DIU stratégies thérapeutiques et préventives en pathologie infectieuse

Nouveaux anti-*Pseudomonas* et bacilles à Gram négatif résistants

Pr. Laurent DORTET

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

Mortalité et resistance aux antibiotiques

5 millions décès associés à la résistance
1,27 millions décès attribuable à la résistance

- Inf. Respiratoires
- Bactériémies
- Inf. intra-abdominales

90% des décès attribuables à la résistance

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

*Antimicrobial Resistance Collaborators**

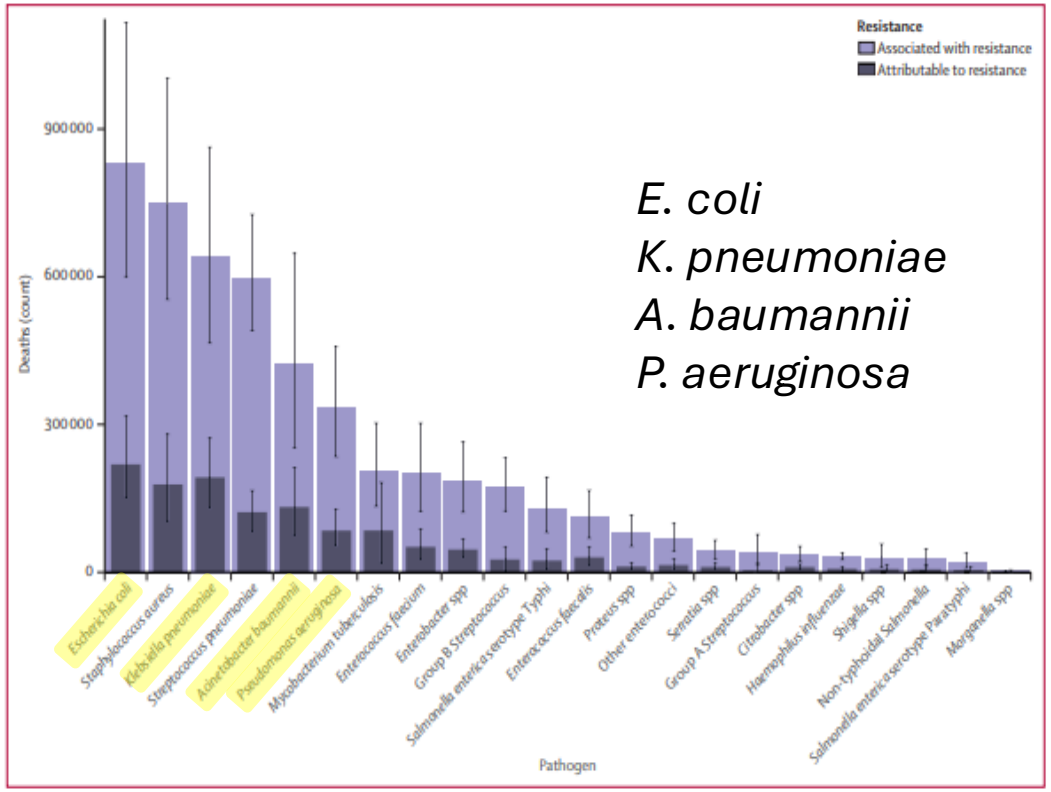


Figure 4: Global deaths (counts) attributable to and associated with bacterial antimicrobial resistance by pathogen, 2019
Estimates were aggregated across drugs, accounting for the co-occurrence of resistance to multiple drugs. Error bars show 95% uncertainty intervals.

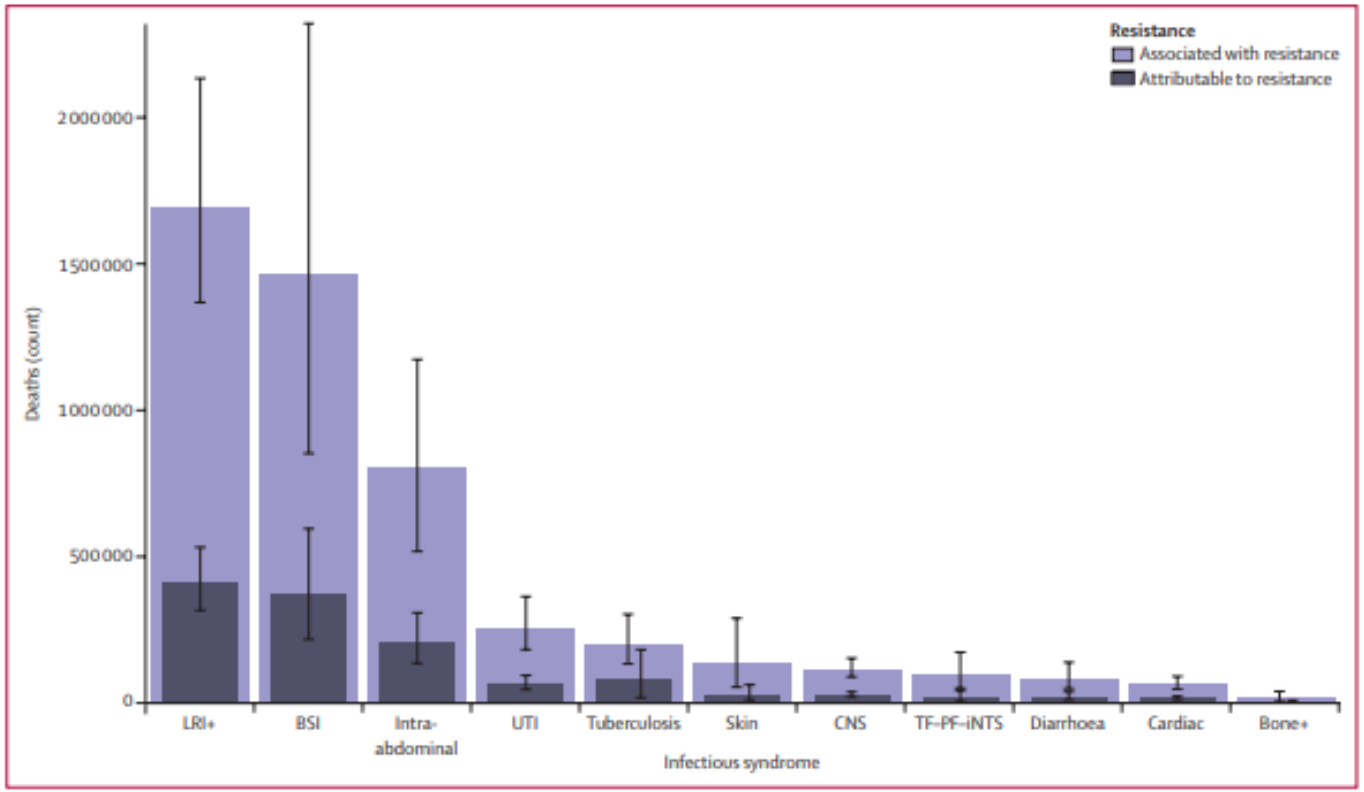
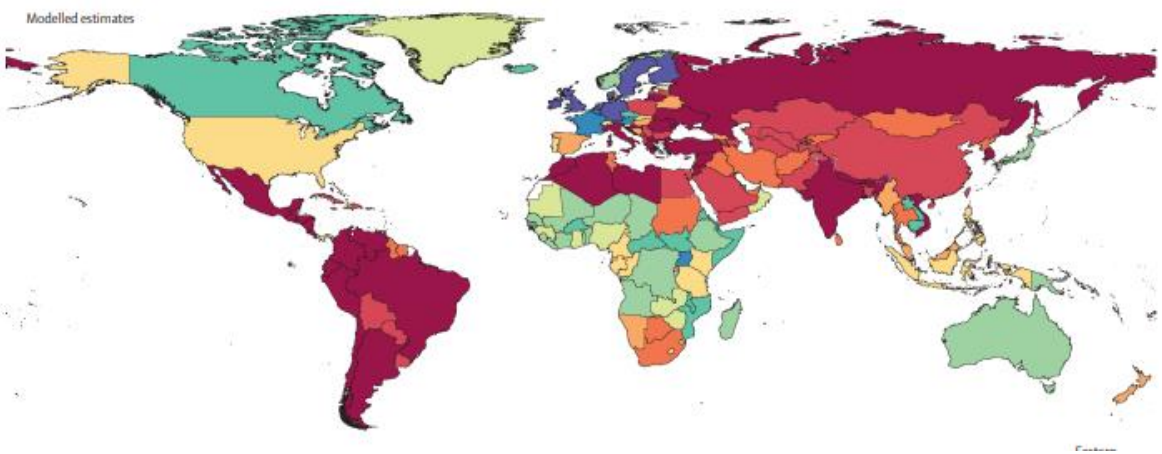
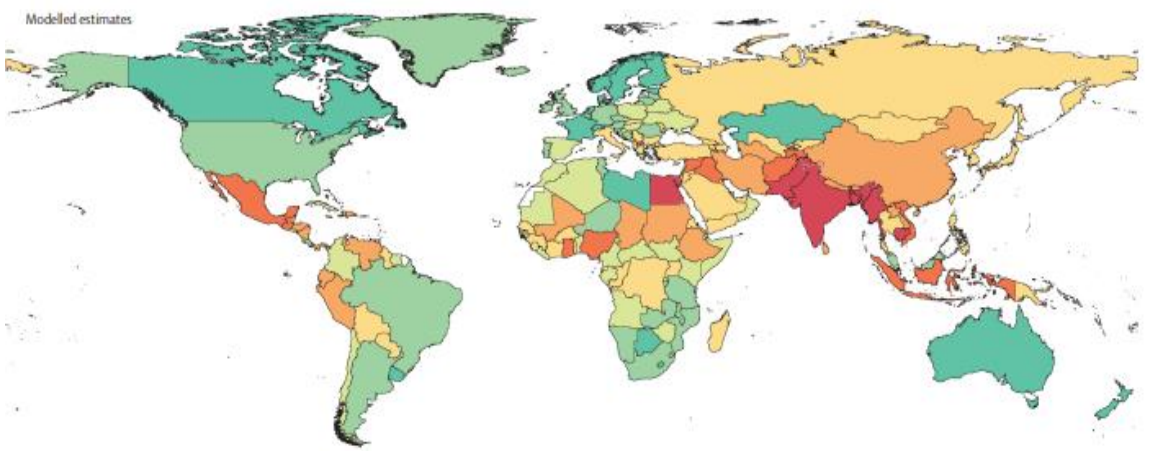


Figure 3: Global deaths (counts) attributable to and associated with bacterial antimicrobial resistance by infectious syndrome, 2019

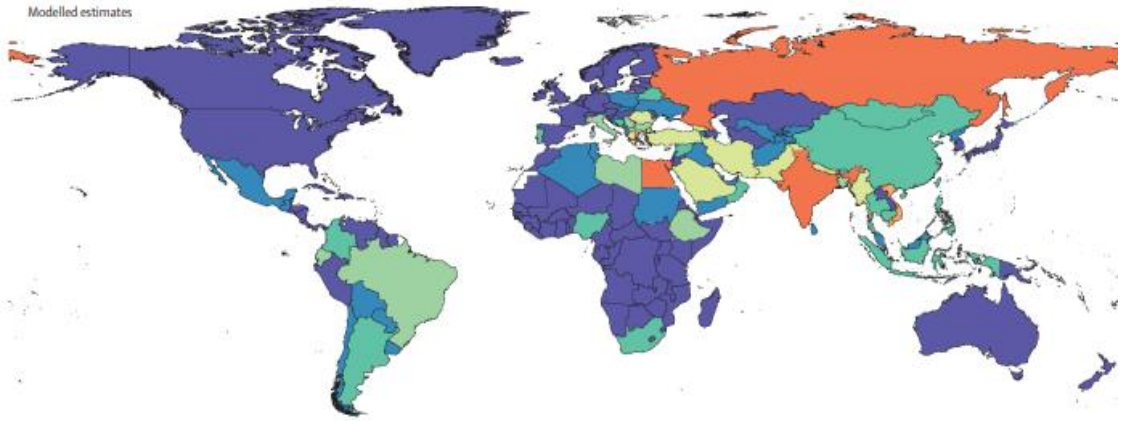
Mortalité et resistance aux antibiotiques : Inégalités territoriales



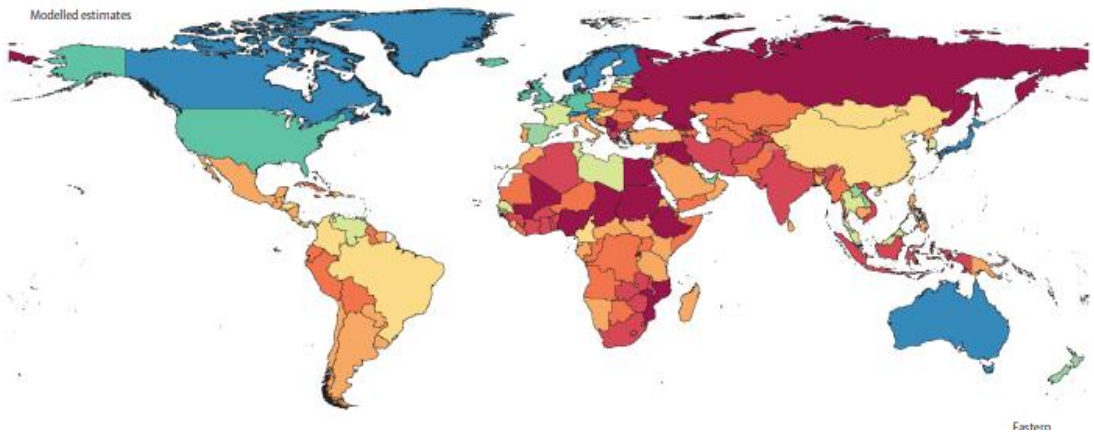
A. baumannii R carbapenèmes



E. coli R Fluoroquinolones



K. pneumoniae R carbapenèmes



K. pneumoniae R C3G

MDR, XDR ou DTR

- Classification MDR et XDR = définition microbiologique peu utile pour le clinicien

- **DTR (difficult-to-treat resistance) = Résistance à tous les antibiotiques de 1ère ligne, spécifiquement les β-lactamines et les fluoroquinolones**

Huh K. et al. Clin Infect Dis. 2020

MDR, XDR ou DTR

- Etude rétrospective sur 14 hôpitaux coréens.
  - **Bactériémies à BGN** : *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *A. baumannii*
  - Objectif : déterminer l'impact de la DTR sur la mortalité à 30 j
  - **4 catégories** :
    - DTR+
    - CR+/DTR- : résistance aux carbapénèmes, non DTR
    - ESCR+/DTR- : résistance aux céphalosporines (CP) et carbapénèmes, non DTR
    - FQR+/ESCR-CR- : résistance aux fluoroquinolones, sans résistance aux CP et carbapénèmes

Huh K. et al. Clin Infect Dis. 2020

MDR, XDR ou DTR

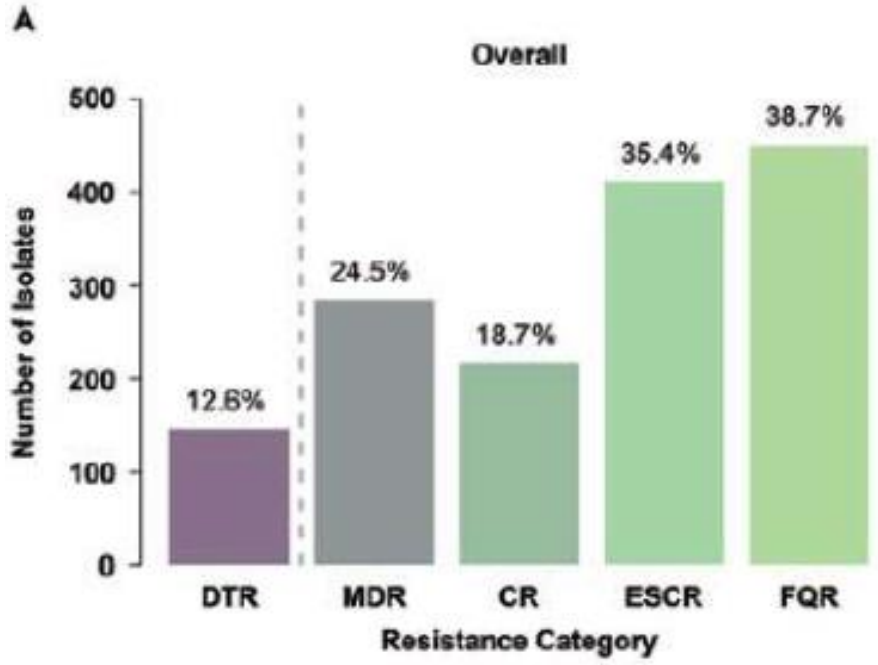
Clinical Infectious Diseases
MAJOR ARTICLE

Impact of Difficult-to-Treat Resistance in Gram-negative Bacteremia on Mortality: Retrospective Analysis of Nationwide Surveillance Data

Kyungmin Huh,[1,2] Doo Ryeon Chung,[1,2] Young Eun Ha,[3] Jae-Hoon Ko,[1] Si-Ho Kim,[1] Min-Ji Kim,[4] Hee Jae Huh,[5] Nam Yong Lee,[5] Sun Young Cho,[1] Cheol-In Kang,[1] Kyong Ran Peck,[1] and Jae-Hoon Song[1,2]; for the Korean Antimicrobial Resistance Surveillance Network (KARS-Net) Investigators*

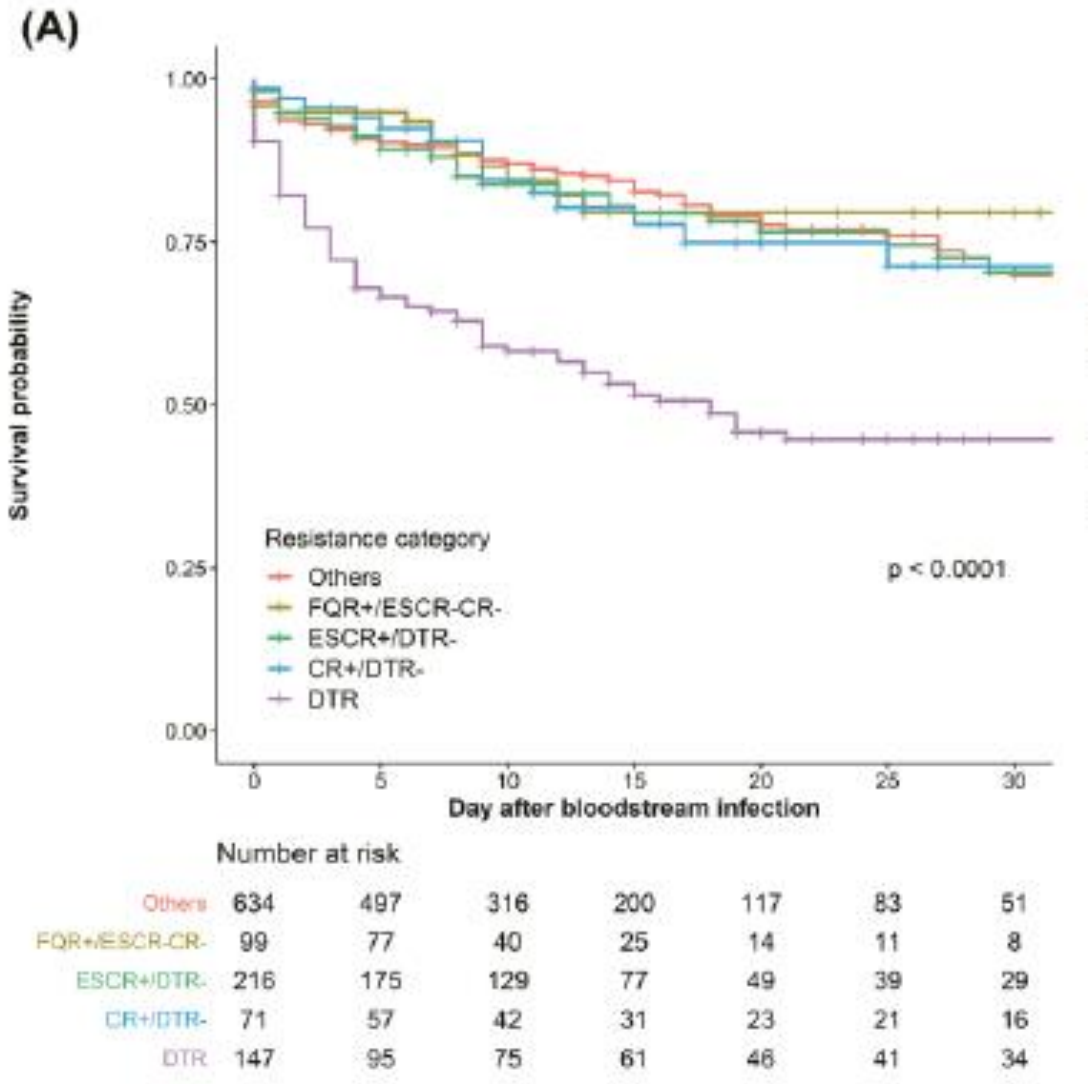
Difficult-to-Treat Resistance (DTR)

- *Acinetobacter baumannii*: 117 (79,6%)
- *Pseudomonas aeruginosa*: 26 (17,7%)
- *Klebsiella pneumoniae*: 4 (1,4%)
- *E. coli*: 0 (0%)



Huh K. et al. Clin Infect Dis. 2020

MDR, XDR ou DTR



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Huh K. et al. Clin Infect Dis. 2020

Dans la vraie vie les souches DTR sont …

- Entérobactéries résistantes aux carbapénèmes
  - Carbapénèmases +++
  - BLSE et/ou AmpC + imperméabilité
- *Pseudomonas aeruginosa* resistants aux carbapénèmes + C3G + C4G
  - AmpC + imperméabilité
  - Carbapénèmases
- *Acinetobacter baumannii* résistants aux carbapénèmes
  - Carbapénèmases

Les nouvelles molecules pour le traitement de ces souches DTR

❑ Nouvelle β-lactamine + ancien inhibiteur

- Ceftolozane - Tazobactam

❑ Anciennes β-lactamines + nouvel inhibiteur

- Ceftazidime – Avibactam
- Imipénème - Relebactam
- Méropénème – Vaborbactam
- Aztréonam - avibactam
- Céfépime – Enmetazobactam

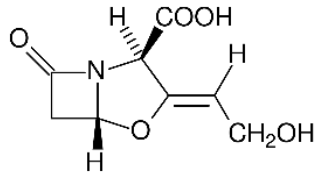
❑ Nouvelle β-lactamine

- Céfidérocol

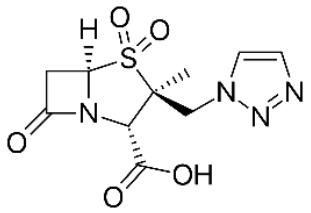
Les inhibiteurs de β-lactamases

β-lactam derivatives

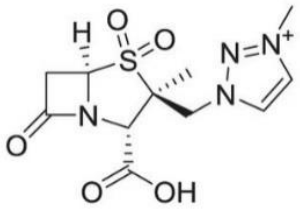
Clavulanic acid



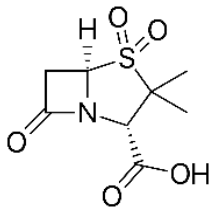
Tazobactam



Enmetazobactam

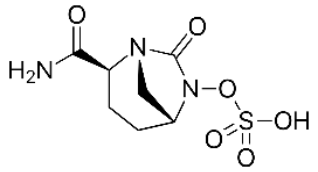


Sulbactam

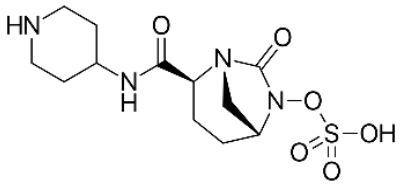


Diazabicyclooctane (DBO)

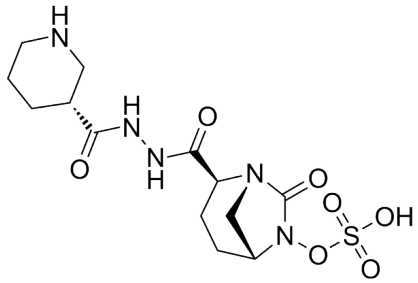
Avibactam



Relebactam

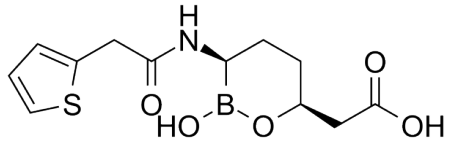


Zidebactam

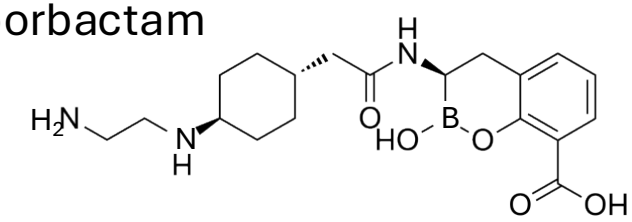


Boronic acid derivatives

Vaborbactam



Taniborbactam



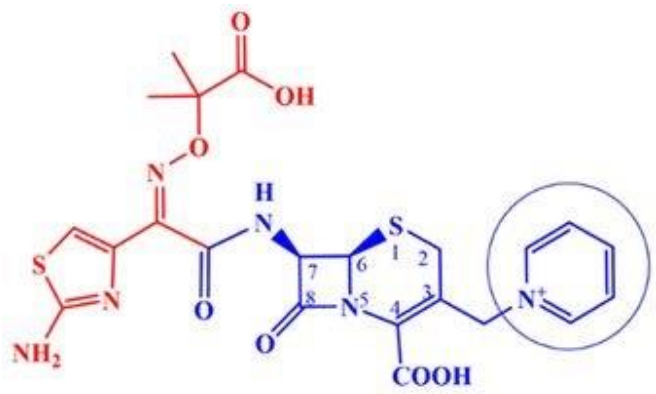
Principe, L. et al. Pharmaceuticals **2022**, 15, 463.

Spectres d'inhibition

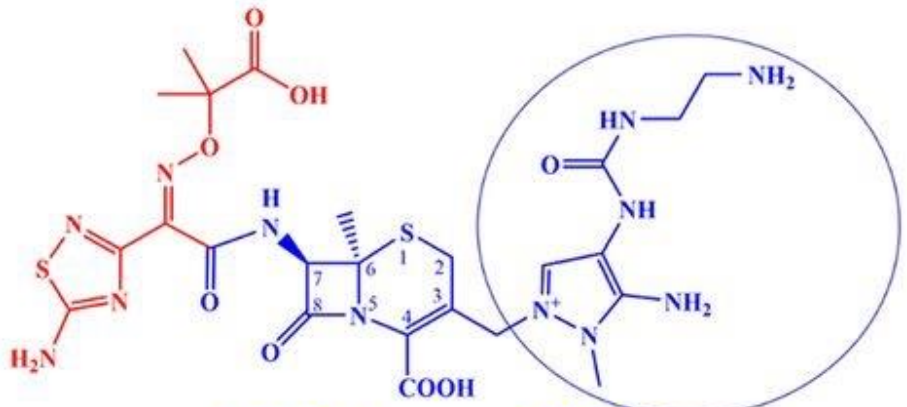
Inhibiteur	ESBL	AmpC	KPC	MBL	OXA-48-like	Intrinsic ATB activity
Clavulanic acid	++	-	+	-	-	-
Sulbactam	++	-	+	-	-	PBP2
Tazobactam	++	-	+	-	-	-
Enmetazobactam	**+++**	**++**	**++**	-	-	-
Avibactam	**+++**	**++**	**+++**	-	**+**	-
Relebactam	**+++**	**++**	**+++**	-	**+/-**	-
Vaborbactam	**+++**	**++**	**+++**	-	**+/-**	-
Zidebactam	+++	++	+++	-	?	PBP2
Taniborbactam	+++	++	+++	++ (except IMP)	?	?

Ceftolozane-tazobactam

Ceftolozane-tazobactam : Structure chimique

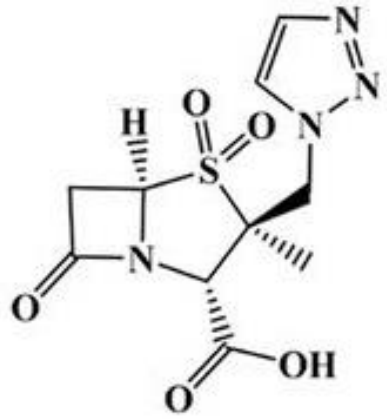


Ceftazidime (CAZ)

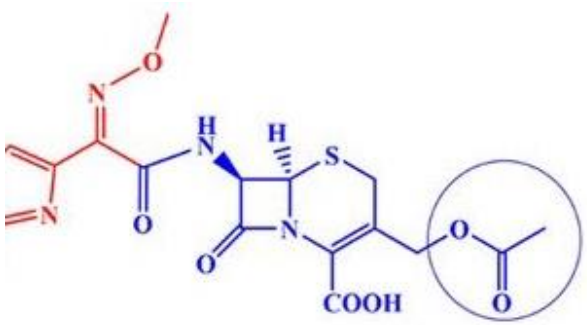


Ceftolozane (TOL)

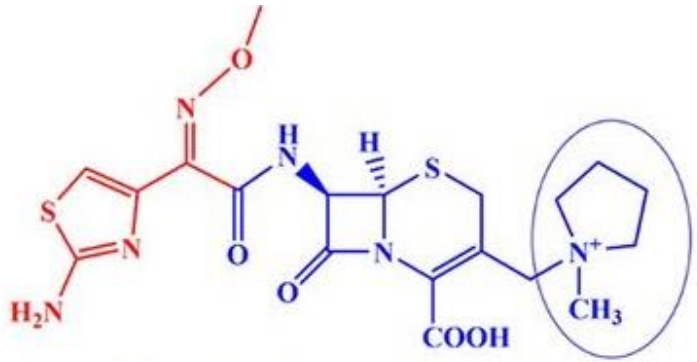
+



Tazobactam



Cefotaxime (TAX)

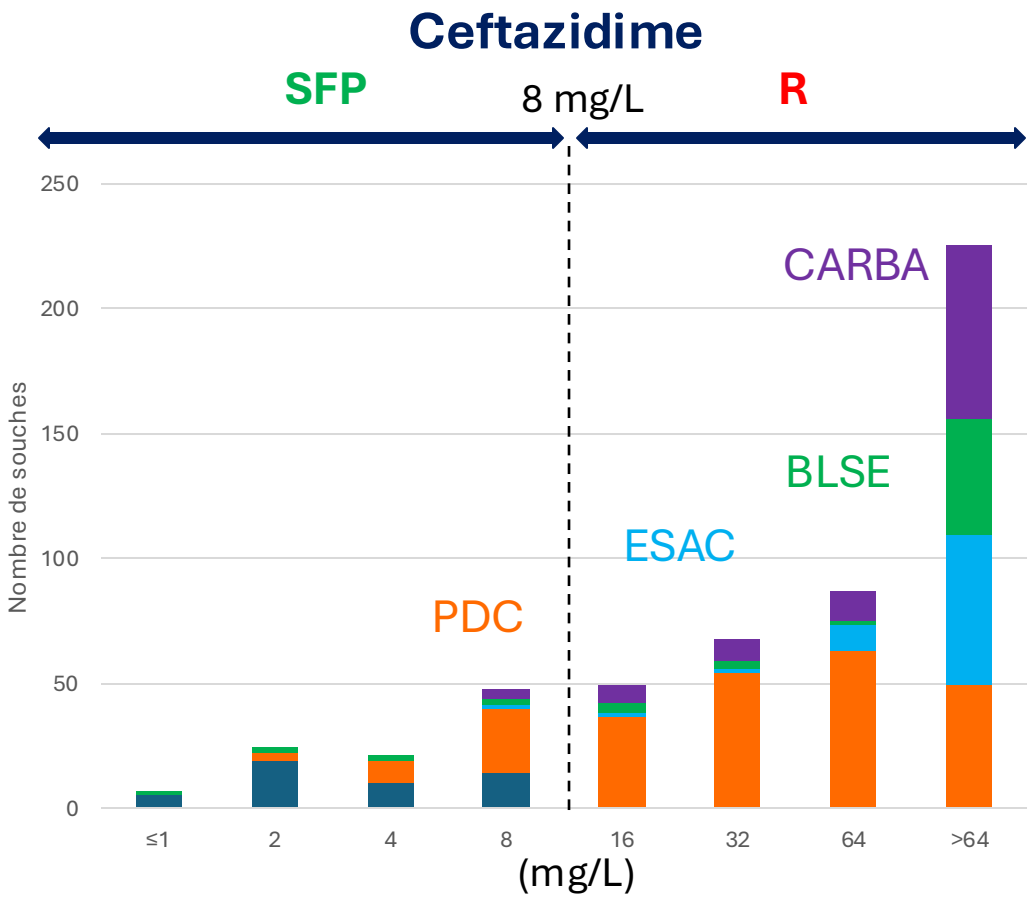


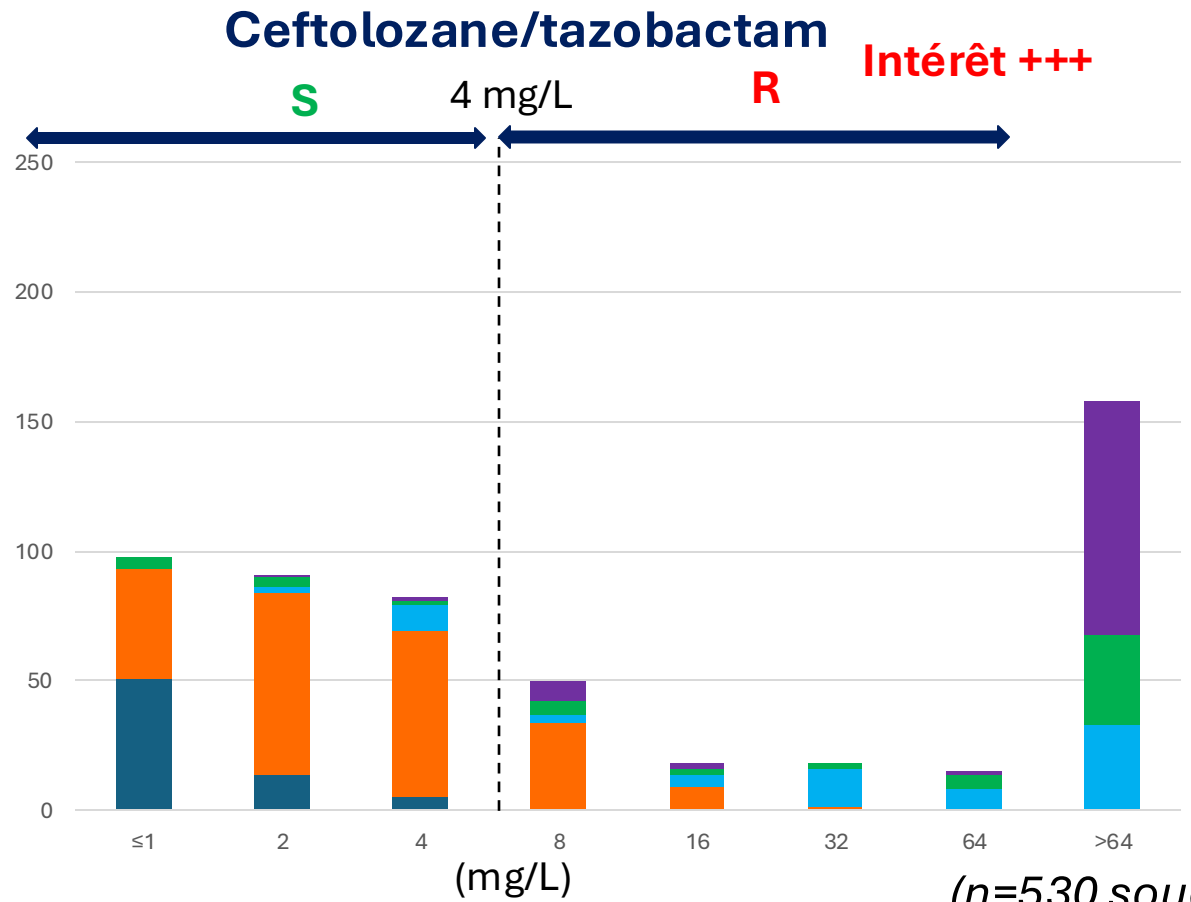
Cefepime (FEP)

Ceftolozane-tazobactam : Spectre d'activité

P. aeruginosa : **Stable en face des principaux mécanismes de résistance**

(Peu / Pas d'intérêt du tazobactam)





(n=530 souches)

Ceftolozane-tazobactam : Spectre d'activité

P. aeruginosa : **Stable en face des principaux mécanismes de résistance**

- OprD, déficience ou mutation
- Pompes d'efflux
- **AmpC hyperproduite**

} **Peu / Pas d'intérêt du tazobactam**

Intérêt +++

Enterobactéries:

- Actif sur entérobactéries BLSE (*E. coli* +++, +/- pour les autres espèces)
- Peu actif sur les AmpC des Enterobacterales (et aucun rôle du tazobactam)
- Inactive contre les carbapénèmases KPC, OXA-48 et MBLs

Acinetobacter baumannii

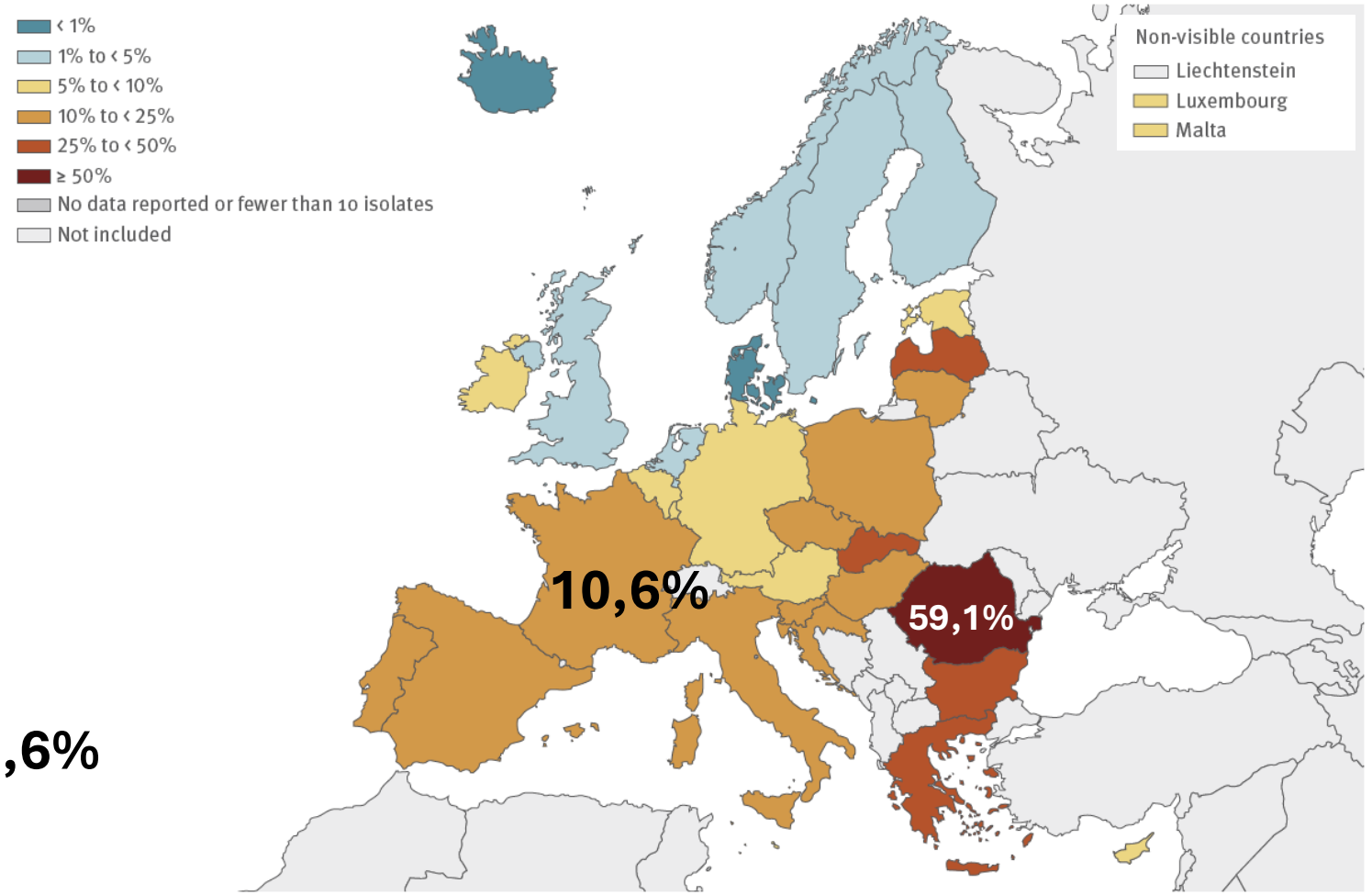
- Inactive contre les principales carbapénèmases NDM (et autre MBLs) ou OXA (OXA-23, OXA-40, OXA-58)

P. aeruginosa MDR en Europe

Taux de résistance en France en 2017

- Pipéraciline-tazobactam : 19,2 %
- Fluoroquinolones : 15,1%
- Ceftazidime : 12,2%
- Aminoglycosides : 10,9%
- Carbapénèmes : 13,9%
- **MDR** = R à 3 *anti-P. aeruginosa* : **10,6%**

European Center for Diseases Prevention



Ceftolozane – tazobactam fait partie de la liste standard des antibiotiques à tester pour *P. aeruginosa*

Comité de l'Antibiogramme de la Société Française de Microbiologie

Liste standard	Liste complémentaire
Ticarcilline	Nétilmicine
Ticarcilline-acide clavulanique	Lévofloxacine
Pipéracilline	Colistine
Pipéracilline-tazobactam	Fosfomycine
Ceftazidime	Ceftazidime-avibactam
Céfépime	Méropénème-vaborbactam
Ceftolozane-tazobactam	
Imipénème	
Méropénème	
Tobramycine	
Amikacine	
Ciprofloxacine	
Aztréonam	
Gentamicine	

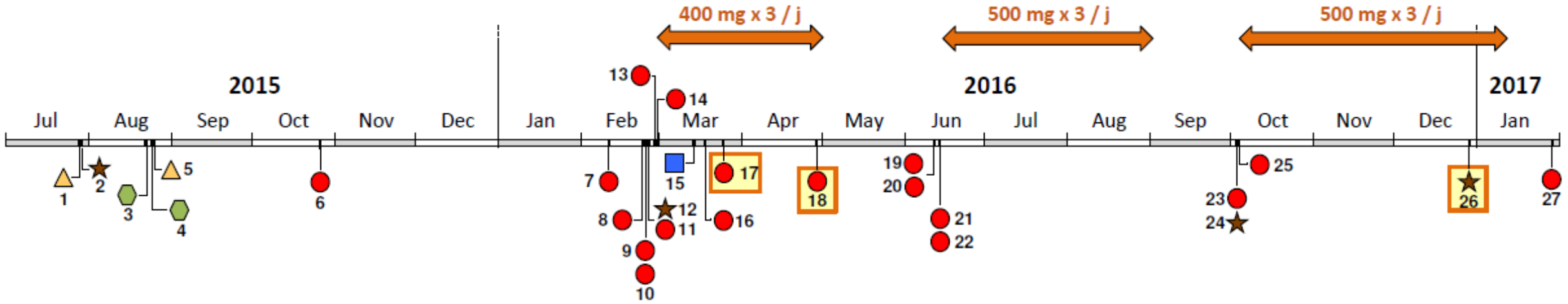
Ceftolozane-tazobactam : Résistance acquise sous traitement

- Enfant de 3 ans
- Atrésie des voies biliaires
- Deux transplantations hépatiques successives
- Pneumonie acquise sou ventilation à *P. aeruginosa* XDR sensible à:
  - **Ceftolozane-tazobactam (C/T): ++++**
  - Ceftazidime-avibactam (CAZ-AVI) : +/-
  - Colistine (COL): ++ (CMI = 1 mg/L)

- Traitement par colistine IV + aérosol

Colonisation / infections à long termes

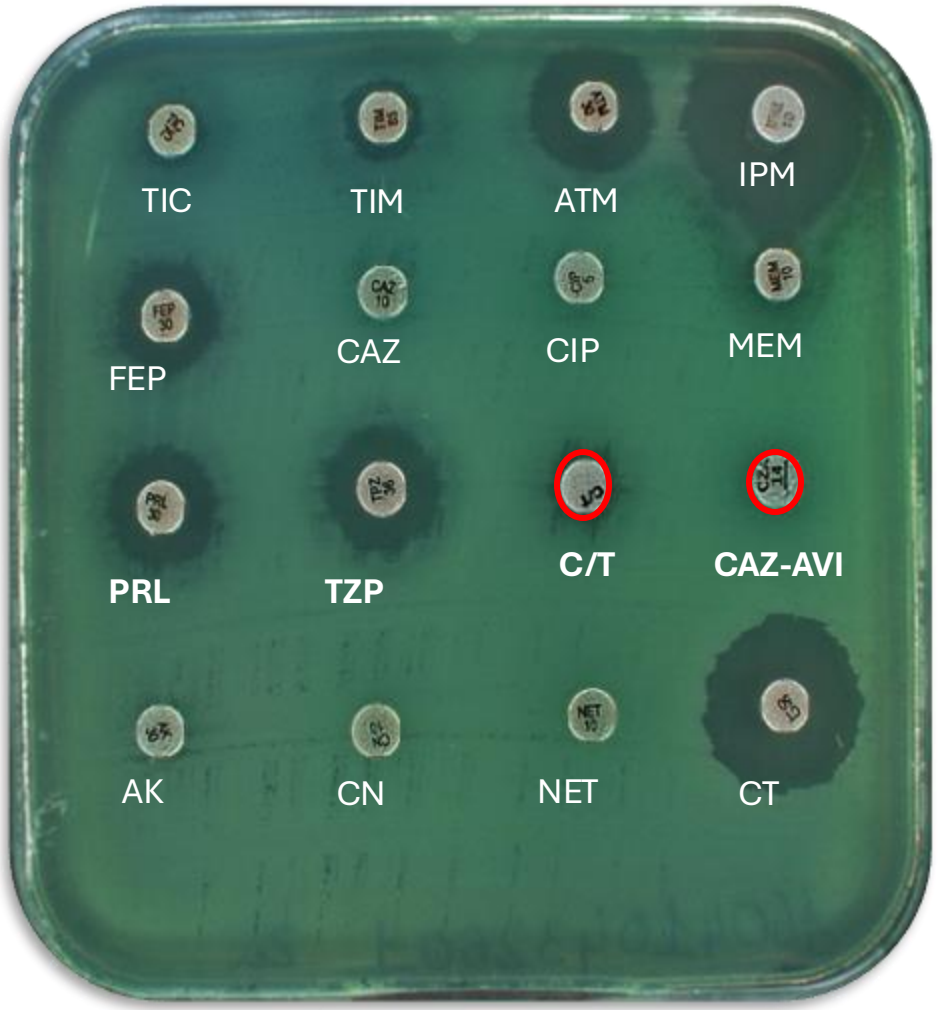
- 53 souches clinique de *P. aeruginosa* sur 2,5 années
- **Acquisition d'une résistance au C/T sous traitement** (3 souches



Hémoculture Bile Plaie LBA Dépistage / selles

Ceftolozane-tazobactam : Résistance acquise sous traitement

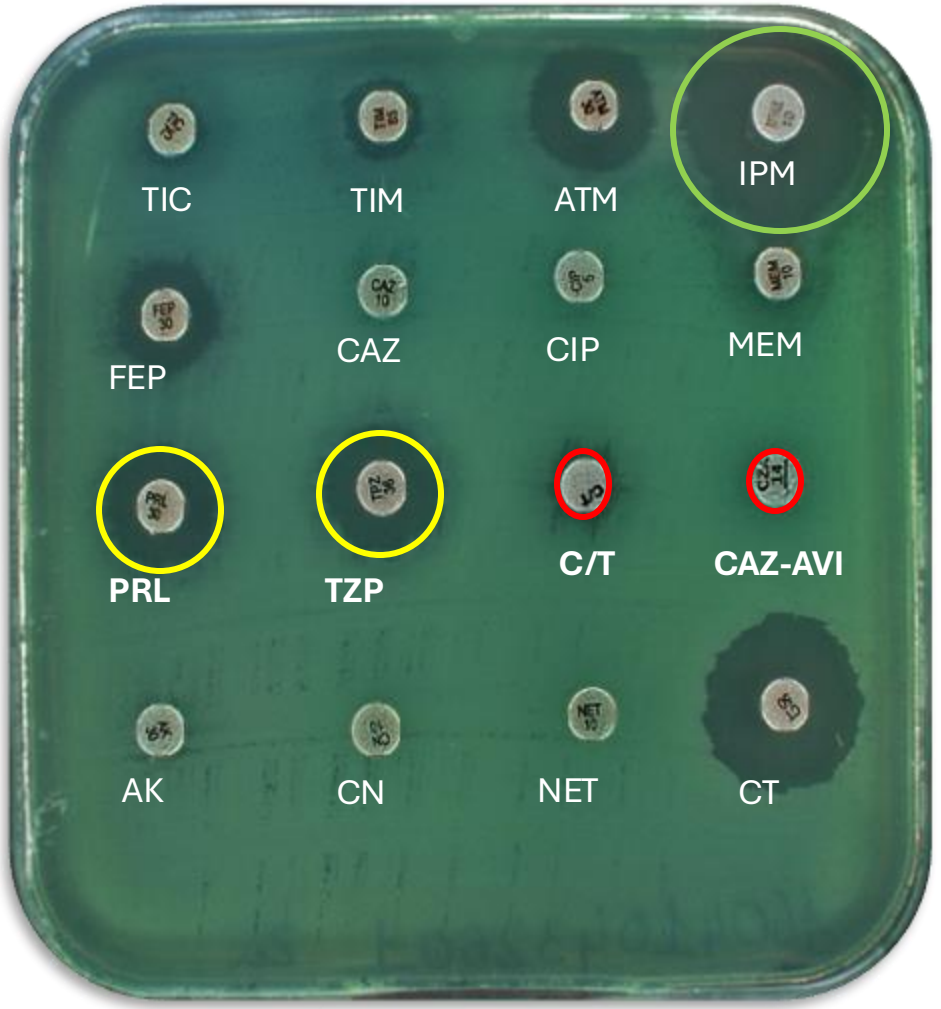
Resistance C/T et CAZ-AVI



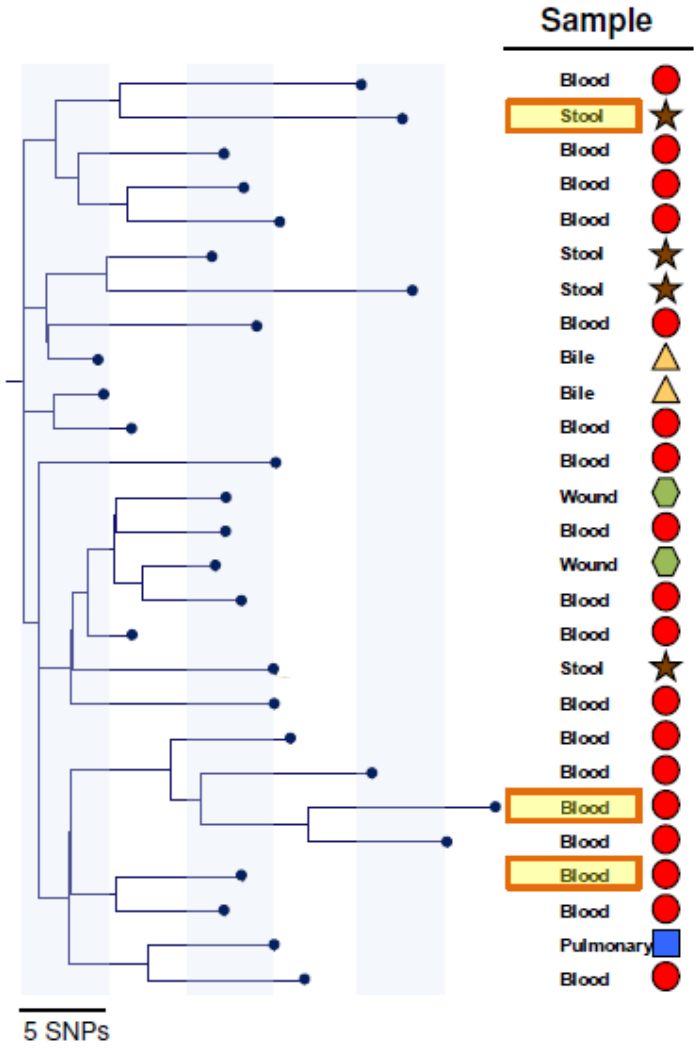
Ceftolozane-tazobactam : Résistance acquise sous traitement

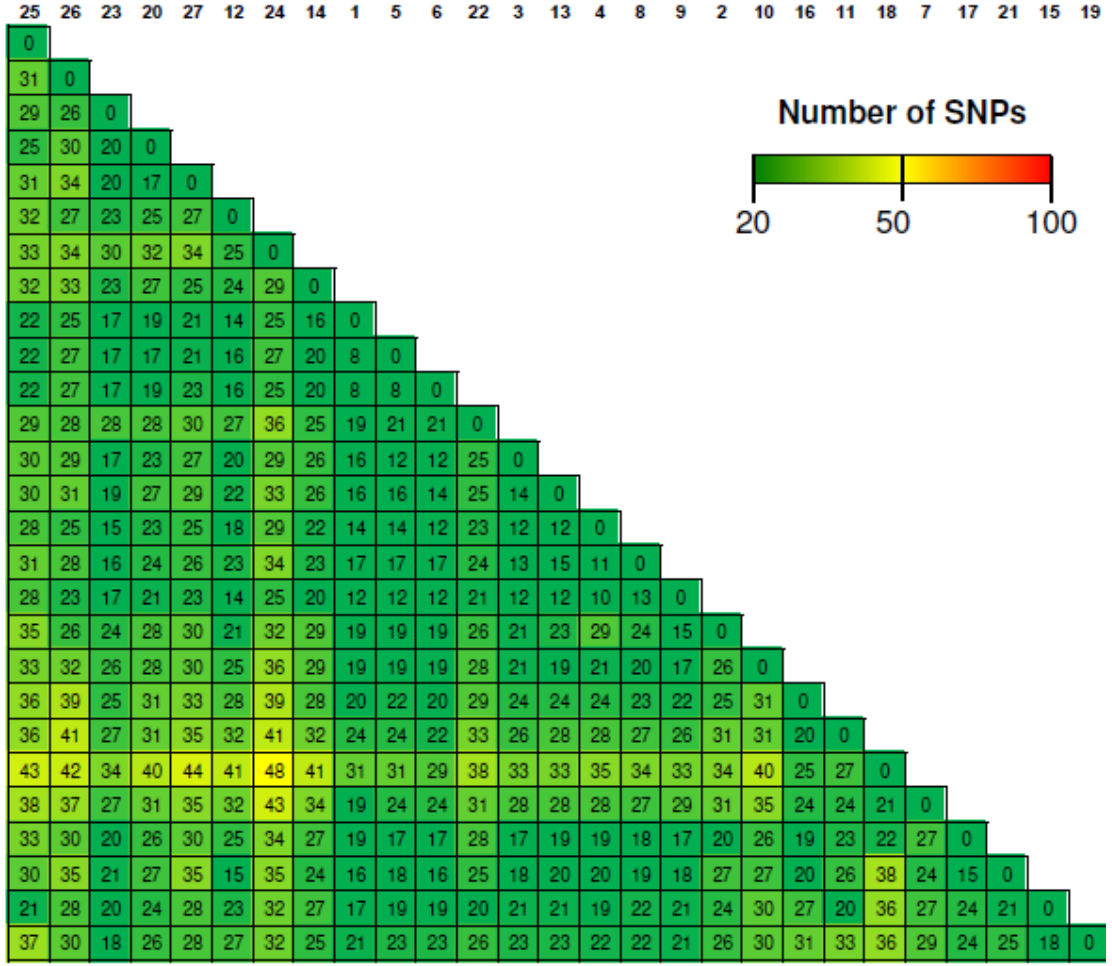
Resistance C/T et CAZ-AVI

Restauration « partielle » sensibilité : Piperacilline ± tazobactam ET Carbapénèmes

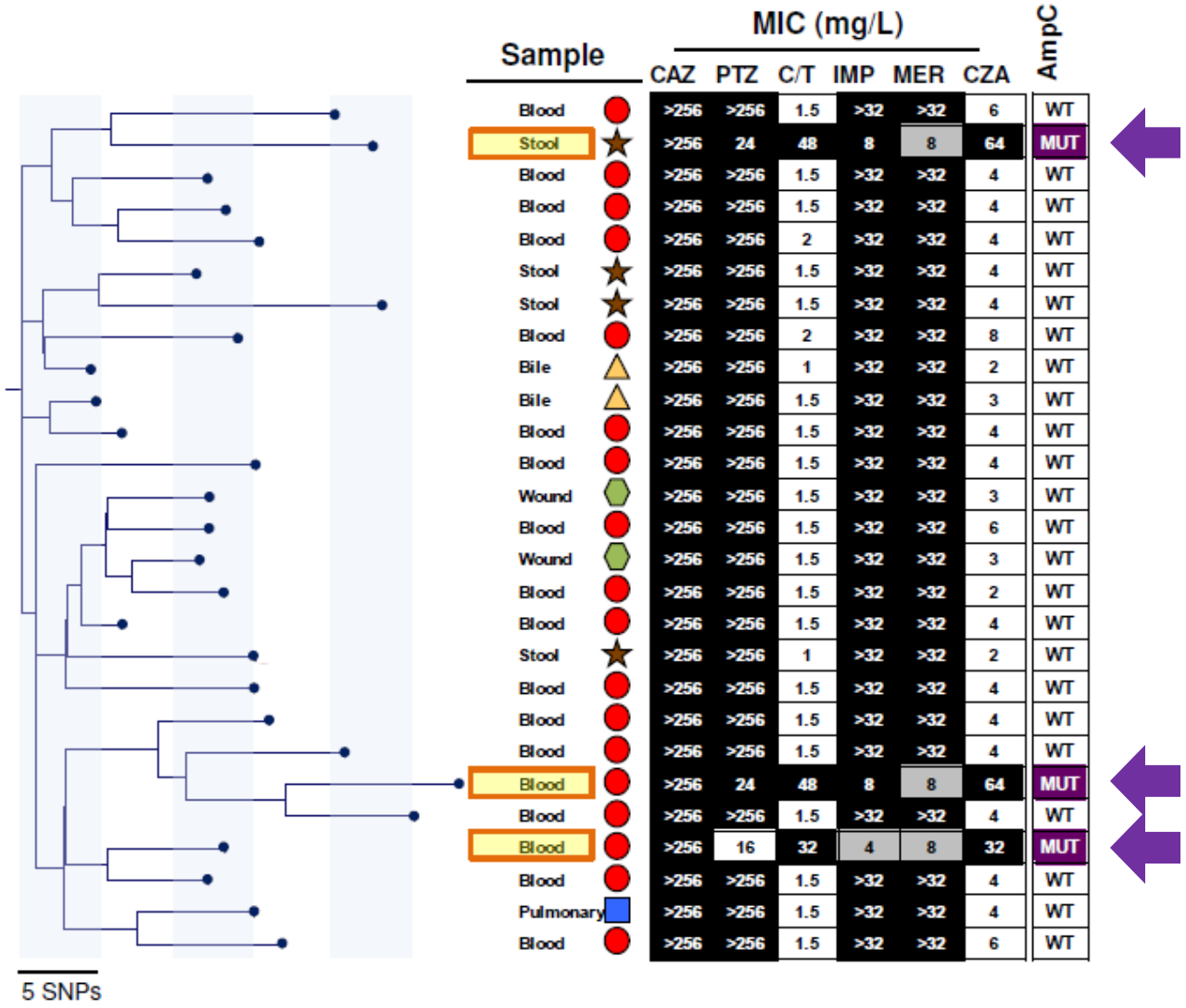


Un seul et unique clone (< 50 SNPs)





Une unique mutation de l'AmpC (G183D)



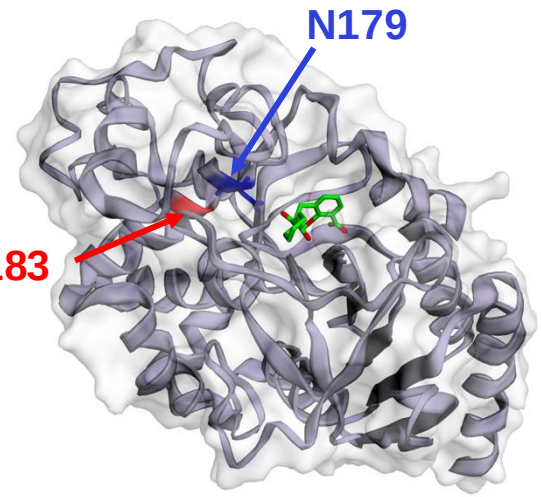
Sample	MIC (mg/L) CAZ	PTZ	C/T	IMP	MER	CZA	AmpC
Blood	>256	>256	1.5	>32	>32	6	WT
Stool	>256	24	48	8	8	64	MUT
Blood	>256	>256	1.5	>32	>32	4	WT
Blood	>256	>256	1.5	>32	>32	4	WT
Blood	>256	>256	2	>32	>32	4	WT
Stool	>256	>256	1.5	>32	>32	4	WT
Stool	>256	>256	1.5	>32	>32	4	WT
Blood	>256	>256	2	>32	>32	8	WT
Bile	>256	>256	1	>32	>32	2	WT
Bile	>256	>256	1.5	>32	>32	3	WT
Blood	>256	>256	1.5	>32	>32	4	WT
Blood	>256	>256	1.5	>32	>32	4	WT
Wound	>256	>256	1.5	>32	>32	3	WT
Blood	>256	>256	1.5	>32	>32	6	WT
Wound	>256	>256	1.5	>32	>32	3	WT
Blood	>256	>256	1.5	>32	>32	2	WT
Blood	>256	>256	1.5	>32	>32	4	WT
Stool	>256	>256	1	>32	>32	2	WT
Blood	>256	>256	1.5	>32	>32	4	WT
Blood	>256	>256	1.5	>32	>32	4	WT
Blood	>256	>256	1.5	>32	>32	4	WT
Blood	>256	24	48	8	8	64	MUT
Blood	>256	>256	1.5	>32	>32	4	WT
Blood	>256	16	32	4	8	32	MUT
Blood	>256	>256	1.5	>32	>32	4	WT
Pulmonary	>256	>256	1.5	>32	>32	4	WT
Blood	>256	>256	1.5	>32	>32	6	WT

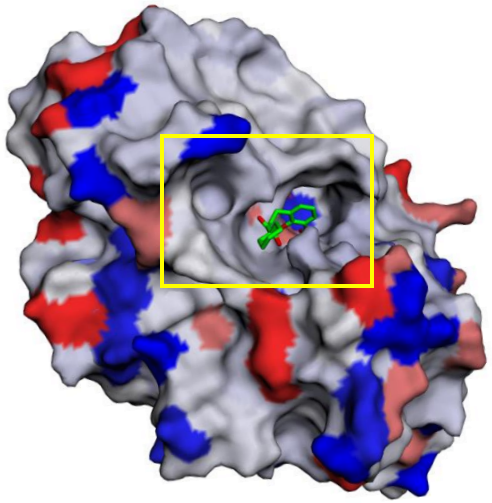
- Les 3 souches résistantes à C/T et CAZ-AVI possèdent la même **mutation dans l'AmpC naturelle : G183D**

- **Trois évènements indépendants**

Changement de la conformation du site actif de l'AmpC

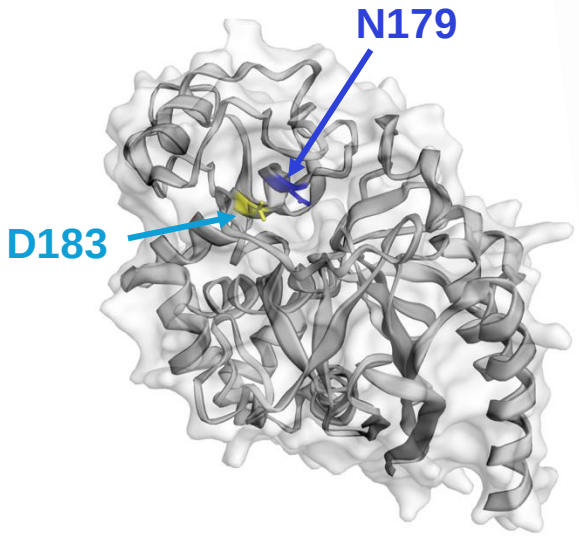
C/T Sensible

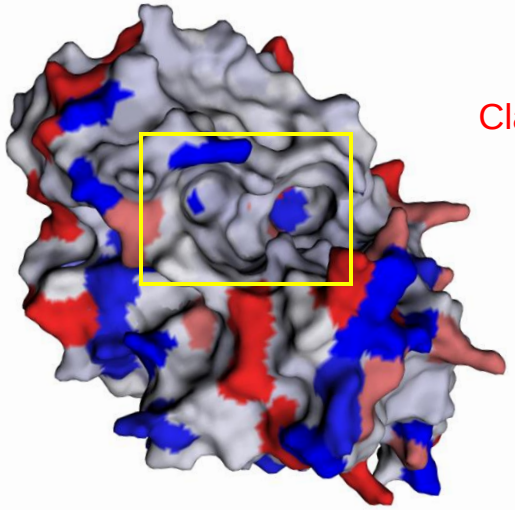


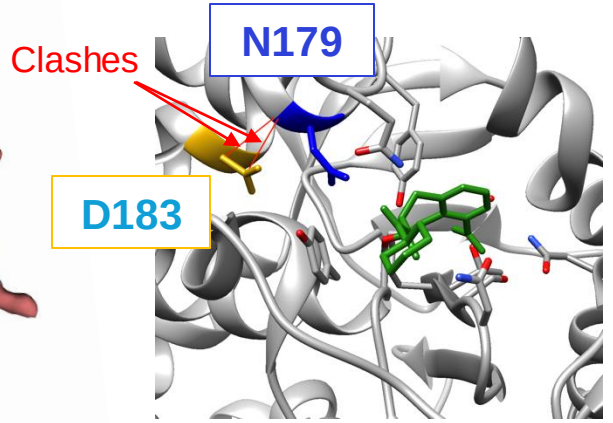


- « Ouverture » du site actif
- Addition d'une charge négative dans la poche catalytique
- Interférence entre D183 et N179 impliqué dans la stabilisation de C/T dans le site actif de l'enzyme

C/T Resistant



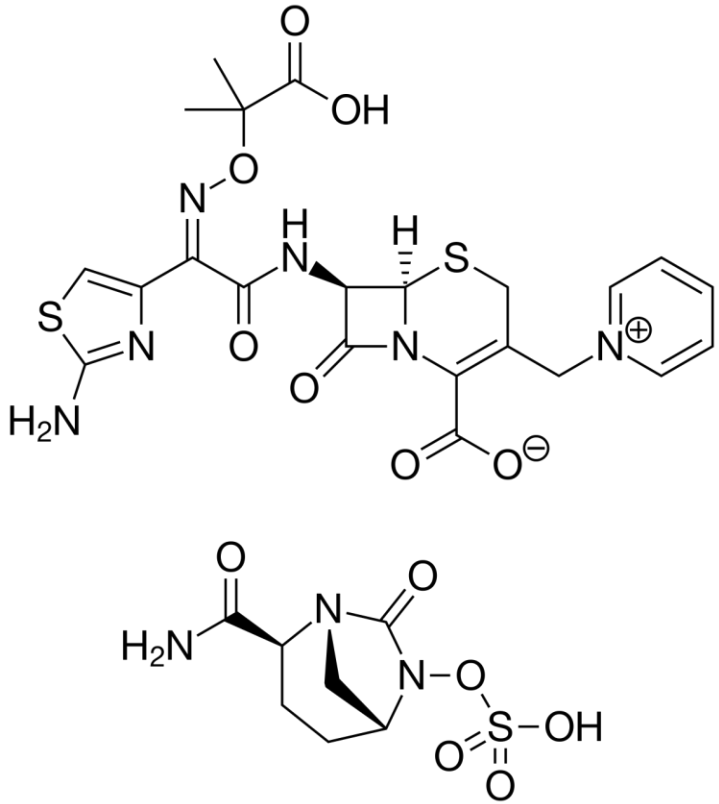




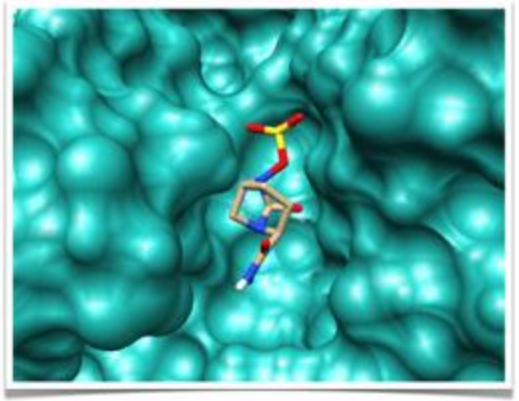
Ceftazidime-avibactam

Ceftazidime-avibactam

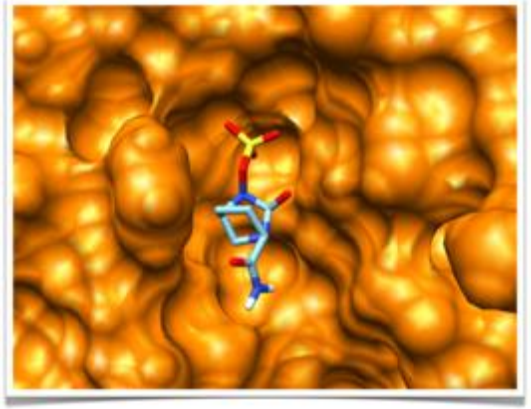
- Actif sur BLSE, AmpC et KPC, OXA-48, porines
- **Inactive sur les MLBs (VIM, IMP, NDM)**
- Elimination rénale
- Infections urinaires, infection intra-abdominales, infection respiratoires (y compris VAP)



Site actif KPC

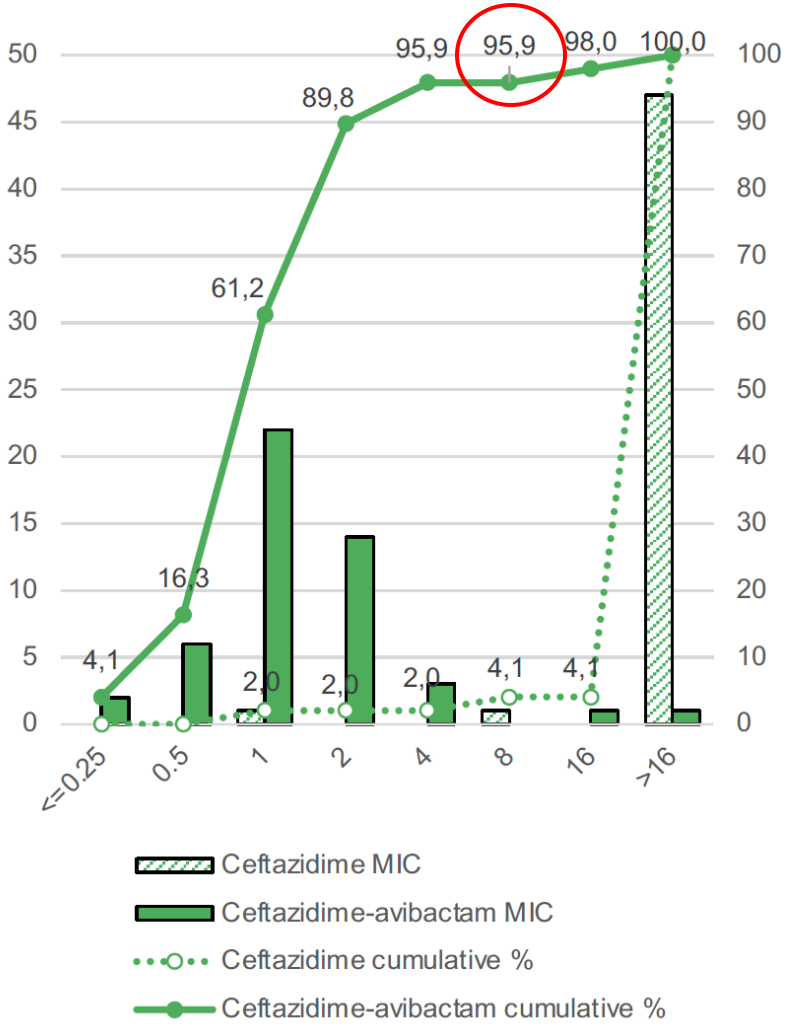


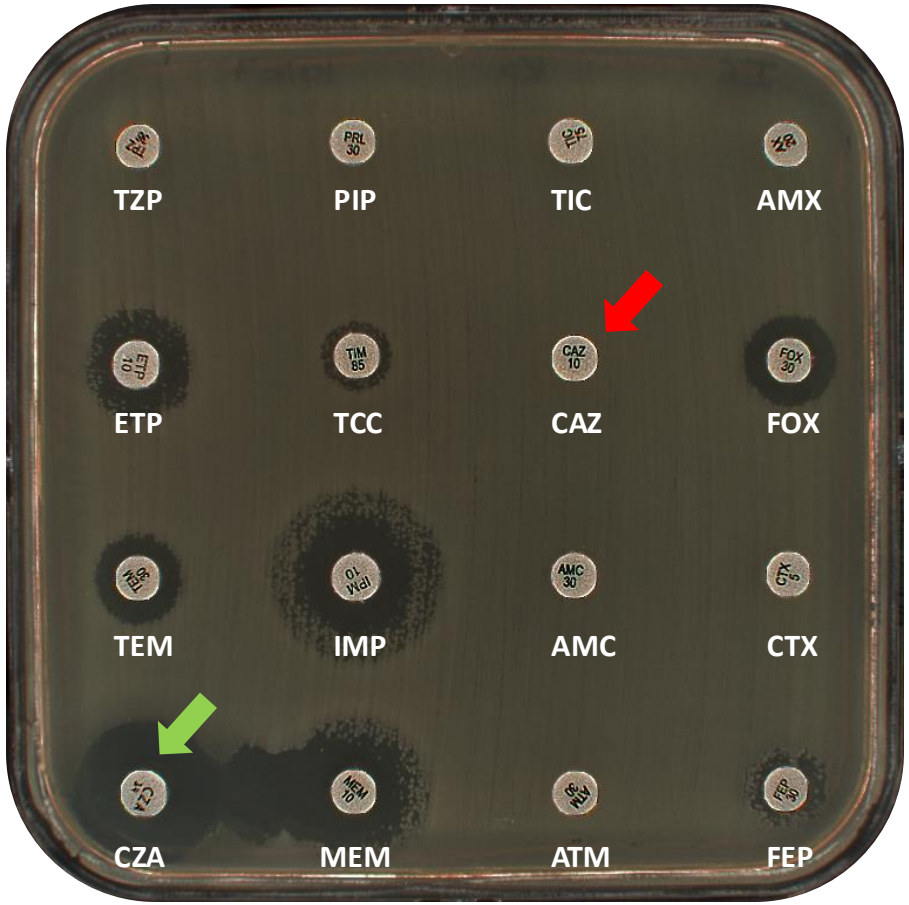
Site actif OXA-48



Lucasti et al. JAC 2013, Riccobene et al. AAC 2013

Ceftazidime-avibactam / KPC

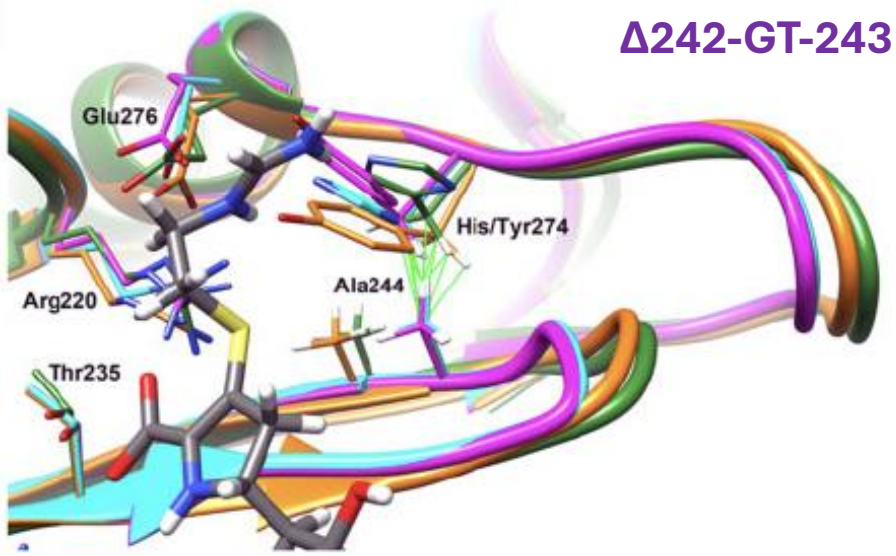




Ceftazidime-avibactam / KPC : Résistance acquise

- **Variants de KPC avec ↗ hydrolyse ceftazidime ou perte activité inhibitrice de l'avibactam MAIS restauration de la sensibilité vis-à-vis des carbapénèmes**

		MIC (mg/L)[a]										
AA changes	Variant	AMX	ATM	CRO	CAZ	CAZ/AVI	CFM	CTX	FEP	IPM	MEM	ETP
–	KPC-2	>256	32	16	4	0.38	4	8	2	8	3	1
H272Y	KPC-3	>256	>256	48	>256	0.75	12	>32	6	8	3	1
P104R	KPC-5	>256	>256	>256	>256	0.5	>256	8	2	1	0.25	0.19
V240G	KPC-6	>256	>256	48	32	0.75	16	>32	4	4	3	1
L168M	KPC-12	>256	12	6	4	0.38	3	4	1	0.75	0.25	0.125
D179Y	KPC-33	12	0.75	1	>256	8	6	1.5	1	0.25	0.032	0.008
H272Y, D179Y	KPC-31	6	0.75	2	>256	12	4	1.5	1	0.25	0.032	0.008



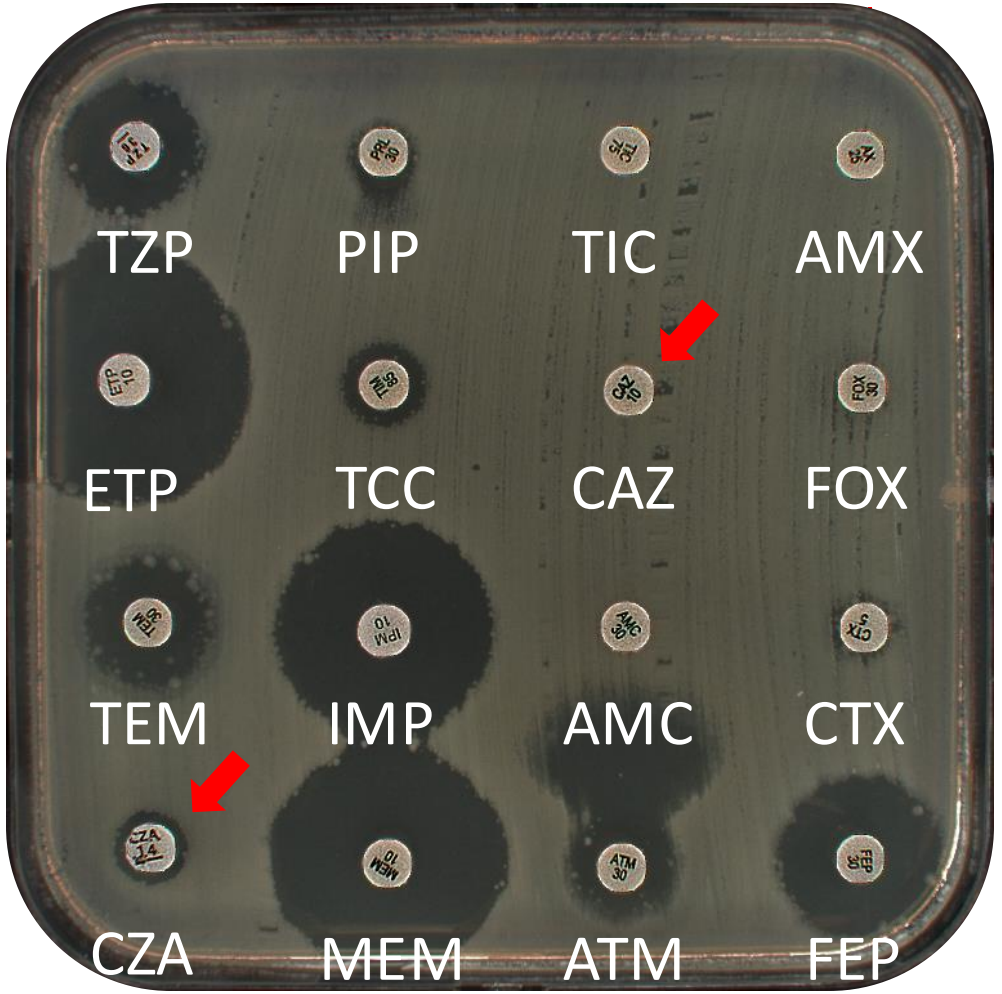
- Jusqu'à 10 % d'émergence de résistance par mutation **D179Y** dans la boucle ω de KPC (site de fixation de l'enzyme)
- Facteurs de risque : hémodialyse, posologies insuffisantes

Shields RK *et al.* Clin Infect Dis 2016
Shields RK *et al.* Antimicrob Ag Chemother 2017

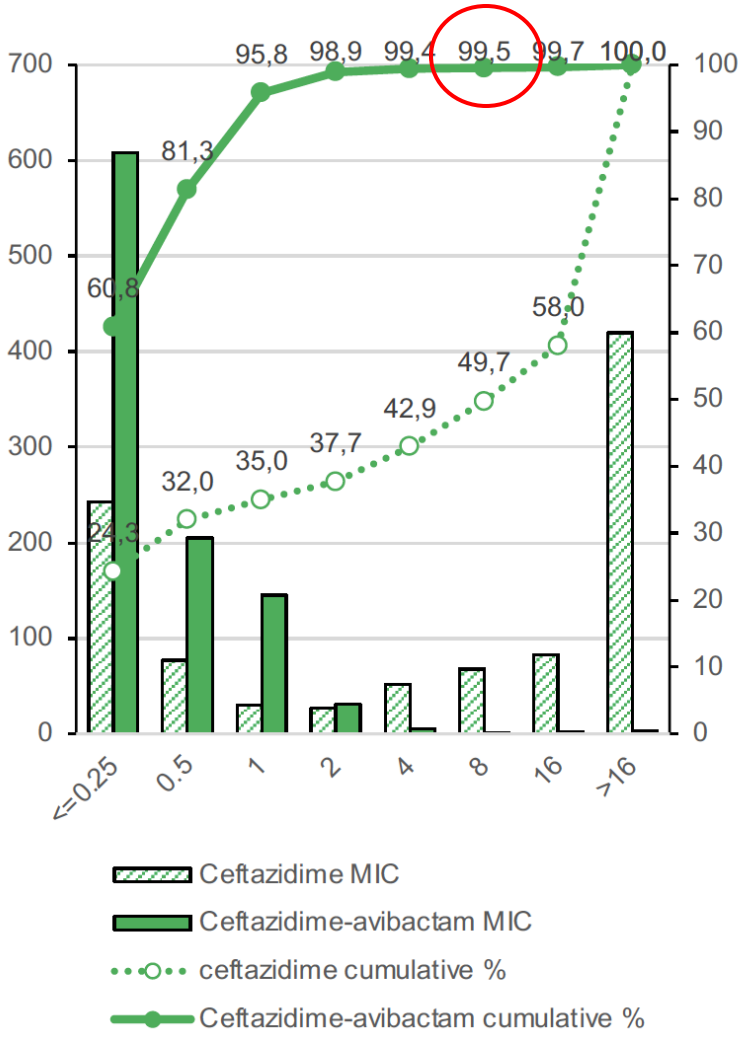
Ceftazidime-avibactam / MBL

NDM + BLSE

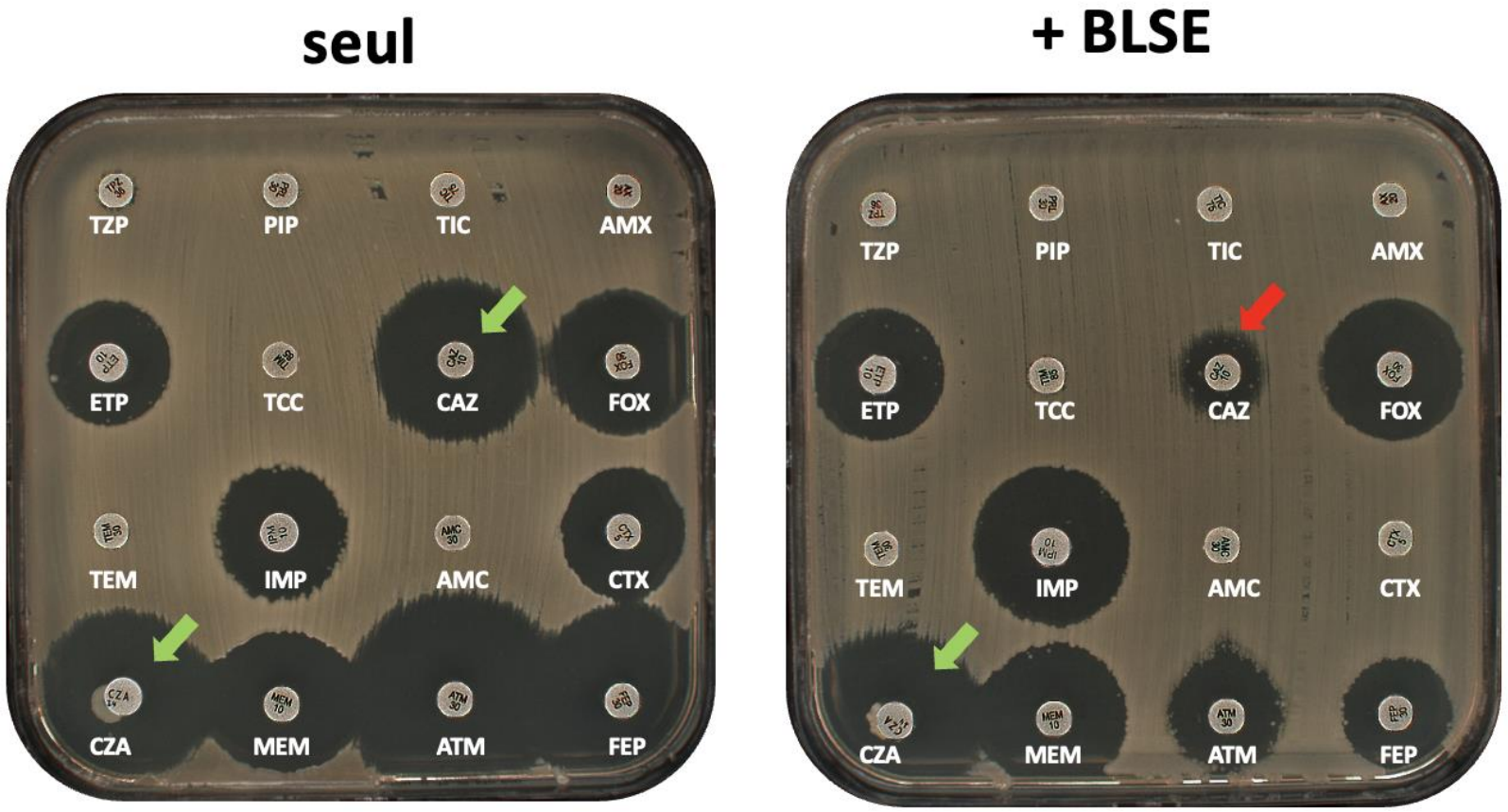
VIM + BLSE



Ceftazidime-avibactam / OXA-48

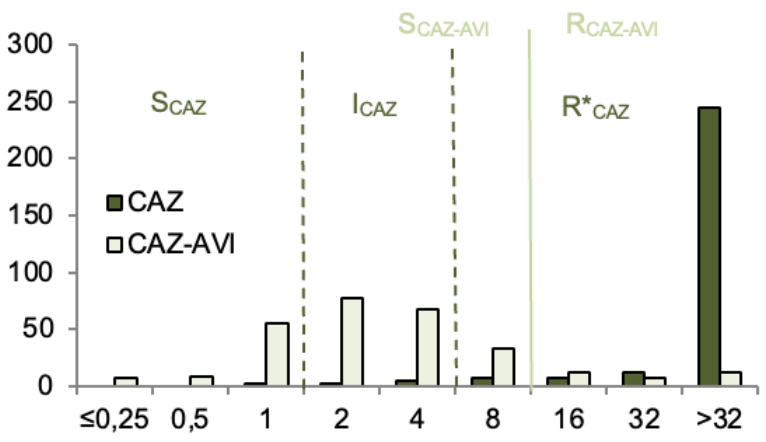


OXA-48 producing *E. coli*

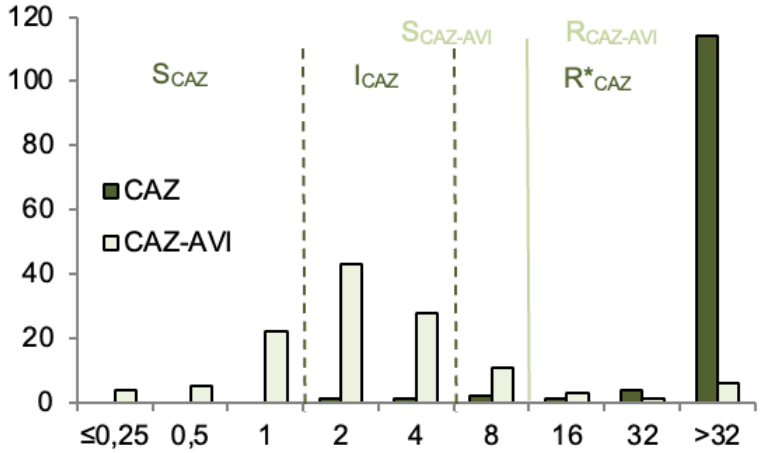


Ceftazidime-avibactam / CRE non EPC

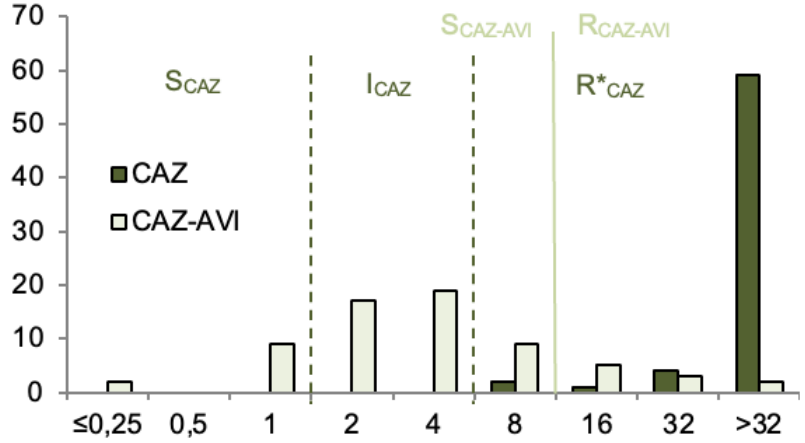
Global n=284



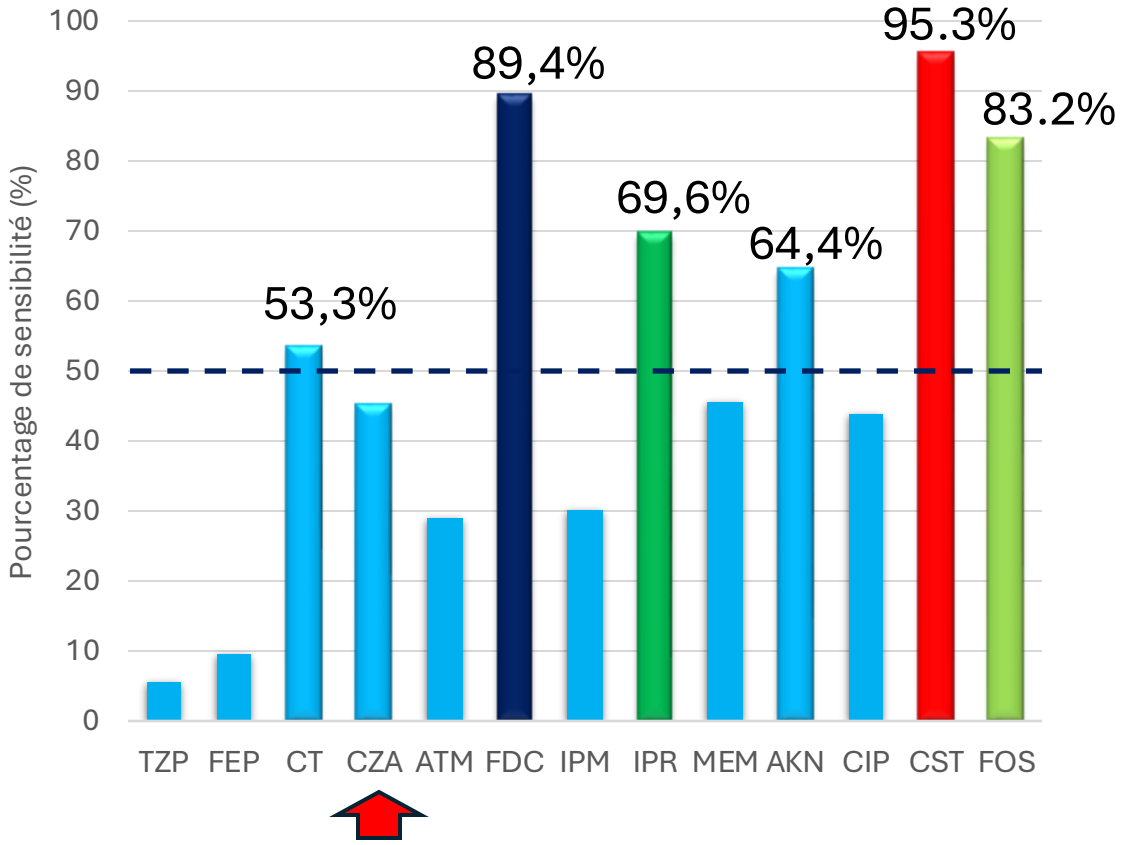
ESBL n=123



CASE n=68

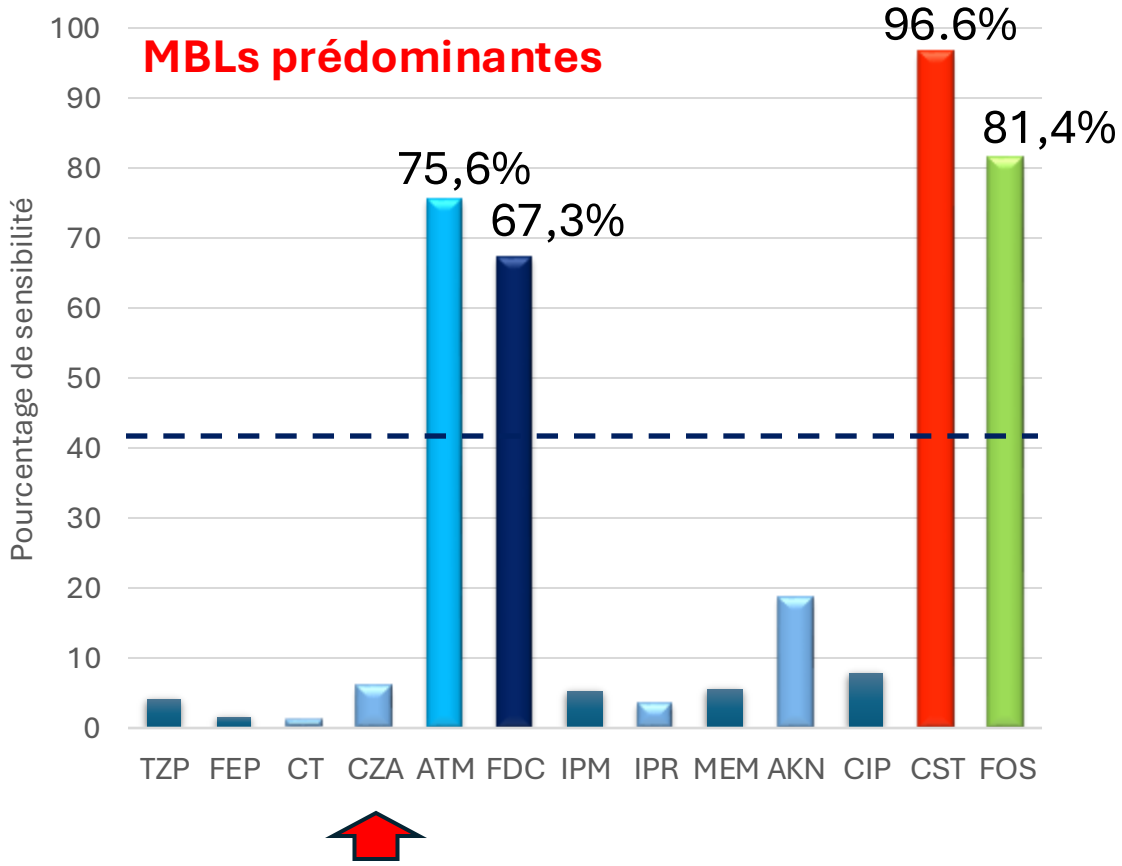


Sensibilité aux antibiotiques des souches de *P. aeruginosa* CAZ^{R} *in vitro*



Isolats CAZ^{R} non producteurs de carbapénèmase
(*n*= 844 isolats)

2022/2023



Isolats producteurs de carbapénèmase
(*n*=307 isolats)

CNR RÉSISTANCE AUX ANTIBIOTIQUES

Imipénème-relebactam

Imipénème-relebactam / KPC

Antimicrobial Agents and Chemotherapy®

Relebactam Is a Potent Inhibitor of the KPC-2 β-Lactamase and Restores Imipenem Susceptibility in KPC-Producing *Enterobacteriaceae*

Krisztina M. Papp-Wallace,[a,b,c] Melissa D. Barnes,[a,b] Jim Alsop,[d] Magdalena A. Taracila,[a,b] Christopher R. Bethel,[a] Scott A. Becka,[a] David van Duin,[e] Barry N. Kreiswirth,[f] Keith S. Kaye,[g] Robert A. Bonomo[a,b,c,h,i]

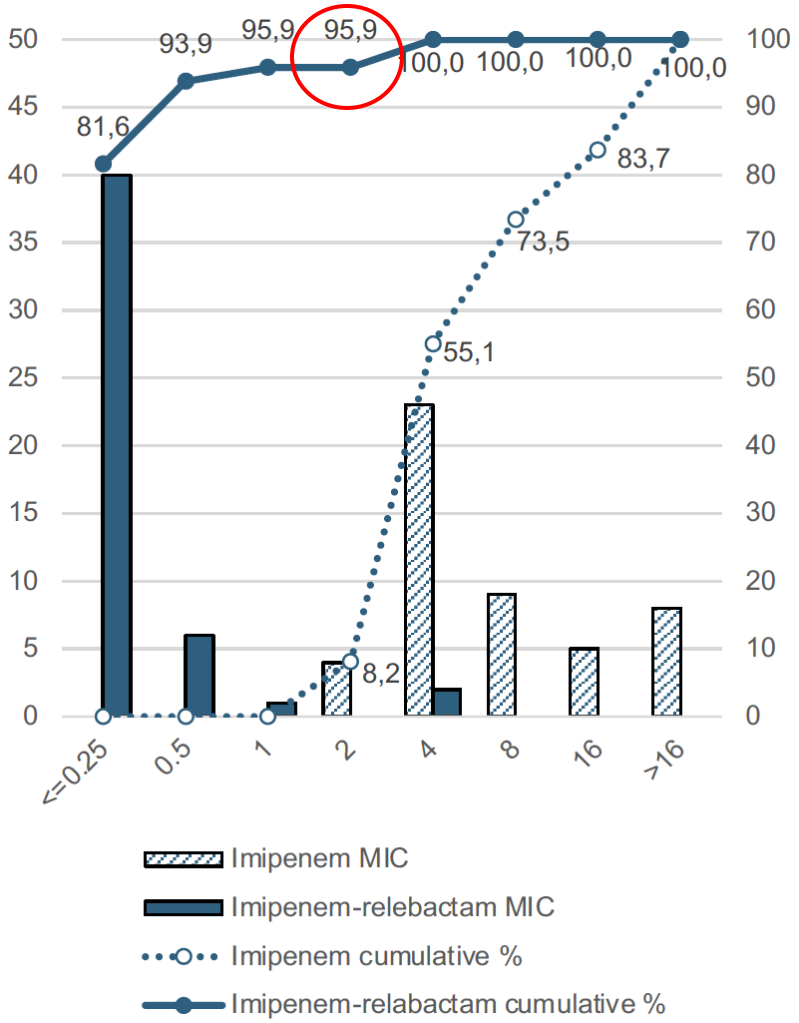
TABLE 3 Kinetic parameters against KPC-2 using relebactam

Kinetic parameter	Value for KPC-2
$K_{i\ app}$ (μM)	2.3 ± 0.3
k_2/K (M^{-1} s^{-1})	24,750 ± 2,475
k_{off} (s^{-1})	0.00020 ± 0.00002
Half-life[a] (min)	58 ± 6
K_d[b] (nM)	8 ± 1
k_{cat}/k_{inact}	1

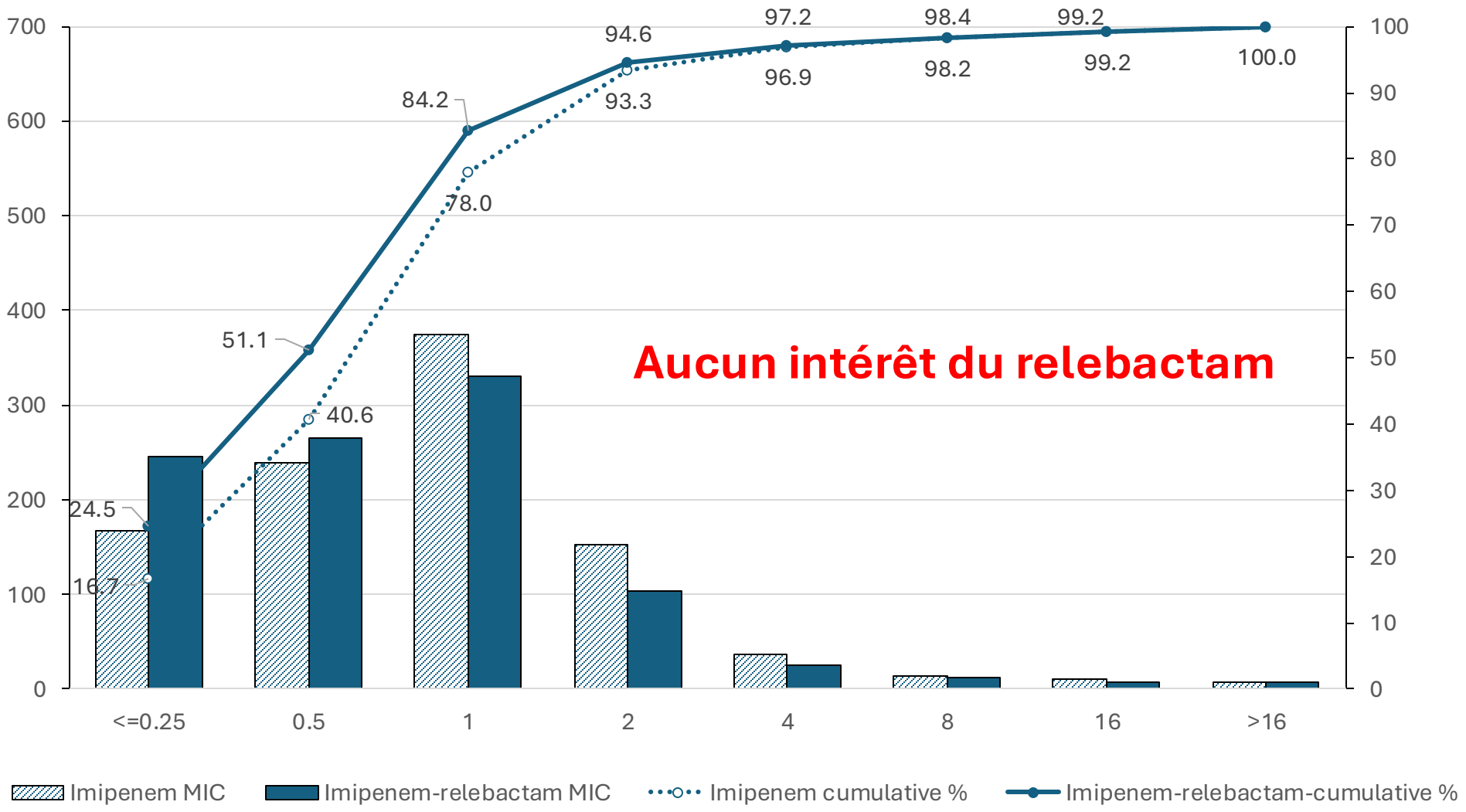
[a]Residence time.
[b]K_d, dissociation constant.

« KPC-2-relebactam complex is more stable than KPC-2-avibactam complex »

IMP *vs* IMP-REL on KPC producers

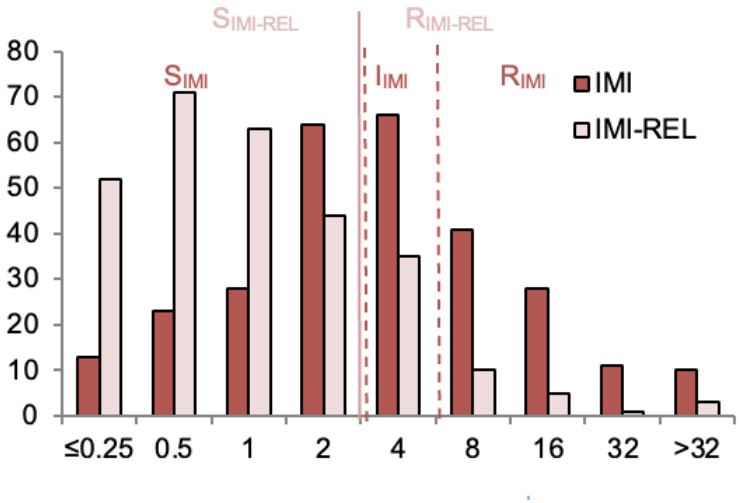


Imipénème-relebactam / OXA-48



Imipénème-relebactam / CRE- non-EPC

Global n=284



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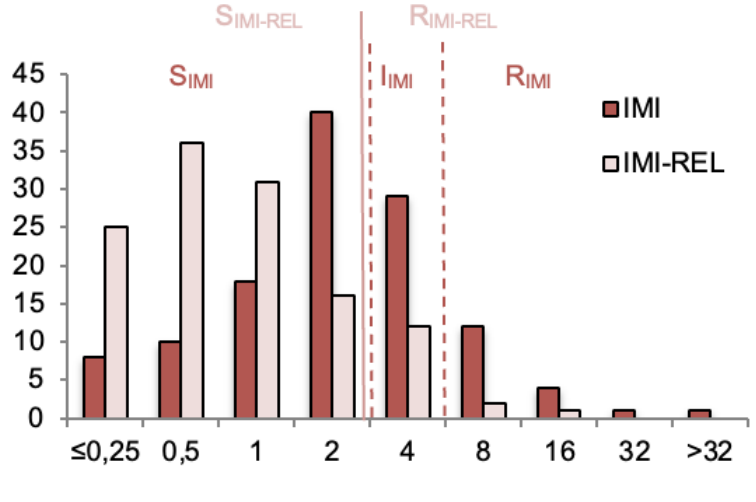
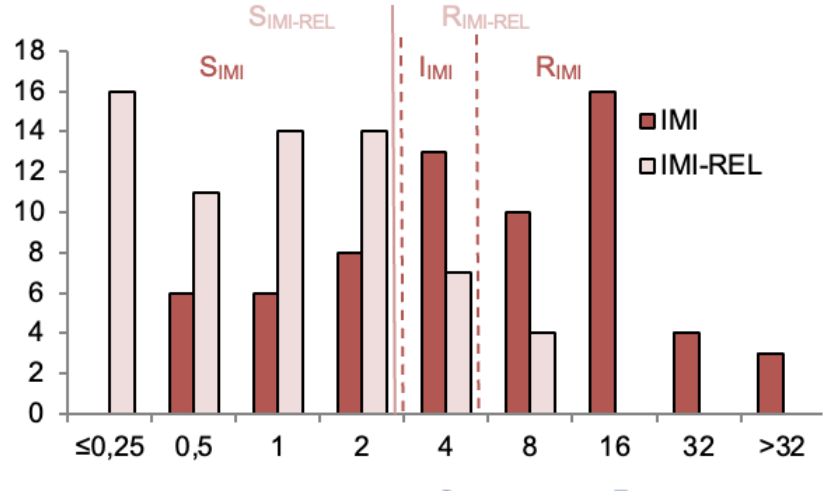
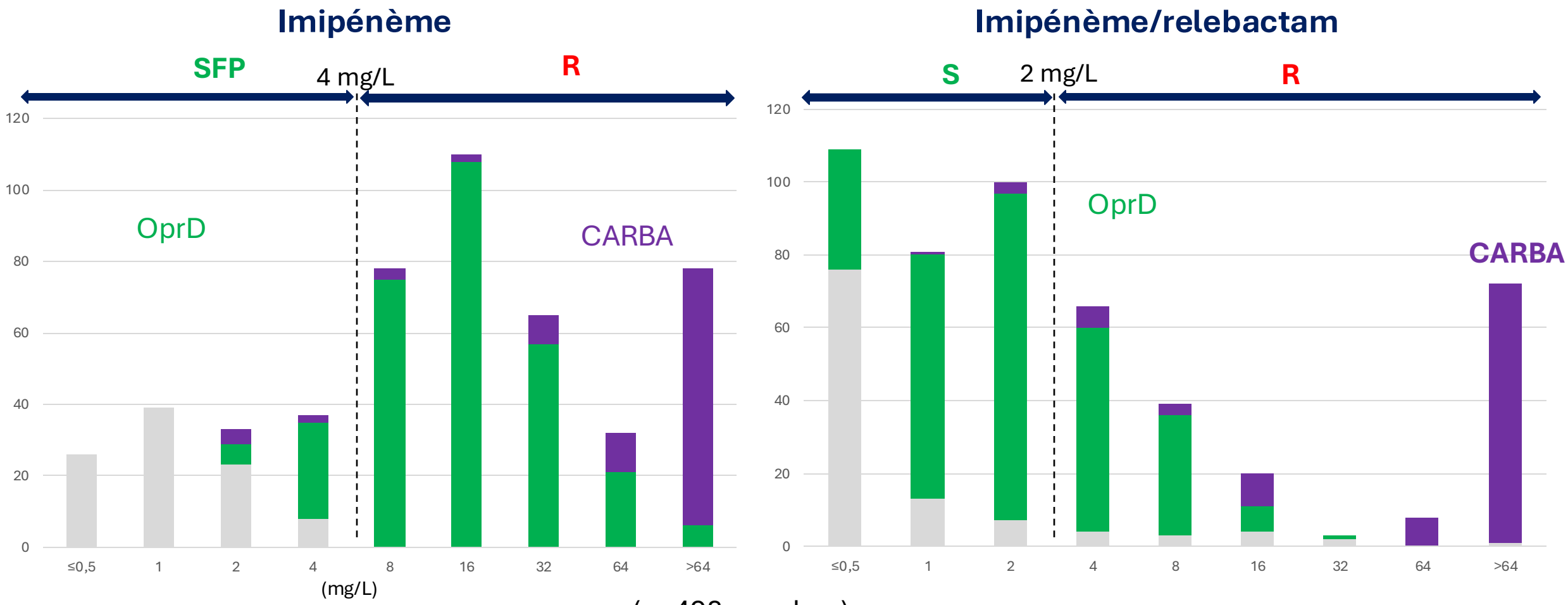


CASE n=68



Imipénème-relebactam / *P. aeruginosa*

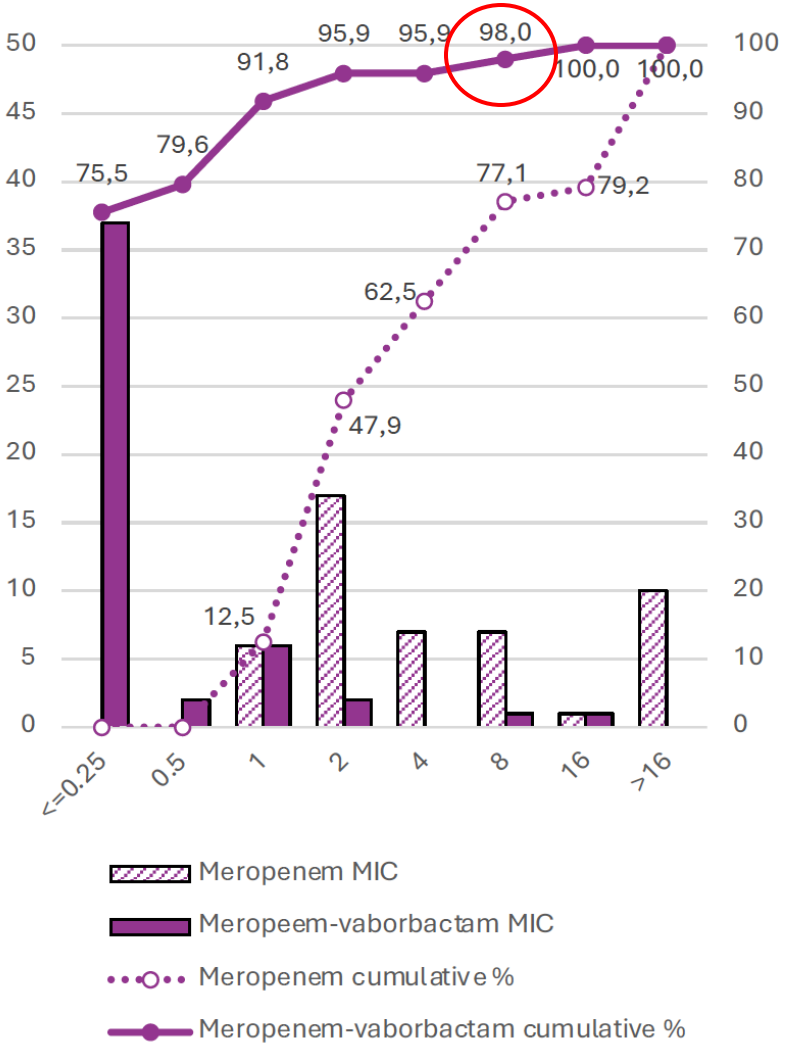


(*n*=498 souches)

intérêt +++ sur les souches OprD + AmpC déréprimée

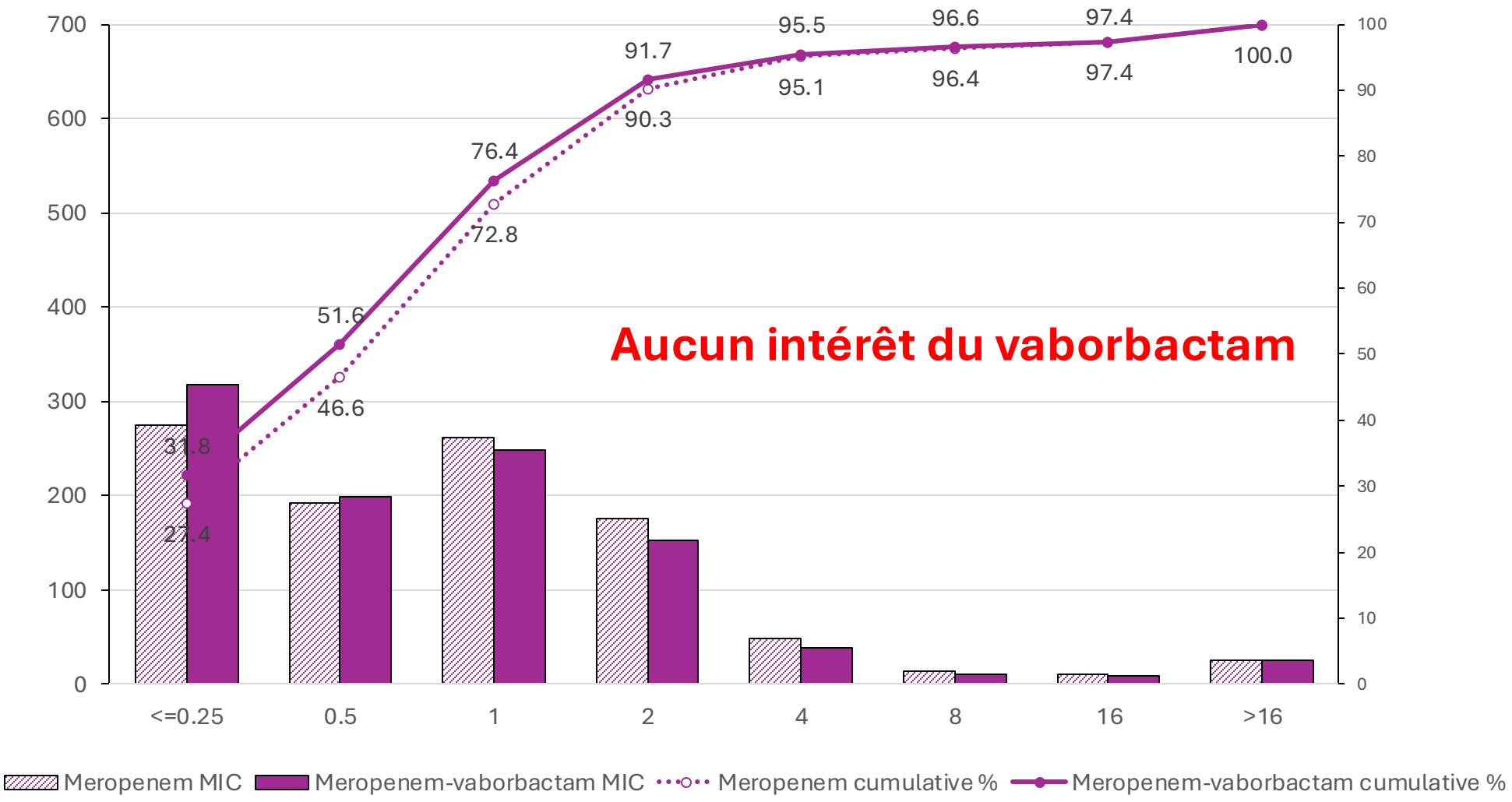
Méropénème-vaborbactam

Méropénème-vaborbactam / KPC



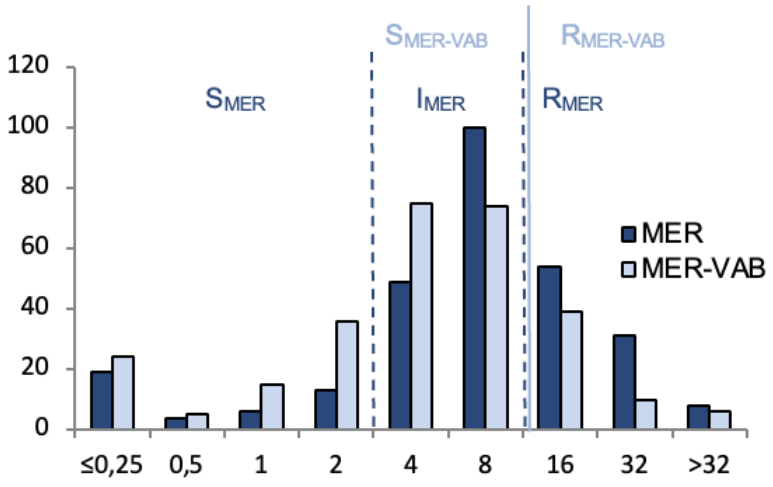
- **Active +++ on KPC**
- **Résiste à la mutation D179Y de KPC: seulement 20% de résistance croisée avec ceftazidime/Avibactam**

Méropénème-vaborbactam / OXA-48



Méropénème-vaborbactam / CRE non-EPC

Global n=284



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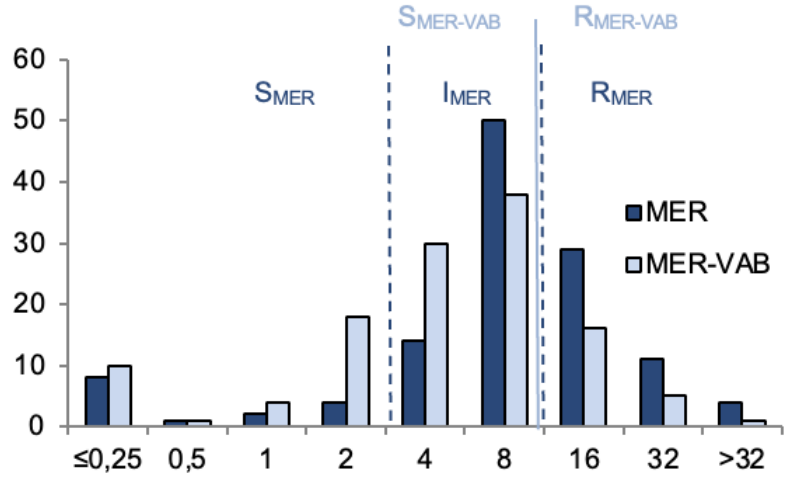
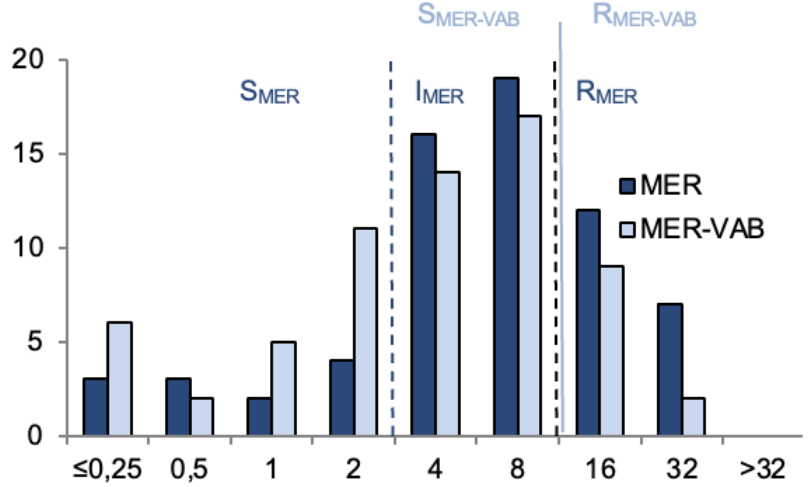
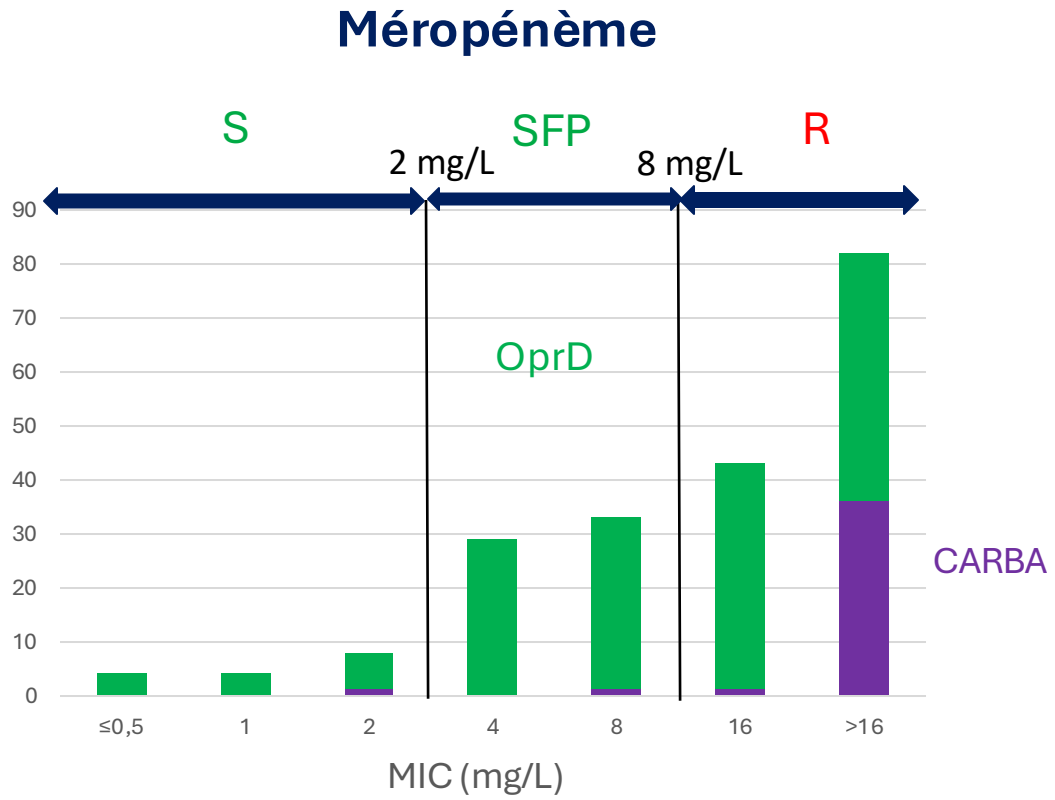
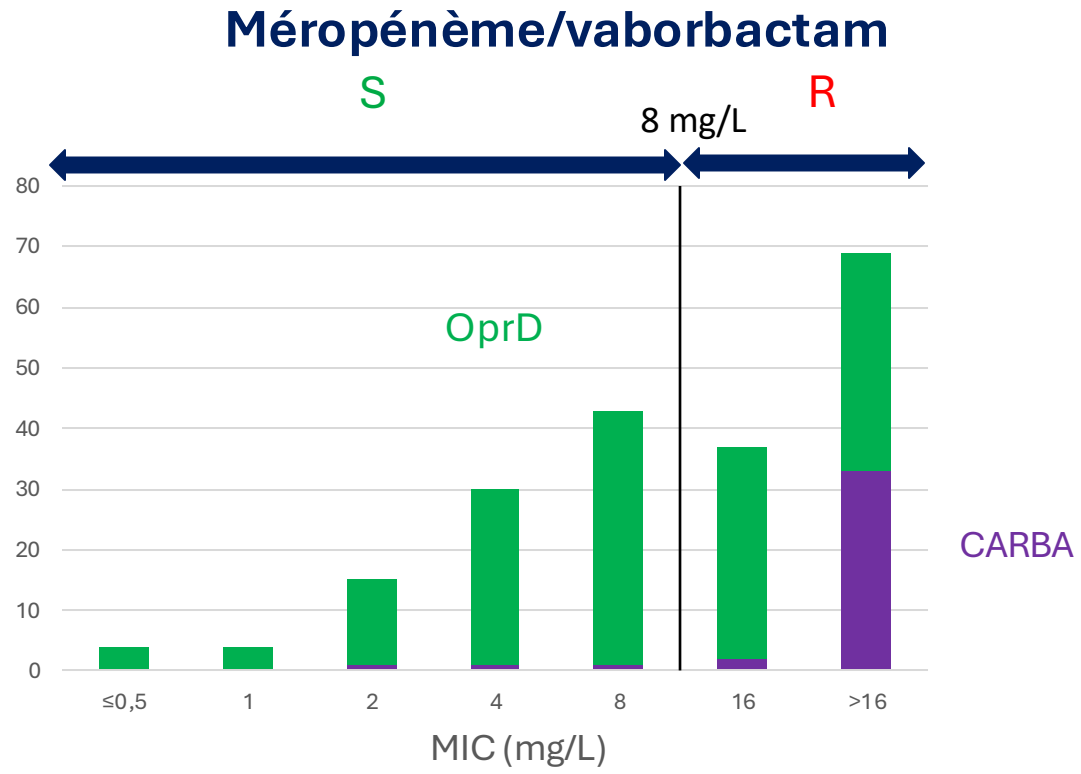


CASE n=68



Méropénème-vaborbactam / *P. aeruginosa*





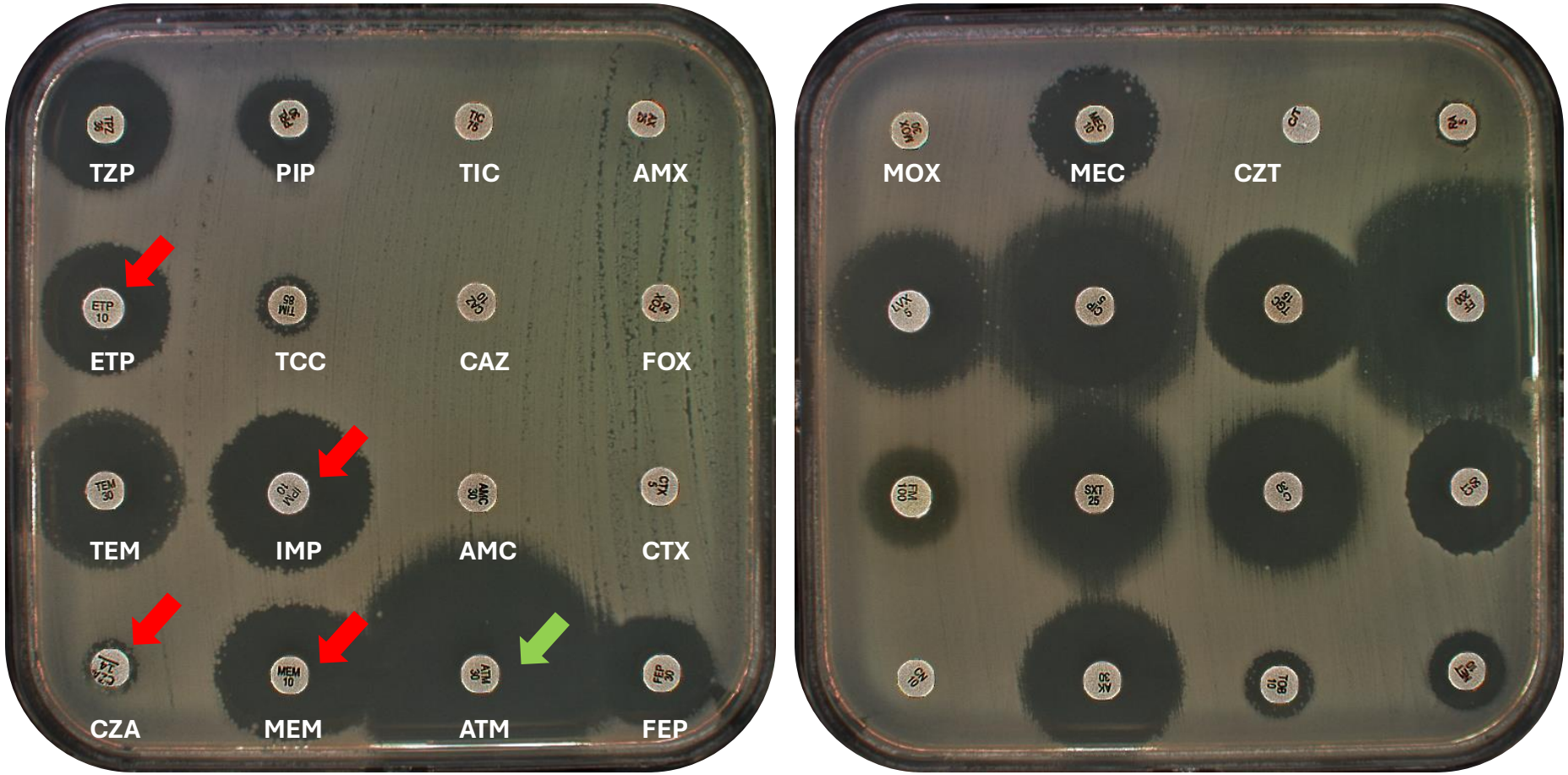
(*n*=263 isolates)

Aucun intérêt du vaborbactam

Aztréonam-avibactam

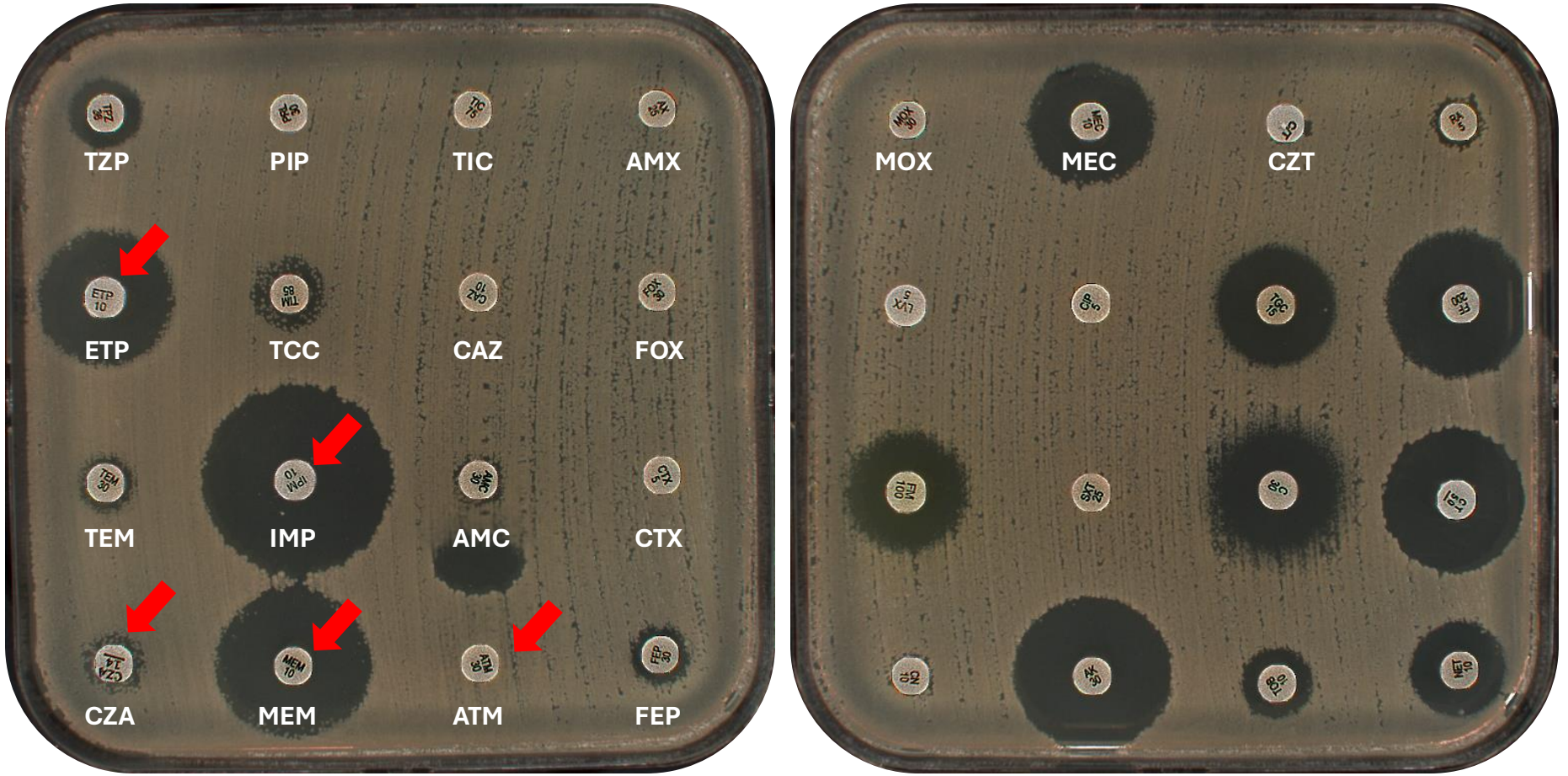
Aztréonam-avibactam

MBL alone



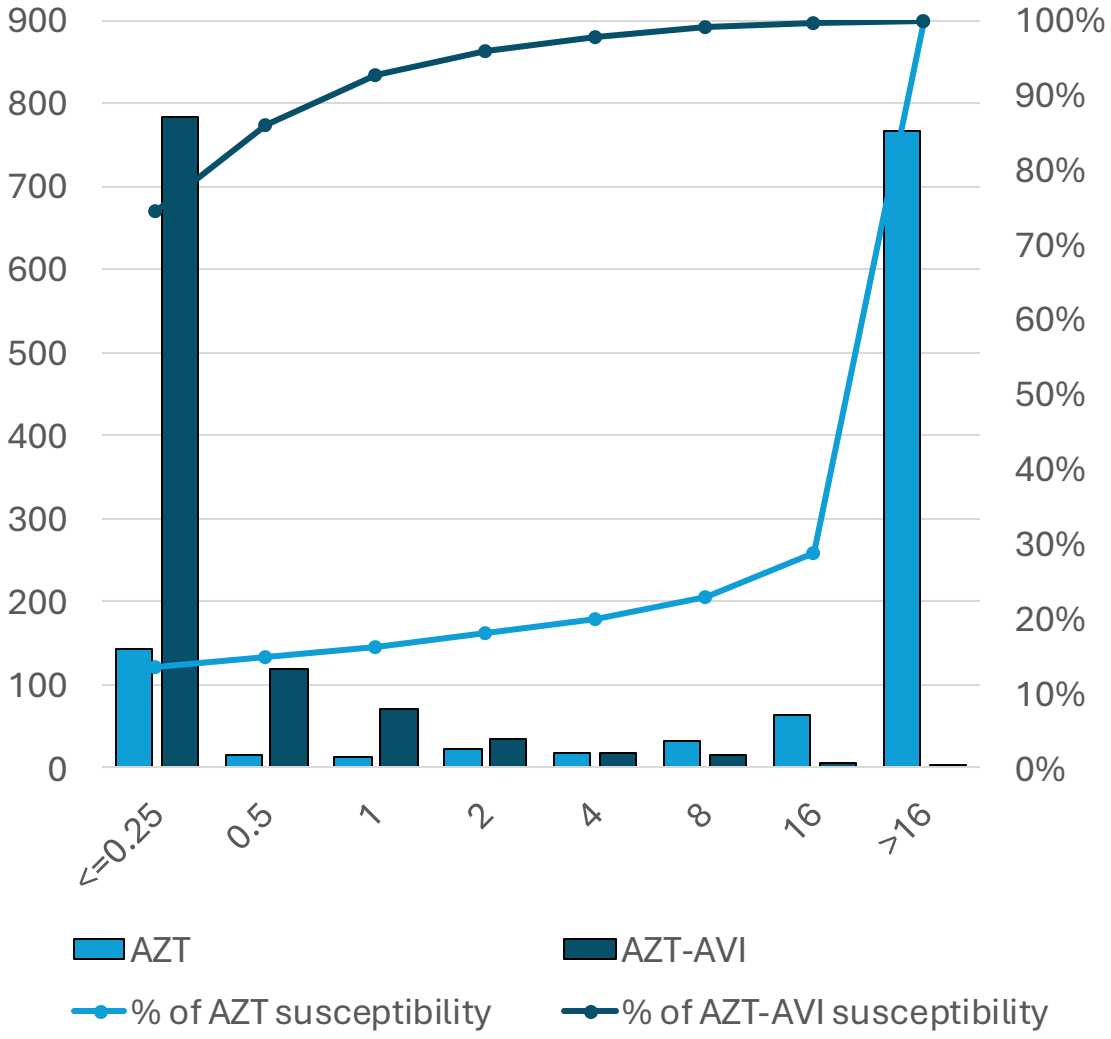
Aztréonam-avibactam

MBL + BLSE



CNR RÉSISTANCE AUX ANTIBIOTIQUES 2023

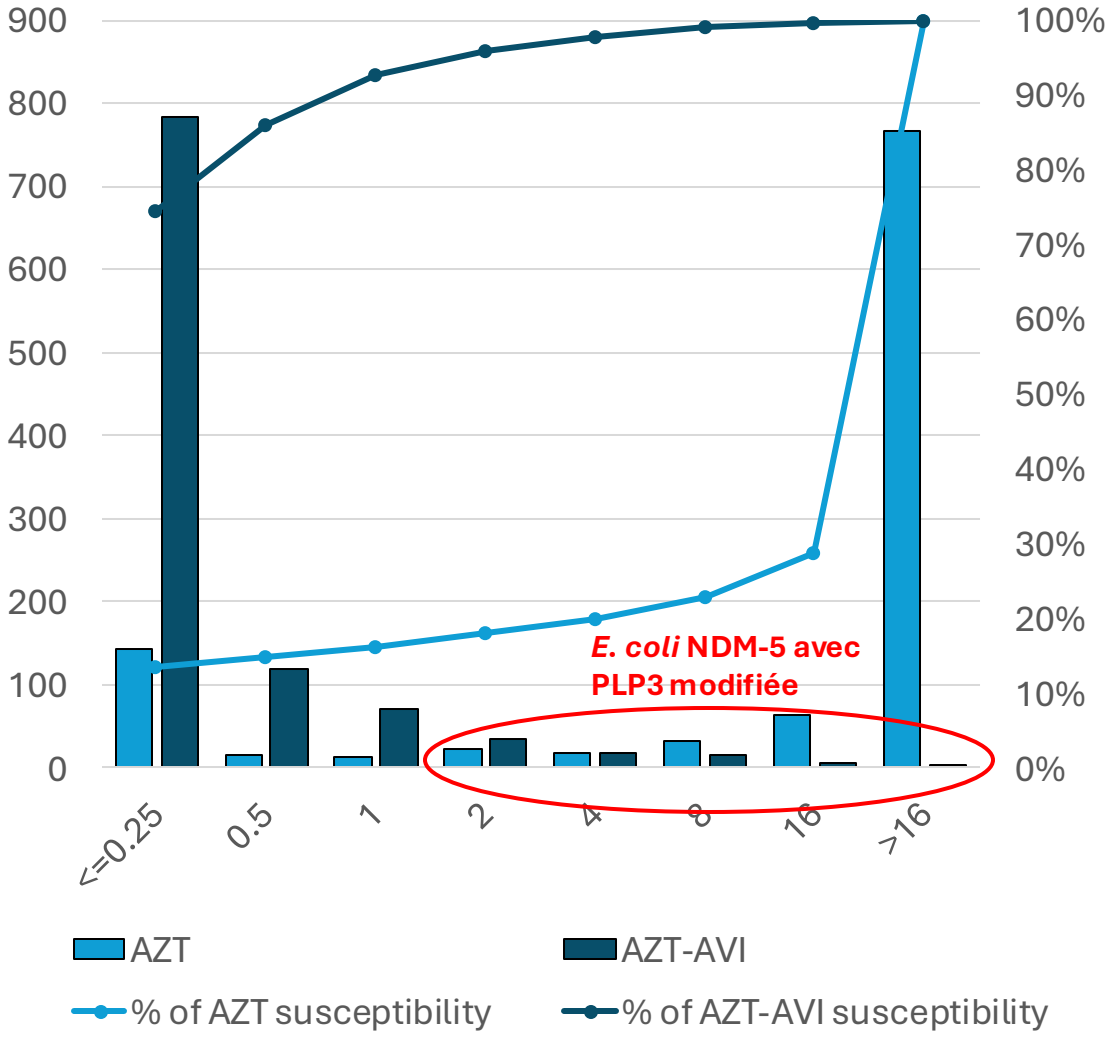
NDM



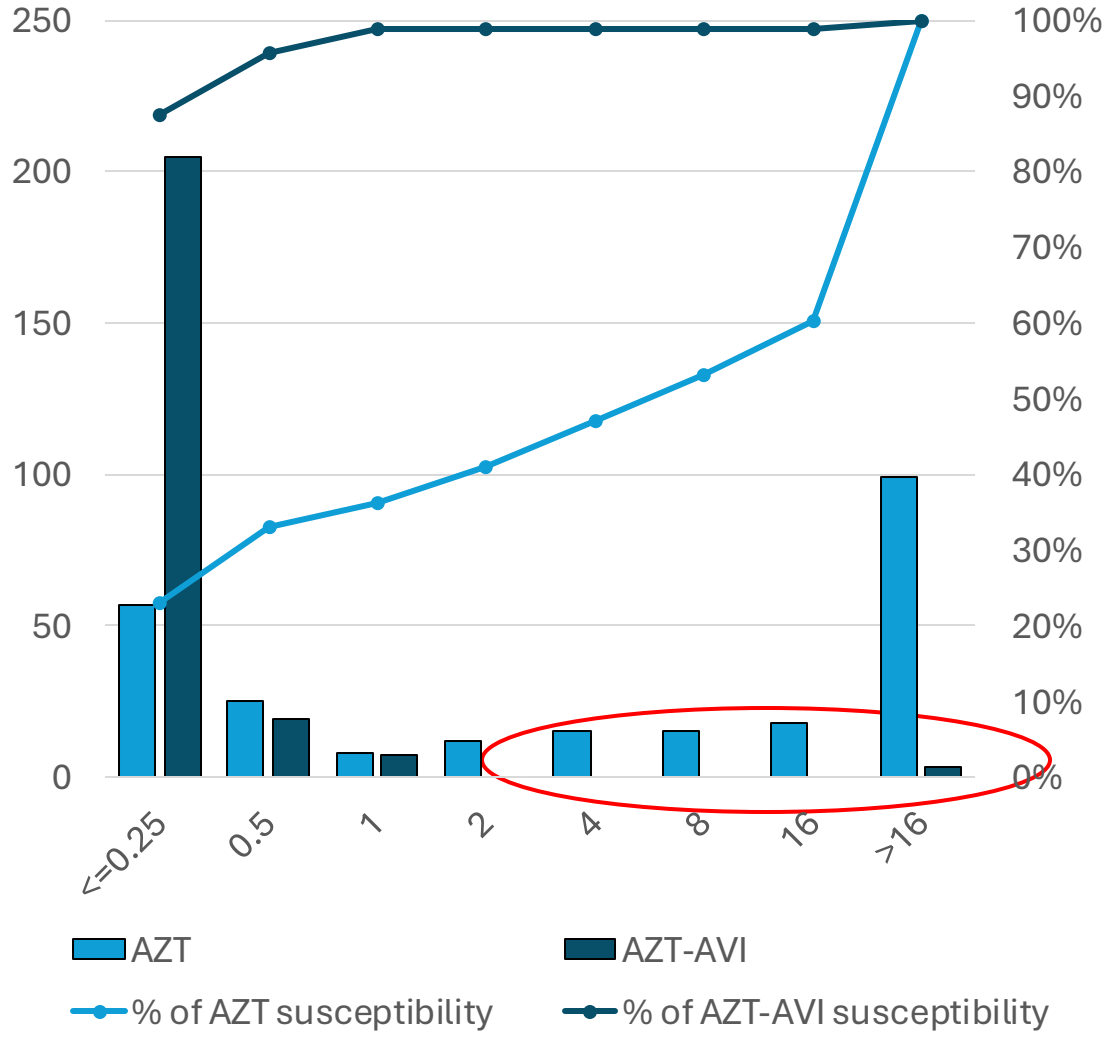
VIM

CNR RÉSISTANCE AUX ANTIBIOTIQUES 2023

NDM

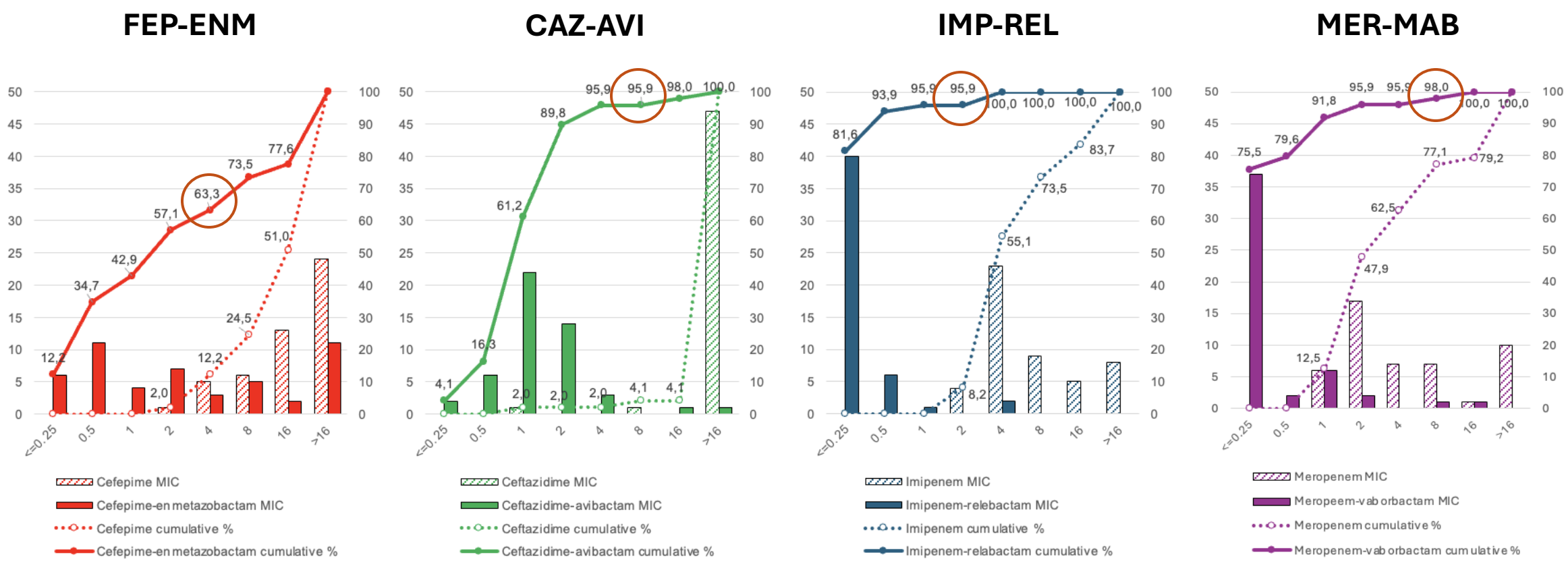


VIM



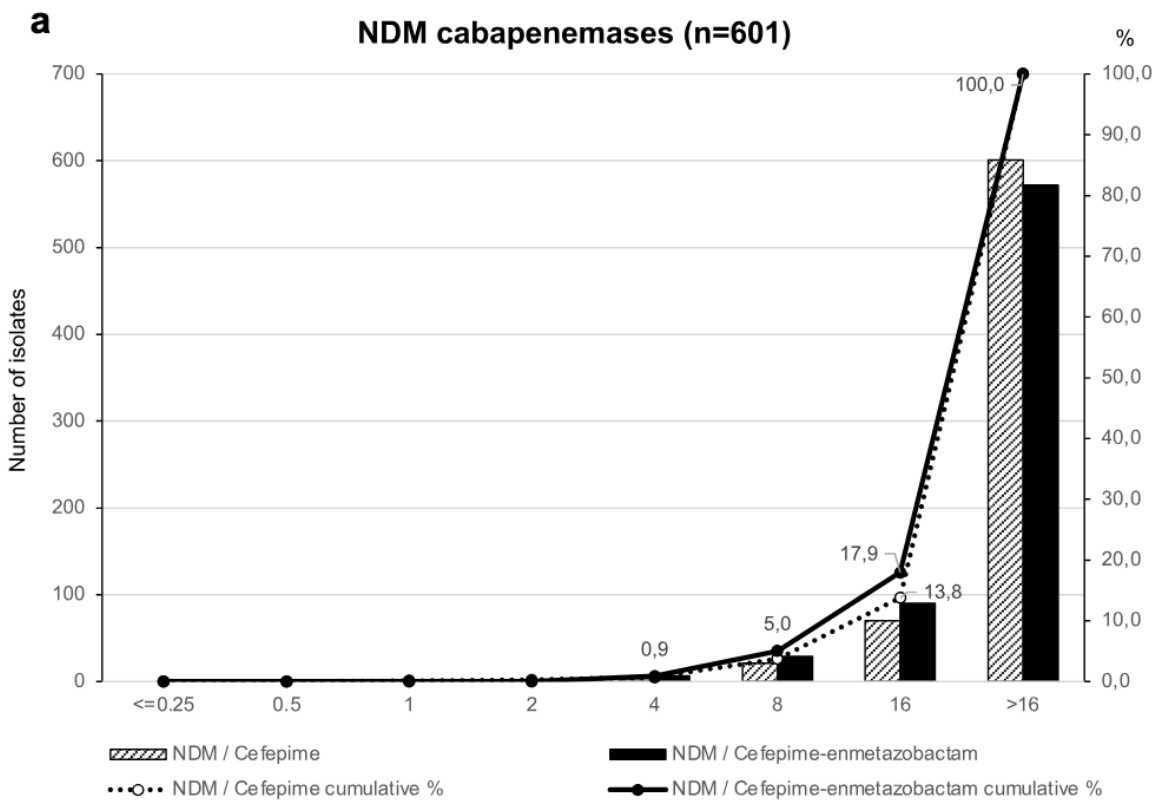
Céfépime-enmetazobactam

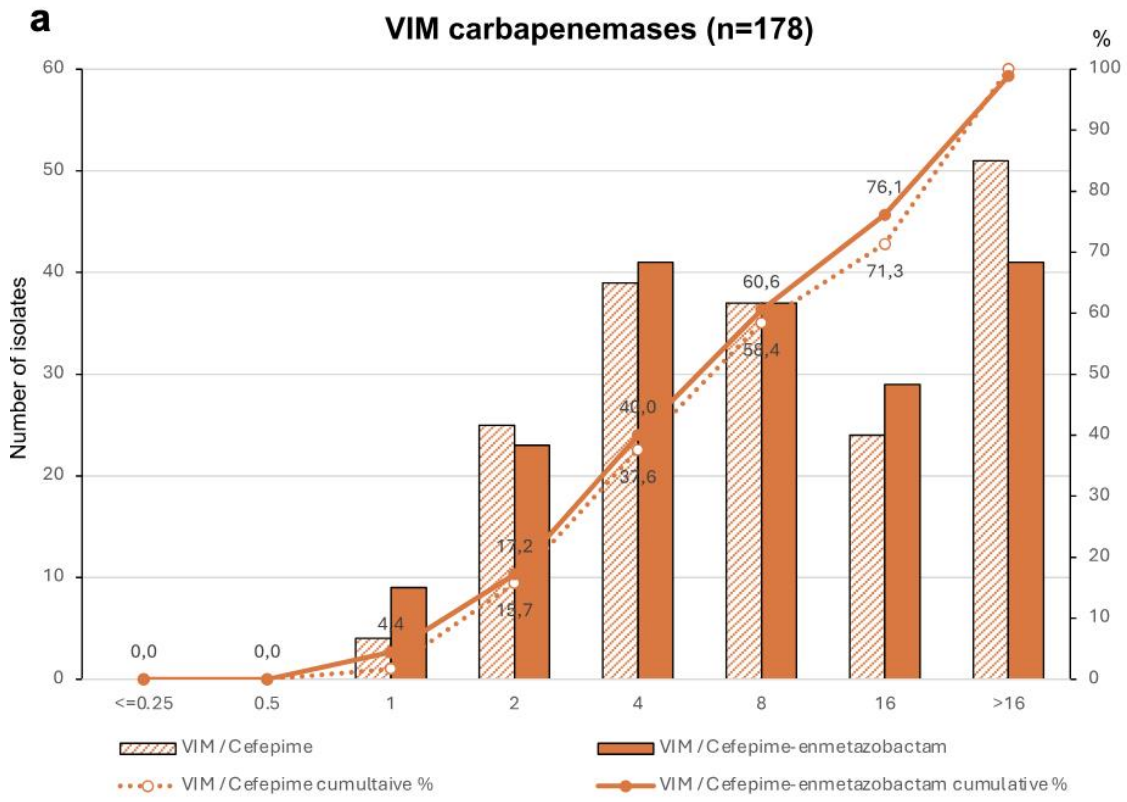
Céfépime-enmétazobactam / KPC



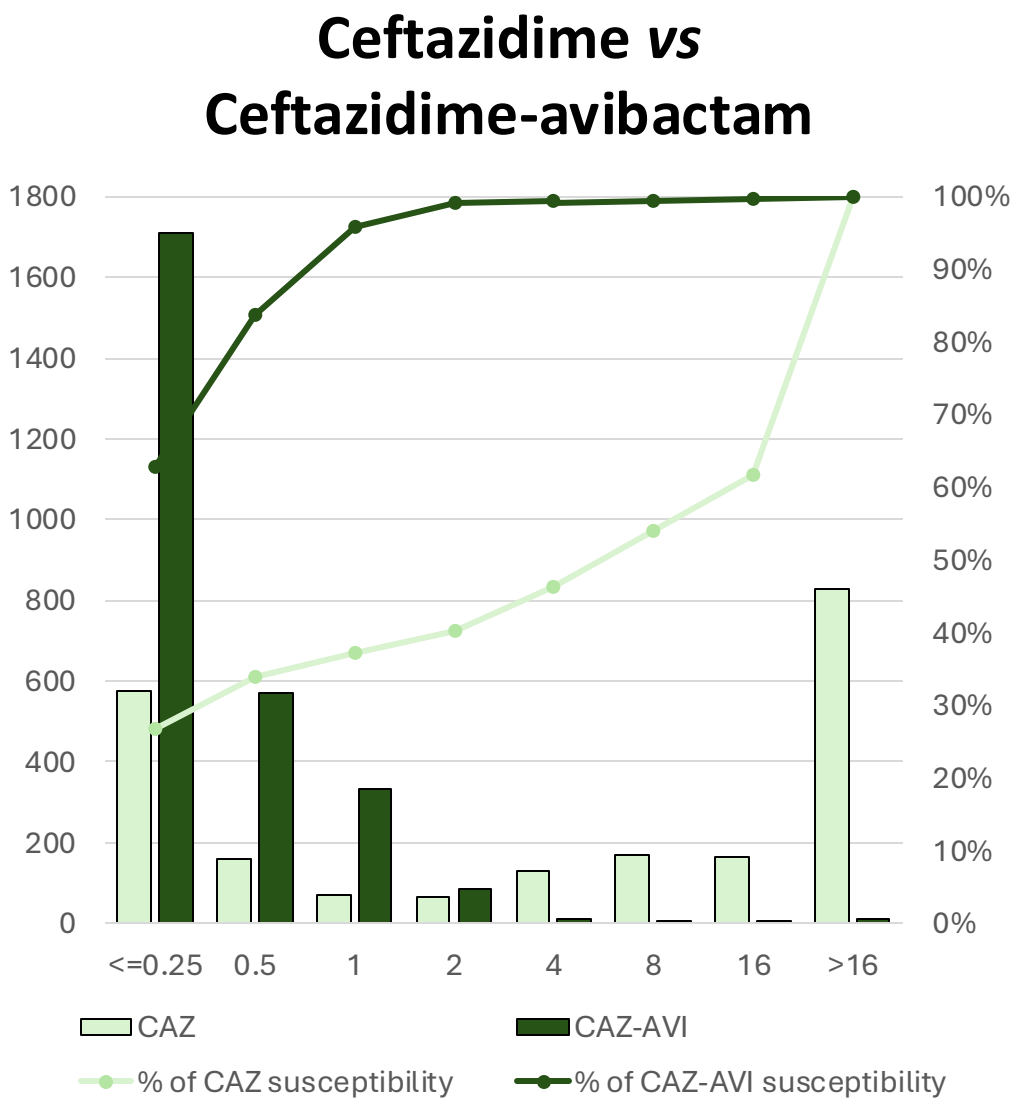
- **Actif +/- sur KPC**
- **Actif sur les KPC résistant à la ceftazidime/avibactam**

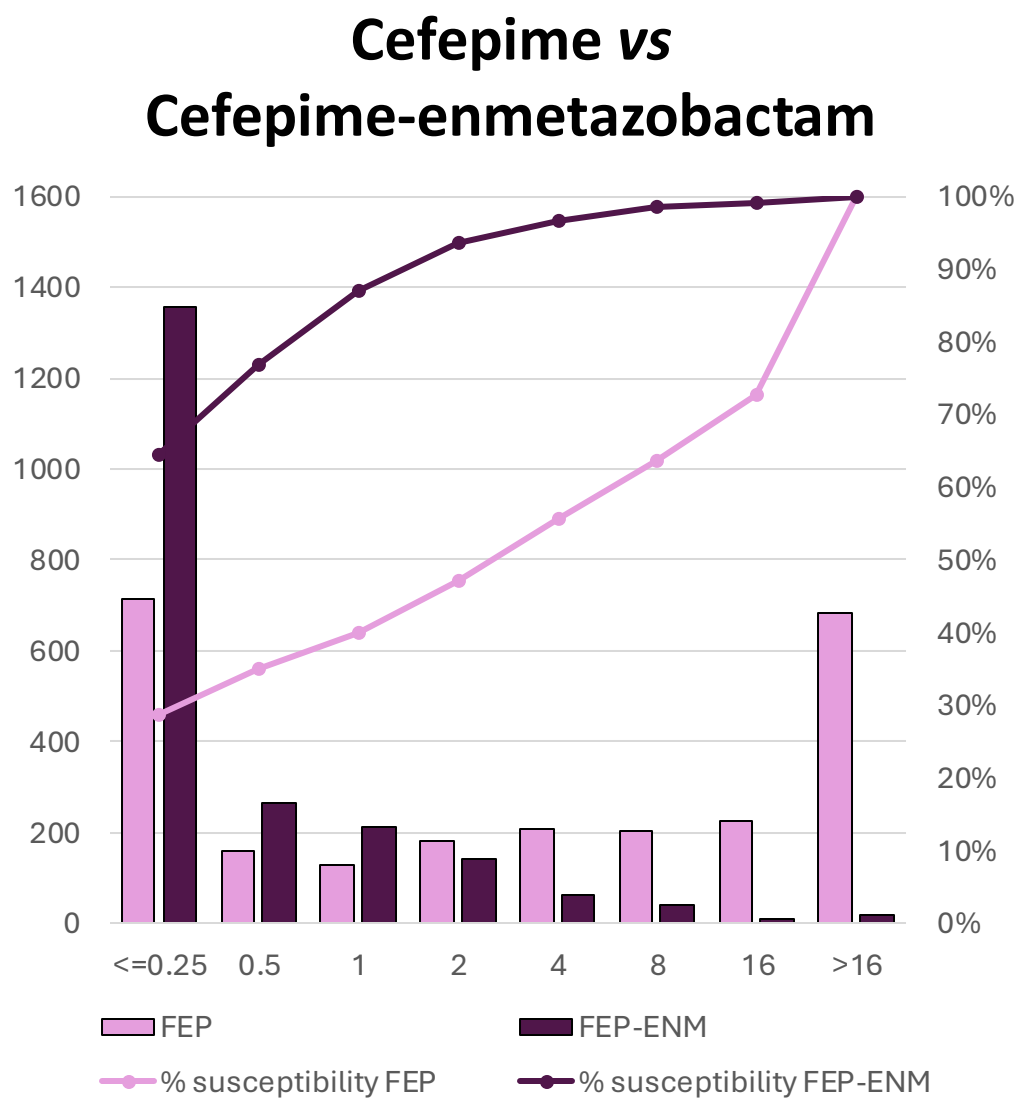
Céfépime-enmétazobactam / MBL





Céfépime-enmétazobactam / OXA-48





Céfépime-enmétazobactam / CRE non-EPC

Antimicrobial	MIC (mg/L)								MIC_{50}	MIC_{90}
	⩽0.25	0.5	1	2	4	8	16	>16		
Cefepime	0.8%	5.0%	6.6%	13.2%	24.8%	35.5%	50.4%	100.0%	16	>16
Cefepime-enmetazobactam	9.9%	21.5%	41.3%	53.7%	66.9%	78.5%	87.6%	100.0%	2	>16
Ceftazidime	0.0%	0.0%	0.8%	2.5%	5.0%	5.8%	11.6%	100.0%	>16	>16
Ceftazidime-avibactam	10.7%	22.3%	52.9%	76.9%	92.6%	96.7%	100.0%	100.0%	1	4
Imipenem	24.0%	41.3%	69.4%	76.9%	87.6%	93.4%	96.7%	100.0%	1	8
Imipenem-relebactam	54.9%	77.9%	89.3%	93.4%	96.7%	100.0%	100.0%	100.0%	≤0.25	2
Meropenem	28.3%	37.5%	49.2%	66.7%	80.8%	92.5%	95.8%	100.0%	2	8
Meropenem-relebactam	47.1%	57.9%	70.2%	86.0%	90.9%	95.9%	99.2%	100.0%	0.5	4
Ertapenem	2.5%	5.8%	22.3%	33.9%	40.5%	57.0%	71.9%	100.0%	8	>16

50 souches de *P. aeruginosa* XDR

Strains	Resistance mechanisms	CAZ	CAZ-AVI	FEP	FEP-ENM	CZT-TAZ	IMP	IMP-REL	MEM	MEM-VAB	CFD
21.9326	SHV-2a, OprD-, AmpC+, PDC-35	16	4/4	>16	8/8	2/4	16	2/4	8	4/8	0.5
23.10743	SHV-2a, VIM-1, PDC-31	>16	>16/4	>16	>16/8	>16/4	>16	>16/4	>16	>16/8	0.5
22.9890	GES-11, AmpC+, PDC-35	>16	8/4	>16	16/8	>16/4	1	1/4	4	4/8	0.12
22.10133	GES-9, OprD-, PDC-11	>16	>16/4	>16	>16/8	>16/4	16	8/4	>16	>16/8	2
23.11087	GES-1, OprD-, PDC-35	>16	16/4	>16	>16/8	>16/4	16	8/4	8	8/8	0.25
23.10807	BEL-1, OprD-, AmpC+, PDC-16	8	1/4	16	8/8	8/4	16	2/4	1	0.5/8	0.12
23.10562	PER-1, OprD-, AmpC+, PDC-35	>16	>16/4	>16	16/8	>16/4	8	2/4	16	16/8	2
21.9021	PER-1, OprD-, AmpC+, PDC-35	>16	8/4	>16	16/8	>16/4	8	1/4	4	4/8	1
23.10482	VEB-1a, PDC-11, OprD-, AmpC+	>16	>16/4	>16	16/8	>16/4	16	2/4	8	8/8	2
23.11040	VEB-1a, PDC-11, OprD-	>16	>16/4	>16	16/8	>16/4	16	4/4	16	16/8	4
23.11148	VIM-2, PDC-3	>16	>16/4	16	16/8	>16/4	>16	>16/4	4	4/8	0.12
23.10456	VIM-4, PDC-36	>16	>16/4	>16	>16/8	>16/4	>16	>16/4	>16	>16/8	0.25
23.11191	NDM-1, PDC-3	>16	>16/4	>16	>16/8	>16/4	>16	>16/4	>16	>16/8	16
21.8592	IMP-13, PDC-35	>16	>16/4	>16	>16/8	>16/4	8	8/4	4	4/8	0.5
20.8130	KPC-2, OXA-2, OXA-779, PDC-35	>16	16/4	>16	>16/8	>16/4	>16	>16/4	>16	>16/8	1
19.7335	KPC-2, OXA-2, OXA-779, PDC-35	>16	8/4	>16	>16/8	>16/4	>16	>16/4	>16	>16/8	1
21.8640	TEM-3, OprD-, AmpC+, PDC-35	8	2/4	16	8/8	1/4	8	0.5/4	2	2/8	0.5
21.9041	PME-1, OprD-, AmpC+, PDC-3	>16	>16/4	>16	>16/8	>16/4	>16	8/4	>16	>16/8	2
22.10009	PME-1, NDM-1, PDC-35	>16	>16/4	>16	>16/8	>16/4	>16	>16/4	>16	>16/8	8
23.10845	OprD-, AmpC+, MexAB+, PDC-19a	>16	16/4	>16	>16/8	16/4	>16	8/4	>16	16/8	8
23.10874	OprD-, AmpC+, MexAB+, PDC-8	>16	>16/4	>16	>16/8	4/4	>16	16/4	>16	>16/8	1
23.10877	OprD-, AmpC++, PDC-3	>16	16/4	>16	>16/8	16/4	>16	4/4	>16	>16/8	0.5
23.10744	OprD-, AmpC+, MexAB+, PDC-16	>16	4/4	16	16/8	2/4	16	2/4	8	4/8	1
23.10650	OprD-, AmpC+, MexAB+, PDC-37	16	16/4	16	16/8	2/4	16	8/4	>16	16/8	4
23.10848	OprD-, AmpC++, PDC-34	>16	>16/4	>16	>16/8	>16/4	8	2/4	>16	16/8	0.5
23.11092	OprD-, AmpC++, PDC-5	>16	>16/4	>16	16/8	8/4	16	16/4	16	16/8	2
23.10483	OprD-, AmpC++, PDC-35	>16	16/4	>16	>16/8	8/4	16	8/4	>16	>16/8	1
22.9871	AmpC+, PDC-67	16	2/4	8	2/8	1/4	0.5	≤0.25/4	≤0.25	≤0.25/8	0.5
22.9809	AmpC+, PDC-30	>16	8/4	16	16/8	4/4	8	1/4	4	4/8	1
22.10326	OprD-, AmpC+, PDC-346 (ESAC)	>16	>16/4	>16	>16/8	>16/4	16	16/4	>16	>16/8	>32
22.9481	OprD-, AmpC+, PDC-511 (ESAC)	>16	>16/4	>16	>16/8	8/4	16	2/4	16	16/8	8
23.10568	AmpC+, PDC-553 (ESAC)	>16	16/4	8	8/8	>16/4	0.5	0.5/4	2	2/8	0.5
23.10885	AmpC+, PDC-562 (ESAC)	>16	2/4	>16	>16/8	4/4	≤0.25	≤0.25/4	≤0.25	≤0.25/8	2
23.10653	AmpC+, PDC-558 (ESAC)	>16	>16/4	>16	16/8	>16/4	1	1/4	16	8/8	2
23.10715	AmpC+, PDC-559 (ESAC)	>16	4/4	>16	>16/8	4/4	0.5	0.5/4	0.5	0.5/8	2
23.10828	OprD-, AmpC+, PDC-561 (ESAC)	>16	≤0.25/4	>16	2/8	2/4	4	1/4	0.5	≤0.25/8	0.25
22.10251	OprD-, AmpC+, PDC-534 (ESAC)	>16	16/4	>16	16/8	>16/4	8	4/4	8	4/8	4
22.9556	PAC-1, OXA-10, OprD-, PDC-98	>16	>16/4	>16	>16/8	>16/4	>16	>16/4	>16	>16/8	16
19.6881	OXA-2, OprD-, PDC-35	>16	16/4	>16	>16/8	2/4	16	8/4	>16	>16/8	0.5
19.6796	OXA-1, PDC-14	16	16/4	>16	>16/8	2/4	16	8/4	>16	>16/8	0.12
22.9883	MexYX+, OprD-, AmpC+, PDC-19a	>16	4/4	16	16/8	4/4	>16	4/4	8	8/8	0.5
23.10588	MexYX+, PDC-19a	2	2/4	8	8/8	1/4	1	0.5/4	≤0.25	≤0.25/8	0.06
23.10638	MexYX+,OprD-, AmpC+, PDC-1	>16	8/4	16	16/8	8/4	16	2/4	8	4/8	1
23.10860	MexAB+, OprD-, PDC-568	>16	0.5/4	16	8/8	4/4	16	4/4	8	4/8	0.12
23.10874	MexAB+, OprD-, AmpC+, PDC-8	>16	>16/4	>16	16/8	4/4	>16	8/4	>16	>16/8	0.5
23.10877	MexAB+, OprD-, AmpC+, PDC-3	>16	>16/4	>16	>16/8	16/4	>16	8/4	>16	>16/8	0.5
15.2986	CTX-M-3, OprD-, AmpC+, PDC-1	>16	8/4	>16	8/8	>16/4	16	2/4	16	16/8	0.5
21.8794	CTX-M-15, OXA-1, OprD-, PDC-11	>16	4/4	>16	4/8	8/4	16	2/4	8	8/8	1

Aucun rôle additionnel du enmetazobactam et du vaborbactam

Strains	Resistance mechanisms	CAZ	CAZ-AVI	FEP	FEP-ENM	CZT-TAZ	IMP	IMP-REL	MEM	MEM-VAB	CFD
21.9326	SHV-2a, OprD-, AmpC+, PDC-35	16	4/4	>16	8/8	2/4	16	2/4	8	4/8	0.5
23.10743	SHV-2a, VIM-1, PDC-31	>16	>16/4	>16	>16/8	>16/4	>16	>16/4	>16	>16/8	0.5
22.9890	GES-11, AmpC+, PDC-35	>16	8/4	>16	16/8	>16/4	1	1/4	4	4/8	0.12
22.10133	GES-9, OprD-, PDC-11	>16	>16/4	>16	>16/8	>16/4	16	8/4	>16	>16/8	2
23.11087	GES-1, OprD-, PDC-35	>16	16/4	>16	>16/8	>16/4	16	8/4	8	8/8	0.25
23.10807	BEL-1, OprD-, AmpC+, PDC-16	8	1/4	16	8/8	8/4	16	2/4	1	0.5/8	0.12
23.10562	PER-1, OprD-, AmpC+, PDC-35	>16	>16/4	>16	16/8	>16/4	8	2/4	16	16/8	2
21.9021	PER-1, OprD-, AmpC+, PDC-35	>16	8/4	>16	16/8	>16/4	8	1/4	4	4/8	1
23.10482	VEB-1a, PDC-11, OprD-, AmpC+	>16	>16/4	>16	16/8	>16/4	16	2/4	8	8/8	2
23.11040	VEB-1a, PDC-11, OprD-	>16	>16/4	>16	16/8	>16/4	16	4/4	16	16/8	4
23.11148	VIM-2, PDC-3	>16	>16/4	16	16/8	>16/4	>16	>16/4	4	4/8	0.12
23.10456	VIM-4, PDC-36	>16	>16/4	>16	>16/8	>16/4	>16	>16/4	>16	>16/8	0.25
23.11191	NDM-1, PDC-3	>16	>16/4	>16	>16/8	>16/4	>16	>16/4	>16	>16/8	16
21.8592	IMP-13, PDC-35	>16	>16/4	>16	>16/8	>16/4	8	8/4	4	4/8	0.5
20.8130	KPC-2, OXA-2, OXA-779, PDC-35	>16	16/4	>16	>16/8	>16/4	>16	>16/4	>16	>16/8	1
19.7335	KPC-2, OXA-2, OXA-779, PDC-35	>16	8/4	>16	>16/8	>16/4	>16	>16/4	>16	>16/8	1
21.8640	TEM-3, OprD-, AmpC+, PDC-35	8	2/4	16	8/8	1/4	8	0.5/4	2	2/8	0.5
21.9041	PME-1, OprD-, AmpC+, PDC-3	>16	>16/4	>16	>16/8	>16/4	>16	8/4	>16	>16/8	2
22.10009	PME-1, NDM-1, PDC-35	>16	>16/4	>16	>16/8	>16/4	>16	>16/4	>16	>16/8	8
23.10845	OprD-, AmpC+, MexAB+, PDC-19a	>16	16/4	>16	>16/8	16/4	>16	8/4	>16	16/8	8
23.10874	OprD-, AmpC+, MexAB+, PDC-8	>16	>16/4	>16	>16/8	4/4	>16	16/4	>16	>16/8	1
23.10877	OprD-, AmpC++, PDC-3	>16	16/4	>16	>16/8	16/4	>16	4/4	>16	>16/8	0.5
23.10744	OprD-, AmpC+, MexAB+, PDC-16	>16	4/4	16	16/8	2/4	16	2/4	8	4/8	1
23.10650	OprD-, AmpC+, MexAB+, PDC-37	16	16/4	16	16/8	2/4	16	8/4	>16	16/8	4
23.10848	OprD-, AmpC++, PDC-34	>16	>16/4	>16	>16/8	>16/4	8	2/4	>16	16/8	0.5
23.11092	OprD-, AmpC++, PDC-5	>16	>16/4	>16	16/8	8/4	16	16/4	16	16/8	2
23.10483	OprD-, AmpC++, PDC-35	>16	16/4	>16	>16/8	8/4	16	8/4	>16	>16/8	1
22.9871	AmpC+, PDC-67	16	2/4	8	2/8	1/4	0.5	≤0.25/4	≤0.25	≤0.25/8	0.5
22.9809	AmpC+, PDC-30	>16	8/4	16	16/8	4/4	8	1/4	4	4/8	1
22.10326	OprD-, AmpC+, PDC-346 (ESAC)	>16	>16/4	>16	>16/8	>16/4	16	16/4	>16	>16/8	>32
22.9481	OprD-, AmpC+, PDC-511 (ESAC)	>16	>16/4	>16	>16/8	8/4	16	2/4	16	16/8	8
23.10568	AmpC+, PDC-553 (ESAC)	>16	16/4	8	8/8	>16/4	0.5	0.5/4	2	2/8	0.5
23.10885	AmpC+, PDC-562 (ESAC)	>16	2/4	>16	>16/8	4/4	≤0.25	≤0.25/4	≤0.25	≤0.25/8	2
23.10653	AmpC+, PDC-558 (ESAC)	>16	>16/4	>16	16/8	>16/4	1	1/4	16	8/8	2
23.10715	AmpC+, PDC-559 (ESAC)	>16	4/4	>16	>16/8	4/4	0.5	0.5/4	0.5	0.5/8	2
23.10828	OprD-, AmpC+, PDC-561 (ESAC)	>16	≤0.25/4	>16	2/8	2/4	4	1/4	0.5	≤0.25/8	0.25
22.10251	OprD-, AmpC+, PDC-534 (ESAC)	>16	16/4	>16	16/8	>16/4	8	4/4	8	4/8	4
22.9556	PAC-1, OXA-10, OprD-, PDC-98	>16	>16/4	>16	>16/8	>16/4	>16	>16/4	>16	>16/8	16
19.6881	OXA-2, OprD-, PDC-35	>16	16/4	>16	>16/8	2/4	16	8/4	>16	>16/8	0.5
19.6796	OXA-1, PDC-14	16	16/4	>16	>16/8	2/4	16	8/4	>16	>16/8	0.12
22.9883	MexYX+, OprD-, AmpC+, PDC-19a	>16	4/4	16	16/8	4/4	>16	4/4	8	8/8	0.5
23.10588	MexYX+, PDC-19a	2	2/4	8	8/8	1/4	1	0.5/4	≤0.25	≤0.25/8	0.06
23.10638	MexYX+,OprD-, AmpC+, PDC-1	>16	8/4	16	16/8	8/4	16	2/4	8	4/8	1
23.10860	MexAB+, OprD-, PDC-568	>16	0.5/4	16	8/8	4/4	16	4/4	8	4/8	0.12
23.10874	MexAB+, OprD-, AmpC+, PDC-8	>16	>16/4	>16	16/8	4/4	>16	8/4	>16	>16/8	0.5
23.10877	MexAB+, OprD-, AmpC+, PDC-3	>16	>16/4	>16	>16/8	16/4	>16	8/4	>16	>16/8	0.5
15.2986	CTX-M-3, OprD-, AmpC+, PDC-1	>16	8/4	>16	8/8	>16/4	16	2/4	16	16/8	0.5
21.8794	CTX-M-15, OXA-1, OprD-, PDC-11	>16	4/4	>16	4/8	8/4	16	2/4	8	8/8	1

Céfépime-enmétazobactam / *P. aeruginosa*

Céfépime-zidebactam

Zidebactam

J Antimicrob Chemother 2017; **72**: 1696–1703
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Journal of Antimicrobial Chemotherapy

WCK 5222 (cefepime/zidebactam) antimicrobial activity tested against Gram-negative organisms producing clinically relevant β-lactamases

Helio S. Sader*, Paul R. Rhomberg, Robert K. Flamm, Ronald N. Jones and Mariana Castanheira

Multiple activities :

- **β-lactamase inhibitor (Ambler class A, AmpC)**
- **Direct antibacterial (PBP2 binding,** such as mecillinam)
- **Enhancer effect with PBP3-targeting β-lactams (e.g. cefepime)**
- Inactive on Proteae

Céfépime-Zidebactam

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Table 3. Cumulative frequency distribution of cefepime, cefepime/zidebactam at 2:1 and 1:1 ratios and zidebactam MIC results when tested against β-lactamase-producing Enterobacteriaceae strains

		No. of isolates (cumulative %) inhibited at MIC (mg/L) of:						S		R						
Organism group/ antimicrobial agent	*n*	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128	MIC_{50}	MIC_{90}
CTX-M-15-producing strains[a]																
cefepime	21	—	—	—	—	—	—	—	—	—	2 (9.5)	4 (28.6)	2 (38.1)	13 (100.0)	>128	>128
cefepime/zidebactam (2:1)	21	—	—	3 (14.3)	12 (71.4)	3 (85.7)	1 (90.5)	1 (95.2)	1 (100.0)	—	—	—	—	—	0.5	2
cefepime/zidebactam (1:1)	21	—	6 (28.6)	8 (66.7)	4 (85.7)	1 (90.5)	1 (95.2)	1 (100.0)	—	—	—	—	—	—	0.25	1
zidebactam	21	—	2 (9.5)	9 (52.4)	4 (71.4)	2 (81.0)	1 (85.7)	0 (85.7)	0 (85.7)	0 (85.7)	0 (85.7)	1 (90.5)	0 (90.5)	2 (100.0)	0.25	64
SHV-producing strains[b]																
cefepime	20	0 (0.0)	1 (5.0)	2 (15.0)	1 (20.0)	2 (30.0)	4 (50.0)	5 (75.0)	3 (90.0)	2 (100.0)	—	—	—	—	2	8
cefepime/zidebactam (2:1)	20	2 (10.0)	6 (40.0)	10 (90.0)	1 (95.0)	0 (95.0)	1 (100.0)	—	—	—	—	—	—	—	0.25	0.25
cefepime/zidebactam (1:1)	20	4 (20.0)	10 (70.0)	5 (95.0)	0 (95.0)	1 (100.0)	—	—	—	—	—	—	—	—	0.12	0.25
zidebactam	20	0 (0.0)	8 (40.0)	2 (50.0)	0 (50.0)	0 (50.0)	0 (50.0)	0 (50.0)	0 (50.0)	0 (50.0)	1 (55.0)	0 (55.0)	0 (55.0)	9 (100.0)	0.25	>128
Strains producing other ESBLs[c]																
cefepime	20	—	—	1 (5.0)	2 (15.0)	2 (25.0)	4 (45.0)	2 (55.0)	3 (70.0)	2 (80.0)	1 (85.0)	1 (90.0)	2 (100.0)	—	4	64
cefepime/zidebactam (2:1)	20	—	3 (15.0)	9 (60.0)	3 (75.0)	4 (95.0)	1 (100.0)	—	—	—	—	—	—	—	0.25	1
cefepime/zidebactam (1:1)	20	1 (5.0)	8 (45.0)	6 (75.0)	2 (85.0)	3 (100.0)	—	—	—	—	—	—	—	—	0.25	1
zidebactam	20	—	3 (15.0)	1 (20.0)	2 (30.0)	2 (40.0)	0 (40.0)	1 (45.0)	0 (45.0)	0 (45.0)	0 (45.0)	1 (50.0)	1 (55.0)	9 (100.0)	64	>128
Plasmidic AmpC-producing strains[d]																
cefepime	10	0 (0.0)	1 (10.0)	5 (60.0)	4 (100.0)	—	—	—	—	—	—	—	—	—	0.25	0.5
cefepime/zidebactam (2:1)	10	6 (60.0)	3 (90.0)	1 (100.0)	—	—	—	—	—	—	—	—	—	—	≤0.06	0.12
cefepime/zidebactam (1:1)	10	9 (90.0)	1 (100.0)	—	—	—	—	—	—	—	—	—	—	—	≤0.06	≤0.06
zidebactam	10	1 (10.0)	2 (30.0)	5 (80.0)	0 (80.0)	0 (80.0)	0 (80.0)	0 (80.0)	0 (80.0)	1 (90.0)	1 (100.0)	—	—	—	0.25	16
Derepressed AmpC-producing strains[e]																
cefepime	23	1 (4.3)	2 (13.0)	0 (13.0)	5 (34.8)	4 (52.2)	0 (52.2)	3 (65.2)	5 (87.0)	1 (91.3)	2 (100.0)	—	—	—	1	16
cefepime/zidebactam (2:1)	23	3 (13.0)	5 (34.8)	6 (60.9)	6 (87.0)	2 (95.7)	1 (100.0)	—	—	—	—	—	—	—	0.25	1
cefepime/zidebactam (1:1)	23	6 (26.1)	9 (65.2)	4 (82.6)	2 (91.3)	2 (100.0)	—	—	—	—	—	—	—	—	0.12	0.5
zidebactam	23	—	5 (21.7)	3 (34.8)	3 (47.8)	0 (47.8)	2 (56.5)	0 (56.5)	0 (56.5)	1 (60.9)	0 (60.9)	0 (60.9)	0 (60.9)	9 (100.0)	2	>128

Zidebactam = inhibiteur efficace des BLSE (CTX-M +++, SHV et autres) mais également activité intrinsèque

Céfépime-Zidebactam

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Table 3. Cumulative frequency distribution of cefepime, cefepime/zidebactam at 2:1 and 1:1 ratios and zidebactam MIC results when tested against β-lactamase-producing Enterobacteriaceae strains

		No. of isolates (cumulative %) inhibited at MIC (mg/L) of:						S		R						
Organism group/ antimicrobial agent	*n*	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128	MIC_{50}	MIC_{90}
CTX-M-15-producing strains[a]																
cefepime	21	—	—	—	—	—	—	—	—	—	2 (9.5)	4 (28.6)	2 (38.1)	13 (100.0)	>128	>128
cefepime/zidebactam (2:1)	21	—	—	3 (14.3)	12 (71.4)	3 (85.7)	1 (90.5)	1 (95.2)	1 (100.0)	—	—	—	—	—	0.5	2
cefepime/zidebactam (1:1)	21	—	6 (28.6)	8 (66.7)	4 (85.7)	1 (90.5)	1 (95.2)	1 (100.0)	—	—	—	—	—	—	0.25	1
zidebactam	21	—	2 (9.5)	9 (52.4)	4 (71.4)	2 (81.0)	1 (85.7)	0 (85.7)	0 (85.7)	0 (85.7)	0 (85.7)	1 (90.5)	0 (90.5)	2 (100.0)	0.25	64
SHV-producing strains[b]																
cefepime	20	0 (0.0)	1 (5.0)	2 (15.0)	1 (20.0)	2 (30.0)	4 (50.0)	5 (75.0)	3 (90.0)	2 (100.0)	—	—	—	—	2	8
cefepime/zidebactam (2:1)	20	2 (10.0)	6 (40.0)	10 (90.0)	1 (95.0)	0 (95.0)	1 (100.0)	—	—	—	—	—	—	—	0.25	0.25
cefepime/zidebactam (1:1)	20	4 (20.0)	10 (70.0)	5 (95.0)	0 (95.0)	1 (100.0)	—	—	—	—	—	—	—	—	0.12	0.25
zidebactam	20	0 (0.0)	8 (40.0)	2 (50.0)	0 (50.0)	0 (50.0)	0 (50.0)	0 (50.0)	0 (50.0)	0 (50.0)	1 (55.0)	0 (55.0)	0 (55.0)	9 (100.0)	0.25	>128
Strains producing other ESBLs[c]																
cefepime	20	—	—	1 (5.0)	2 (15.0)	2 (25.0)	4 (45.0)	2 (55.0)	3 (70.0)	2 (80.0)	1 (85.0)	1 (90.0)	2 (100.0)	—	4	64
cefepime/zidebactam (2:1)	20	—	3 (15.0)	9 (60.0)	3 (75.0)	4 (95.0)	1 (100.0)	—	—	—	—	—	—	—	0.25	1
cefepime/zidebactam (1:1)	20	1 (5.0)	8 (45.0)	6 (75.0)	2 (85.0)	3 (100.0)	—	—	—	—	—	—	—	—	0.25	1
zidebactam	20	—	3 (15.0)	1 (20.0)	2 (30.0)	2 (40.0)	0 (40.0)	1 (45.0)	0 (45.0)	0 (45.0)	0 (45.0)	1 (50.0)	1 (55.0)	9 (100.0)	64	>128
Plasmidic AmpC-producing strains[d]																
cefepime	10	0 (0.0)	1 (10.0)	5 (60.0)	4 (100.0)	—	—	—	—	—	—	—	—	—	0.25	0.5
cefepime/zidebactam (2:1)	10	6 (60.0)	3 (90.0)	1 (100.0)	—	—	—	—	—	—	—	—	—	—	≤0.06	0.12
cefepime/zidebactam (1:1)	10	9 (90.0)	1 (100.0)	—	—	—	—	—	—	—	—	—	—	—	≤0.06	≤0.06
zidebactam	10	1 (10.0)	2 (30.0)	5 (80.0)	0 (80.0)	0 (80.0)	0 (80.0)	0 (80.0)	0 (80.0)	1 (90.0)	1 (100.0)	—	—	—	0.25	16
Derepressed AmpC-producing strains[e]																
cefepime	23	1 (4.3)	2 (13.0)	0 (13.0)	5 (34.8)	4 (52.2)	0 (52.2)	3 (65.2)	5 (87.0)	1 (91.3)	2 (100.0)	—	—	—	1	16
cefepime/zidebactam (2:1)	23	3 (13.0)	5 (34.8)	6 (60.9)	6 (87.0)	2 (95.7)	1 (100.0)	—	—	—	—	—	—	—	0.25	1
cefepime/zidebactam (1:1)	23	6 (26.1)	9 (65.2)	4 (82.6)	2 (91.3)	2 (100.0)	—	—	—	—	—	—	—	—	0.12	0.5
zidebactam	23	—	5 (21.7)	3 (34.8)	3 (47.8)	0 (47.8)	2 (56.5)	0 (56.5)	0 (56.5)	1 (60.9)	0 (60.9)	0 (60.9)	0 (60.9)	9 (100.0)	2	>128

Céfépime est déjà efficace sur les AmpC mais gain de CMI sur les AmpC déréprimées + imperméabilité

Cefepime-Zidebactam

J Antimicrob Chemother 2017; **72**: 1696–1703
doi:10.1093/jac/dkx050 Advance Access publication 18 March 2017

Journal of Antimicrobial Chemotherapy

WCK 5222 (cefepime/zidebactam) antimicrobial activity tested against Gram-negative organisms producing clinically relevant β-lactamases

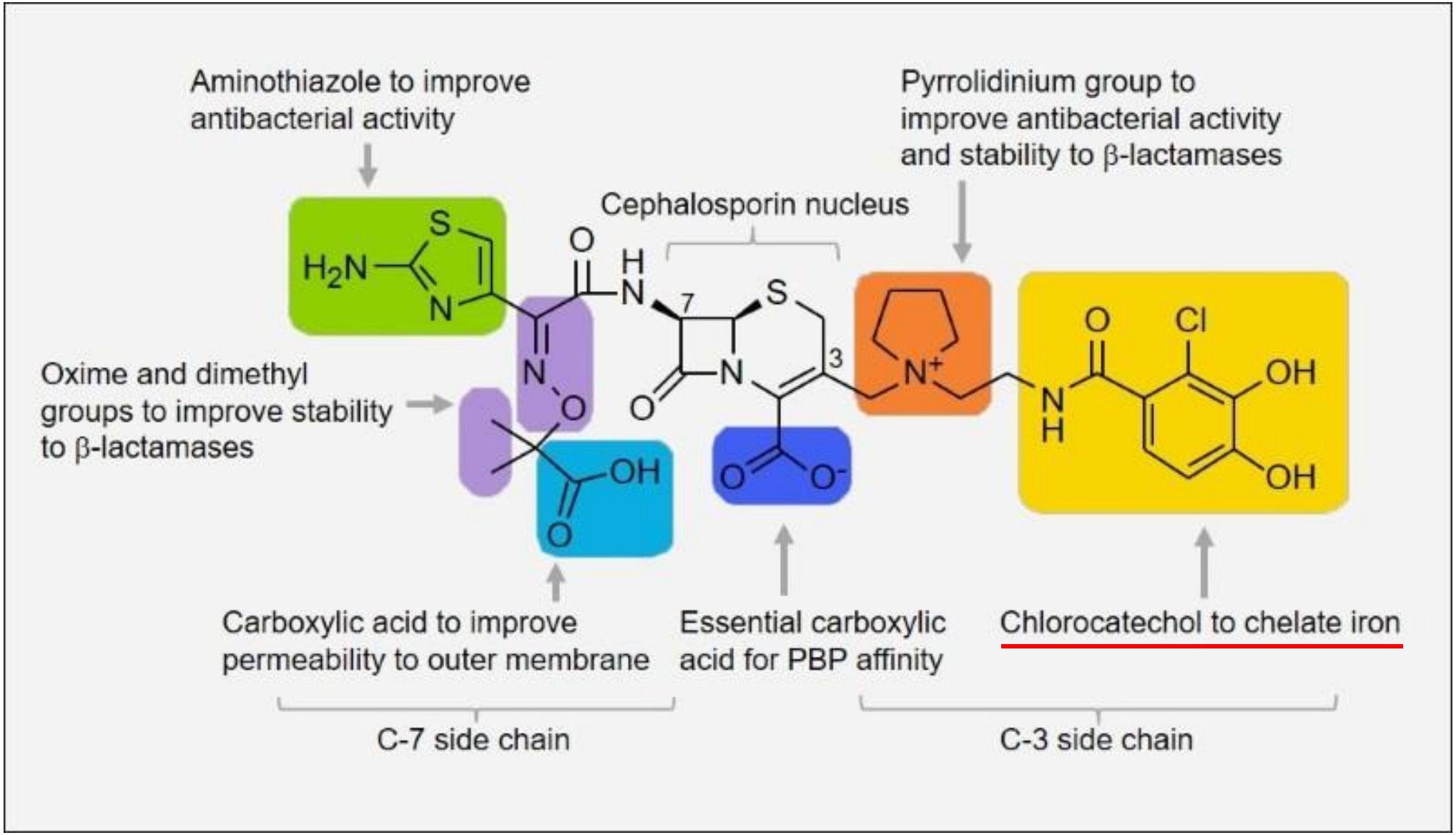
Helio S. Sader*, Paul R. Rhomberg, Robert K. Flamm, Ronald N. Jones and Mariana Castanheira

Actif sur KPC, OXA-48, MBL (*via* son activité directe sur PLP2)

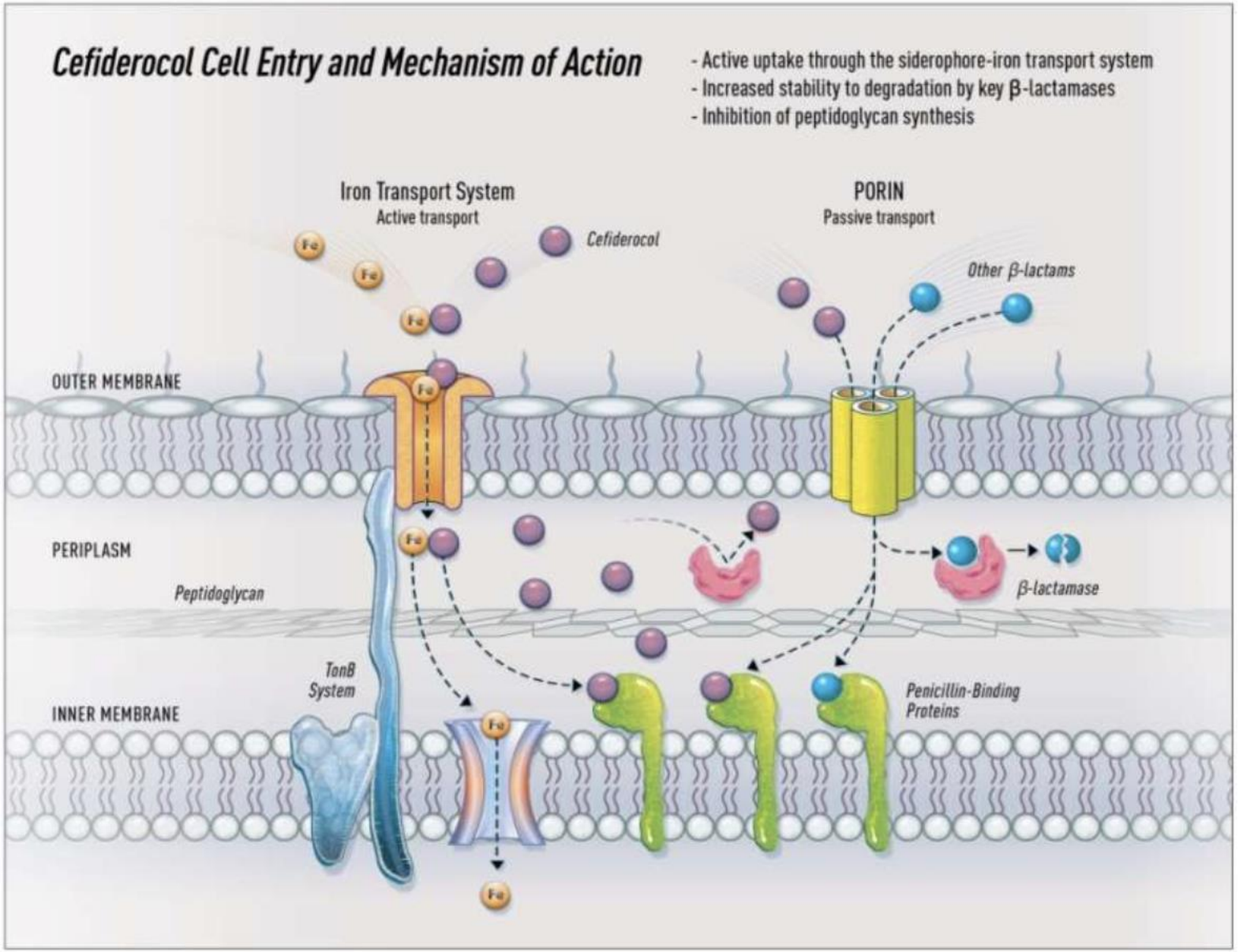
Table 3. Cumulative frequency distribution of cefepime, cefepime/zidebactam at 2:1 and 1:1 ratios and zidebactam MIC results when tested against β-lactamase-producing Enterobacteriaceae strains

		No. of isolates (cumulative %) inhibited at MIC (mg/L) of:														
Organism group/ antimicrobial agent	*n*	≤0.06	0.12	0.25	0.5	1	2	S 4	R 8	16	32	64	128	>128	MIC_{50}	MIC_{90}
KPC-producing strains[f]																
cefepime	35	—	—	—	—	—	2 (5.7)	5 (20.0)	2 (25.7)	5 (40.0)	5 (54.3)	3 (62.9)	3 (71.4)	10 (100.0)	32	>128
cefepime/zidebactam (2:1)	35	—	—	8 (22.9)	14 (62.9)	7 (82.9)	5 (97.1)	1 (100.0)	—	—	—	—	—	—	0.5	2
cefepime/zidebactam (1:1)	35	—	7 (20.0)	12 (54.3)	11 (85.7)	4 (97.1)	1 (100.0)	—	—	—	—	—	—	—	0.25	1
zidebactam	35	—	1 (2.9)	7 (22.9)	3 (31.4)	5 (45.7)	1 (48.6)	1 (51.4)	0 (51.4)	3 (60.0)	1 (62.9)	1 (65.7)	1 (68.6)	11 (100.0)	4	>128
MBL-producing strains[g]																
cefepime	20	—	—	—	—	—	—	—	1 (5.0)	0 (5.0)	2 (15.0)	2 (25.0)	1 (30.0)	14 (100.0)	>128	>128
cefepime/zidebactam (2:1)	20	—	—	2 (10.0)	5 (35.0)	6 (65.0)	2 (75.0)	0 (75.0)	2 (85.0)	1 (90.0)	2 (100.0)	—	—	—	1	16
cefepime/zidebactam (1:1)	20	—	1 (5.0)	6 (35.0)	3 (50.0)	1 (55.0)	4 (75.0)	1 (80.0)	2 (90.0)	1 (95.0)	1 (100.0)	—	—	—	0.5	8
zidebactam	20	—	1 (5.0)	4 (25.0)	5 (50.0)	1 (55.0)	0 (55.0)	1 (60.0)	0 (60.0)	0 (60.0)	0 (60.0)	0 (60.0)	0 (60.0)	8 (100.0)	0.5	>128

Céfidérocol : Le cheval de Troie



Céfidérocol : Le cheval de Troie



Céfidérocol / Enterobacterales

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SUSCEPTIBILITY

In Vitro Activity of the Siderophore Cephalosporin, Cefiderocol, against Carbapenem-Nonsusceptible and Multidrug-Resistant Isolates of Gram-Negative Bacilli Collected Worldwide in 2014 to 2016

Meredith A. Hackel,[a] Masakatsu Tsuji,[b] Yoshinori Yamano,[c] Roger Echols,[d] James A. Karlowsky,[e] Daniel F. Sahm[a]

Actif sur toutes les EPC y compris les MBLs

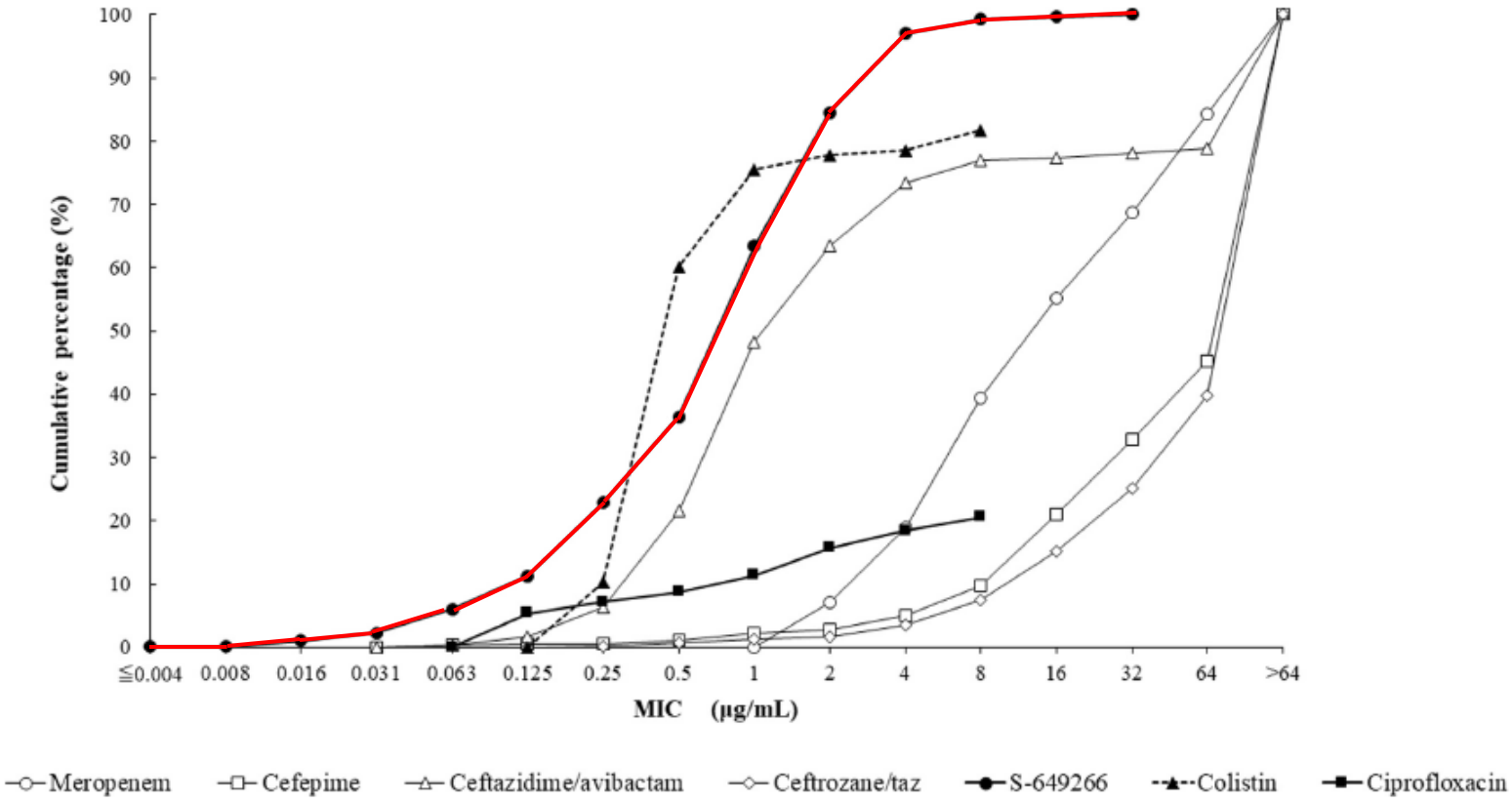


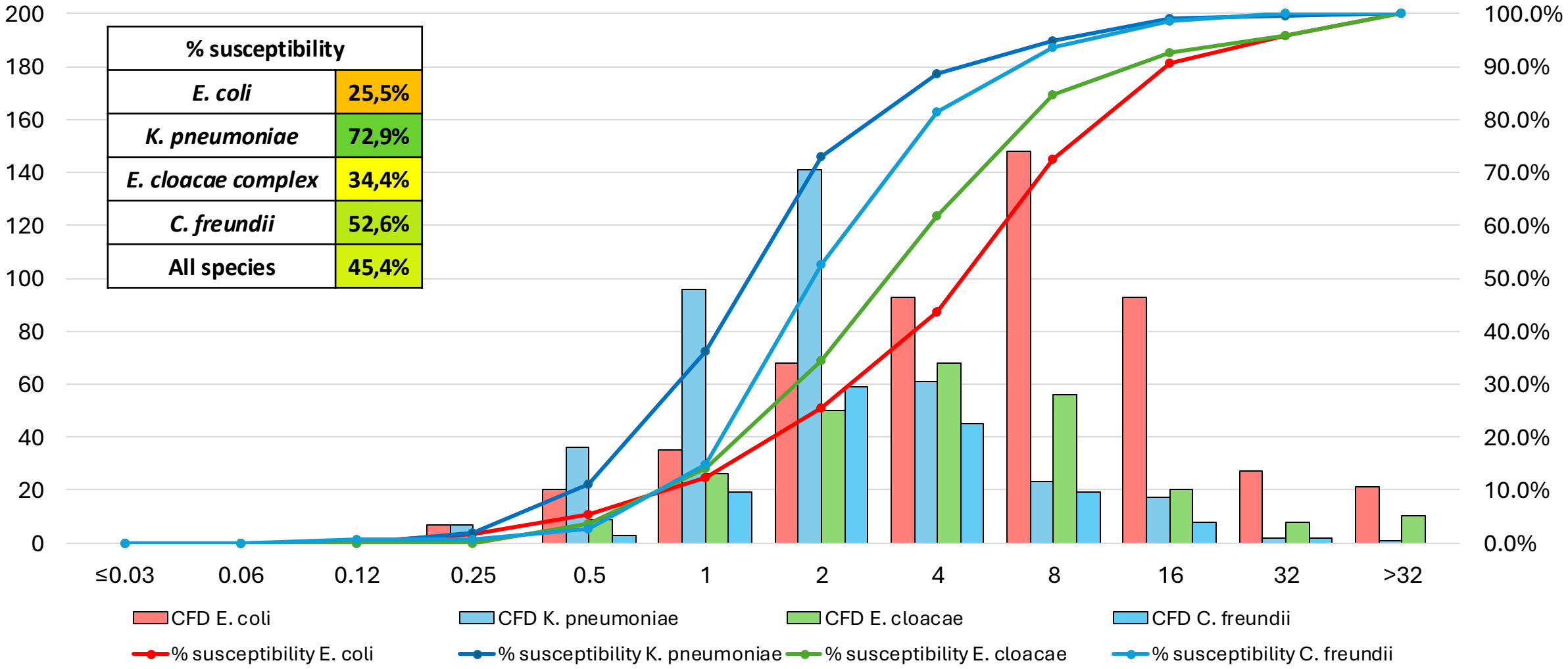
FIG 1 Cumulative cefiderocol MIC distribution (percentage of isolates) for 1,022 isolates of meropenem-nonsusceptible *Enterobacteriaceae*.

NDM

Céfidérocol / Espèce

CNR RÉSISTANCE AUX ANTIBIOTIQUES

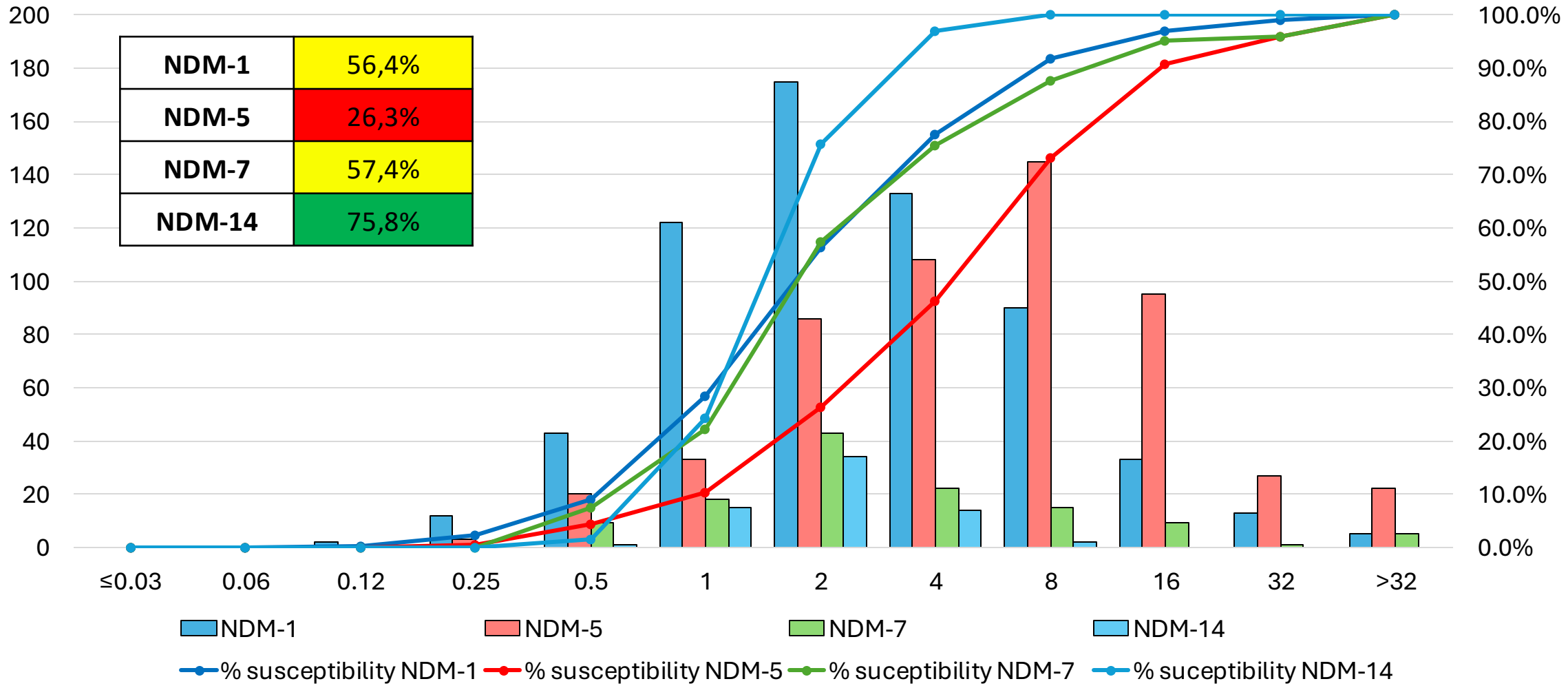
2023



NDM

Céfidérocol / NDM variant

2023



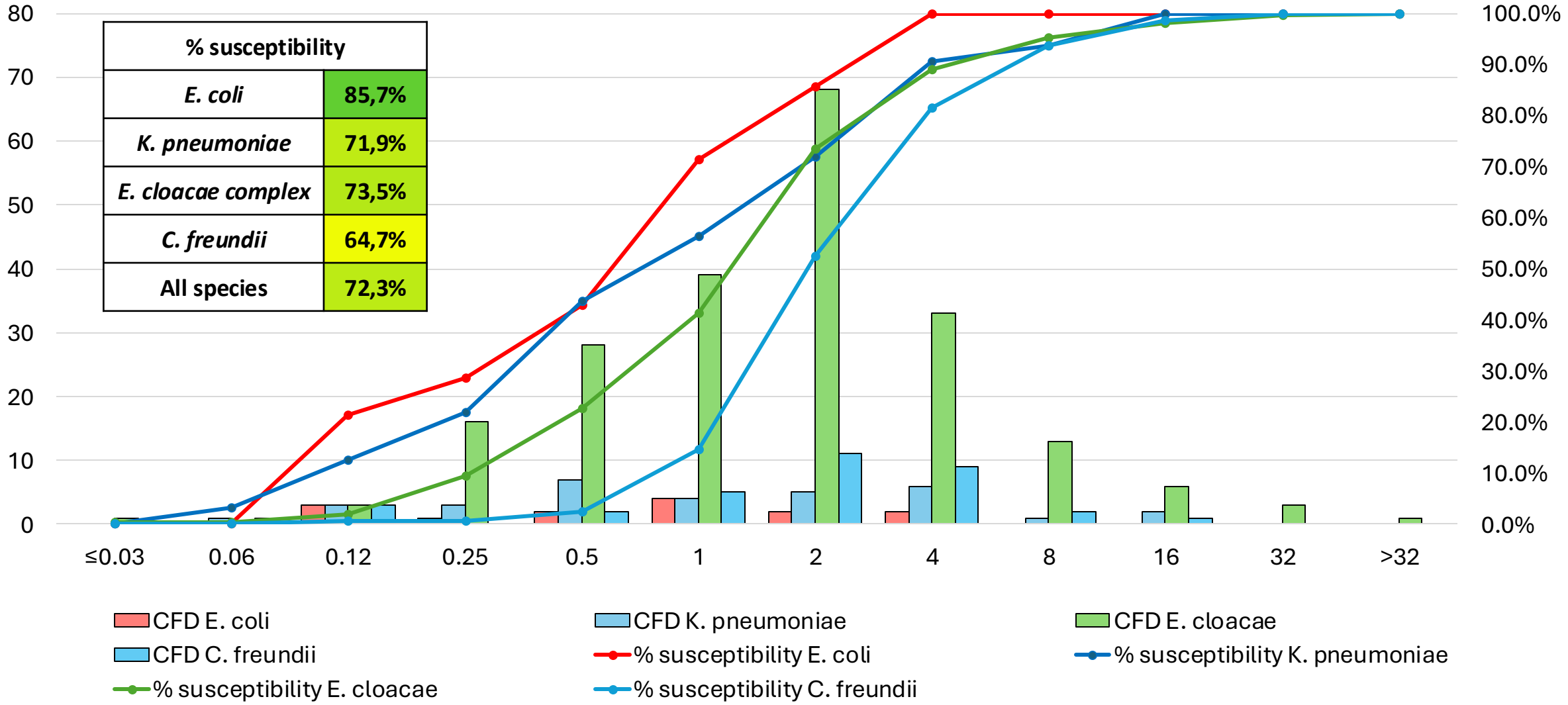
VIM

CNR RÉSISTANCE AUX ANTIBIOTIQUES

Céfidérocol / Espèce

2023

% susceptibility	
E. coli	85,7%
K. pneumoniae	71,9%
E. cloacae complex	73,5%
C. freundii	64,7%
All species	72,3%



Céfidérocol / *P. aeruginosa*

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Très bonne activité sur *P. aeruginosa*

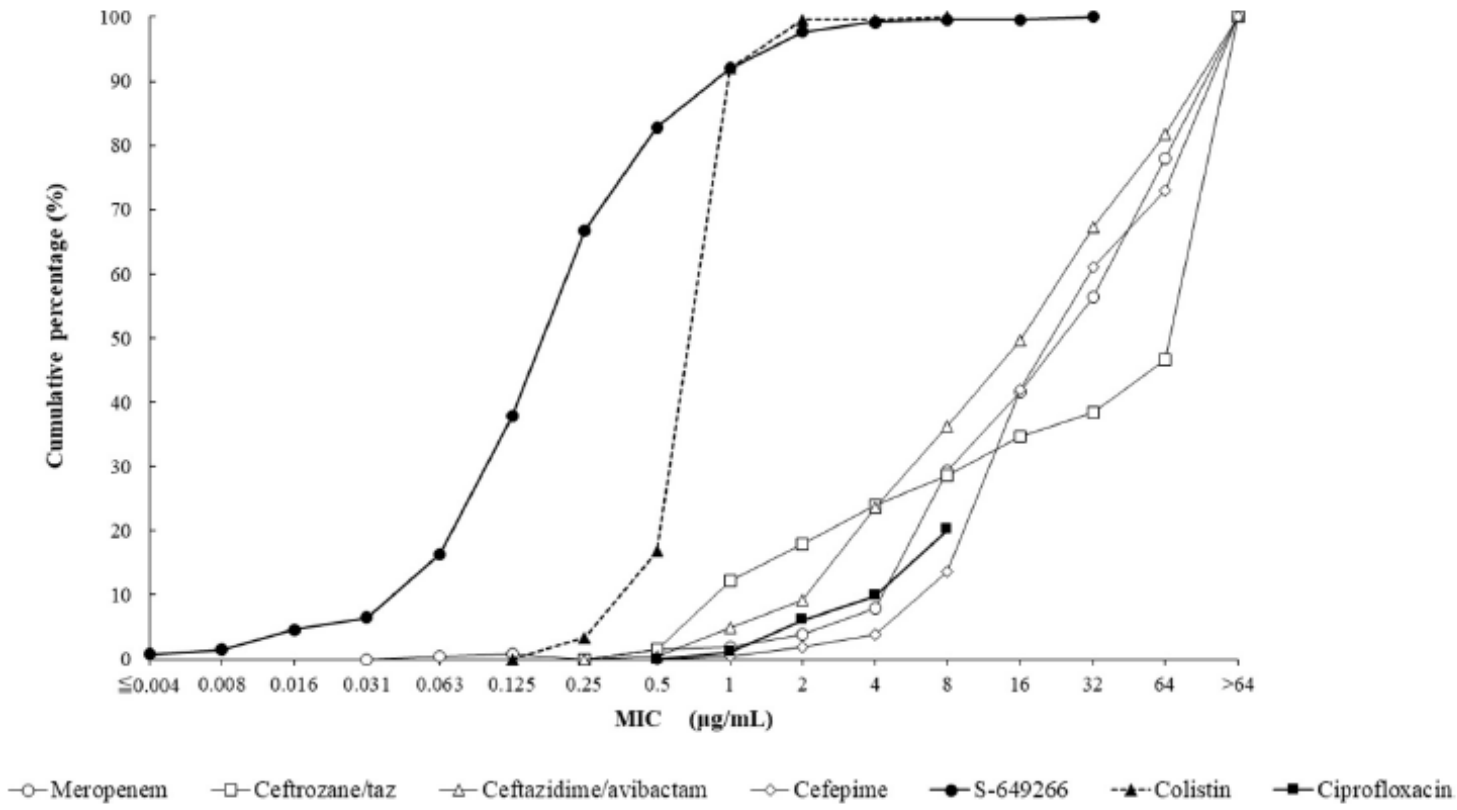
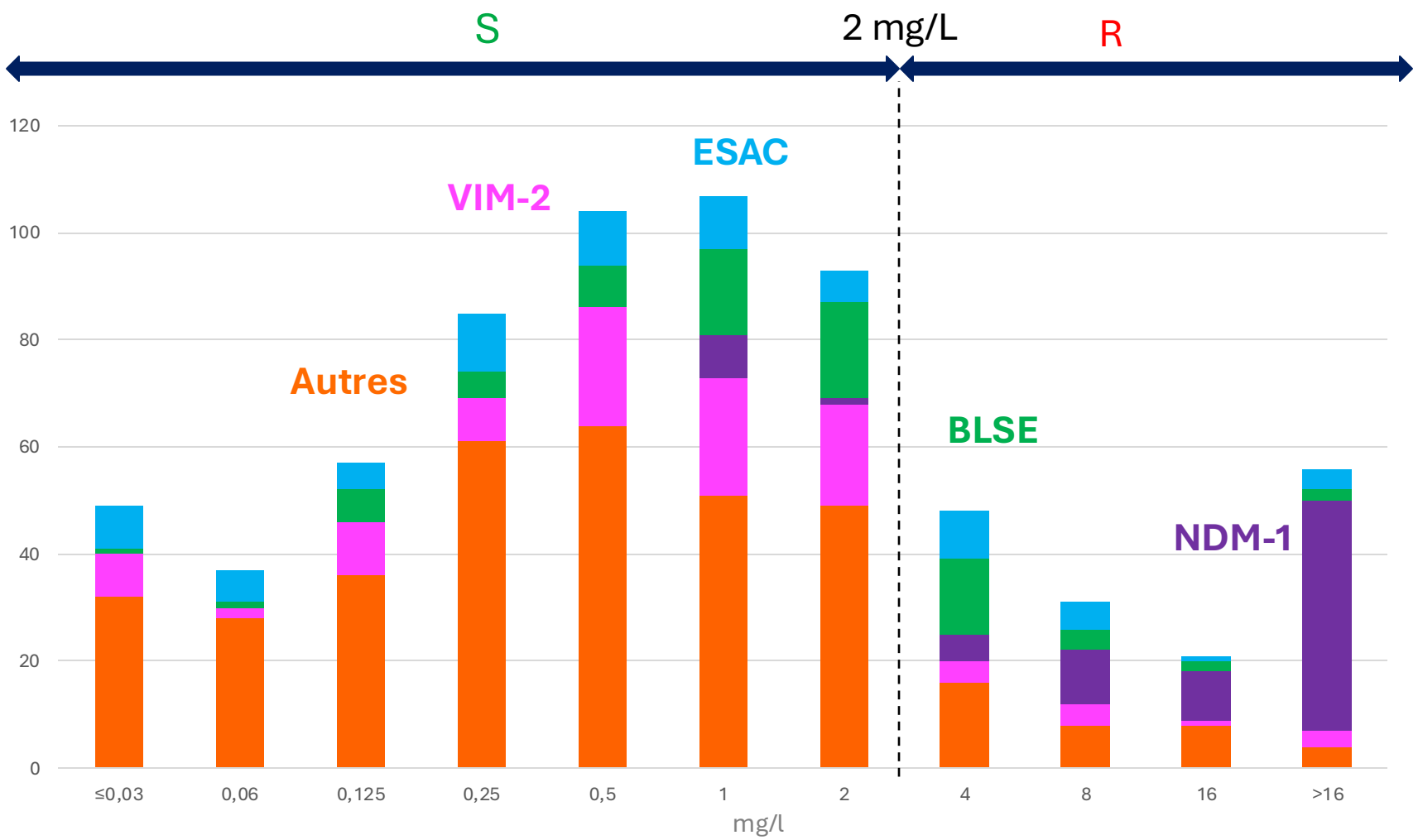


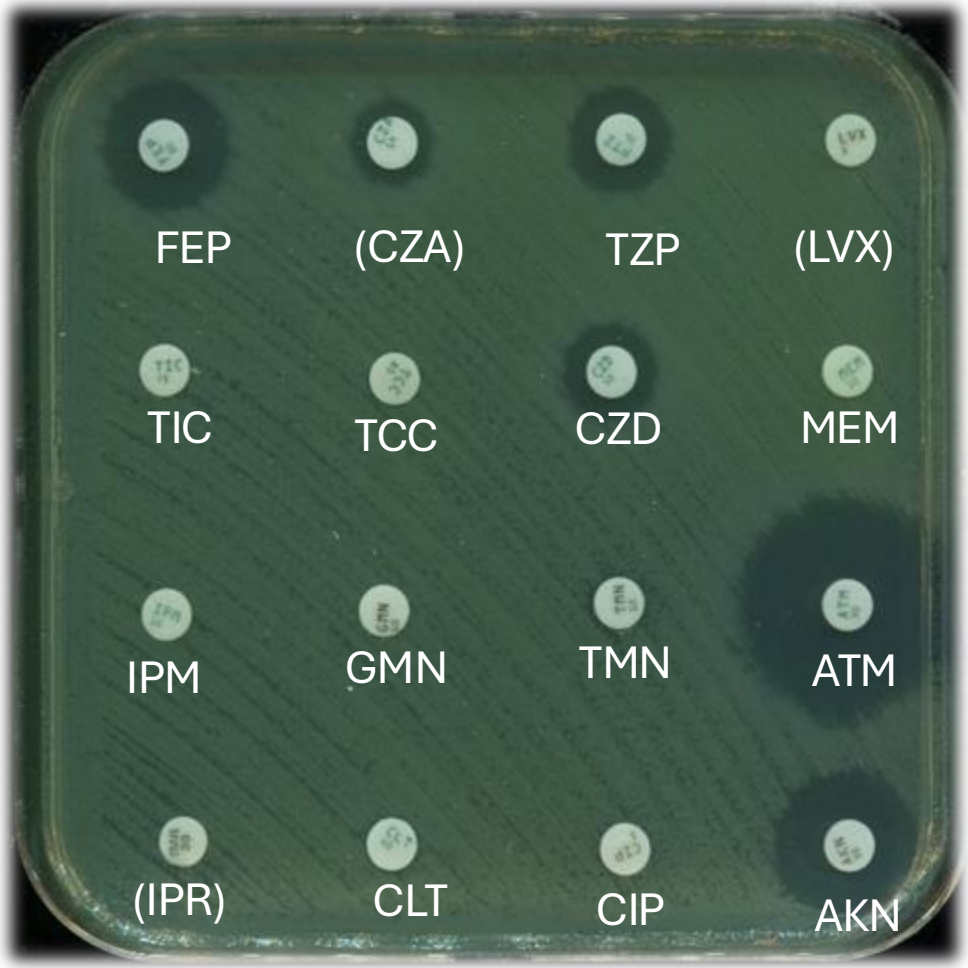
FIG 5 Cumulative cefiderocol MIC distribution (percentage of isolates) for 262 isolates of MDR *P. aeruginosa*.

Céfidérocol / *P. aeruginosa*

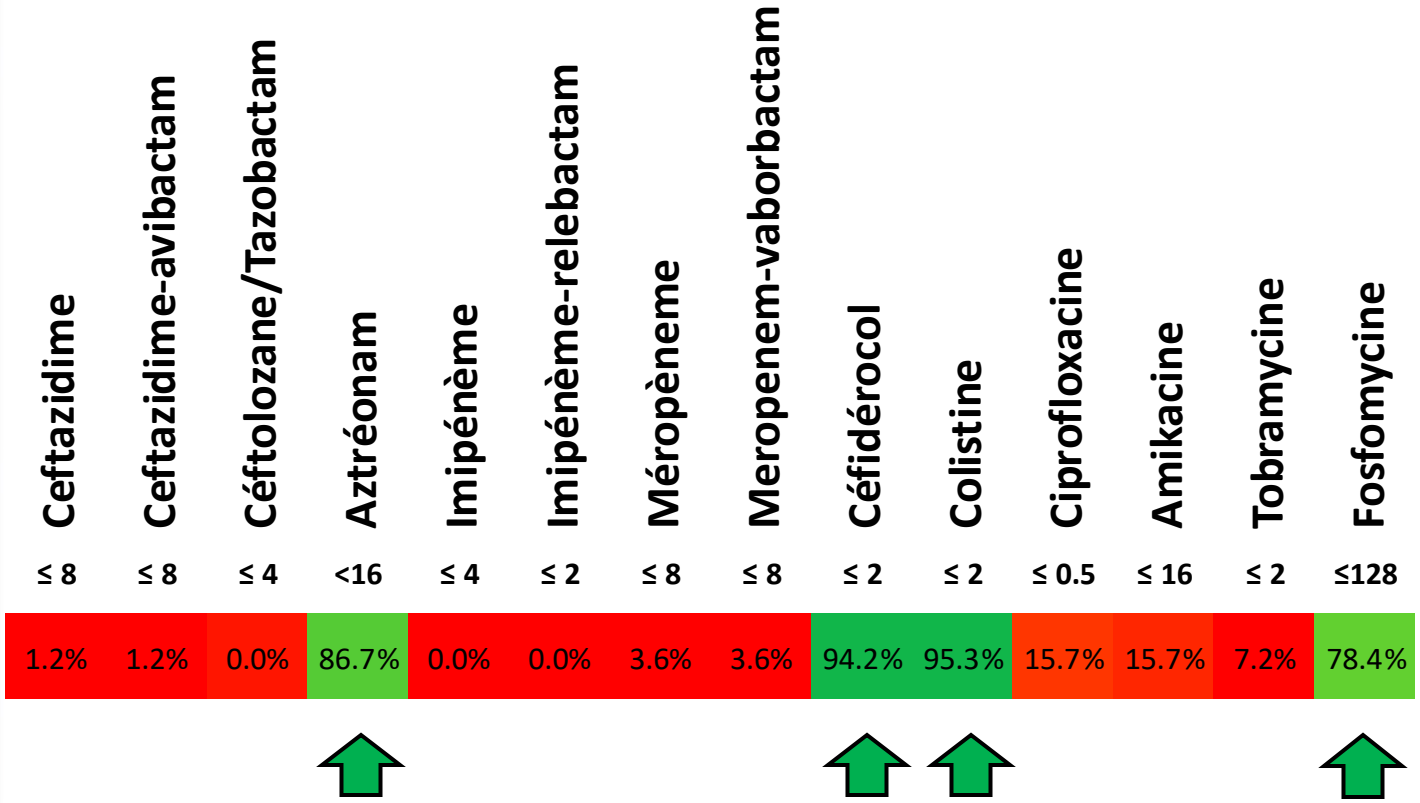


n=678 souches

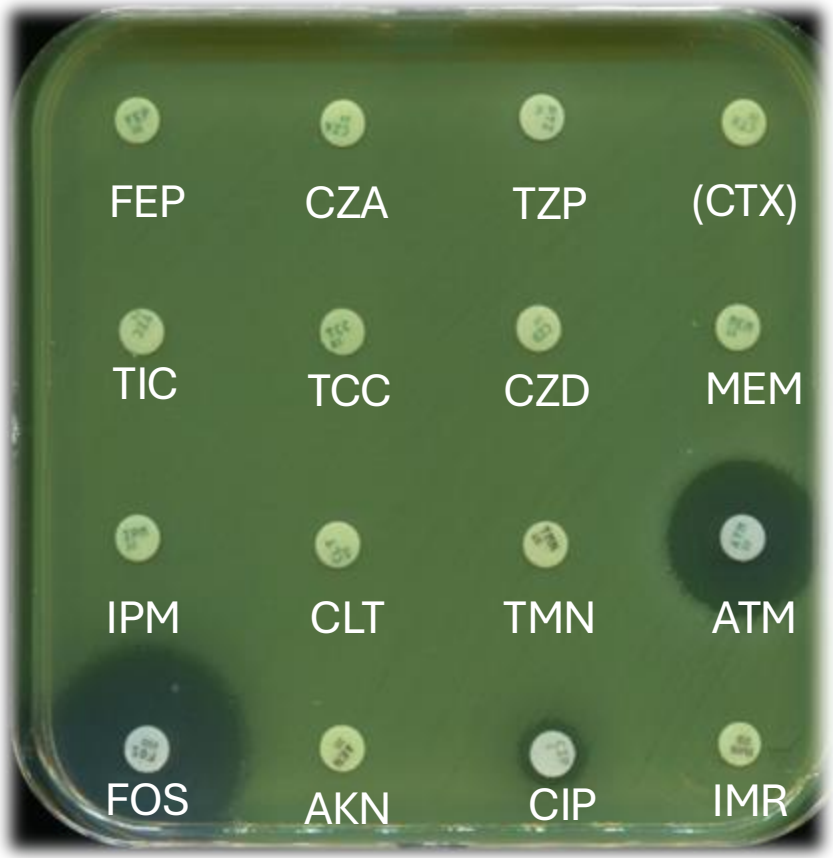
Sensibilité des souches de *P. aeruginosa* productrices de l'enzyme VIM-

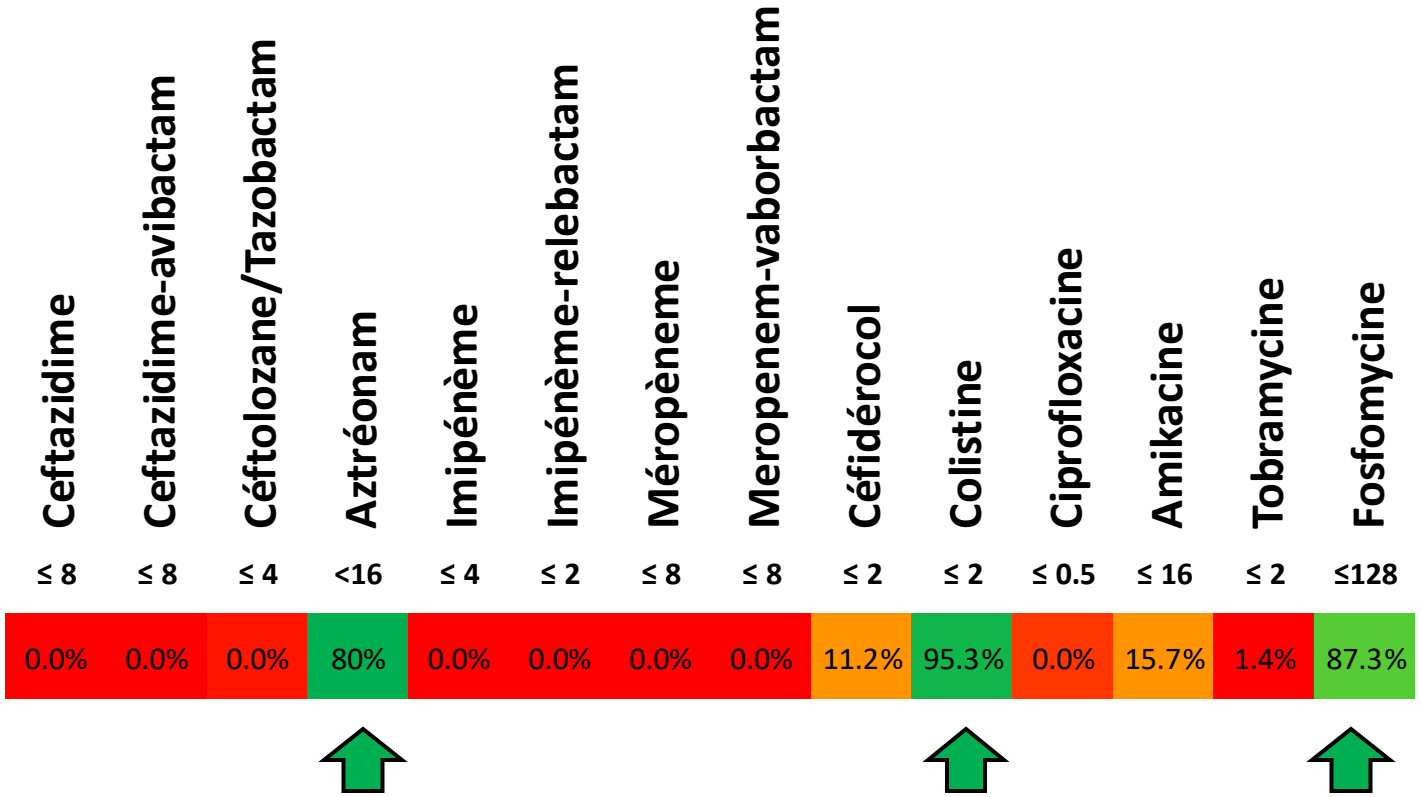


VIM-2



Sensibilité des souches productrices de l'enzyme NDM-





Résumé : Enterobacterales

	Ceftazidime Céfépime	Aztréonam	Carbapénème	Ceftazidime / avibactam	Imipénème / relebactam	Méropénème / vaborbactam	Céfidérocol	Aztréonam / avibactam
KPC				1ère intention	1ère intention	1ère intention	2ème intention	3ème intention
MBL		1ère intention					2ème intention	2ème intention
MBL + BLSE							1ère intention	1ère intention
OXA-48 seul	1ère intention	1ère intention					2ème intention	3ème intention
OXA-48 + BLSE				1ère intention			2ème intention	3ème intention
Non EPC			1ère intention	1ère intention	1ère intention	1ère intention	2ème intention	3ème intention

Disques	✓	✓	✓	✓	✓	**ND**	✗	**ND**
ATB automatisé	✓	✓	✓	✓	✓	✓	**ND**	**ND**
Bandelette CMI	✓	✓	✓	✓	✓	✓	✗	✓
CMI microdilution	✓	✓	✓	✓	✓	✓	✓	✓

https://www.cnr-resistance-antibiotiques.fr/ressources/actualite/lien_CNR_cefiderocol.pdf

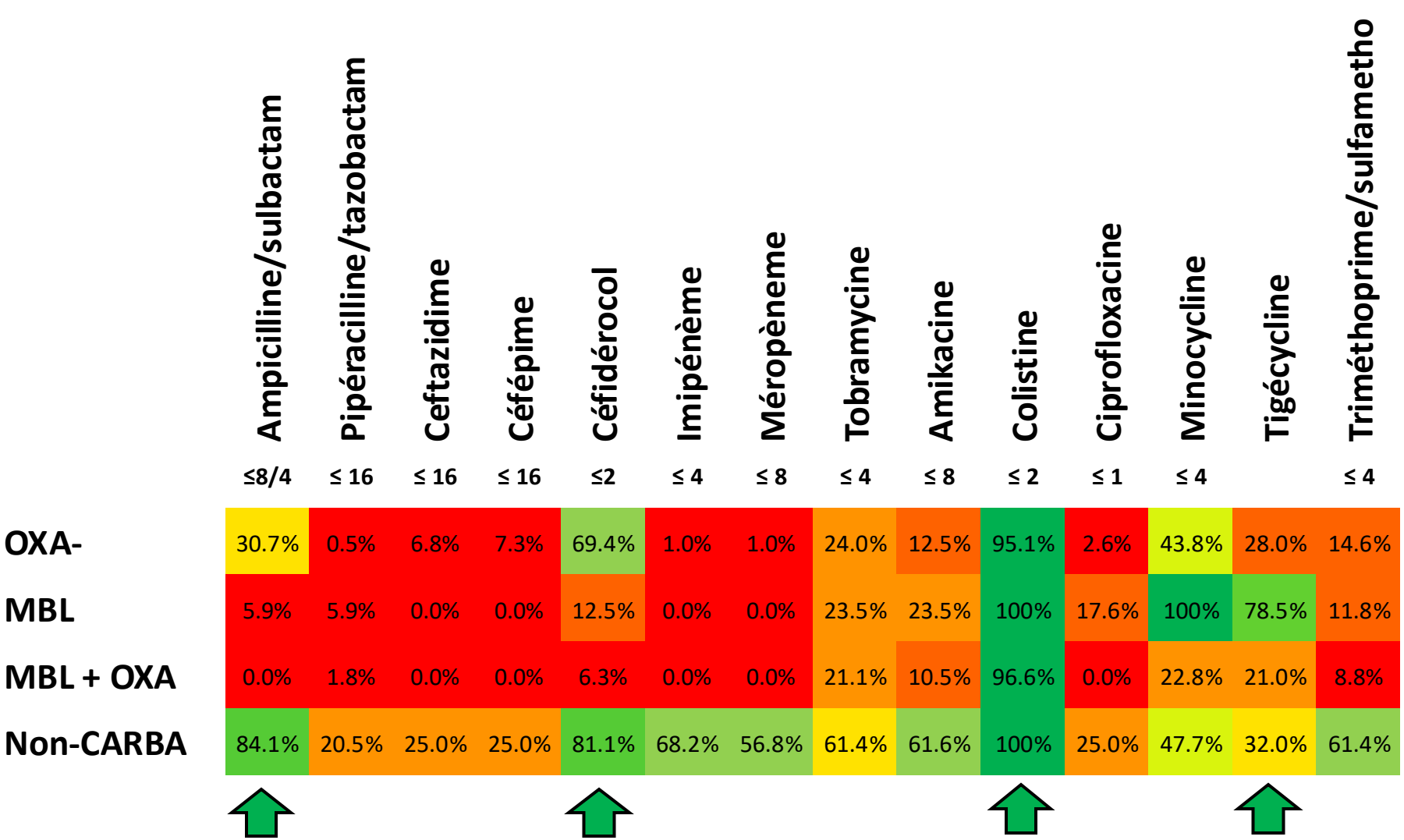
Résumé: *Pseudomonas aeruginosa*

	Ceftolozane/ tazobactam	Ceftazidime / avibactam	Aztréonam	Méropénème	Imipénème / relebactam	Céfidérocol	Colistine	Fosfomycine
OprD + AmpC	1ère intention	1ère intention		1ère intention	1ère intention	2ème intention	3ème intention	3ème intention
PDC variant + OprD		1ère intention		1ère intention	1ère intention	2ème intention	3ème intention	3ème intention
BLSE + OprD		1ère intention (A)		1ère intention	1ère intention	2ème intention	3ème intention	3ème intention
MBL			1ère intention			1ère intention	1ère intention	1ère intention

Disques	✓	✓	✓	✓	✓	**Screening**	✗	✓
Bandelette CMI	✓	✓	✓	✓	✓	✗	✗	✓

Le problème *Acinetobacter*

Sensibilité de *A. baumannii* selon les mécanismes de résistance



Minocycline
CA-SFM/CLSI (c)
CMI S≤ 0.001, R >4 mg/L

Tigécycline
CA-SFM
PK/PD, S≤0.5 mg/L

Triméthoprime/
sulfametoxazol
EUCAST
CMI S≤ 2, R >4 mg/L

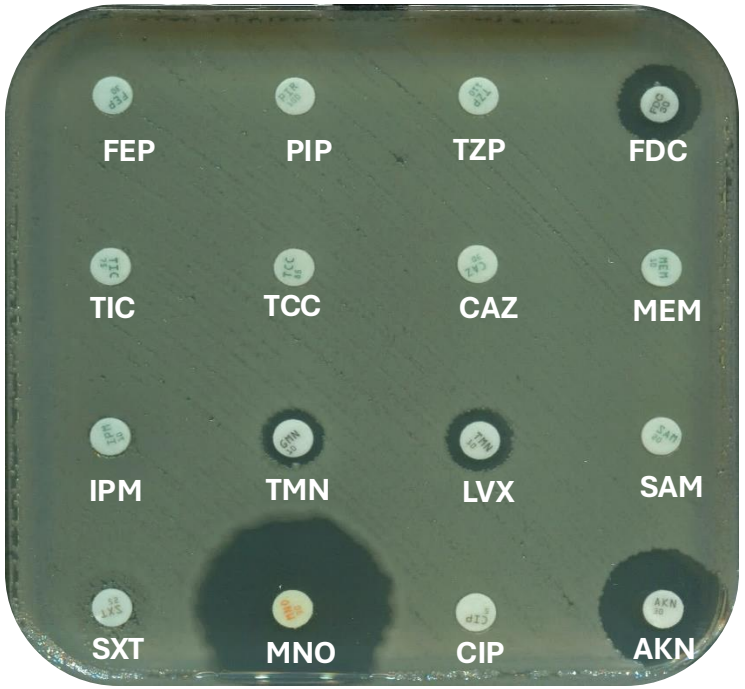
Céfidérocol
EUCAST
PK/PD S≤ 2 mg/L

Colistine
CA-SFM
CMI S≤ 2, R >2 mg/L

Clones NDM-1

IC9 – $ST^{Pas}85$

OXA-94

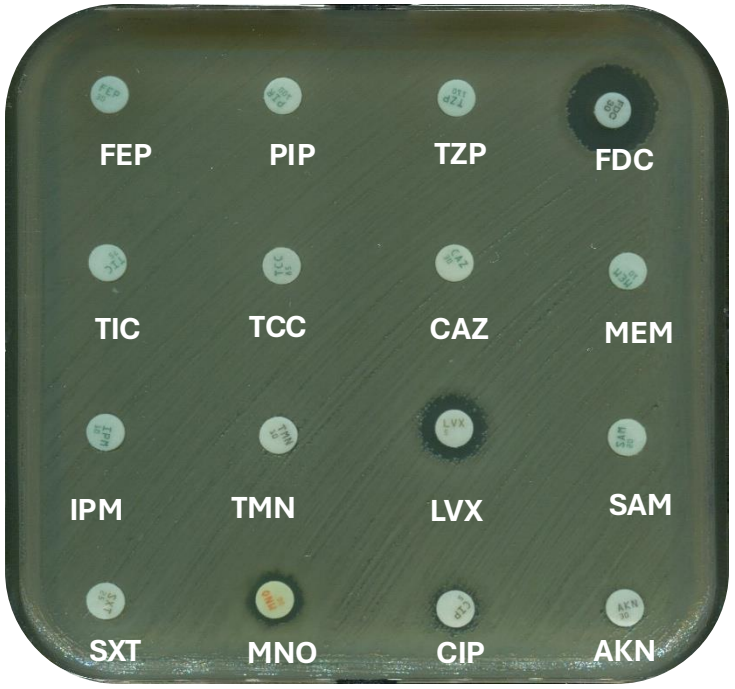


NDM-1

82% Afrique

IC1 – $ST^{Pas}1$

OXA-69

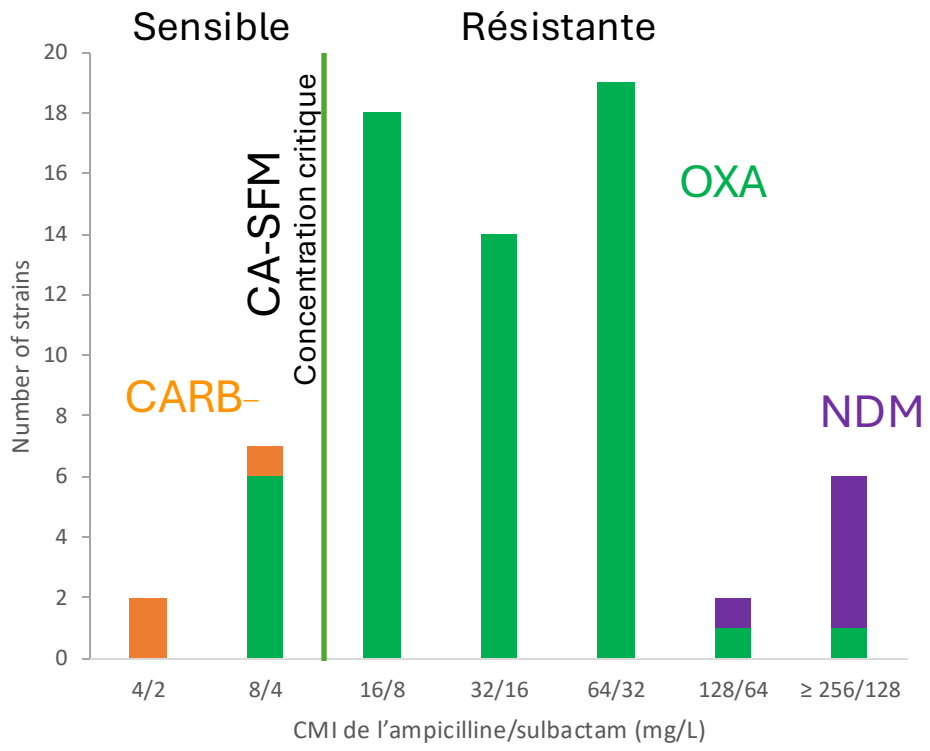


NDM-1/OXA-23

63% Océan Indien

30% Afrique

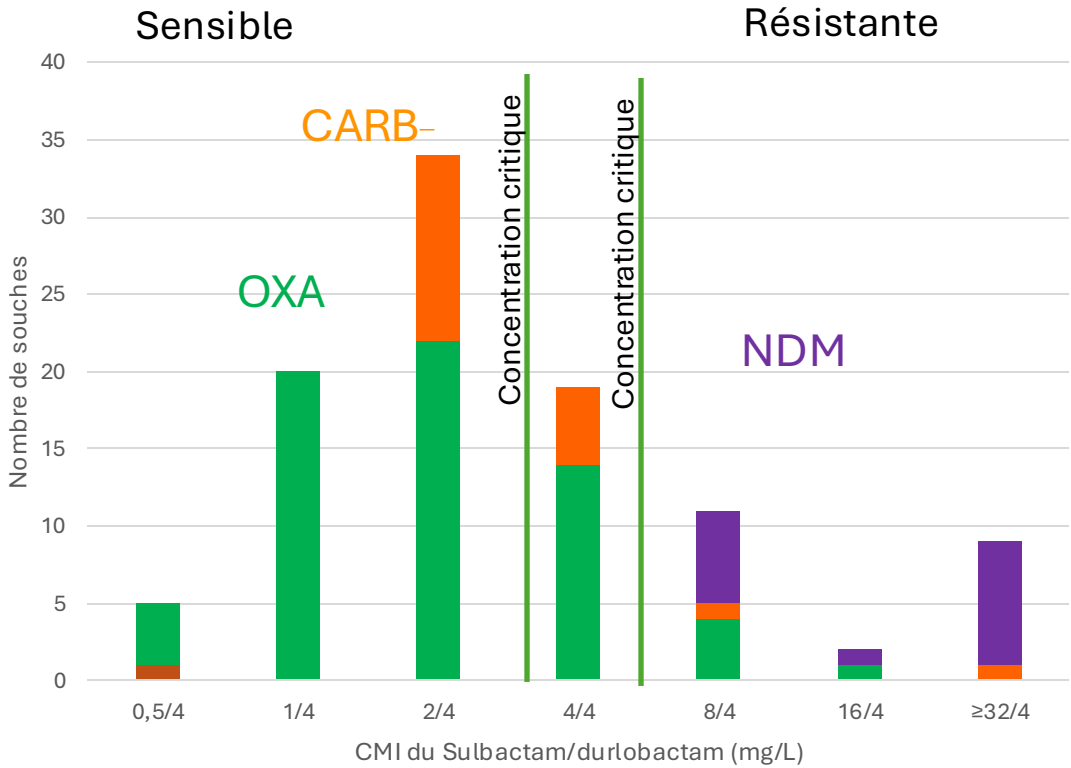
Sensibilité Ampicilline/sulbactam, Sulbactam/durlobactam



CLSI
8/4 (S) ≤-≥32/16 (R)

n=68

Sulbactam PBP-1, PBP-1b, PBP-3



CLSI
4/4 (S) ≤-≥16/4 (R)

n=100

Durlobactam PBP-1, PBP-1b, PBP-2, PBP-3

29 souches de *A. baumannii* XDR

Strains	Resistance mechanisms	CAZ	CAZ-AVI	FEP	FEP-ENM	IMP	IMP-REL	MEM	MEM-VAB	CFD
23A.3614	NDM-1	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	4
23A.3871	OXA-23, ArmA	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	0.25
22A.3576	OXA-24, ArmA	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	32
22A.3386	OXA-72	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	>32
23A.3693	OXA-58, NDM-1	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	2
20A.2935	KPC-2, CTX-M-15	>16	>16/4	>16	>16/8	>16	8/4	>16	8/8	2
23A.3804	OXA-72, CARB-16, ArmA	>16	>16/4	16	8/8	>16	>16/4	>16	>16/8	0.06
22A.3434	OXA-23, NDM-1	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	8
23A.3728	OXA-23, ArmA	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	8
23A.3674	OXA-23, OXA-24, PER-7, ArmA	>16	16/4	>16	16/8	>16	>16/4	>16	>16/8	>32
23A.3639	ADC-30 +	>16	>16/4	>16	16/8	16	16/4	>16	>16/8	0.25
19A.2817	TEM-206	>16	>16/4	>16	>16/8	16	16/4	>16	16/8	2
22A.3380	OXA-23, TEM-206, ArmA	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	0.25
22A.3410	ADC-267 +	>16	>16/4	>16	1/8	2	1/4	16	8/8	0.5
22A.3561	CARB-16, ADC-199+	>16	>16/4	>16	>16/8	4	1/4	2	2/8	32
22A.3565	ADC-200+	>16	>16/4	>16	>16/8	8	4/4	16	16/8	4
22A.3312	OXA-72, ADC-276+	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	8
20A.2935	KPC-2, CTX-M-15	>16	>16/4	>16	>16/8	>16	4/4	>16	8/8	2
21A.3262	OXA-72, CTX-M-115, Carb-14, ArmA	>16	>16/4	>16	16/8	>16	>16/4	>16	>16/8	0.25
16A.1303	GES-7	>16	>16/4	>16	>16/8	4	4/4	16	8/8	>32
22A.3421	GES-11	>16	>16/4	>16	>16/8	4	4/4	16	8/8	4
20A.2875	OXA-23, PER-7, ArmA	>16	>16/4	>16	>16/8	8	>16/4	>16	>16/8	16
21A.3253	NDM-1, PER-7	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	>32
22A.3413	VEB-1a, OXA-10	>16	>16/4	>16	>16/8	4	1/4	2	2/8	8
23A.3672	AdeABC+	8	8/4	16	0.5/8	0.5	0.5/4	1	0.5/8	0.12
20A.3070	Ade IJK +	>16	>16/4	>16	>16/8	2	2/4	16	16/8	>32
22A.3498	TEM-1, IS-OXA-66	>16	>16/4	>16	8/8	4	2/4	4	4/8	0.5
23A.3639	IS-OXA-201	>16	>16/4	>16	2/8	16	16/4	>16	>16/8	0.25

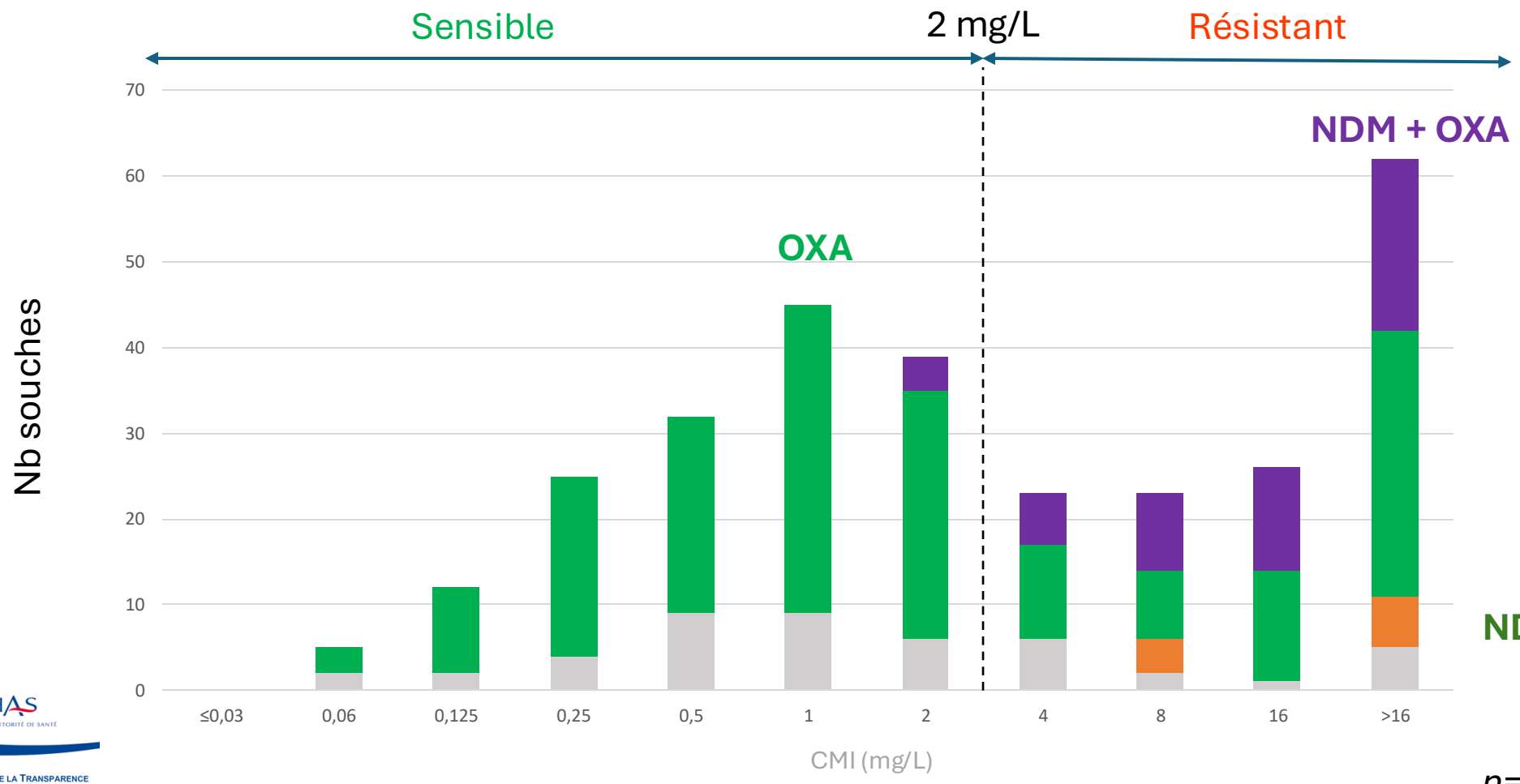
Aucun rôle significatif des inhibiteurs

Strains	Resistance mechanisms	CAZ	CAZ-AVI	FEP	FEP-ENM	IMP	IMP-REL	MEM	MEM-VAB	CFD
23A.3614	NDM-1	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	4
23A.3871	OXA-23, ArmA	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	0.25
22A.3576	OXA-24, ArmA	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	32
22A.3386	OXA-72	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	>32
23A.3693	OXA-58, NDM-1	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	2
20A.2935	KPC-2, CTX-M-15	>16	>16/4	>16	>16/8	>16	8/4	>16	8/8	2
23A.3804	OXA-72, CARB-16, ArmA	>16	>16/4	16	8/8	>16	>16/4	>16	>16/8	0.06
22A.3434	OXA-23, NDM-1	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	8
23A.3728	OXA-23, ArmA	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	8
23A.3674	OXA-23, OXA-24, PER-7, ArmA	>16	16/4	>16	16/8	>16	>16/4	>16	>16/8	>32
23A.3639	ADC-30 +	>16	>16/4	>16	16/8	16	16/4	>16	>16/8	0.25
19A.2817	TEM-206	>16	>16/4	>16	>16/8	16	16/4	>16	16/8	2
22A.3380	OXA-23, TEM-206, ArmA	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	0.25
22A.3410	ADC-267 +	>16	>16/4	>16	1/8	2	1/4	16	8/8	0.5
22A.3561	CARB-16, ADC-199+	>16	>16/4	>16	>16/8	4	1/4	2	2/8	32
22A.3565	ADC-200+	>16	>16/4	>16	>16/8	8	4/4	16	16/8	4
22A.3312	OXA-72, ADC-276+	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	8
20A.2935	KPC-2, CTX-M-15	>16	>16/4	>16	>16/8	>16	4/4	>16	8/8	2
21A.3262	OXA-72, CTX-M-115, Carb-14, ArmA	>16	>16/4	>16	16/8	>16	>16/4	>16	>16/8	0.25
16A.1303	GES-7	>16	>16/4	>16	>16/8	4	4/4	16	8/8	>32
22A.3421	GES-11	>16	>16/4	>16	>16/8	4	4/4	16	8/8	4
20A.2875	OXA-23, PER-7, ArmA	>16	>16/4	>16	>16/8	8	>16/4	>16	>16/8	16
21A.3253	NDM-1, PER-7	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	>32
22A.3413	VEB-1a, OXA-10	>16	>16/4	>16	>16/8	4	1/4	2	2/8	8
23A.3672	AdeABC+	8	8/4	16	0.5/8	0.5	0.5/4	1	0.5/8	0.12
20A.3070	Ade IJK +	>16	>16/4	>16	>16/8	2	2/4	16	16/8	>32
22A.3498	TEM-1, IS-OXA-66	>16	>16/4	>16	8/8	4	2/4	4	4/8	0.5
23A.3639	IS-OXA-201	>16	>16/4	>16	2/8	16	16/4	>16	>16/8	0.25

Céfidérocol (en association)

Strains	Resistance mechanisms	CAZ	CAZ-AVI	FEP	FEP-ENM	IMP	IMP-REL	MEM	MEM-VAB	CFD
23A.3614	NDM-1	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	4
23A.3871	OXA-23, ArmA	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	0.25
22A.3576	OXA-24, ArmA	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	32
22A.3386	OXA-72	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	>32
23A.3693	OXA-58, NDM-1	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	2
20A.2935	KPC-2, CTX-M-15	>16	>16/4	>16	>16/8	>16	8/4	>16	8/8	2
23A.3804	OXA-72, CARB-16, ArmA	>16	>16/4	16	8/8	>16	>16/4	>16	>16/8	0.06
22A.3434	OXA-23, NDM-1	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	8
23A.3728	OXA-23, ArmA	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	8
23A.3674	OXA-23, OXA-24, PER-7, ArmA	>16	16/4	>16	16/8	>16	>16/4	>16	>16/8	>32
23A.3639	ADC-30 +	>16	>16/4	>16	16/8	16	16/4	>16	>16/8	0.25
19A.2817	TEM-206	>16	>16/4	>16	>16/8	16	16/4	>16	16/8	2
22A.3380	OXA-23, TEM-206, ArmA	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	0.25
22A.3410	ADC-267 +	>16	>16/4	>16	1/8	2	1/4	16	8/8	0.5
22A.3561	CARB-16, ADC-199+	>16	>16/4	>16	>16/8	4	1/4	2	2/8	32
22A.3565	ADC-200+	>16	>16/4	>16	>16/8	8	4/4	16	16/8	4
22A.3312	OXA-72, ADC-276+	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	8
20A.2935	KPC-2, CTX-M-15	>16	>16/4	>16	>16/8	>16	4/4	>16	8/8	2
21A.3262	OXA-72, CTX-M-115, Carb-14, ArmA	>16	>16/4	>16	16/8	>16	>16/4	>16	>16/8	0.25
16A.1303	GES-7	>16	>16/4	>16	>16/8	4	4/4	16	8/8	>32
22A.3421	GES-11	>16	>16/4	>16	>16/8	4	4/4	16	8/8	4
20A.2875	OXA-23, PER-7, ArmA	>16	>16/4	>16	>16/8	8	>16/4	>16	>16/8	16
21A.3253	NDM-1, PER-7	>16	>16/4	>16	>16/8	>16	>16/4	>16	>16/8	>32
22A.3413	VEB-1a, OXA-10	>16	>16/4	>16	>16/8	4	1/4	2	2/8	8
23A.3672	AdeABC+	8	8/4	16	0.5/8	0.5	0.5/4	1	0.5/8	0.12
20A.3070	Ade IJK +	>16	>16/4	>16	>16/8	2	2/4	16	16/8	>32
22A.3498	TEM-1, IS-OXA-66	>16	>16/4	>16	8/8	4	2/4	4	4/8	0.5
23A.3639	IS-OXA-201	>16	>16/4	>16	2/8	16	16/4	>16	>16/8	0.25

Sensibilité de *A. baumannii* au céfidérocol



4,9% → CMI ≤ 2 mg/L
7.4% → CMI = 4 mg/L
87.8% → CMI ≥ 8 mg/L

n=292 souches

HAS HAUTE AUTORITÉ DE SANTÉ
COMMISSION DE LA TRANSPARENCE
AVIS
20 JANVIER 2021
céfidérocol

*Avis CT du cefiderocol du 20 janvier 2021 : https://www.has-sante.fr/upload/docs/evamed/CT-18908_FETCROJA_PIC_INS_AvisDef_CT18908.pdf

Résumé : Acinetobacter baumannii

	Céfidérocol	Carbapénème	Triméthoprime /sulfamethoxazol	Colistine	Tigécycline	Minocycline
OXA-23	1ère intention			1ère intention		
NDM-1				1ère intention	1ère intention	1ère intention
Non-CARBA	1ère intention	1ère intention	1ère intention	1ère intention		

Disques	**Screening**	✓	✓	✗	✗	✓
Bandelette CMI	✗	✓	✓	✗	✓	✓

Céfiderocol, traitement de dernier recours des infections a BGN multirésistants (notamment entéobactéries et Pseudomonas), à l'exception d'A. baumanii et S. maltophilia (HAS 2021)