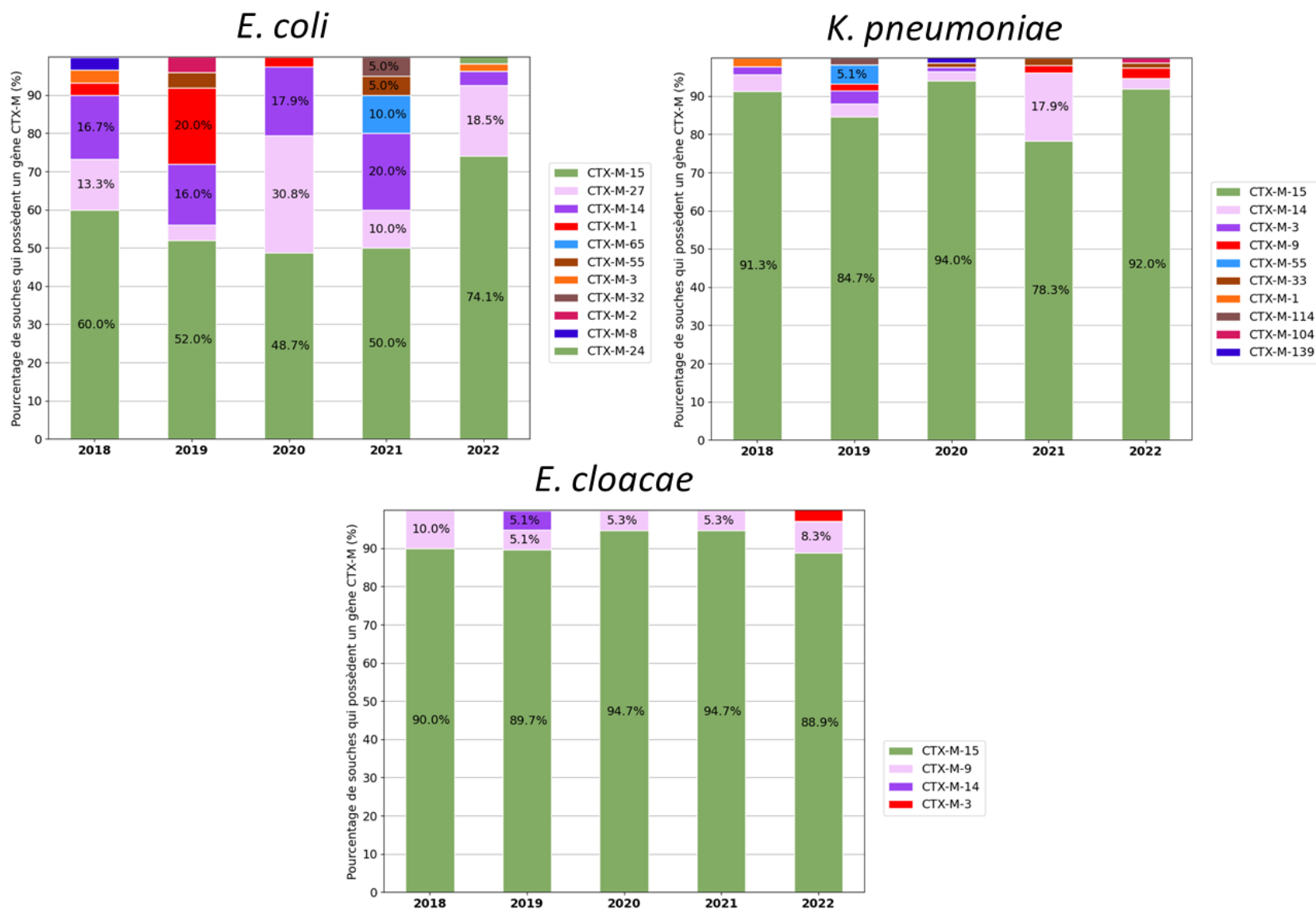
Résistances aux céphalosporines de 3^{ème} génération chez les entérobactéries en France

2022	<i>E. coli</i>				<i>K. pneumoniae</i>				<i>E. cloacae</i>			
	Tous prélèvements		Hémocultures		Tous prélèvements		Hémocultures		Tous prélèvements		Hémocultures	
	Nb souches	% (R+)	Nb souches	% (R+)	Nb souches	% (R+)	Nb souches	% (R+)	Nb souches	% (R+)	Nb souches	% (R+)
Amoxicilline-acide clavulanique	198 141	30,1	18 945	27,3	45 464	33,9	5 773	35,3				
Pipéracilline-tazobactam	184 277	8,2	18 431	9,3	42 614	25,5	5 772	28,8	23 920	40,4	3 633	38,6
C3G	215 504	7,3	20 261	9,5	48 323	24,5	6 040	27,0	24 747	47,0	3 728	46,1
Gentamicine	191 004	5,1	18 030	5,5	43 545	12,4	5 715	14,4	23 289	20,2	3 475	21,2
Quinolones	210 049	16,5	20 204	17,5	47 980	26,1	6 011	28,2	25 753	28,5	3 859	28,5
Ciprofloxacine	117 921	11,2	18 927	12,3	31 948	22,4	5 655	23,6	20 018	23,0	3 615	24,5
Cotrimoxazole	192 802	24,4	17 964	28,2	43 645	23,7	5 429	27,0	23 811	23,2	3 529	23,0

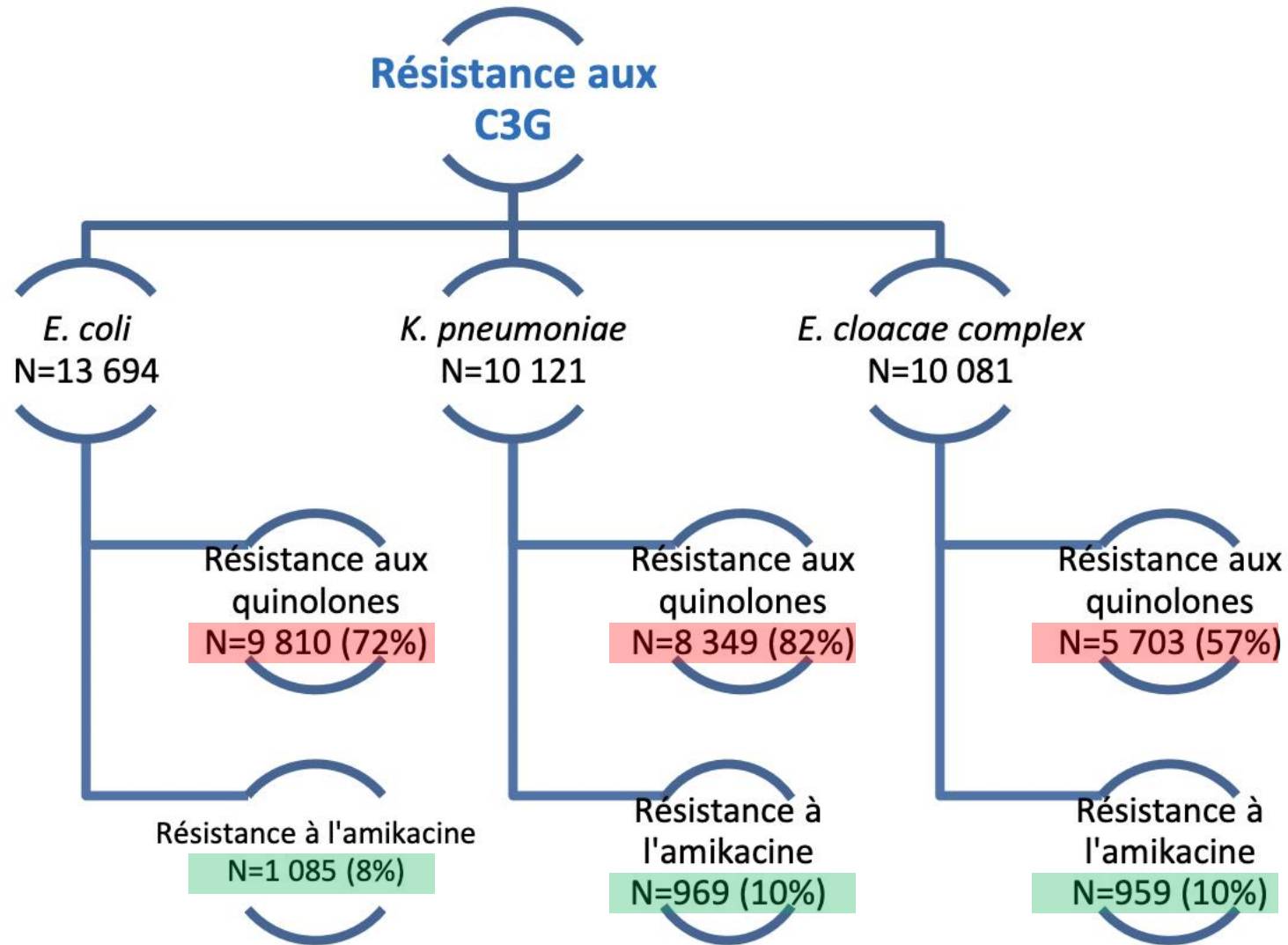
BLSE

Céphalosporinase +++
16,7% de BLSE

Les BLSE de type CTX-M prédominantes ... CTX-M-15 +++



Co-résistances fréquentes : quinolones, aminosides



CTX-M : a community acquired ESBL

Increasing carriage of ESBLs in the community

Faecal carriage of extended-spectrum β -lactamase-producing and AmpC β -lactamase-producing bacteria among Danish army recruits

A. M. Hammerum¹, C. H. Lester¹, L. Jakobsen¹, L. J. Porsbo²

Article first published online: 3 DEC 2010

DOI: 10.1111/j.1469-0691.2010.03340.x

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Issue



Clinical Microbiology and Infection

Volume 17, Issue 4, pages 566–568, April 2011

4% carriage in Denmark

J Antimicrob Chemother 2013; **68**: 562–568
doi:10.1093/jac/dks429 Advance Access publication 9 November 2012

Journal of Antimicrobial Chemotherapy

10-Fold increase (2006–11) in the rate of healthy subjects with extended-spectrum β -lactamase-producing *Escherichia coli* faecal carriage in a Parisian check-up centre

Marie-Hélène Nicolas-Chanoine^{1-3*}, Coraline Gruson³, Suzanne Bialek-Davenet¹⁻³, Xavier Bertrand⁴, Frédérique Thomas-Jean⁵, Frédéric Bert¹, Mati Moyat¹, Elodie Meiller¹, Estelle Marcon¹, Nicolas Danchin⁵, Latifa Noussair¹, Richard Moreau³ and Véronique Leflon-Guibout¹

6% carriage in France

ESBLs : our worst nightmare ?

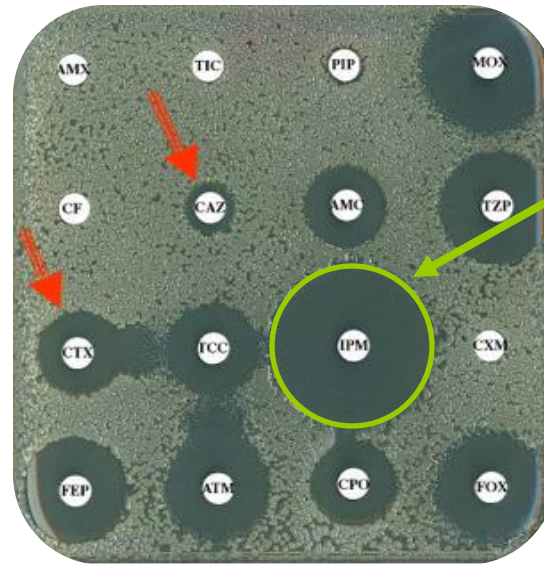


Carbapenems : the last resort antimicrobials

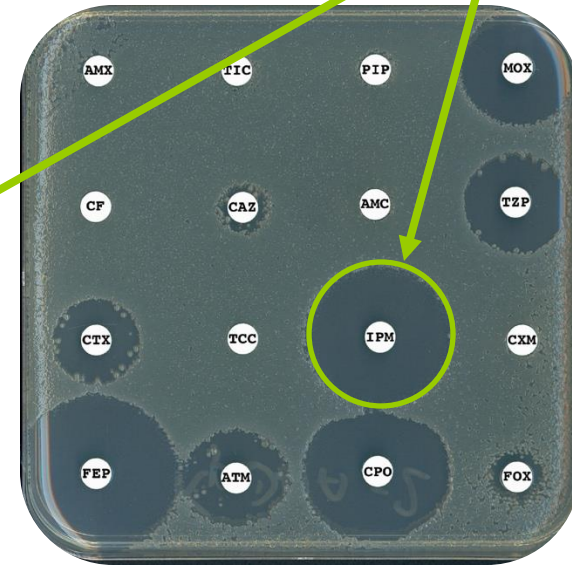
E. coli
of our childhood



E. coli
modern strains

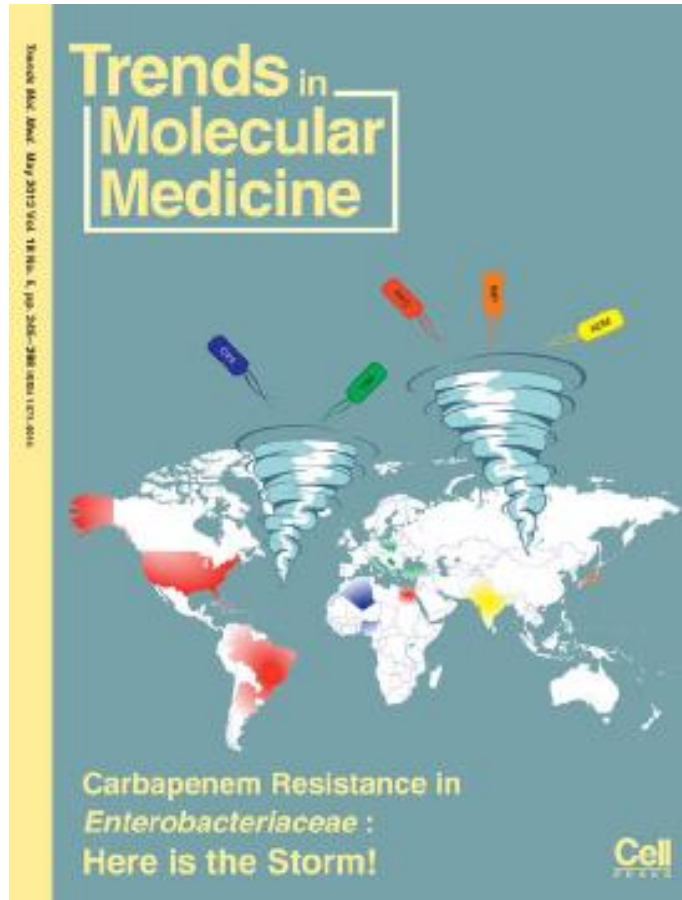


ESBL



Plasmidic AmpC

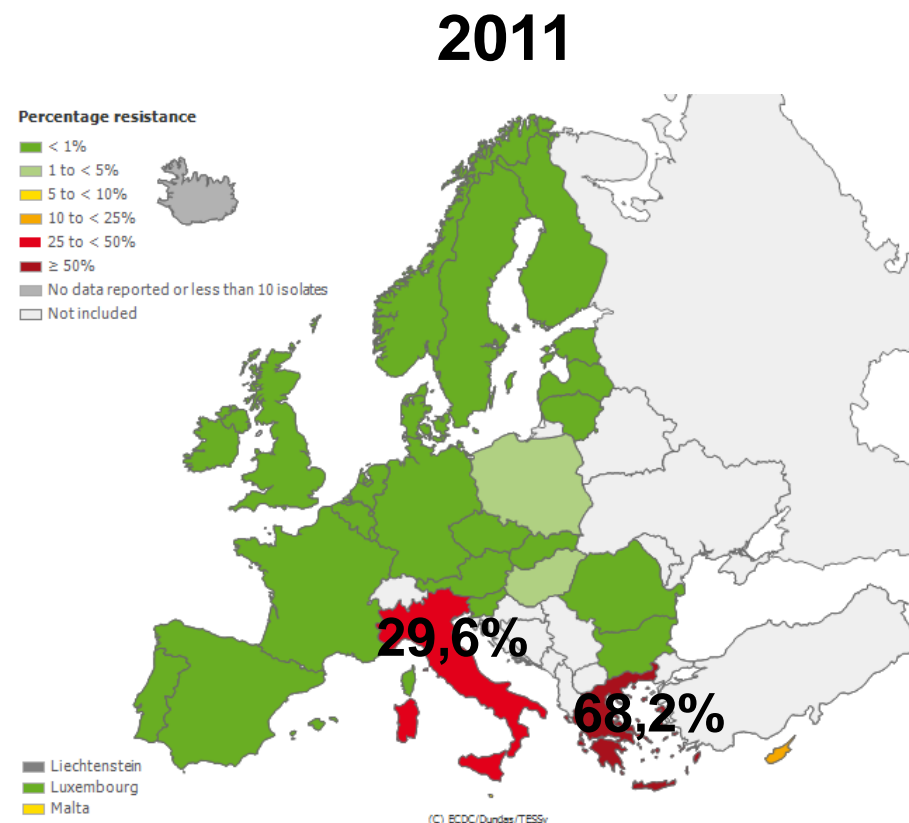
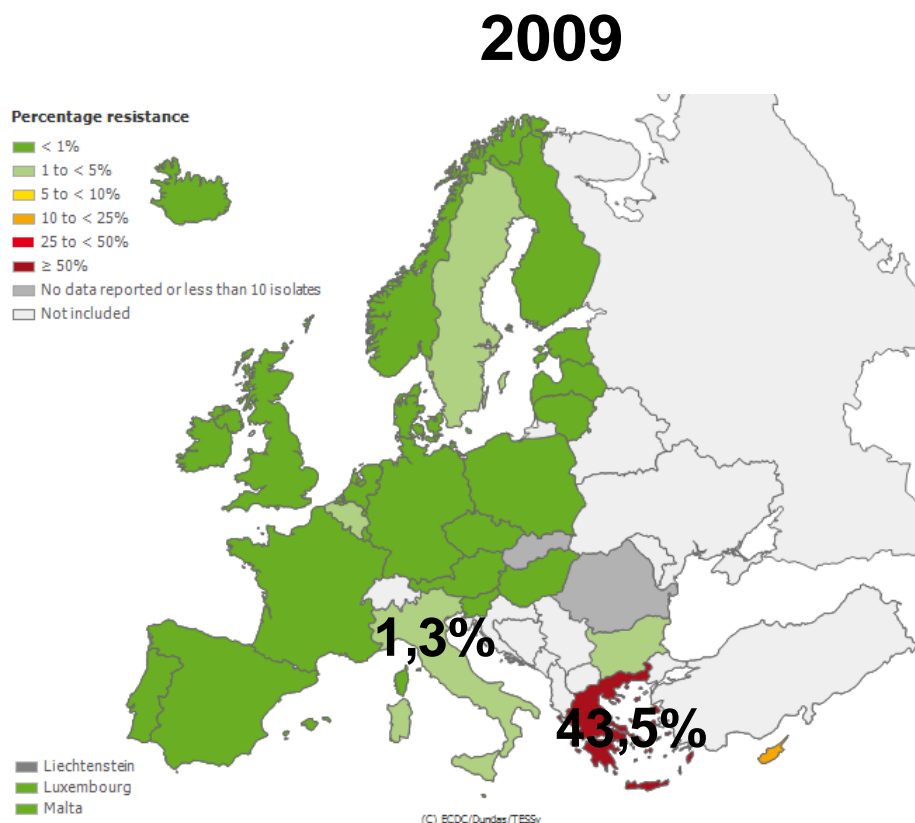
Résistance aux carbapénèmes : Les ennuis commencent...



P. Nordmann, L. Dortet, L. Poirel

Penicillins	Cephalosporins	Carbapenems
ESBLs : CTX-Ms		
		Carbapenemases : KPC, NDM, OXA-48 ...

Increase of carbapenem resistance in *Enterobacterales* in Europe



K. pneumoniae I+R to carbapenems

Carbapenem resistance in *Enterobacterales*

1 CARBAPENEMASE PRODUCTION

Significant hydrolysis activity towards carbapenems
(KPC > MBL > OXA-48-like > OXA-23)

2 WITHOUT CARBAPENEMASE PRODUCTION

ESBL +/- AmpC overproduction

Very weak hydrolysis activity towards carbapenems

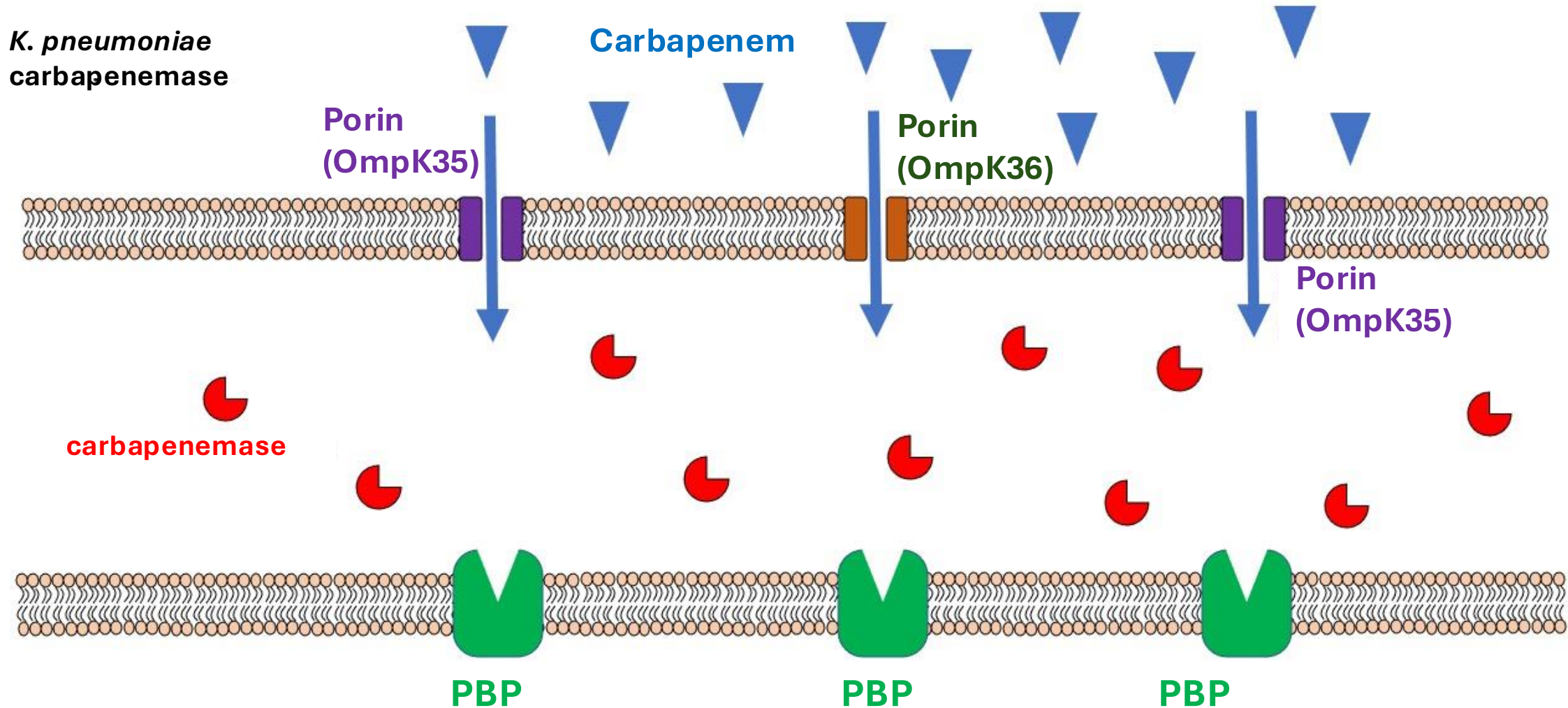
+

Decreased outer-membrane permeability

Porins deficiency +/- Efflux

Carbapenem resistance in *Enterobacteriales*

1 CARBAPENEMASE PRODUCTION (CRE CPE)

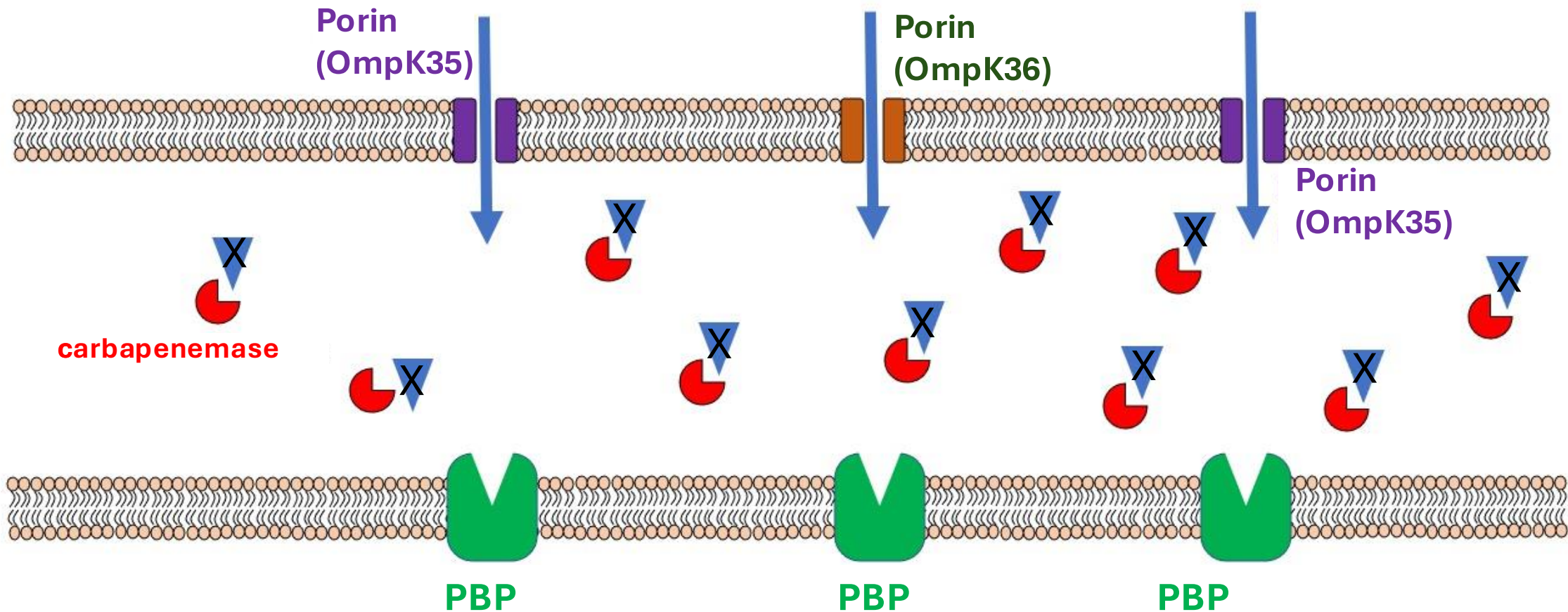


Carbapenem resistance in *Enterobacteriales*

1 CARBAPENEMASE PRODUCTION (CRE CPE)

K. pneumoniae
carbapenemase

Carbapenem

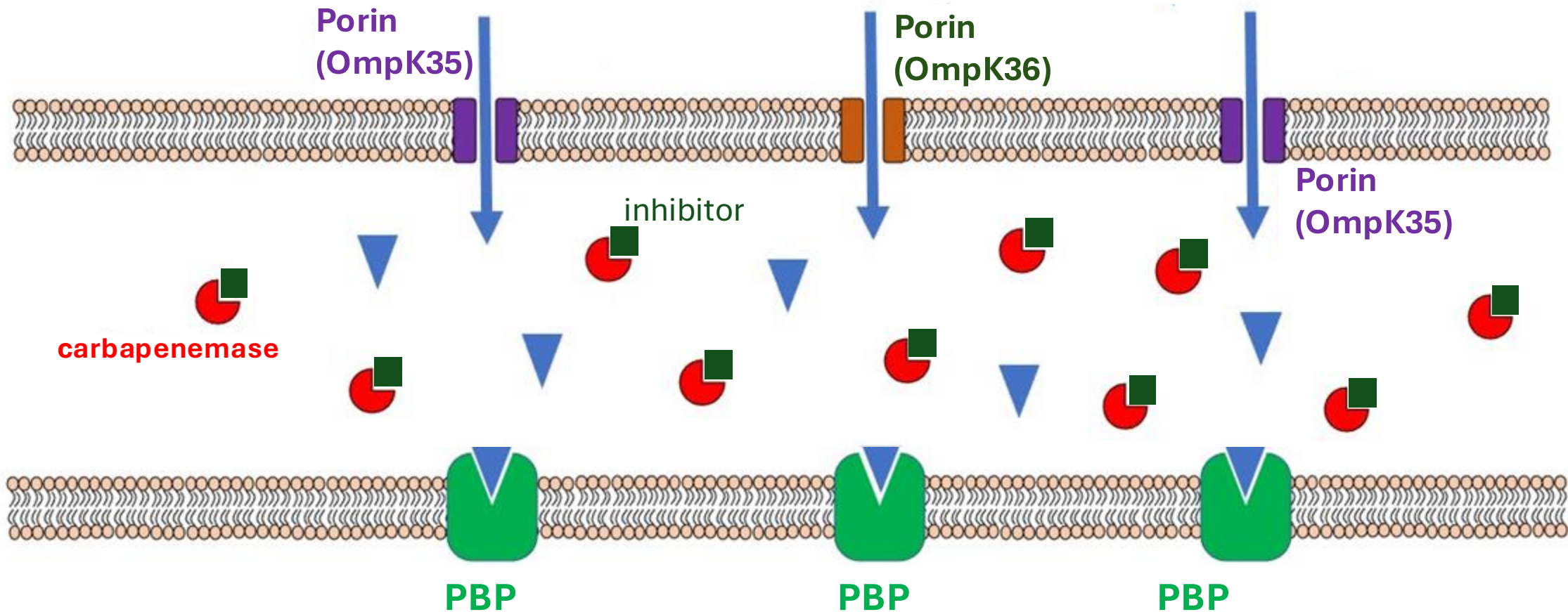


Carbapenem resistance in *Enterobacteriales*

1 CARBAPENEMASE PRODUCTION (CRE CPE)

K. pneumoniae
carbapenemase

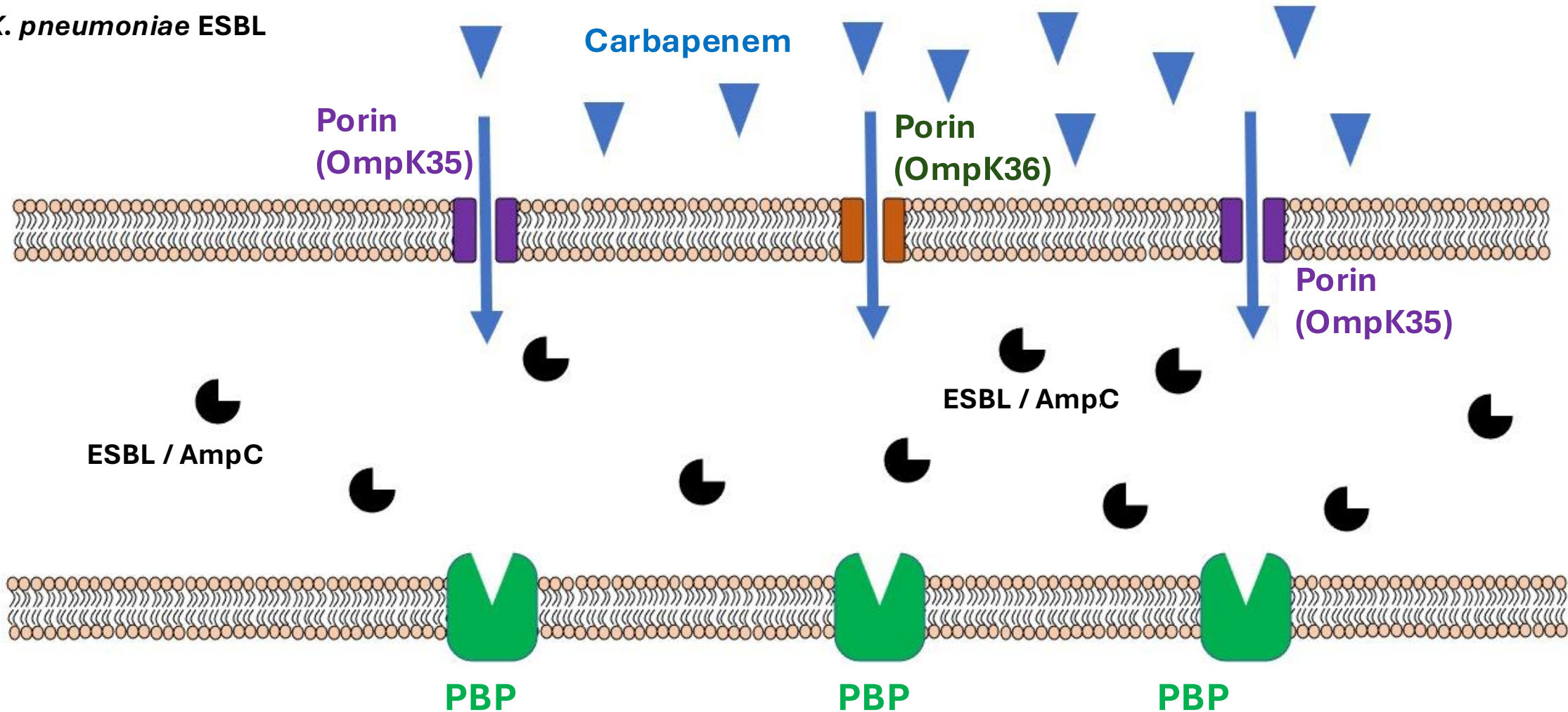
Carbapenem



Carbapenem resistance in *Enterobacteriales*

2 WITHOUT CARBAPENEMASE PRODUCTION (CRE non-CPE)

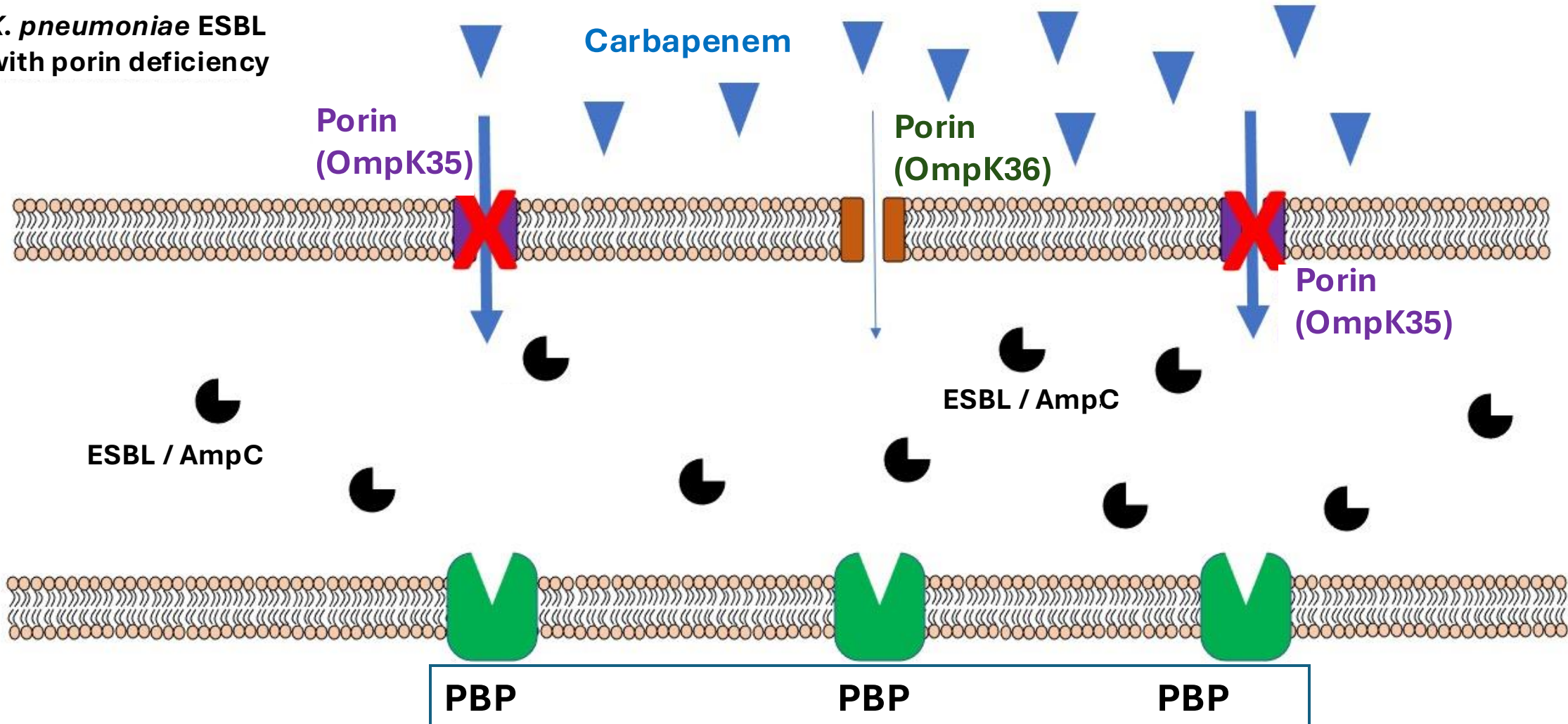
K. pneumoniae ESBL



Carbapenem resistance in *Enterobacteriales*

2 WITHOUT CARBAPENEMASE PRODUCTION (CRE non-CPE)

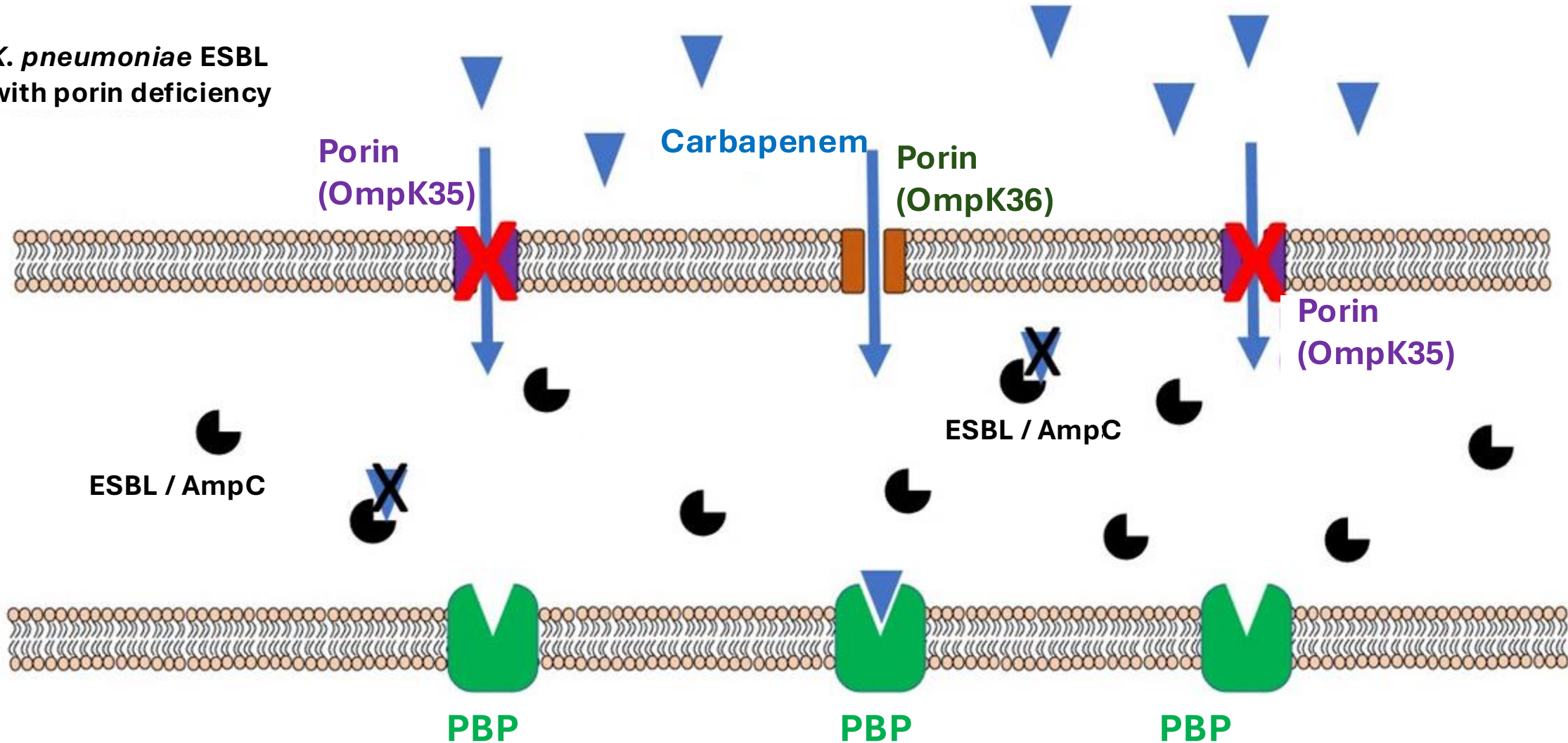
K. pneumoniae ESBL with porin deficiency



Carbapenem resistance in *Enterobacteriales*

2 WITHOUT CARBAPENEMASE PRODUCTION (CRE non-CPE)

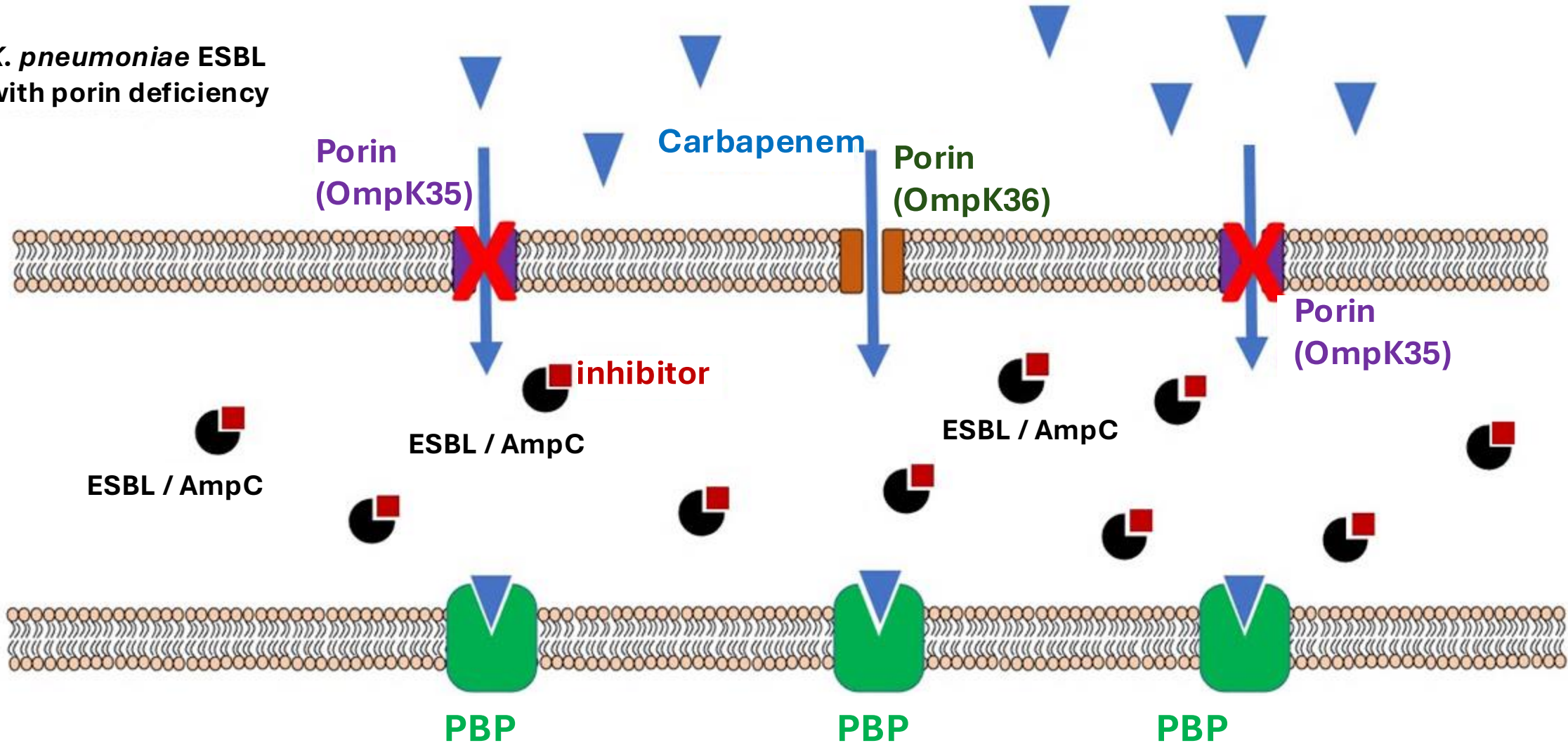
K. pneumoniae ESBL
with porin deficiency



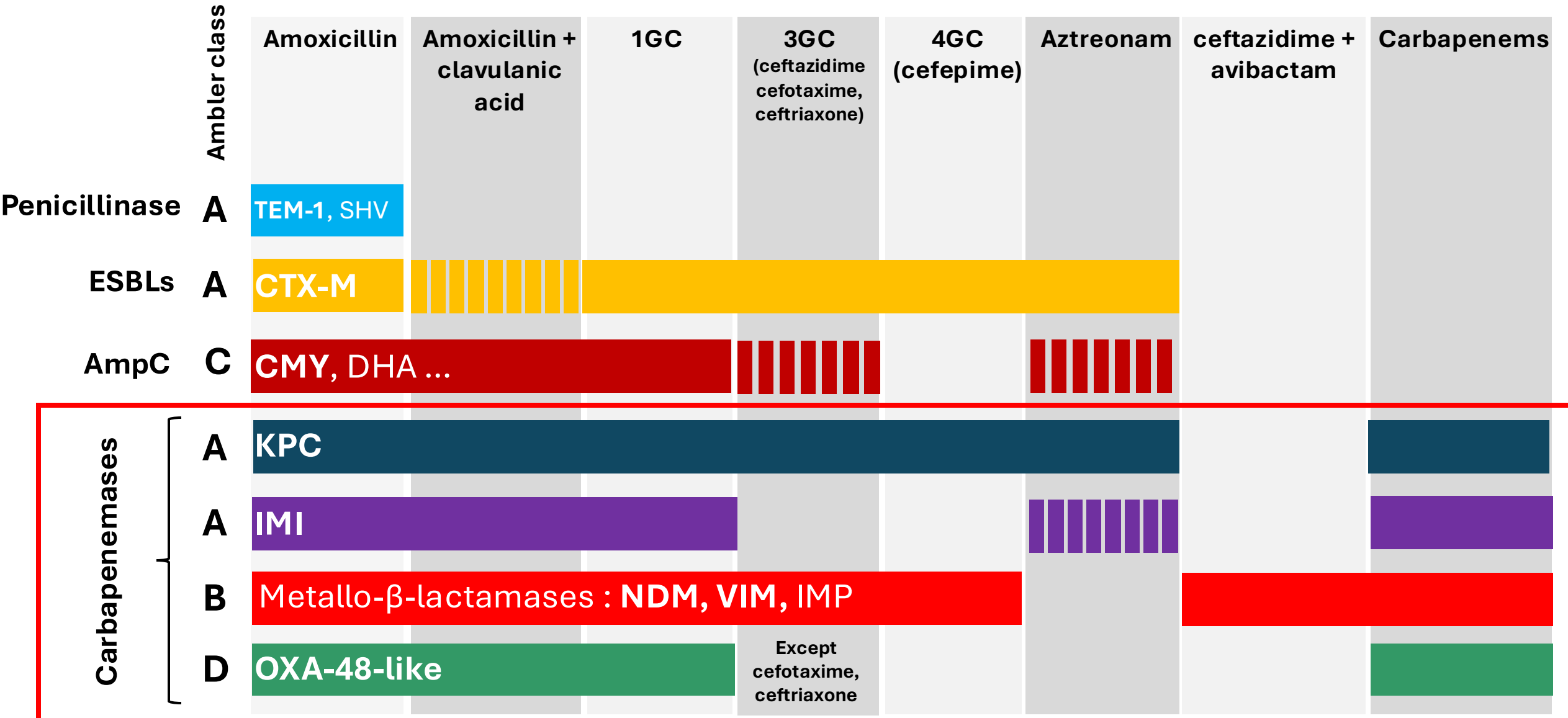
Carbapenem resistance in *Enterobacterales*

2 WITHOUT CARBAPENEMASE PRODUCTION (CRE non-CPE)

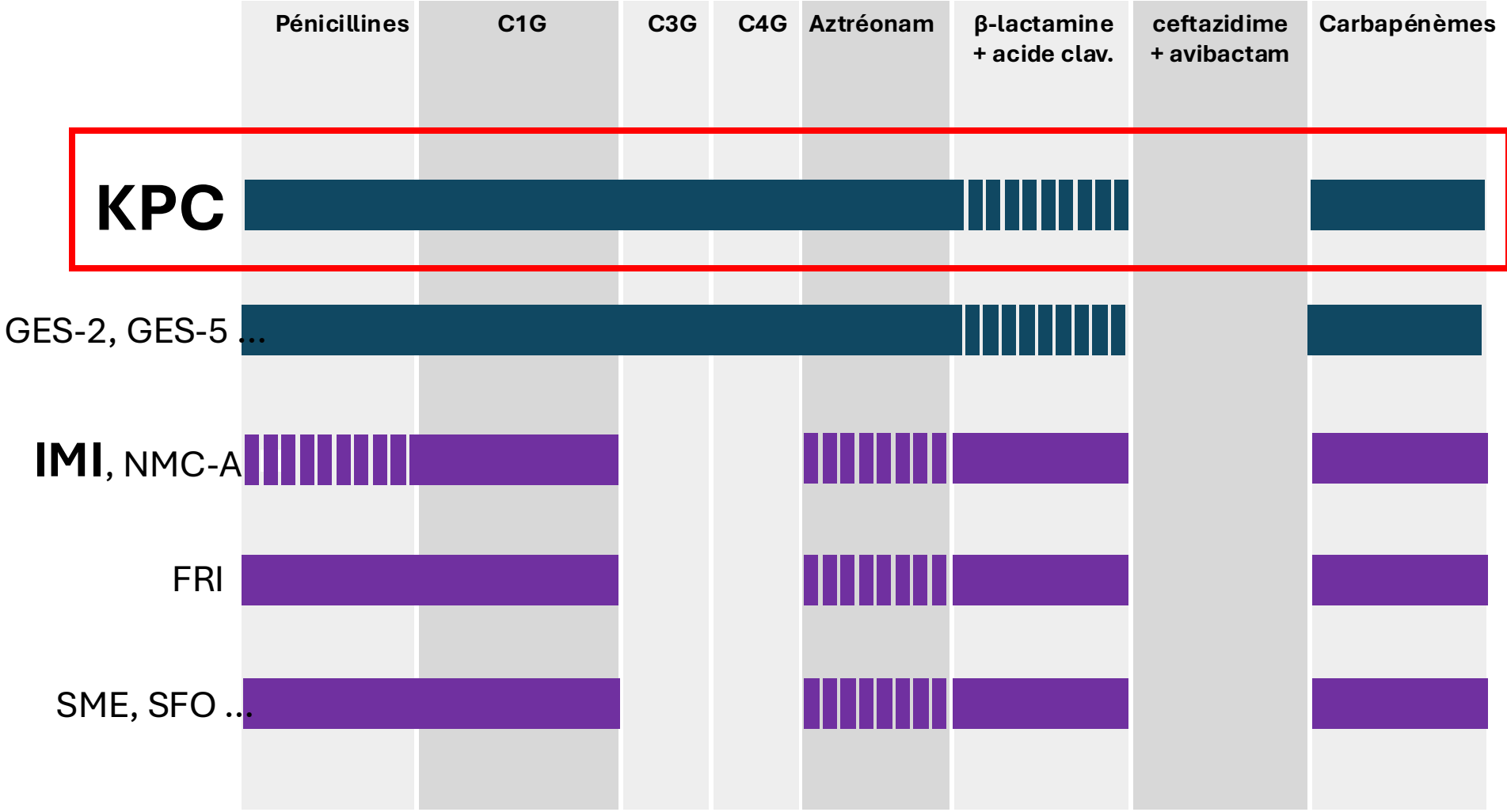
K. pneumoniae ESBL
with porin deficiency



Hydrolytic profile of β -lactamases in Enterobacterales



Class A carbapenemases in Enterobacteriales



KPC-3 producing *K. pneumoniae*



KPC : *Klebsiella Pneumoniae* Carbapenemase

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2001, p. 1151–1161
0066-4804/01/\$04.00+0 DOI: 10.1128/AAC.45.4.1151-1161.2001
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Vol. 45, No. 4

Novel Carbapenem-Hydrolyzing β -Lactamase, KPC-1, from a Carbapenem-Resistant Strain of *Klebsiella pneumoniae*

HESNA YIGIT,¹ ANNE MARIE QUEENAN,² GREGORY J. ANDERSON,¹
ANTONIO DOMENECH-SANCHEZ,³ JAMES W. BIDDLE,¹ CHRISTINE D. STEWARD,¹
SEBASTIAN ALBERTI,⁴ KAREN BUSH,² AND FRED C. TENOVER^{1*}

Hospital Infections Program, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia 30333¹; The R. W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey 08869²; and Unidad de Investigacion, Hospital Son Dureta, Andrea Doria, Palma de Mallorca, 07014,⁴ and Área de Microbiología, Universidad de las Islas Baleares, Crta. Valldemosa, Palma de Mallorca, 07071,³ Spain

2001



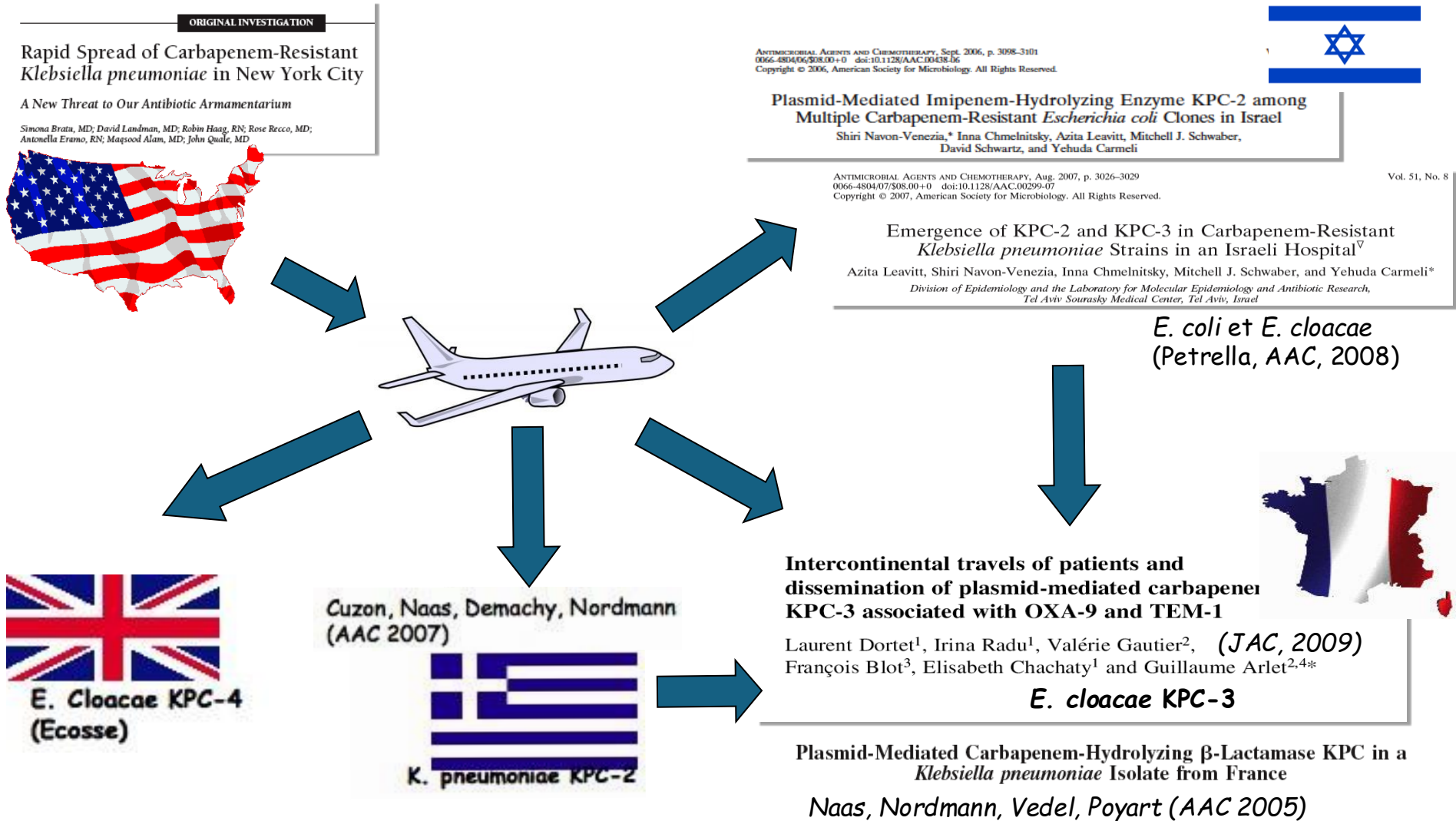
ORIGINAL INVESTIGATION

Rapid Spread of Carbapenem-Resistant *Klebsiella pneumoniae* in New York City

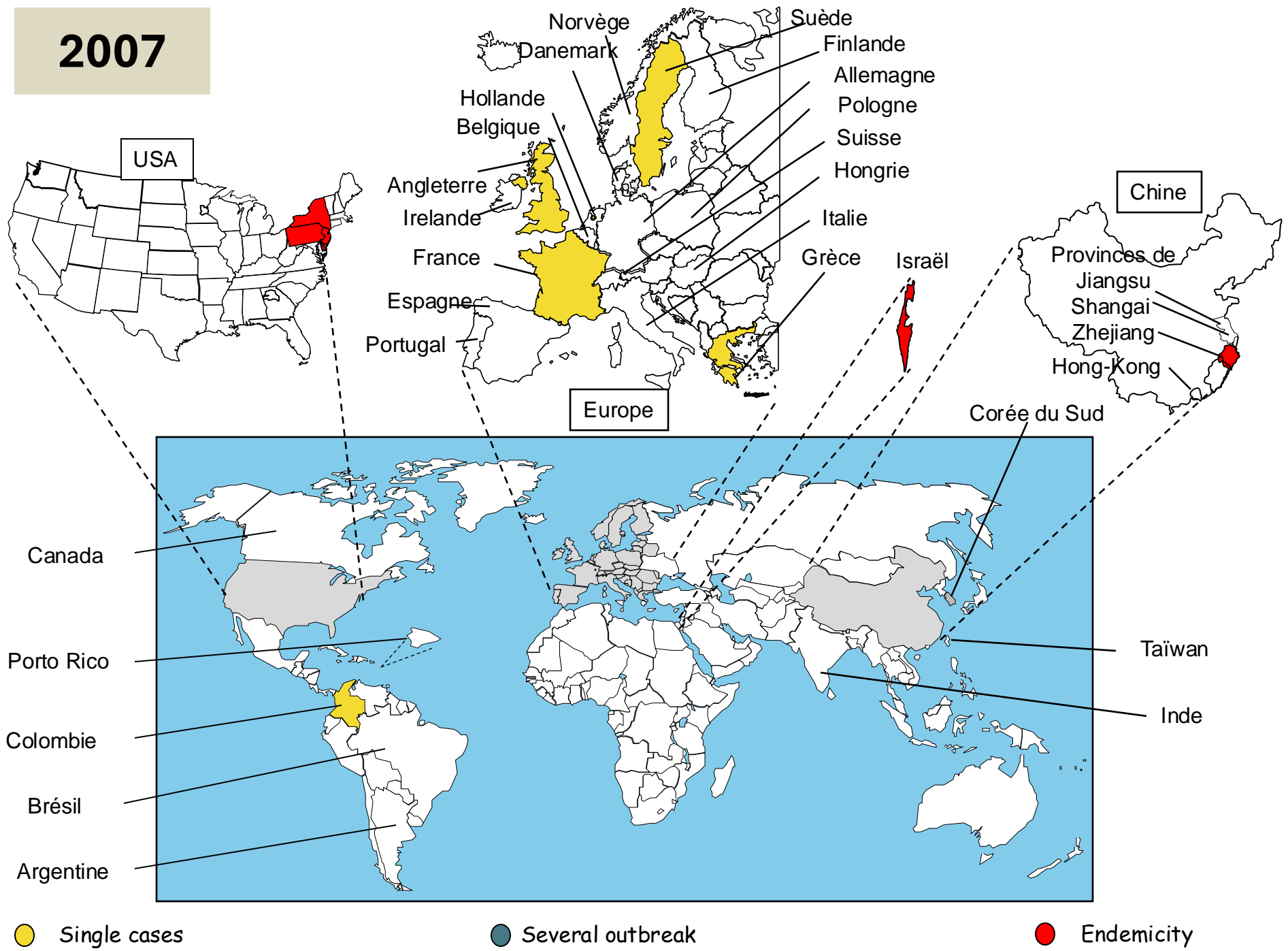
A New Threat to Our Antibiotic Armamentarium

*Simona Bratu, MD; David Landman, MD; Robin Haag, RN; Rose Recco, MD;
Antonella Eramo, RN; Maqsood Alam, MD; John Quale, MD*

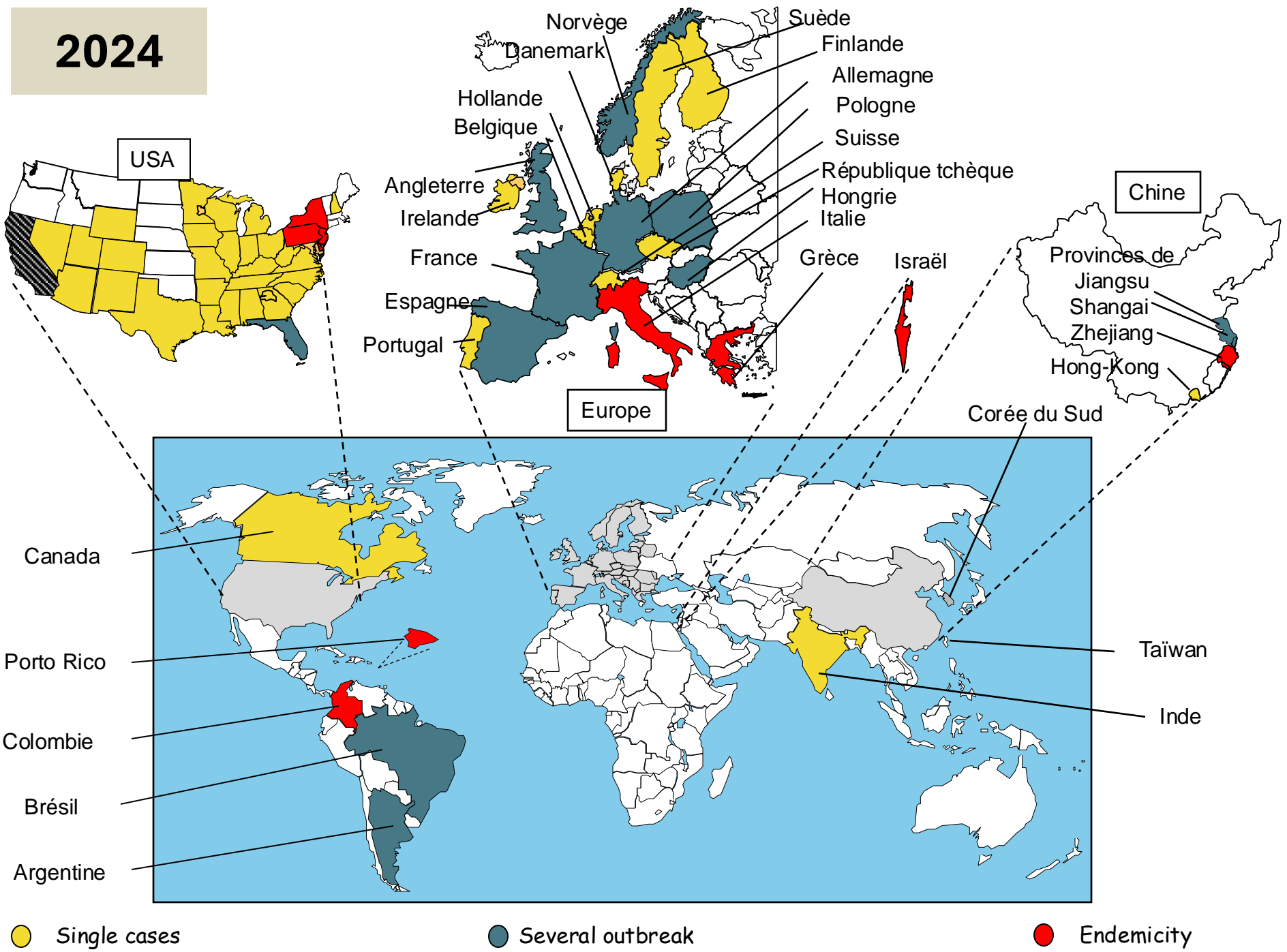
KPC dissemination



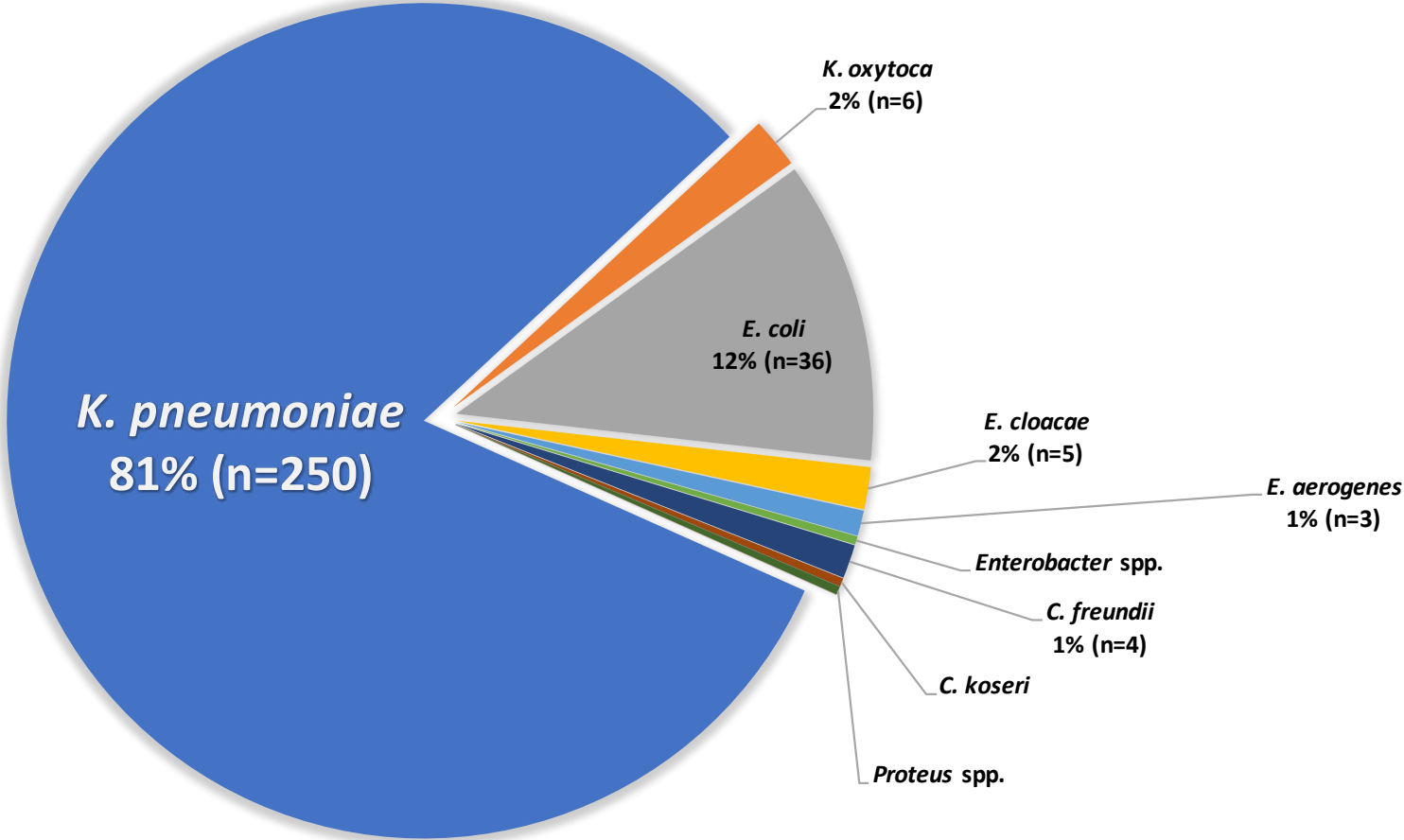
2007



2024

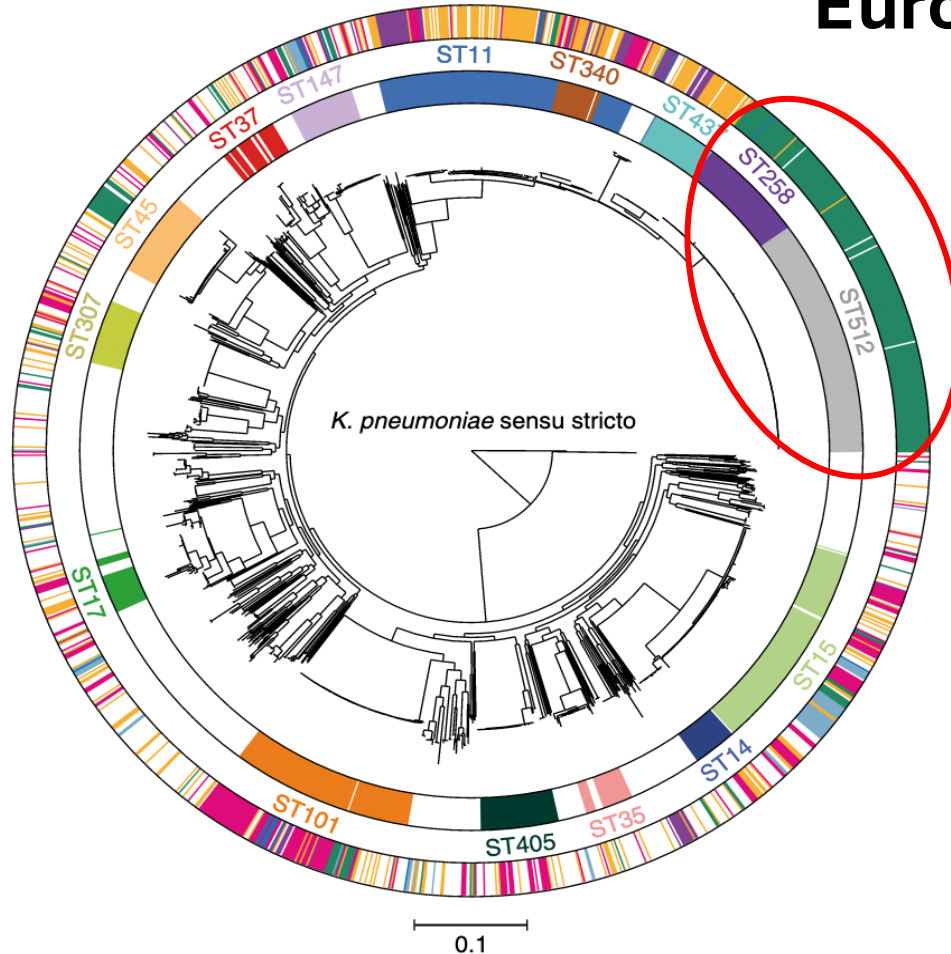


KPC carbapenemases are strongly associated with *K. pneumoniae*

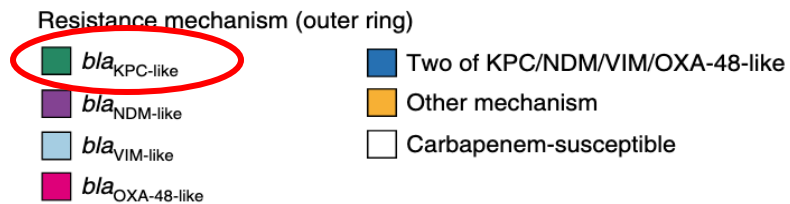


KPC-type carbapenemase producing Enterobacteriales from France 2014-2019

Dissemination of ST258/512 *K. pneumoniae* in Europe

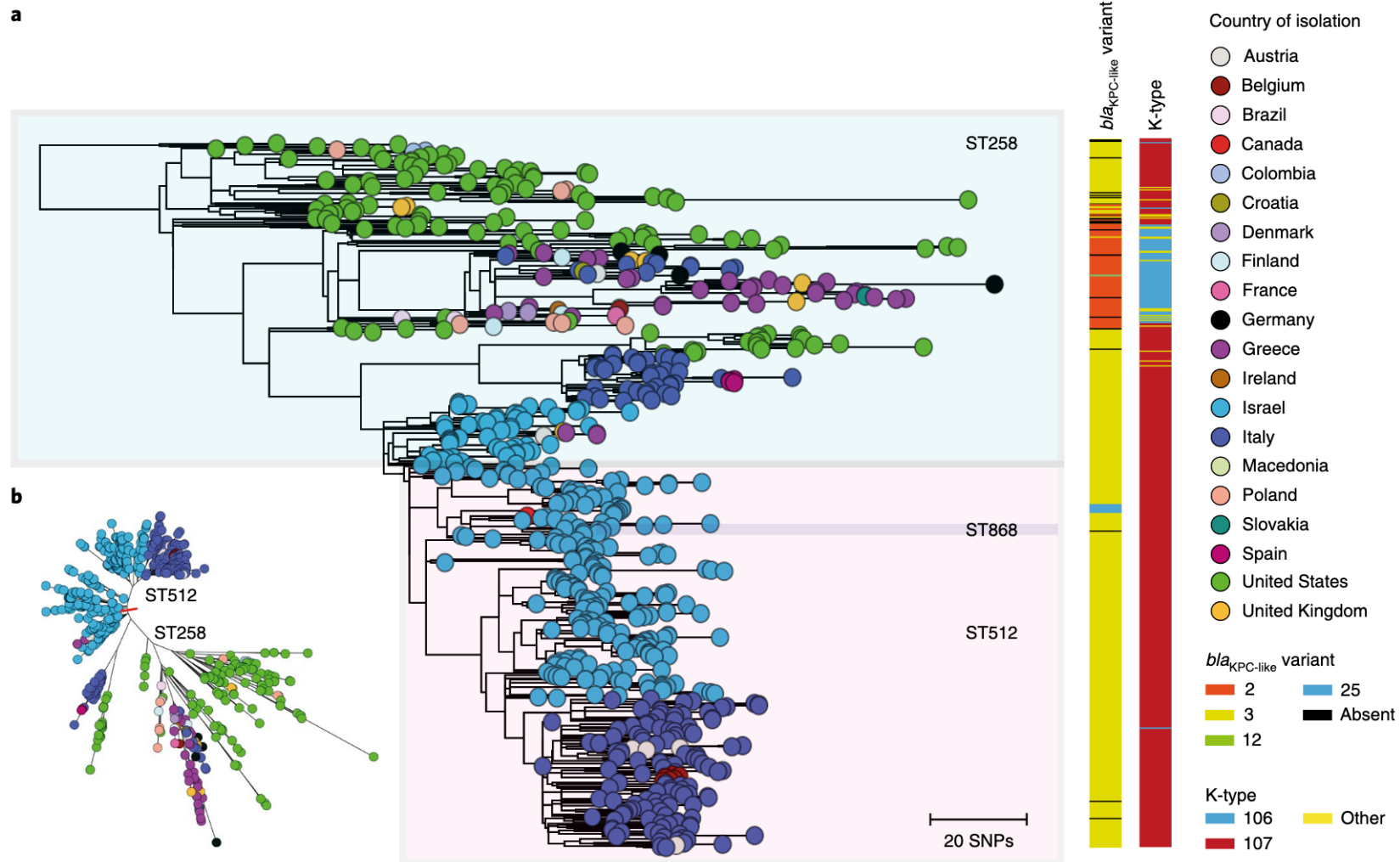


In 2013, in Europe most of KPC-producing *K. pneumoniae* were of ST258/512

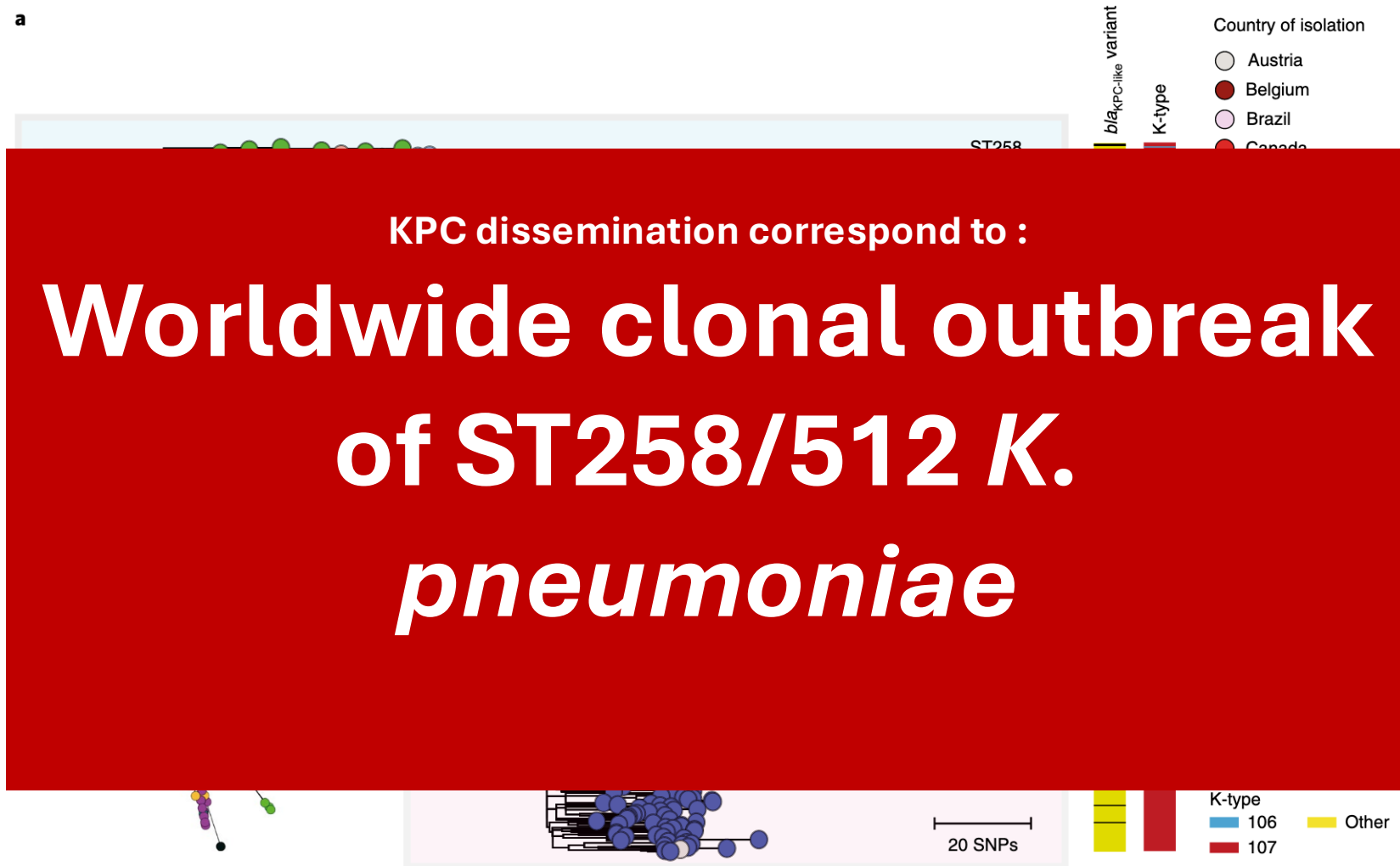


Phylogenetic tree of 1,649 isolates belonging to *K. pneumoniae* of the EuSCAPE study (2013)

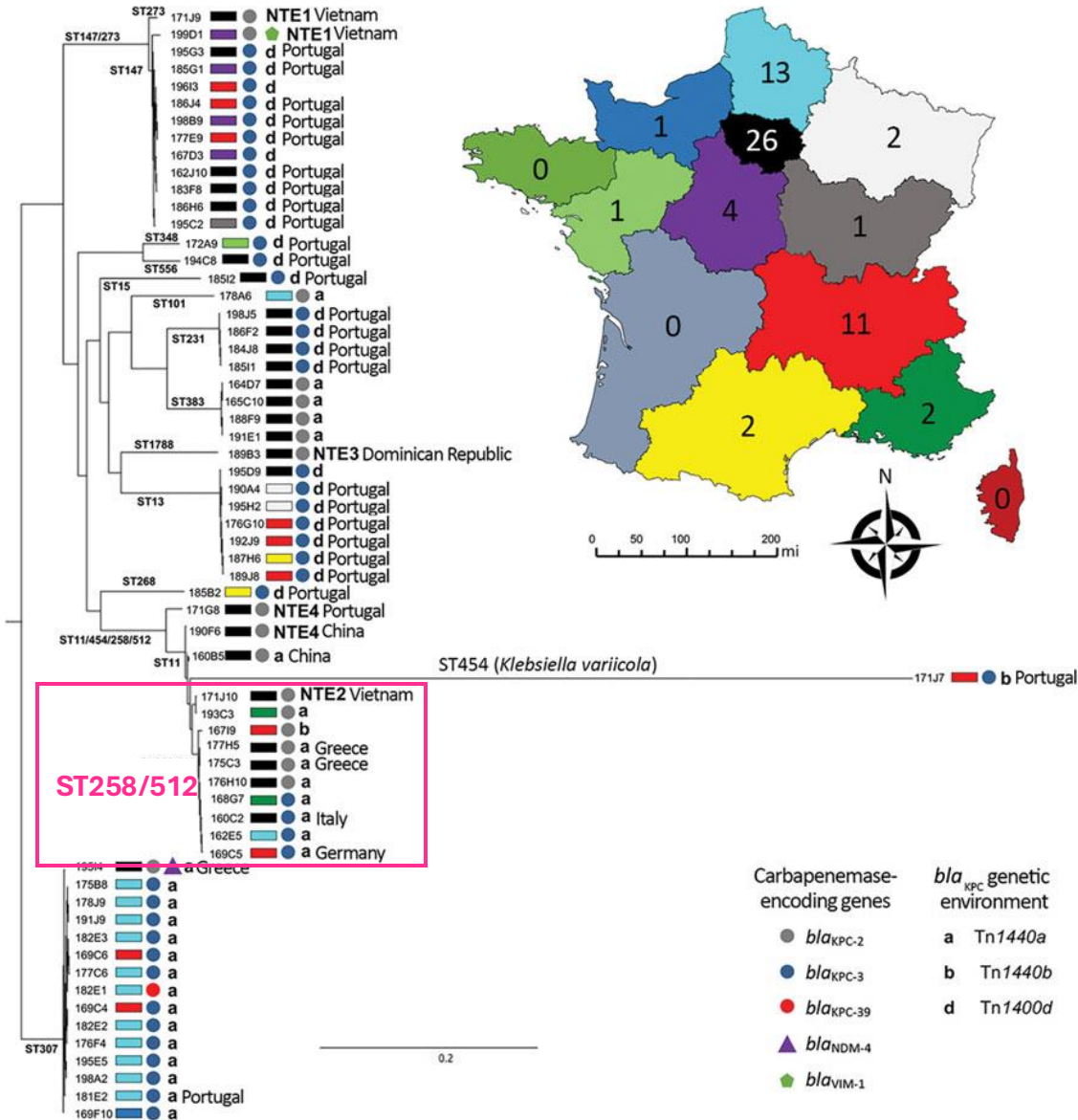
International spread of the epidemic ST258/512 clone of *K. pneumoniae*



International spread of the epidemic ST258/512 clone of *K. pneumoniae*

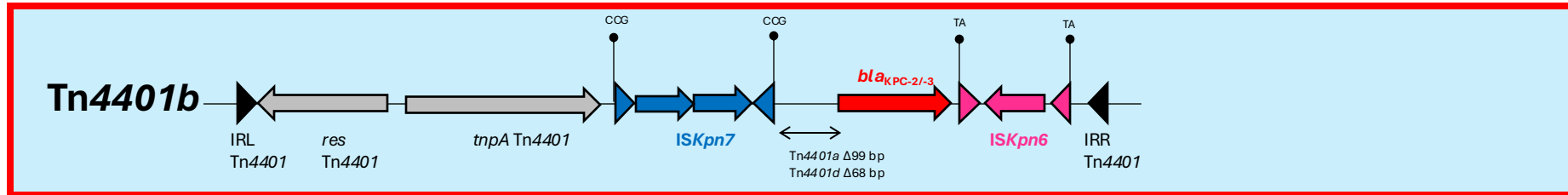


KPC-producing *K. pneumoniae* : the French and « Portuguese » paradox

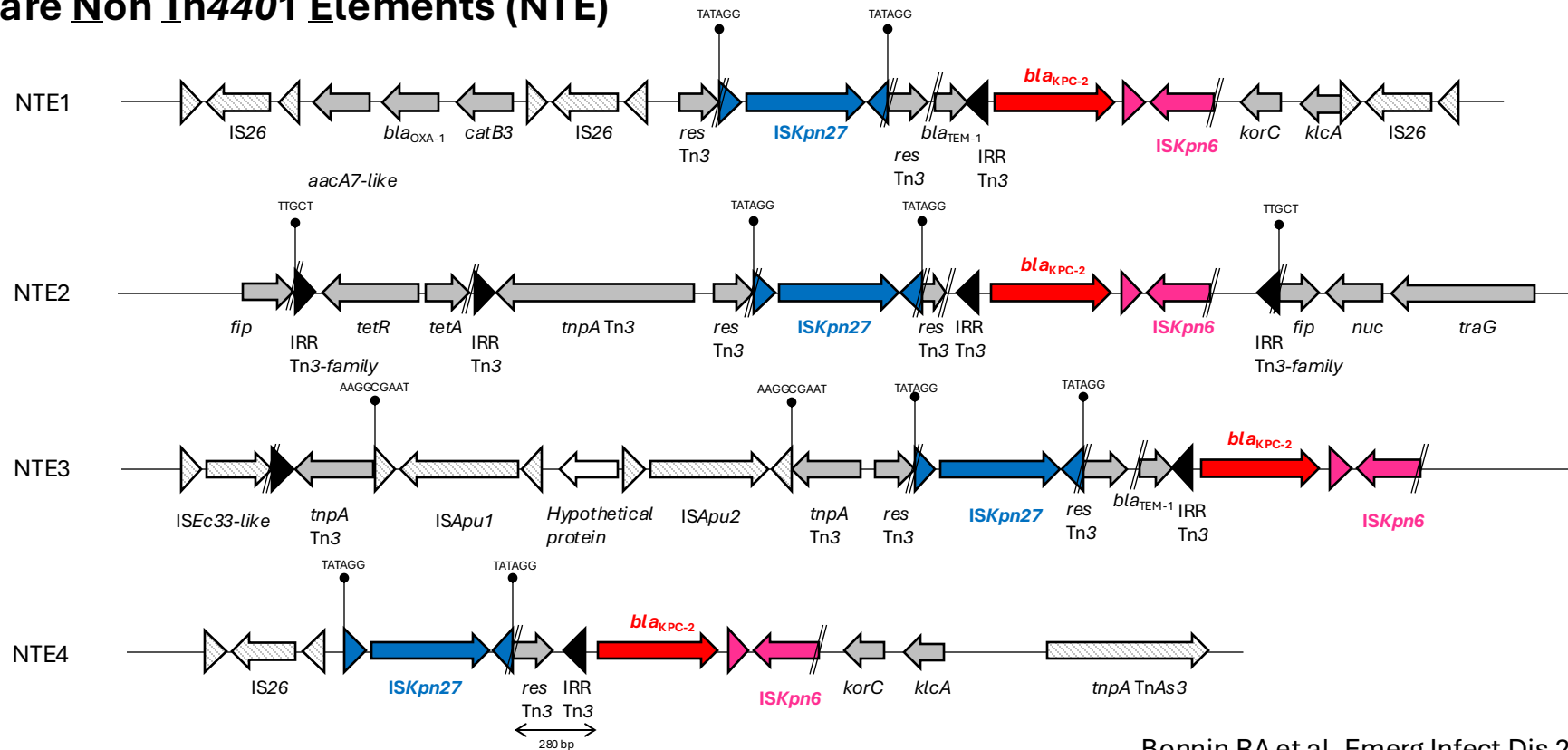


In 2018, ST258/512 KPC-producing *K. pneumoniae* are not the most prevalent STs in France and Portugal

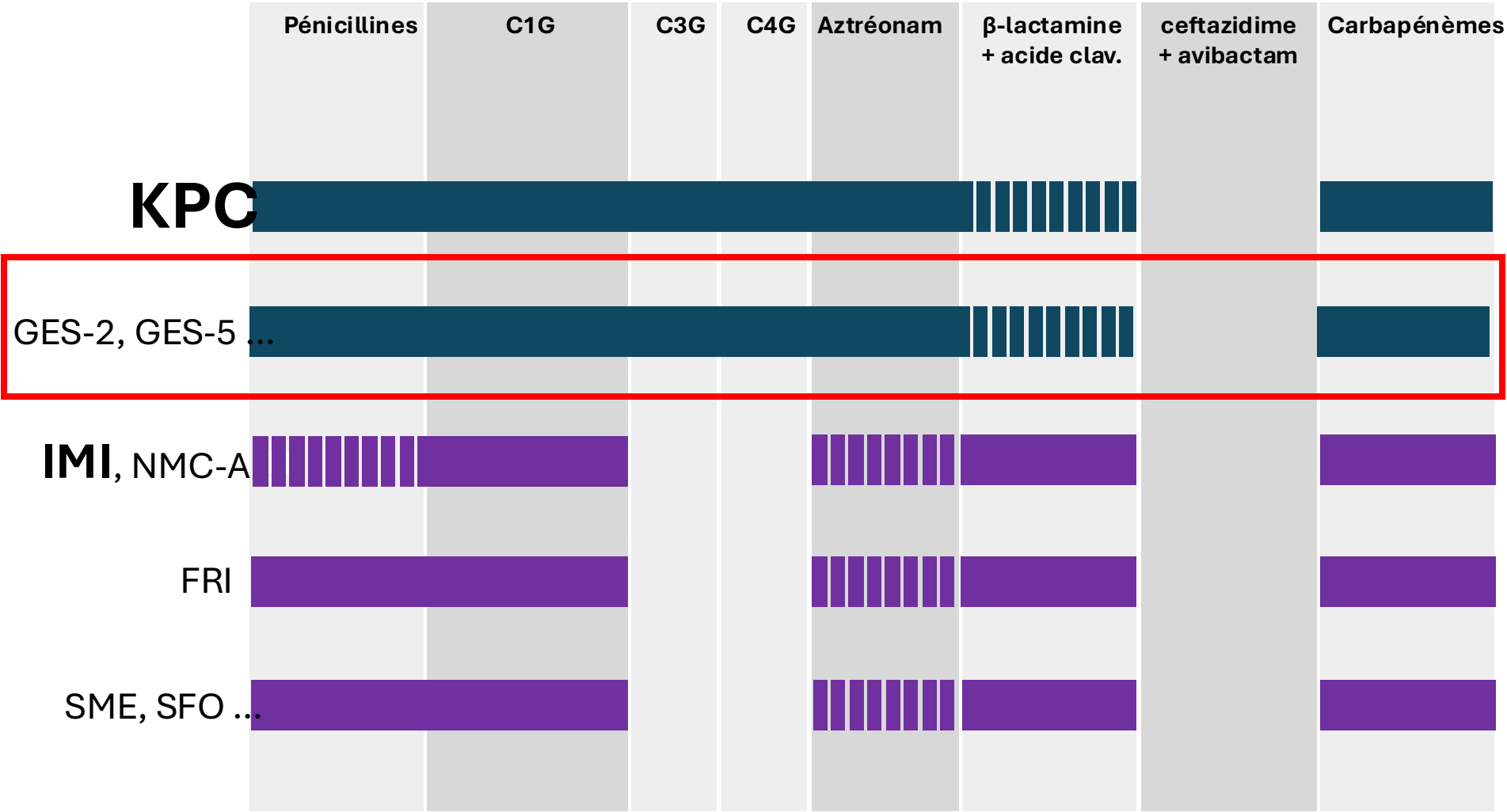
Genetic environments of *bla*_{KPC}



Rare Non Tn4401 Elements (NTE)



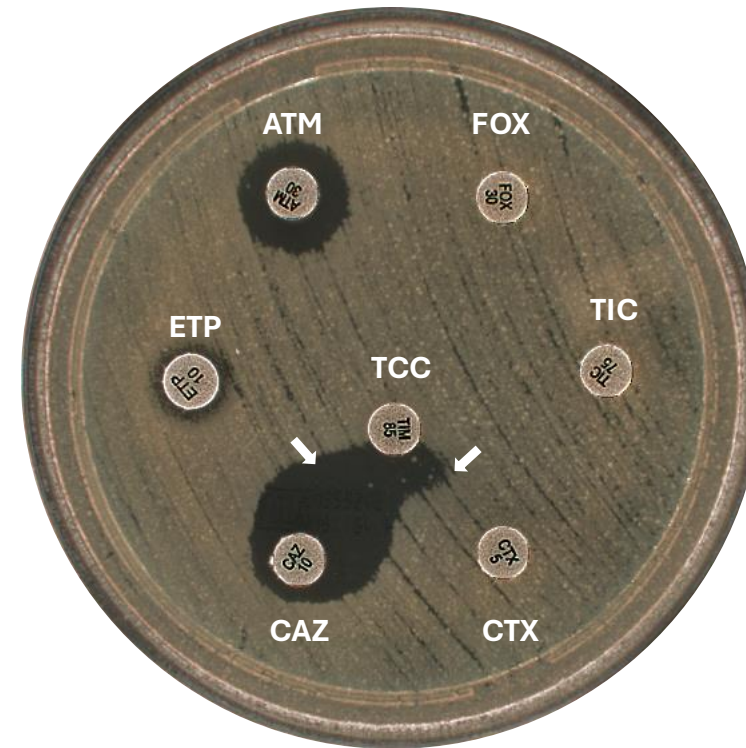
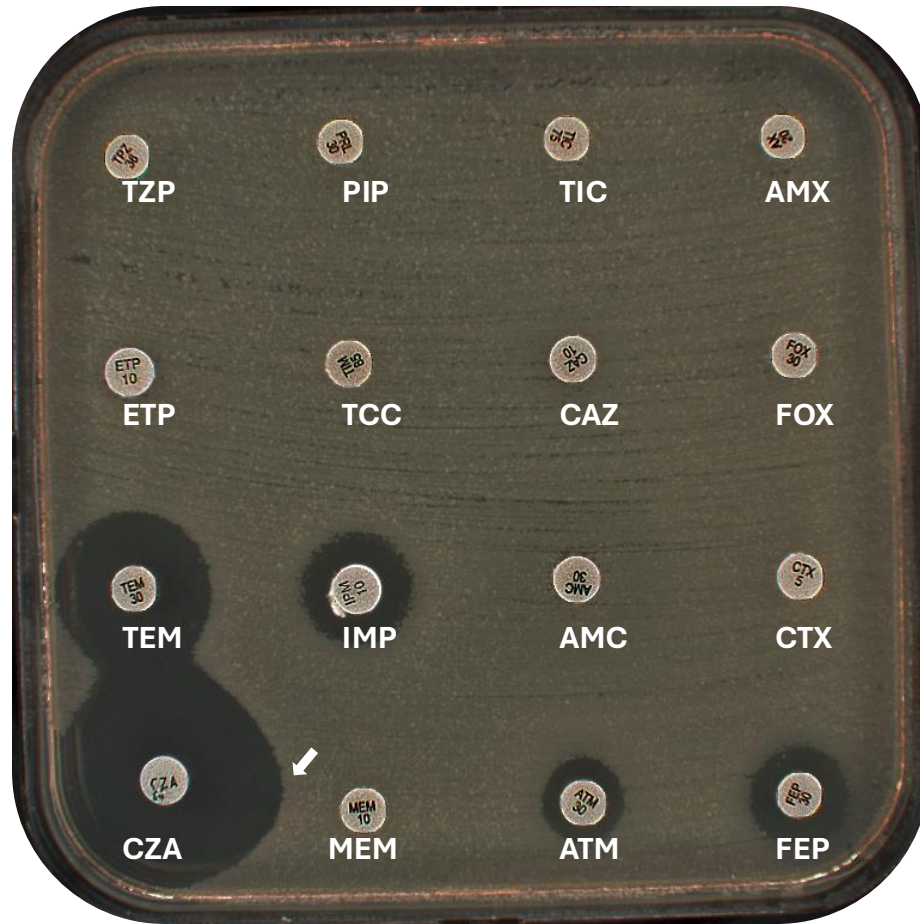
Class A carbapenemases in Enterobacteriales



GES-5 producing *K. pneumoniae*



GES-5 producing *K. pneumoniae*



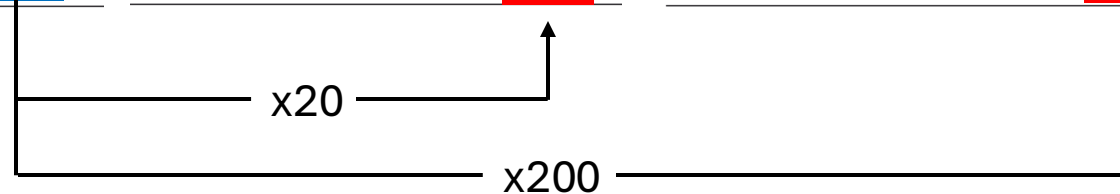
Gly170 mutation transforms ESBL in carbapenemase

TABLE 1. Studied GES variants differing from GES-1 by one or two residues at Ambler positions 104 and 170

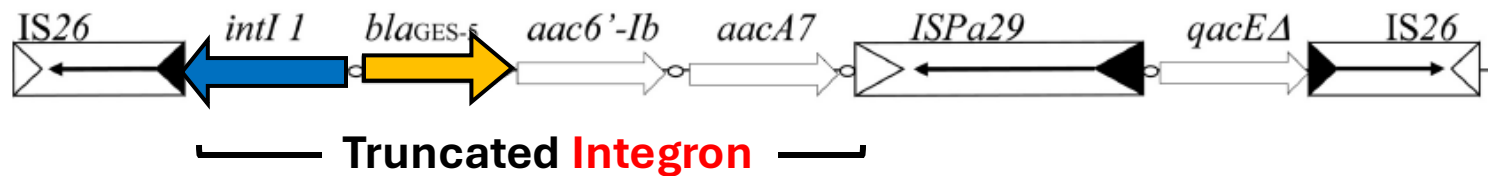
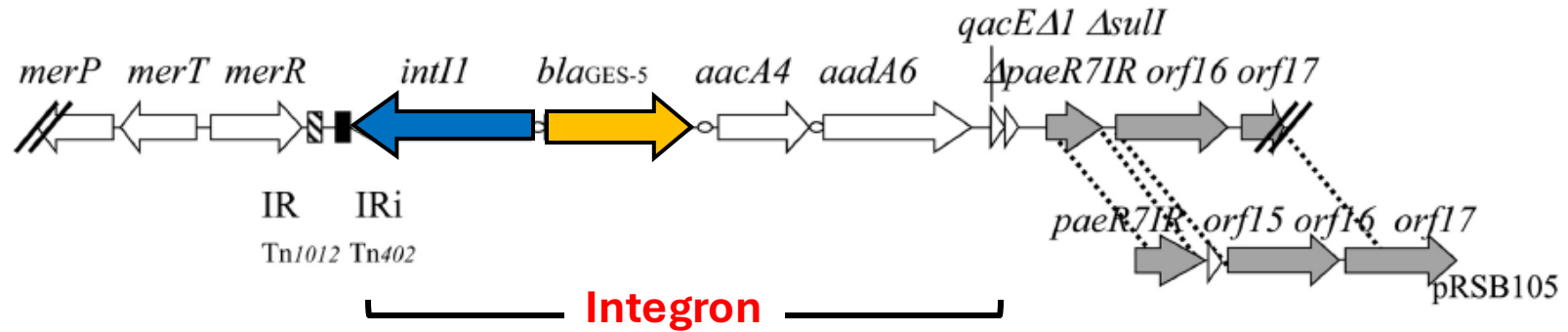
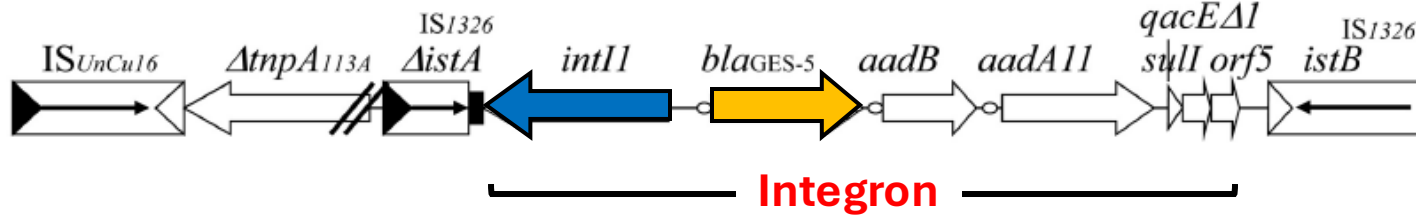
β -Lactamase	Amino acid residue at position:	
	104	170
GES-1	Glu	Gly
GES-7 ^a	Lys	Gly
GES-2	Glu	Asn
GES-5	Glu	Ser
GES-6	Lys	Ser

} ESBLs (GES-1, GES-7)
} Carbapenemases (GES-2, GES-5, GES-6)

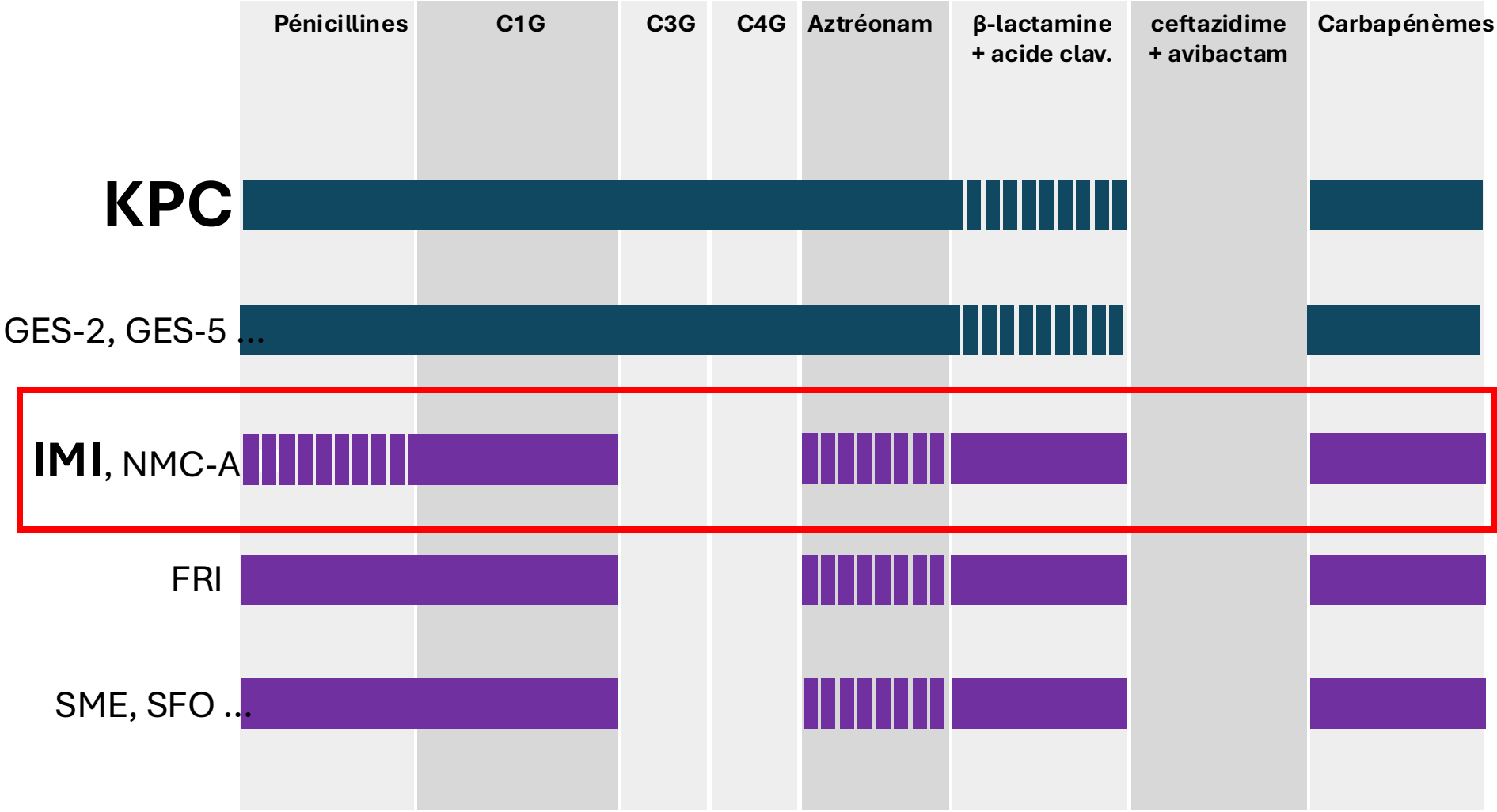
β -Lactam	GES-1 (E104, G170)			GES-2 (E104, N170)			GES-5 (E104, S170)		
	k_{cat} (s ⁻¹)	K_m (μ M)	$\frac{k_{cat}}{K_m}$ (μ M ⁻¹ · s ⁻¹)	k_{cat} (s ⁻¹)	K_m (μ M)	$\frac{k_{cat}}{K_m}$ (μ M ⁻¹ · s ⁻¹)	k_{cat} (s ⁻¹)	K_m (μ M)	$\frac{k_{cat}}{K_m}$ (μ M ⁻¹ · s ⁻¹)
Penicillin G	30.5	120	0.26	5.75	87.6	0.07	28.6	88.9	0.32
Cephalothin	218	87.8	2.48	2.94	53.9	0.05	167	61.1	2.73
Cefoxitin	ND	ND	ND	ND	ND	ND	7.50	221	0.03
Ceftazidime	10.5	137	0.077	0.21	98.2	0.002	0.24	135	0.002
Aztreonam	ND	ND	ND	ND	ND	ND	ND	ND	ND
Cefotaxime	56.8	152	0.37	37.2	261	0.14	3.55	133	0.03
Imipenem	0.006	1.2	0.005	0.016	0.87	0.02	0.332	1.27	0.26



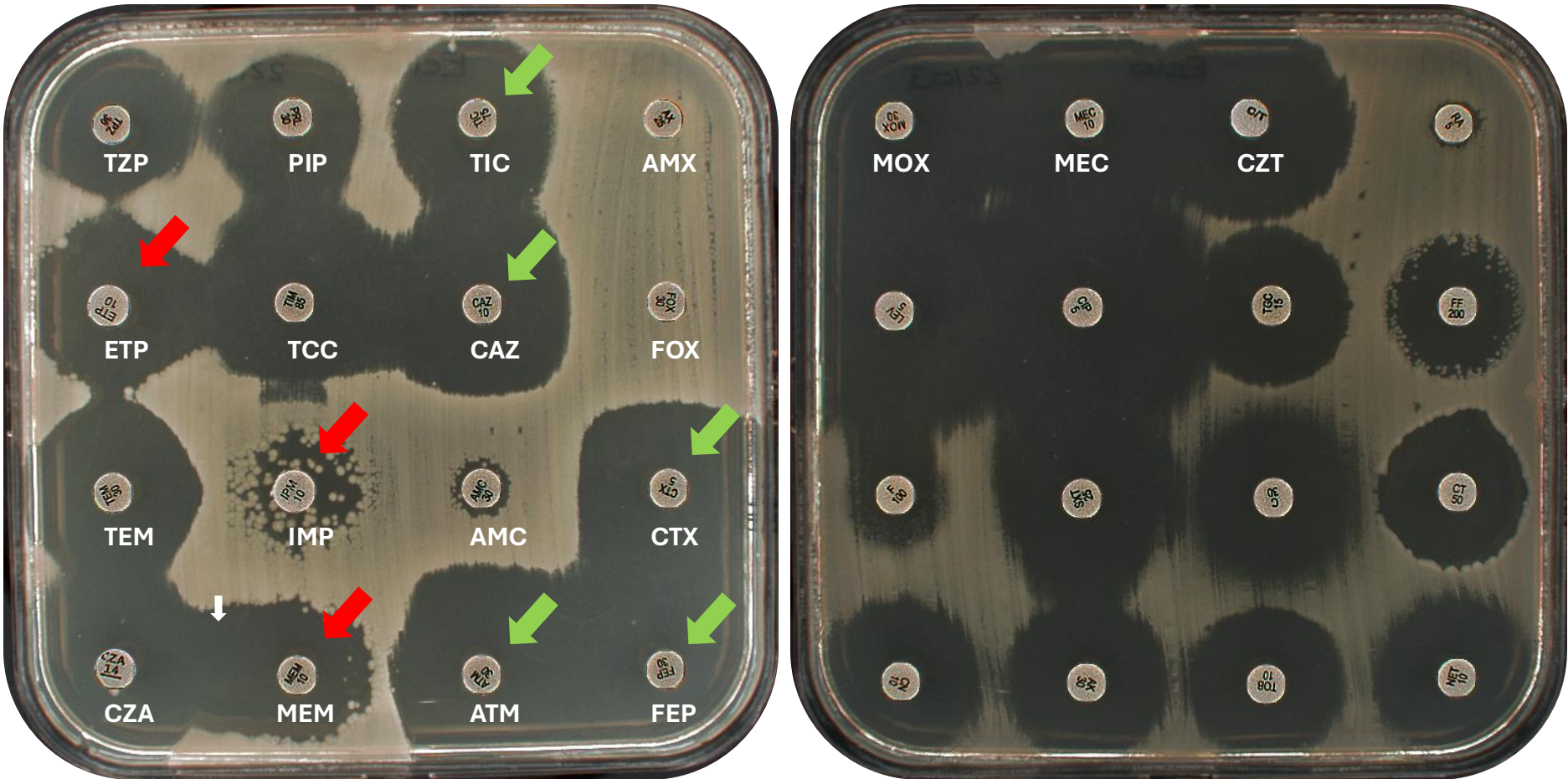
Genetic environments of *bla*_{GES-2/-5}



Class A carbapenemases in Enterobacteriales



IMI-1 producing *E. cloacae* complex



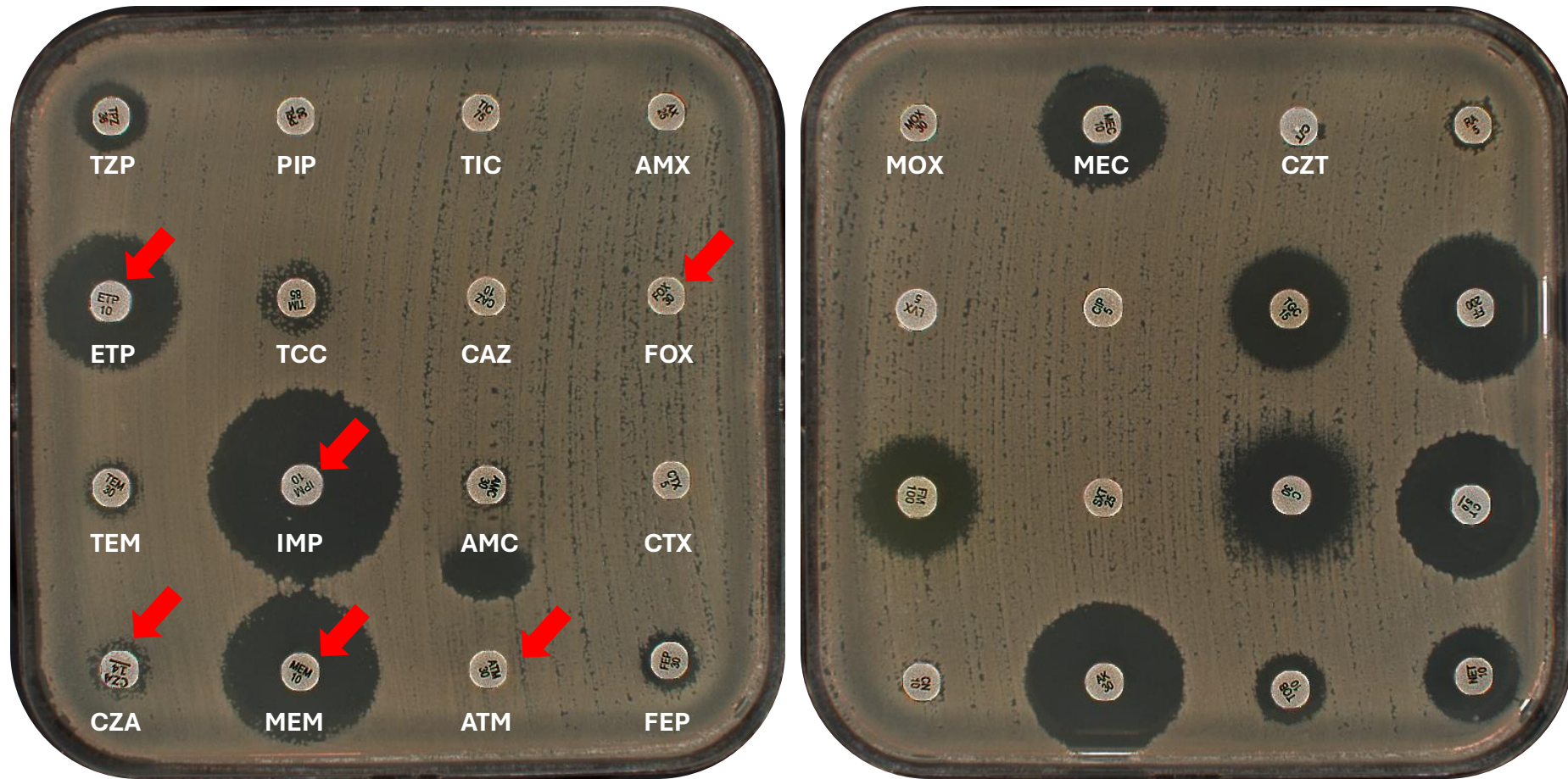
Métallo- β -lactamases in Enterobacterales

Pénicillines	C1G	C3G	C4G	Aztréonam	β -lactamine + acide clav.	ceftazidime + avibactam	Carbapénèmes
Métallo- β -lactamases : NDM, VIM, IMP							

IMP-4 producing *E. cloacae*



IMP-4 + CTX-M-15 producing *K. pneumoniae*



VIM, IMP and GIM-type metallo- β -lactamases



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 1999, p. 1584–1590
0066-4804/99/\$04.00+0
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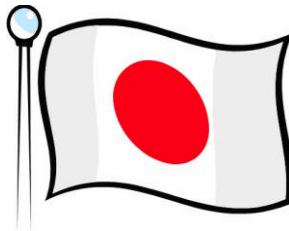
Vol. 43, No. 7

Cloning and Characterization of *bla*_{VIM}, a New Integron-Borne Metallo- β -Lactamase Gene from a *Pseudomonas aeruginosa* Clinical Isolate

LAURA LAURETTI,¹ MARIA LETIZIA RICCIO,¹ ANNARITA MAZZARIOL,² GIUSEPPE CORNAGLIA,² GIANFRANCO AMICOSANTE,³ ROBERTA FONTANA,² AND GIAN MARIA ROSSOLINI^{1*}

Dipartimento di Biologia Molecolare, Sezione di Microbiologia, Università di Siena, 53100-Siena,¹ Istituto di Microbiologia, Università di Verona, 37134-Verona,² and Dipartimento di Scienze e Tecnologie Biomediche e Biometria, Università dell'Aquila, 67100-L'Aquila,³ Italy

VIM 1999



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 1995, p. 824–829
0066-4804/95/\$04.00+0
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Vol. 39, No. 4

Plasmid-Mediated Dissemination of the Metallo- β -Lactamase Gene *bla*_{IMP} among Clinically Isolated Strains of *Serratia marcescens*

HIDEO ITO,^{1,2} YOSHICHIKA ARAKAWA,^{1*} SHINJI OHSUKA,¹ ROCHAPORN WACHAROTAYANKUN,[†] NOBUO KATO,¹ AND MICHIO OHTA¹

Department of Bacteriology, Nagoya University School of Medicine, Nagoya 466,¹ and College of Medical Technology, Nagoya University, Nagoya 461,² Japan

IMP 1995



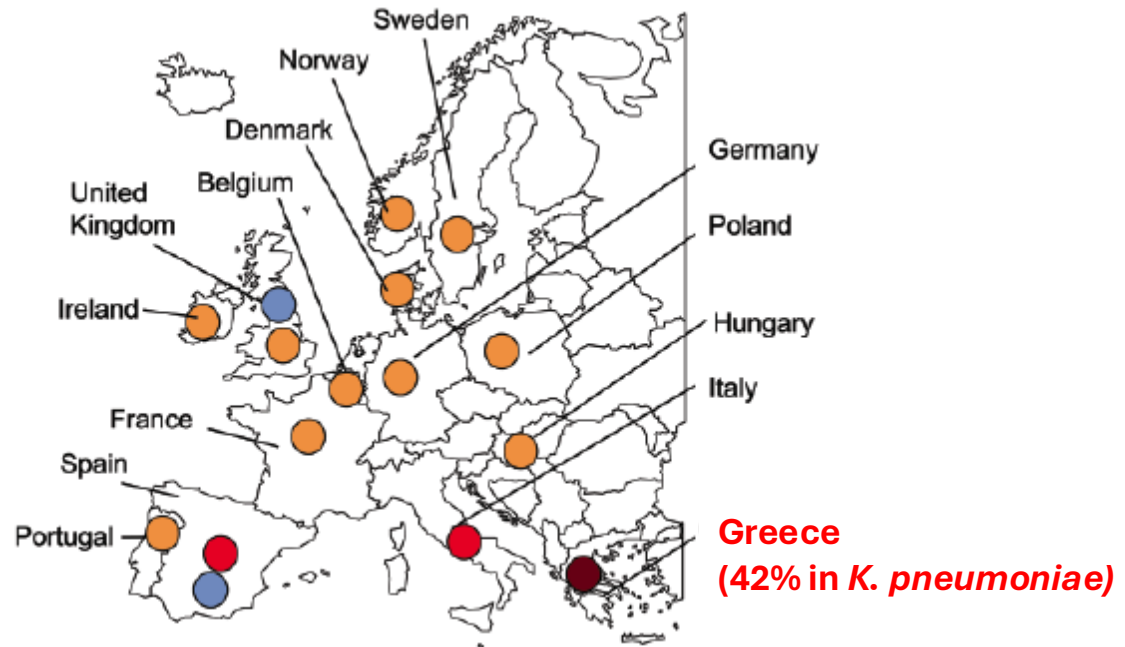
Emergence of Metallo- β -Lactamase GIM-1 in a Clinical Isolate of *Serratia marcescens*

Helme Rieber,^a Andre Frontzek,^a and Yvonne Pfelfer^b

GIM 2012

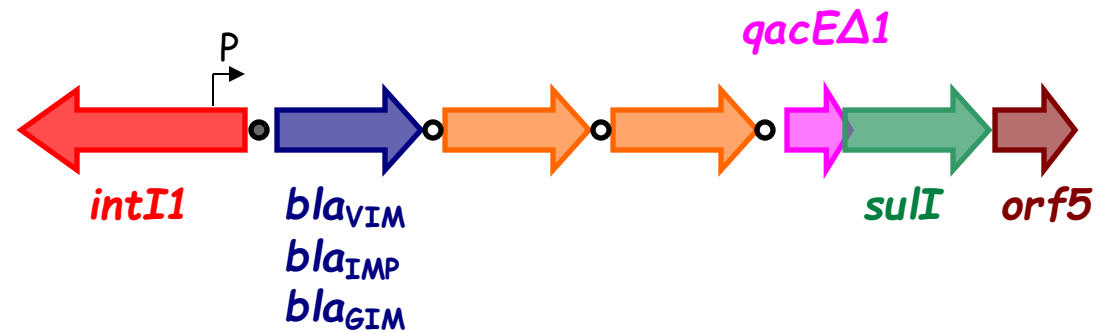
Dissemination of IMP and VIM carbapenemases

- VIM-producing isolates/outbreaks
- VIM interhospital spread
- VIM high prevalence
- IMP-producing isolates/outbreaks
- IMP high prevalence



Genetic environment of *bla*_{VIM}, *bla*_{IMP} et *bla*_{GIM}

- Class 1 integron



- Diversity of plasmids

- ***Pseudomonas aeruginosa* and Enterobacterales**

NDM : New Dehli Metallo- β -lactamase



2009

Carriage in population prevalence = 18,5%

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2009, p. 5046–5054
0066-4804/09/\$12.00 doi:10.1128/AAC.00774-09
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Vol. 53, No. 12

Characterization of a New Metallo- β -Lactamase Gene, *bla*_{NDM-1}, and a Novel Erythromycin Esterase Gene Carried on a Unique Genetic Structure in *Klebsiella pneumoniae* Sequence Type 14 from India[∇]

Dongeun Yong,^{1,2} Mark A. Toleman,² Christian G. Giske,³ Hyun S. Cho,⁴ Kristina Sundman,⁵ Kyungwon Lee,¹ and Timothy R. Walsh^{2,4}

Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study

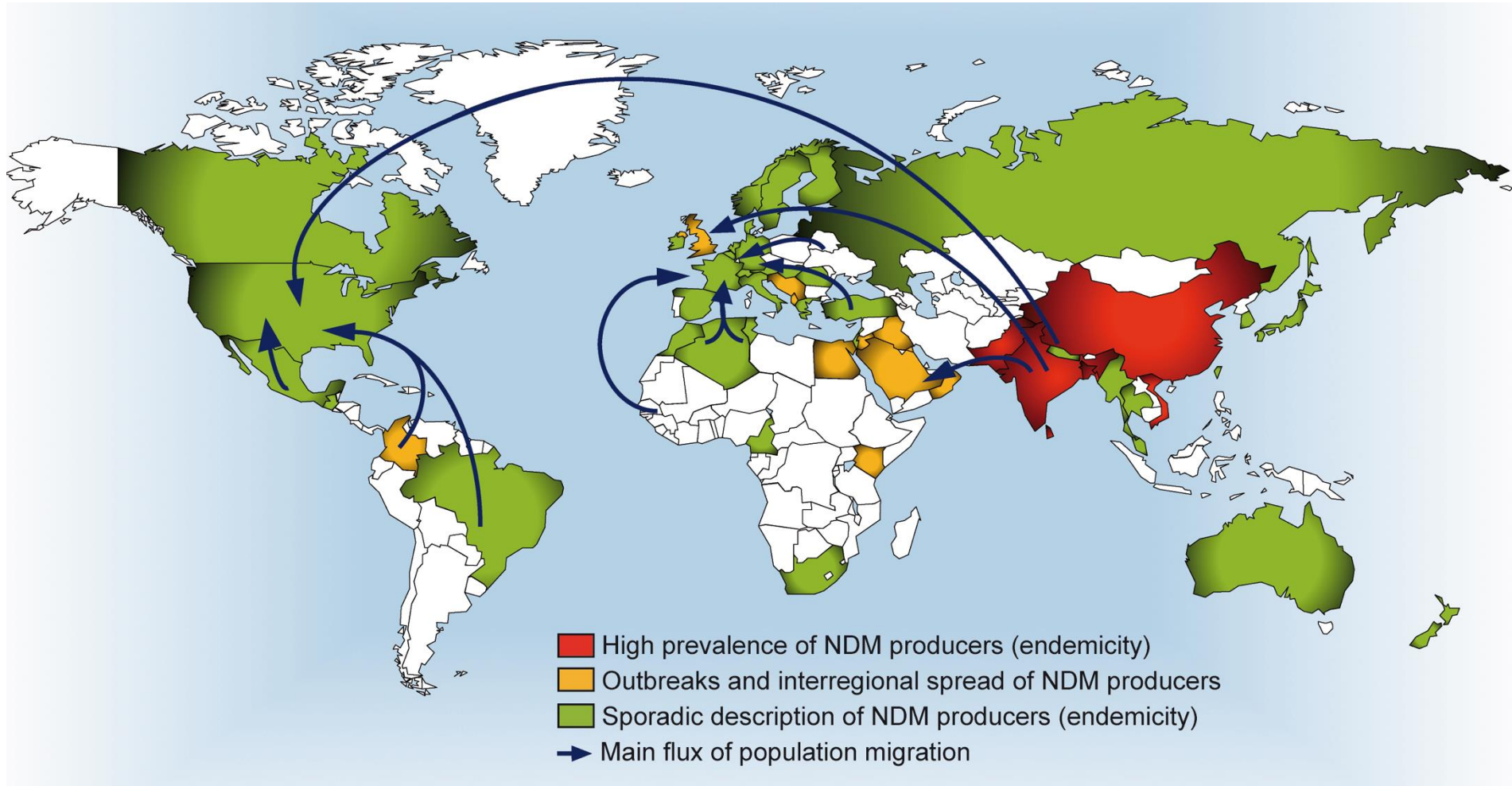
Timothy R Walsh, Janis Weeks, David M Livermore, Mark A Toleman

Lancet Infectious Diseases 2011

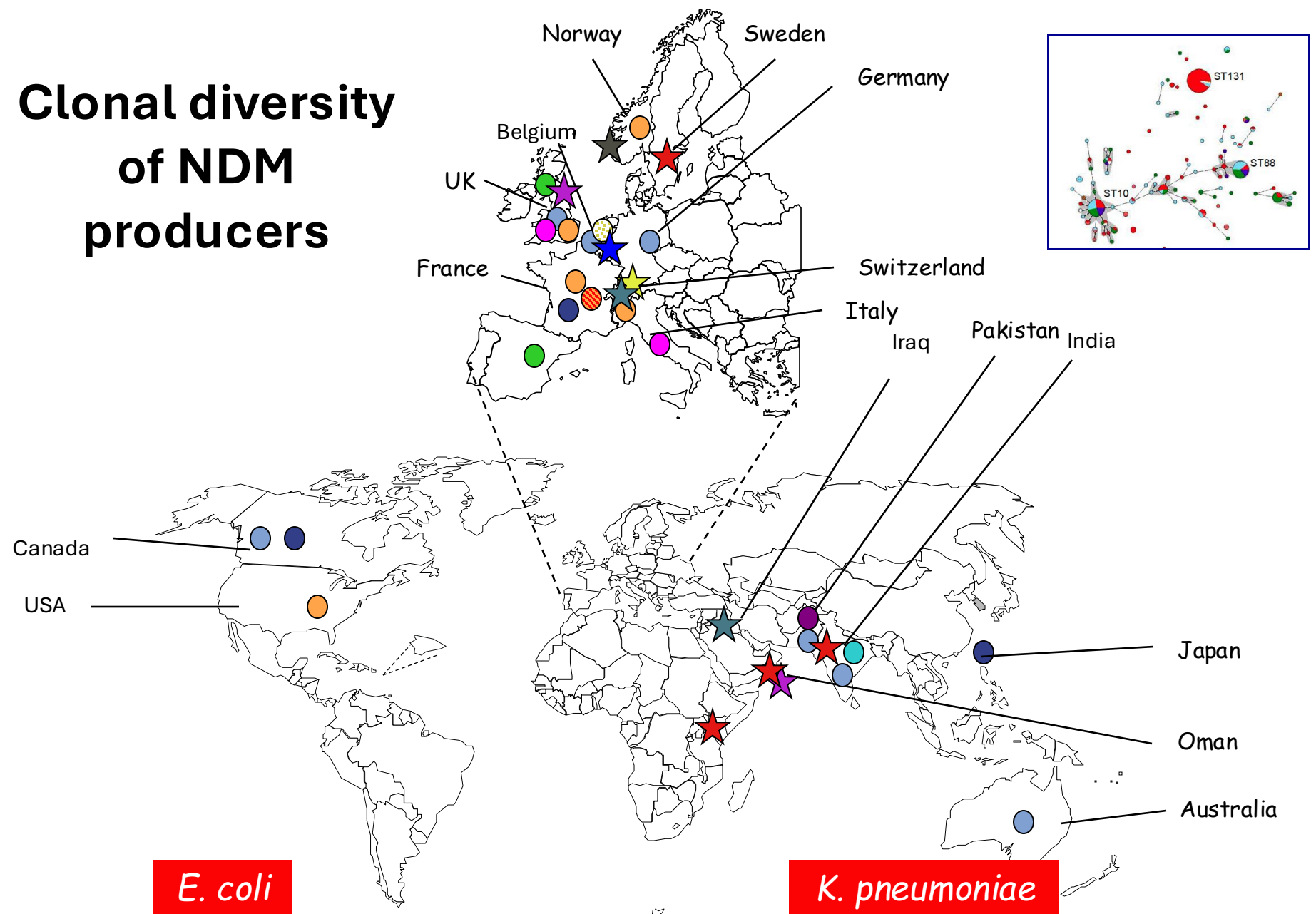
Prevalence of faecal carriage of Enterobacteriaceae with NDM-1 carbapenemase at military hospitals in Pakistan, and evaluation of two chromogenic media

John D. Perry^{1*}, Sakeenah Hussain Naqvi², Irfan Ali Mirza², Shehla Ambreen Alizai², Aamir Hussain², Sandrine Ghirardi³, Sylvain Orenga³, Kathryn Wilkinson¹, Neil Woodford⁴, Jiancheng Zhang⁴, David M. Livermore⁴, Shahid Ahmad Abbasi² and Muhammad W. Raza¹

Dissemination of NDM producers from the Indian subcontinent



Clonal diversity of NDM producers

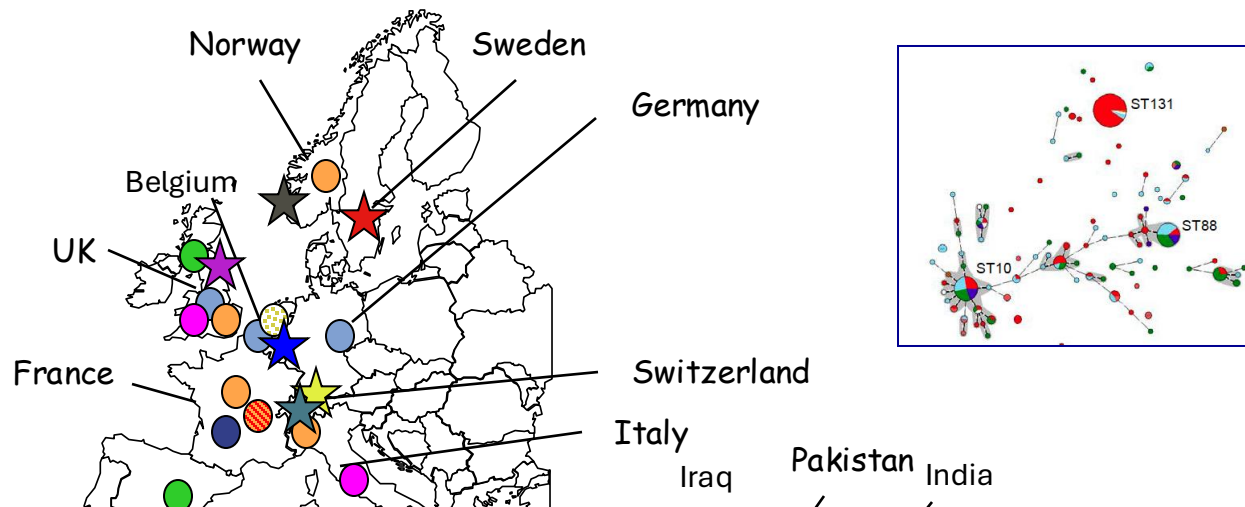


E. coli

K. pneumoniae

- | | | | | | | | | | | | | | | | |
|--|------|--|-------|--|-------|--|-------|--|-------|--|------|--|------|--|-------|
| | ST10 | | ST101 | | ST156 | | ST410 | | ST782 | | ST11 | | ST15 | | ST147 |
| | ST90 | | ST131 | | ST405 | | ST648 | | | | ST14 | | ST25 | | ST340 |

Clonal diversity of NDM producers



Gene outbreak
Worldwide dissemination of diverse strains with diversity of plasmids

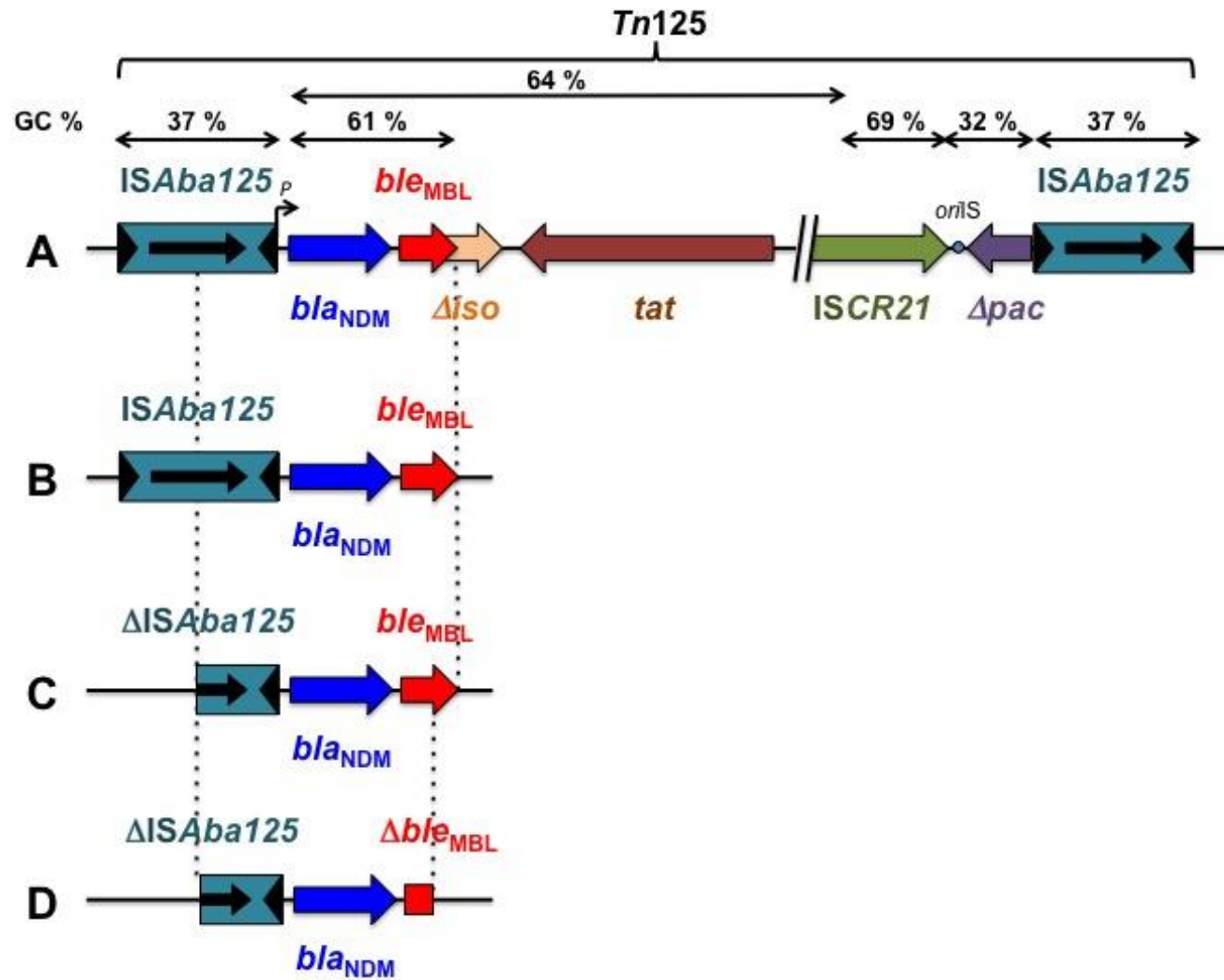
E. coli

K. pneumoniae

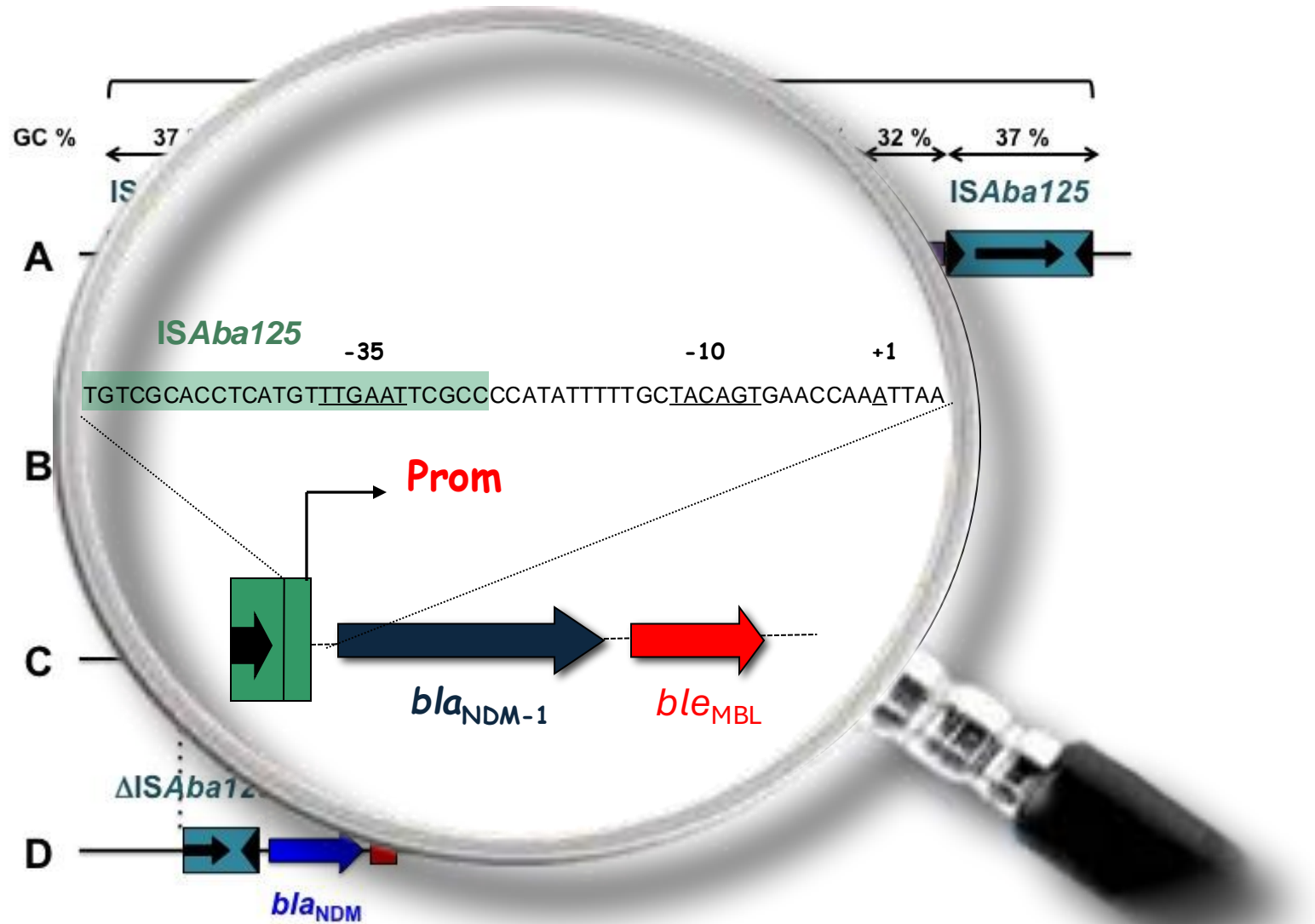
- ST10
- ST101
- ST156
- ST410
- ST782
- ST90
- ST131
- ST405
- ST648

- ST11
- ST14
- ST15
- ST25
- ST147
- ST340

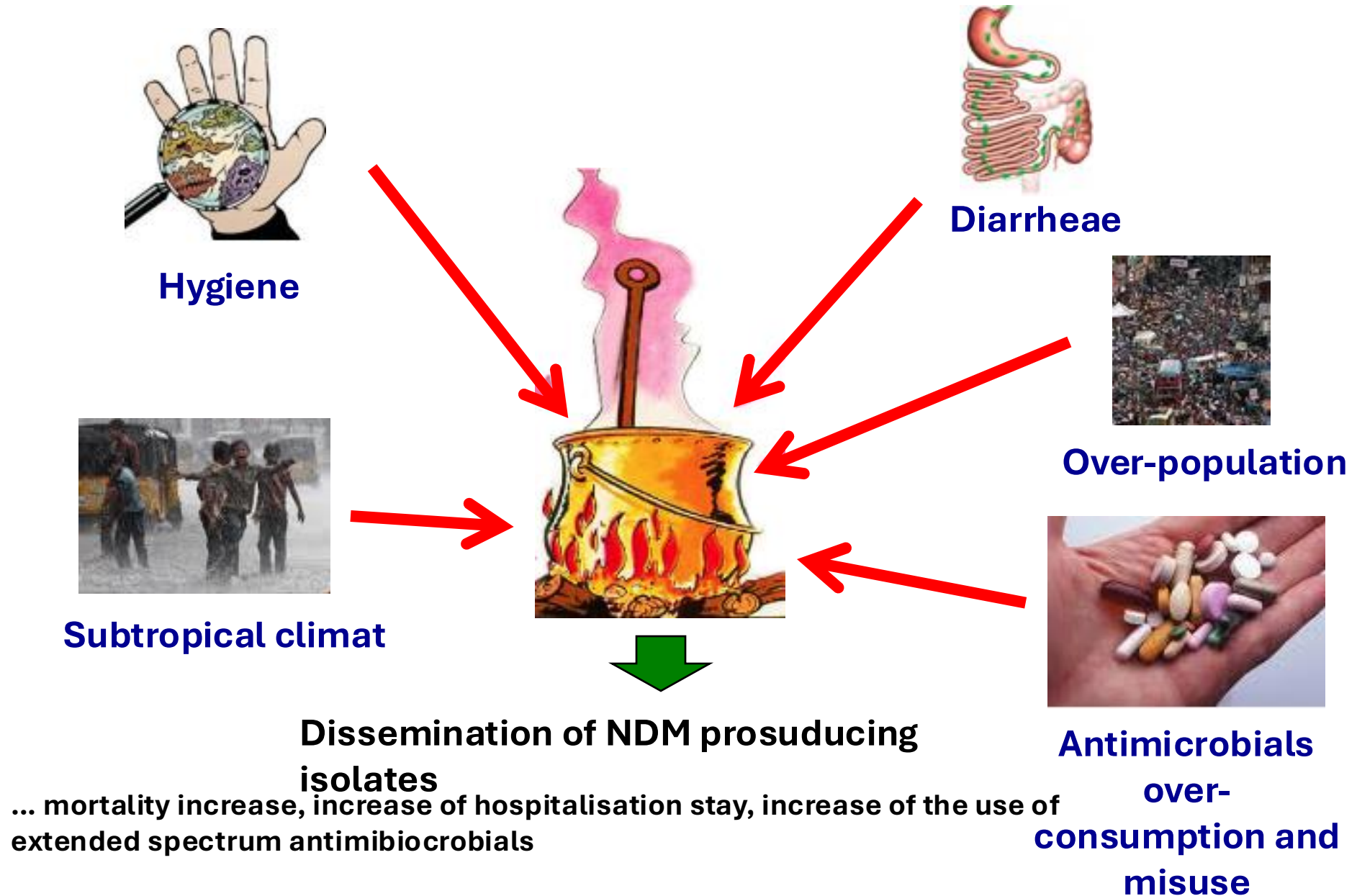
Genetic environment of *bla*_{NDM}



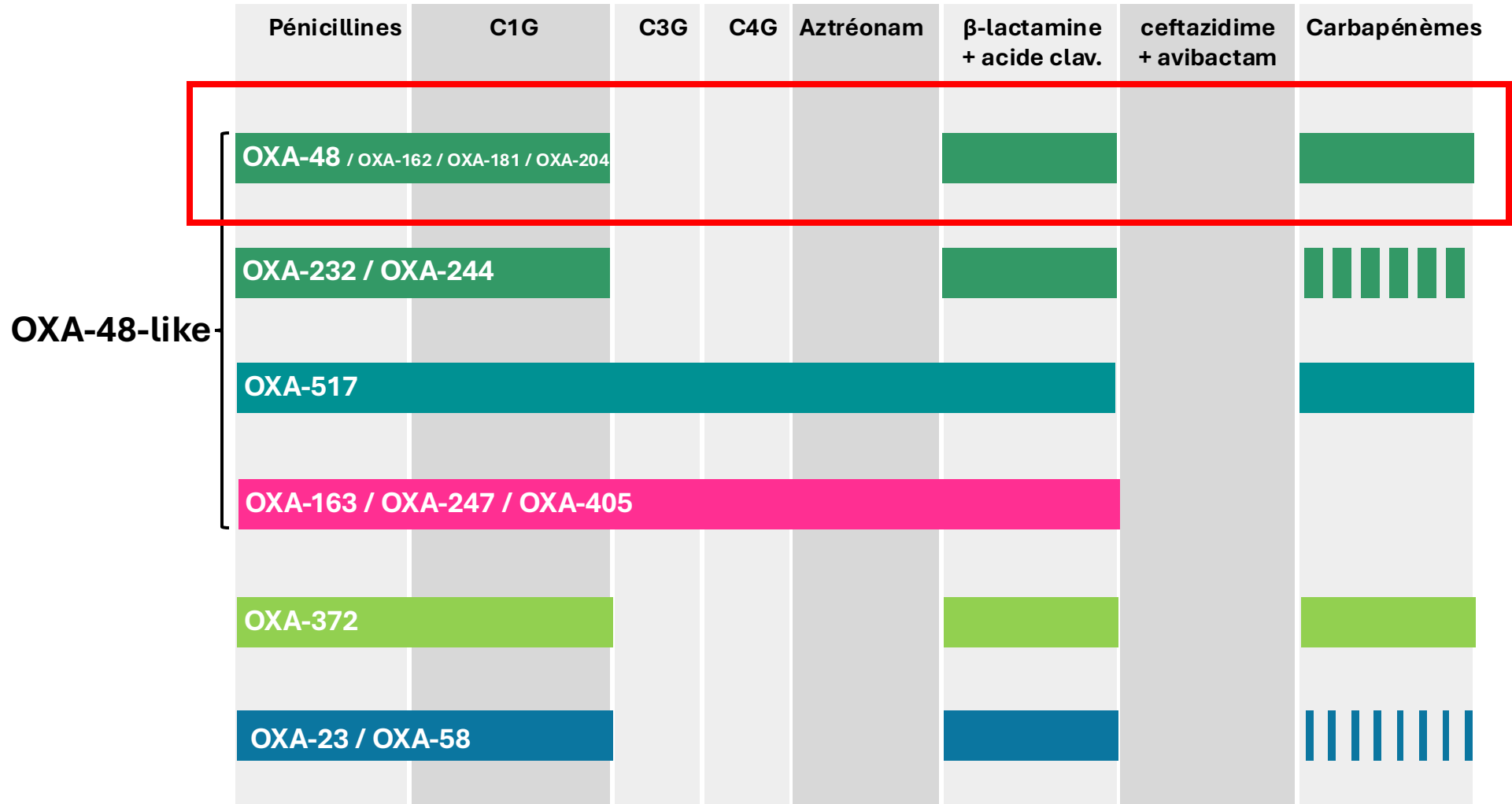
Genetic environment of *bla*_{NDM}



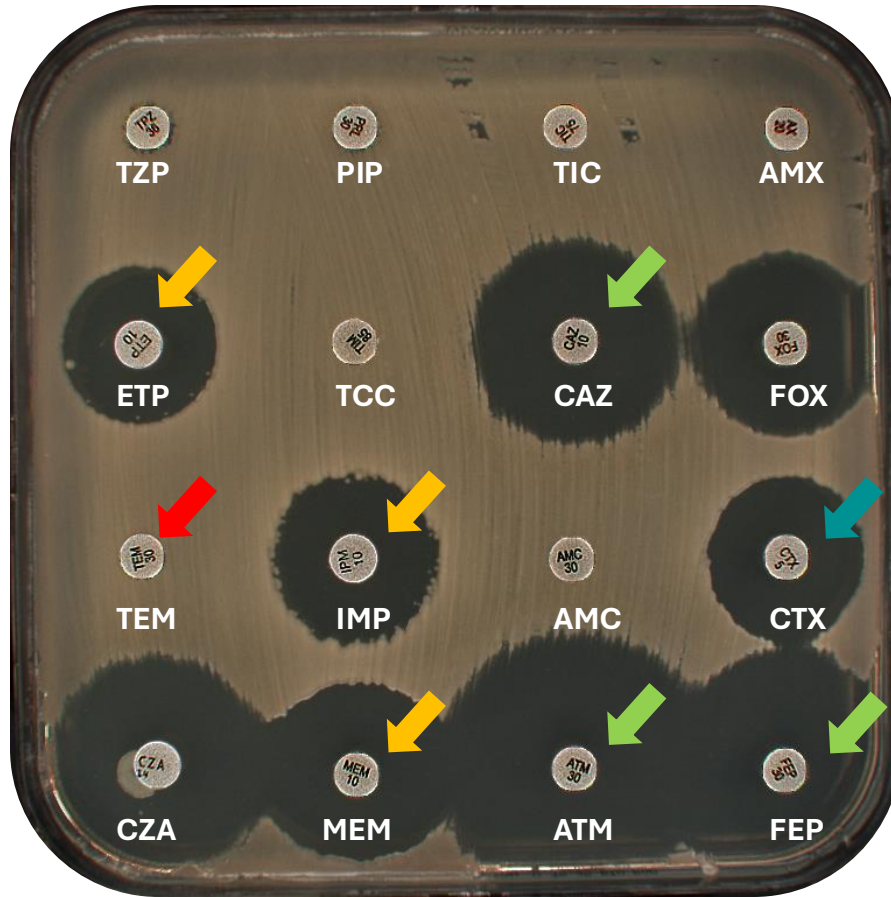
La successful story de NDM



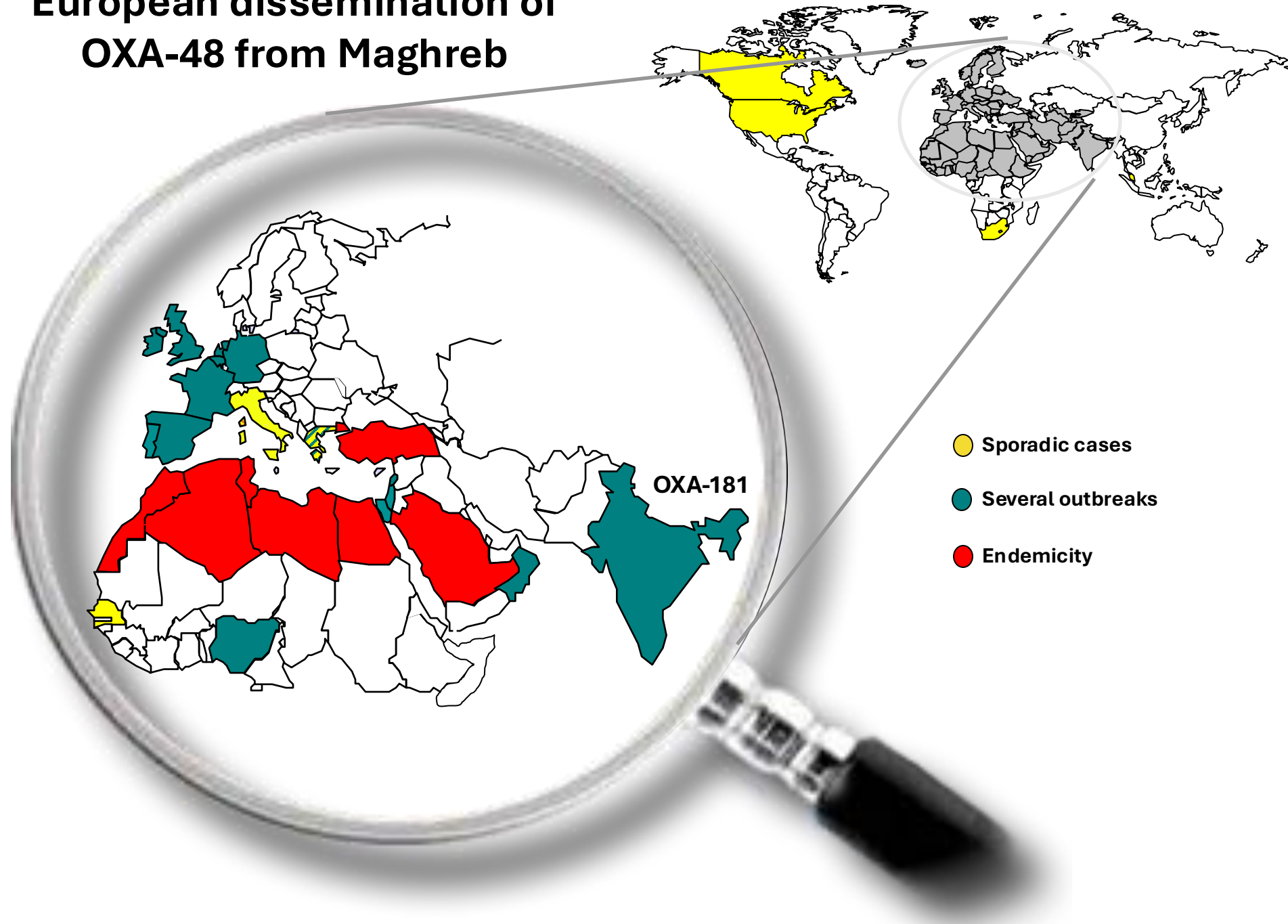
Class D carbapenemases in Enterobacteriales



OXA-48 producing *E. coli*



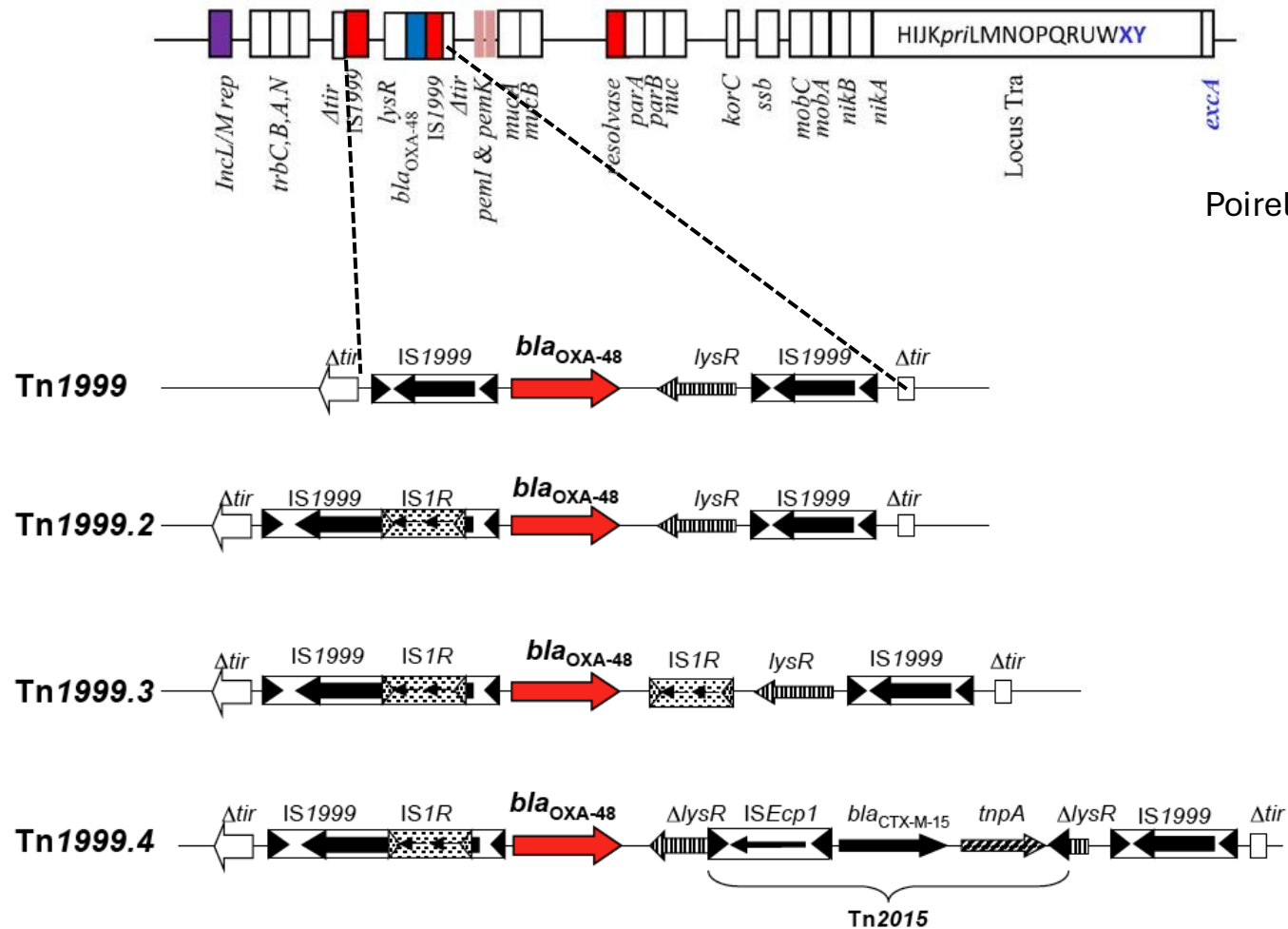
European dissemination of OXA-48 from Maghreb



Genetic environment of *bla*_{OXA-48}

same 62,5 kb plasmid of Inc L-type

IncL/M pOXA-48, *Klebsiella pneumoniae*, 61,881 bp



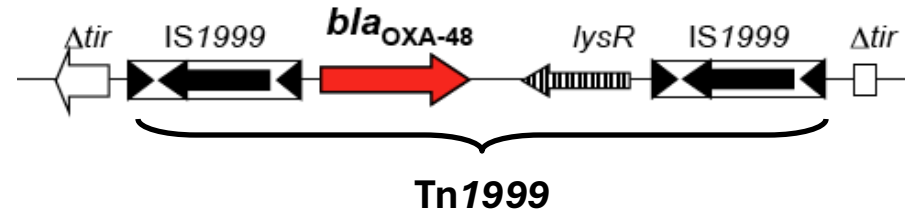


TABLE 2 Transfer frequencies in *E. coli* JM109 and *E. cloacae* SB^a

Donor strain	Recipient strain	Mean transfer frequency \pm SD	
<i>E. coli</i> TOP10(pOXA-48a)	<i>E. coli</i> JM109	$1.1 \times 10^{-1} \pm 0.02$	Δtir (Tn1999)
<i>E. coli</i> TOP10(pNDM-OM)	<i>E. coli</i> JM109	$2.6 \times 10^{-5} \pm 0.016$	
<i>E. coli</i> TOP10(pOXA-48a, pTOPO-Nc)	<i>E. coli</i> JM109	$1.7 \times 10^{-1} \pm 0.03$	$\Delta tir + \text{control DNA}$
<i>E. coli</i> TOP10(pOXA-48a, pTOPO-TIR)	<i>E. coli</i> JM109	$1.6 \times 10^{-3} \pm 0.0005$	$\Delta tir + tir$
<i>E. coli</i> TOP10(pOXA-48a, pTOPO-Nc)	<i>E. cloacae</i> SB	$4.9 \times 10^{-2} \pm 0.018$	
<i>E. coli</i> TOP10(pOXA-48a, pTOPO-TIR)	<i>E. cloacae</i> SB	$1.2 \times 10^{-3} \pm 0.00004$	

% 100



TAB

Dono

E. coli

E. coli

E. coli

p1

E. coli

pT

E. coli

pT

E. coli

pT

E. coli

Plasmid outbreak
Dissemination of the same hyper conjugative plasmid among diverse species of Enterobacterales

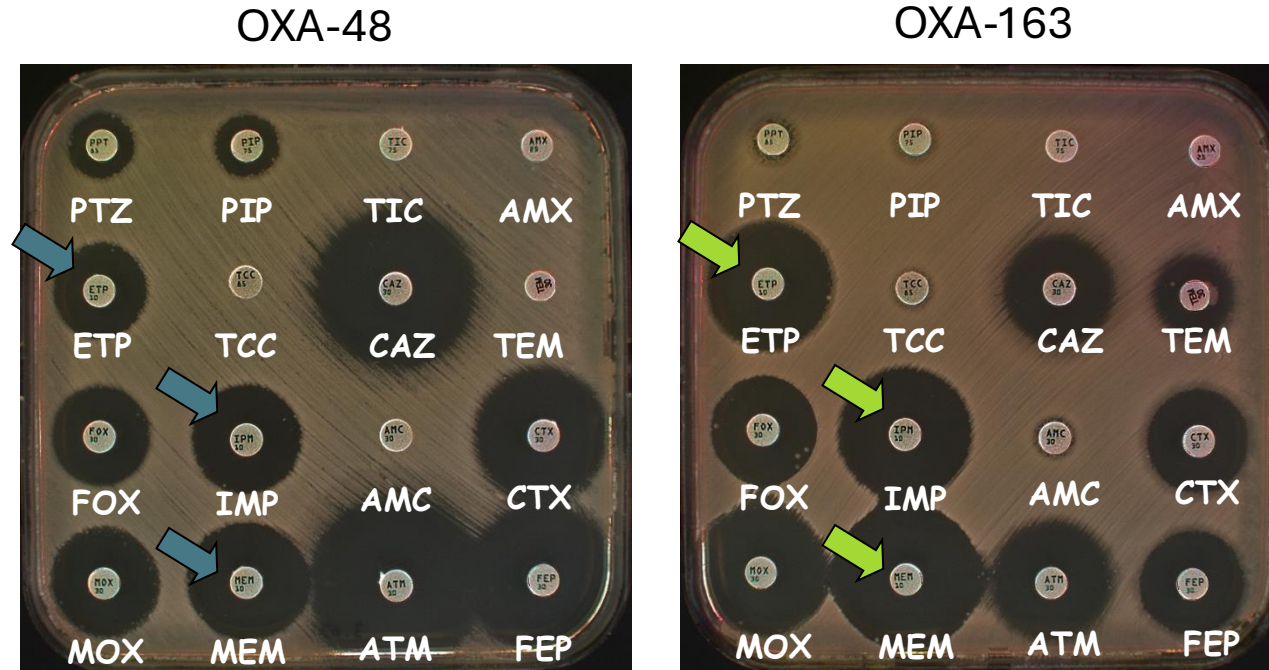
% 100

<i>E. coli</i> TOP10(pOXA-48a, pTOPO-TIR)	<i>E. cloacae</i> SB	$1.2 \times 10^{-3} \pm 0.00004$
---	----------------------	----------------------------------

OXA-48 variants without carbapénemase activity :

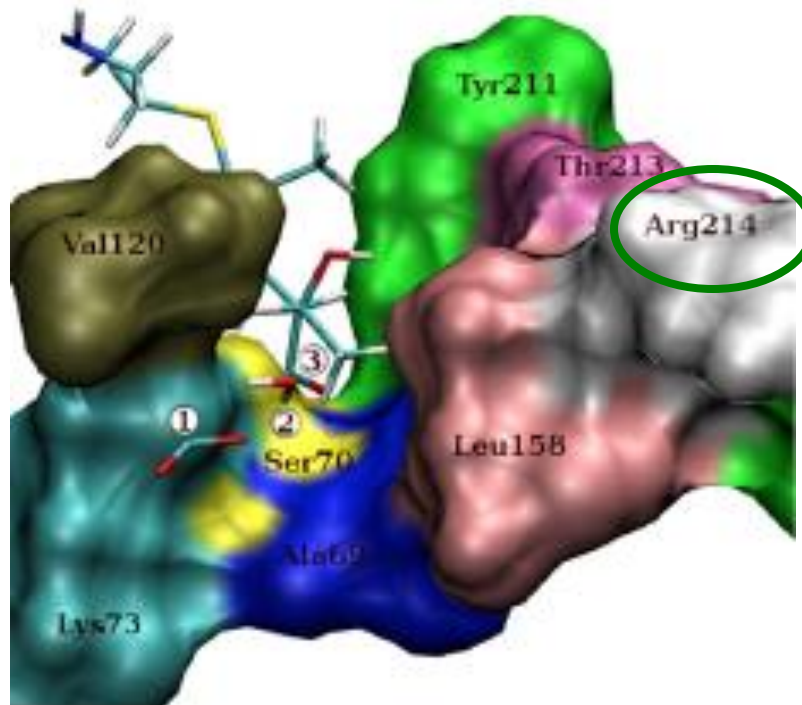
OXA-163, OXA-247, OXA-405

- No carbapenemase activity : deletion in the active site



		210	220	230	240	250	260
Carbapenemase	OXA-204	GDYIIRAKTGYS	TRIEPKIGWVVGWV	ELDDNVVFFAMNMDM	PTSDGLGLRQAITKEV	LKQEKIIP	
	OXA-245	GDYIIRAKTGYS	TRIEPKIGWVVGWV	ELDDNVVFFAMNMDM	PTSDGLGLRQAITKEV	LKQEKIIP	
	OXA-48	GDYIIRAKTGYS	TRIEPKIGWVVGWV	ELDDNVVFFAMNMDM	PTSDGLGLRQAITKEV	LKQEKIIP	
	OXA-370	GDYIIRAKTGYE	TRIEPKIGWVVGWV	ELDDNVVFFAMNMDM	PTSDGLGLRQAITKEV	LKQEKIIP	
	OXA-162	GDYIIRAKTGYS	ARIEPKIGWVVGWV	ELDDNVVFFAMNMDM	PTSDGLGLRQAITKEV	LKQEKIIP	
	OXA-181	GDYIIRAKTGYS	TRIEPKIGWVVGWV	ELDDNVVFFAMNMDM	PTSDGLGLRQAITKEV	LKQEKIIP	
	OXA-232	GDYIIRAKTGYS	TSIEPKIGWVVGWV	ELDDNVVFFAMNMDM	PTSDGLGLRQAITKEV	LKQEKIIP	
Non Carbapenemase	OXA-244	GDYIIRAKTGYS	TGIEPKIGWVVGWV	ELDDNVVFFAMNMDM	PTSDGLGLRQAITKEV	LKQEKIIP	
	OXA-163	GDYIIRAKTGYD	-----	KIGWVVGWV	ELDDNVVFFAMNMDM	PTSDGLGLRQAITKEV	LKQEKIIP
	OXA-247	GDYIIRAKTGSN	-----	KIGWVVGWV	ELDDNVVFFAMNMDM	PTSDGLGLRQAITKEV	LKQEKIIP
	OXA-405	GDYIIRAKTGYS	-----	PKIGWVVGWV	ELDDNVVFFAMNMDM	PTSDGLGLRQAITKEV	LKQEKIIP
		*****	..	*****	*****	*****	*****

OXA-48
active site

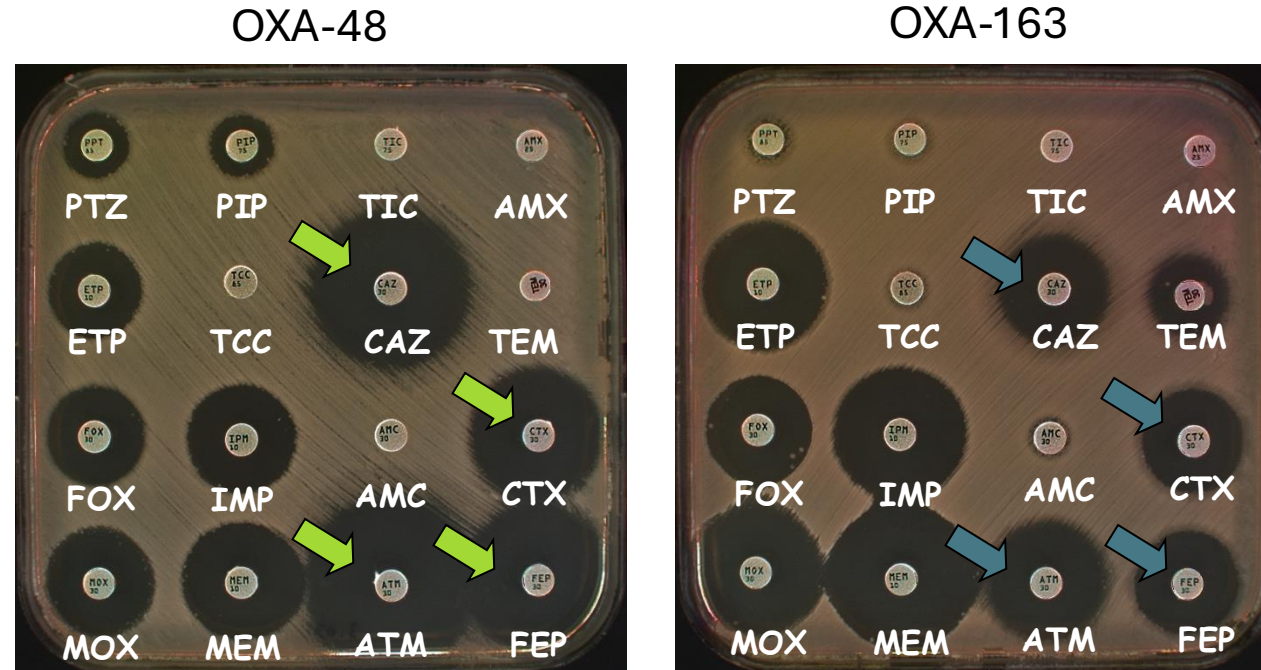


Deletion in OXA-163,
OXA-247 and OXA-405

OXA-48 variants without carbapénemase activity :

OXA-163, OXA-247, OXA-405

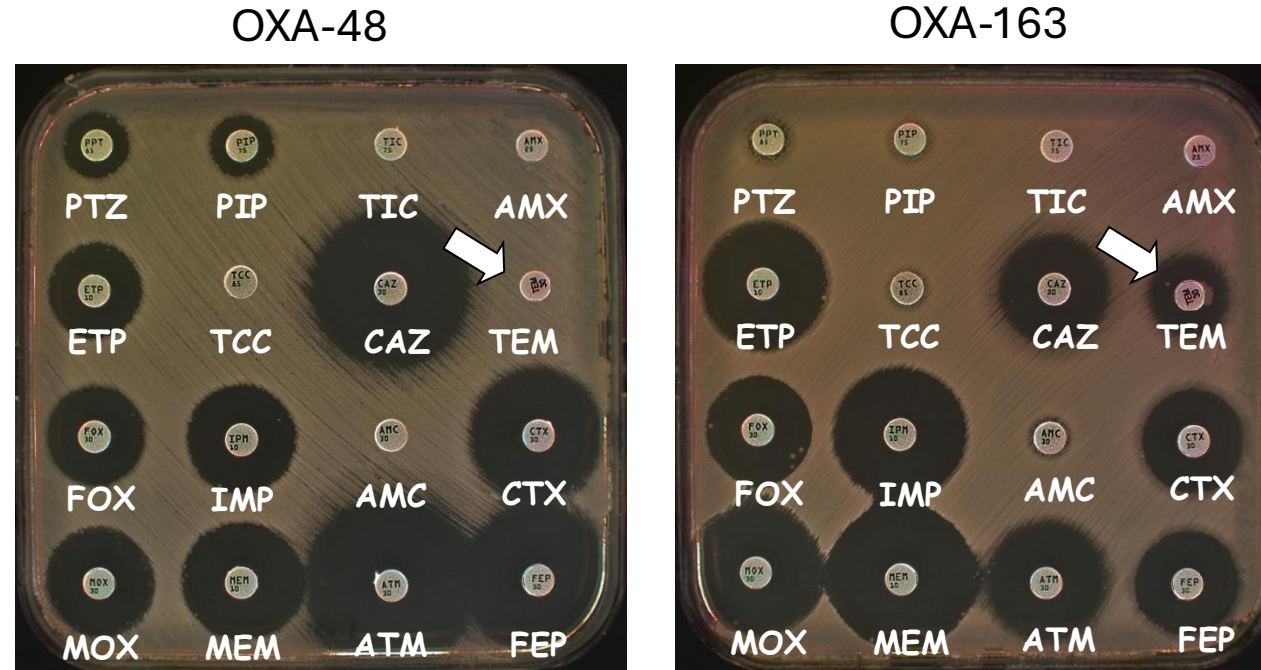
- No carbapenemase activity : deletion in the active site
- 3rd generation cephalosporins hydrolysis (ESBL-like)



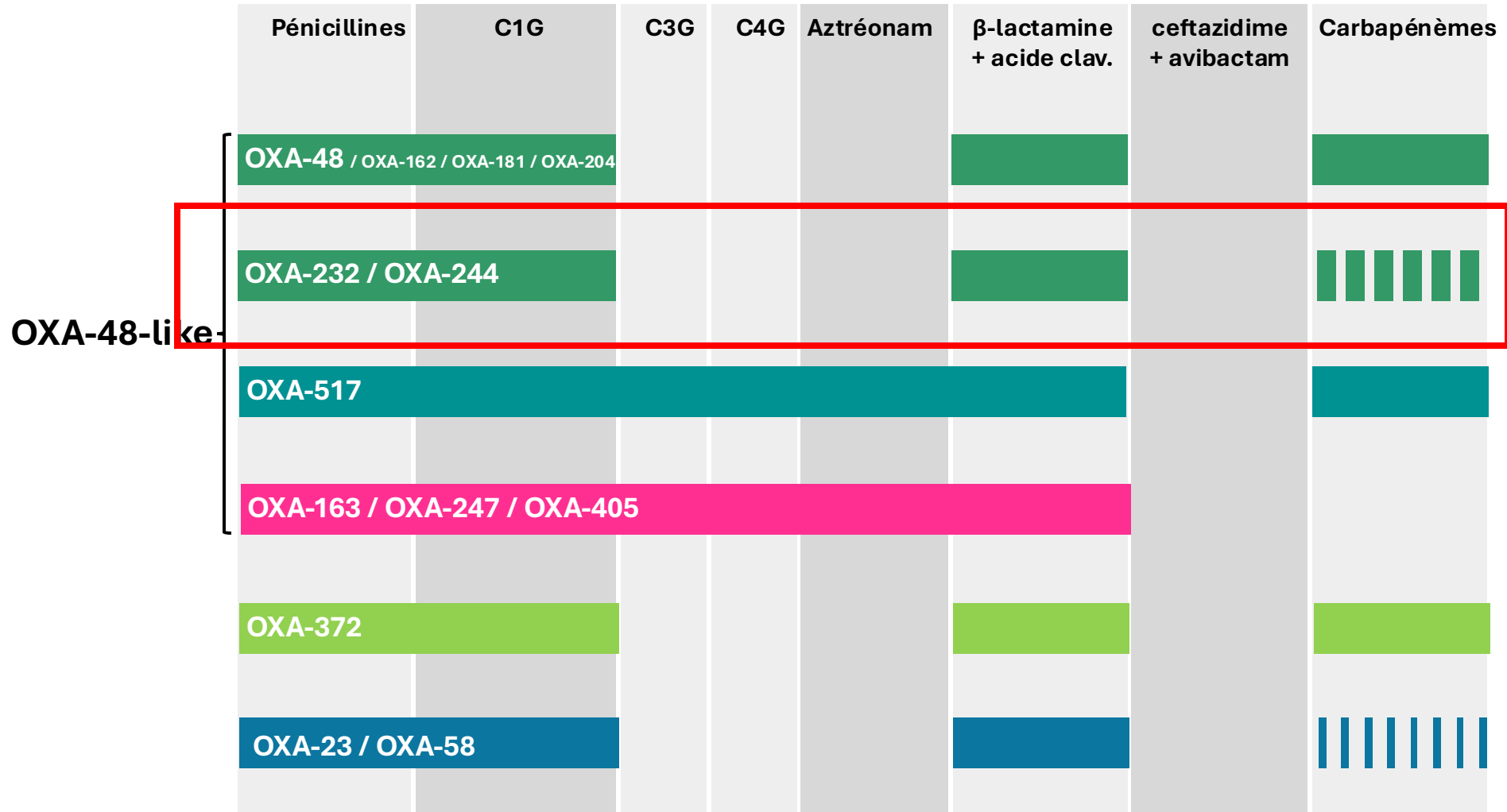
OXA-48 variants without carbapénemase activity :

OXA-163, OXA-247, OXA-405

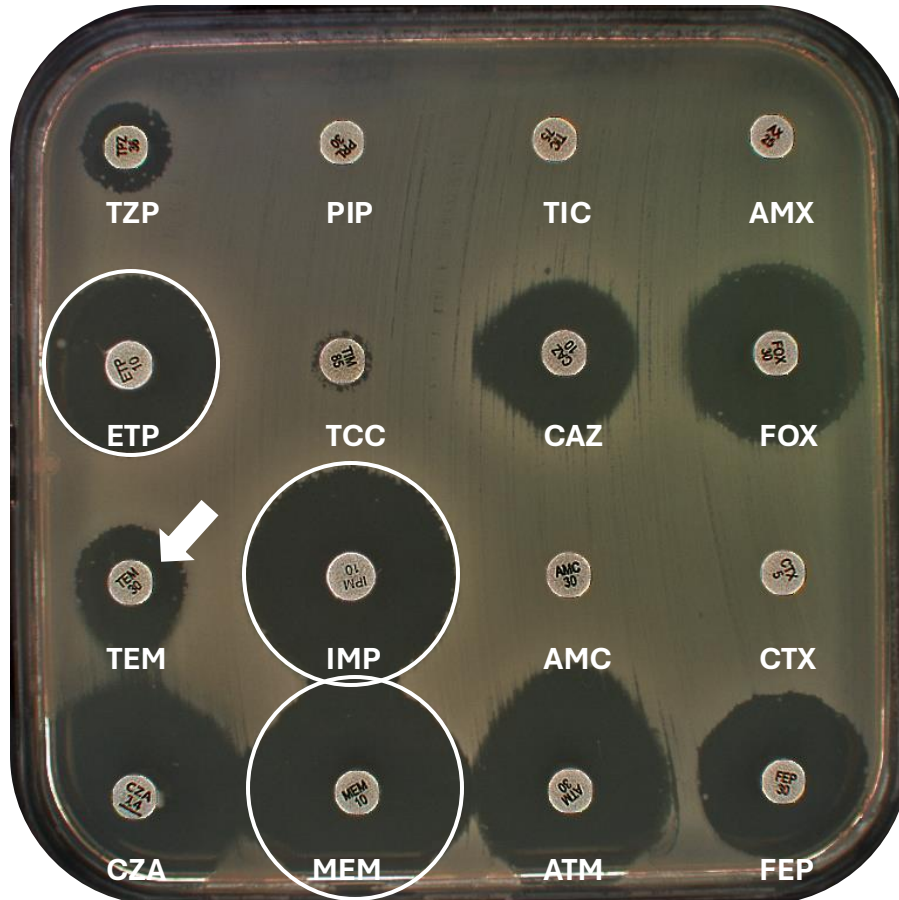
- **No carbapenemase activity** : deletion in the active site
- **3rd generation cephalosporins hydrolysis** (ESBL-like)
- **Temocillin increased susceptibility**



Class D carbapenemases in Enterobacterales



OXA-244



OXA-48

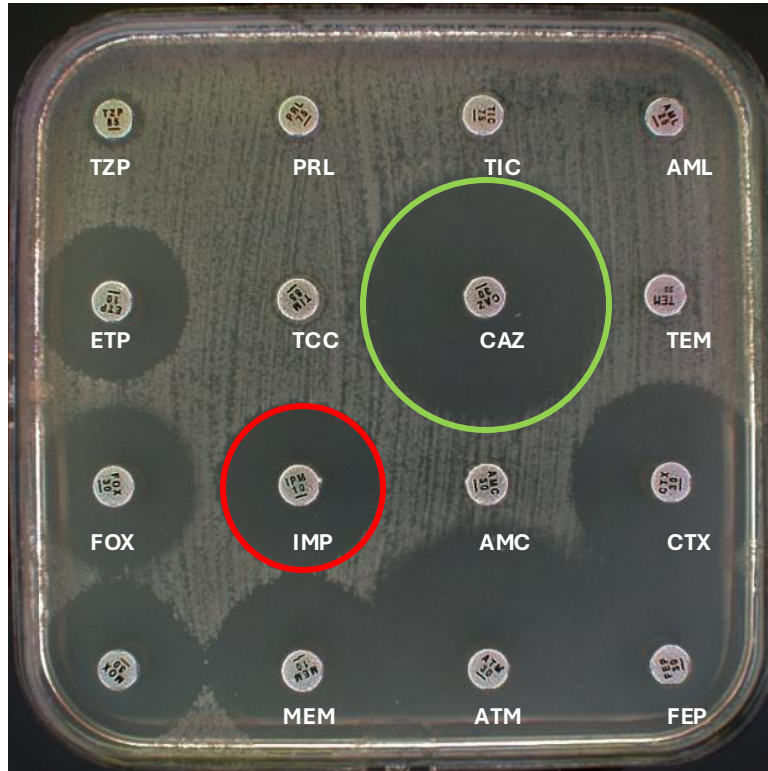


Low hydrolytic activity compare to OXA-48

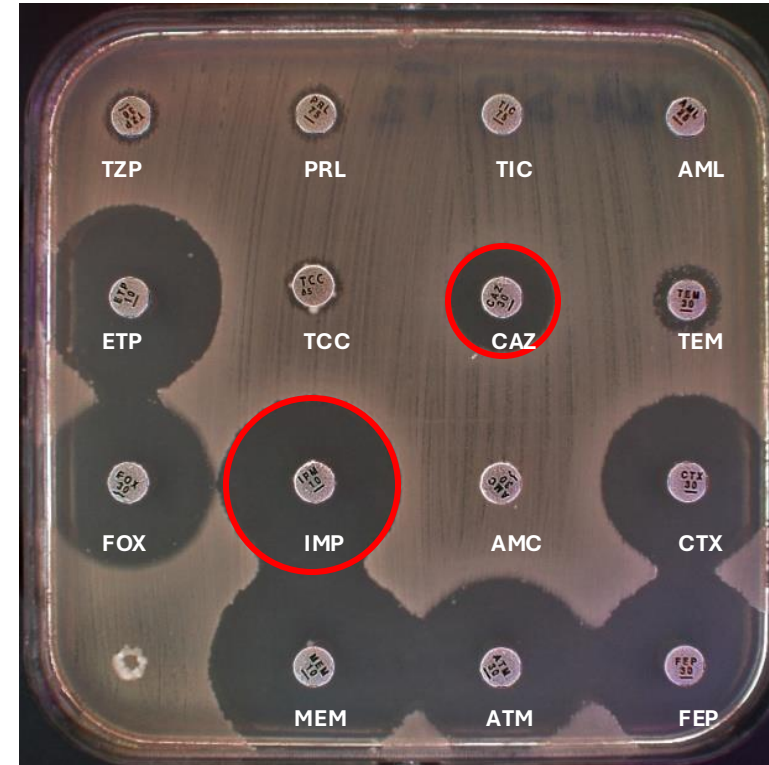
Variant	Amino acid at position (DBL numbering system)															Hydrolysis	
	98	99	104	110	120	122	127	127	129	221	222	222	222	223	224	225	IMI
OXA-48	Q	T	T	N	V	E	E	S	Y	S	T	R	I	E	P	+	-
OXA-162											A					++	-
OXA-244											G					+/-	-
OXA-245						T										+	-
OXA-204	H	R														+	-
OXA-181			A	D			Q	A								+	-
OXA-232			A	D			Q	A			S					+/-	-
OXA-163										D	*	*	*	*		-	+
OXA-247									S	D	*	*	*	*		-	+
OXA-405											*	*	*	*		-	+

Loop β 5- β 6

OXA-48



OXA-517

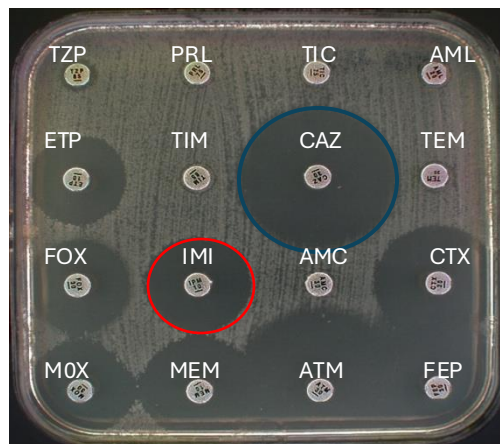


Carba ESBL

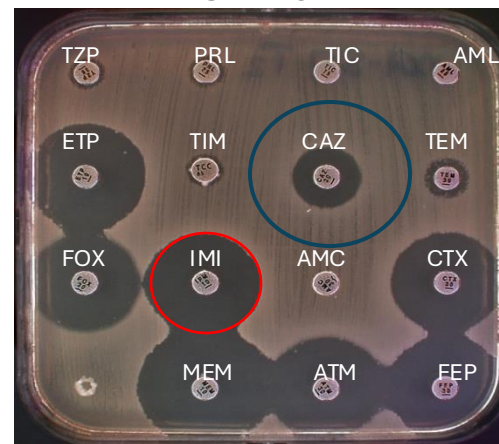
OXA-48	GDYIIRAKTGYSTRIE	PKIGWWVGWVELDDNVWFFAMNMDMPTSDGLGLRQAITKEVLKQEKIIP
OXA-517	GDYIIRAKTGYST K ..	PKIGWWVGWVELDDNVWFFAMNMDMPTSDGLGLRQAITKEVLKQEKIIP
OXA-247	GDYIIRAKTGSNT....	PKIGWWVGWVELDDNVWFFAMNMDMPTSDGLGLRQAITKEVLKQEKIIP
OXA-405	GDYIIRAKTGYS....	PKIGWWVGWVELDDNVWFFAMNMDMPTSDGLGLRQAITKEVLKQEKIIP
OXA-163	GDYIIRAKTGYDT....	PKIGWWVGWVELDDNVWFFAMNMDMPTSDGLGLRQAITKEVLKQEKIIP

Loop β 5- β 6

OXA-48



OXA-517



Antibiotic	MIC (mg/L)					
	<i>K.pneumoniae</i> 1219	<i>E.coli</i> top10 (pOXA-517)	<i>E.coli</i> top10 (pTOPO OXA-48)	<i>E.coli</i> top10 (pTOPO OXA-517)	<i>E.coli</i> top10 (pTOPO OXA-163)	<i>E.coli</i> top10
Amoxicillin	>256	>256	>256	>256	>256	2
Amoxicillin + CLA ^a	64	64	192	32	96	2
Piperacillin	>256	>256	128	>256	>256	1.5
Piperacillin + TZB ^b	96	96	12	32	32	1
Cefotaxime	>32	2	0.094	0.38	3	0.06
Ceftazidime	48	16	0.19	4	16	0.12
Cefepime	12	1	0.047	0.25	0.5	0.023
Imipenem	8	0.75	0.38	0.38	0.25	0.19
Meropenem	3	0.125	0.047	0.047	0.023	0.016
Ertapenem	3	0.125	0.047	0.047	0.032	0.002
Doripenem	3	0.094	0.094	0.094	0.023	0.06
Temocillin	192	192	>256	32	32	4

^aCLA, clavulanic acid (4mg/L)

^bTZB, tazobactam (4mg/L)

***Shewanella* spp. are progenitors of OXA-48-like enzymes**

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2004, p. 348–351
0066-4804/04/\$08.00+0 DOI: 10.1128/AAC.48.1.348–351.2004
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Vol. 48, No. 1

Chromosome-Encoded Ambler Class D β -Lactamase of *Shewanella oneidensis* as a Progenitor of Carbapenem-Hydrolyzing Oxacillinase

Laurent Poirel, Claire Héritier, and Patrice Nordmann*

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2011, p. 4405–4407
0066-4804/11/\$12.00 doi:10.1128/AAC.00681-11
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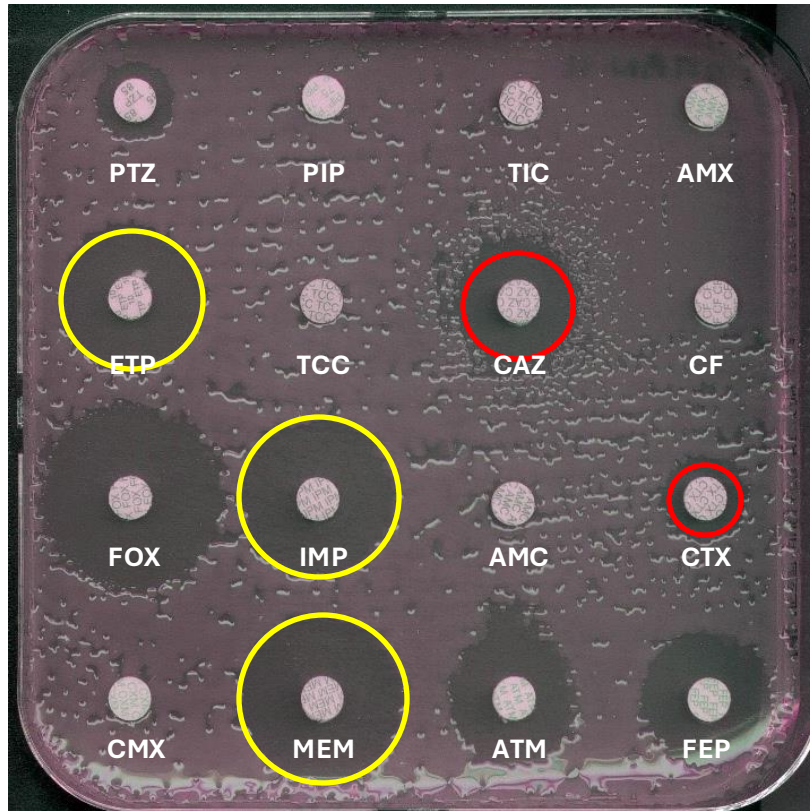
Vol. 55, No. 9

Origin of OXA-181, an Emerging Carbapenem-Hydrolyzing Oxacillinase, as a Chromosomal Gene in *Shewanella xiamenensis*[∇]

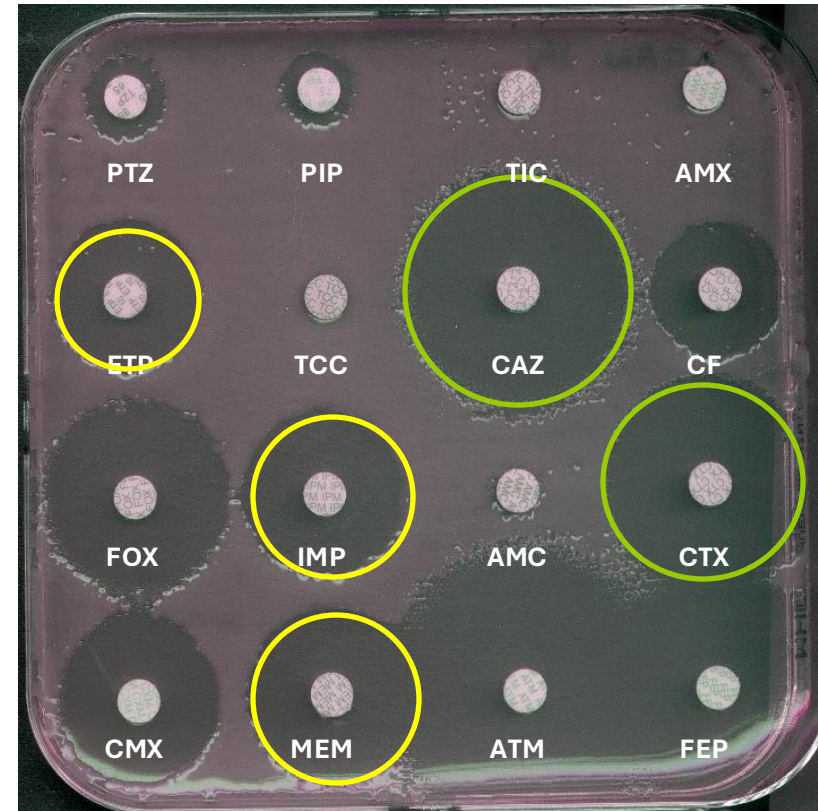
Anaïs Potron, Laurent Poirel, and Patrice Nordmann*

OXA-48 success story

Low hydrolysis of carbapenems + no hydrolysis of 3GC \Rightarrow
Detection difficulties

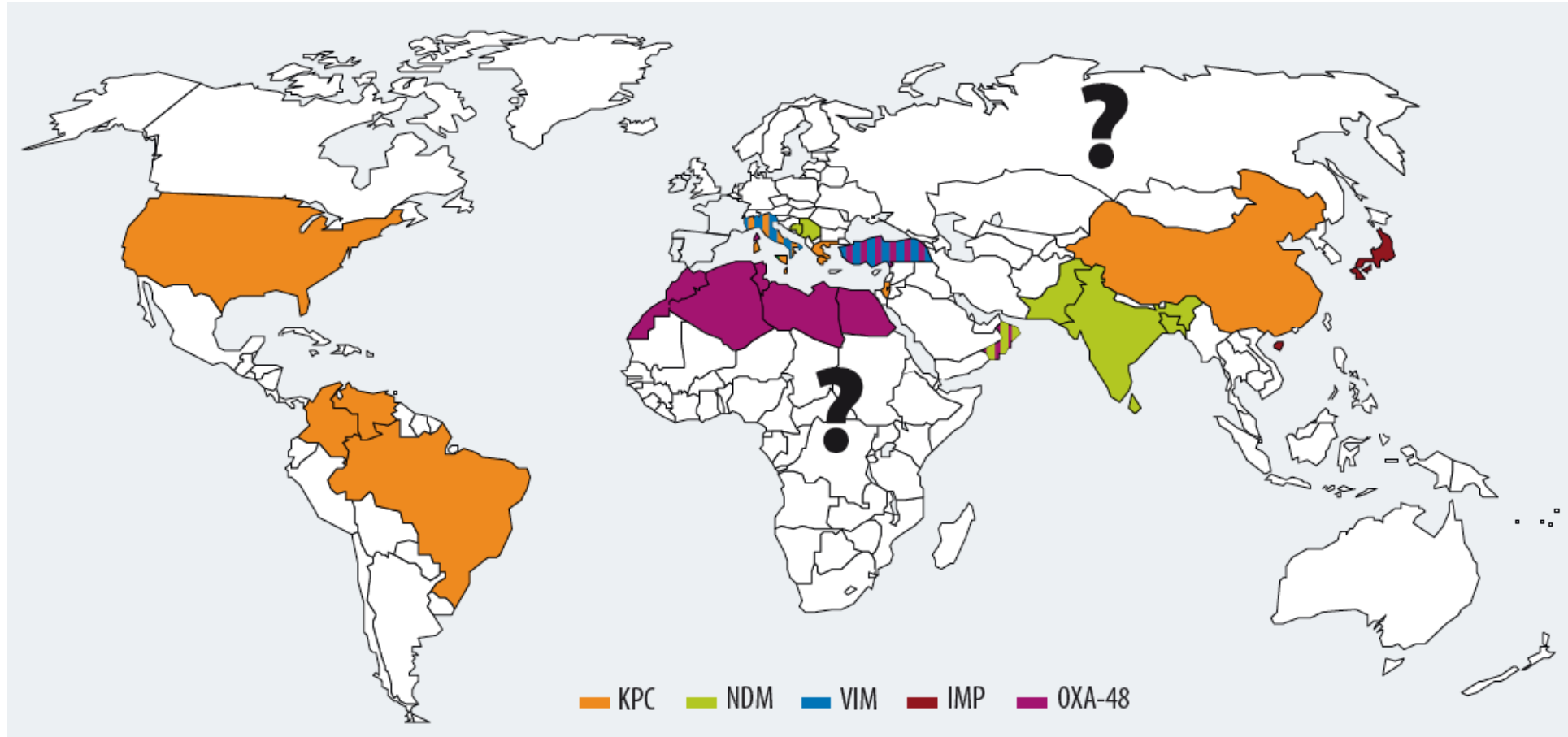


K. pneumoniae OXA-48
BLSE +

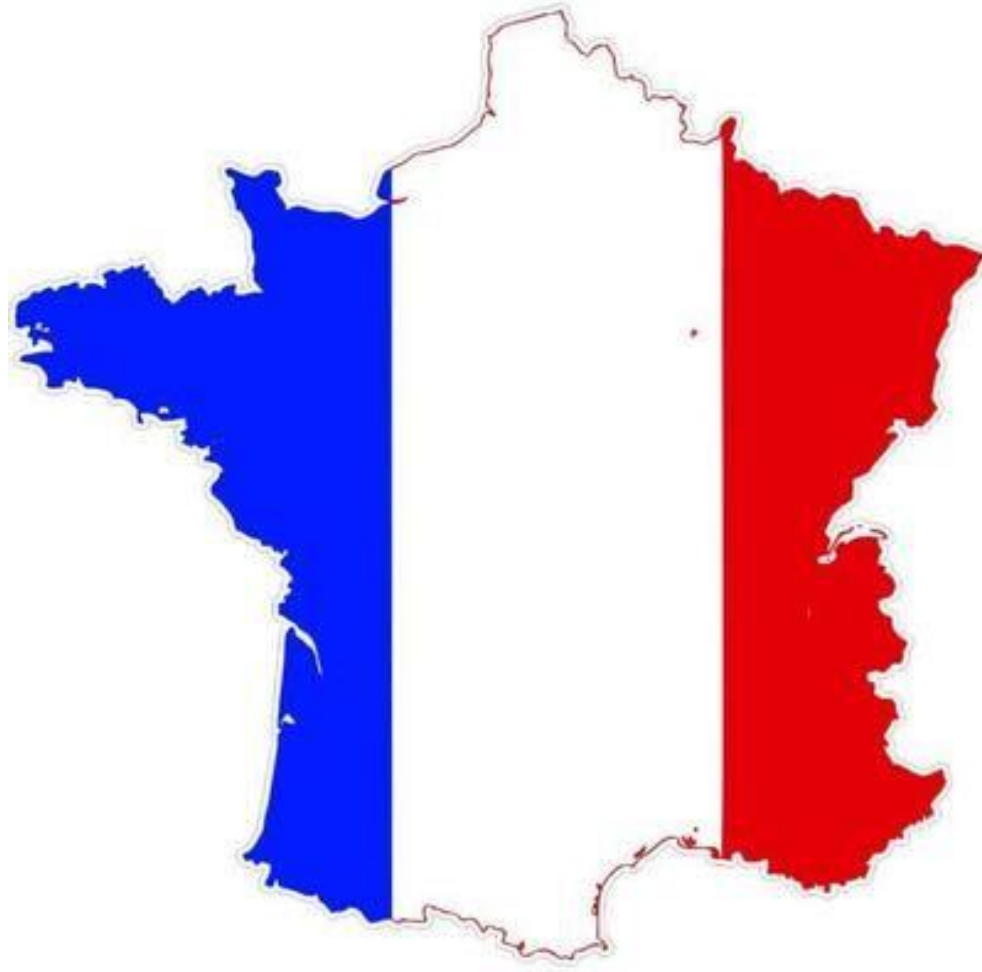


K. pneumoniae OXA-48
BLSE -

Global epidemiology of CPE

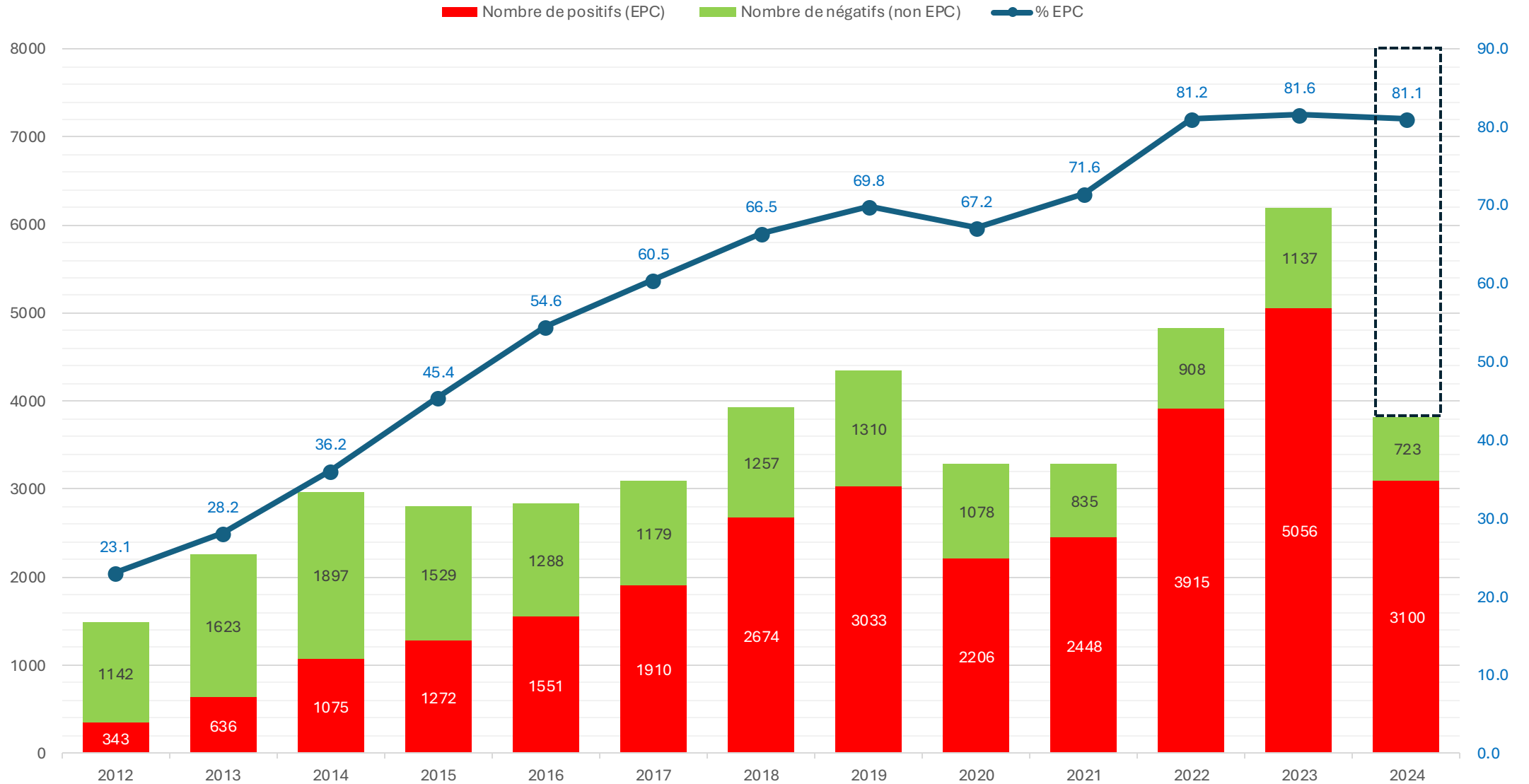


Epidemiology of CPE in France

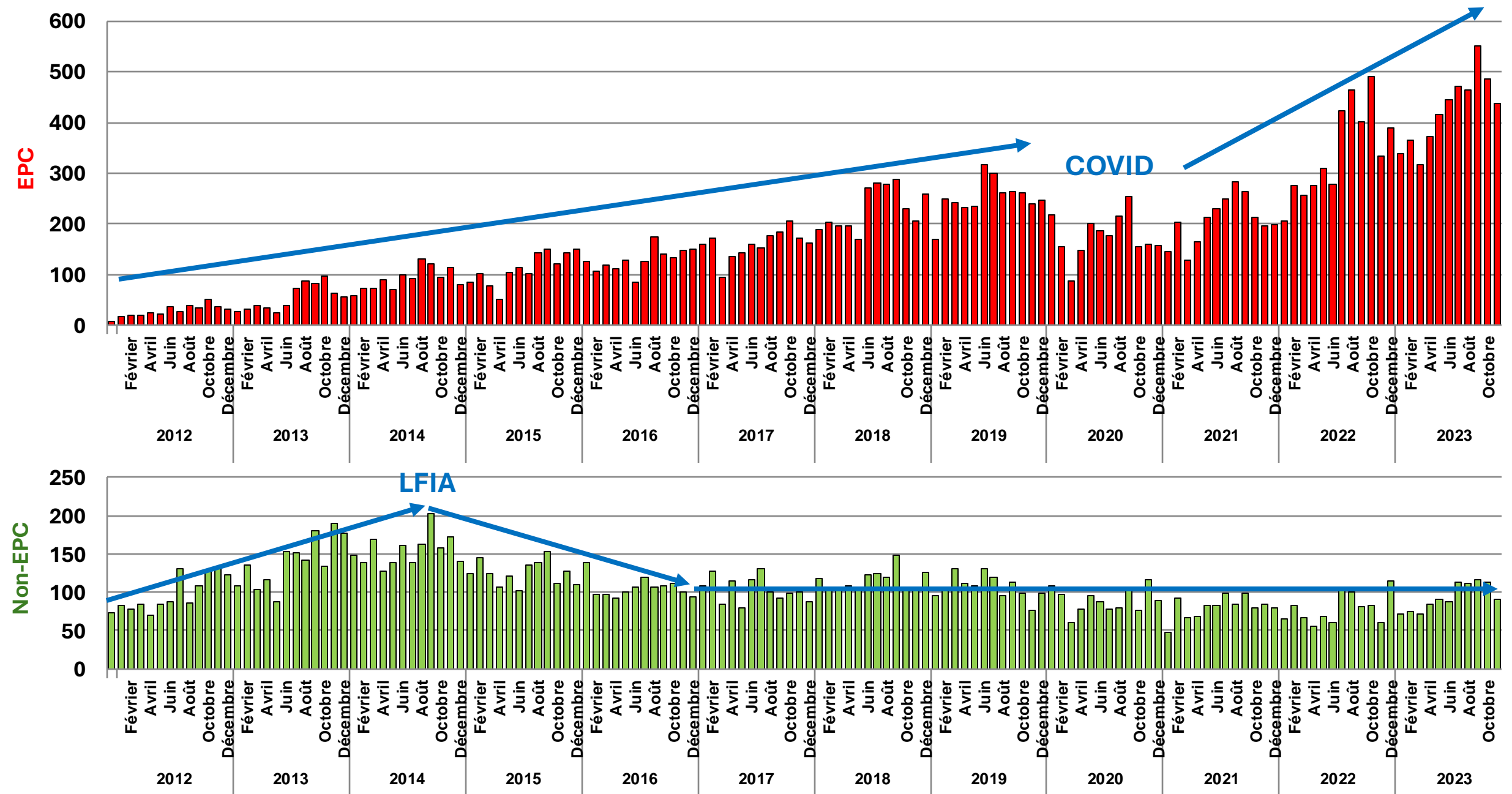


2023

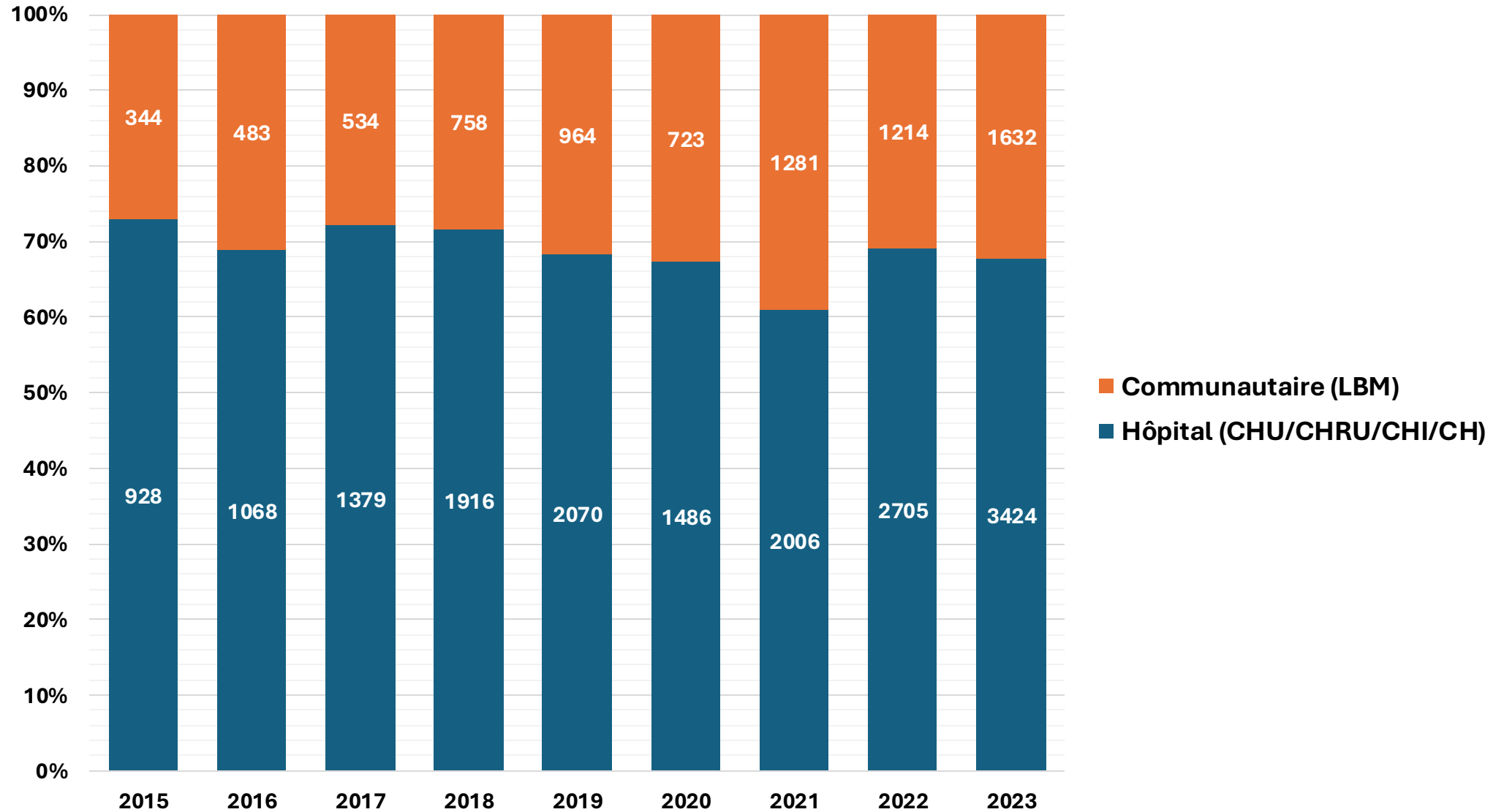
Répartition des souches reçues au CNR entre 2012 et 2024



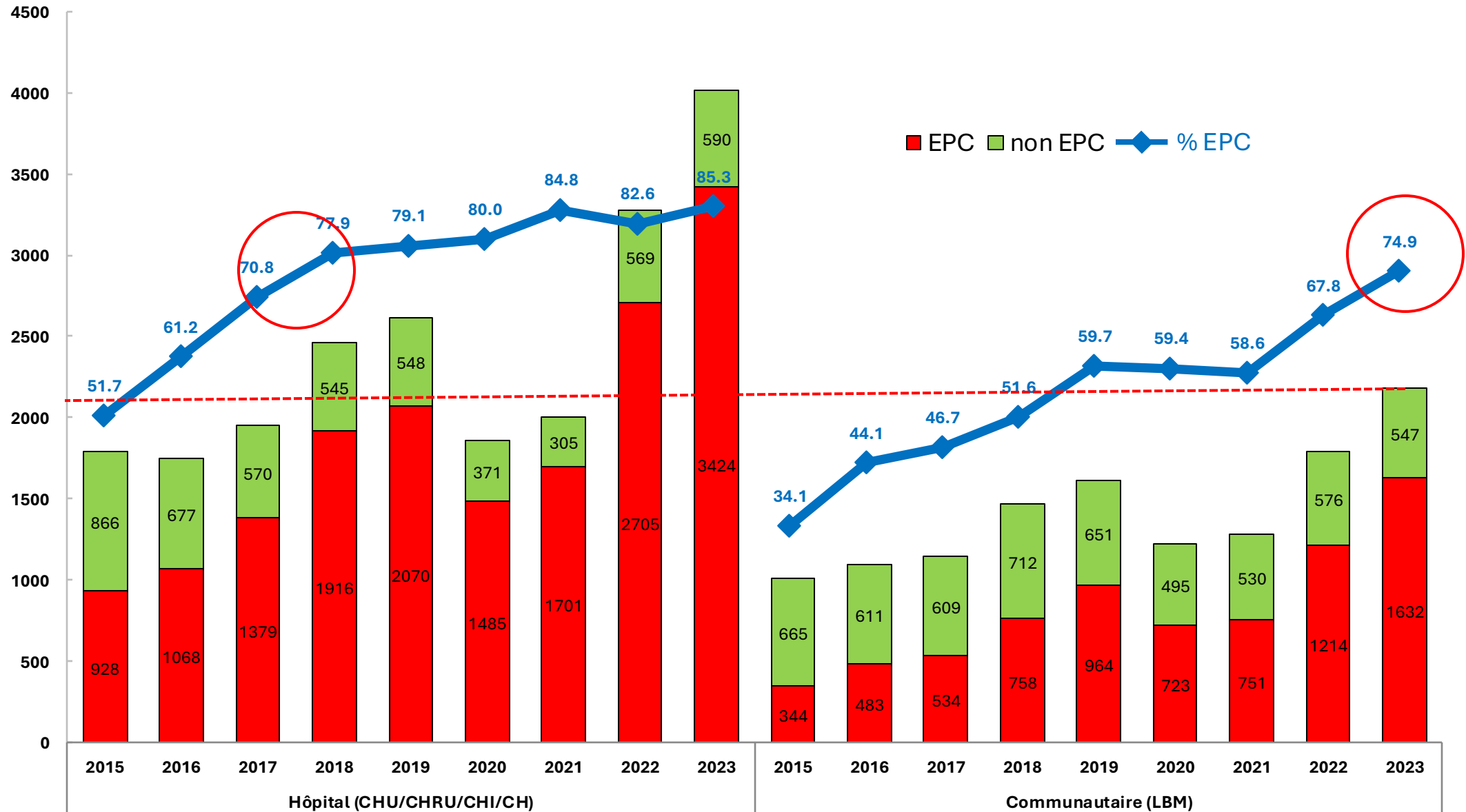
Evolution du nombre de souches reçues au CNR par mois de 2012 à 2023



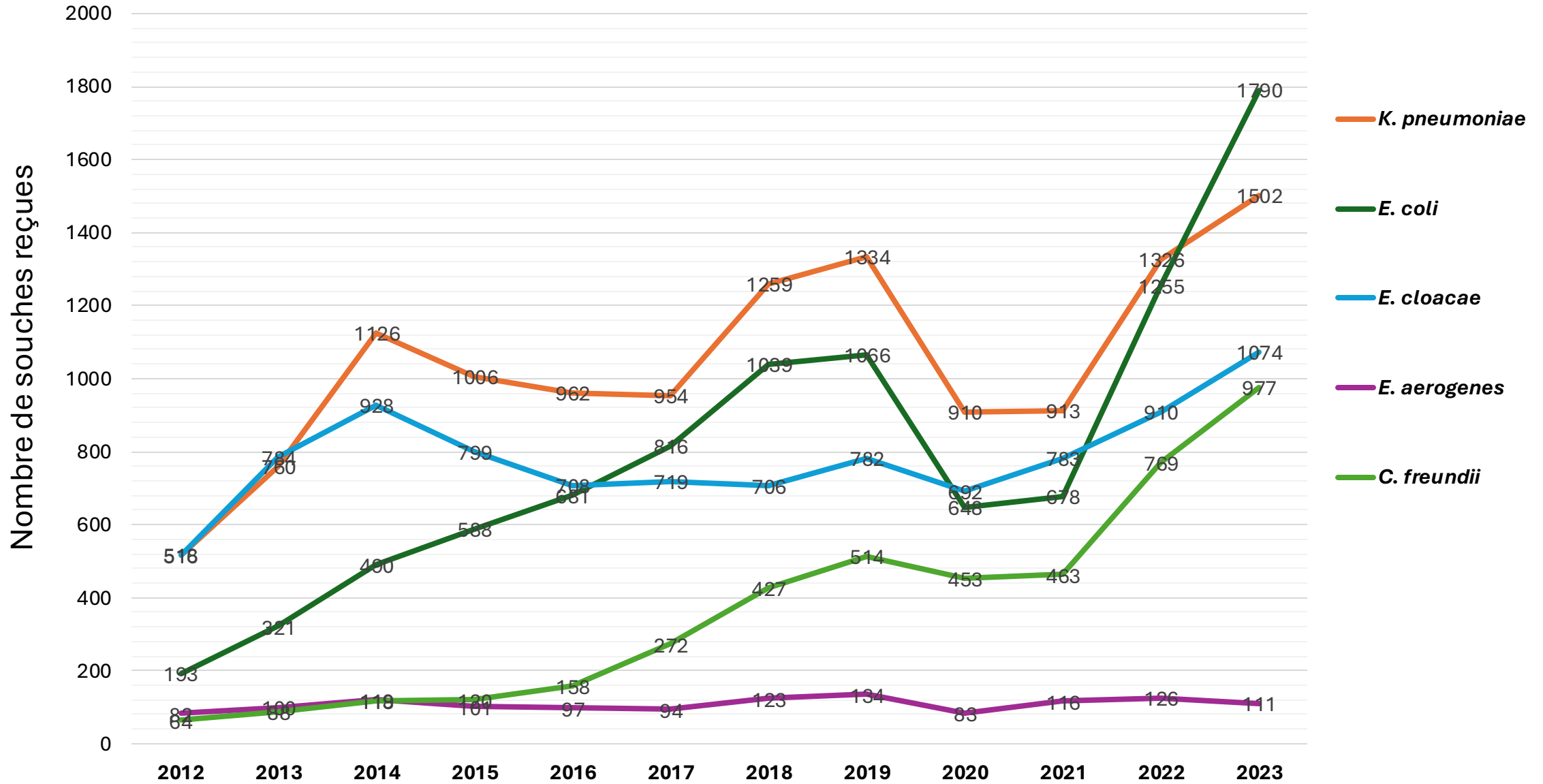
Répartition des EPC en fonction du laboratoire expéditeur



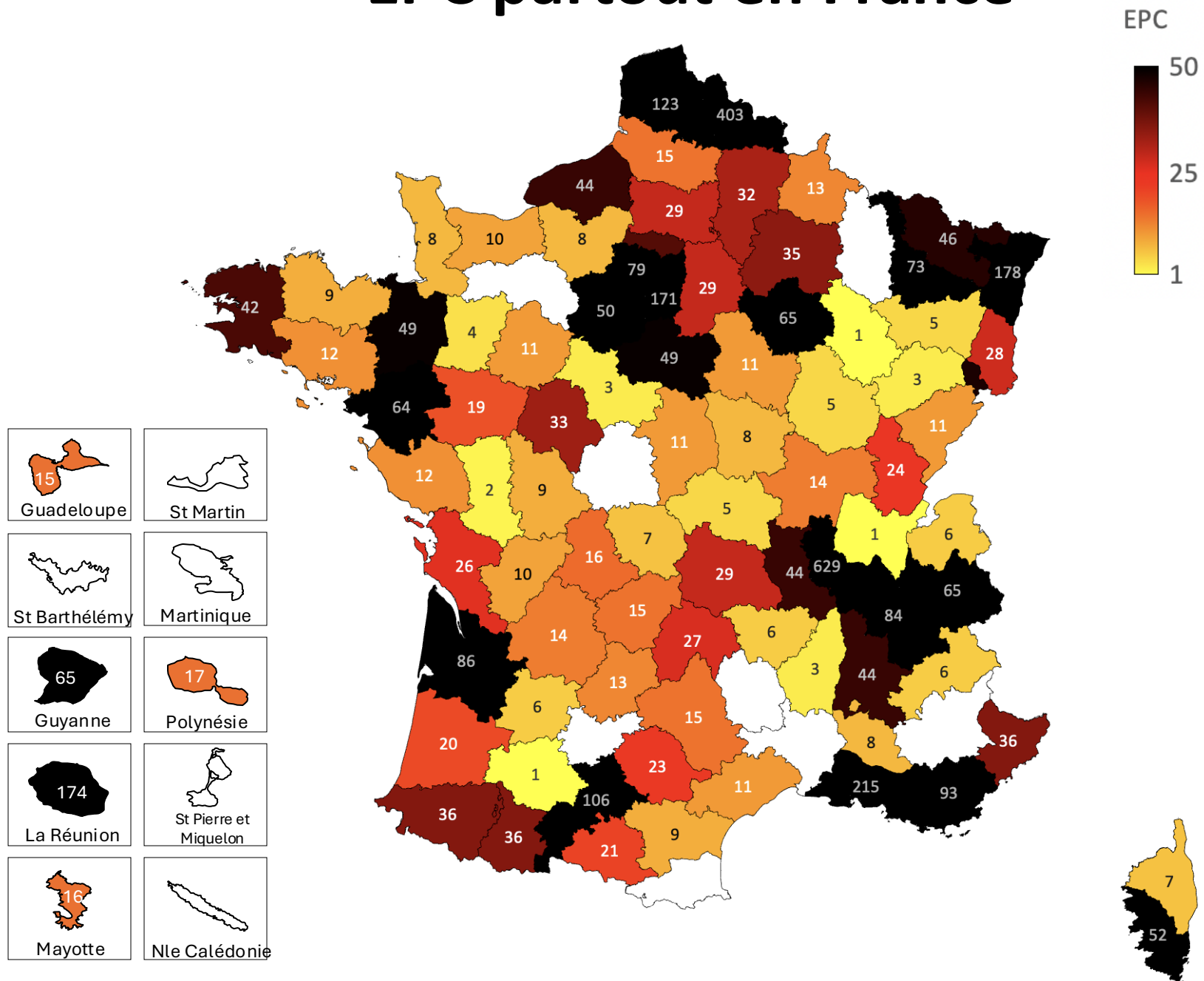
La ville a environ 5 ans de retard sur l'hôpital ... explosion à craindre !!!



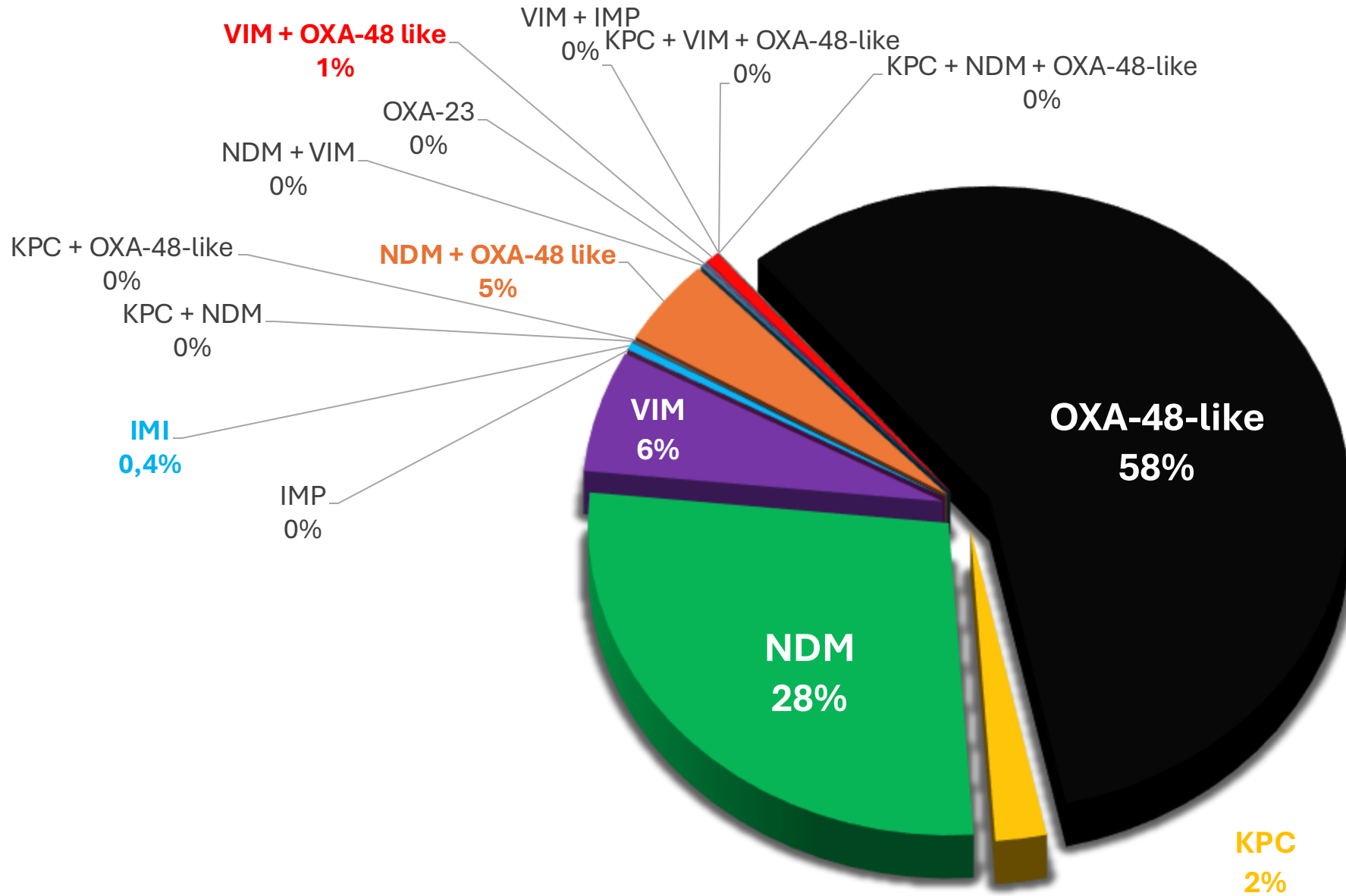
Evolution des principales espèces reçues par année



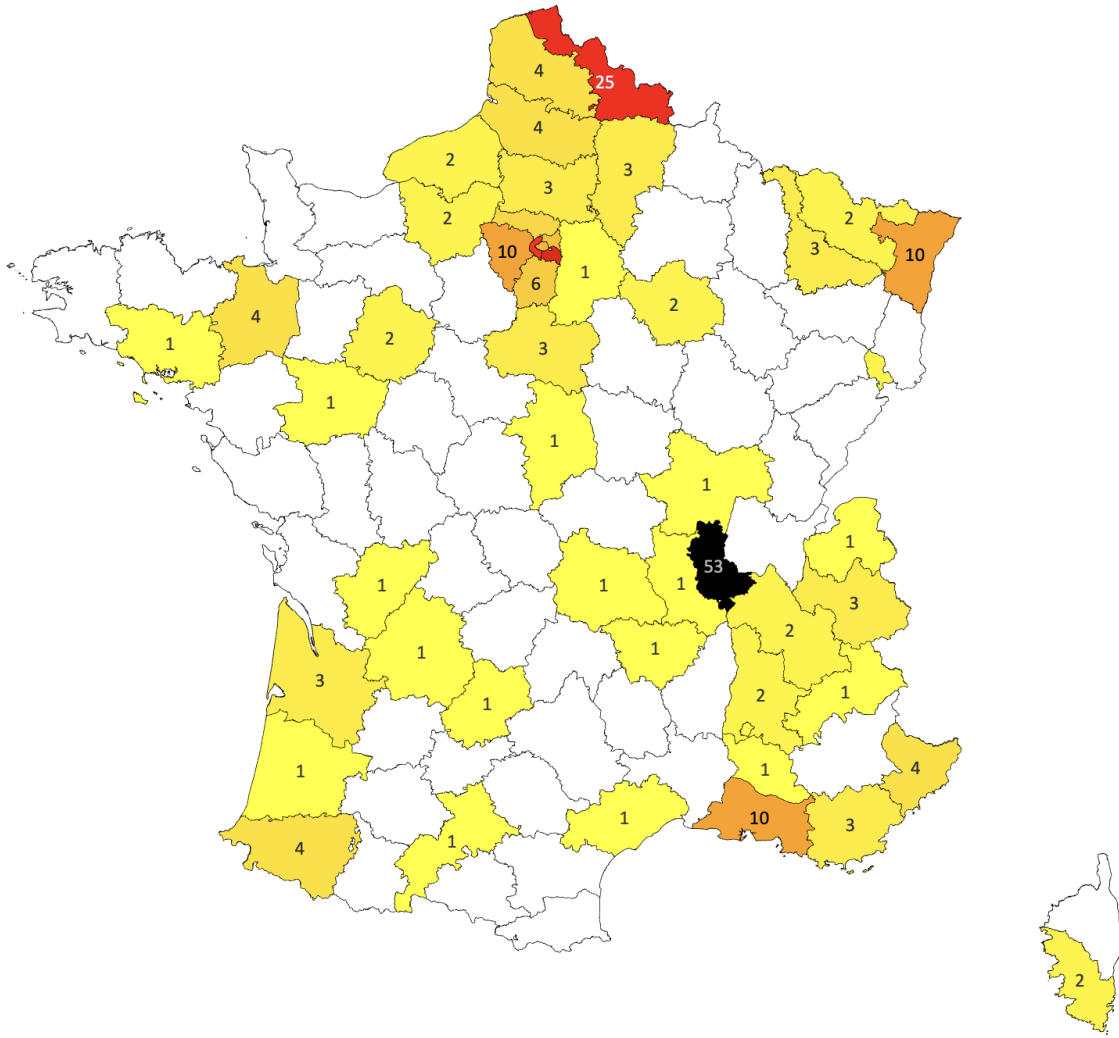
EPC partout en France



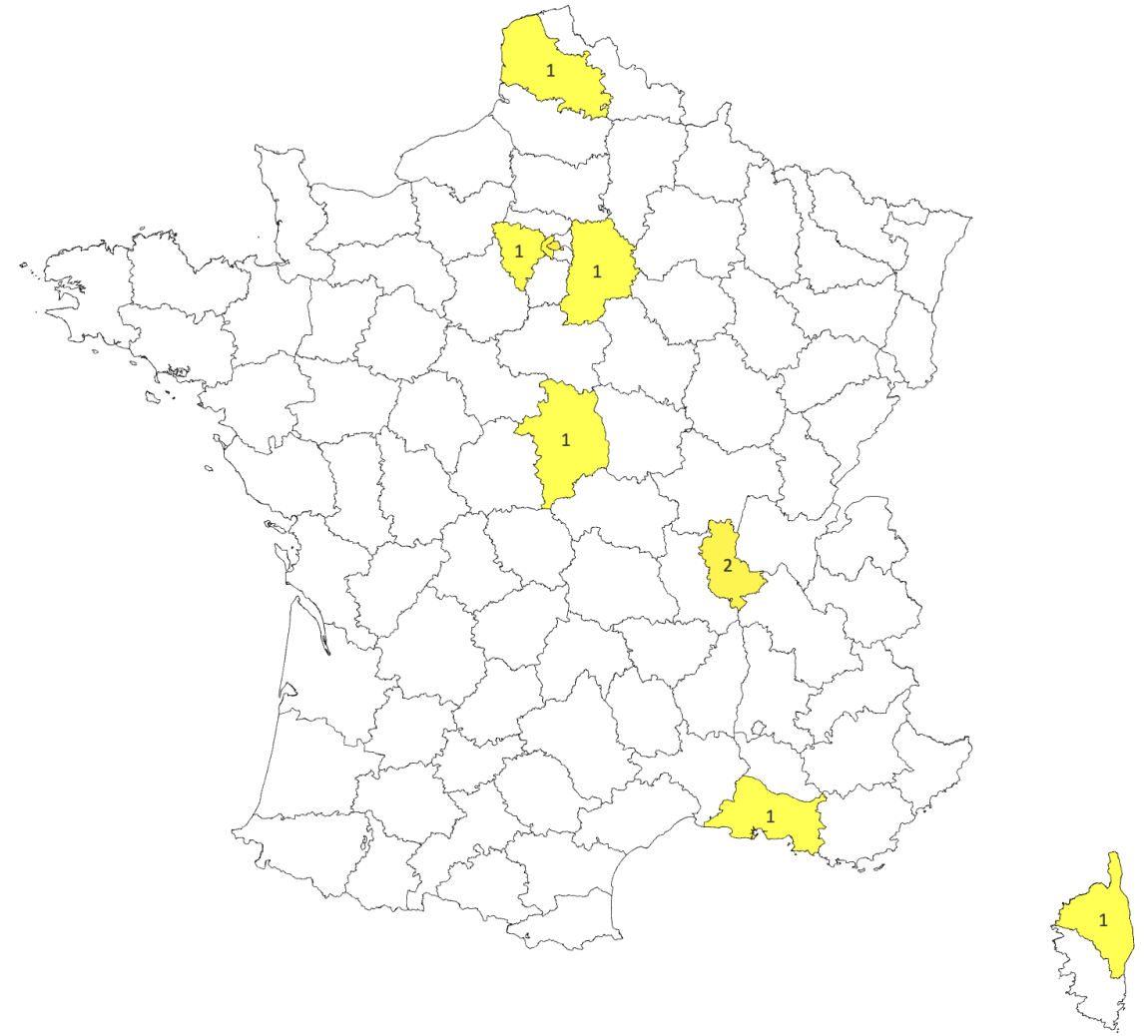
Distribution des souches reçues en 2023 par mécanisme de résistance



Multiple

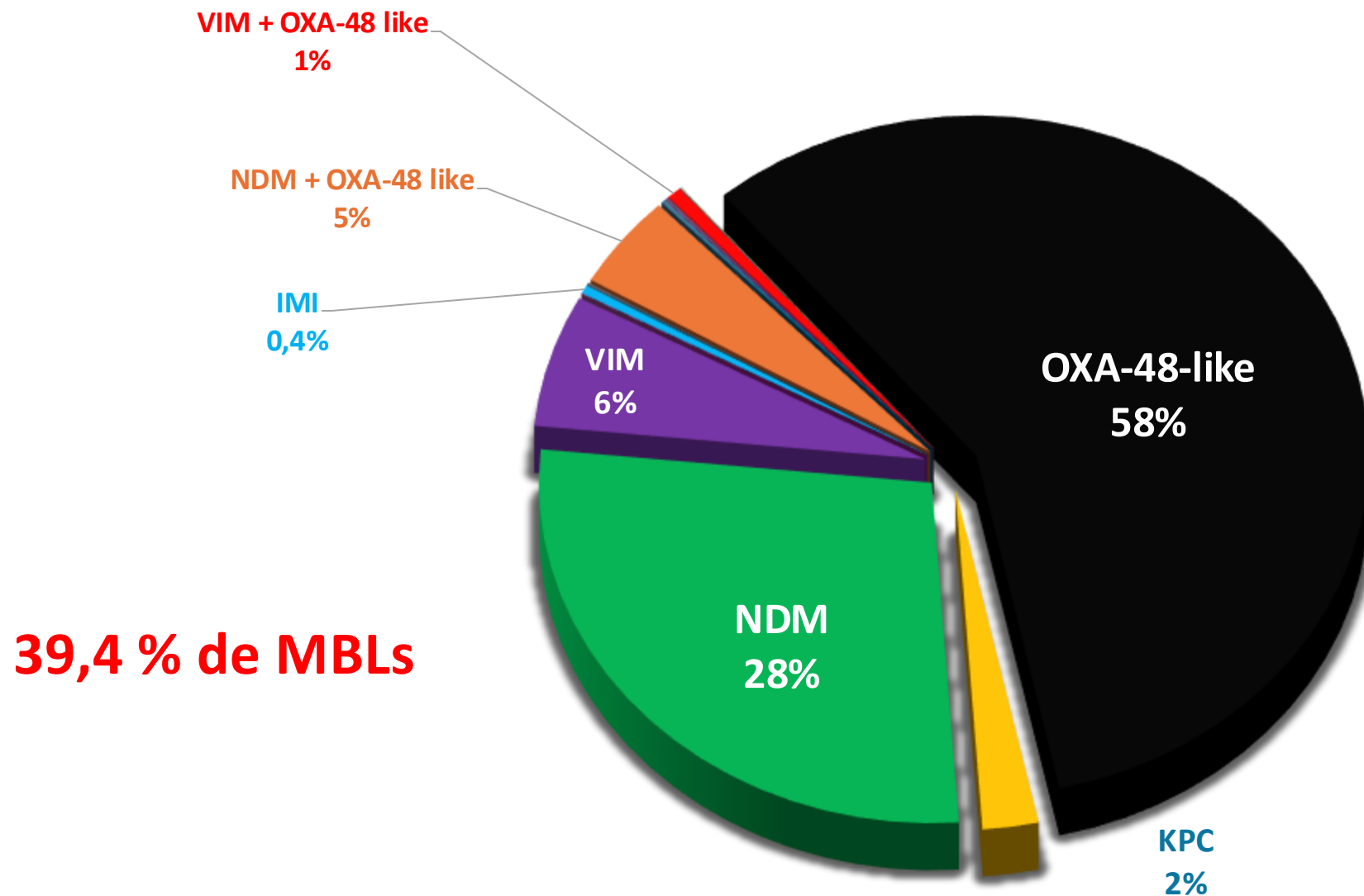


IMI

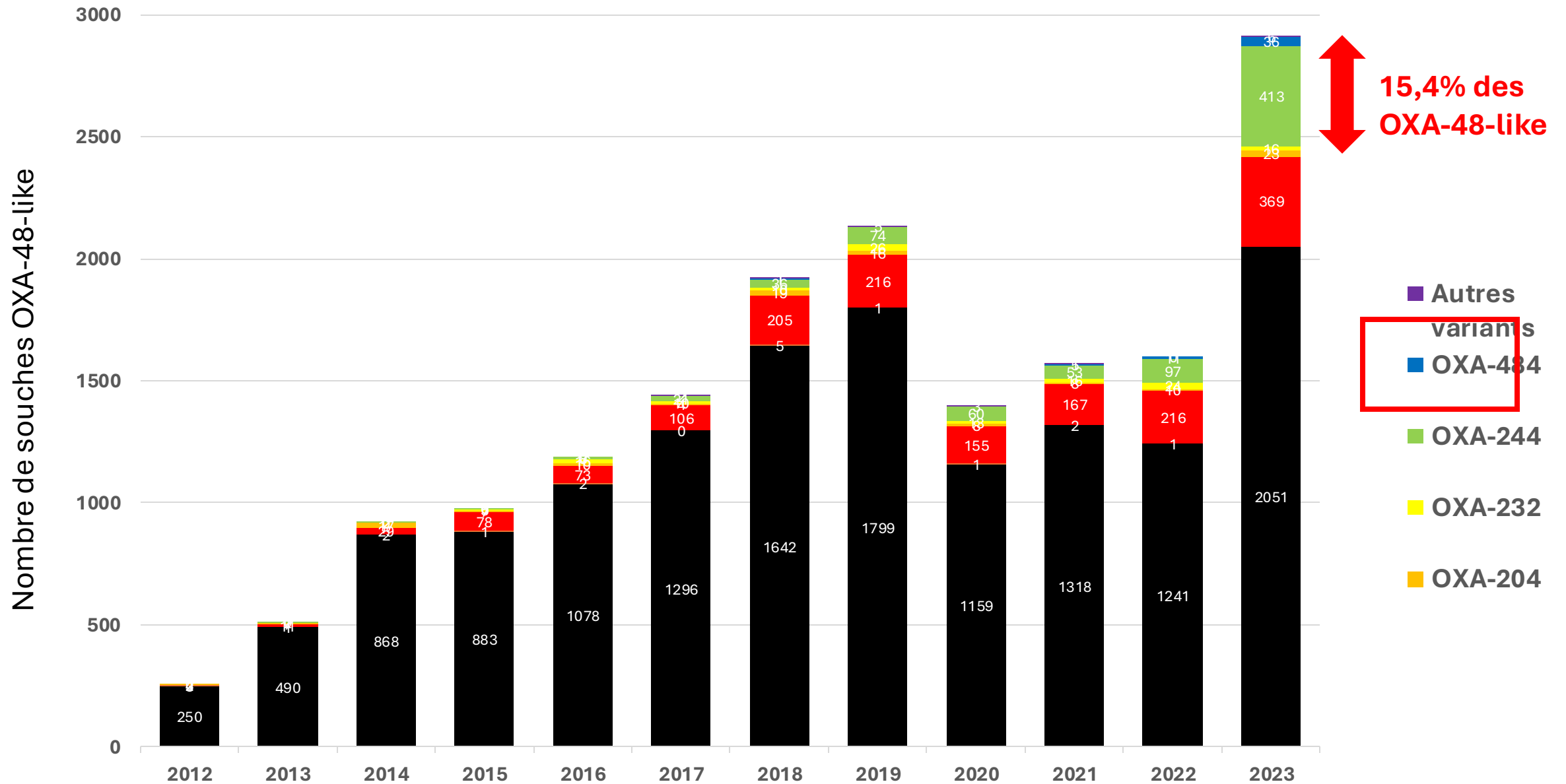


Epidémiologie de la résistance aux carbapénèmes chez les Enterobact

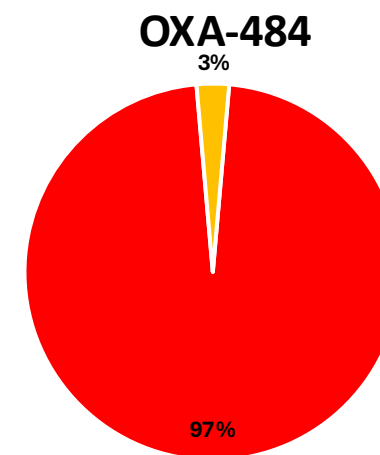
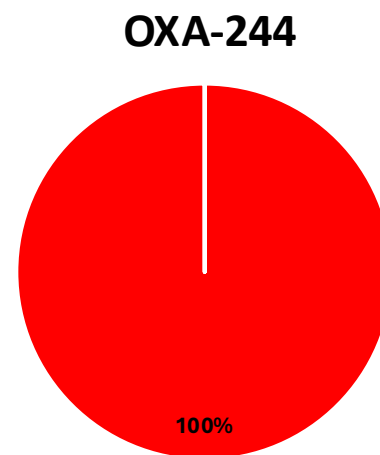
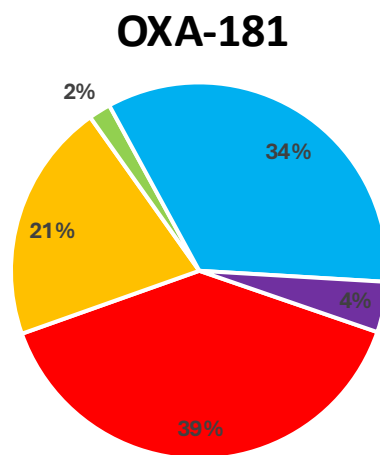
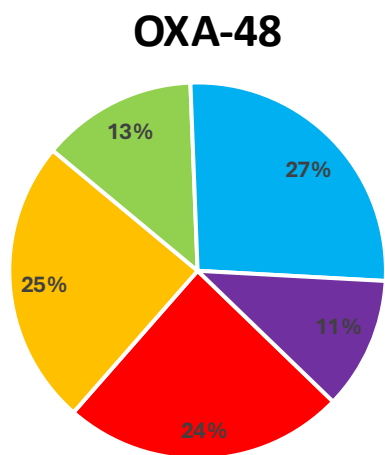
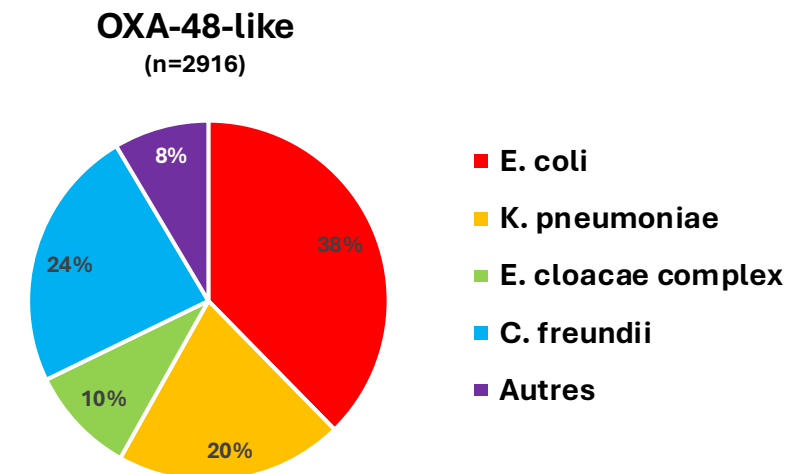
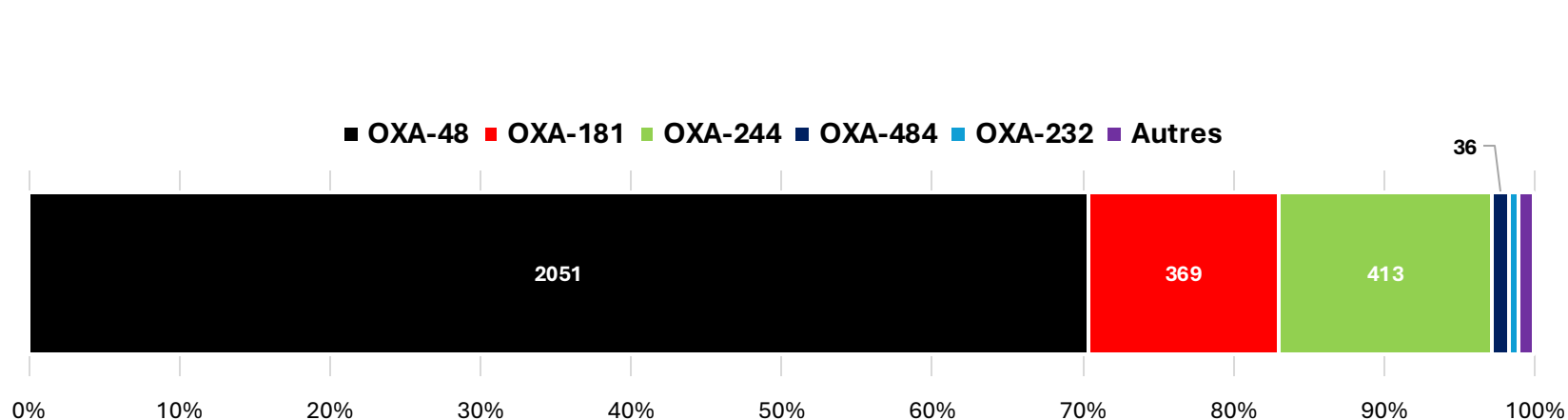
2023



Forte augmentation des OXA-48-like à activité hydrolytique réduite



E. coli comme véhicule de dissémination des OXA-48-like émergents (OXA-181, OXA-244 et OXA-484)



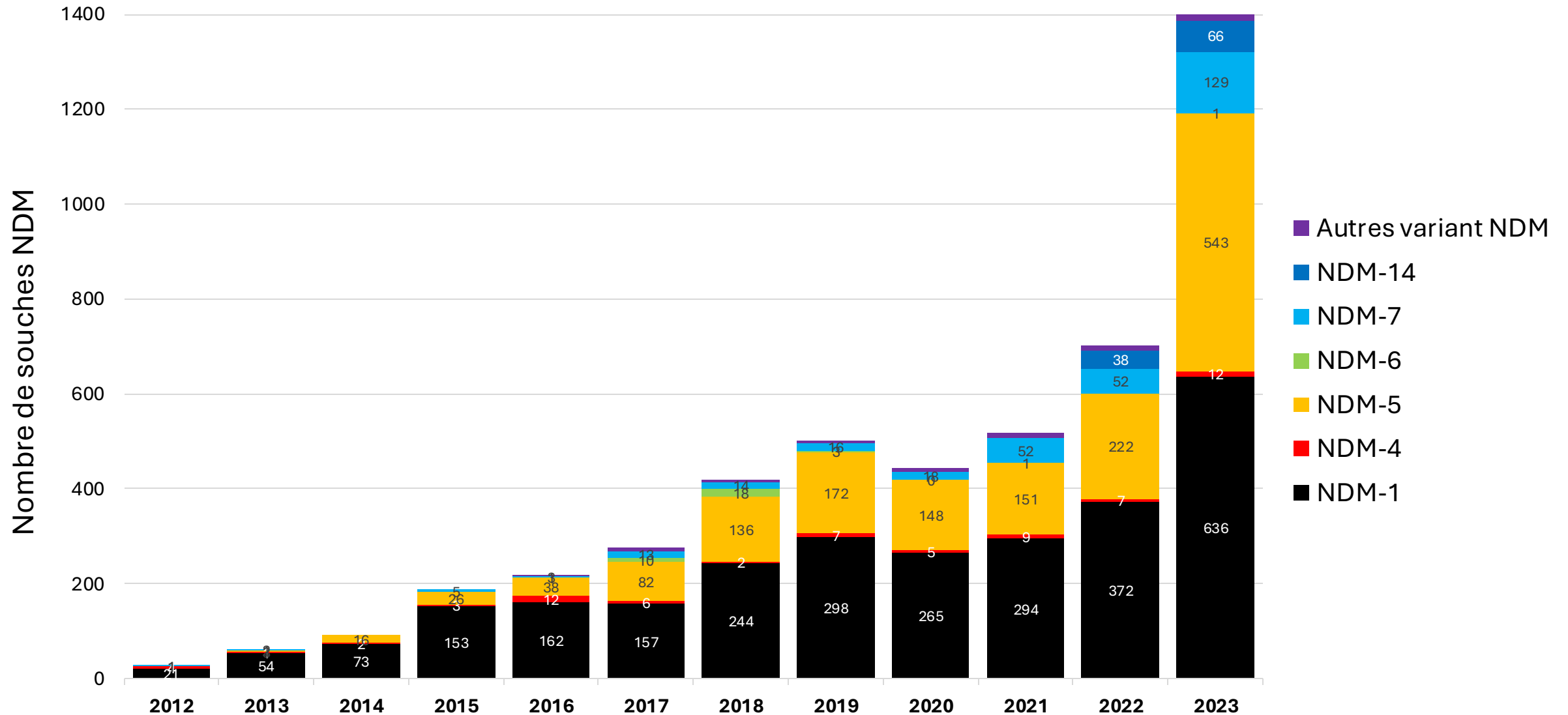
* PLP3 mutée

E. coli ST-410*

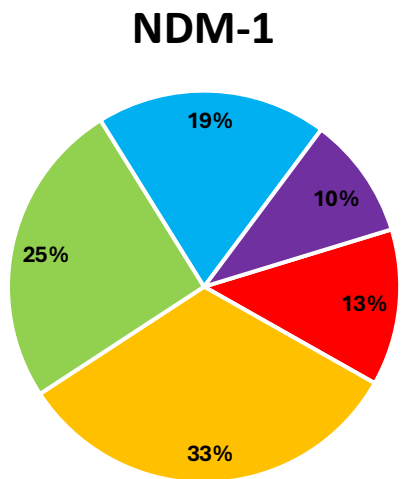
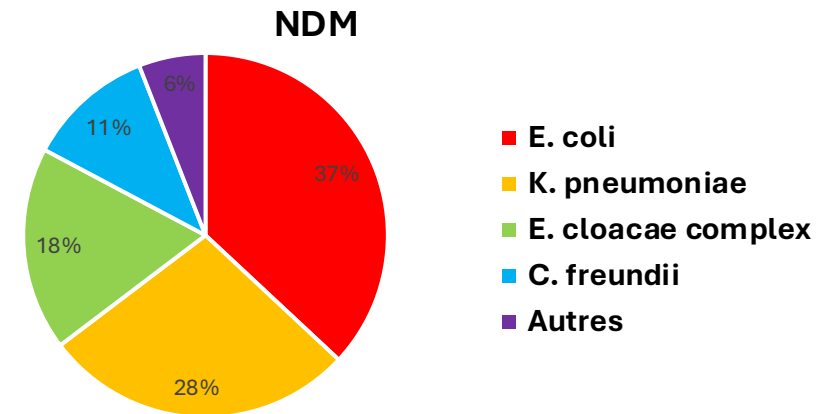
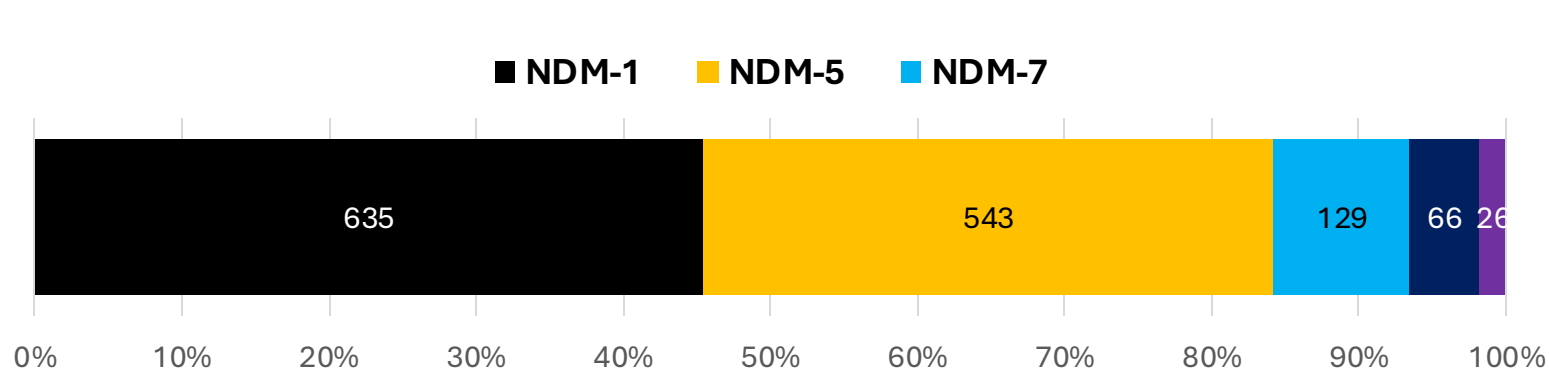
E. coli ST-38
E. coli ST-131

E. coli ST-410*

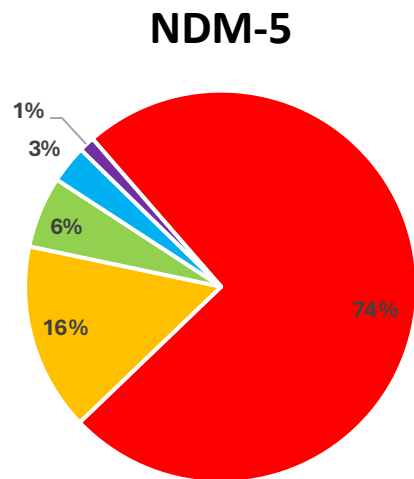
Forte augmentation des variants NDM-5, NDM-7 et NDM-14



A chaque variant sont « clone à risque »

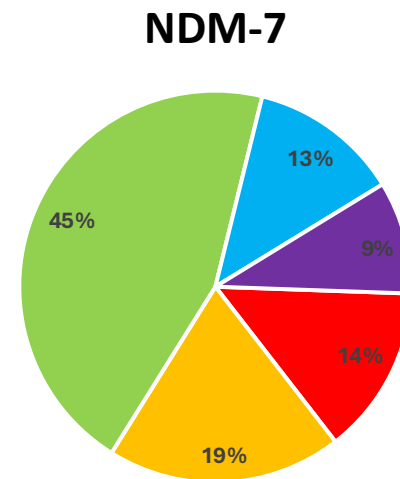


K. pneumoniae ST-147

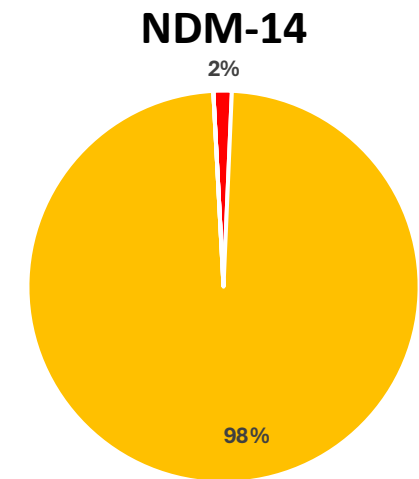


E. coli ST-167*
E. coli ST-410*

* PLP3 mutée

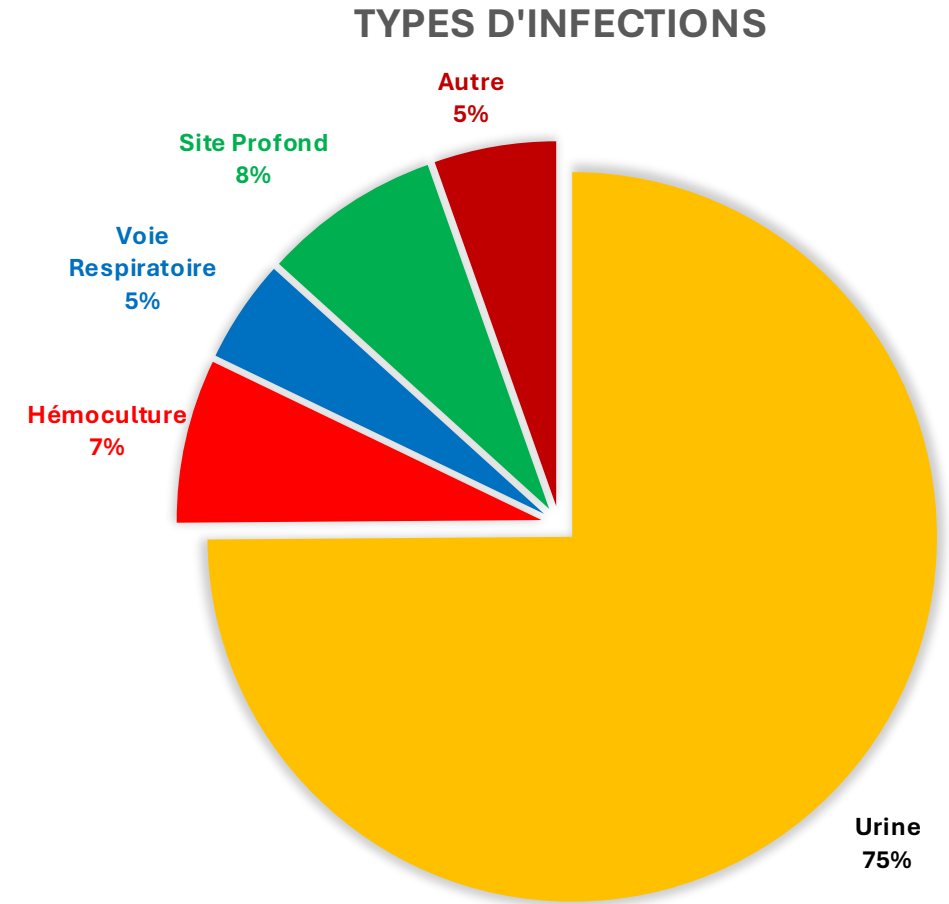
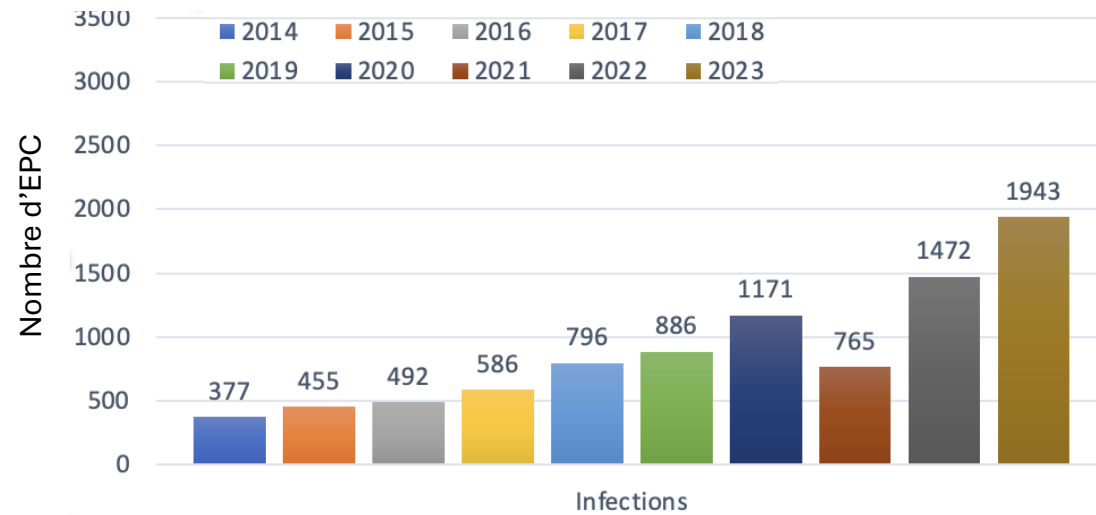
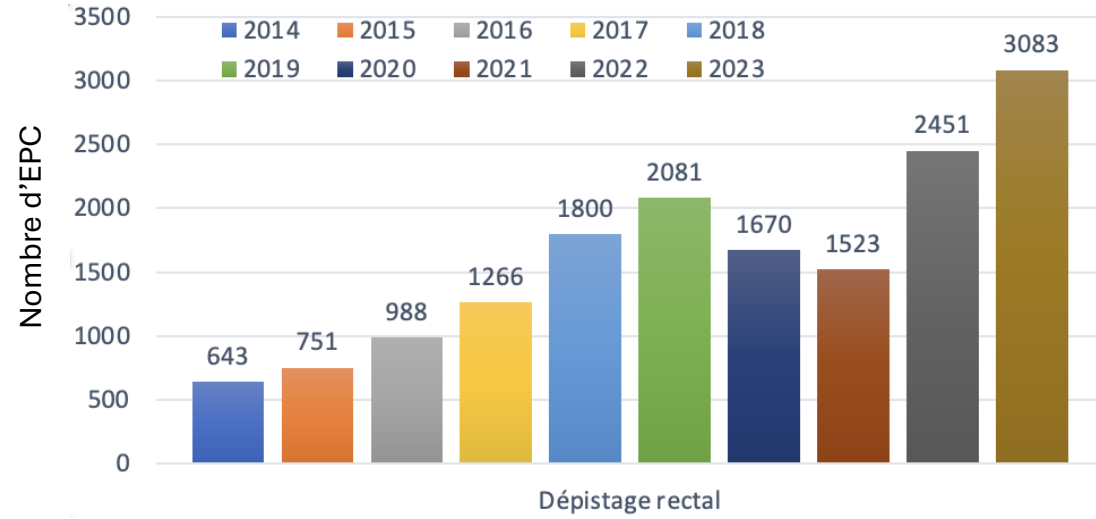


Divers
E. cloacae complex



K. pneumoniae ST-147

Infections vs colonisation



High level resistance to aminoglycosides due to 16S RNA methylsases

- **2003** : description of **armA** a 16S rRNA methylase in a *K. pneumoniae* BM4336 (Paris, 2000) conjugative plasmid pAT780 80 kb (*bla*_{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
- 2007: **npmA** (*E. coli*, 2003, Japan) Wachino, AAC, 2007, 51, 4401-09
- **rmtE, F, G, H et**

High-level resistance to:

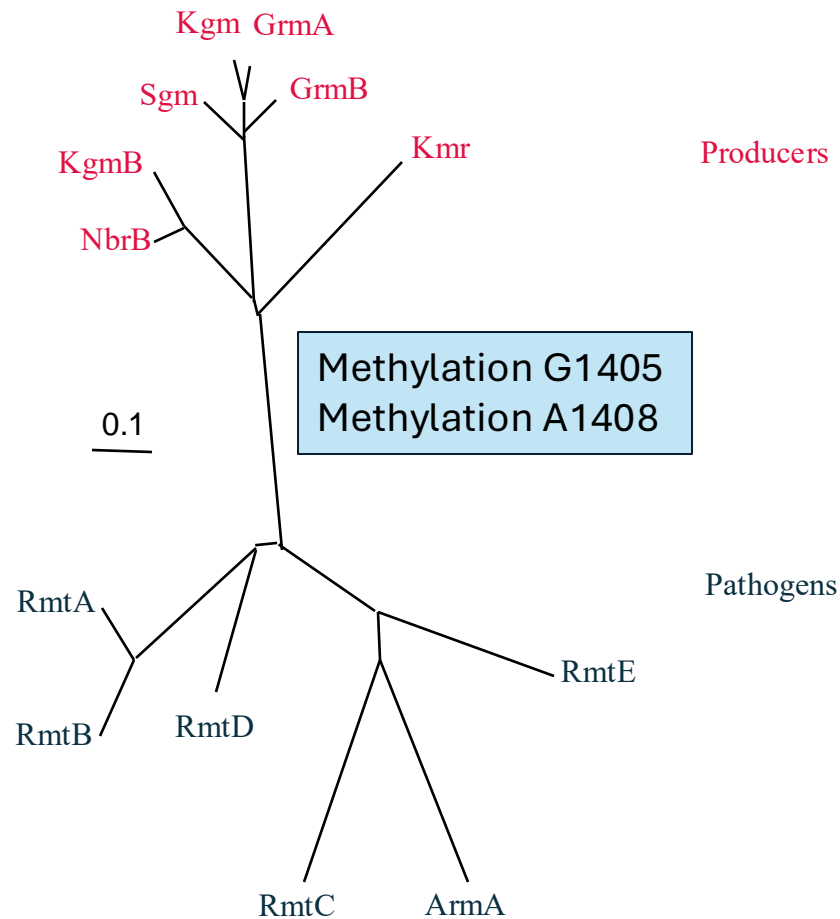
Gentamicin, Tobramycin, Amikacin,
Isepamicin, Kanamycin, Netilmicin, arbekacin

Spares:

Neomycin, Apramycin, Streptomycin

Relations phylogénétiques des 16S rRNA méthyl-transférases

Actinomycetes -> self-defence mechanisms



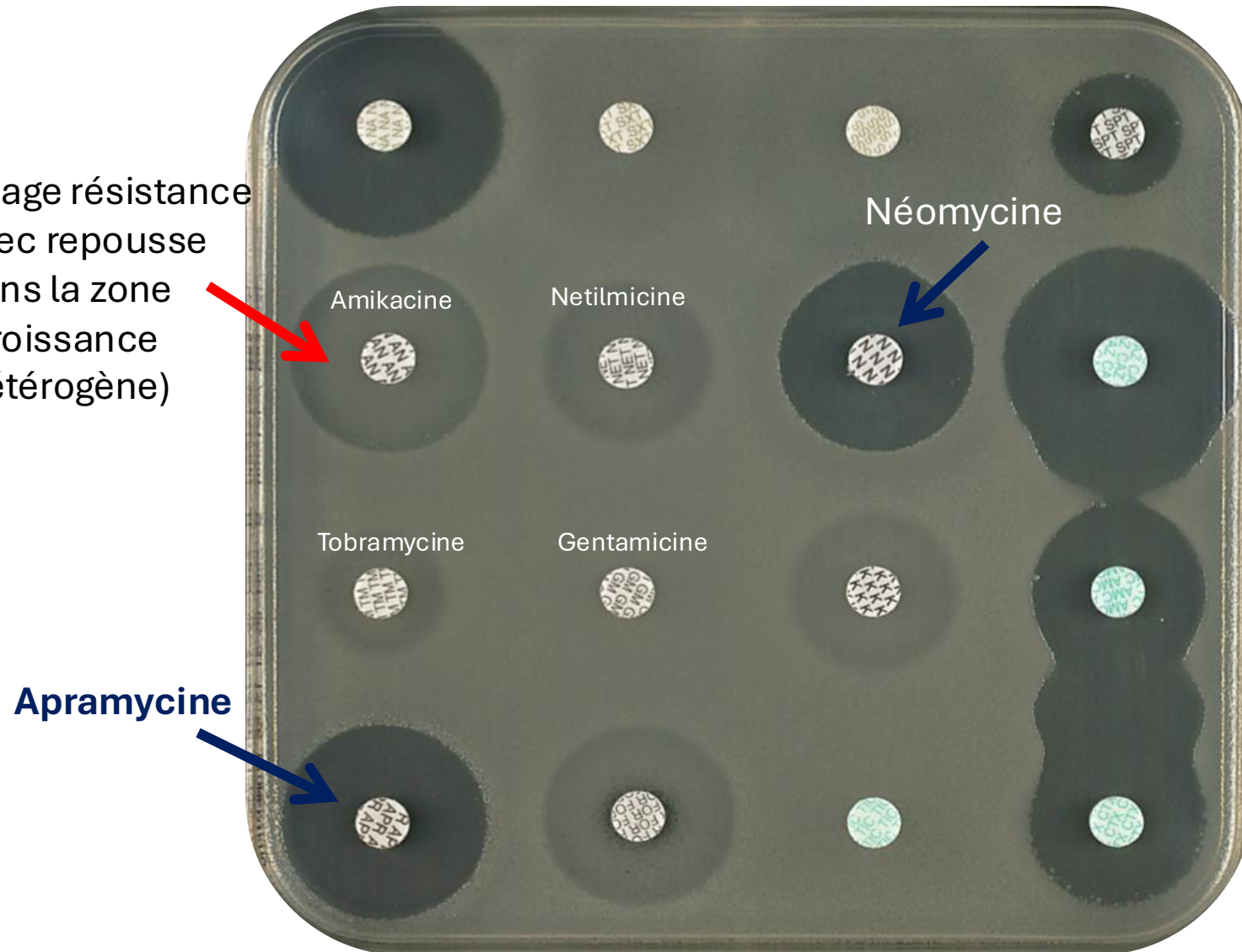
NbrB	<i>Streptoalloteichus hindustanus</i>	nebramycin
KgmB	<i>Streptomyces tenebrarius</i>	nebramycin
Sgm	<i>Micromonospora zionensis</i>	sisomicin
Kgm	<i>Streptomyces lividans</i>	kanamycin
GrmA	<i>Micromonospora purpurea</i>	gentamicin
GrmB	<i>Micromonospora rosea</i>	sisomicin
Kmr	<i>Streptomyces kanamyceticus</i>	kanamycin
FmrO	<i>Micromonospora olivasterospora</i>	fortimicin

RtmA	<i>Pseudomonas aeruginosa</i>
RtmB	<i>Enterobacteriaceae</i>
RtmC	<i>Proteus mirabilis</i>
RtmD	<i>Pseudomonas aeruginosa</i>
RmtE	<i>Escherichia coli</i>
ArmA	<i>Enterobacteriaceae</i>

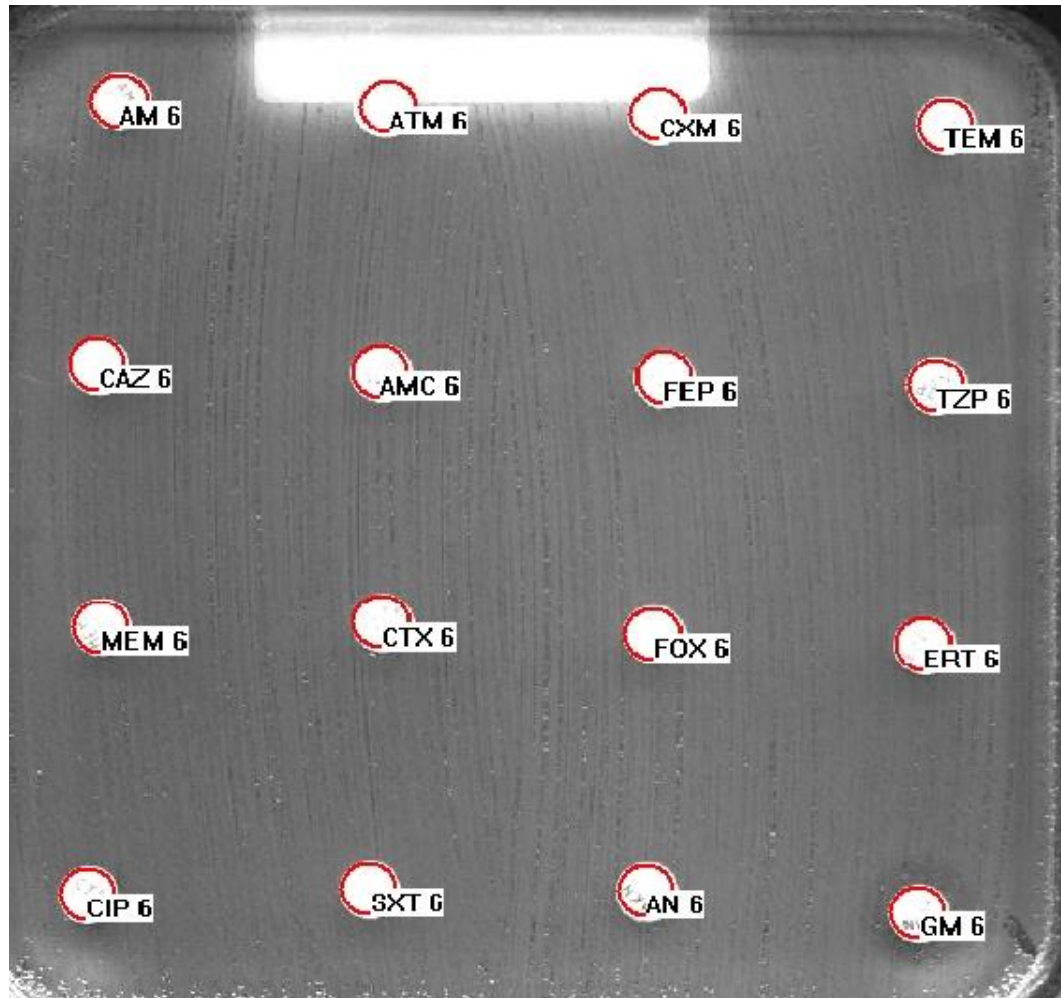
NB: RmtF, RmtG et RmtH have been recently reported

Résistance à tous les aminoglycosides (2-DOS, 4,6 disubst.)
Sensibilité conservée à apramycine et néomycine

Image résistance
avec repousse
dans la zone
(croissance
Hétérogène)



Souvent associées à des BLSE (CTX-M ++++) et/ou des carbapénèmases (NDM +++)



K. pneumoniae

OXA-48

NDM-1

CTX-M-15

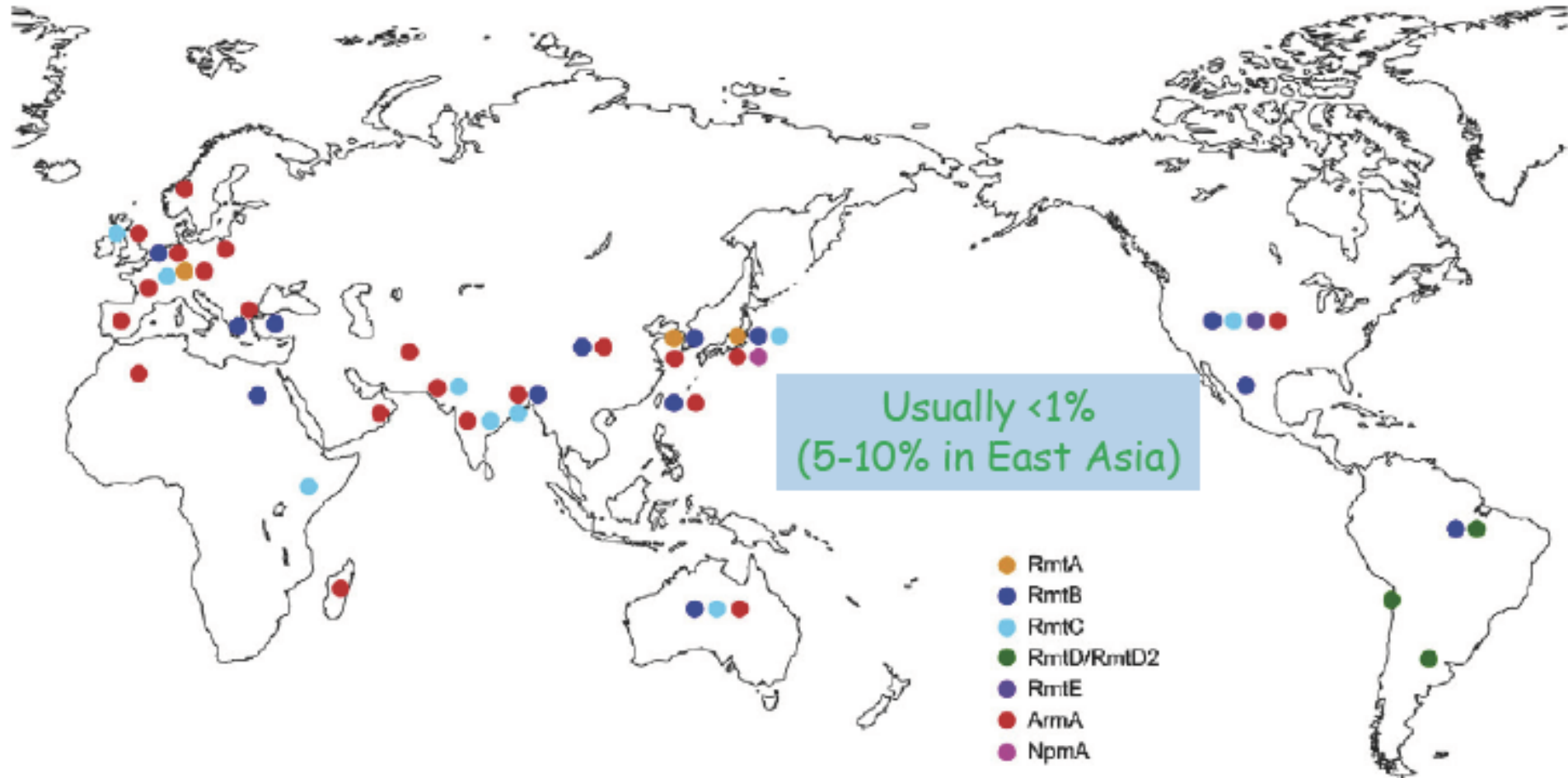
RmtC (ARNr methylase

16S)

SHV-11

TEM-1

Worldwide distribution of 16S rRNA methylases



ArmA, RmtB and RmtC are predominant among Enterobacteriaceae

Résistances émergentes chez
Pseudomonas aeruginosa

Infections causées par *P. aeruginosa*

Tableau 31. Répartition des souches de *P. aeruginosa* par type de prélèvement (n=42 035)

<i>Pseudomonas aeruginosa</i>		
Type de prélèvement	Nb souches	Répartition (%)
Hémoculture	4 119	9,1%
Dispositif intravasculaire	1 072	2,3%
Urine	16 445	36,2%
Prélèv. respi. non protégé	9 179	20,2%
Prélèv. respi. protégé ou distal	2 848	6,3%
Pus profond et séreuses	5 191	11,4%
Autre	6 603	14,5%
Tous prélèvements confondus	42 035 ¹	100,0%

¹ Un seul isolat ayant le même antibiotype quel que soit le prélèvement est retenu ; ne correspond donc pas à la somme des isolats par type de prélèvement (45 457), un patient pouvant présenter un isolat de même antibiotype dans des prélèvements de natures différentes.

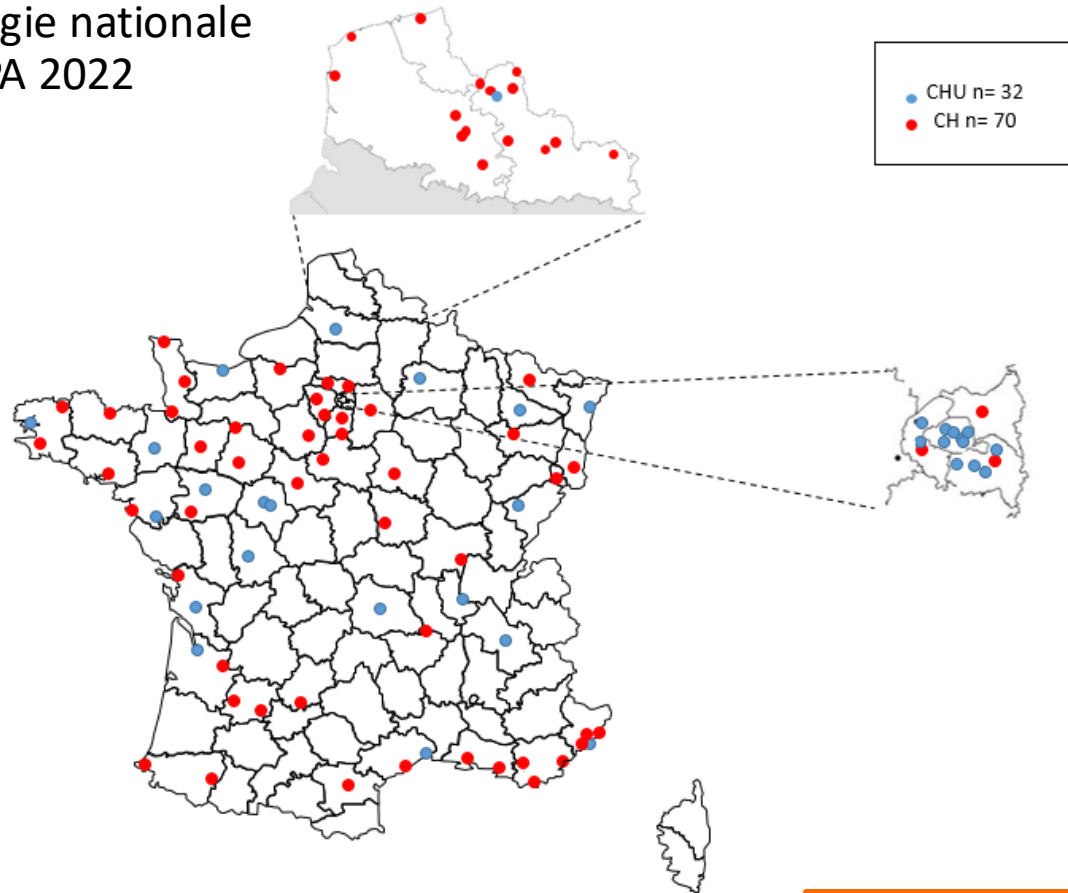
Résistance aux antibiotiques chez *P. aeruginosa*

Tableau 30. Résistance de *P. aeruginosa* aux antibiotiques, tous prélèvements confondus (n=42 035) et hémocultures (n=4 119)

Antibiotique	Tous prélèvements confondus		Hémocultures	
	Nb total de souches	% (R+I)	Nb total de souches	% (R+I)
Ticarcilline	25 754	28,5	2 622	26,2
Pipéracilline - tazobactam	36 434	20,7	3 588	20,1
Ceftazidime	39 199	15,5	3 870	14,5
Céfépime	35 784	14,3	3 534	13,3
Imipénème	39 059	15,5	3 832	13,4
Méropénème	33 853	11,6	3 294	10,1
Amikacine	39 752	5,0	3 844	4,0
Ciprofloxacine	39 161	14,8	3 846	11,8

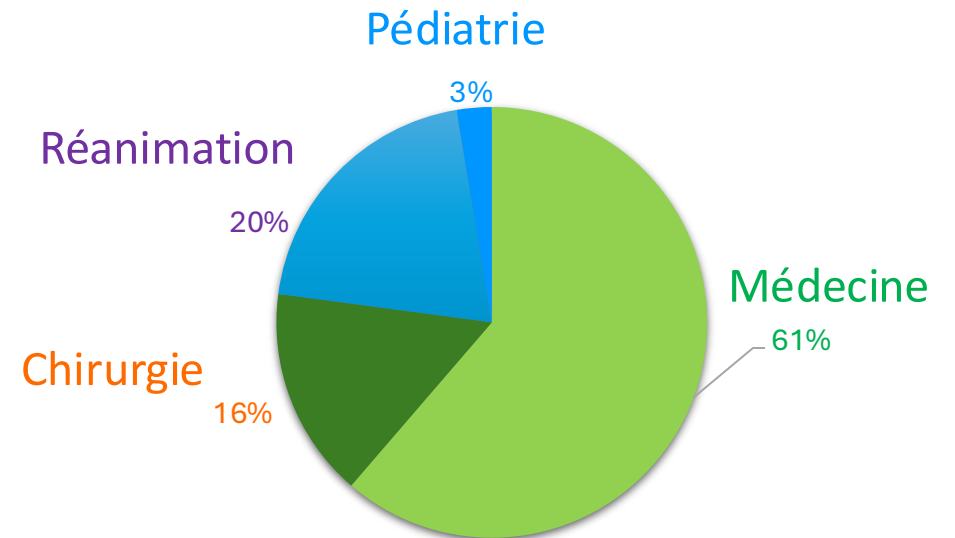
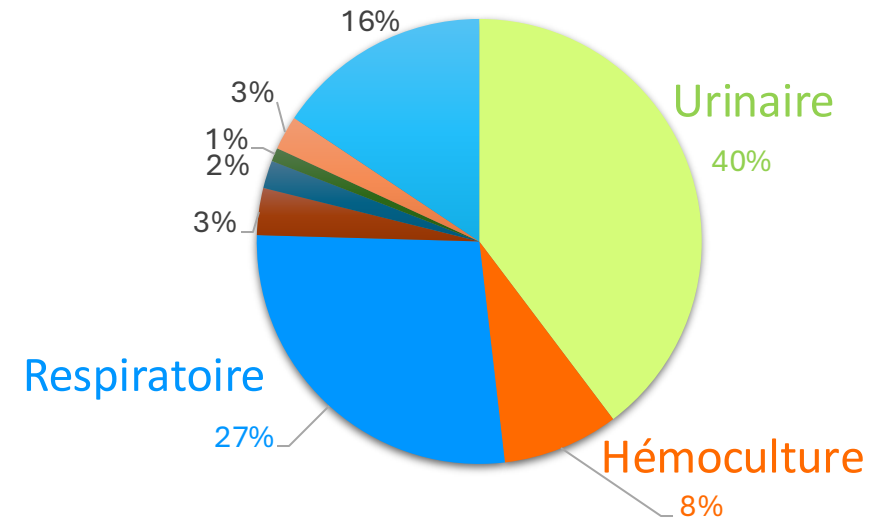
La résistance aux carbapénèmes chez *P. aeruginosa*

Epidémiologie nationale
GERPA 2022

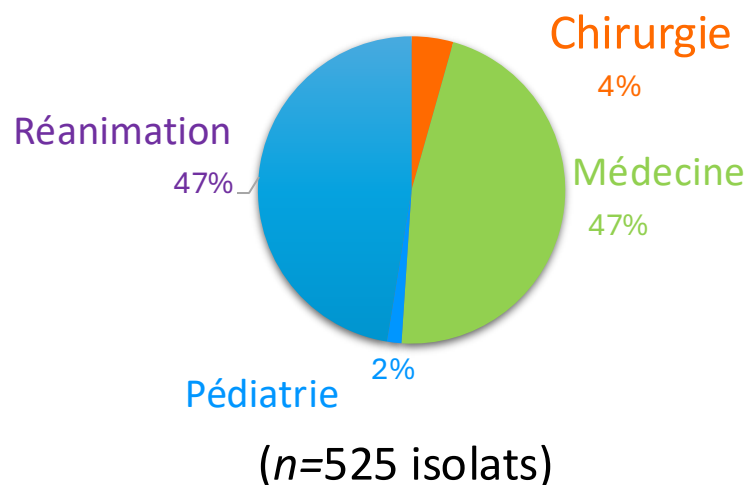


n=102 centres
(1 au 28 février 2022)

1 931 isolats



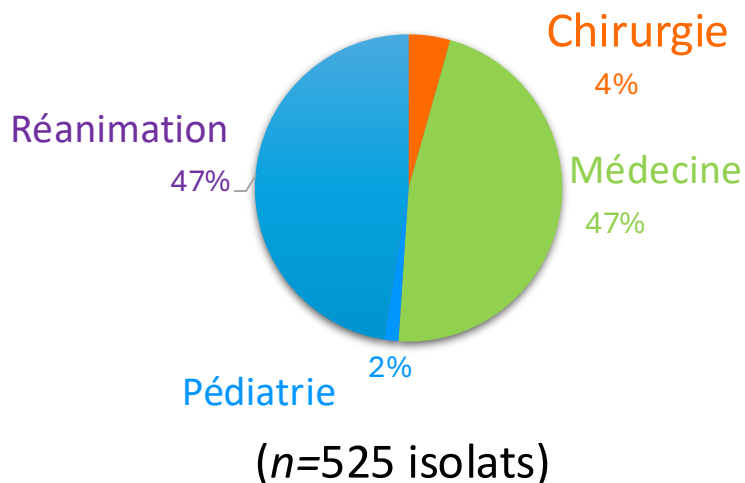
Sensibilité des souches de *P. aeruginosa* isolées des prélèvements respiratoires



	CMI (mg/L)*											
	0.5	1	2	4	8	16	32	64	128	256	512	
Pipéracilline/tazobactam				281	67	40	46	28	31	25	7	26.1 %
Ceftazidime		73	224	82	39	35	38	22	9	3		20.4 %
Céfépime		88	189	90	69	49	32	6	1	1		17.0 %
Imipénème	135	232	53	27	40	33	2	0	3			14.9 %
Méropénème	327	75	40	25	28	21	4	2	3			5.7 %

*CMI déterminées par microdilution en milieu liquide et interprétées selon les recommandations de l'EUCAST 2023

Sensibilité des souches de *P. aeruginosa* isolées des prélèvements respiratoires



CMI (mg/L)*	0.5	1	2	4	8	16	32	64	128	256	512	
Pipéracilline/tazobactam				281	67	40	46	28	31	25	7	26.1 %
Ceftazidime		73	224	82	39	35	38	22	9	3		20.4 %
Céfépime		88	189	90	69	49	32	6	1	1		17.0 %
Imipénème	135	232	53	27	40	33	2	0	3			14.9 %
Méropénème	327	75	40	25	28	21	4	2	3			5.7 %

*CMI déterminées par microdilution en milieu liquide et interprétées selon les recommandations de l'EUCAST 2023

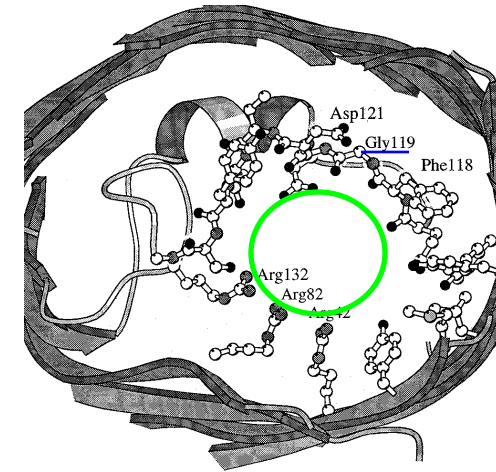
CMI (mg/L)*	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	
Ceftazidime/avibactam					31	124	245	67	37	12	5	1	3	4.0 %
Ceftolozane/tazobactam					196	228	65	21	9	0	1	5		2.9 %
Céfidérol	94	75	136	114	62	31	6	3	3	1				1.8 %
Imipénème/relebactam					451	38	27	3	3	0	0	0	3	1.7 %
Colistine					35	298	181	7	1	2	1			0.8 %

➔ < 5% de résistance aux nouvelles associations, au céfidérol et à la colistine

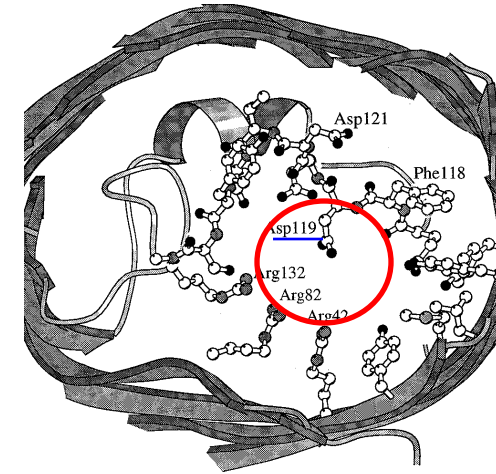
La résistance aux carbapénèmes chez *P. aeruginosa*



**Perte /
modification
porine OprD**



Porine sauvage



Porine mutée (G119D)

La résistance aux carbapénèmes chez *P. aeruginosa*



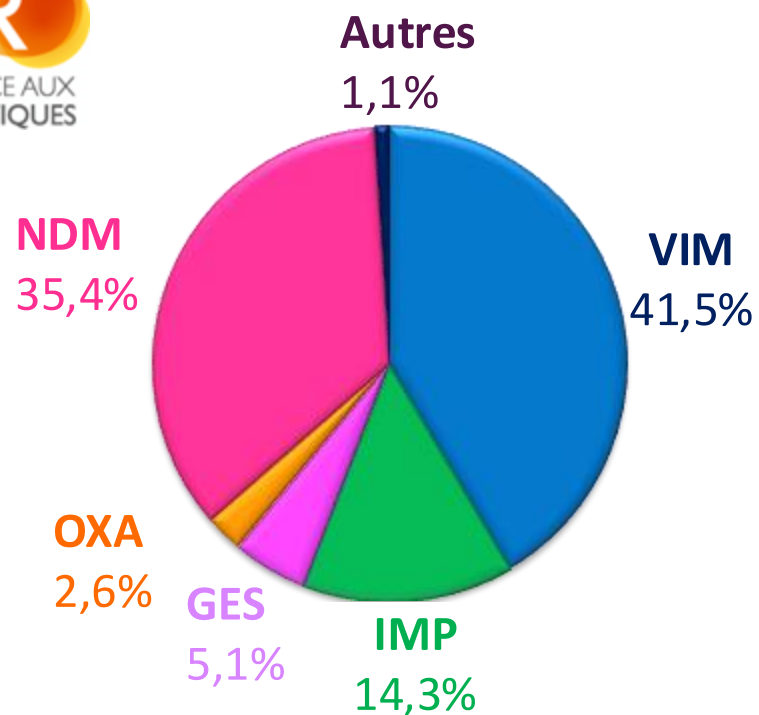
**AmpC
déréprimée
+
Perte de
porine OprD**

La résistance aux carbapénèmes chez *P. aeruginosa*

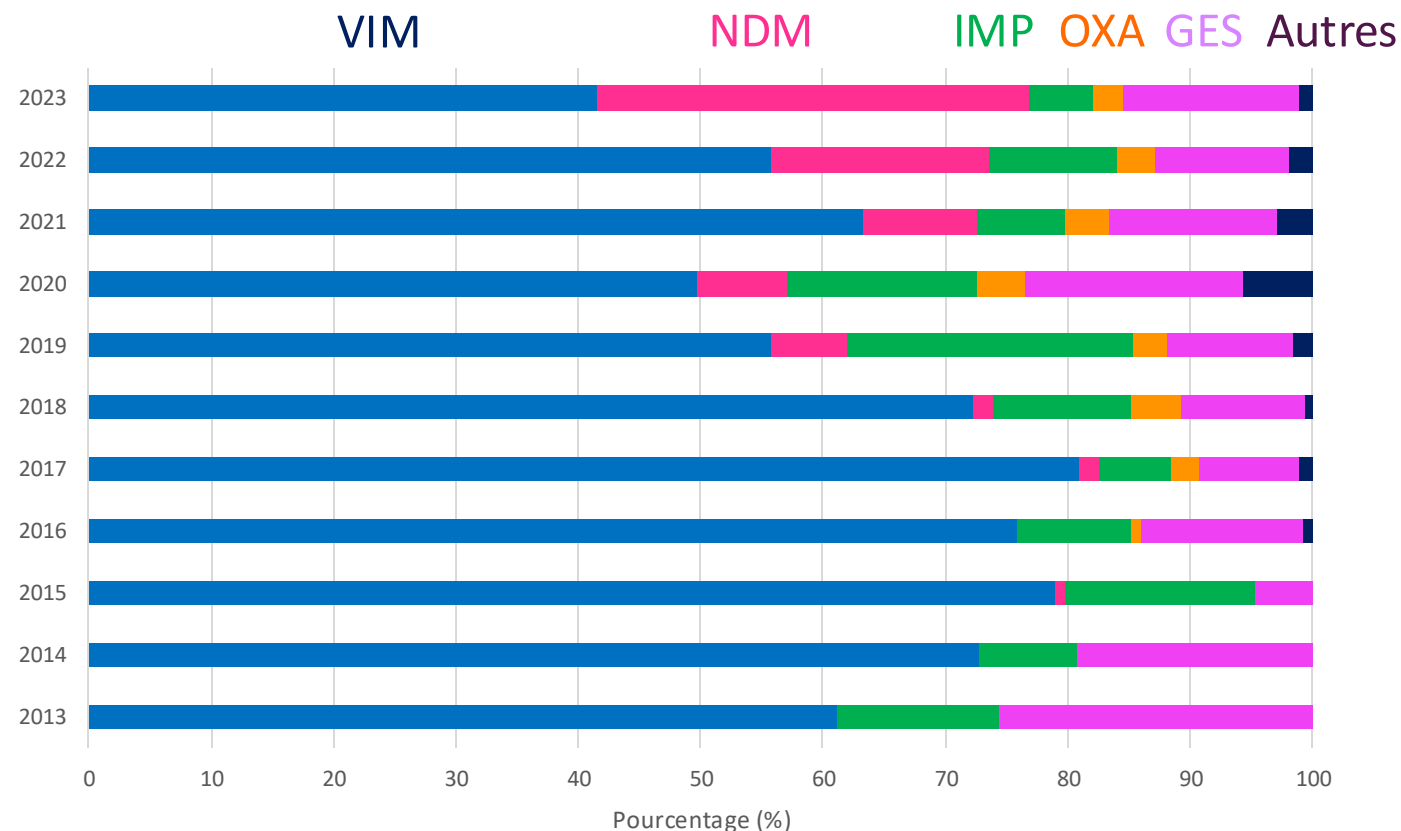


BLSE VEB
+
Perte OprD
+
**Autres mécanismes
pour Aminosides et FQ**

La résistance aux carbapénèmes chez *P. aeruginosa*



n = 221 souches

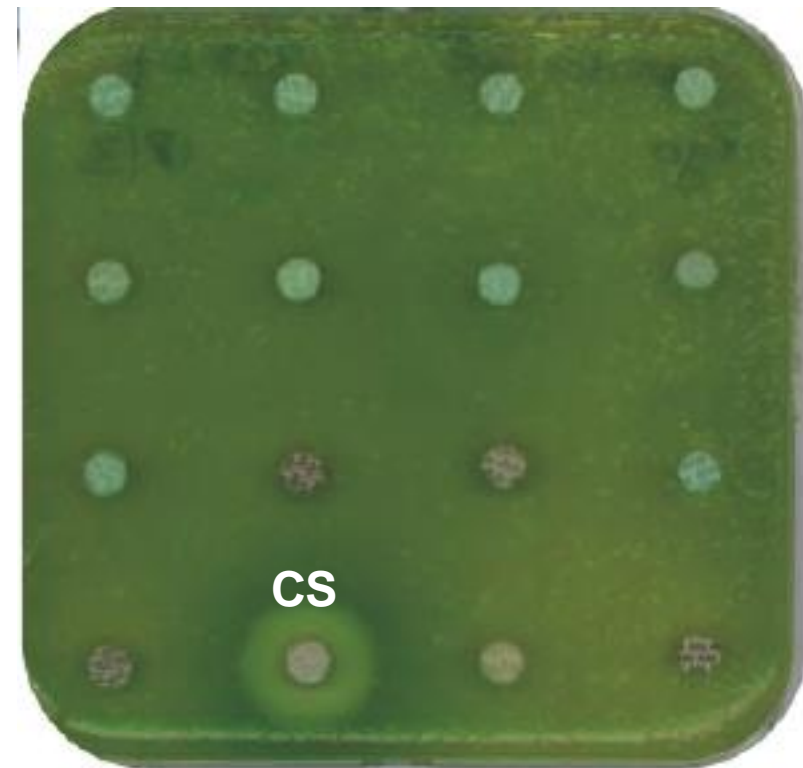
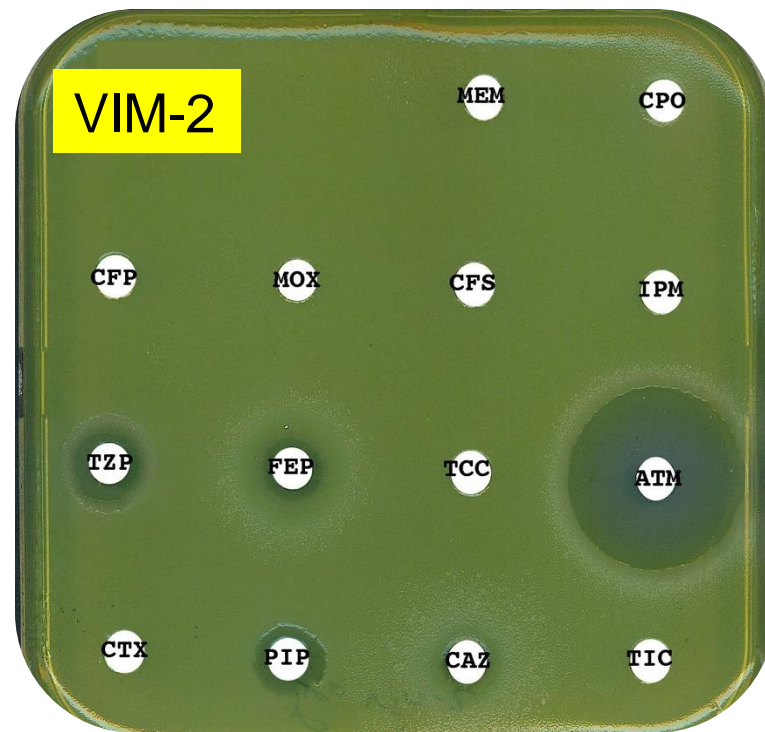


En 2022, **19,1%** des souches résistantes aux carbapénèmes expertisées par le CNR produisaient au moins une carbapénémase. **Forte progression de NDM-1**

La résistance aux carbapénèmes chez *P. aeruginosa*

VIM and VIM carbapenemases are predominant in *P. aeruginosa*

XDR *P. aeruginosa* isolate



Colistin : an antibiotic of last resort

Résistances émergentes chez
Acinetobacter baumannii

Infections causées par *A. baumannii*

Tableau 33. Répartition des souches d'*A. baumannii* par type de prélèvement (n=1 521)

Type de prélèvement	<i>Acinetobacter baumannii</i>	
	Nb souches	Répartition (%)
Hémoculture	311	19,0%
Dispositif intravasculaire	89	5,4%
Urine	375	22,8%
Prélèv. respi. non protégé	325	19,8%
Prélèv. respi. protégé ou distal	163	9,9%
Pus profond ou séreuses	160	9,8%
Autre	218	13,3%
Tous prélèvements confondus	1 521 ¹	100,0%

Résistance aux antibiotiques chez *A. baumannii*

Tableau 32. Résistance d'*A. baumannii* aux antibiotiques (n=1 521), tous prélèvements confondus et hémocultures (n=311)

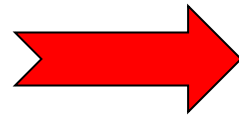
Antibiotique	Tous prélèvements confondus		Hémocultures	
	Nb total de souches	% (R+I)	Nb total de souches	% (R+I)
Ticarcilline	1347	13,1	270	11,5
Pipéracilline - tazobactam	879	16,6	170	20,6
Ceftazidime	1001	15,5	205	20,0
Céfépime	1390	11,8	284	10,9
Imipénème	1469	6,9	306	7,8
Méropénème	1177	7,7	246	8,1
Amikacine	1053	10,9	219	10,5
Ciprofloxacine	1270	29,3	253	23,3

Acinetobacter baumannii

In the early 1980' s



In 2000' s



Towards 100% of carbapenem resistance?

Table 1. Antimicrobial resistance of *Acinetobacter baumannii* isolates from patients in intensive care units in Greece

	Proportion of isolates with full or intermediate resistance										
	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006 ^a
Ampicillin-sulbactam	ND	46	40	ND	ND	ND	44	65	63	55	57
Piperacillin-tazobactam	ND	ND	ND	ND	ND	ND	84	91	96	96	98
Ceftazidime	ND	96	92	93	88	85	88	94	98	95	95
Cefepime	ND	81	84	ND	ND	ND	91	95	97	92	94
Imipenem	0	16	17	ND	10	27	44	66	64	78	91
Amikacin	ND	78	82	81	79	82	86	86	86	84	90
Ciprofloxacin	93	88	86	86	90	91	94	97	98	99	98
MDR ^b	ND	ND	ND	73	68	63	74	79	86	86	86

^aData available for the first semester of 2006.

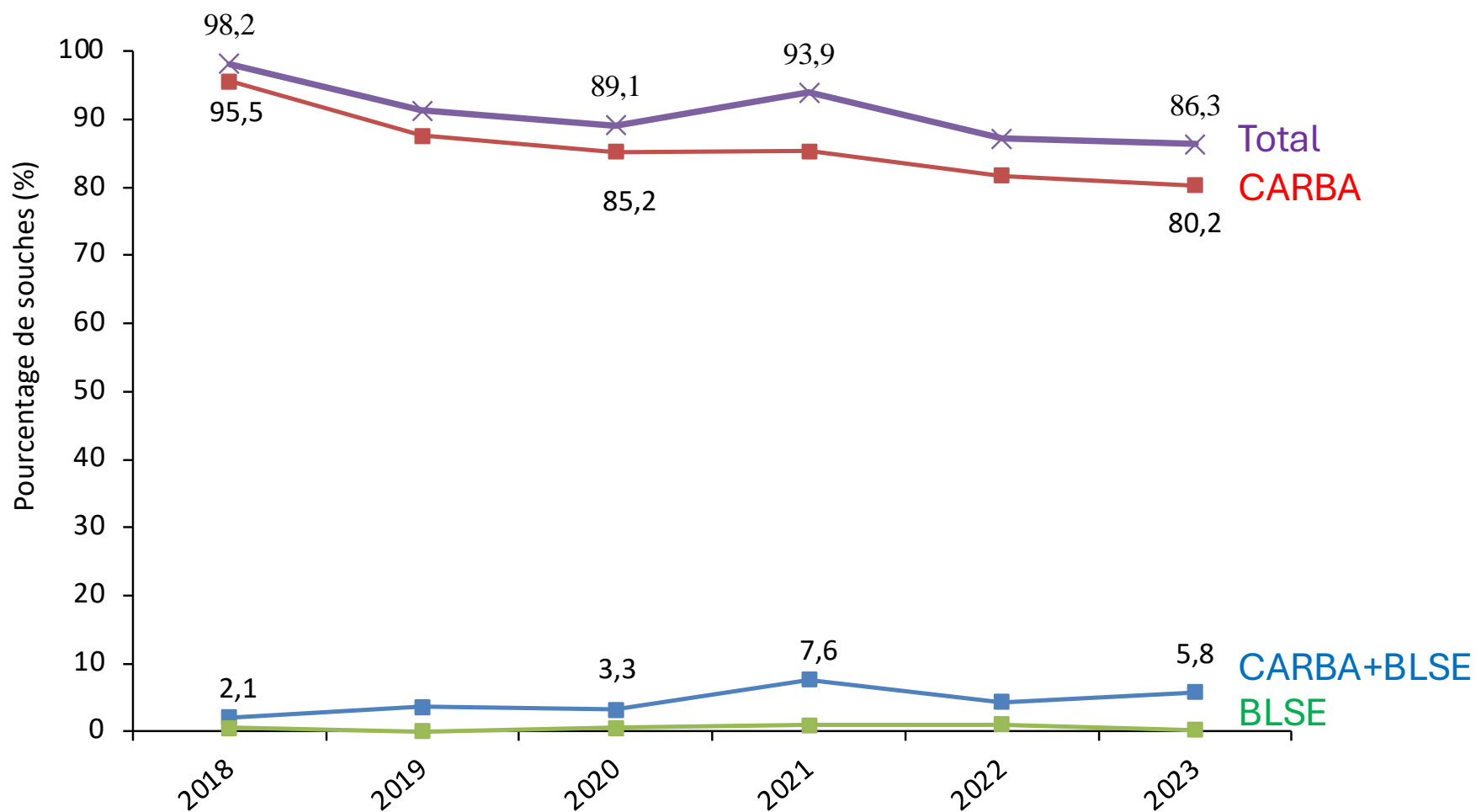
^bMultidrug-resistant (resistance to ceftazidime, ciprofloxacin, and amikacin).

La résistance aux carbapénèmes chez *A. baumannii*

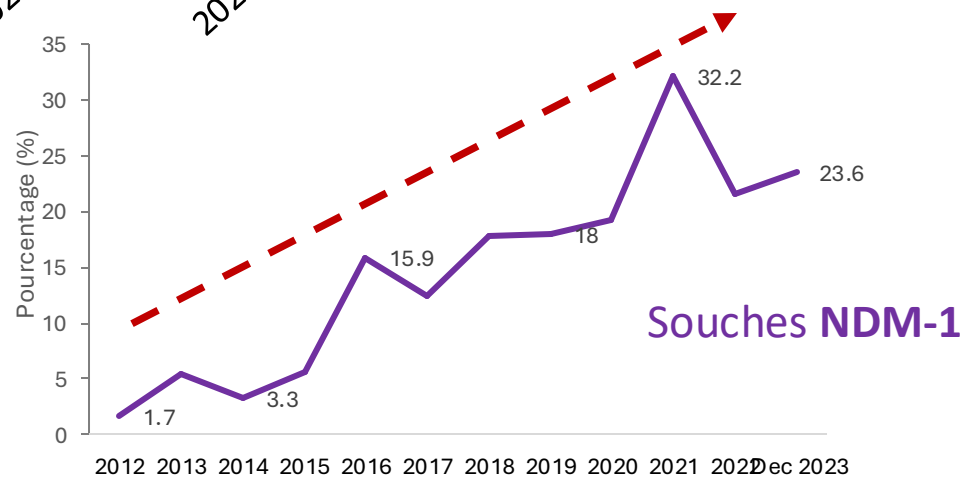
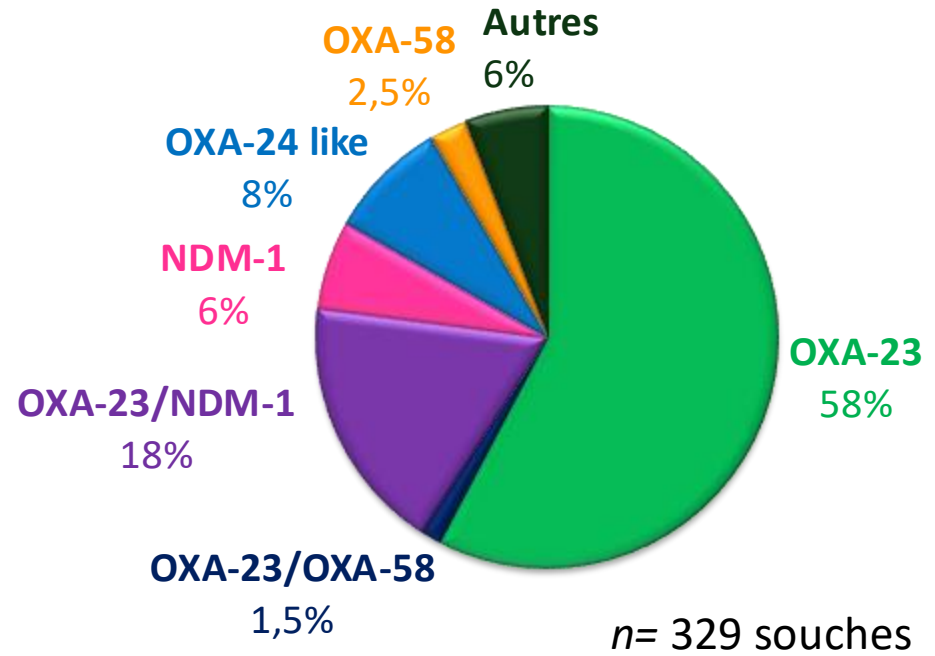
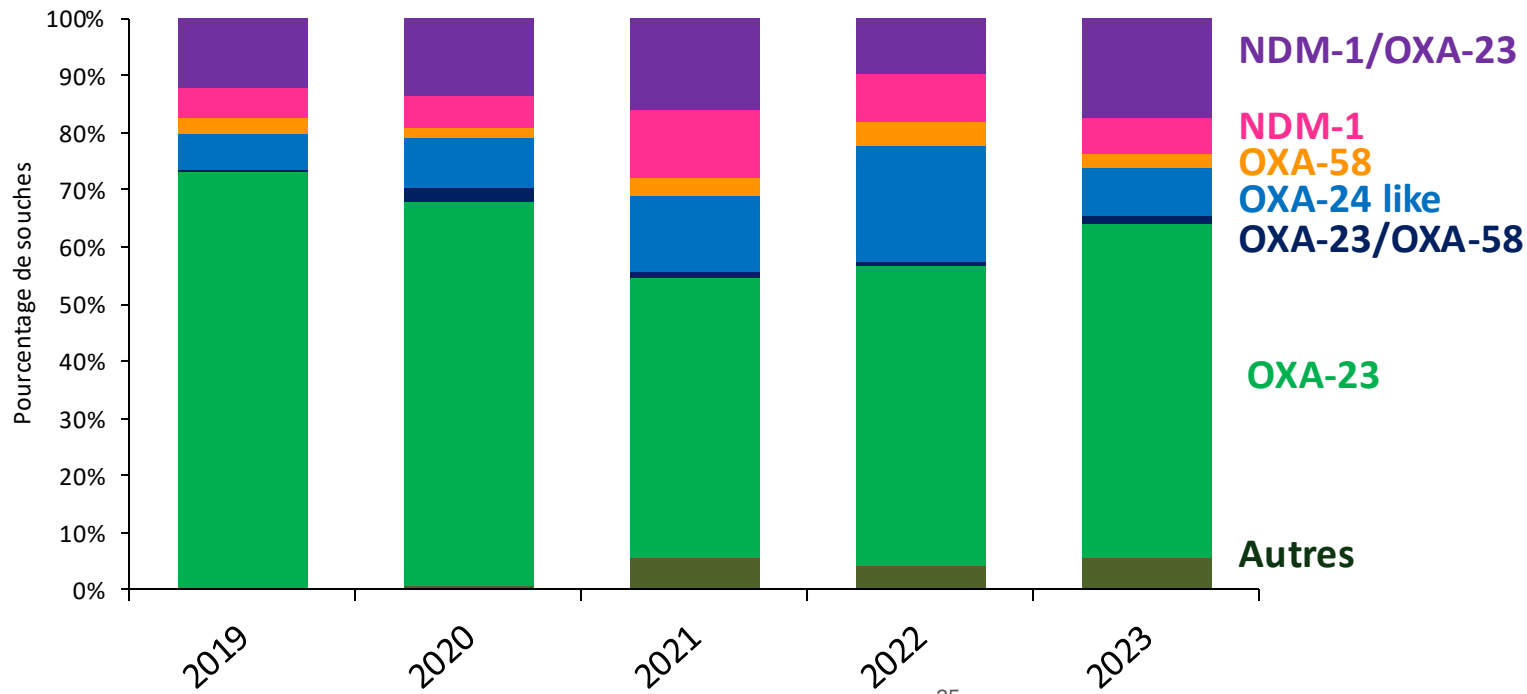
Les carbapénémases +++



2023

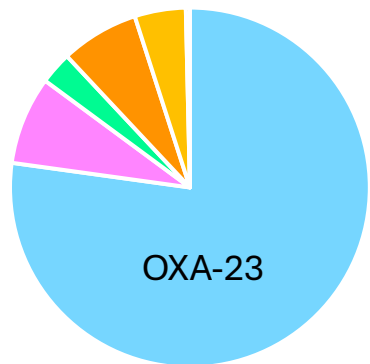


Les carbapénèmases chez *A. baumannii*

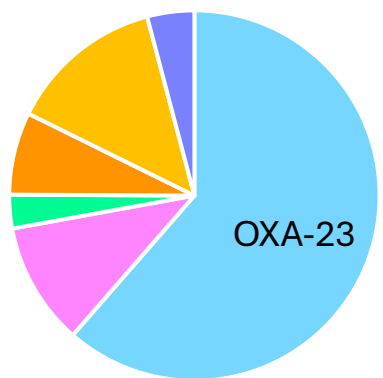


Carbapénèmases identifiées chez *A. baumannii* en Europe

France 2014-2018 ($n=1\ 653$)



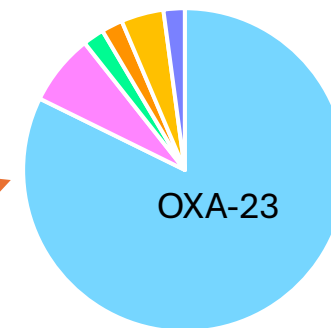
France 2019-2023 $n=1\ 192$



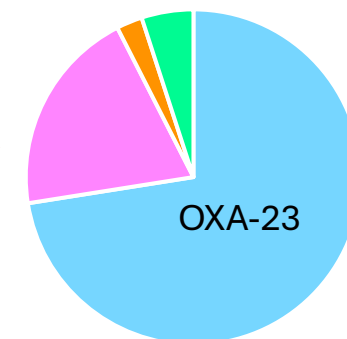
- OXA-23
- OXA-24/40
- OXA-58
- NDM-1
- NDM-1 + OXA-23
- Autres

Hansen *et al*, 2023; Kostyanov *et al*, 2021 (EURECA Study), Zarrilli *et al*, 2021, Valcek *et al*, 2022, Galani *et al*, 2023

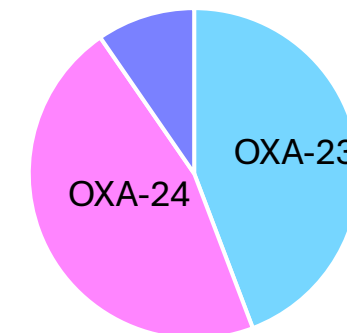
Danemark 2014-2021 ($n=141$)



Belgique 2014-2017 ($n=40$)



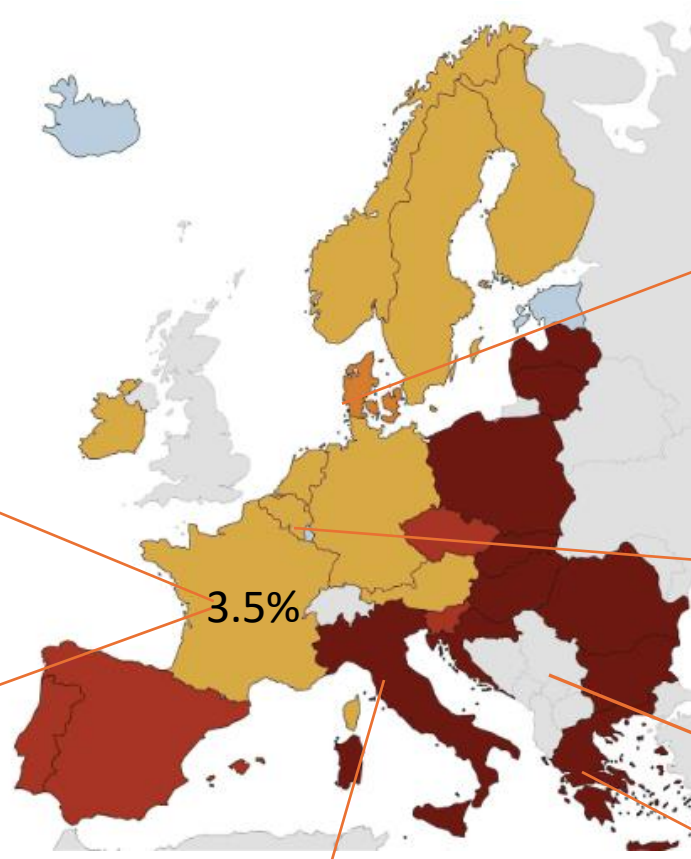
Serbie 2016-2018 ($n=104$)



Italie 2014-2018 ($n=37$)



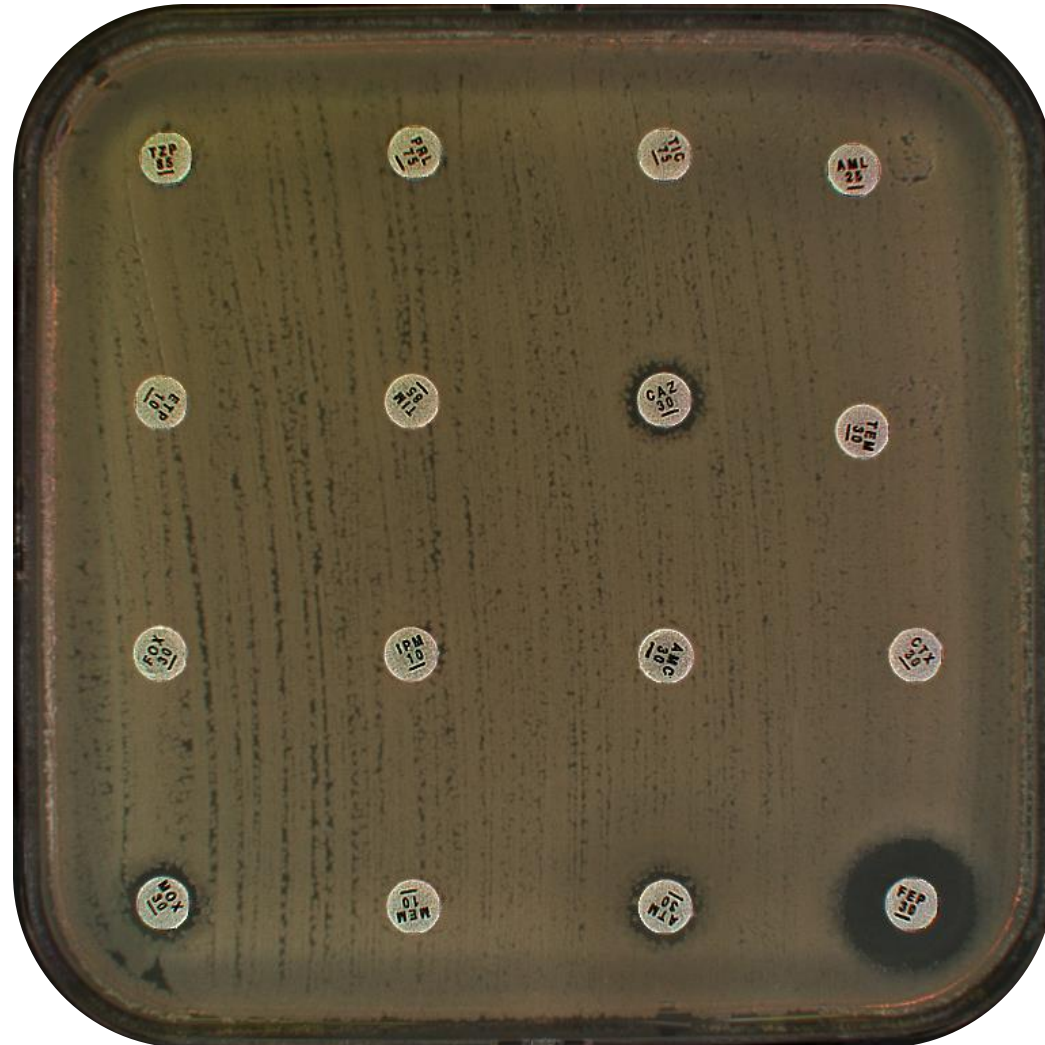
Grèce 2020-2021 ($n=271$)



Carbapenemase-producing *Acinetobacter* spp.

OXA-23

Carbapenem hydrolyzing β -lactamases (**CHDLs**) and mostly **OXA-23** are predominant in *Acinetobacter* spp.

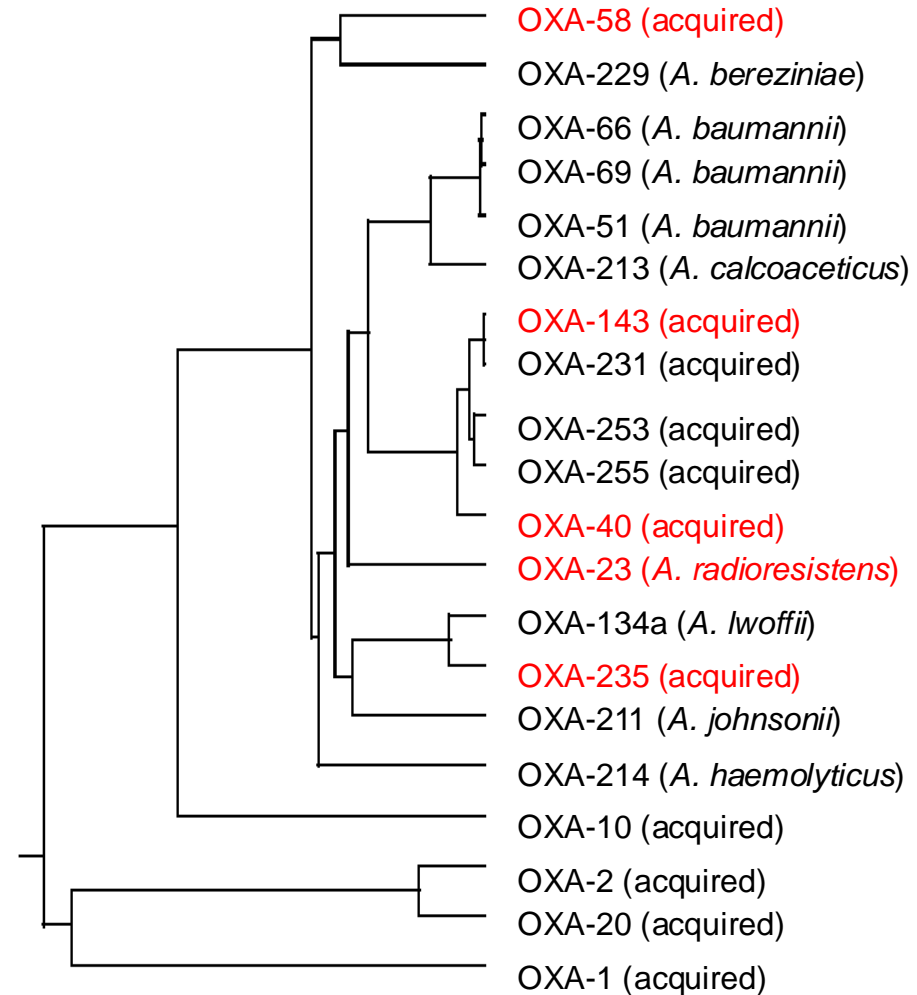


Acquired class D carbapenemases

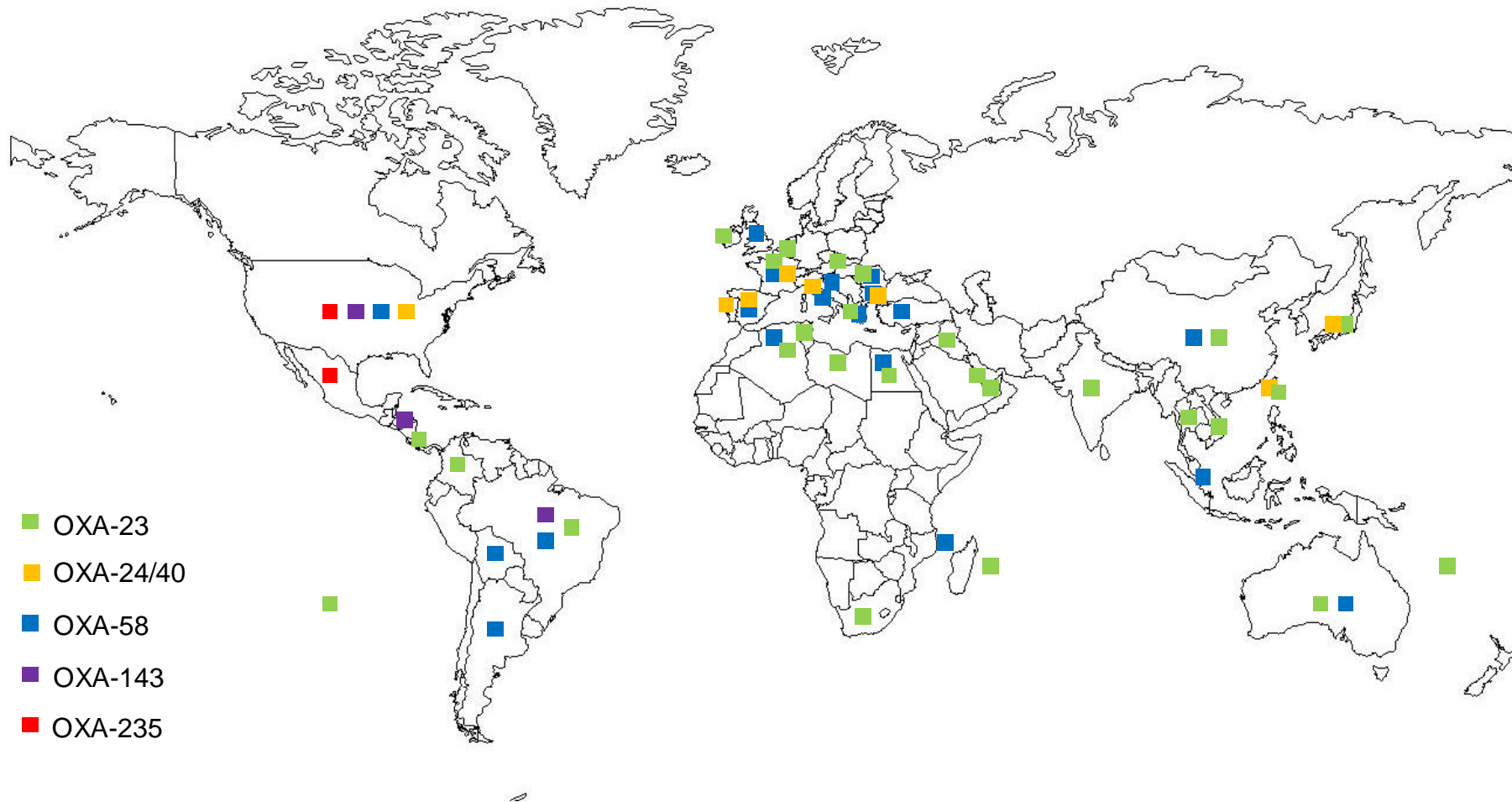
- 5 main groups of acquired CHDL:

OXA-23, OXA-40, OXA-58,
OXA-143 and OXA-235

- Hydrolysis of penicillins and carbapenems
- Not inhibited by clavulanate

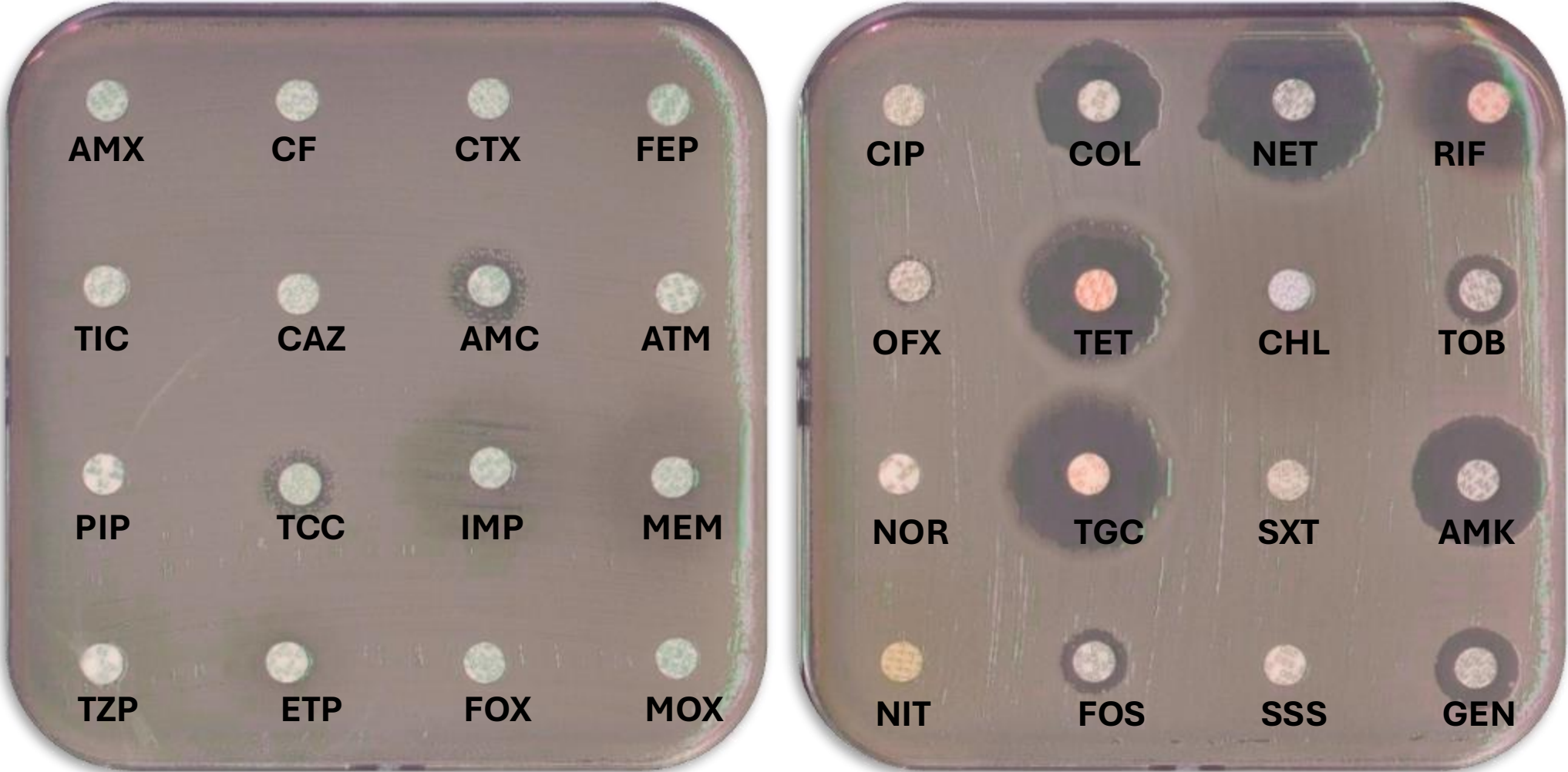


Global distribution of OXA-type carbapenemases in *Acinetobacter* spp.



MBL-producing *Acinetobacter* spp.

NDM-1



Global distribution of MBL-type carbapenemases in *Acinetobacter* spp.

