51e JBP Journées de Biologie Praticienne

51ème Journées de Biologie Praticiennes

LA RÉSISTANCE BACTÉRIENNE AUX CARBAPÉNÈMES, UN PROBLÈME DE SANTÉ PUBLIQUE MONDIAL

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ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

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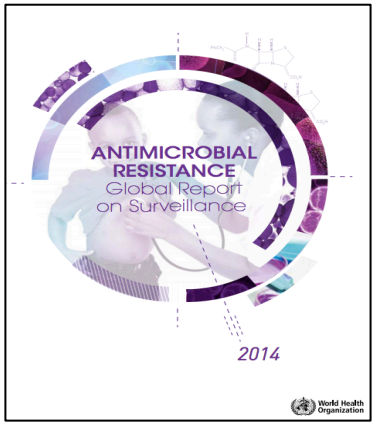
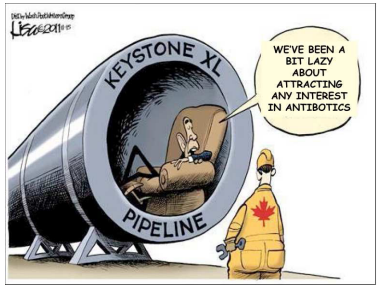
Le fardeau des bactéries multi-résistantes (BMR)

MDR
- 23,000 morts
- 2 million infections par an (USA).
=> 1,2 milliard $

- « Antibiotic Resistance Just Became Public Enemy Number One, Will Likely Kill More People Than Cancer By 2050 »
- MDR: 700,000 mort/ an globalement.
- En 2050 - 10 millions mort/ mort- cout de 100 000 billions $

En 2012
- 158 000 MDR infections
- 12 500 morts associées à ces infections. (étude Burden, InVS)





"Antimicrobial resistance: The problem is so serious that it threatens the achievements of modern medicine (WHO global report, 2014). « post-antibiotic era »

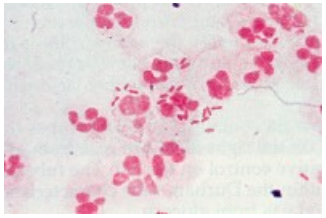
Impact on PIB : **decrease of 1,1 % in an «optimistic» scenario (low impact on antimicrobial resistance) and 3,8 % in the worst scenario ; (even 5 % in low income countries)**

THE CLINICALLY-SIGNIFICANT BACTERIA (WHO)

- Echecs thérapeutiques et taux de mortalité élevés
- Maladies infectieuses restent la 2ème cause de mortalité dans le monde.

Enterobacteriaceae

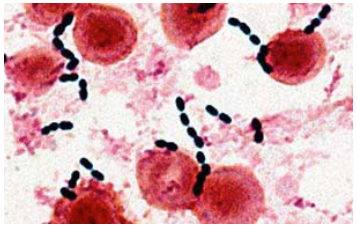
1) KPC, OXA-48, NDM
2) ESBL/AMPC + impermeability
3) VIM, IMP



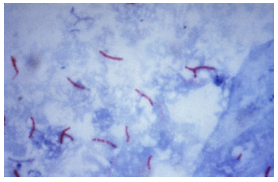
E. faecium

BHRe

1) VanA et VanB



M. tuberculosis
MDR and XDR

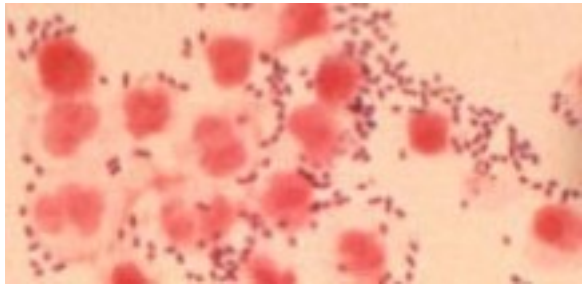


P. aeruginosa

1) VIM, IMP
2) KPC, NDM
3) ESBL,

A. baumannii

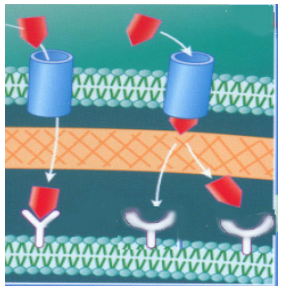
1) Oxacillinases (OXA-23)
2) NDM,
3) GES, KPC

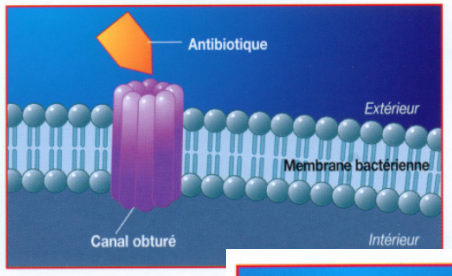


S. aureus

1) Methicilin R

Resistance to β-lactams in Gram negatives



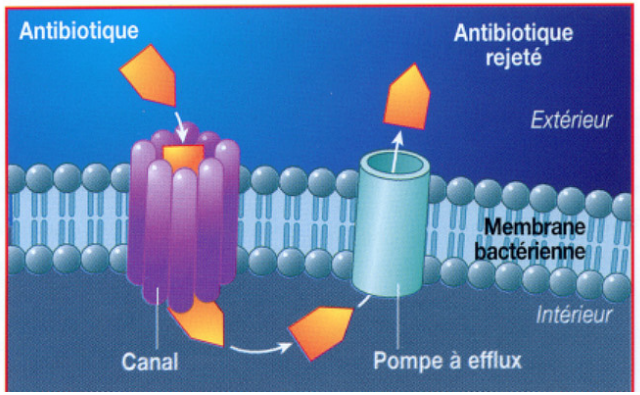


Decrease in permeability

Modification of PBPs

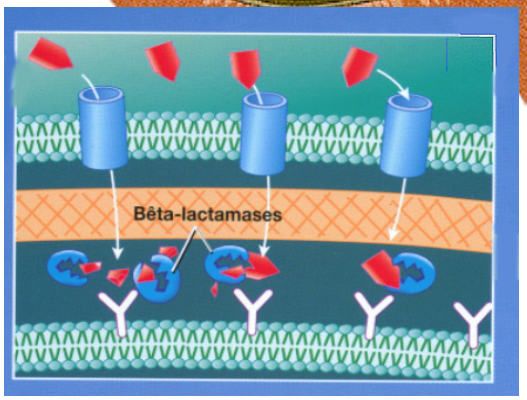
Overexpression Efflux pumps

Antibiotic

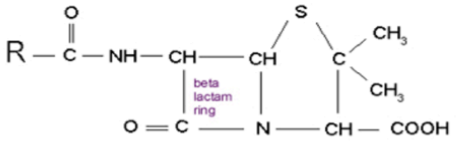


Pumps

Antibiotic



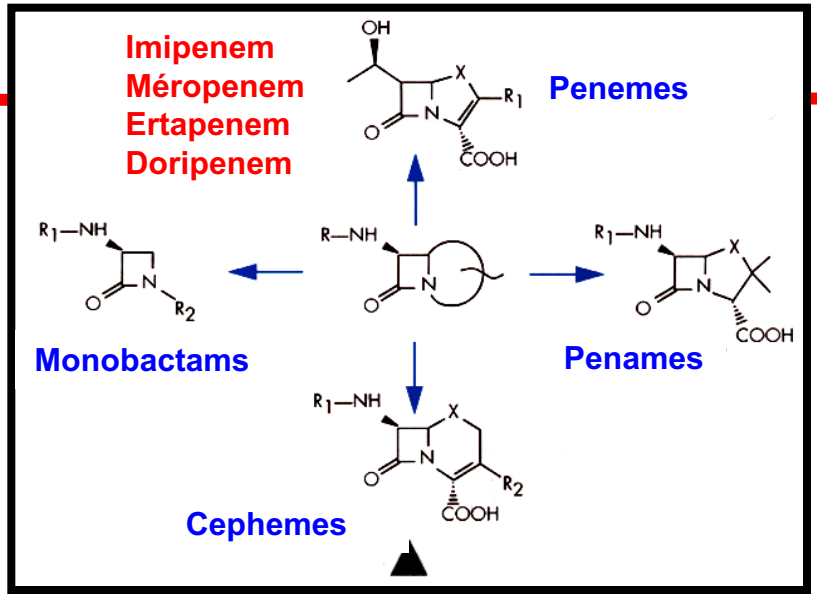
β-Lactamases



Site of penicillinase action (break in β lactam ring)

Resistance to β-lactams: β-lactamases

β-lactams

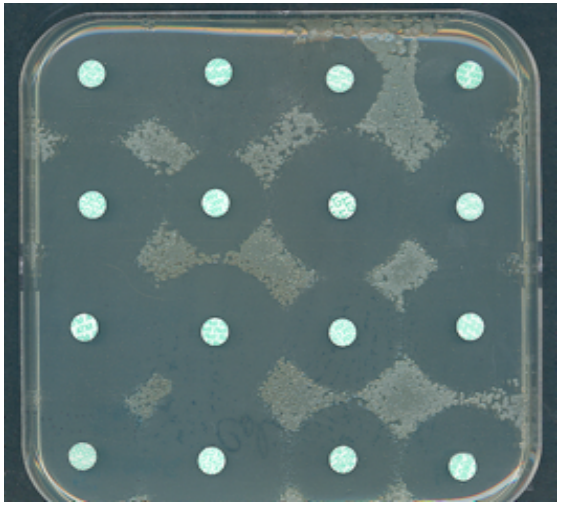


β-lactamases

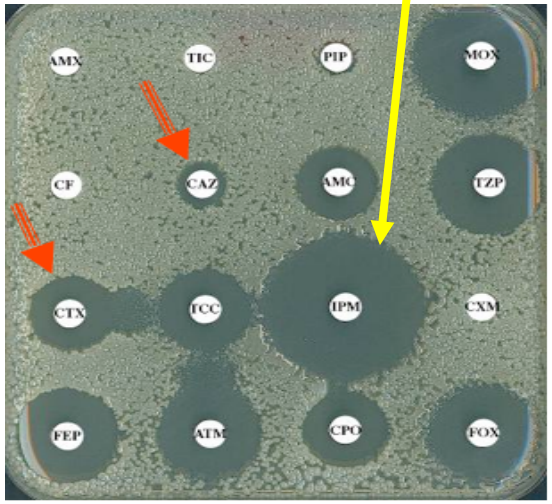
	Active site		G		KTG	Groupe	Inhibitors	
A	SXXK 70-73	SXN 130-132	156	Ωloop 164-179	234-236	Penicillinase	clavulanic acid	KPC
C	SXXK 64-67	YXN		Ωloop 208-213	315-317	Cephalosporinase	Cloxacillin	
D	SXXK 70-73	YGN 144-146		WxExxL 164-169	216-218	Oxacillinase	no inhibitor	OXA-48
B Zn++	61-65	Zn1 ligand His116, 118,196		Zn2 ligand Asp120, Cys221,His263		Metallo-enzyme	EDTA	NDM/VIM/IMP

Multi-resistance and therapeutic dead-ends
E. coli our best friend, and our worst ennemi

E. coli
Of our youth

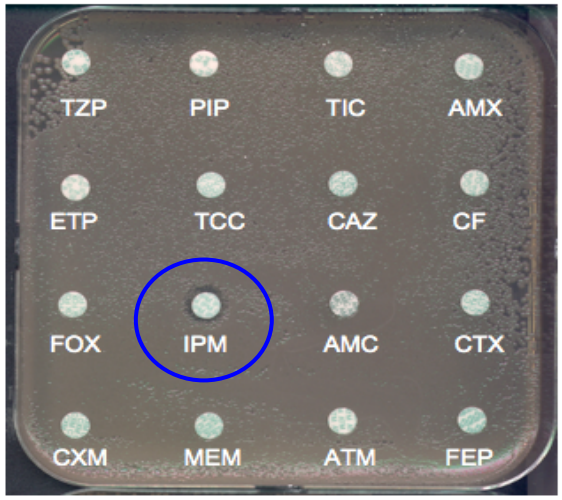


E. coli
of modern times



ESBLs

E. coli
of tomorrow

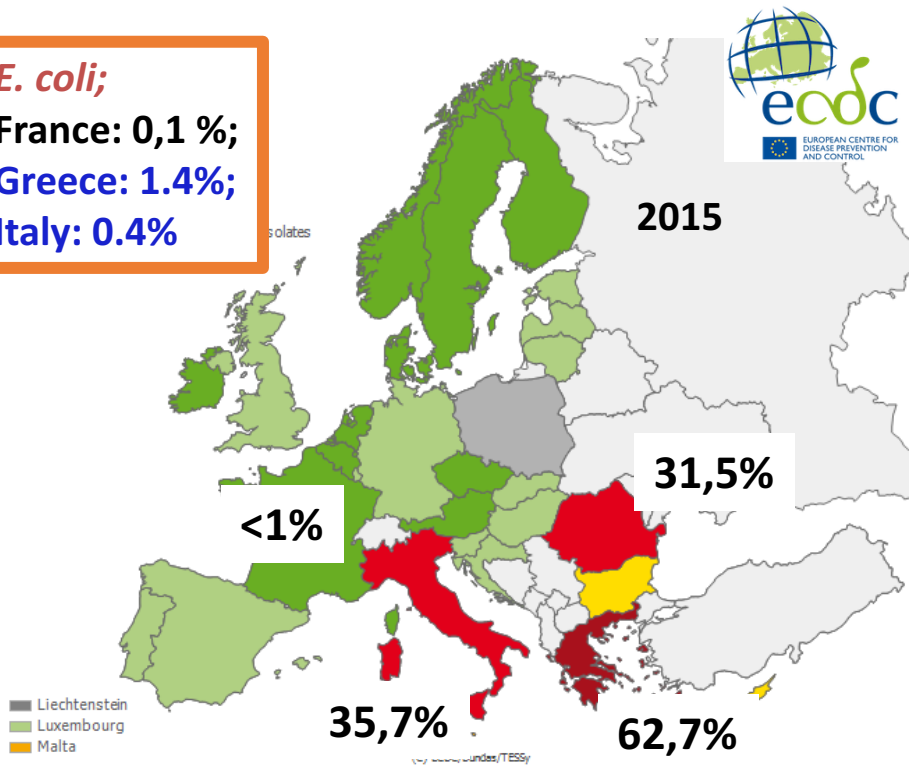


Carbapenemases

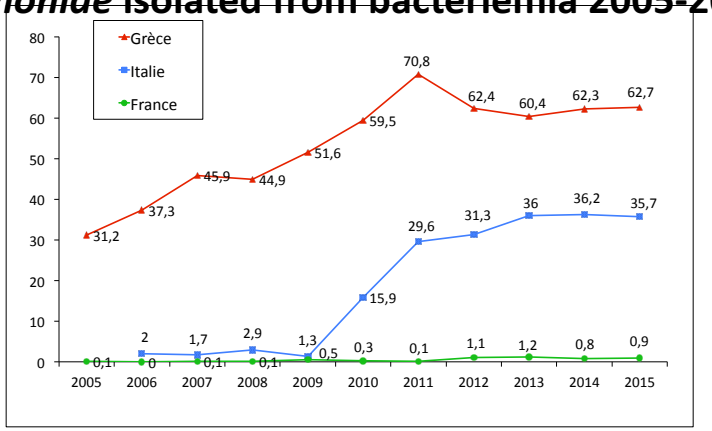
Carbapenem resistant Enterobacteriaceae (CRE)
Here we are !!!

Bacterimia with Enterobacteria resistant to carbapenems (CRE) in Europe 2015 (ECDC)

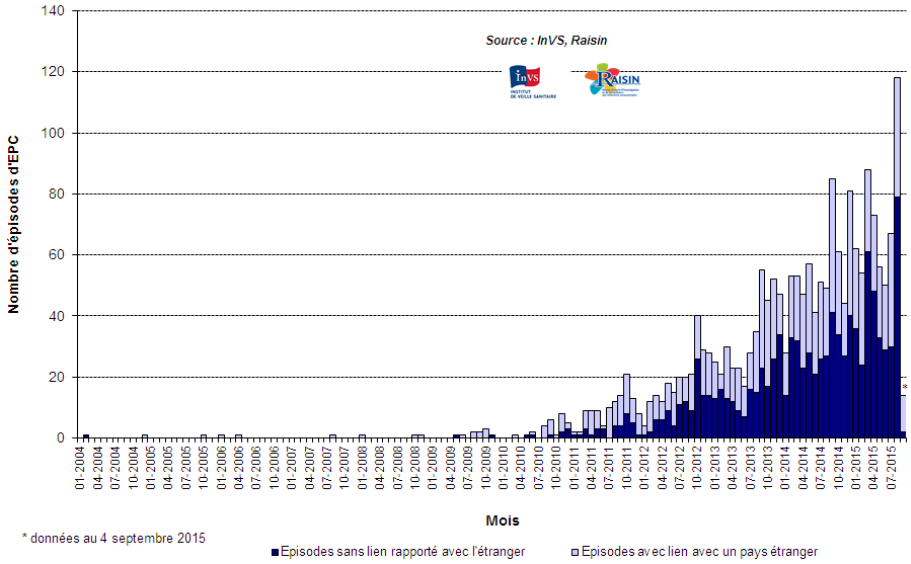
E. coli;
France: 0,1 %;
Greece: 1.4%;
Italy: 0.4%



Evolution of carbapenem-resistance in *K. pneumoniae* isolated from bacteriemia 2005-2015



Number of CRE Episodes, France, 2004 – 2015, per month of notification, 4 septembre 2015 (SPF; N= 2026 épisodes)



CRE remain susceptible to colistin, but frequent resistances described in Italy and Greece.

⇒ **pan-resistance, therapeutic dead-end**

⇒ **High mortality rates (50-70%)**

CRE : Carbapenem resistance in enterobacteriaceae

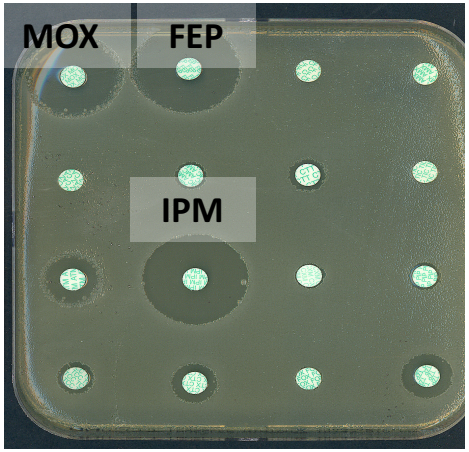
1) Decreased outer membrane permeability + β-lactamase with no (or very poor) hydrolytic activity against carbapenems

Resistance to Expanded spectrum cephalosporins BUT Carbapenem susceptible,

→

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

Resistance to carbapenems by decreased permeability



after 21 days of imipenem mono therapy

International Journal of Antimicrobial Agents 35 (2010) 265–268

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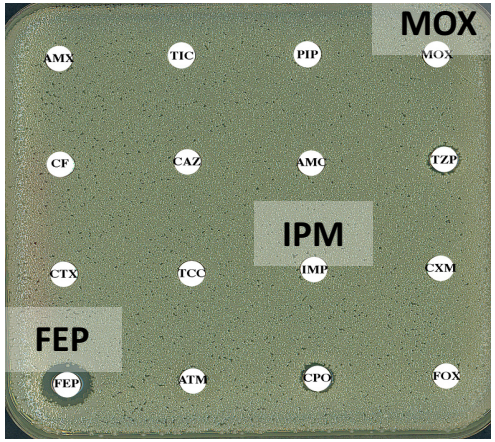
journal homepage: http://www.elsevier.com/locate/ijantimicag

Short communication

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

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

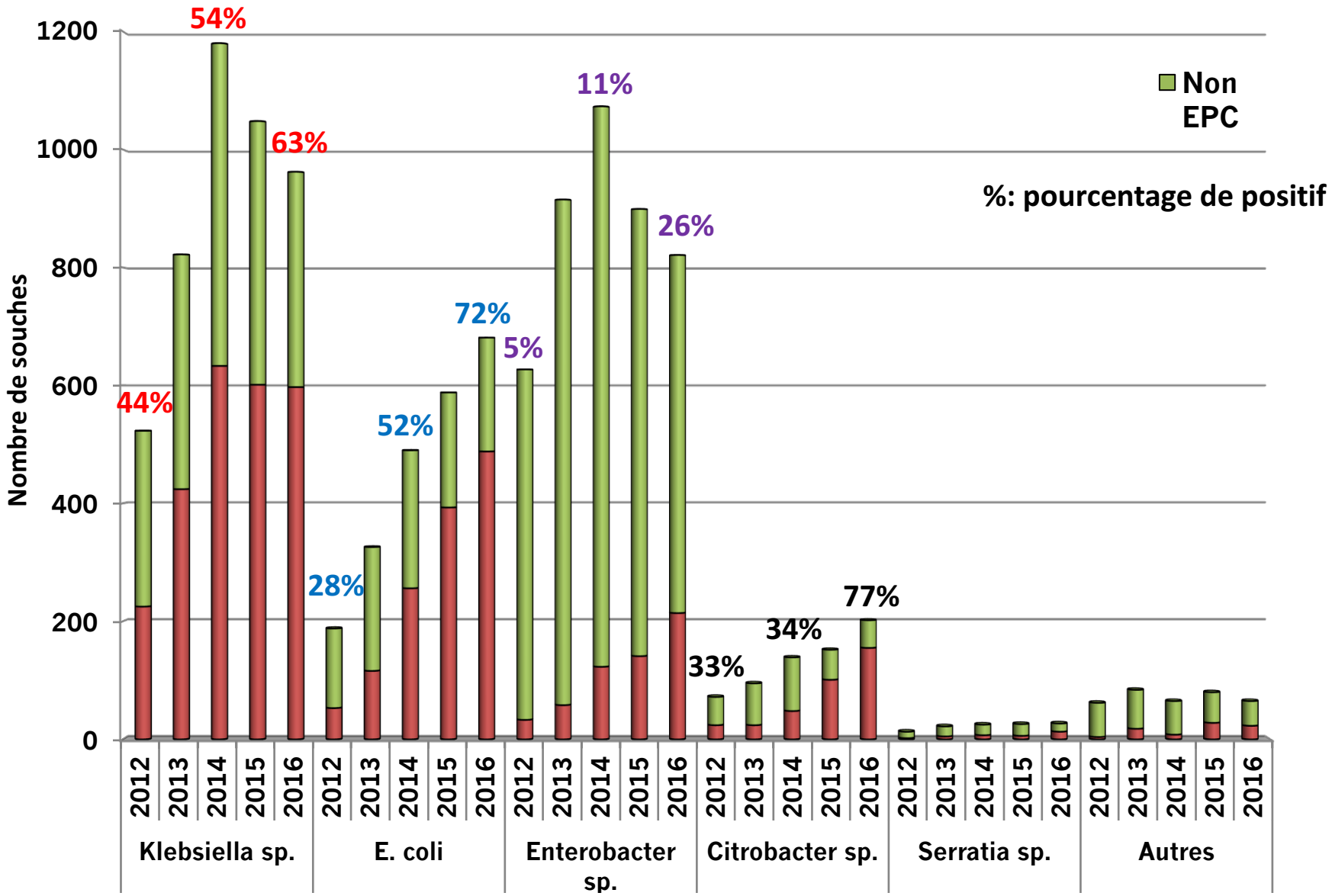


Important in terms of treatment issues, but no epidemic dissemination,

=> chromosomal mutations with important fitness cost

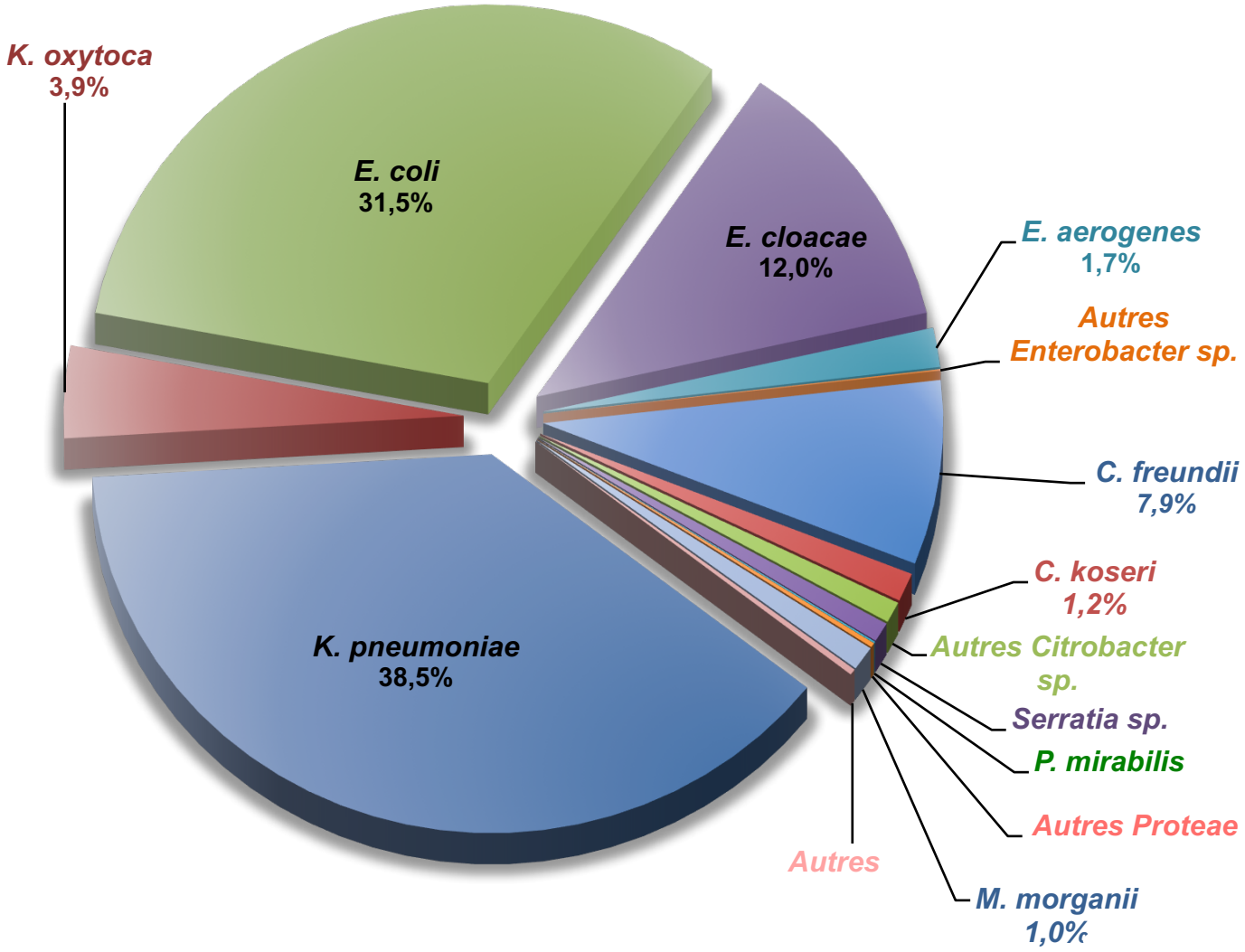
2) Carbapenemases (CPE)

Evolution of the number of CPEs received at the NRC between 2012 -2016 according to species



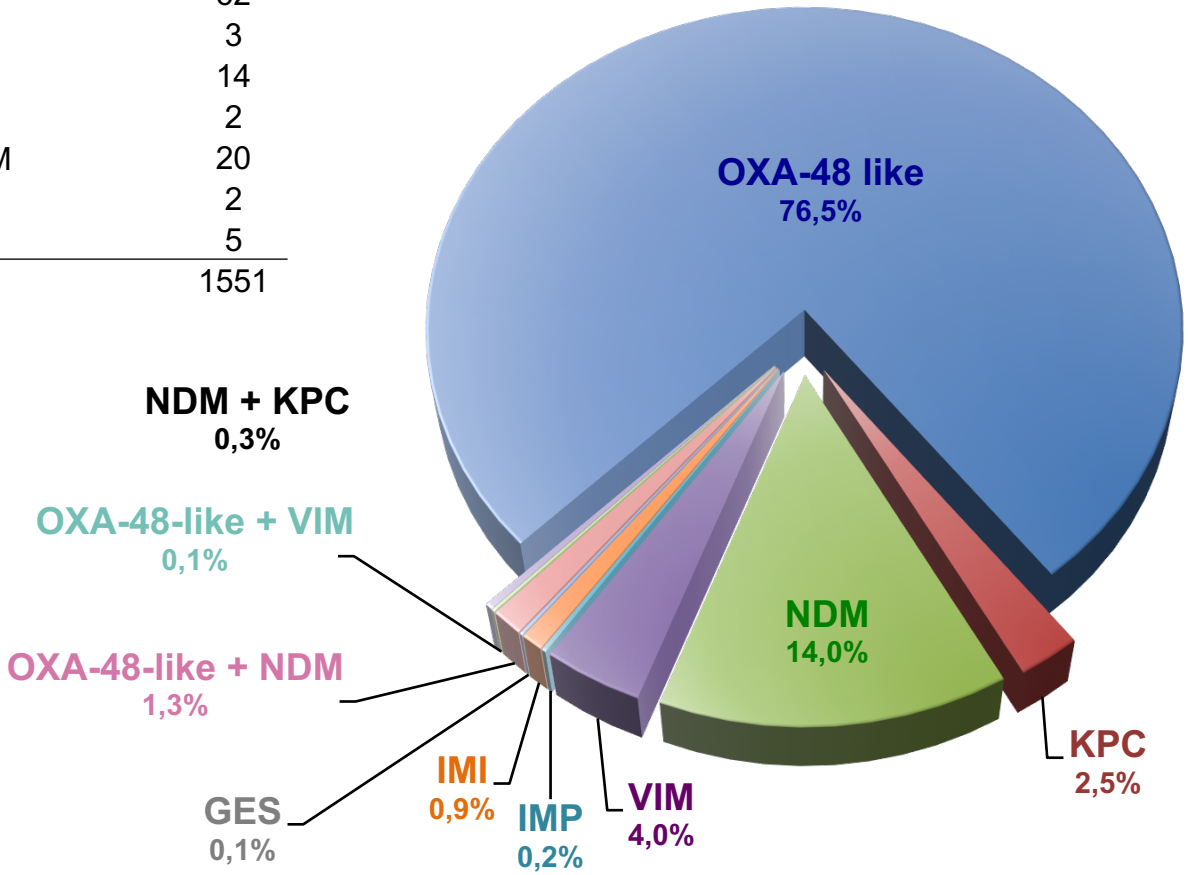
Distribution of CPEs per species in France (2016)

Espèce	n
K. pneumoniae	597
K. oxytoca	61
E. coli	488
E. cloacae	186
E. aerogenes	26
Autres *Enterobacter sp.*	1
C. freundii	122
C. koseri	19
Autres *Citrobacter sp.*	14
Serratia sp.	13
P. mirabilis	1
Autres *Proteae*	3
M. morganii	16
Autres	4
Total	1551



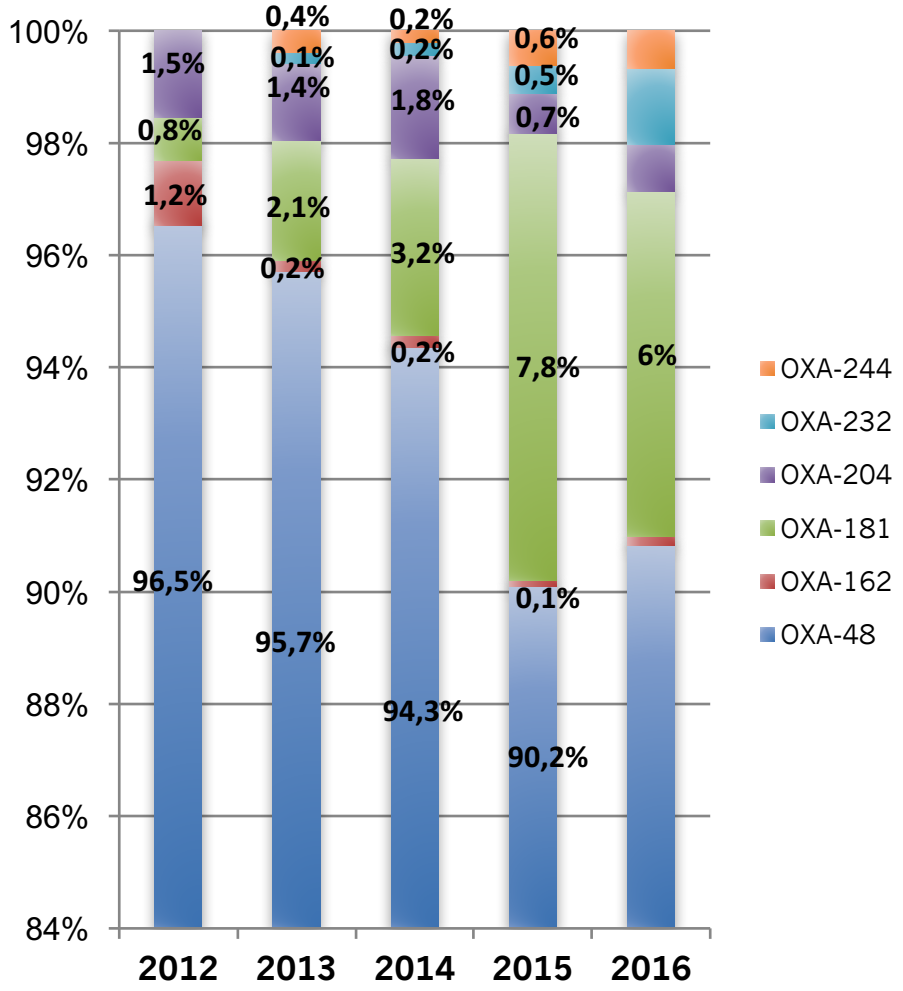
Distribution des CPEs per carbapenemase in France (2016)

Type of carbapenemase	n
OXA-48 like	1187
KPC	39
NDM	217
VIM	62
IMP	3
IMI	14
GES	2
OXA-48-like + NDM	20
OXA-48-like + VIM	2
NDM + KPC	5
Total	1551

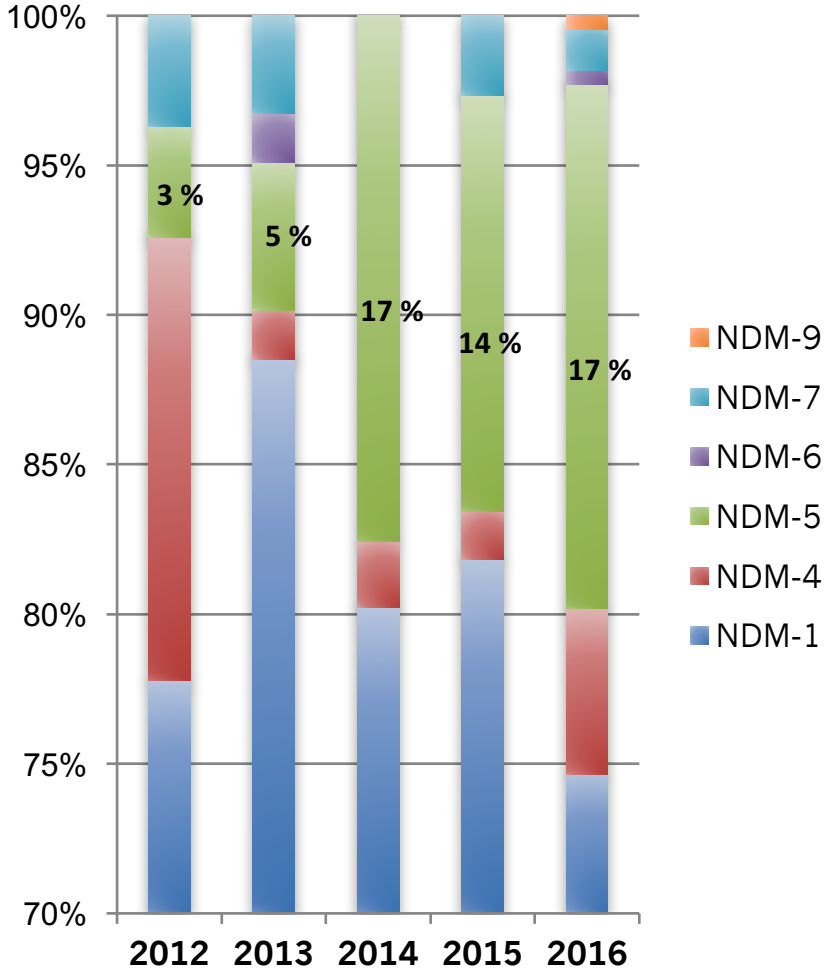


MBLs= 19,9 %

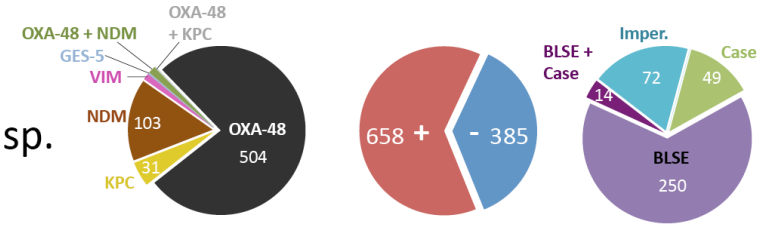
Variants OXA-48 : progression of OXA-181



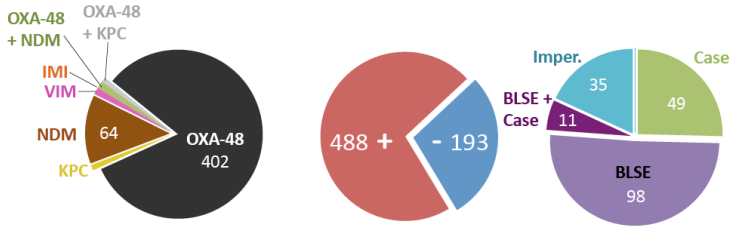
Variants NDM : progression of NDM-5



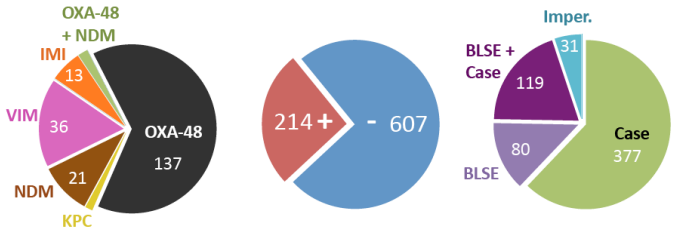
Klebsiella sp.
(n=1043)



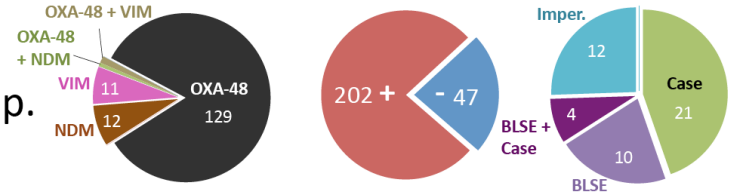
E. coli
(n=681)



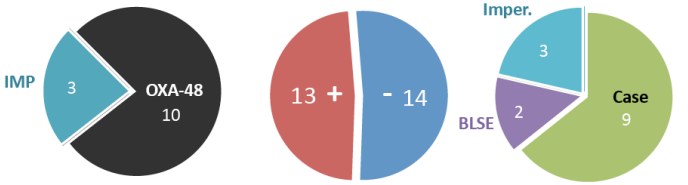
Enterobacter sp.
(n=821)



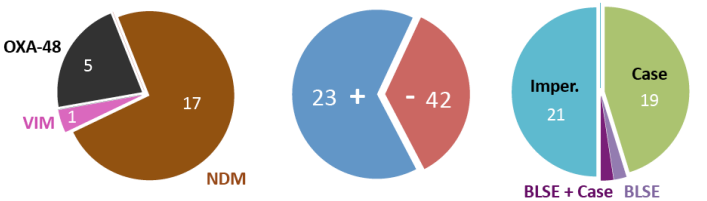
Citrobacter sp.
(n=202)

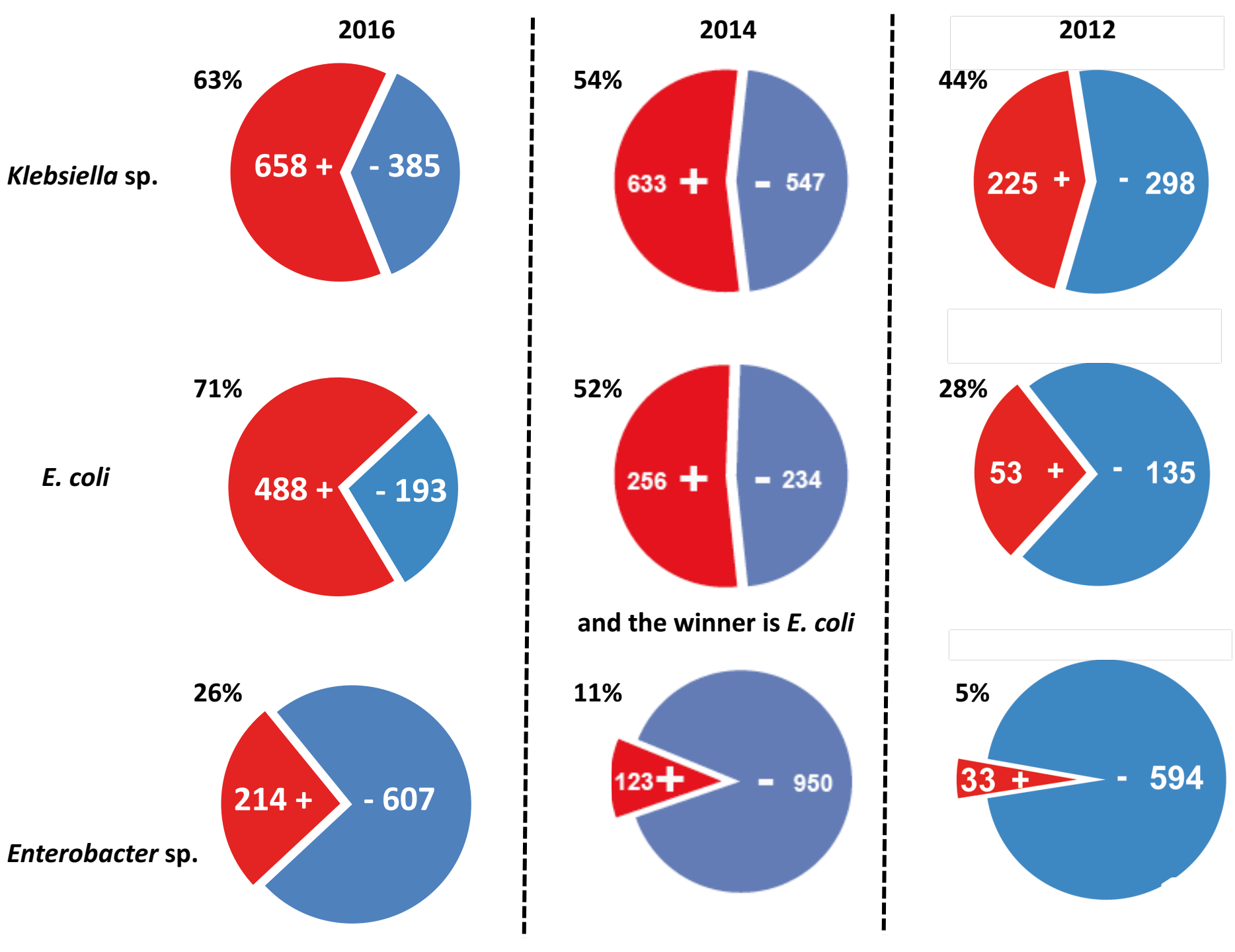


Serratia sp.
(n=27)

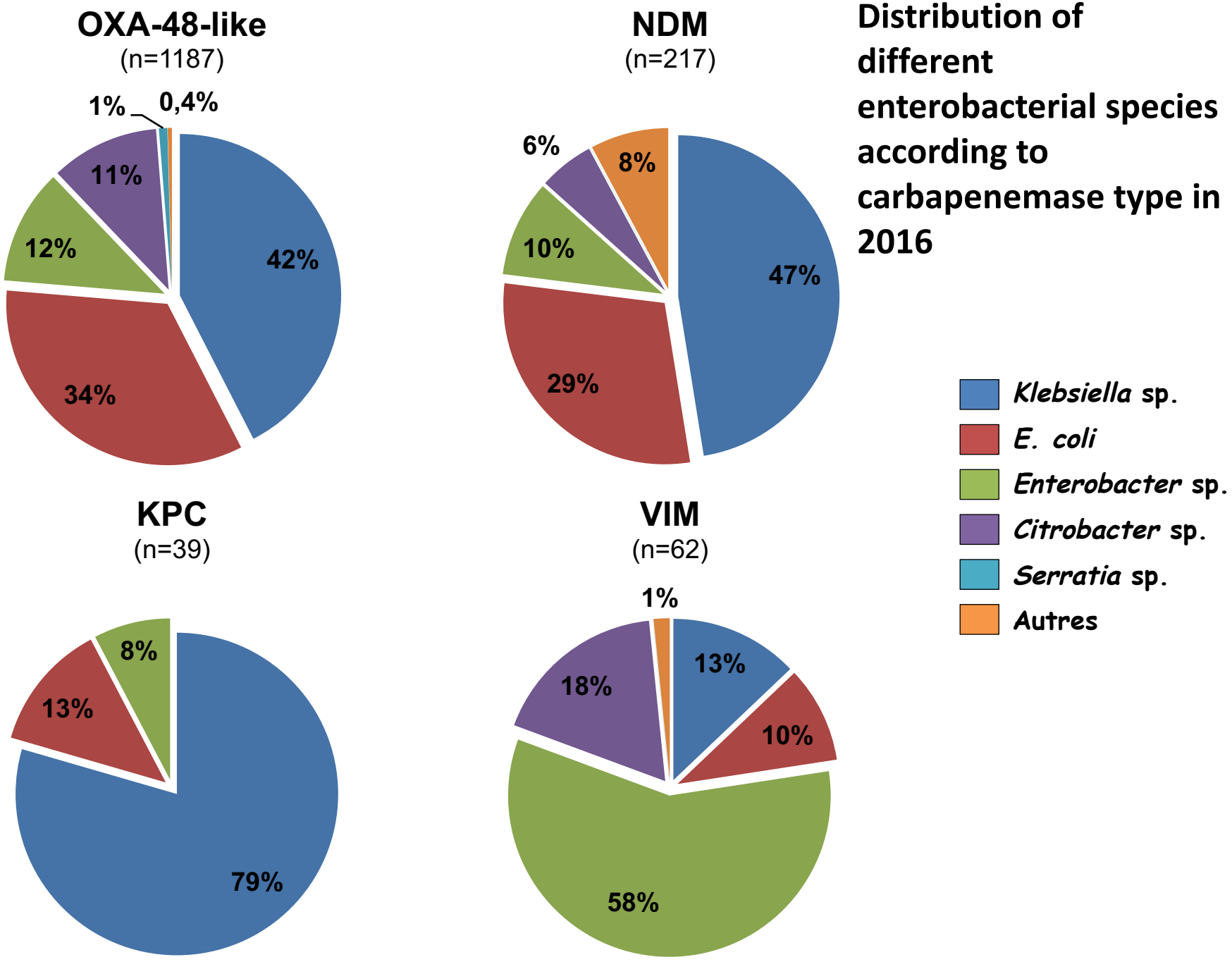


Autres
(n=65)

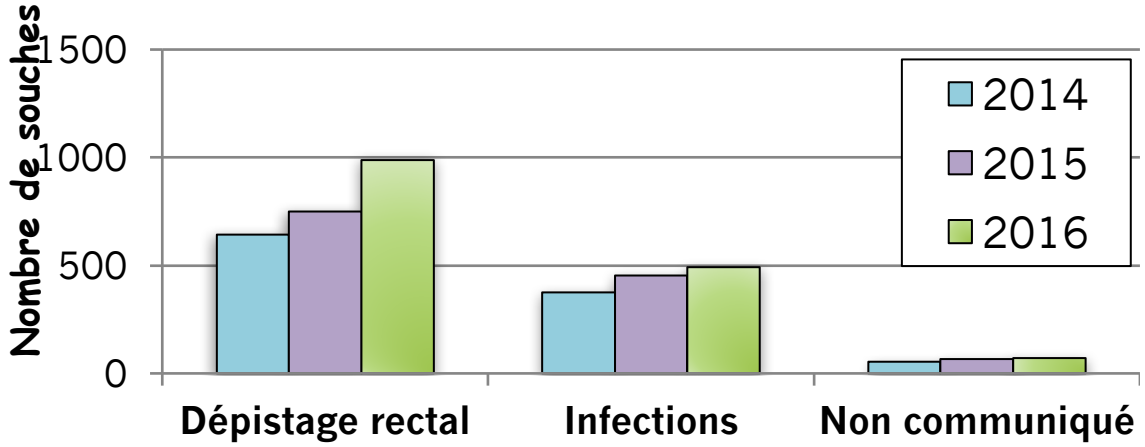


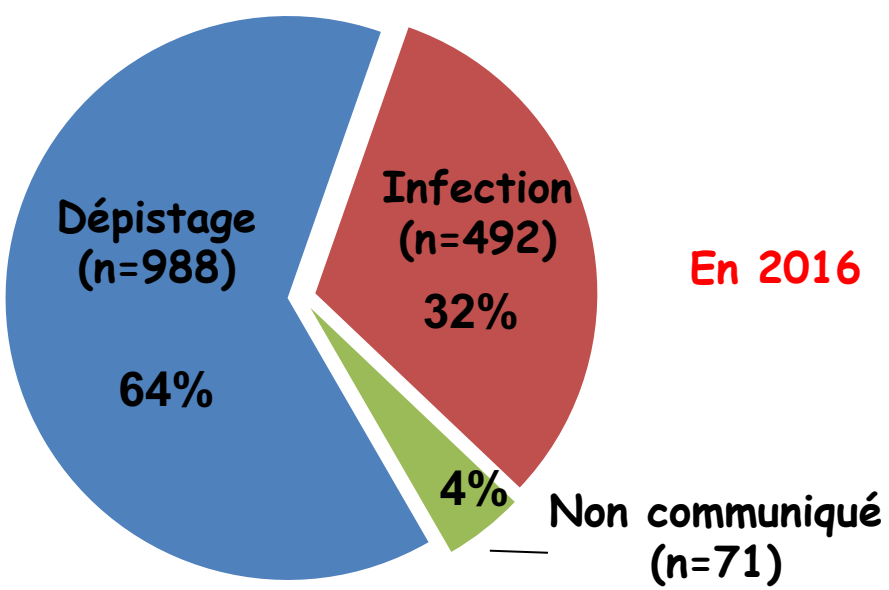

2016
2014
2012
63%
54%
44%
Klebsiella sp.
658 +
- 385
633 +
- 547
225 +
- 298
71%
52%
28%
E. coli
488 +
- 193
256 +
- 234
53 +
- 135
and the winner is E. coli
26%
11%
5%
Enterobacter sp.
214 +
- 607
123 +
- 950
33 +
- 594

Distribution of different enterobacterial species according to carbapenemase type in 2016

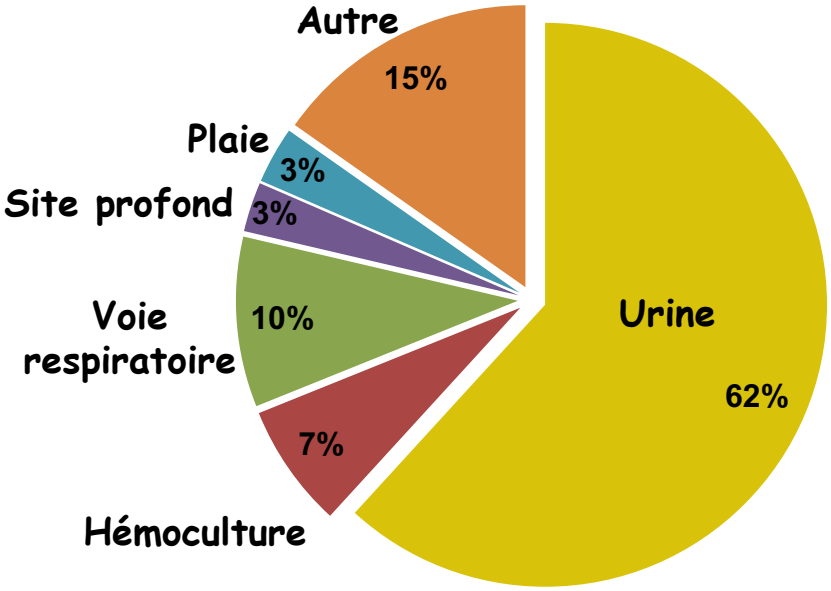


volution of the CPE per sample type: 2014-2016

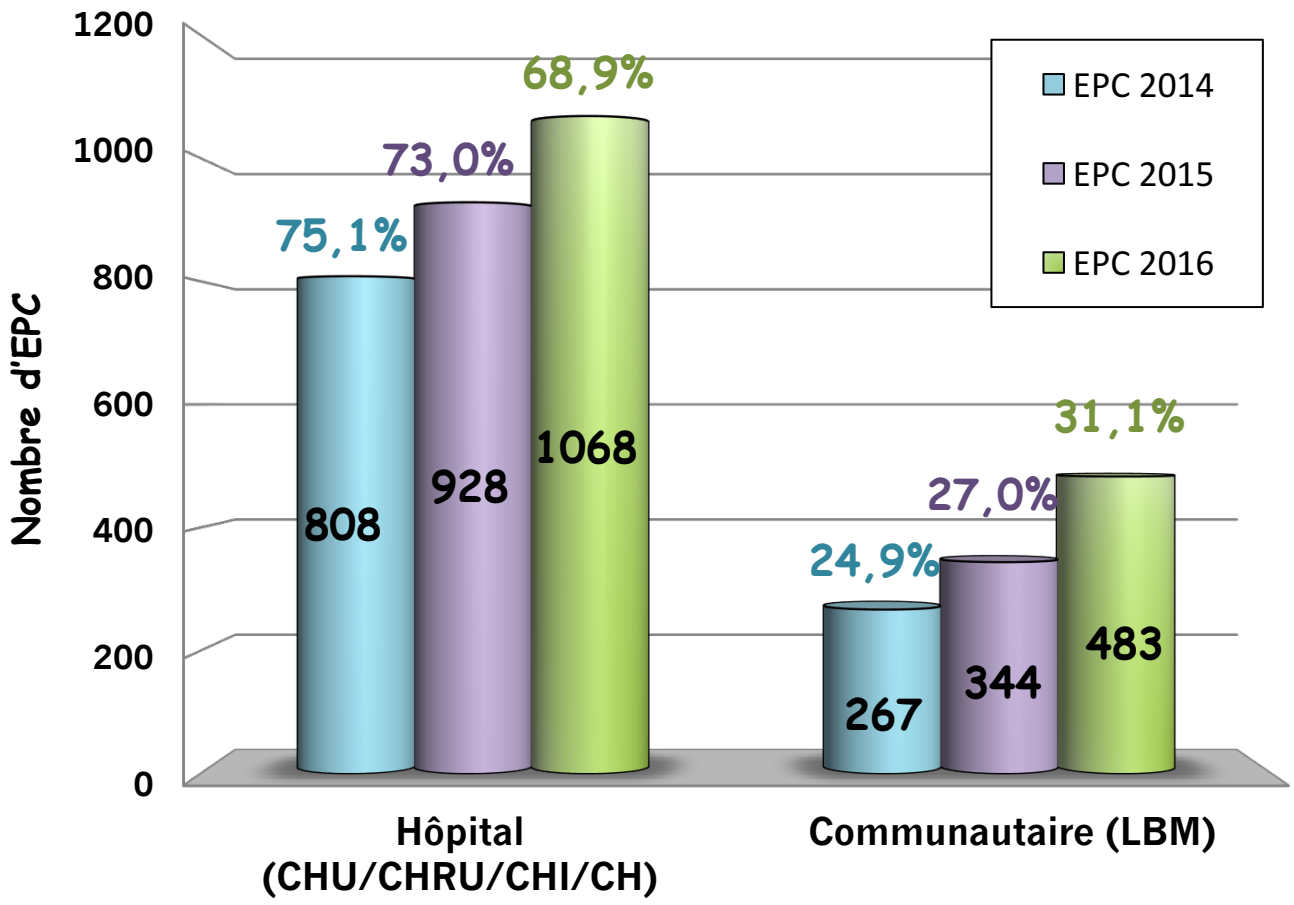




En 2016

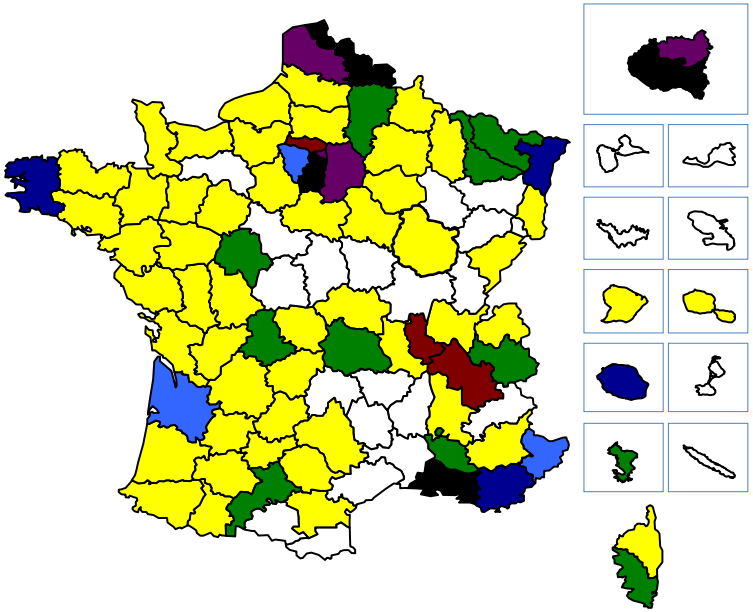


Hospitals / private labs 2014-2015



Répartition des EPC reçues au CNR Bicêtre en 2014 (n=1075), 2015 (n=1272) et 2016 (n=1551) en fonction du laboratoire expéditeur.

Number of CPEs according to departements in 2016



Number of isolates :

0	20 - 29	50 - 59
1 - 9	30 - 39	60 - 69
10 - 19	40 - 49	≥ 70

Epidodes of CPEs, France, 2004 – 2015, Per country of origin and type of carbapenemase, Dec 2015 (InVS; N= 971 episodes)

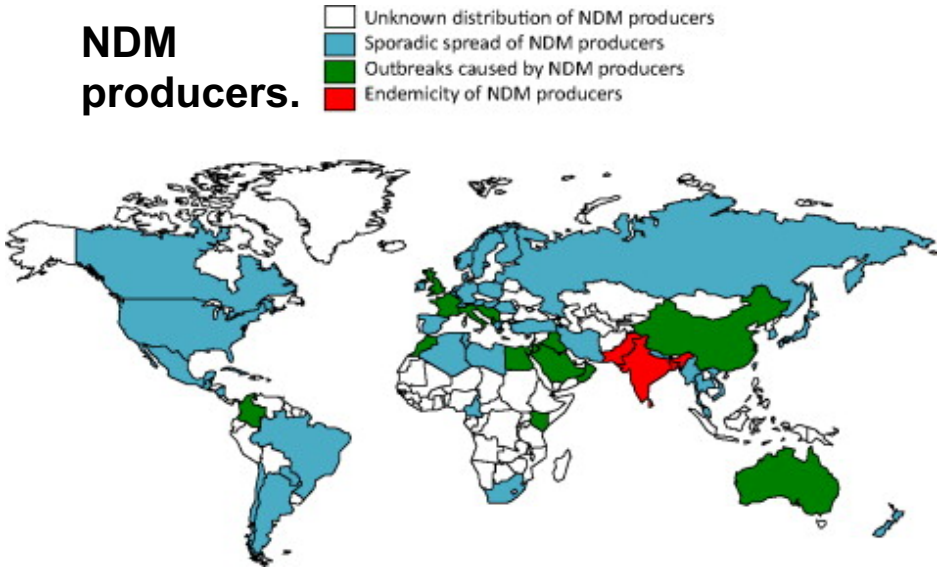
Pays	Mécanismes de résistance (carbapénèmases)					Nombre total d'épisodes*
	OXA-48 et OXA-48-like	NDM	KPC	VIM	IMI	
Maroc	237	19	2			246
Algérie	159	4	2	1		166
Tunisie	87	21	1	1		105
Inde	19	63	2			73
Égypte	44	16	1	3		59
Turquie	44	2	1	2		47
Sénégal	39	5				43
Grèce	1	1	28	10		39
Italie	5	1	27	6		39
Libye	22	1				22
Roumanie	14	2	1	1		18
Koweït	11	5	2	2		17
Cambodge	12	4				14
Congo	9	5				13
Ile Maurice	3	10				12
Vietnam	3	8	2		1	12
Espagne	7	1		2		10
Cameroun	8	1				9
Côte d'Ivoire	8				1	9
Israël	2	1	6			9
Liban	9					9

* *Nombre total d'épisodes pour lesquels le pays a été cité.*

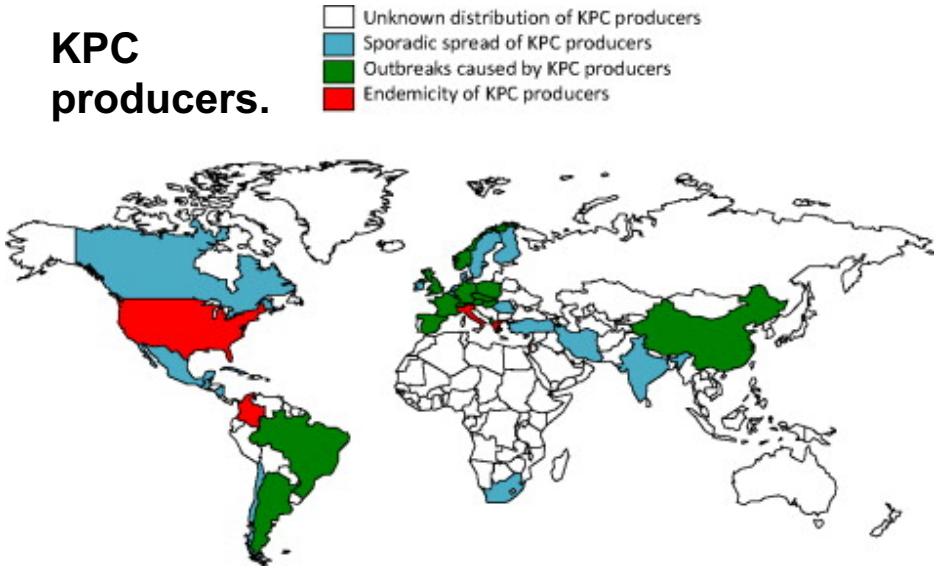
NB : pour un même épisode, plusieurs mécanismes de résistance différents peuvent être impliqués.

The tourist guide of carbapenemase-producing *Enterobacteriaceae*

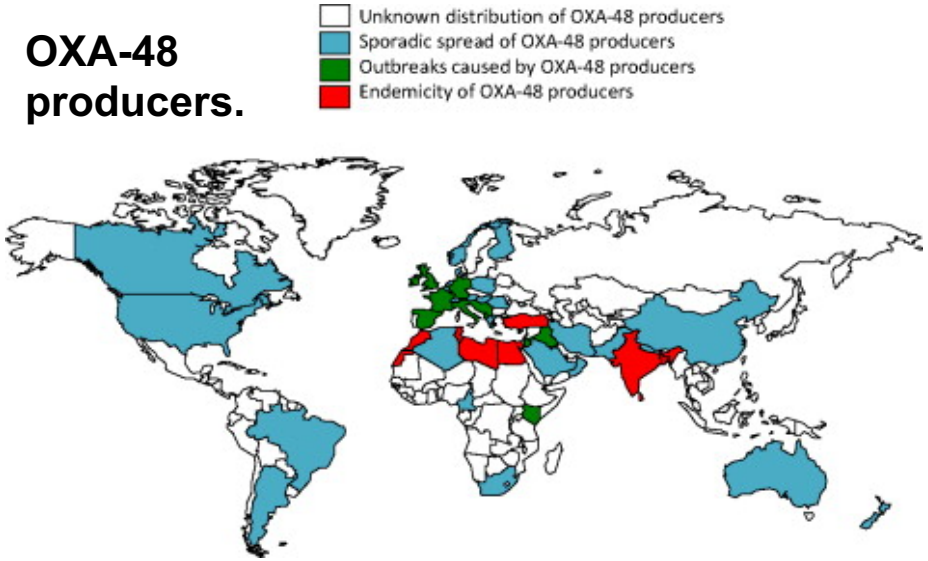
NDM producers.



KPC producers.

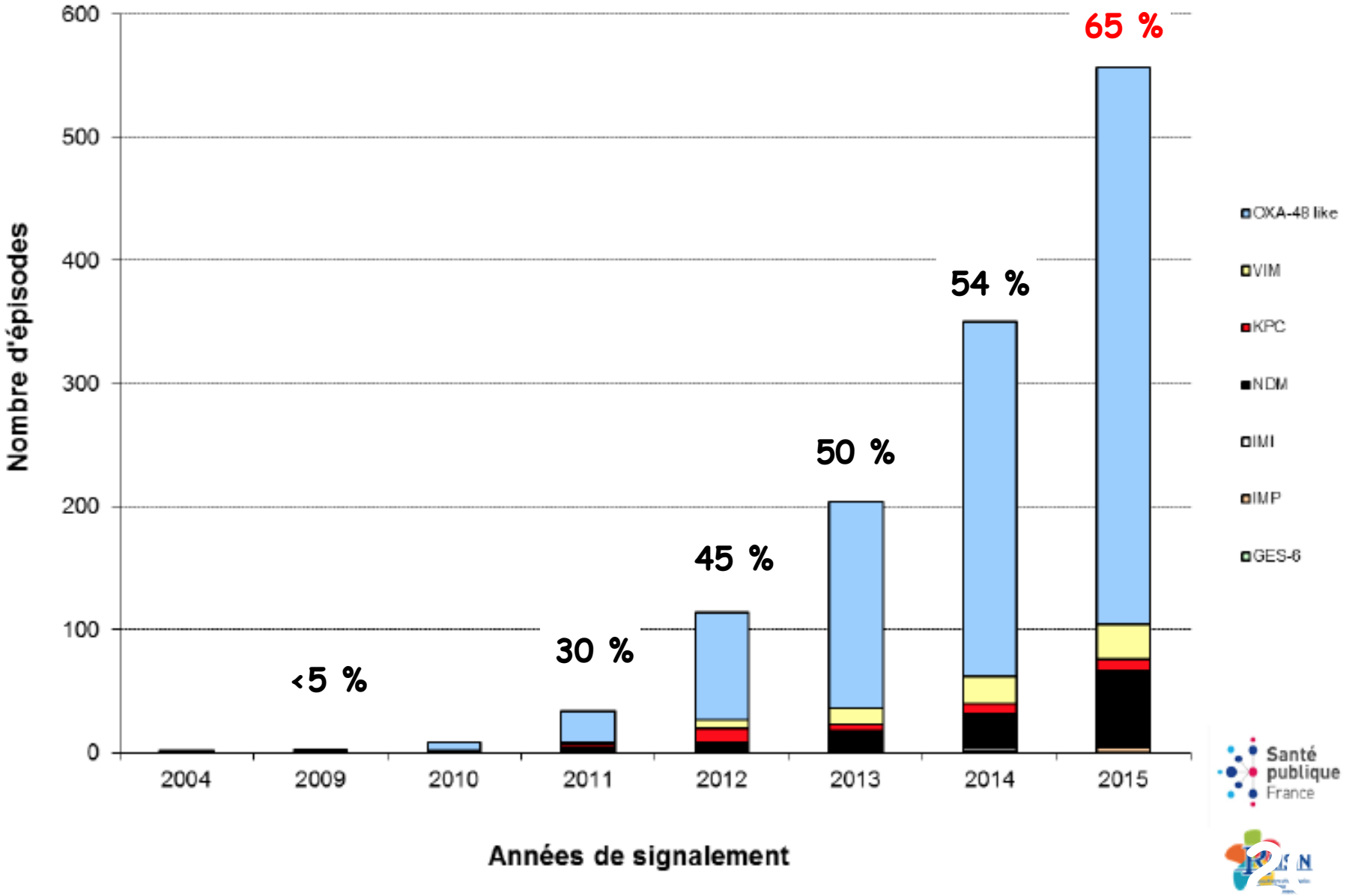


OXA-48 producers.



P. Nordmann, L. Poirel
CMI, 2014, 20, 821–830

Figure 10. Mécanismes de résistance impliqués dans les épisodes sans lien rapporté avec l'étranger, entre 2004 et 2015, par année de signalement (N=1 254 épisodes).



Colistin resistance ? Is the very last defence line about to fall?

- SENTRY study of the years **2014-2015**, have shown a prevalence of **0,4% among *E. coli*** isolates (n=13526) and **4,4% among *K. pneumoniae*** (n=7480) collected in 183 hospitals worldwide (Castaheira et al. AAC, 2016)

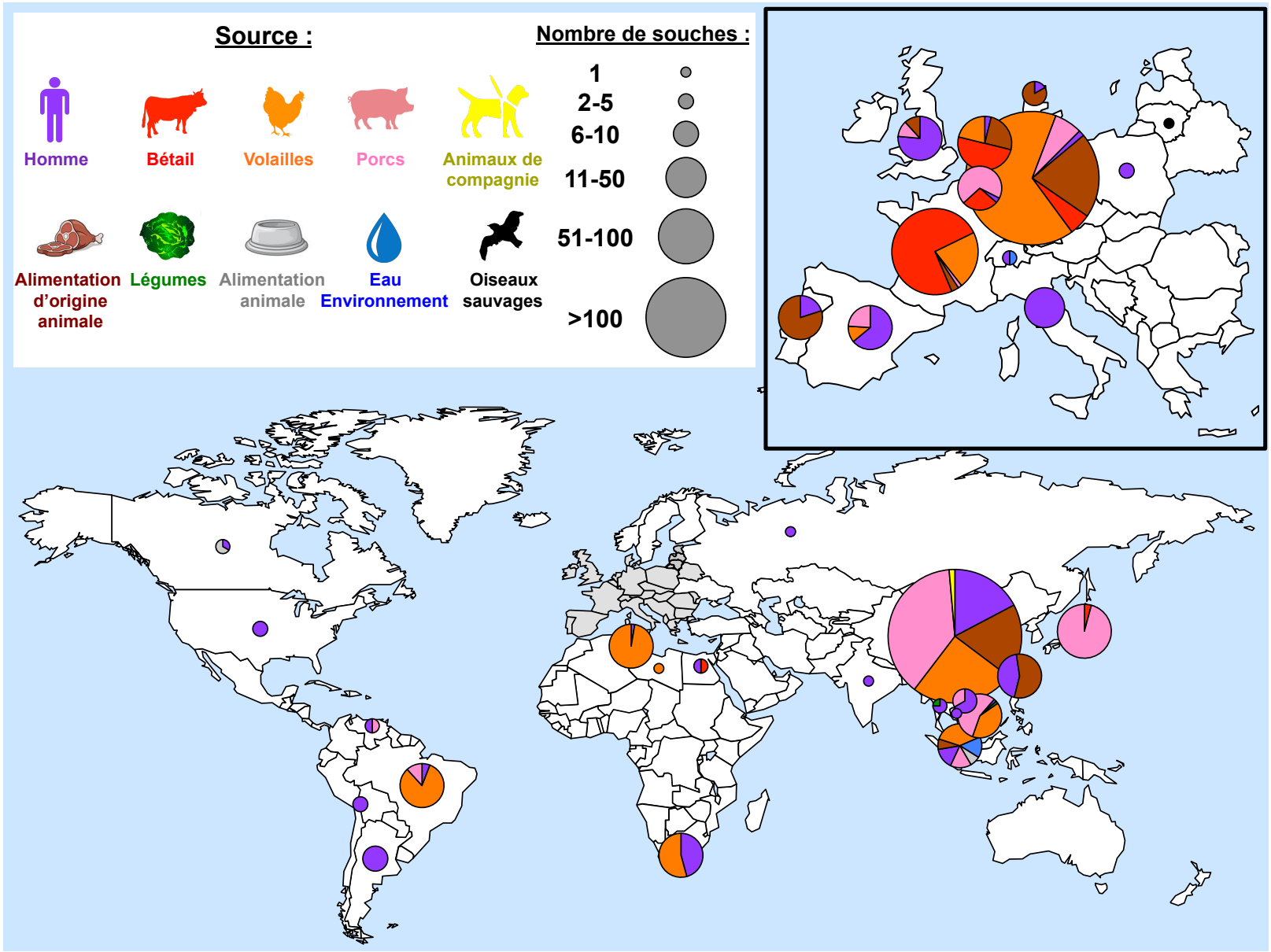
- This prevalence is however increasing as compared to the previous study performed in **Latin America between 2008 and 2010 (0,2% for *E. coli* and 3,0% for *K. pneumoniae)*** (Gales et al. DMID 2012)

- **In Europe 15% to 25% colistine resistance are reported in countries were carbapenem-resistance is already very high (Greece –Italy)**

- **In Greece colistin consumption has increased 6 times between 2009 -2013, while colistin resistant *K. pneumoniae* isolates from ICU patients rose from 0% over 2007-2010 to 21,8% over 2010-2013 period (Meletis et al, New Microbiol, 2015)**

- **Emergence of plasmid encoded colistine resistance mcr-1, mcr-1.2, mcr-2, mcr-5 ….. (Nov 2015)**

Geographic distribution of MCR-1-producing *Enterobacteriaceae* as of the 1st August 2016



What can be done?

IDENTIFICATION of CPEs

- As a source of infections

- As a source of gastro-intetinal colonisation

How?, Who?, When?, Why?

Treatment of infections

Novel alternatives to antibiotics?

Numerous approaches (antimicrobial peptides, phagotherapy, immunotherapy, vaccination, bacterial cannibalism, phototherapy, essentila oils)

Almost no clinical phase studies, or non validated by authorities (EMA, FDA, etc..)

Many in early stage of develpment développement (proof of concept, need for clinical studies)

=> NOVEL ANTIBIOTICS

Méthodes de détection des entérobactéries productrices de carbapénèmases

1) A partir d'un prélèvement clinique (infection)

2) Dépistage des patients porteurs

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

WHEN TO SCREEN FOR A CRE

Clinical breakpoints and screening cut-off values for CPE (according to EUCAST methodology)

	MIC (mg/L)		Disk diffusion zone diameter (mm)	
Carbapenem	S/I breakpoint	Screening cut-off	S/I breakpoint	Screening cut-off
Meropenem (10 µg)[1]	**≤2**	**>0.125**	**≥22**	**<25[2]**
Imipenem (10 µg)[3]	≤2	>1	≥22	<23
Ertapenem (10 µg)[4]	≤0.5	>0.125	≥25	<25

[1] **Best balance of sensitivity and specificity.**

[2] **In some cases OXA-48 producers have zone diameters up to 26 mm, so <27 mm may be used as a screening cut-off during outbreaks caused by OXA-48-producing Enterobacteriaceae, but with reduction in specificity.**

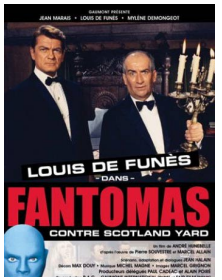
[3] **With imipenem the separation between the wild-type and carbapenemase-producers is relatively poor. Imipenem is therefore not recommended to use as a stand-alone screening test compound.**

[4] **High sensitivity, but low specificity, and therefore not routinely recommended.**

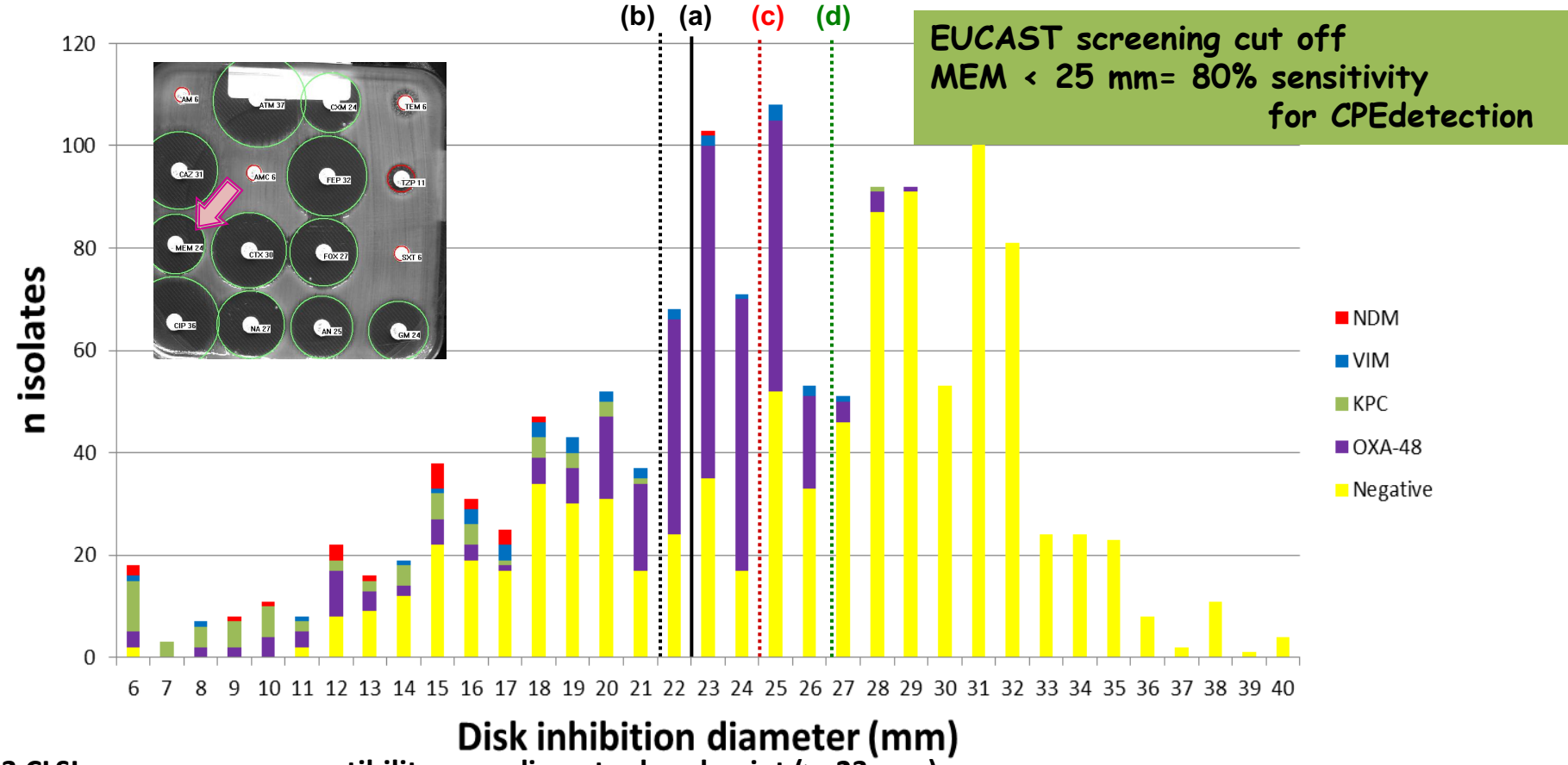
EUCAST Clinical breakpoints (v 6.0) (2016-01-01)

ARE EUCAST GUIDELINES SUFFICIENT?

Meropenem zone size distribution for suspected CPE isolates referred at two NRLs in Belgium and in France



« OXA-48 »



(a) 2013 CLSI meropenem susceptibility zone diameter breakpoint (>=23 mm)

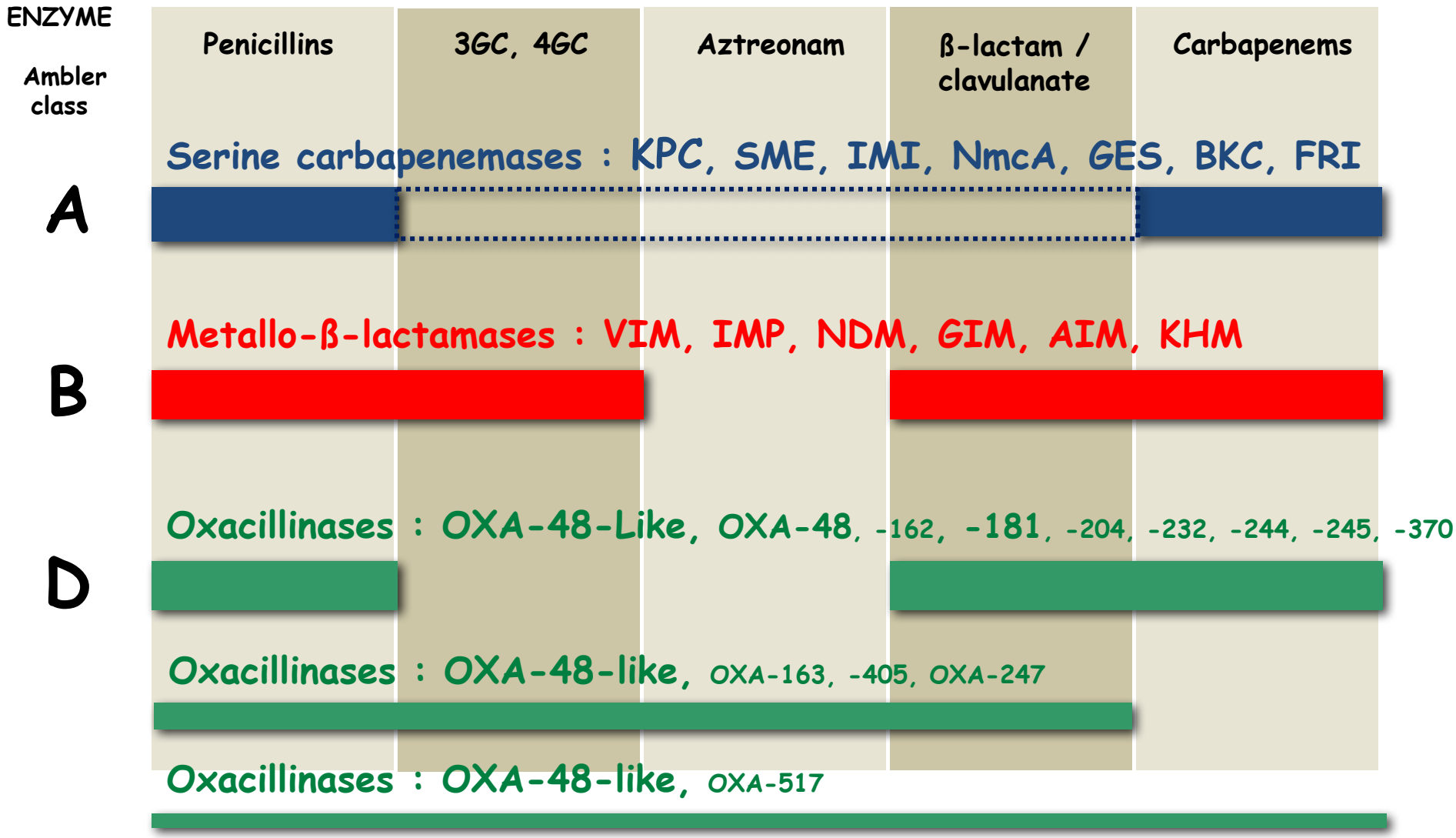
(b) 2013 EUCAST meropenem susceptibility zone diameter breakpoint (>=22 mm)

(c) 2013 EUCAST meropenem screening cut-off for the detection of CPE (<25 mm)

(d) 2013 EUCAST meropenem screening cut-off for the detection of CPE – epidemics (<27 mm)

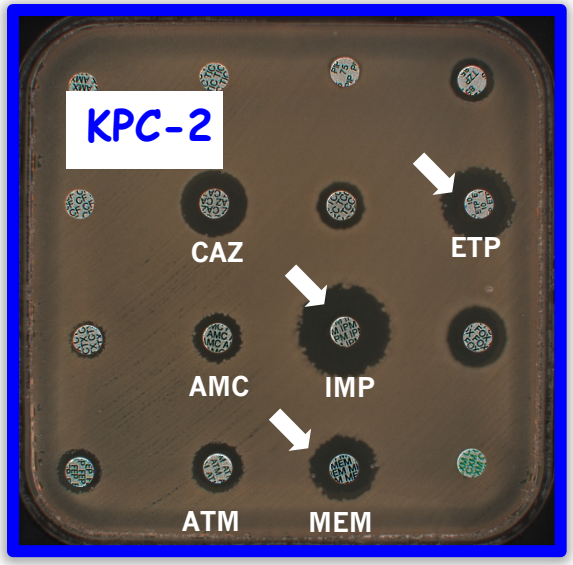
Huang TD et al., JAC 2013
(Courtesy Y Glupczynski)

Carbapenemases and *Enterobacteriaceae*
Hydrolysis profile

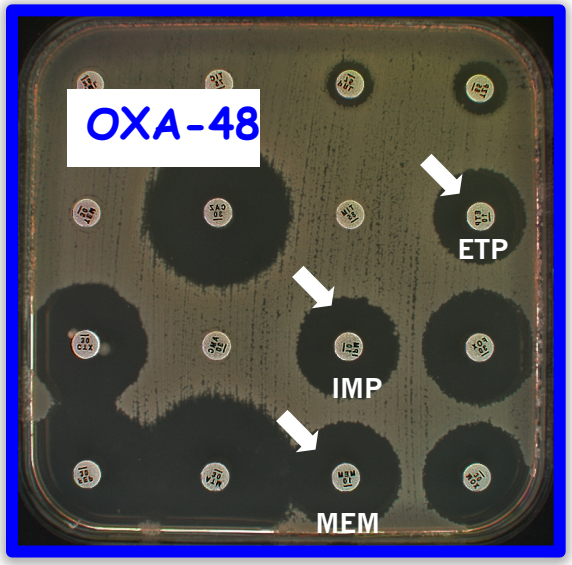


TO BE OR NOT TO BE A CARBAPENEMASE PRODUCER, THAT IS THE QUESTION IN CLINICAL MICROBIOLOGY !!!

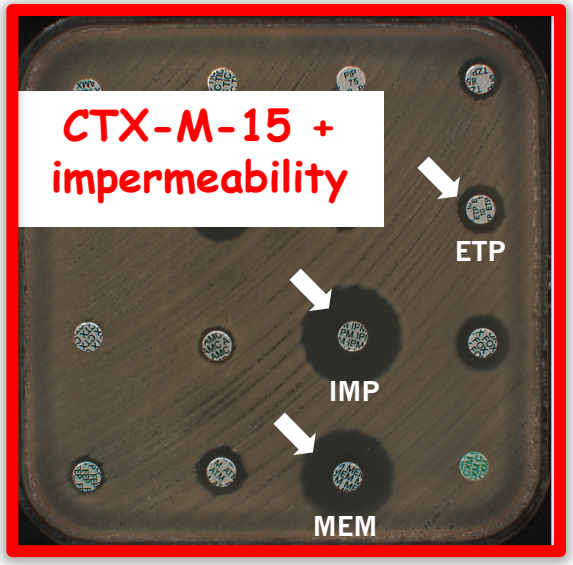
K. pneumoniae 1



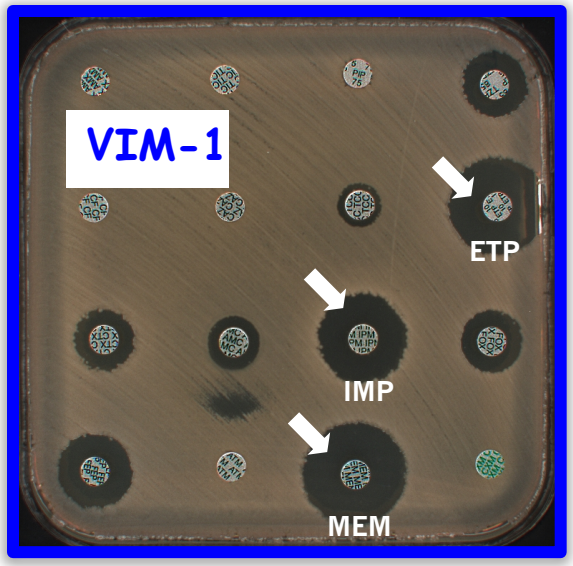
K. pneumoniae 2



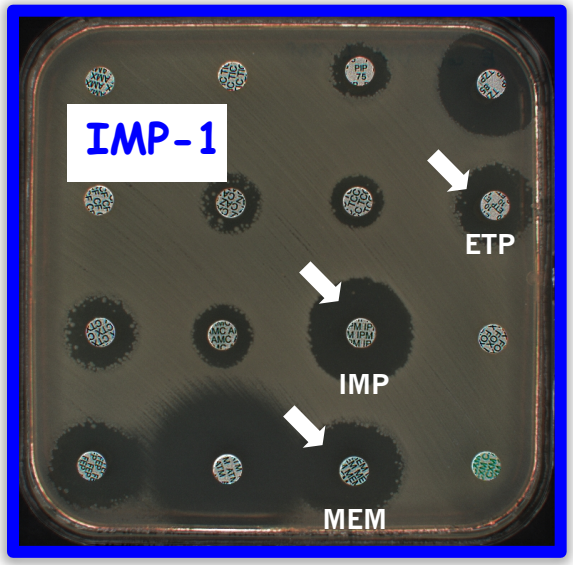
K. pneumoniae 3



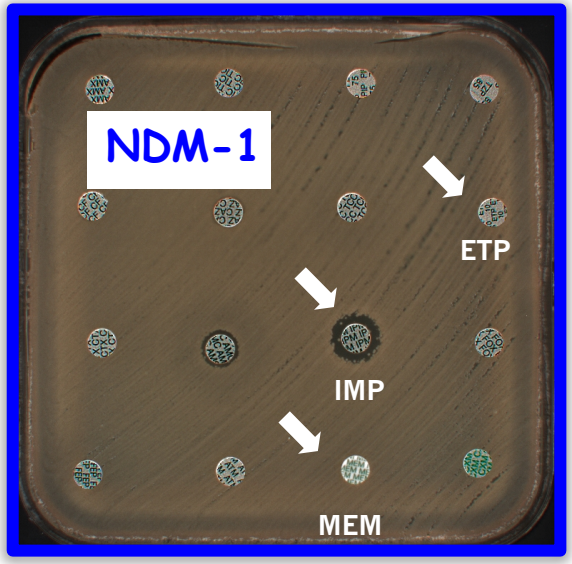
E. coli A



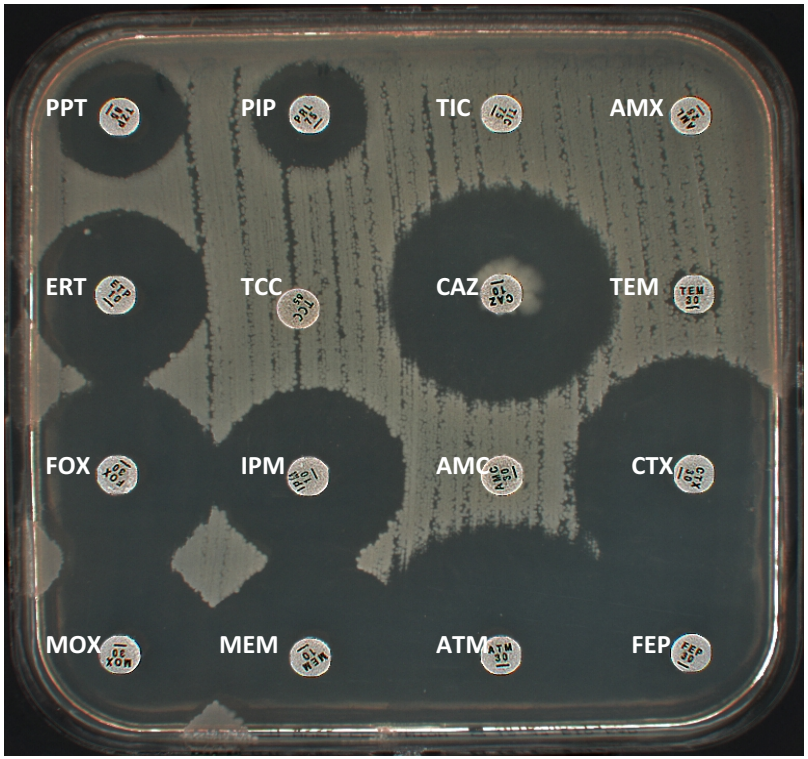
E. coli B

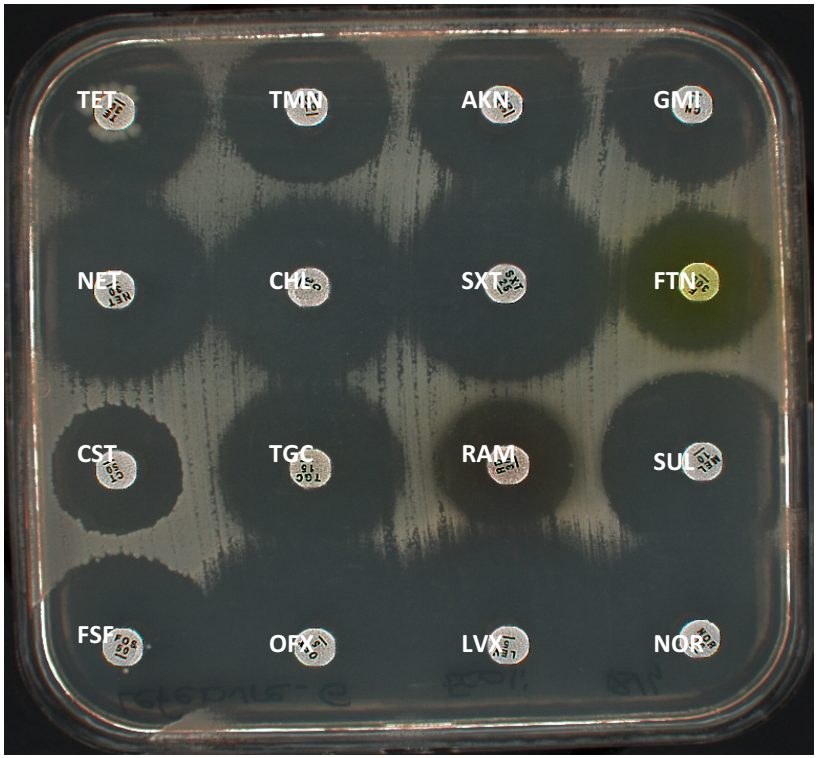


E. coli C



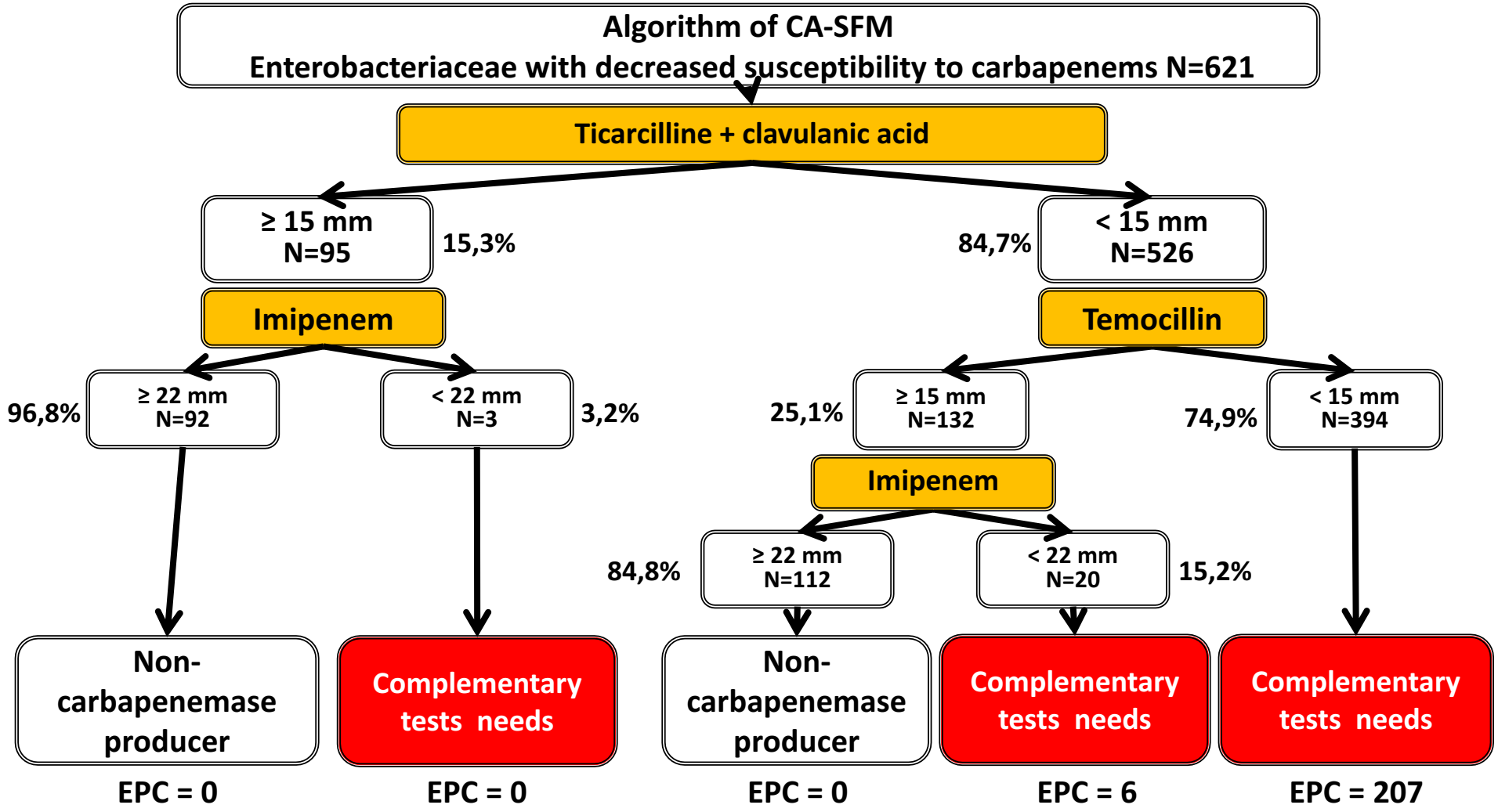
Urine with 10^7 *Escherichia coli*/ml.
Multi-susceptible





PPT : Pipéracilline-Tazobactam ; PIP : Pipéracilline ; TIC : Ticarcilline ; AMX : Amoxicilline ; ERT : Ertapénème; TCC : Ticarcilline-Acide clavulanique ; CAZ : Ceftazidime ; TEM : Temocilline ; FOX : Céfoxitine ; IPM : Imipénème; AMC : Amoxicilline-Acide clavulanique ; CTX : Céfotaxime ; MOX : Moxalactam ; ATM : Aztréonam; FEP : Céfépime ; TET : Tétracycline ; TMN : Tobramycine ; AKN : Amikacine ; GMI : Gentamycine ; NET : Netilmycine ; CHL : Chloramphénicol ; SXT : Bactrim ; FTN : Furanes ; CST : Colistine ; TGC : Tigécycline ; RAM : Rifampicine ; SUL : Sulfamide ; FSF : Fosfomycine ; OFX : Ofloxacine ; LVX : Lévofloxacine ; NOR : Norfloxacine

CMI ertapénème à 0,38 mg/l et imipénème 0,25mg/l)



5 NDM-1
1 NDM-5

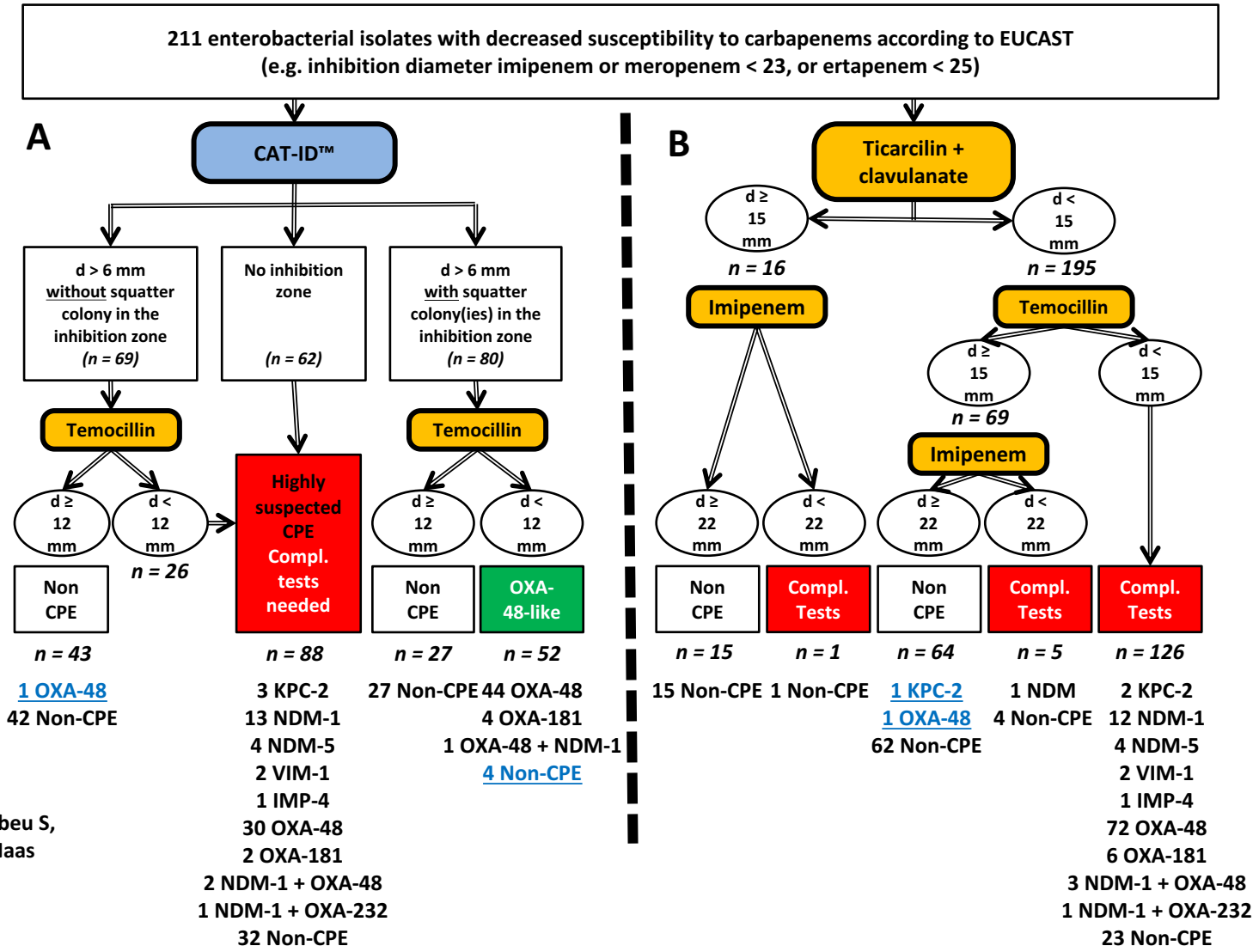
2 KPC-2, 1 KPC-3
10 NDM-1, 5 NDM-5
3 VIM-1, 1 VIM-4
166 OXA-48, 1 OXA-162
8 OXA-181, 9 OXA-204
1 OXA-232
1 NDM-1 + VIM-2
1 NDM-1 + OXA-48
1 NDM-1 + OXA-232

=> Eliminates 1/3 of putative CPEs (watch out for SME; IMI)

Prospective evaluation of an algorithm for the phenotypic screening of carbapenemase-producing Enterobacteriaceae

Dortet L, Cuzon G, Plésiat P, Naas T, JAC, 2016

Evaluation of an algorithm based on faropenem, and temocillin for the phenotypic detection and characterization of carbapenemase-producing *Enterobacteriaceae*



Dortet L, Bernabeu S, Gonzalez C, Naas
AAC 2017

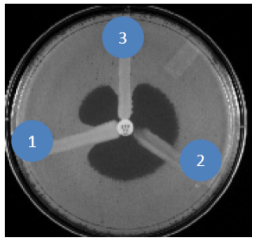
- Similar Performances (98.8% (Faro) *vs* 97.5% (CA-SFM) negative predictive value).
- Algorithm faropenem/témocillin detects well OXA-48-like producers => significant decrease of complementary tests (42.2% of isolates *vs* 62.6% with algorithme of CA-SFM).

Methods of CPE detection : confirmation tests

CNR RÉSISTANCE AUX ANTIBIOTIQUES

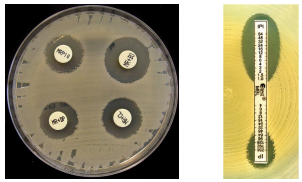
Phenotypic

Hodge test



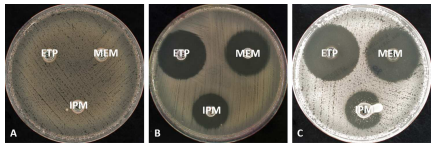
Girlich D. JCM 2012, **24h**

Inhibition tests



Girlich D. DMID 2013
Bonnin RA. JCM 2012
24h

CIM test



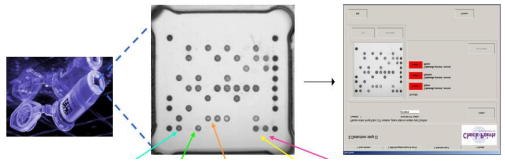
Gauthier, PlosOne, 2017
24h

Molecular

PCR et RT-PCR

Naas T. AAC 2011, 2016, **< 1h**

DNA micro-array



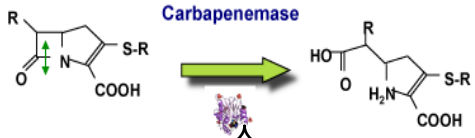
Naas T. JCM 2011, **7h**

Immuno-chromatography

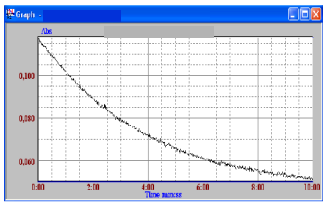
KPC
OXA-48,
NDM
(IMP
VIM)

Bogaerts, JAC, 2016, in press 2017
Dortet, JAC,, 2016, **15'**

Carbapenem -hydrolysis

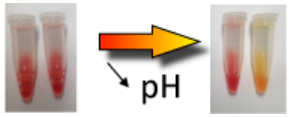


UV spectrophotometry



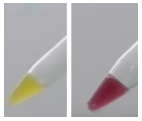
Bernabeu S. DMID 2012, **>2h**

Colorimetry



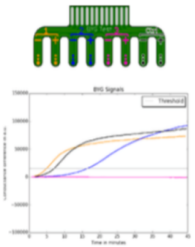
Dortet, AAC, 2012
Pires J, JCM, 2013
Dortet. JAC 2015, **2h**

β-Carba



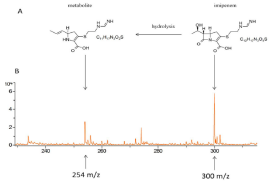
Bernabeu. JAC 2017 **<30'**

PH-metry



Bogaerts. JCM 2015, **<1h**

MALDI-TOF



Tandé D. JCM 2015, **30'**

rCIM

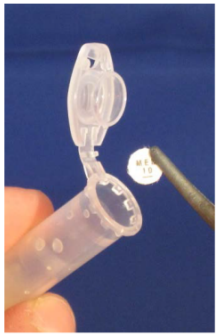
Muntean M. JAC, in press, **3h**

rCIM
(rapid Carbapenemase Inactivation Method)

Protocol

Bacteria of interest

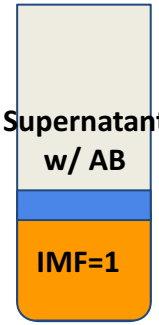
2 loopfulls



2 Meropenem discs

Incubate 30 minutes

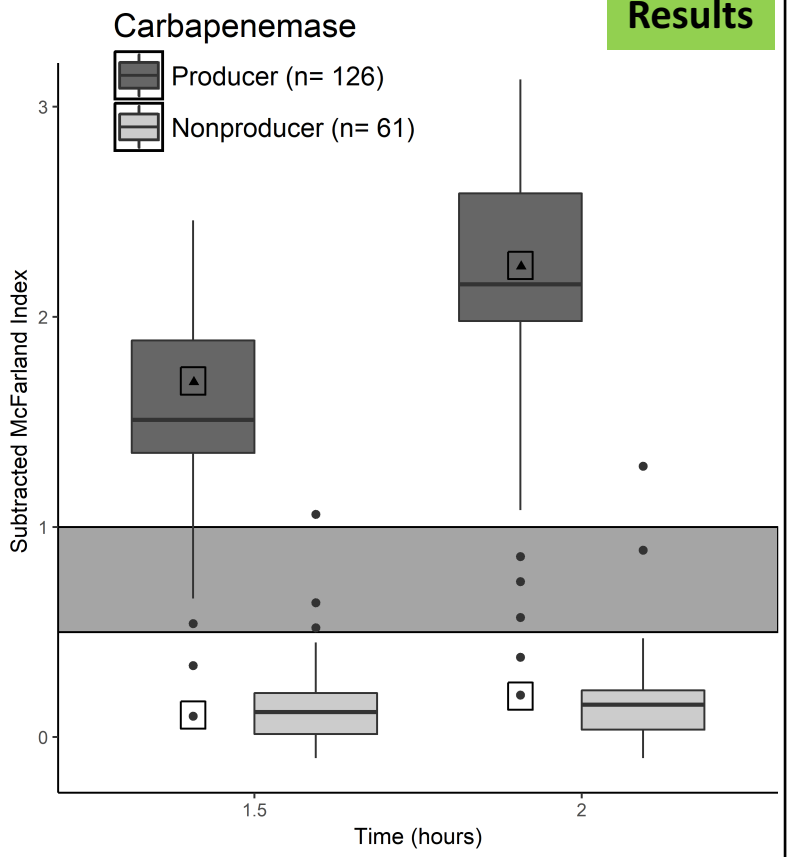
Centrifuge 5 minutes



E. coli ATCC 25922

Incubate 1.5 - 2h

Results



The rCIM correctly identified 62/63 of CPEs and 23/23 non-CPEs

⇒ rCIM: sensitivity of 98%, and specificity of 100%,

⇒ CIM and Carba NP test: 94% sensitivity and 100% specificity.

Muntean M. JAC, in press

Méthodes de détection des entérobactéries productrices de carbapénèmases

1) A partir d'un prélèvement clinique (infection)

2) Dépistage des patients porteurs

HOW? STOOLS / SWABS

AAC
Journals.ASM.org

Rectal Swabs Are Suitable for Quantifying the Carriage Load of KPC-Producing Carbapenem-Resistant *Enterobacteriaceae*

A. Lerner,[a,b] J. Romano,[a]* I. Chmelnitsky,[a] S. Navon-Venezia,[a] R. Edgar,[a] Y. Carmeli[a]

Molecular Epidemiology and Antimicrobial Resistance Laboratory, Division of Epidemiology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel[a]; Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel[b]

It is more convenient and practical to collect rectal swabs than stool specimens to study carriage of colon pathogens. In this study, we examined the ability to use rectal swabs rather than stool specimens to quantify *Klebsiella pneumoniae* carbapenemase (KPC)-producing carbapenem-resistant *Enterobacteriaceae* (CRE). We used a quantitative real-time PCR (qPCR) assay to determine the concentration of the bla_{KPC} gene relative to the concentration of 16S rRNA genes and a quantitative culture-based method to quantify CRE relative to total aerobic bacteria. Our results demonstrated that rectal swabs are suitable for quantifying the concentration of KPC-producing CRE and that qPCR showed higher correlation between rectal swabs and stool specimens than the culture-based method.

***AAC*, 2013, 57: 1474–1479.**

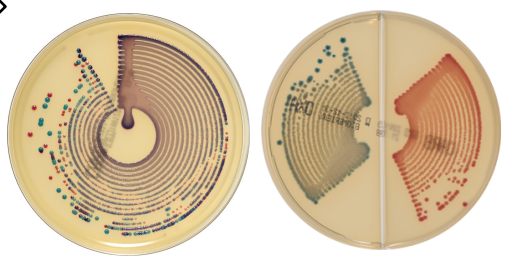
CPE colonisation detection

Stool, Rectal swabs

24-48h

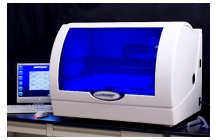
Enrichment culture

Selective Chromogenic media

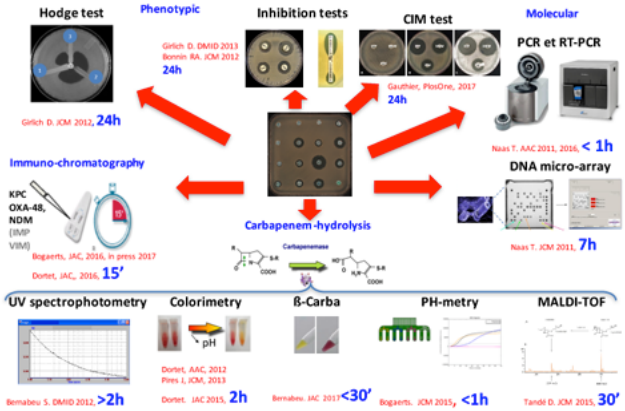


1-2h

Single- or Multi-plex Real time PCR



Girlich D. DMID. 2013
Réglier-Poupet H. JMM. 2008
Cuzon G. JCM. 2008



Naas T. AAC. 2013
Naas T. AAC. 2011
Oxacelay C. JAC. 2009
Hoyos, IJAA, 2017

HOW TO SCREEN? : CULTURE / MOLECULAR

- Culture: cheap, but lack of specificity and sensitivity, and LONG

- Molecular tools are often perceived as:

FASTER
Less then one hour

MORE ACCURATE:
Highly Sensitive and Specific

EASIER
Reduced hands-on-time, user friendly

MORE EXPENSIVE,
BUT WITH A MEDICAL ADDED VALUE

The answer is in the CPE prevalence

MOLECULAR METHODS FOR RAPID SCREENING OF CRE FROM RECTAL SWAB/STOOLS

Most studies in endemic areas with high prevalence, outbreak setting (infection control purposes)

Author (yr)	N° of specimens (pts)	Targeted bla genes	Method	Sens. %	Spec. %	Detection limit (CFU/PCR)	Process Time
Hindiyeh (2008)	189 (127)	KPC	RT PCR (TaqMan)	100	95	1	4h
Schechner (2009)	755 (650)	KPC	In house end -point PCR	92.6	99.6	-	30h* (culture: 144-192 h)
Giani (2012)	101 (65)	KPC	In house end-point PCR	100	86	1	3-4h
Pournaras (2012)	189 (NR)	KPC, VIM,	In house end-point PCR	94.4	86	NR	4h
Singh (2012)	95 (95)	KPC	RT PCR (TaqMan) FAM labeled reporter probes	97	96.6	1-10	24 h* (culture: 64-72h)
Richter (2012)	216 (125)	KPC-2/-12	Fast RT PCR (TaqMan) MGB probe	100	98	1	≤ 2h
Vasoo (2013)	126 (126)	KPC, NDM	RT PCR (Light Cycler) Simple lysis extraction (soiled spec.)	89.1 100	-	2-10	1.5-4 h

*** PCR performed from overnight enrichment broth culture**

CARBAPENEMASE GENE ASSAYS

	Check-Direct CPE on ABI 7500	Check-Direct CPE on BD MAX™	eazyplex SuperBug Complete	Xpert® Carba-R
Assay coverage	KPC, OXA-48-like, NDM/VIM	KPC, OXA-48-like, NDM, VIM	KPC, OXA-48, NDM, VIM	KPC, OXA-48, NDM, VIM, IMP-1-like
'Big 5' carbapenemases NOT detected	IMP family	IMP family	IMP family	some IMP subgroups
Hands on time per sample	<5 min	<5 min	<5 min	<5 min
Assay run time	~1.75 h	~2.5 h	20 min	~50 min
Sample throughput	Up to 94 tests in a batch	Up to 22 tests in a batch	1 or 2 independent tests	1 to 80 independent tests

Findlay J, et al. J Antimicrob Chemother. 2015 May;70(5):1338-42

Commercially available tests: the bloming of novel tests

- **Carbaplex (Brucker)**
  - IMP, KPC, NDM, OXA-48, VIM
  - (sens 96,3%, spec 99,5%) < 3h (de l'ADN extrait)
  - Ecouvillon
- **Carba Assay (Elitech)**
- **LightMix® modular carbapenemase kits (TIB Molbiol, Berlin, Germany)**
- **Amplidiag CarbaR-VRE (Mobidiag, Finlande)**
  - Détecte tous les variants IMP
  - Détecte les principales carbapénèmases des EPC, *P. aeruginosa* et *A. baumannii* (KPC, VIM, OXA-48/-181, IMP, NDM, ISAbal-OXA-51, OXA-23, OXA-40, OXA58, VanA, VanB)
  - Détecte toutes les BHREs en trois PCRs.
  - Sur colonies uniquement (nouvelle version incluant *mcr* et sur ecouvillon)

Extraction and independant PCR

⇒ **Avantages**

- **Open Systemes**
- **Good performances**

⇒ **But**

- **Long (4h),**
- **Trained personel**
- **Risk of contamination ++**

XPERT® CARBA-R

Détection simultanée de bla_{KPC}, bla_{NDM}, bla_{VIM}, bla_{IMP-1} and $bla_{OXA-48\ like}$ incluant les carbapénèmase OXA-181, OXA-232.

RAPIDE
Résultats en: 48 min

PRÉCIS:
Sensibilité 96 %
Spécificité 98 %

FACILE
Temps de manip. < 1 minute
« PCR pour les nuls »

Xpert Carba-R package insert

XPERT® CARBA-R V2 KIT FOR THE DETECTION OF CARBAPENEMASE-PRODUCING ENTEROBACTERIACEAE

CNR RÉSISTANCE AUX ANTIBIOTIQUES

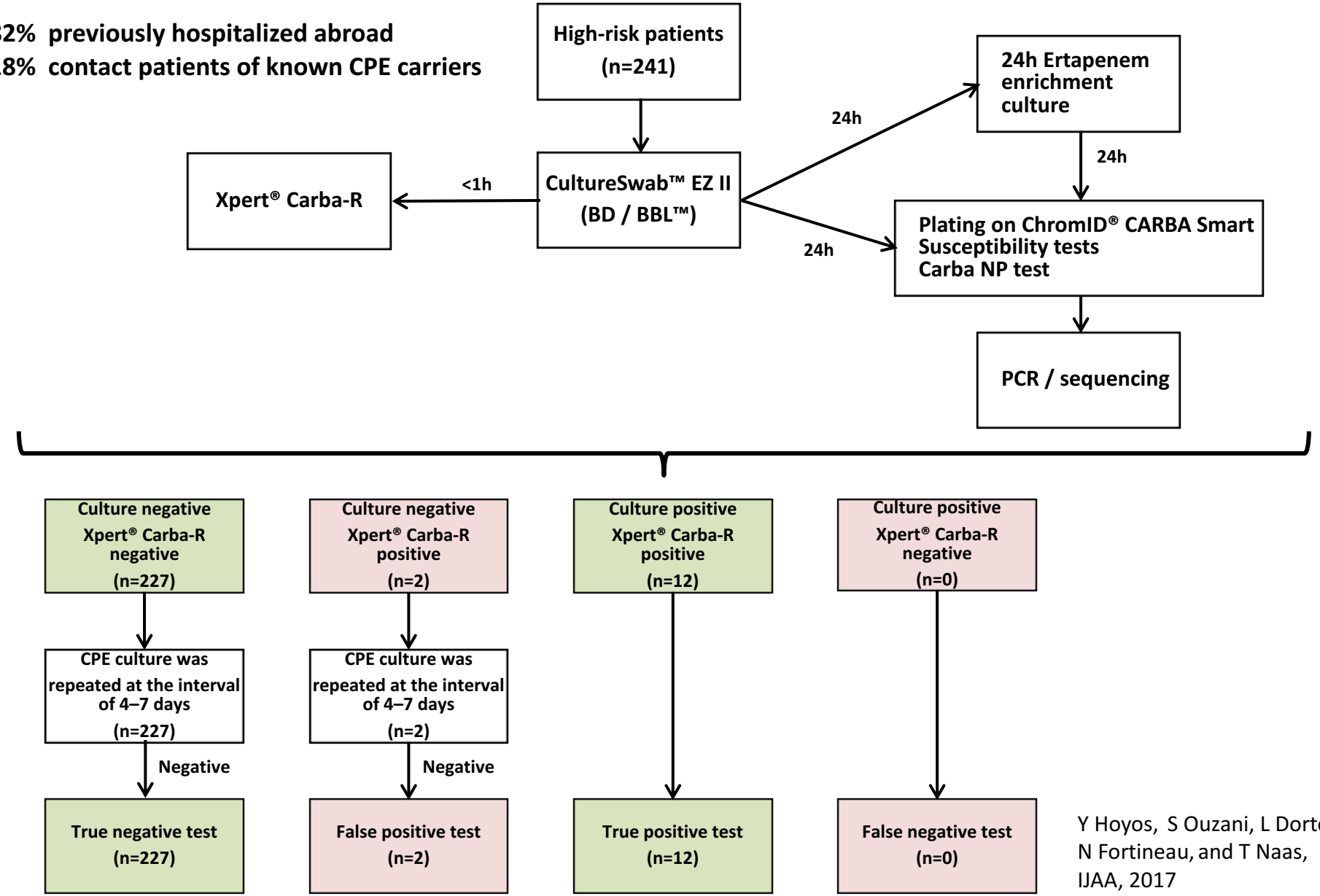
- **150 enterobacterial isolates including 130 isolates with decreased susceptibility to at least one carbapenem)**
- **61 non-carbapenemase producers**
- **89 carbapenemases producers :**

Performances	Xpert® Carba-R v2	
	This study	Global French CPE epidemiology (2012-2014)*
Sensitivity	97.8 %	99.61 %
Specificity	94.1 %	99.98 %
False positive	1 OXA-405 2 OXA-163	1 OXA-405
False negative	2 IMP-8	7 IMI 1 FRI-1

*** 2026 isolates**

Performances of the Xpert® Carba-R v2, in the daily workflow of a hygiene unit in a country with low prevalence of carbapenemase-producing *Enterobacteriaceae* (Sept 2015 - March 2016)

82% previously hospitalized abroad
18% contact patients of known CPE carriers



Y Hoyos, S Ouzani, L Dortet, N Fortineau, and T Naas, IJAA, 2017

Performances of the Xpert® Carba-R v2, in the daily workflow of a hygiene unit in a country with low prevalence of carbapenemase-producing *Enterobacteriaceae* (Sept 2015 - March 2016) (suite)

Patient	Xpert® Carba-R v2	Cultured CPE	Origin of patients
1	OXA-48 + VIM	*K. pneumoniae* OXA-48 and *E. cloacae* OXA-48 + NDM-1	Serbia
2	OXA-48	*K. pneumoniae* OXA-181	Algeria
3			France (contact patient of OXA-48 carrier)
4			
5			
6		OX	
7			
8			XA-48 carrier)
9			
10	OXA-48	*E. coli* OXA-181	India
11	OXA-48	*E. coli* OXA-204	France
12	OXA-48	*E. coli* OXA-48	Morocco
13	OXA-48	None	France (contact patient of OXA-48 carrier)
14	OXA-48	None	Cambodia
15	OXA-48	*E. aerogenes* OXA-48	France (patient contact)
16	OXA-48	*K. pneumoniae* OXA-48	Tunisie
17	OXA-48	*E. coli* OXA-48	Liban
18	NDM	*E. coli* NDM-5	Inde
19	OXA-48	*E. coli* OXA-48 *E. aerogenes* OXA-48	France (patient contact)
20	**NEG**	***C. freundii* OXA-48**	**France**

Performances biologiques
100% sensitivity,
99.13% specificity
85.71% positive predictive value
100% negative predictive value

2 false positives: What to do with these results?

⇒ **nothin? No diffusion to toher patients**
⇒ **Increased awareness (if antibiotherapy?)**

⇒ **Sept 2015 et nov 2016: 449 patients considered as high risk for CPE**
⇒ **Xpert® Carba-R v2 presents a sensibility of 94,44%, a specificity of 99.53%, a positive predictive value of 89.47% and a negative prédictive value of 99,76%.**
⇒ **CARE with false negatives: culture remains useful +++**

Explanations of PCR positive et culture negative

1. Antibiotic susceptibilities and phenotypic characteristics of the OXA-244-producing *E.coli* isolates.

Isolates	MLST[a]	Clones[b]	Plasmids size (c.a)	Date of isolation	Source of isolation	Origin	Susceptibility[c]					OXA-48 K-SeT®	Carba NP test[d]	RAPIDEC®Carba NP[d]	MALDI-TOF MS hydrolysis assay[d]	ChromID® ESBL[e]	Chrom ID® CARBA SMART[f]
							IMP (mg/L)	MEM (mg/L)	ETP (mg/L)	TEM (mg/L)	MOX (mm)						
86J1	ST-361	1	160 110 70	28/05/15	rectal	Egypt	0.5	0.5	2	>1024	**7**	+	+	+	+	+	+ | -
62D3	ST-1722	2	Abs	08/10/14	urine	unknown	0.38	0.38	1	128	21	+	+	+	+	+	- | -
69E6	ST-38	3	Abs	23/12/14	rectal	unknown	0.25	0.38	3	128	20	+	+/-	+	+	+	- | -
78B5	ST-38	3	Abs	15/04/15	rectal	unknown	0.38	0.5	3	256	21	+	+	+	+	+	- | -
35J9	ST-38	3	120 60 10	13/11/13	urine	France	0.5	0.75	2	96	21	+	-	+/-	-	-	- | -
73 G4	ST-3541	4	115	16/02/15	unknown	Egypt	0.25	0.19	0.75	128	20	+	+	+	+	+	- | -
85 H4	ST-3541	4	115	11/08/15	rectal	Egypt	0.38	0.25	2	384	20	+	+/-	+/-	-	+	- | -

2. CTX-M-15-producing *Shewanella bicestrii* sp. nov. clinical isolate harboring a chromosome encoded OXA-48 variant, progenitor of plasmid encoded OXA-436. (Jousset et al. AAC submitted)

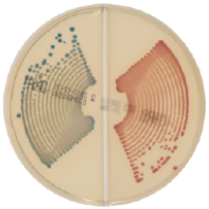
=> isolated from a 7-year-old immune-compromised child suffering from cholangitis.

3. *A. hermannii* VIM-1, no expression of the carbapenemase in that background, but PCR + , plasmid transferable

CNR
RÉSISTANCE AUX ANTIBIOTIQUES

Version mai 2016

Fiche résumée globale: Recommandations pour la détection des EPC à partir d'une colonies suspecte (d'après l'épidémiologie française des EPC)



Dépistage
Pousse sur milieu de screening EPC

Antibiogramme
Diminution de sensibilité à au moins un carbapénème

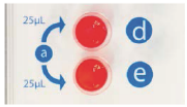
***K-Set* OXA-48**

(+) **Carbapénèmase de type OXA-48**

(-) **RAPIDEC CARBA NP**

(+) **Carbapénèmase de type NDM, KPC, VIM, IMI, ou IMP**

Envoi de la souche au CNR pour typage définitif



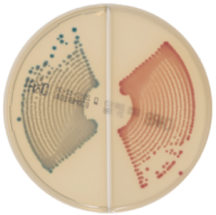
(-) **Absence de carbapénèmase**

http://www.cnr-resistance-antibiotiques.fr/exp-des-souches-1.html

CNR
RÉSISTANCE AUX ANTIBIOTIQUES

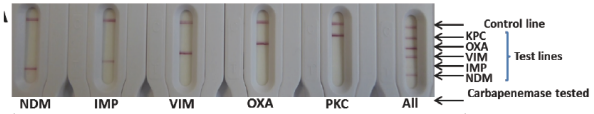
Version 2018

Fiche résumée globale: Recommandations pour la détection des EPC à partir d'une colonies suspecte (d'après l'épidémiologie française des EPC)



Dépistage
Pousse sur milieu de screening EPC

Antibiogramme
Diminution de sensibilité à au moins un carbapénème



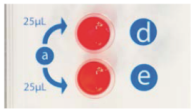
(+) **Carbapénèmase de type: KPC, NDM, VIM, IMP, OXA-48-like**

Envoi de la souche au CNR pour typage définitif

(+) 

Carbapénèmase de type IMI +++, FRI, GES ou autre

(-) **RAPIDEC CARBA NP**

(-) 

Absence de carbapénèmase

http://www.cnr-resistance-antibiotiques.fr/exp-des-souches-1.html

CNR
RÉSISTANCE AUX ANTIBIOTIQUES

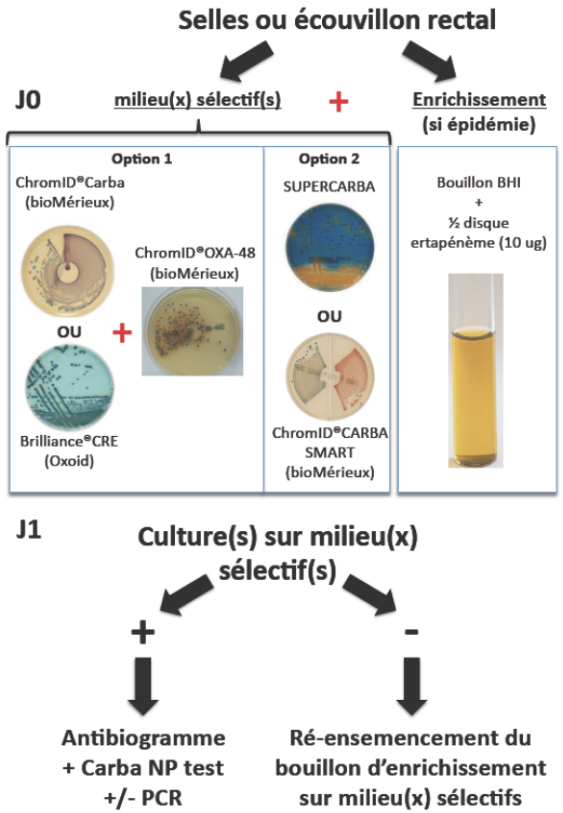
Fiche résumée : Recommandations pour le dépistage des patients porteurs d'une souche d'EPC (patients colonisés)

1) Patient ayant eu dans les 12 derniers mois une hospitalisation de plus de 24 h quel que soit le secteur ou de prise en charge dans une filière de soins spécifique (dialyse) à l'étranger.

2) Types de prélèvements : **selles** ou **écouvillonnages rectaux.** il est important de **vérifier visuellement la présence de matières fécales sur l'écouvillon.**

3) Il est conseillé de **répéter les prélèvements** en cas de forte suspicion de colonisation par une EPC (3 prélèvements à 3-4 jours d'intervalle). Ne pas hésiter à réaliser un nouveau dépistage après la mise sous antibiothérapie.

4) Méthodologie recommandée pour le dépistage des patients porteur d'une EPC :



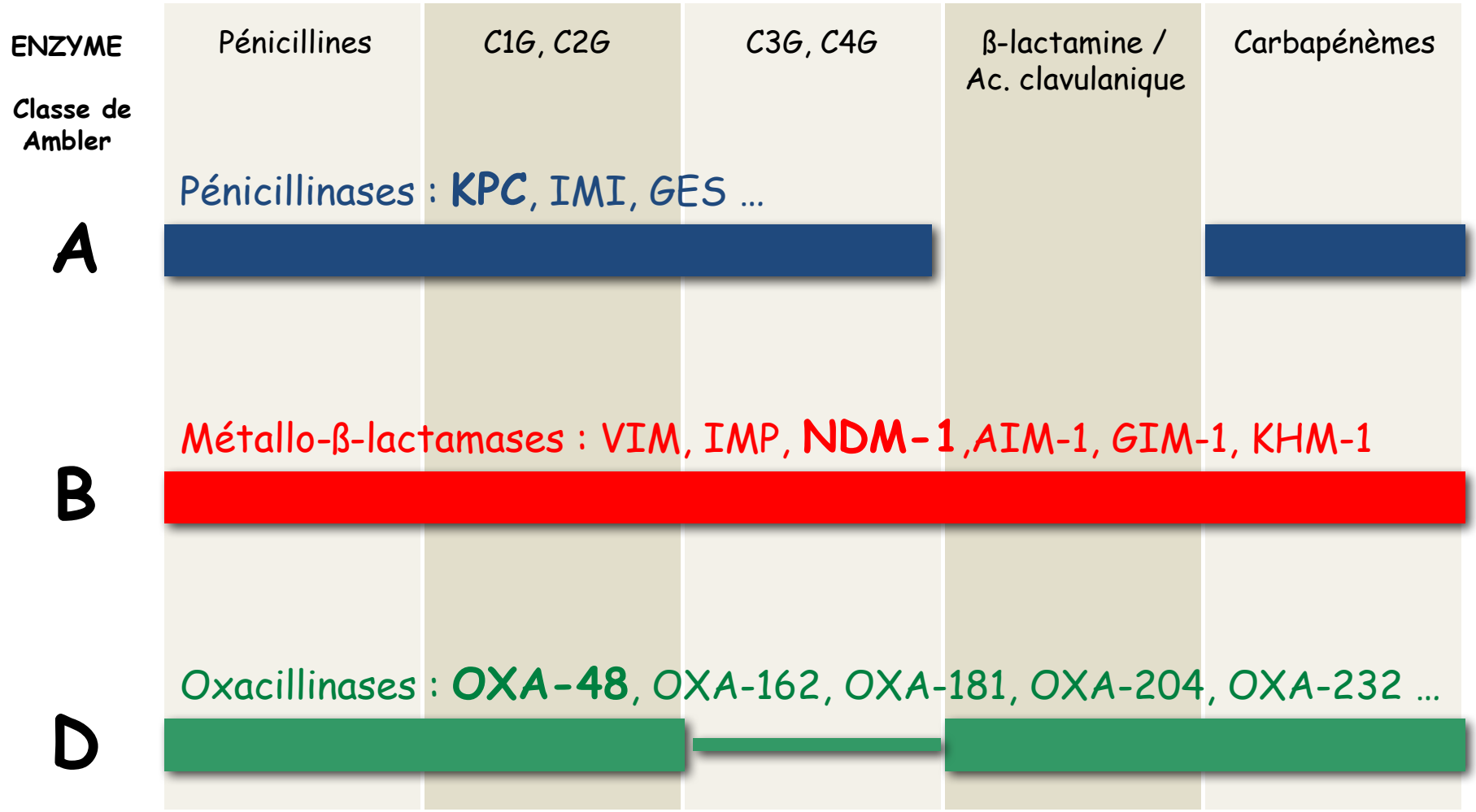
5) **La détection moléculaire de EPC directement à partir du prélèvement** permet de gagner une journée sur la détection des EPC. Etant donné la non détection de certaines carbapénèmases par biologie moléculaire il est conseillé de **réserver ce type de technique au dépistage des patients contact lors d'épidémies**. Il conviendra alors de vérifier que le kit de biologie moléculaire est capable de détecter efficacement la souche épidémique avant utilisation directe sur les prélèvements cliniques.

http://www.cnr-resistance-antibiotiques.fr/exp-des-souches-1.html

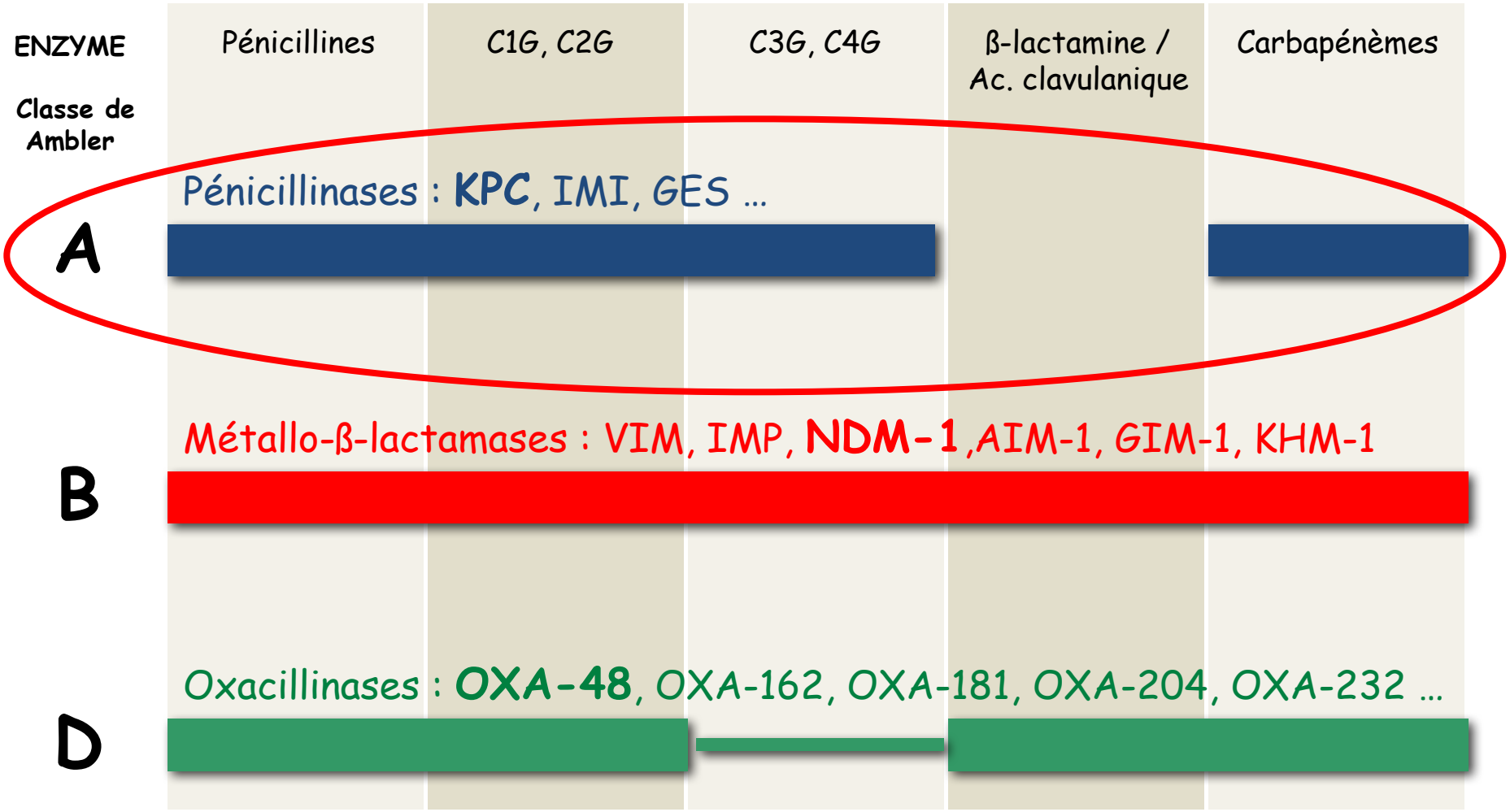
Acknowledgements

- Dr Agnès Jousset
- Dr Rémy Bonnin
- Dr Delphine Girlich
- Dr Lauraine Gauthier
- Dr Gaëlle Cuzon
- Dr Nicolas Fortineau
- Dr Thierry Naas

Les carbapénèmases chez les entérobactéries



Les carbapénèmases chez les entérobactéries



KPC : *Klebsiella Pneumoniae* Carbapenemase

2001

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2001, p. 1151–1161
0066-4804/01/$04.00+0 DOI: 10.1128/AAC.45.4.1151–1161.2001

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 30333[1]; The R. W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey 08869[2]; and Unidad de Investigacion, Hospital Son Dureta, Andrea Doria, Palma de Mallorca, 07014,[4] and Área de Microbiologia, Universidad de las Islas Baleares, Crtra. Valldemosa, Palma de Mallorca, 07071,[3] Spain

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

Dissémination de KPC

ORIGINAL INVESTIGATION

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ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2006, p. 3098–3101
0066-4804/06/$08.00+0 doi:10.1128/AAC.00438-06
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Plasmid-Mediated Imipenem-Hydrolyzing Enzyme KPC-2 among Multiple Carbapenem-Resistant *Escherichia coli* Clones in Israel

Shiri Navon-Venezia,* Inna Chmelnitsky, Azita Leavitt, Mitchell J. Schwaber, David Schwartz, and Yehuda Carmeli

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2007, p. 3026–3029 Vol. 51, No. 8
0066-4804/07/$08.00+0 doi:10.1128/AAC.00299-07
Copyright © 2007, American Society for Microbiology. All Rights Reserved.

Emergence of KPC-2 and KPC-3 in Carbapenem-Resistant *Klebsiella pneumoniae* Strains in an Israeli Hospital▽

Azita Leavitt, Shiri Navon-Venezia, Inna Chmelnitsky, Mitchell J. Schwaber, and Yehuda Carmeli*

Division of Epidemiology and the Laboratory for Molecular Epidemiology and Antibiotic Research, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

E. coli et *E. cloacae* (Petrella, AAC, 2008)

E. Cloacae KPC-4 (Ecosse)

Cuzon, Naas, Demachy, Nordmann (AAC 2007)

K. pneumoniae KPC-2

Intercontinental travels of patients and dissemination of plasmid-mediated carbapenem KPC-3 associated with OXA-9 and TEM-1

Laurent Dortet[1], Irina Radu[1], Valérie Gautier[2], François Blot[3], Elisabeth Chachaty[1] and Guillaume Arlet[2,4]*

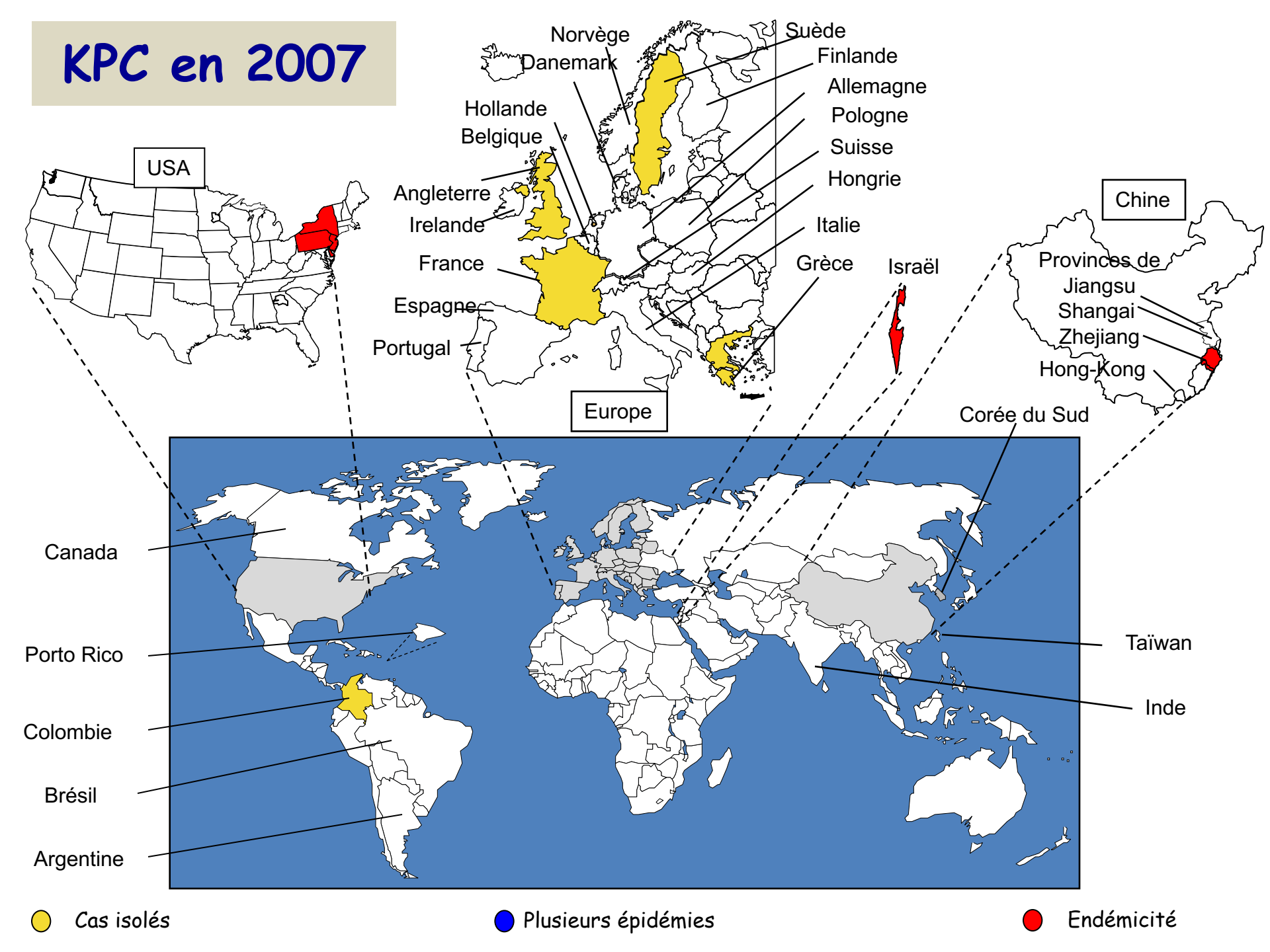
(JAC, 2009)

***E. cloacae* KPC-3**

Plasmid-Mediated Carbapenem-Hydrolyzing β-Lactamase KPC in a *Klebsiella pneumoniae* Isolate from France

Naas, Nordmann, Vedel, Poyart (AAC 2005)

KPC en 2007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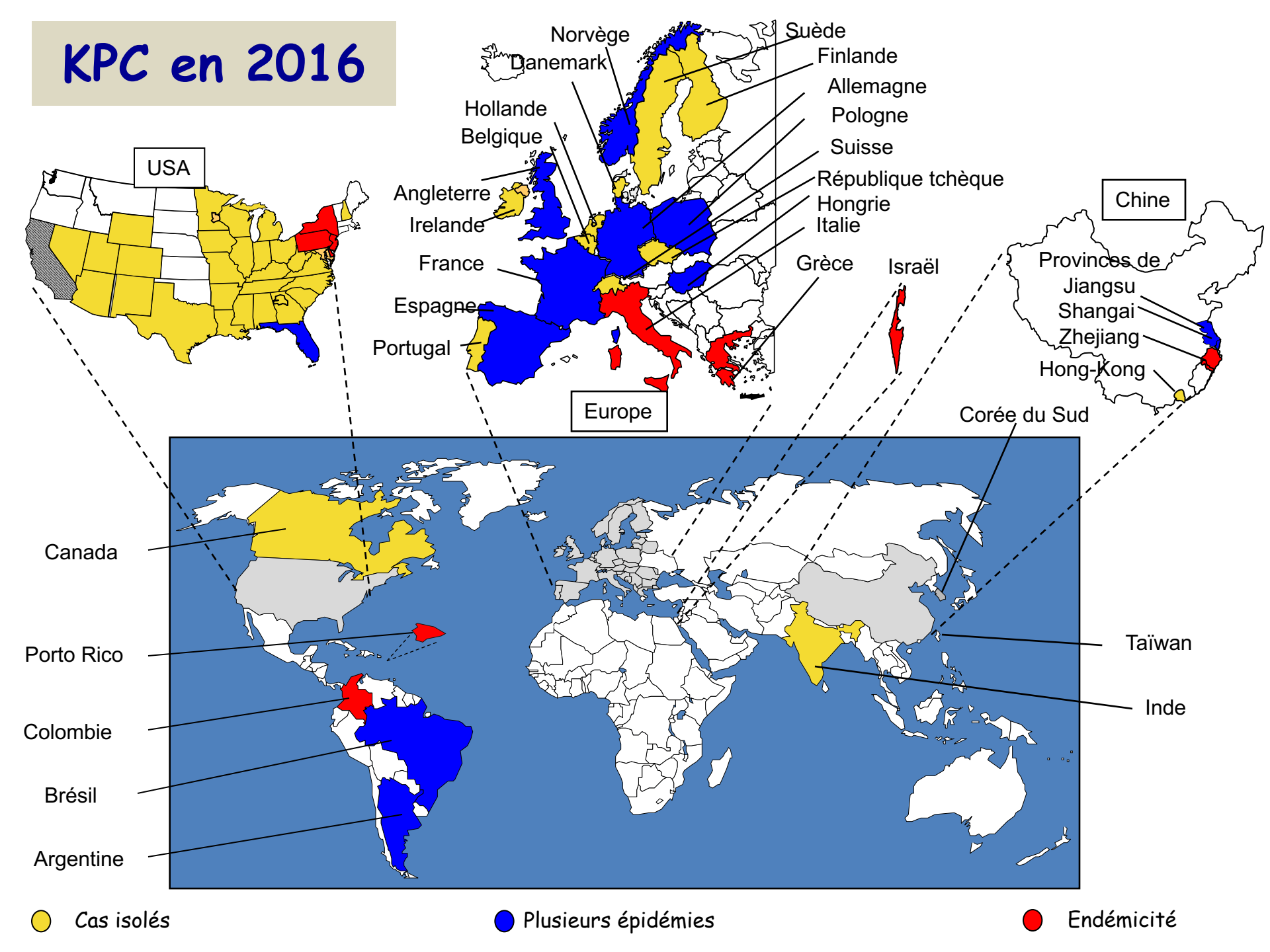
Irelande
France
Espagne
Portugal
Europe
Israël
Chine
Provinces de
Jiangsu
Shangai
Zhejiang
Hong-Kong
Corée du Sud
Canada
Porto Rico
Colombie
Brésil
Argentine
Taïwan
Inde
Cas isolés
Plusieurs épidémies
Endémicité

KPC en 2016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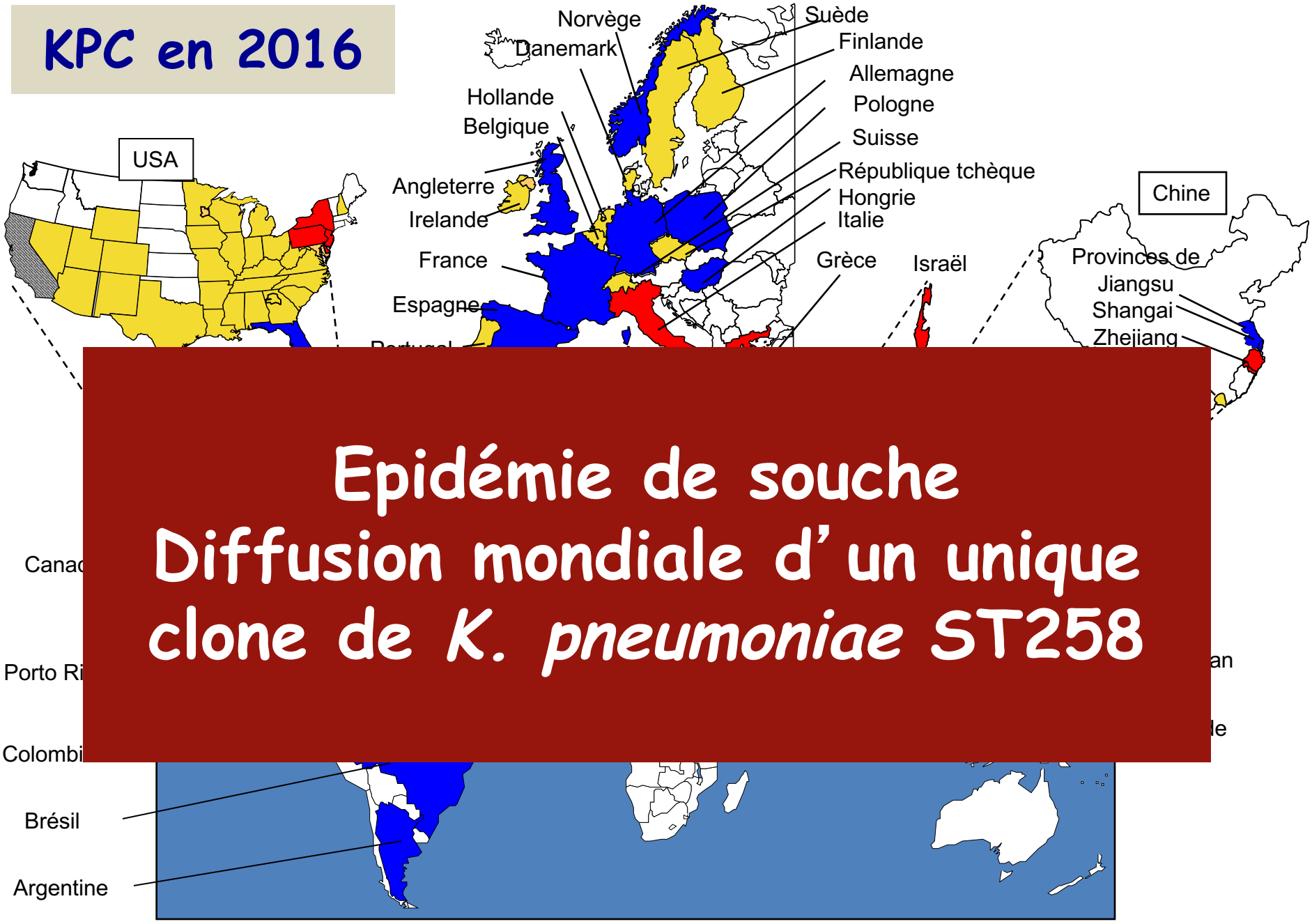
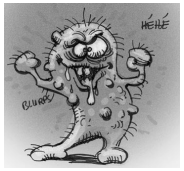
Colombie
Brésil
Argentine
Cas isolés
Plusieurs épidémies
Endémicité

KPC en 2016



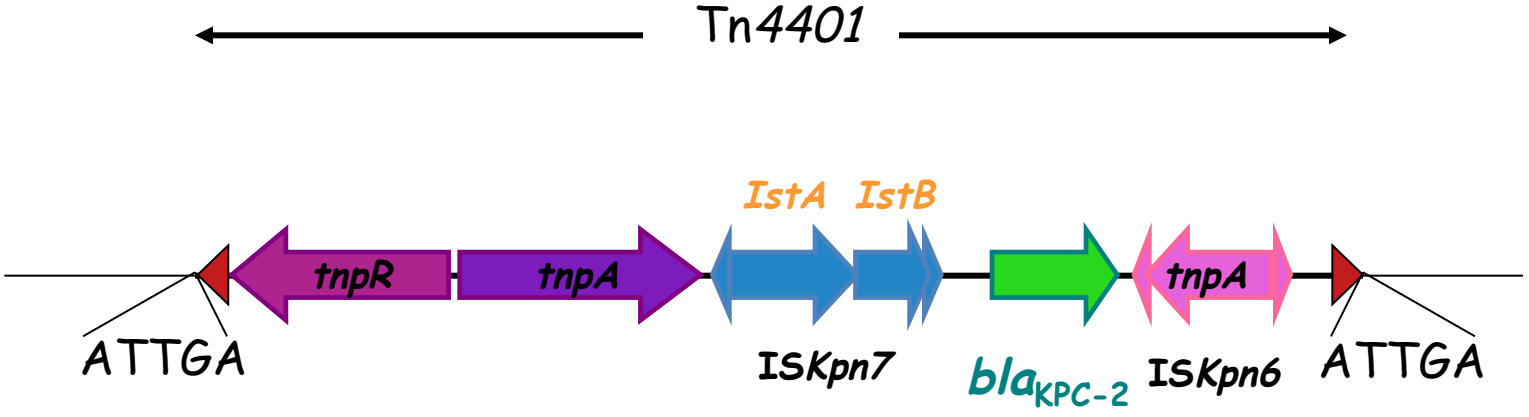
Epidémie de souche
Diffusion mondiale d'un unique clone de *K. pneumoniae* ST258



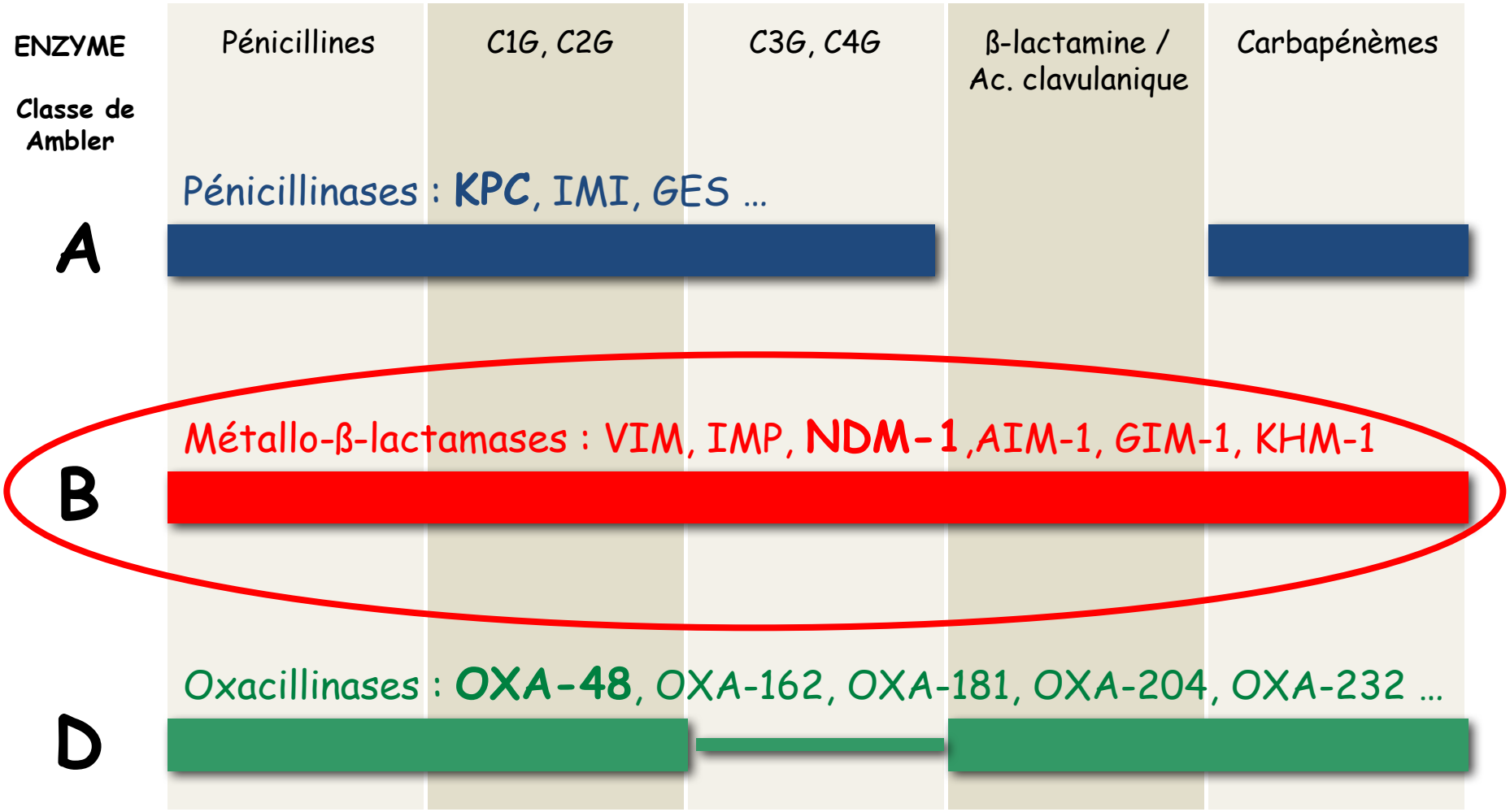
Diffusion mondiale du clone ST-258

- *K. pneumoniae* KPC+ : 33% de ST-258 ⇒ **Diffusion clonale**

- Grande diversité de plasmides mais environemmt génétique conservé (Tn*4401*)



Les carbapénèmases chez les entérobactéries



Metallo-ß-lactamases de type VIM, IMP et GIM

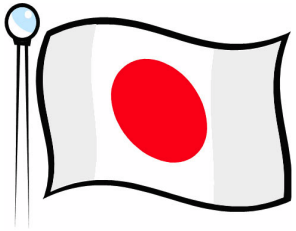
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 1999, p. 1584–1590 Vol. 43, No. 7
0066-4804/99/$04.00+0

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 Vol. 39, No. 4
0066-4804/95/$04.00+0

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 OHTA[1]

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

IMP 1995

AAC
Journals.ASM.org

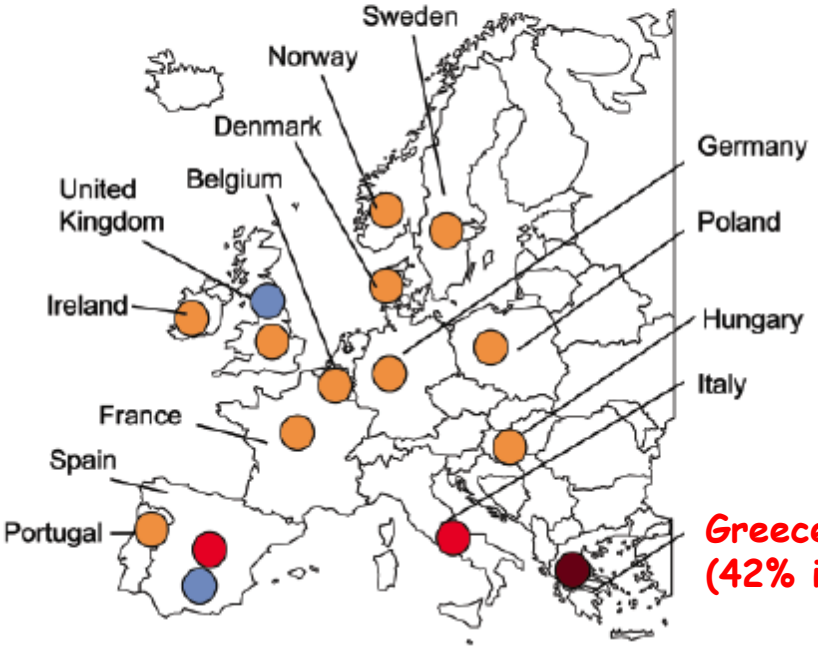
Emergence of Metallo-β-Lactamase GIM-1 in a Clinical Isolate of *Serratia marcescens*

Heime Rieber,* Andre Frontzek,* and Yvonne Pfeifer[b]

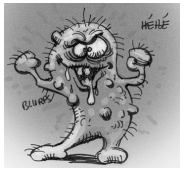
GIM 2012

Dissémination mondiale des MBLs de type IMP et VIM

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

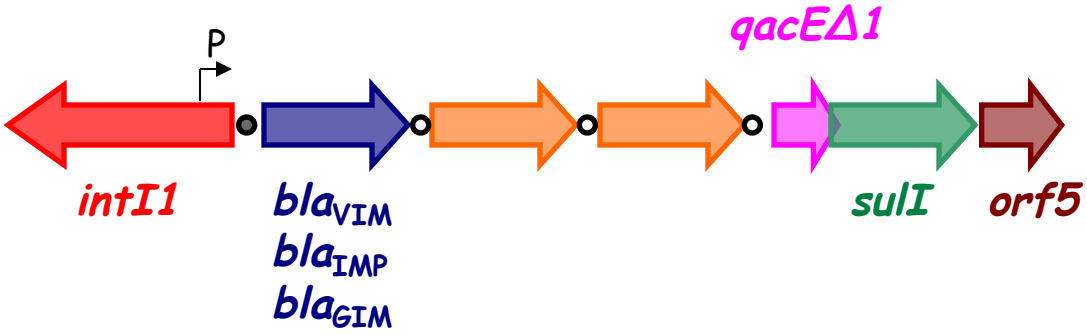


Greece
(42% in *K. pneumoniae*)



Environnement génétique de bla_{VIM} , bla_{IMP} et bla_{GIM}

- **Intégron de class 1**



- Diversité de plasmides

- ***Pseudomonas aeruginosa*** **et entérobactéries**

NDM : New Dehli Metallo-ß-lactamase

2009

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

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]*

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

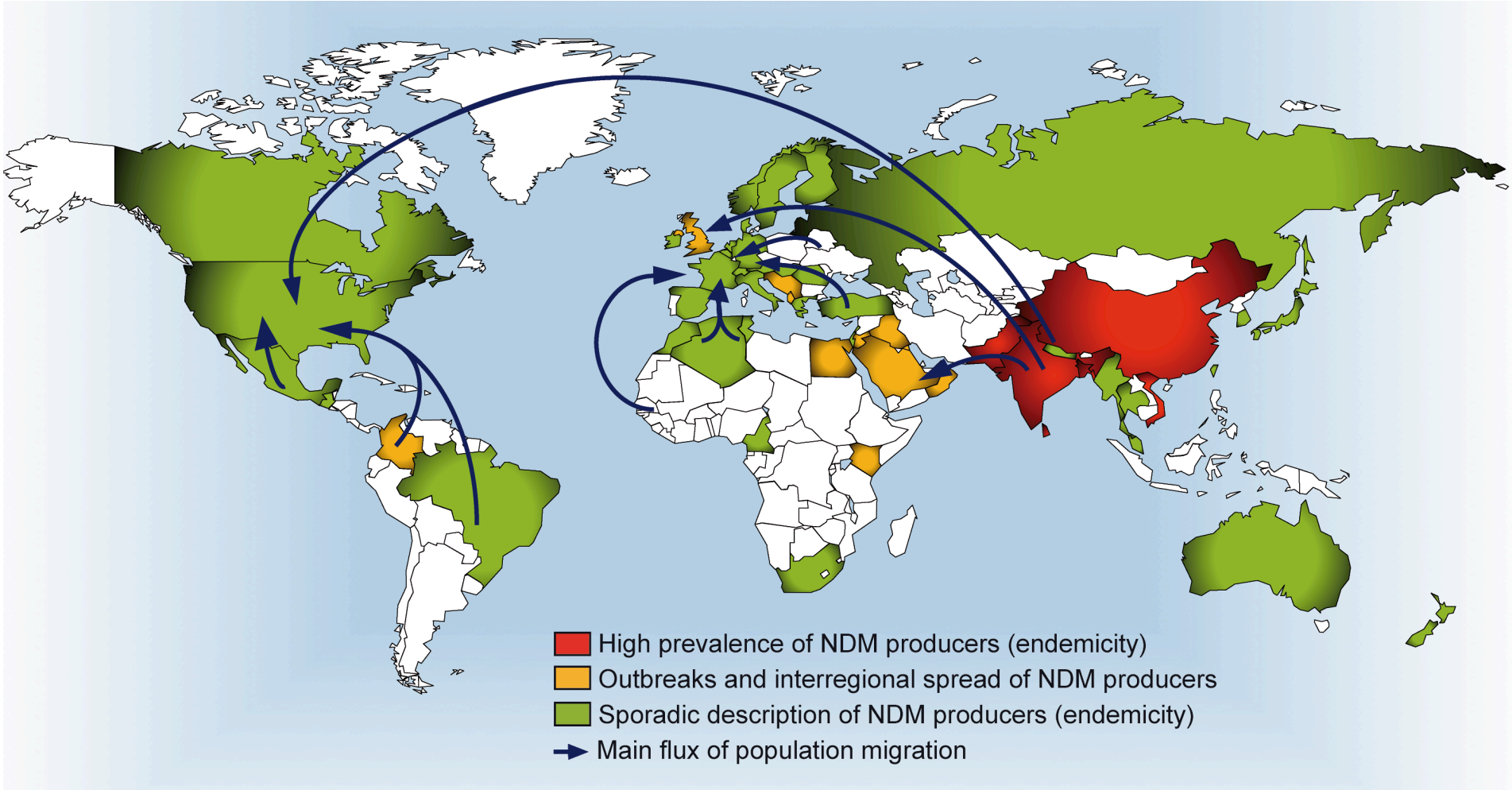
Lancet Infectious Diseases 2011

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

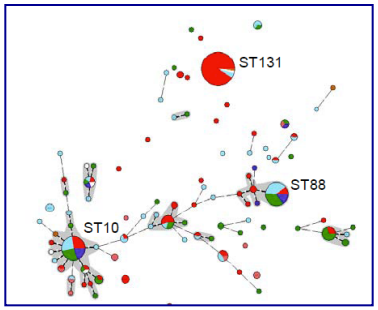
John D. Perry[1]*, Sakeenah Hussain Naqvi[2], Irfan Ali Mirza[2], Shehla Ambreen Alizai[2], Aamir Hussain[2], Sandrine Ghirardi[3], Sylvain Orenga[3], Kathryn Wilkinson[1], Neil Woodford[4], Jiancheng Zhang[4], David M. Livermore[4], Shahid Ahmad Abbasi[2] and Muhammad W. Raza[1]

Portage intestinal
prévalence = 18,5%

Dissémination de NDM depuis le contient indien



Diversité clonale des souches productrices de NDM



Norway
Sweden
Germany
Belgium
UK
France
Switzerland
Italy
Iraq
Pakistan
India
Canada
USA
Japan
Oman
Australia

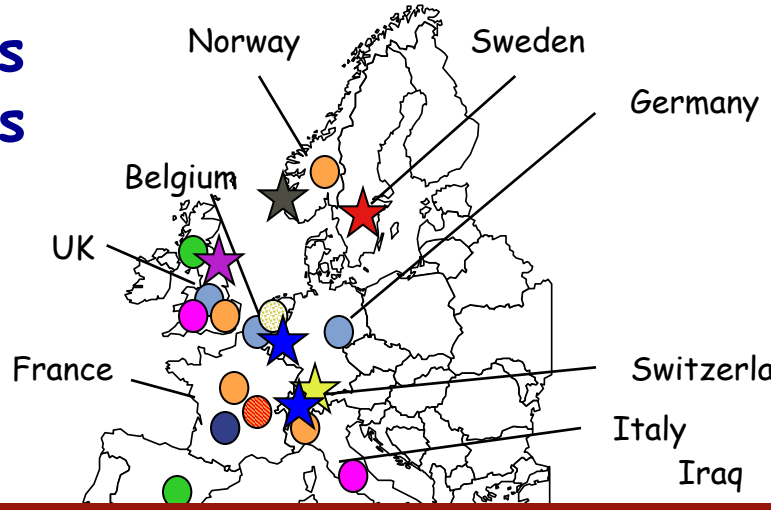
E. coli

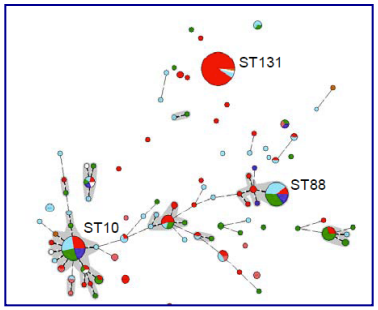
ST10 ST101 ST156 ST410 ST782
ST90 ST131 ST405 ST648

K. pneumoniae

ST11 ST15 ST147
ST14 ST25 ST340

Diversité clonale des souches productrices de NDM





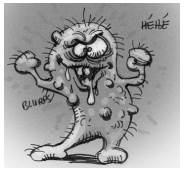
Epidémie de gène
Diffusion mondiale de souches diverses possédant des des plasmides variés

E. coli

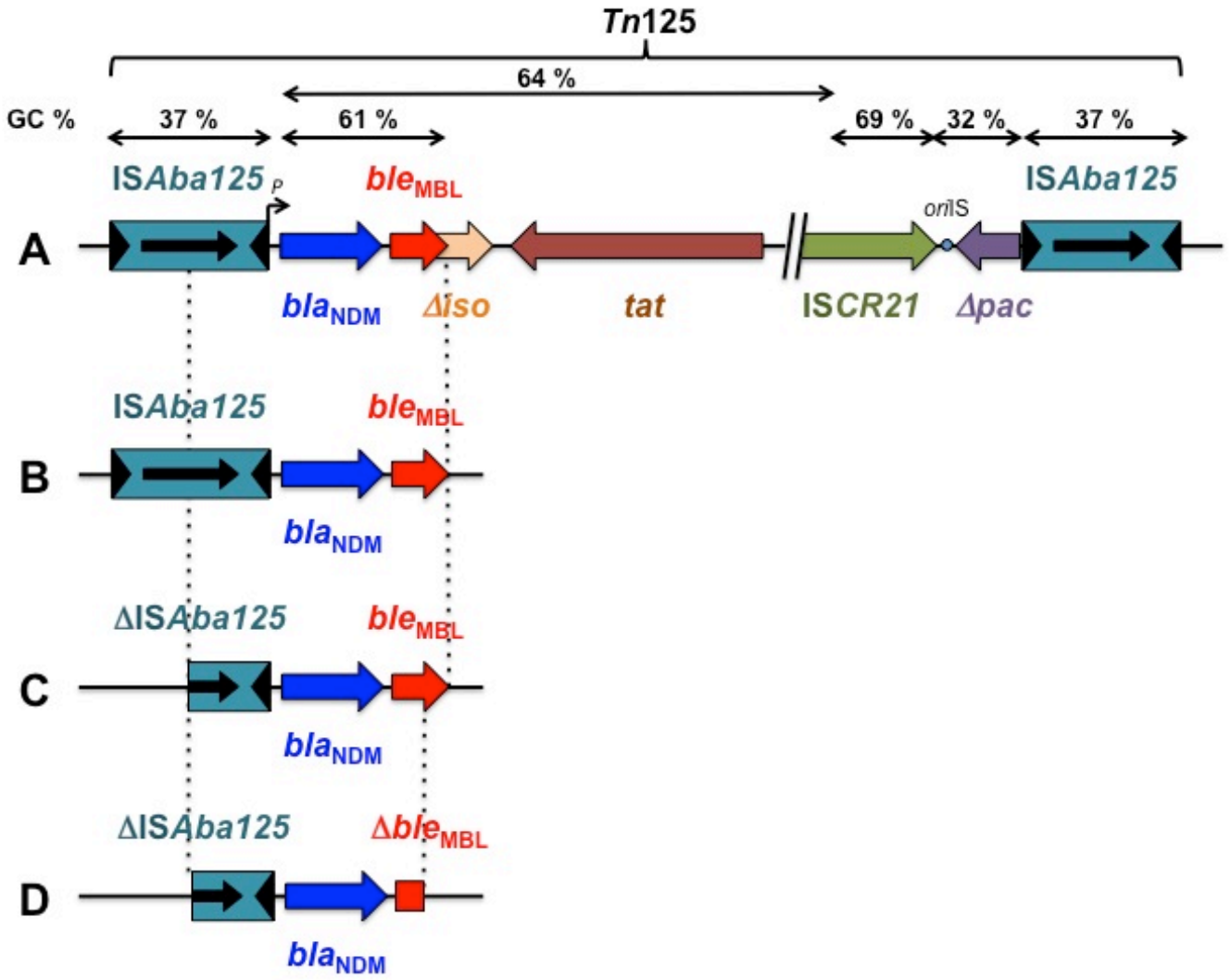
ST10 ST90 ST101 ST131 ST156 ST405 ST410 ST648 ST782

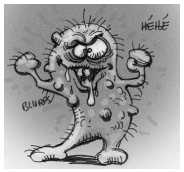
K. pneumoniae

ST11 ST14 ST15 ST25 ST147 ST340

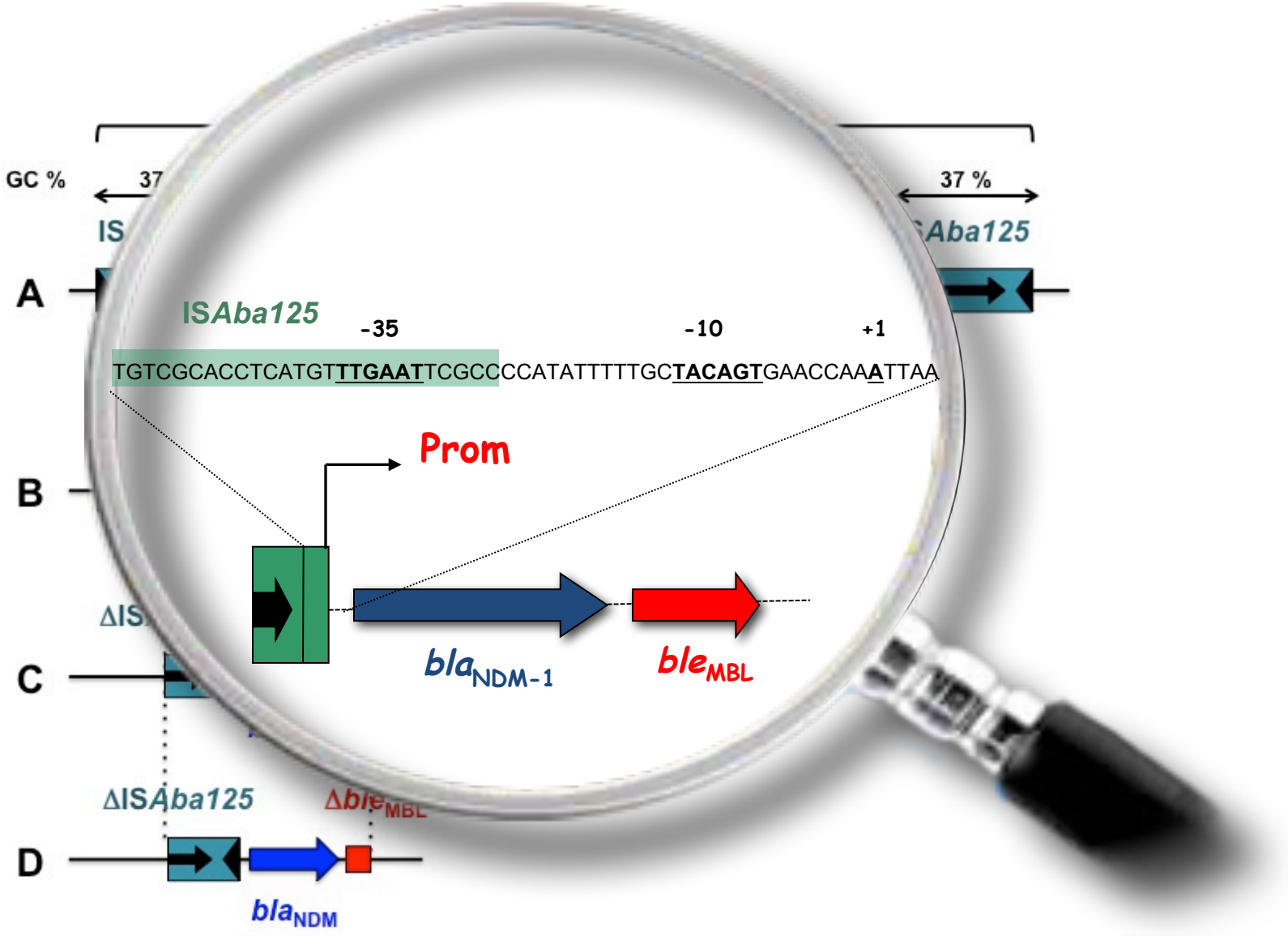


Environnement génétique de *bla*$_{NDM}$





Environnement génétique de bla_{NDM}



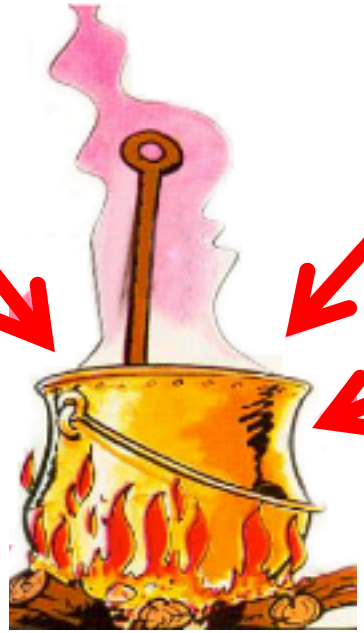
La successful story de NDM

Hygiène

Diarrhées

Surpopulation

Climat subtropical

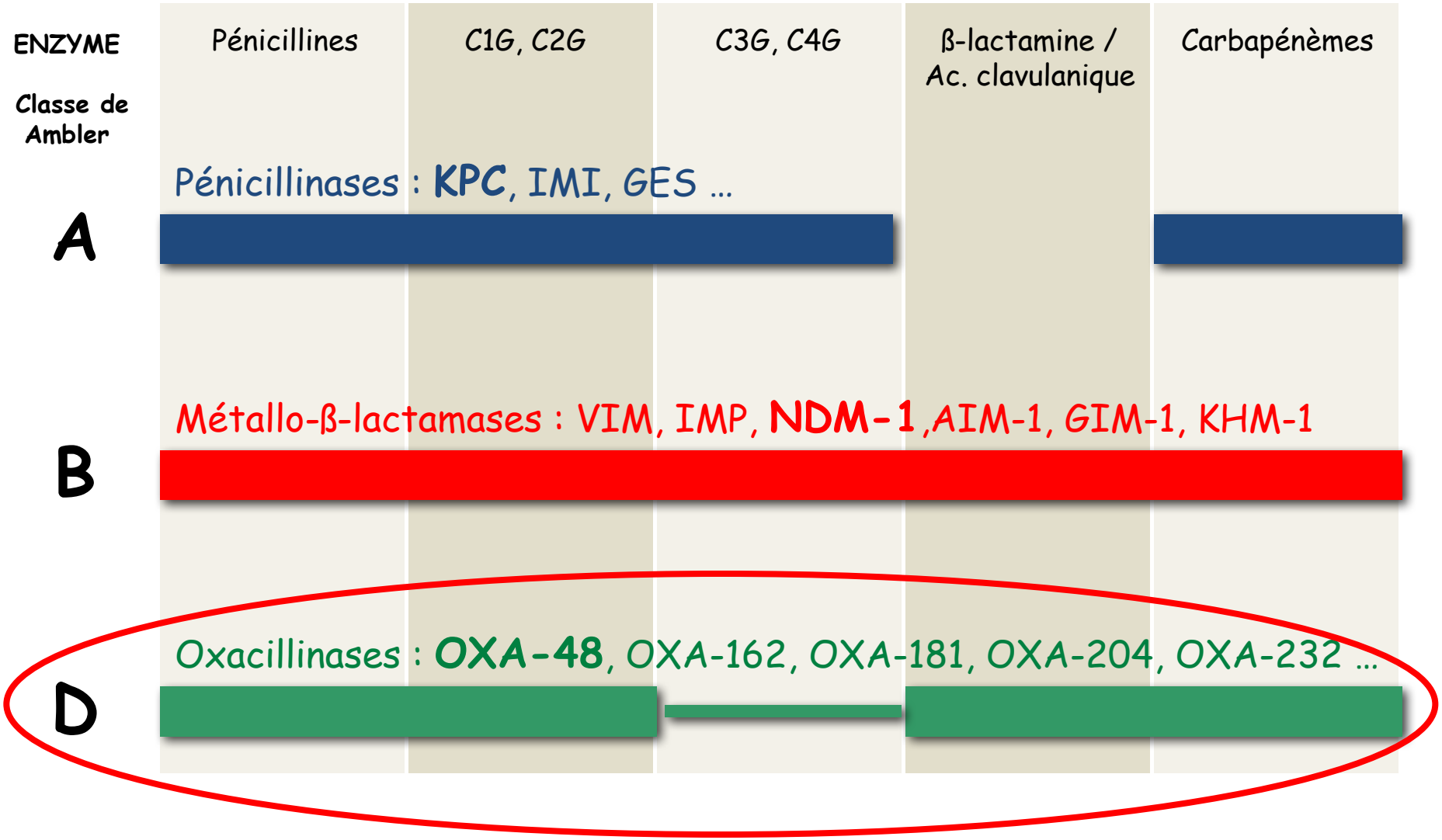


Surconsommation et mésusage des antibiotiques

Dissémination des souches NDM…

… augmentation de la mortalité, augmentation du temps d'hospitalisation, augmentation de l'usages des antibiotiques à large spectre

Les carbapénèmases chez les entérobactéries



OXA-48 / OXA-162 / OXA-181 / OXA-204 / OXA-232 / OXA-244 / OXA-245

1ère description en 2004

Turquie

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2004, p. 15–22 Vol. 48, No. 1
0066-4804/04/$08.00+0 DOI: 10.1128/AAC.48.1.15–22.2004

Emergence of Oxacillinase-Mediated Resistance to Imipenem in *Klebsiella pneumoniae*

Laurent Poirel,[1] Claire Héritier,[1] Venus Tolün,[2] and Patrice Nordmann[1]*

Endémique en Turquie et des les pays du Maghreb

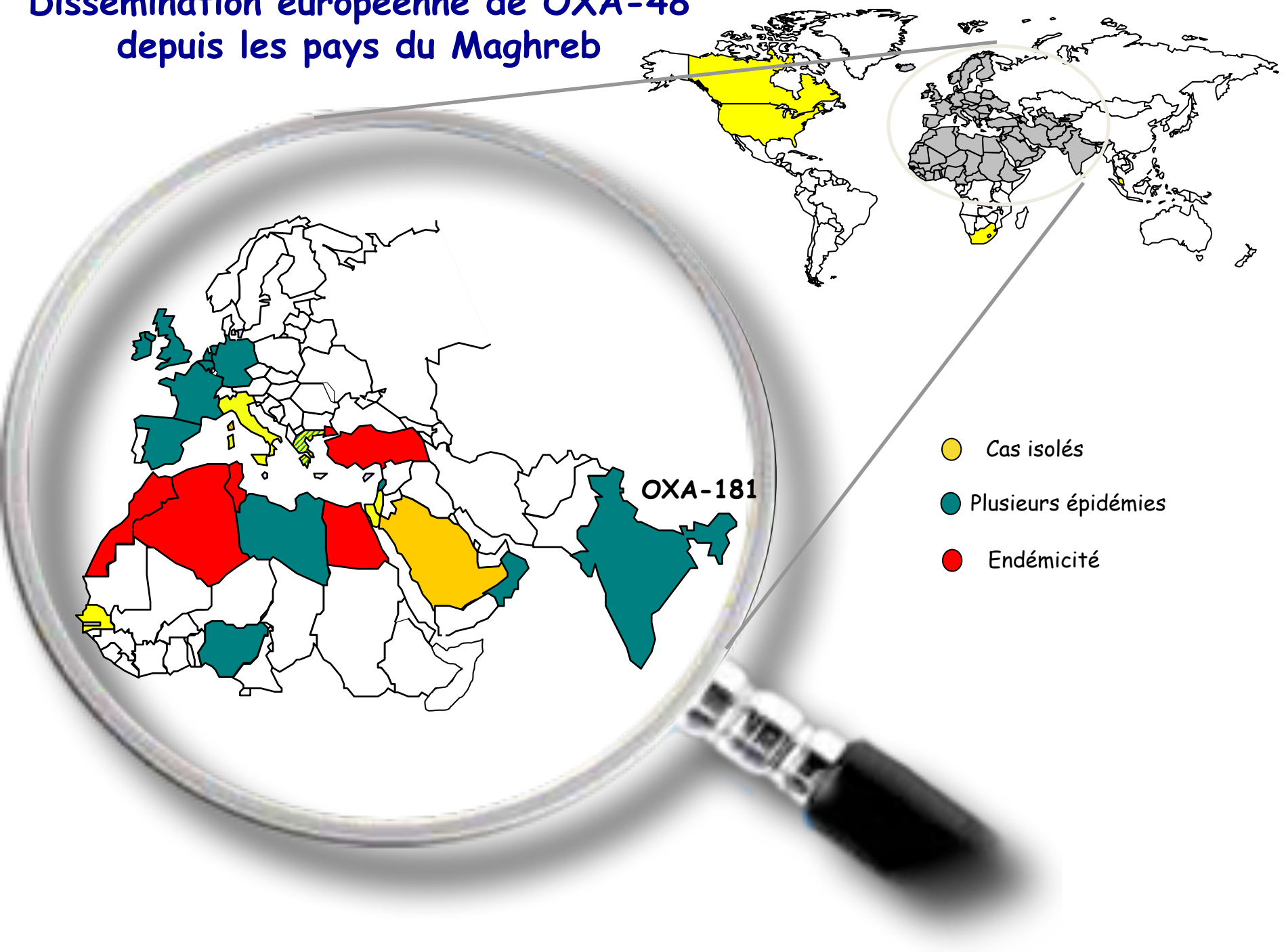
Anaïs Potron
Laurent Poirel
Florence Bussy
Patrice Nordmann*

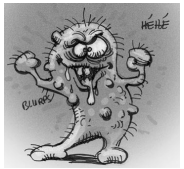
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2011, p. 5413–5414 Vol. 55, No. 11
0066-4804/11/$12.00 doi:10.1128/AAC.05120-11

Letter to the Editor

Occurrence of the Carbapenem-Hydrolyzing β-Lactamase Gene bla_{OXA-48} in the Environment in Morocco▽

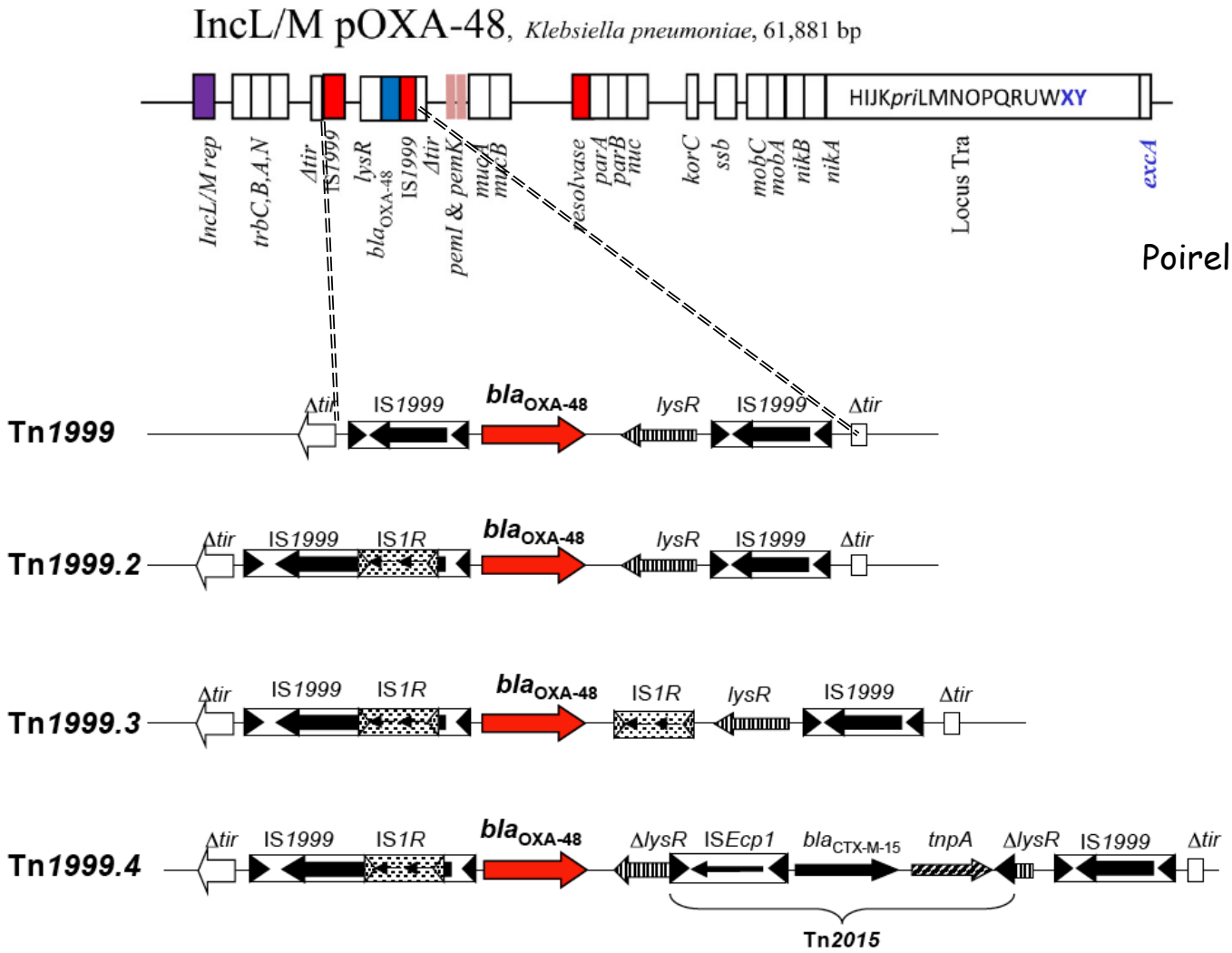
Dissémination européenne de OXA-48 depuis les pays du Maghreb





Environnement génétique de *bla*$_{OXA-48}$

Plasmide unique Inc L/M de 62,5 kb

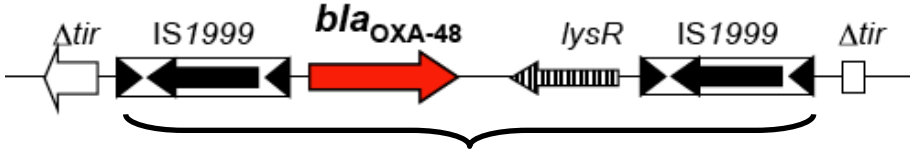


Poirel et al. *AAC* 2012

AAC Journals.ASM.org
January 2014 Volume 58 Number 1

Derepressed Transfer Properties Leading to the Efficient Spread of the Plasmid Encoding Carbapenemase OXA-48

Potron A. et al.



Transposon Tn*1999*

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

Donor strain	Recipient strain	Mean transfer frequency ± SD	
E. coli TOP10(pOXA-48a)	*E. coli* JM109	$1.1 \times 10^{-1} \pm 0.02$	**Δ*tir* (Tn*1999*)**
E. coli TOP10(pNDM-OM)	*E. coli* JM109	$2.6 \times 10^{-3} \pm 0.016$	
E. coli TOP10(pOXA-48a, pTOPO-Nc)	*E. coli* JM109	$1.7 \times 10^{-1} \pm 0.03$	**Δ*tir* + control DNA**
E. coli TOP10(pOXA-48a, pTOPO-TIR)	*E. coli* JM109	$1.6 \times 10^{-3} \pm 0.0005$	**Δ*tir* + *tir***
E. coli TOP10(pOXA-48a, pTOPO-Nc)	*E. cloacae* SB	$4.9 \times 10^{-2} \pm 0.018$	
E. coli TOP10(pOXA-48a, pTOPO-TIR)	*E. cloacae* SB	$1.2 \times 10^{-3} \pm 0.00004$	

% 100

AAC Journals.ASM.org
January 2014 Volume 58 Number 1

Derepressed Transfer Properties Leading to the Efficient Spread of the Plasmid Encoding Carbapenemase OXA-48

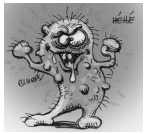
Potron A. et al.

Epidémie de plasmide
Diffusion chez de souches d'entérobactéries diverses d'un même plasmide hyper-conjugatif

TABL

Donor		
E. coli		
E. coli		
E. coli pTO		
E. coli pTO		
E. coli pTOPO-Nc)		
E. coli TOP10(pOXA-48a, pTOPO-TIR)	*E. cloacae* SB	$1.2 \times 10^{-3} \pm 0.00004$

% 100



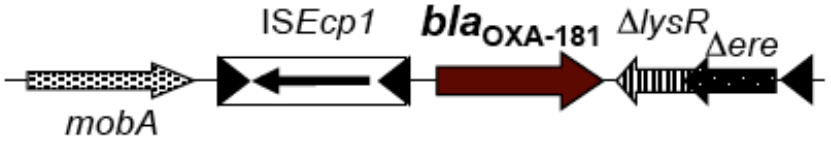
Variants carbapénèmase de OXA-48 : OXA-162, OXA-181, OXA-204, « OXA-232, OXA-244, OXA-245, OXA-247 »

Plasmides différents de celui qui porte *bla*$_{OXA-48}$

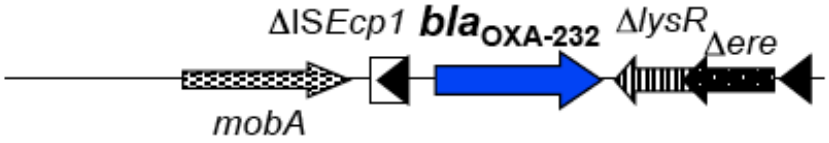
Environnement génétique différent de celui de *bla*$_{OXA-48}$

Mobilisation par **IS*Ecp1*** probable comme décrit pour *bla*$_{CTX-M}$

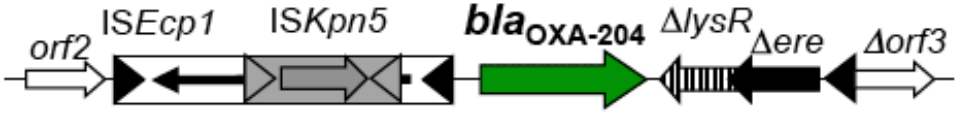
OXA-181 **Tn*2013***

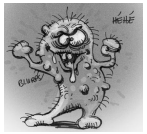


OXA-232



OXA-204 **Tn*2016***

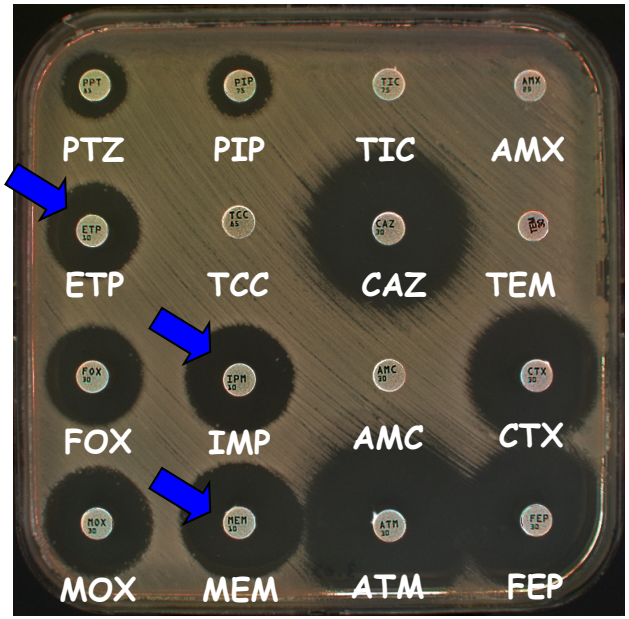




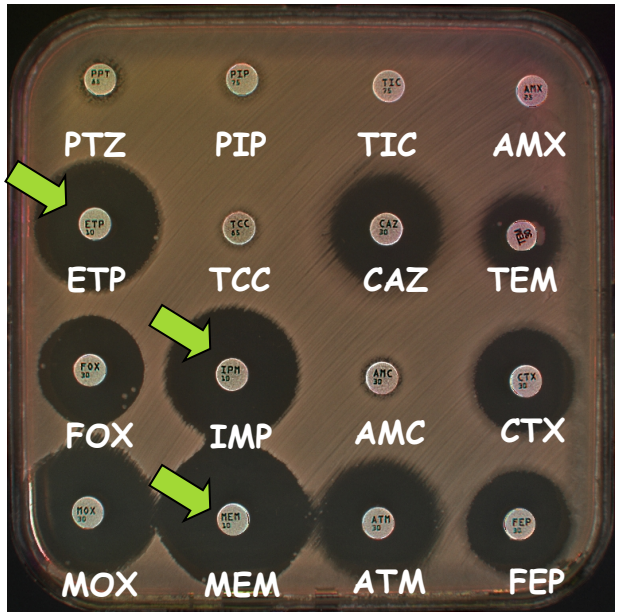
Variants non carbapénèmase de OXA-48 : OXA-163, OXA-247, OXA-405

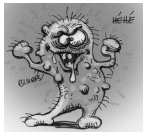
- **Perte activité carbapénèmase** : délétions acides aminés dans le site actif / OXA-48

OXA-48



OXA-163

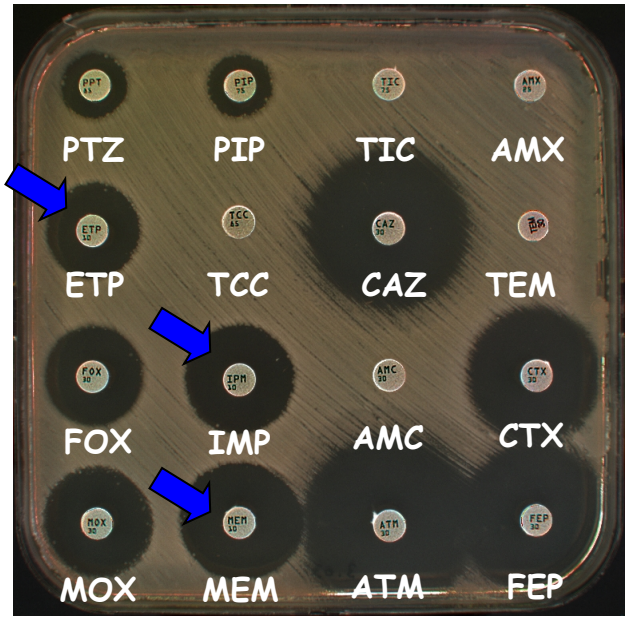




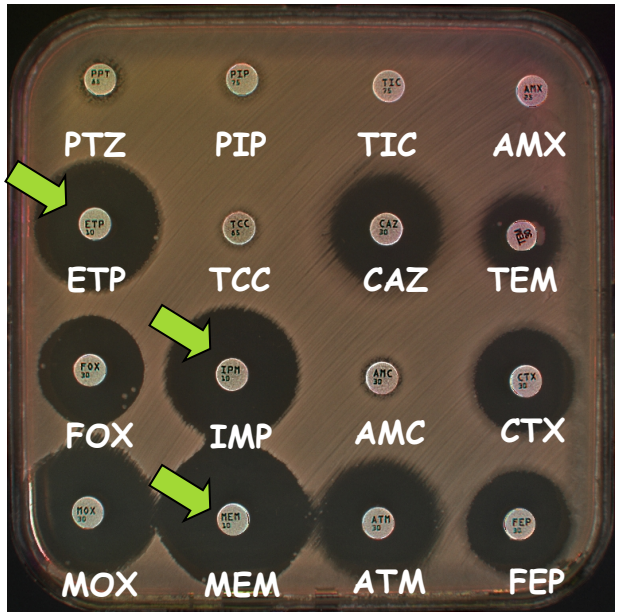
Variants non carbapénèmase de OXA-48 : OXA-163, OXA-247, OXA-405

- **Perte activité carbapénèmase** : délétions acides aminés dans le site actif / OXA-48

OXA-48



OXA-163



```
                                 210        220        230        240        250        260
                                  |          |          |          |          |          |
Carbapenemase   OXA-204  GDYIIRAKTGYSTRIEPKIGWWVGWVELDDNVWFFAMNMDMPTSDGLGLRQAITKEVLKQEKIIP
                OXA-245  GDYIIRAKTGYSTRIEPKIGWWVGWVELDDNVWFFAMNMDMPTSDGLGLRQAITKEVLKQEKIIP
                OXA-48   GDYIIRAKTGYSTRIEPKIGWWVGWVELDDNVWFFAMNMDMPTSDGLGLRQAITKEVLKQEKIIP
                OXA-370  GDYIIRAKTGYETRIEPKIGWWVGWVELDDNVWFFAMNMDMPTSDGLGLRQAITKEVLKQEKIIP
                OXA-162  GDYIIRAKTGYSARIEPKIGWWVGWVELDDNVWFFAMNMDMPTSDGLGLRQAITKEVLKQEKIIP
                OXA-181  GDYIIRAKTGYSTRIEPKIGWWVGWVELDDNVWFFAMNMDMPTSDGLGLRQAITKEVLKQEKIIP
                OXA-232  GDYIIRAKTGYSTSIEPKIGWWVGWVELDDNVWFFAMNMDMPTSDGLGLRQAITKEVLKQEKIIP
                OXA-244  GDYIIRAKTGYSTGIEPKIGWWVGWVELDDNVWFFAMNMDMPTSDGLGLRQAITKEVLKQEKIIP
Non             OXA-163  GDYIIRAKTGYDT----KIGWWVGWVELDDNVWFFAMNMDMPTSDGLGLRQAITKEVLKQEKIIP
Carbapenemase   OXA-247  GDYIIRAKTGSNT----KIGWWVGWVELDDNVWFFAMNMDMPTSDGLGLRQAITKEVLKQEKIIP
                OXA-405  GDYIIRAKTGYS----PKIGWWVGWVELDDNVWFFAMNMDMPTSDGLGLRQAITKEVLKQEKIIP
                         **********..    **********************************************
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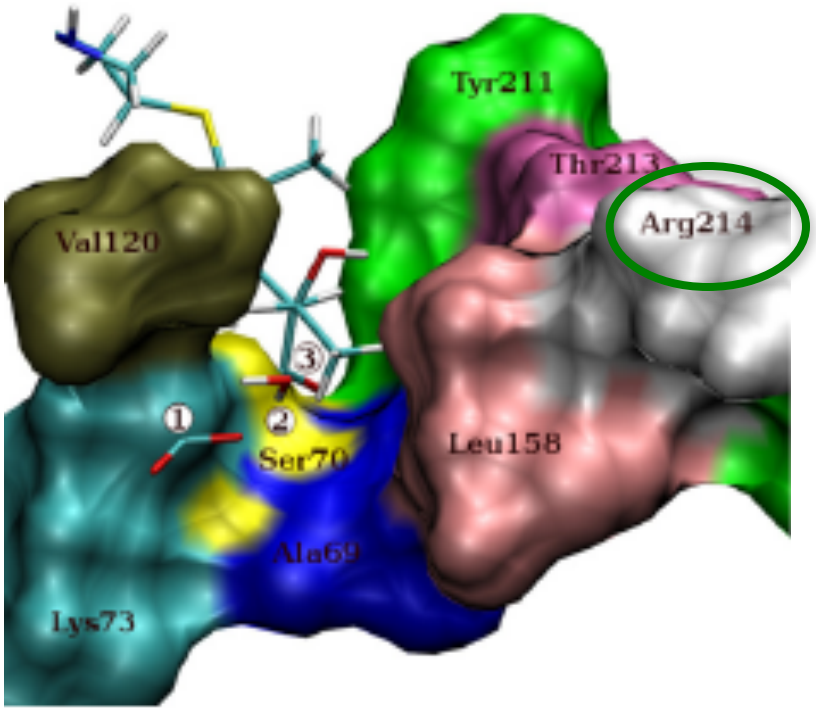
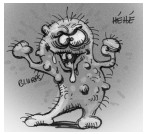


OXA-48 active site

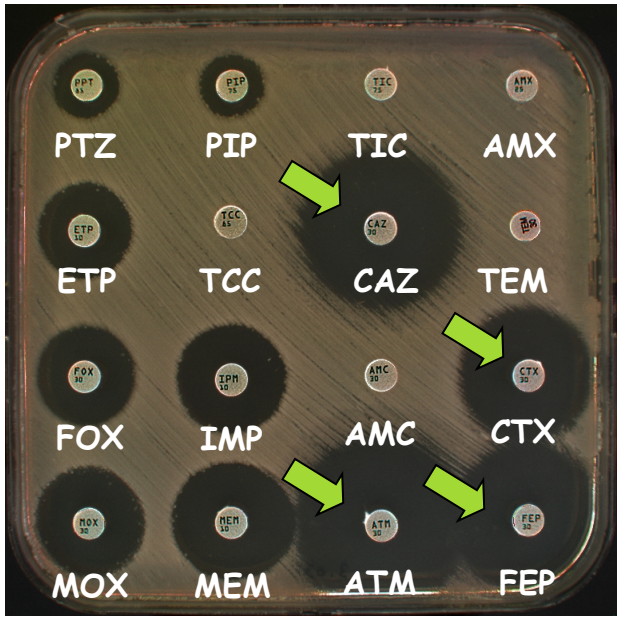
Deletion in OXA-163, OXA-247 and OXA-405



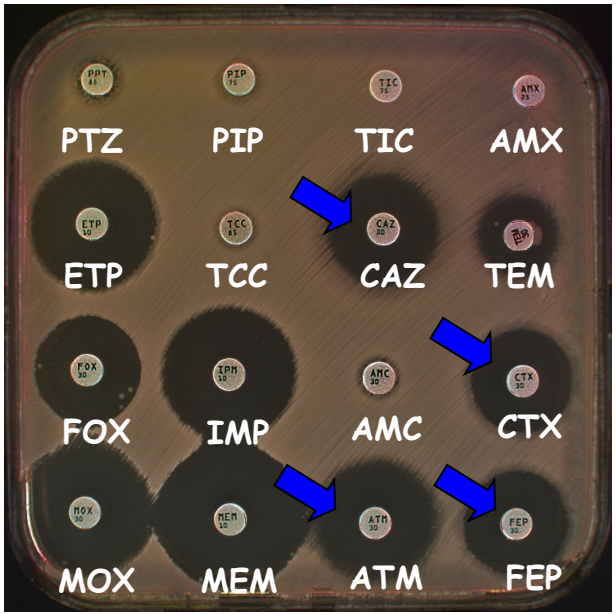
Variants non carbapénèmase de OXA-48 : OXA-163, OXA-247, OXA-405

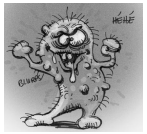
- **Perte activité carbapénèmase** : délétions acides aminés dans le site actif / OXA-48
- **Hydrolyse accrue des C3G** contrairement à OXA-48 (BLSE-like)

OXA-48



OXA-163

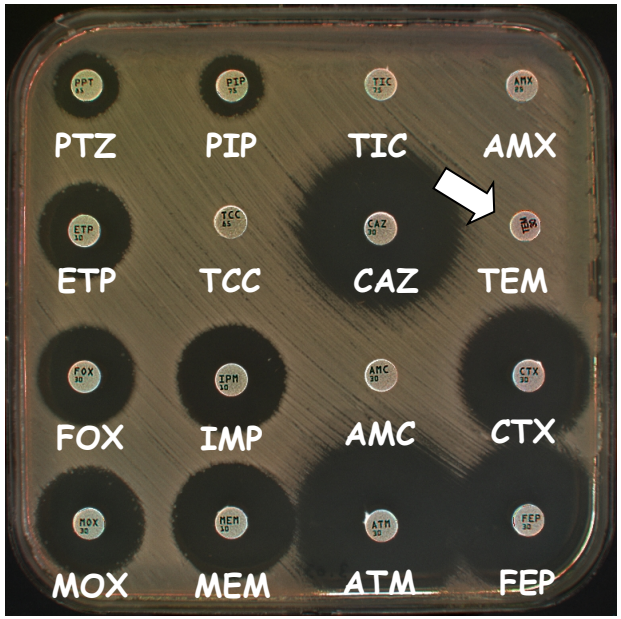




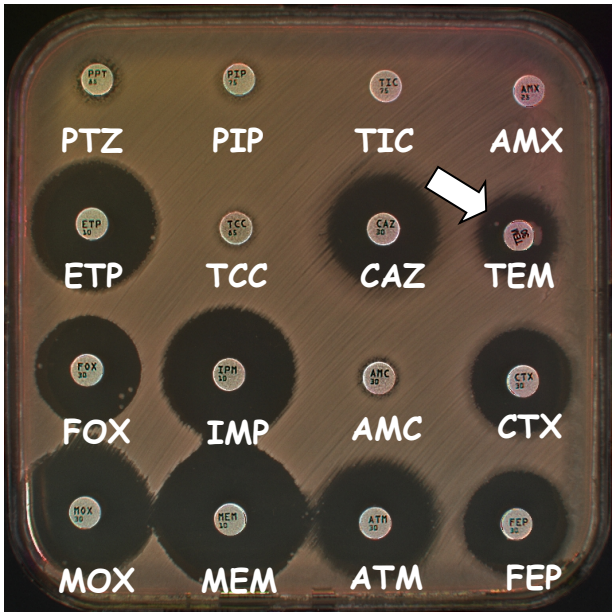
Variants non carbapénèmase de OXA-48 : OXA-163, OXA-247, OXA-405

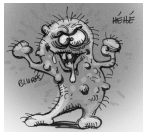
- **Perte activité carbapénèmase** : délétions acides aminés dans le site actif / OXA-48
- **Hydrolyse accrue des C3G** contrairement à OXA-48 (BLSE-like)
- **Hydrolyse réduite de la Témocilline**

OXA-48



OXA-163

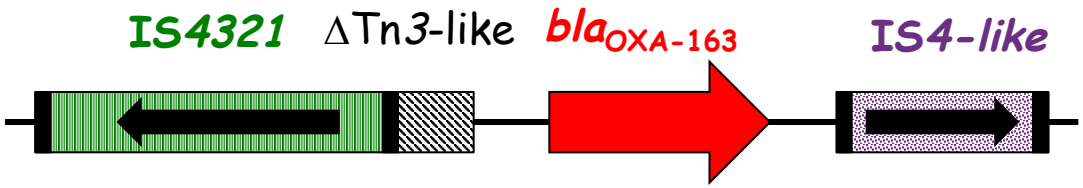




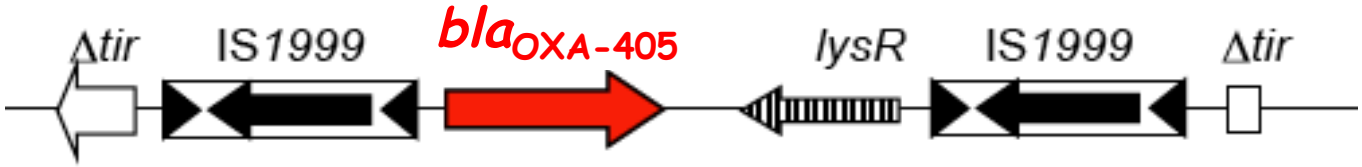
Variants non carbapénèmase de OXA-48 : OXA-163, OXA-247, OXA-370, OXA-405

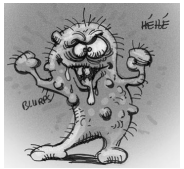
- Environnements génétiques et plasmides variables

OXA-163
OXA-247



OXA-405





Shewanella spp. progéniteurs des carbapénèmases de type OXA-48

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

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

Laurent Poirel, Claire Héritier, and Patrice Nordmann*

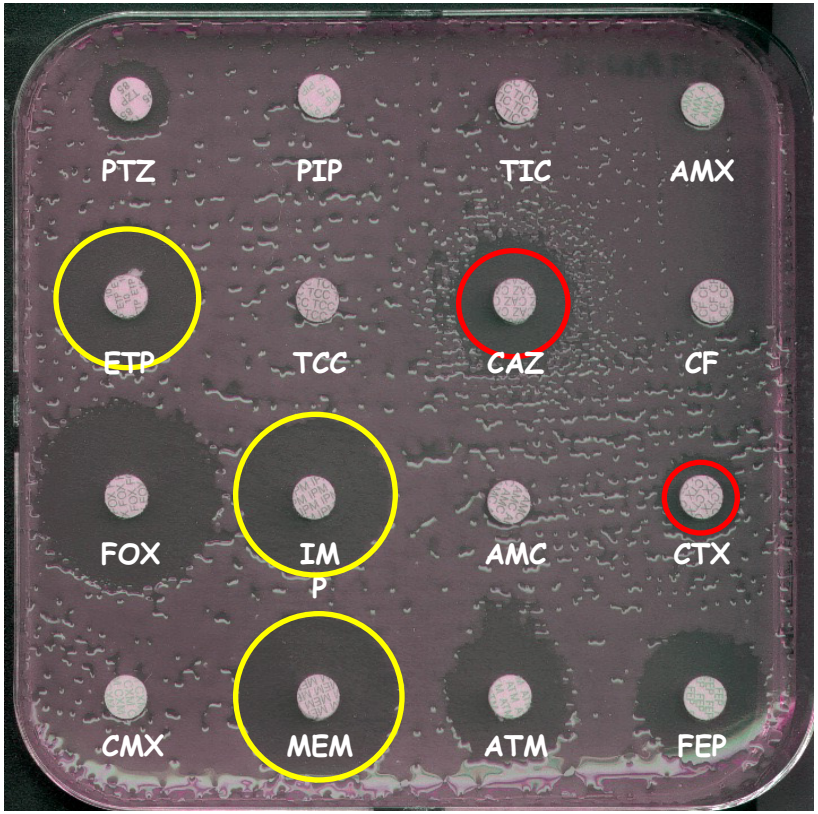
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2011, p. 4405–4407 Vol. 55, No. 9
0066-4804/11/$12.00 doi:10.1128/AAC.00681-11

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

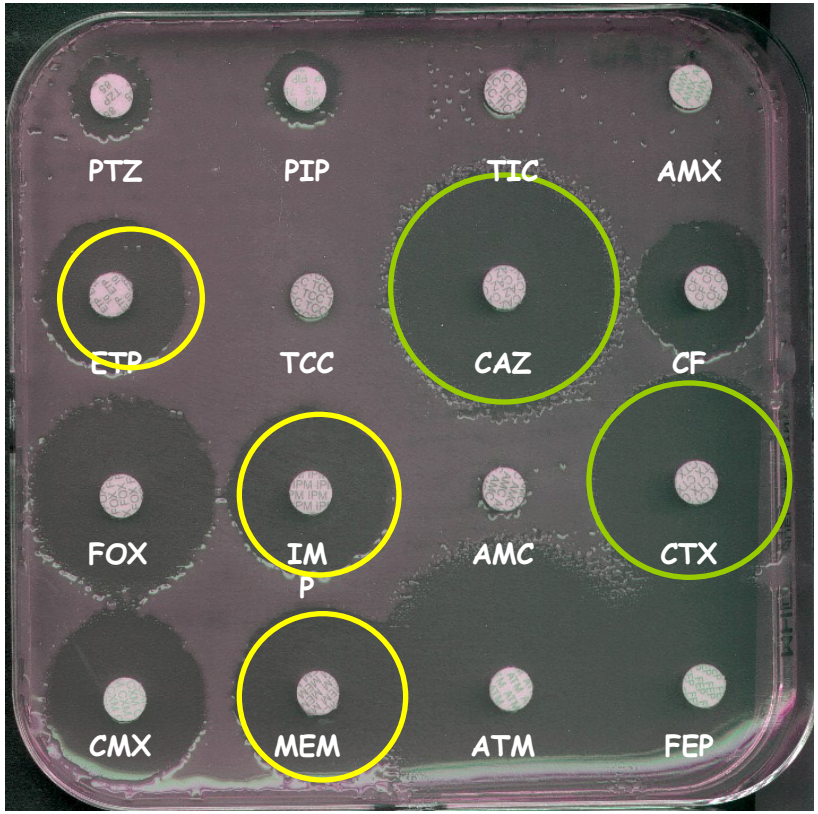
Anaïs Potron, Laurent Poirel, and Patrice Nordmann*

OXA-48 les secrets de son succès

Faible hydrolyse des carbapénèmes et pas d'hydrolyse des C3G
⇒ Difficultés de détection

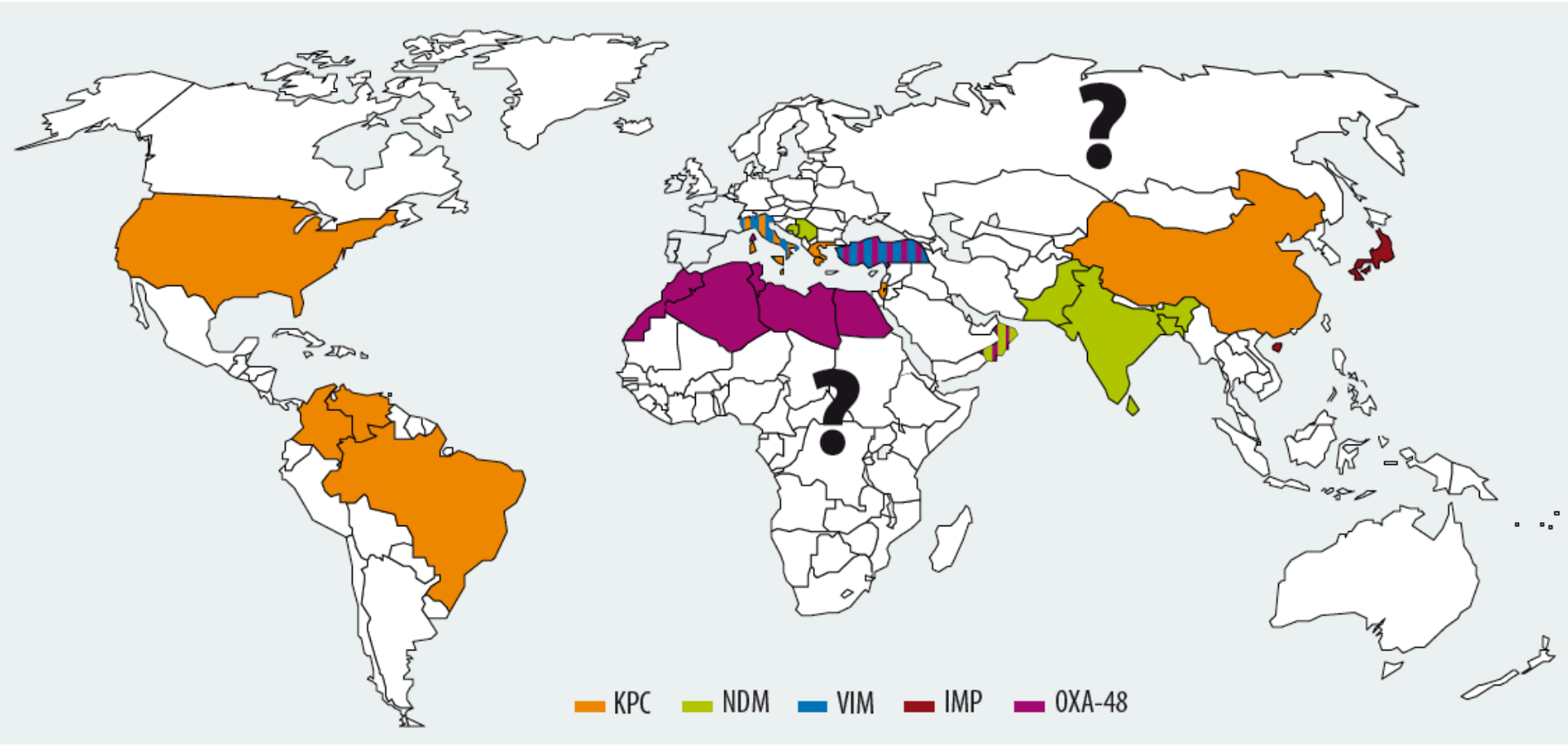


K. pneumoniae OXA-48
BLSE +



K. pneumoniae OXA-48
BLSE -

Epidémiologie globale des EPC



PLAN

Epidémiologie et dissémination des entérobactéries productrices de carbapénèmases

Méthodes de détection des entérobactéries productrices de carbapénèmases

1) A partir d'un prélèvement clinique (infection)

2) Dépistage des patients porteurs

J 0

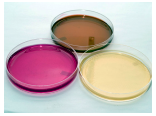
Infections

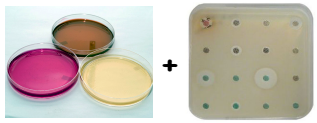
Urine

Autres prélèvements

Hémoculture

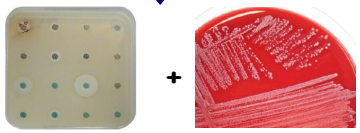
J 1





Antibiogramme

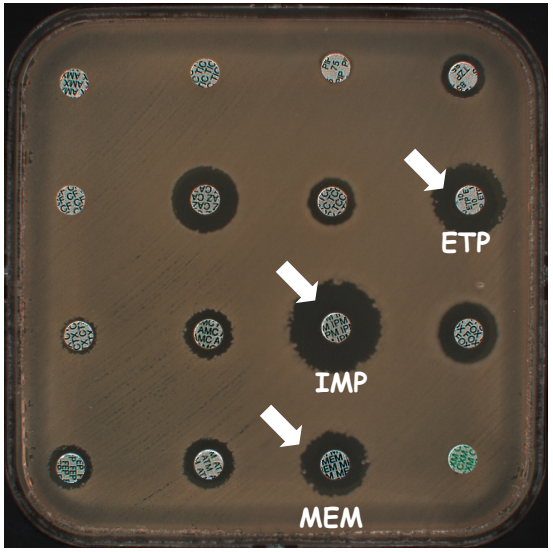
J 2



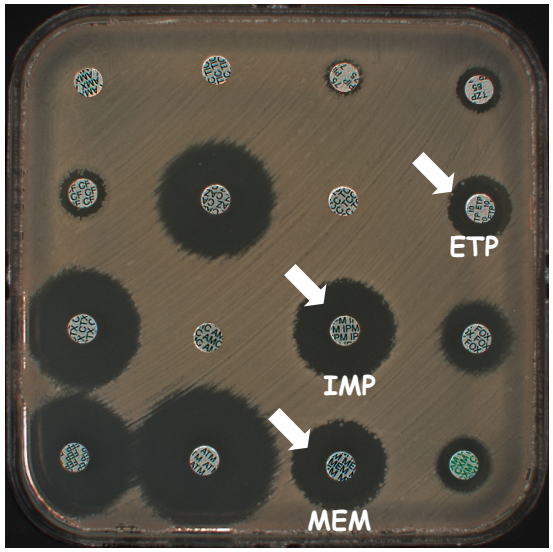
Antibiogramme

Question : quelle souche (ne) produit (pas) de carbapenemase ?

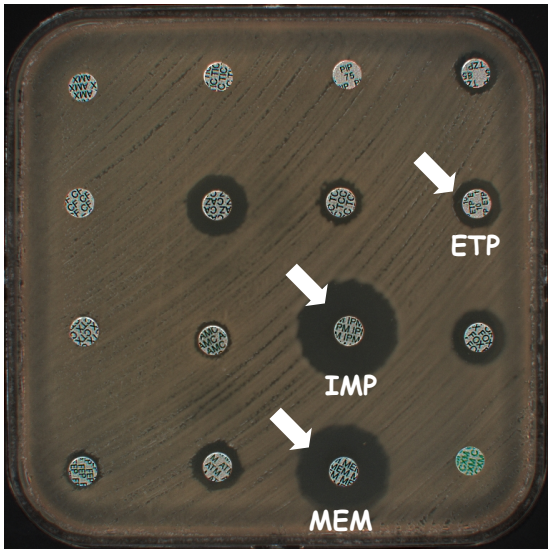
K. pneumoniae



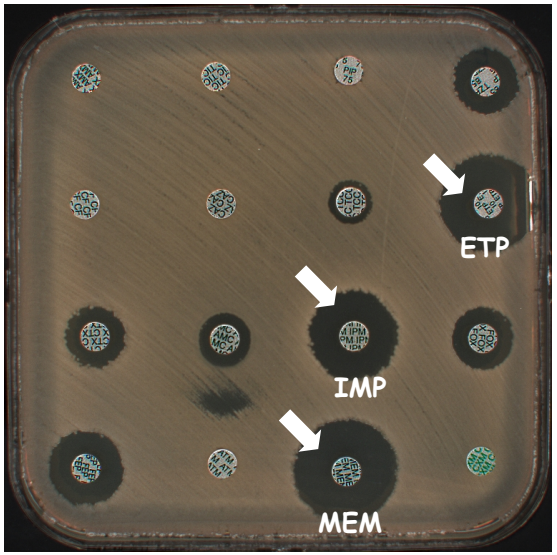
K. pneumoniae



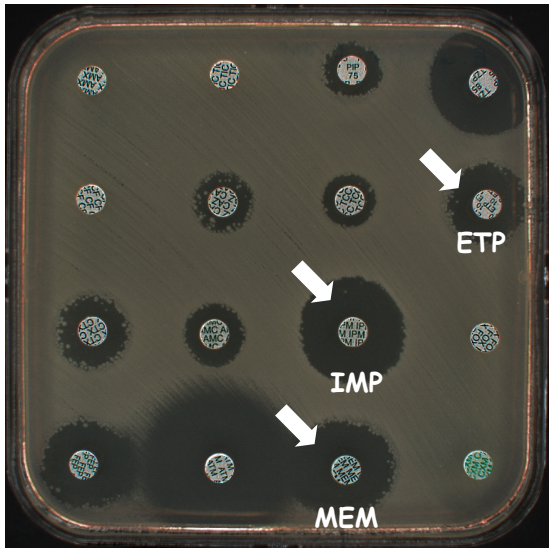
K. pneumoniae



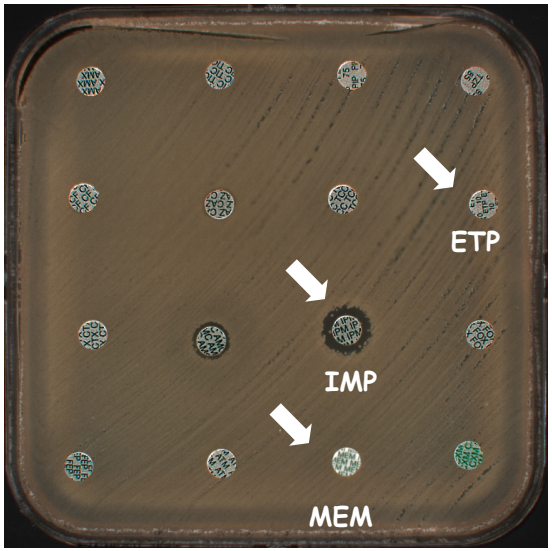
E. coli



E. coli



E. coli



J 0

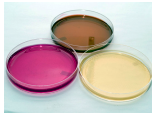
Infections

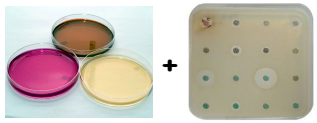
Urine

Autres prélèvements

Hémoculture

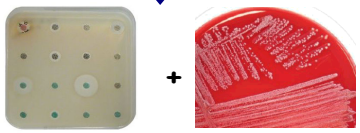
J 1





Carba NP test / β-CARBA test

J 2

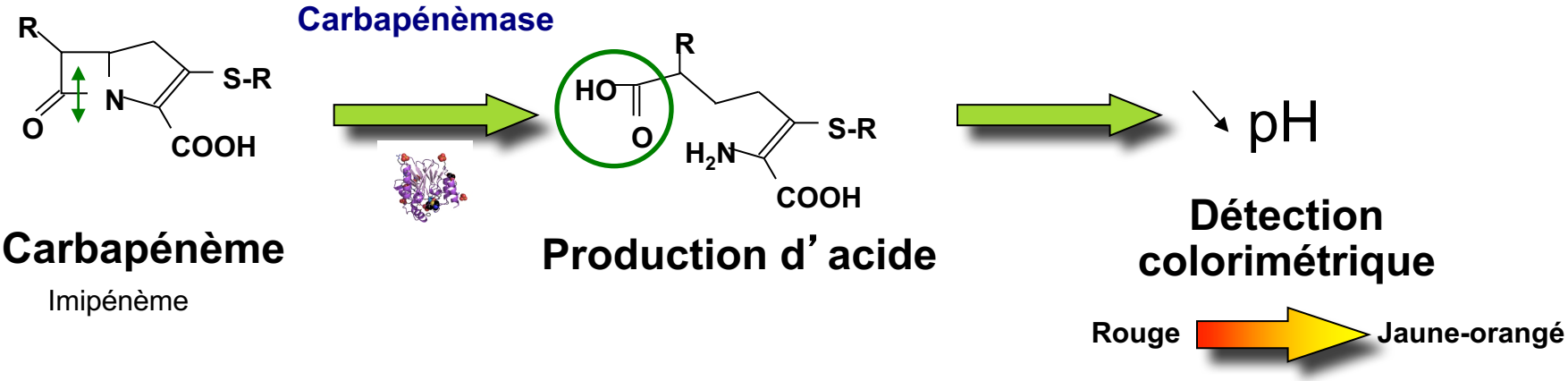


Carba NP test / β-CARBA test

http://www.cnr-resistance-antibiotiques.fr/expertise-des-souches-1.html

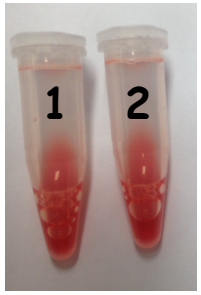
Carba NP test

Principe: Hydrolyse in vitro d'un carbapénème

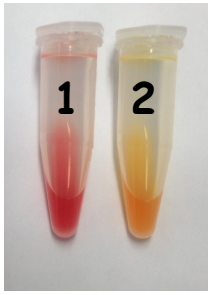


Interprétation:

Absence de carbapénèmase



Production d'une carbapénèmase



1 : solution de révélation (contrôle négatif interne)

2 : Solution de révélation + imipénème

Carba NP test

Avantages:

- Peu onéreux
- Rapidité +++ (< 2h)
- Simple

Sur 6682 souches testées :

- Sensiblilité 98.6%
- Spécificité 99.9%
- PPV 99.8%
- NPV 99.4%

Inconvénient:

- Non utilisable directement à partir du prélèvement rectal
- Difficulté de lecture pour quelques souches OXA-48

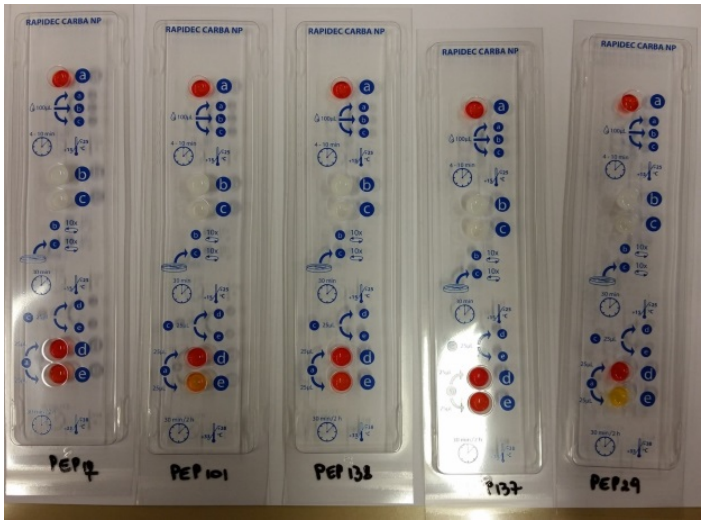
Résultats:

Ambler class	Carbapenemase type	Mean time for positivity
A	KPC	1-15 min
A	GES-2, -5	1h-1h30
B	NDM	20-50 min
B	VIM	20-50 min
B	IMP	5-30 min
D	OXA-48	30-40 min

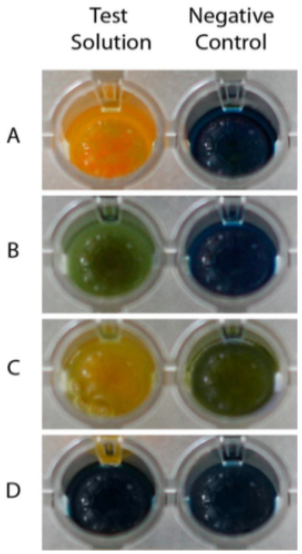
Nordmann, Poirel, Dortet. 2012. Emerg Infect Dis
Dortet, Bréchard, Poirel, Nordmann. 2014. JMM
Vasoo et al. 2013. JCM
Huang TD et al 2014. JCM

Versions dérivées et versions commerciales du Carba NP test

RAPIDEC® CARBA NP (bioMérieux)

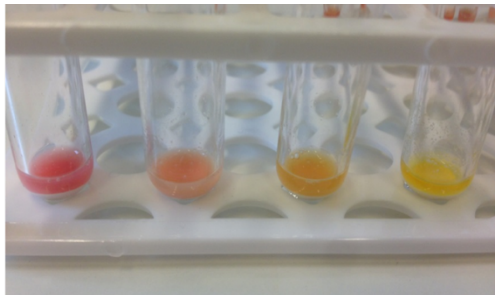


Blue Carba



Pires et al., JCM 2013
Pasteran, JCM 2015

RAPID CARB Screen® (ROSCO)



Neo RAPID CARB Screen® (ROSCO)

Evaluation Carba NP test et dérivés

Test	Company	n	Sen %	Spe %	PPV %	NPV %	NI %	reference
Carba NP test	-	235	97	100	100	95	0	Huang, JCM 2014
	-	150	96.8	100	-	-	0	Dortet, JAC 2015
	-	31	100	100	-	-	0	Denis, ECCMID 2015
RAPIDEC CARBA NP	bioMérieux	110	99	97	-	-	0	Poirel, ECCMID 2015
		150	99	100	-	-	0	Dortet, JAC 2015 submitted
Rapid CARB screen	ROSCO	235	98	83	81	95	11.8	Huang, JCM 2014
		150	89.5	70.9	-	-	16.7	Dortet, JAC 2015
Neo Rapid CARB screen	ROSCO	31	66.7	50	-	-		Denis, ECCMID 2015

J 0

Infections

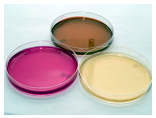
Urine

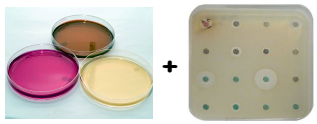
Autres prélèvements

Hémoculture

→ Carba NP test

J 1





Carba NP test

J 2

Carba NP test

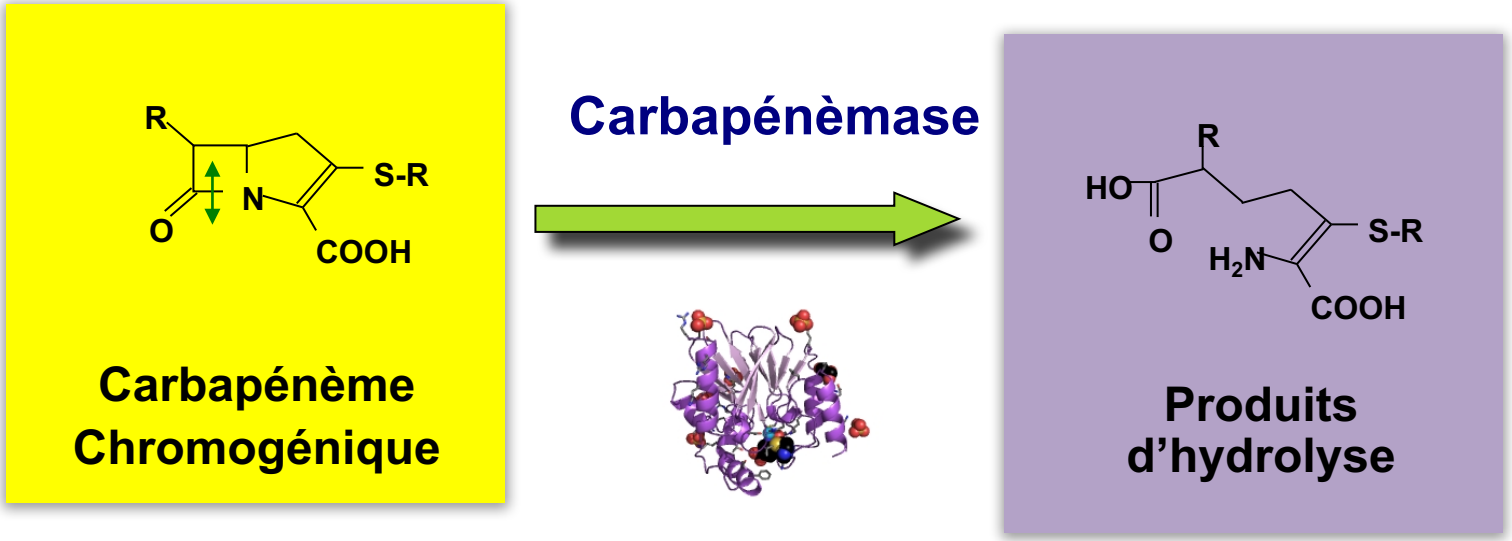
ORIGINAL ARTICLE 10.1111/1469-0691.12318

Rapid detection of carbapenemase-producing Enterobacteriaceae from blood cultures

L. Dortet, L. Bréchard, L. Poirel and P. Nordmann

β-CARBA test

Principe: Hydrolyse in vitro d'un carbapénème chromogénique



Avantages:

- Simple
- Rapide (30 min)

Inconvénients:

- **Absence de détection** des enzymes de type **IMI**, NmcA, SME
- Non utilisable directement à partir du prélèvement rectal
- Difficulté de lecture pour quelques souches OXA-48

J 0

Infections

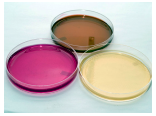
Urine

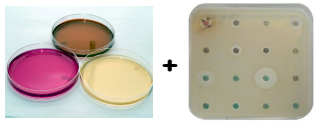
Autres prélèvements

Hémoculture

→ Carba NP test

J 1

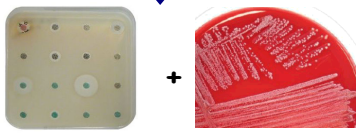




Carba NP test

BYG test

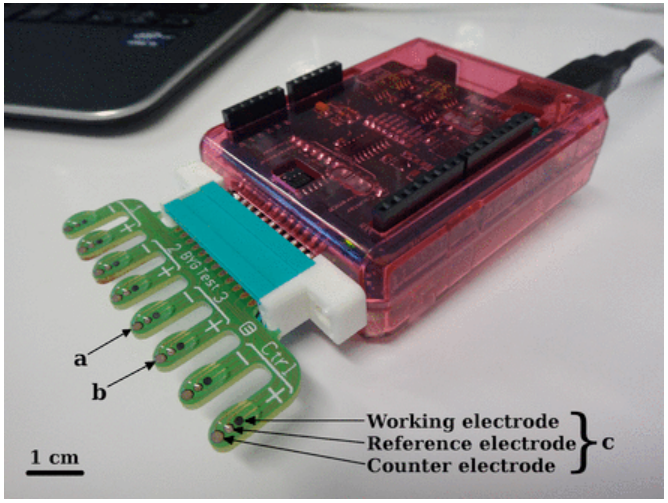
J 2



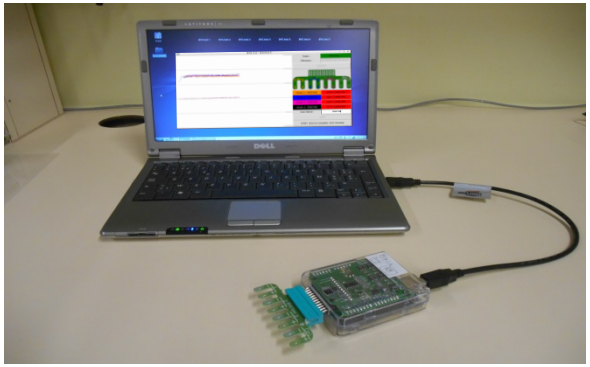
Carba NP test

BYG test

BYG Carba test for CPE detection

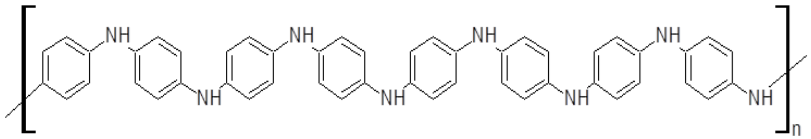


Sytème global incluant le software

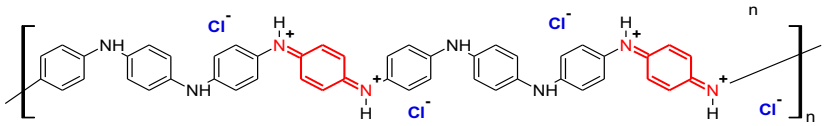


Détection Electrochimique de l'hydrolyse de l'imipénème

Senseur Polyaniline (PA)



Senseur Polyaniline



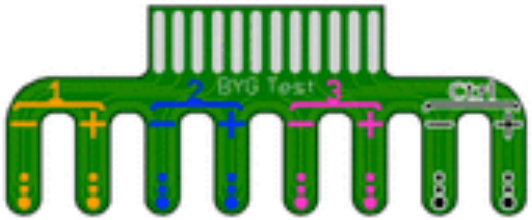
Mesure en temps réel des modifications de la conductivité de la Polyaniline

Mesure en temps réel des modifications de la conductivité de la polyaniline avec et sans imipénème

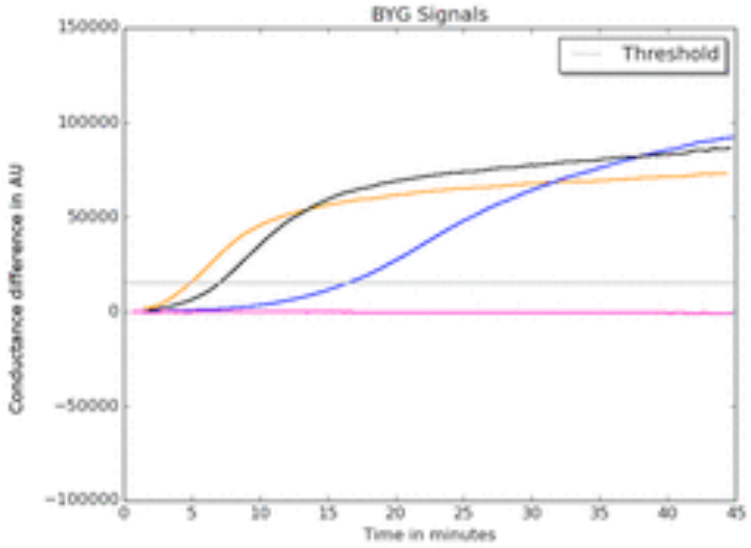
BYG Test Report

CHU Dinant Godinne UCL NAMUR

DATE : 18/03/2015
TIME : 08:46:02
User Name : MARTIN



Strain 1	:	NEQAS 1943	(POSITIVE)
Strain 2	:	NEQAS 1945	(POSITIVE)
Strain 3	:	CNR20150311	(NEGATIVE)
Strain 4 (Ctrl)	:	CNR20150325	(POSITIVE)



For any information concerning the BYG test please contact pierre.bogaert@uclouvain.be or wani.yunus@uclouvain.be

Bogaert *et al*. Evaluation of the BYG Carba Test, a New Electrochemical Assay for Rapid Laboratory Detection of Carbapenemase-Producing Enterobacteriaceae. J Clin Microbiol. 2016 Feb;54(2):349-58.

J 0

Infections

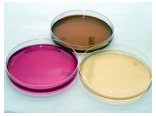
Urine

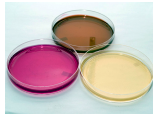
Autres prélèvements

Hémoculture

→ Carba NP test

J 1





+

Carba NP test
BYG test
MALDI-TOF

J 2

+

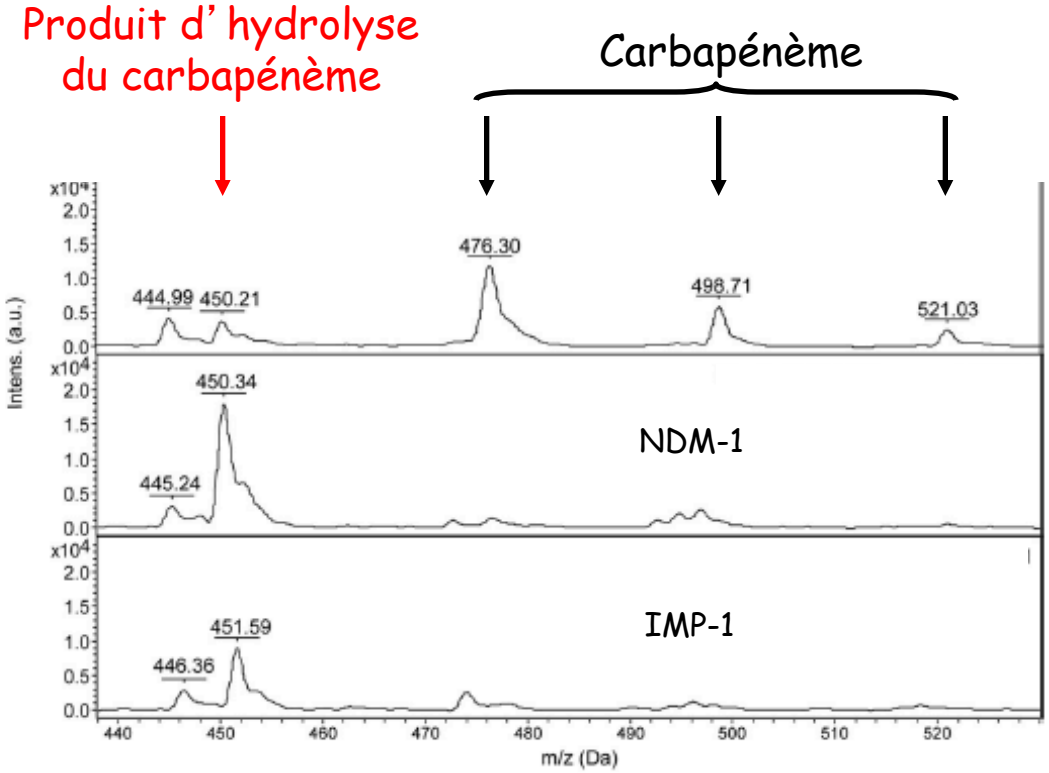
Carba NP test
BYG test
MALDI-TOF

Spectrométrie de masse : MALDI-TOF

Hrabák et al. JCM. 2011
Burckhardt et al. JCM. 2011
Hrabák et al. JCM. 2012
Lasserre et al. JCM 2015

En pratique :

1) Bouillon contenant la bactérie à étudier + carbapénème : 20 min – 4h incubation
2) Spectromètre de masse
3) Si carbapénémase + :
hydrolyse du carbapénème et apparition d' un produit de dégradation



Avantages :

Spécifique / sensible
Rapidité +
Coût hors matériel

Inconvénients :

Matériel
Expertise

Spectrométrie de masse : MALDI-TOF

Hrabák et al. JCM. 2011
Burckhardt et al. JCM. 2011
Hrabák et al. JCM. 2012
Lasserre et al. JCM 2015

En pratique :

1) Bouillon contenant la bactérie à étudier + carbapénème : 20 min – 4h incubation
2) Spectromètre de masse
3) Si c
hydroly
apparit
dégrad

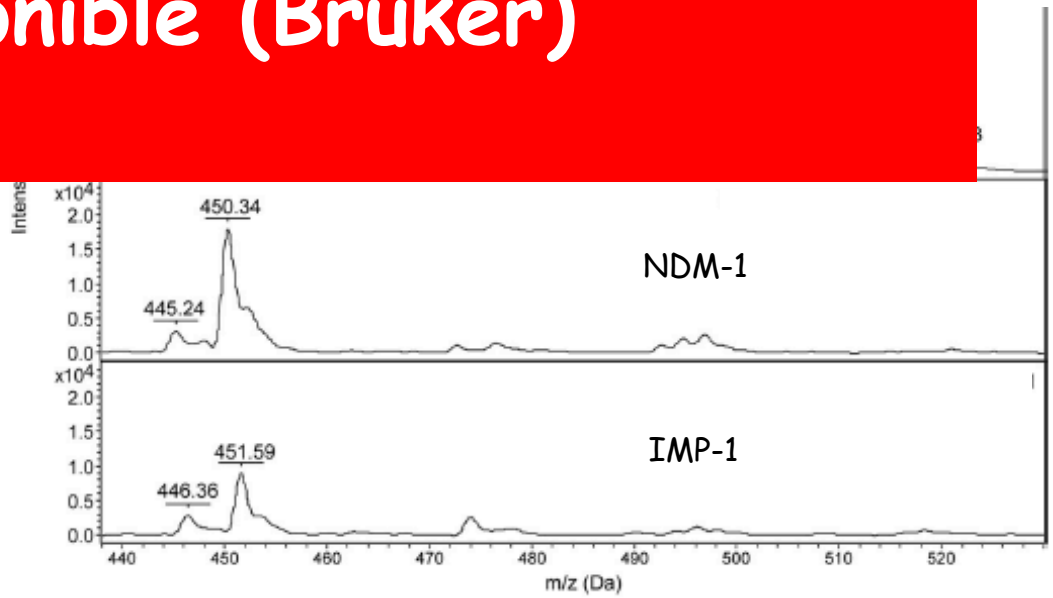
Version commerciale bientôt disponible (Bruker)

Avan

Spécif
Rapidité +
Coût hors matériel

Inconvénients :

Matériel
Expertise



J 0

Infections

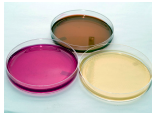
Urine

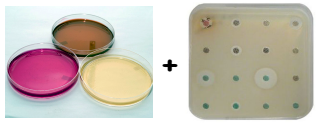
Autres prélèvements

Hémoculture

→ Carba NP test

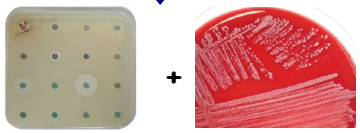
J 1





Carba NP test
BYG test
MALDI-TOF
Détection par biologie moléculaire (PCR, RT-PCR)

J 2



Carba NP test
BYG test
MALDI-TOF
Détection par biologie moléculaire (PCR, RT-PCR)

Biologie Moléculaire : Techniques PCR

ex: Check-MDR Real-Time PCR / GeneXpert / …

Détermine la présence ou non d'une carbapénémase +/- type

Inconvévients :

- Coût +++
- Ne détecte que ce qu'il cherche (attention aux variants et enzymes rares : IMI)

Avantages :

- Rapidité (en fonction des techniques) : 45 min Xpert Carba-R
- Utilisable directement sur prélèvement
- Bien adapté à l'épidémiologie française

GeneXpert®

Xpert® Carba-R
On-demand detection and differentiation of KPC, NDM, VIM, IMP-1 and OXA-48 (now covering OXA-181 & OXA-232)

Dortet et al. Improvement of the Xpert Carba-R Kit for the Detection of Carbapenemase-Producing Enterobacteriaceae.AAC 2016 23;60(6):3832-7.

J 0

Infections

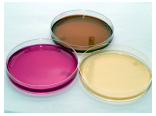
Urine

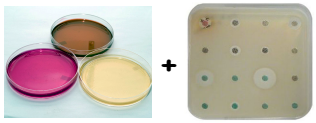
Autres prélèvements

Hémoculture

→ Carba NP test

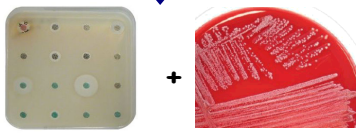
J 1





Carba NP test
BYG test
MALDI-TOF
Détection par biologie moléculaire (PCR, RT-PCR)
K-SeT OXA-48

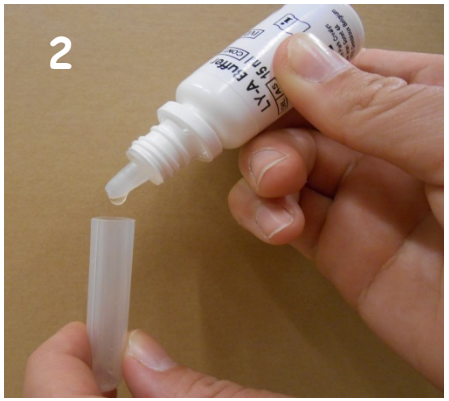
J 2



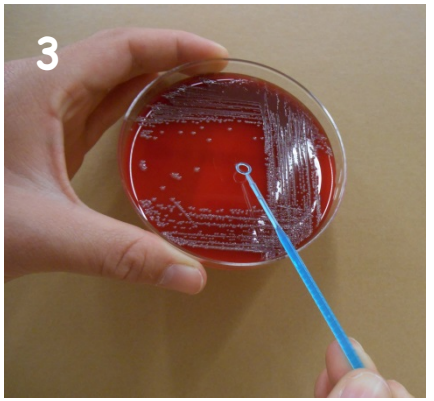
Carba NP test
BYG test
MALDI-TOF
Détection par biologie moléculaire (PCR, RT-PCR)
K-seT OXA-48

OXA-48 K-SeT

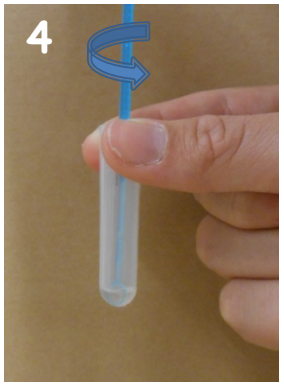
The Kit



10 drops lysis buffer

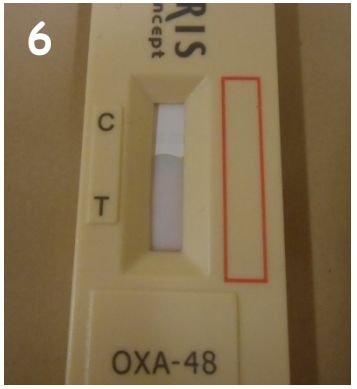


Just touch one colony



Scratch the colony
on the bottom (3-5 sec)

Load 3 drops

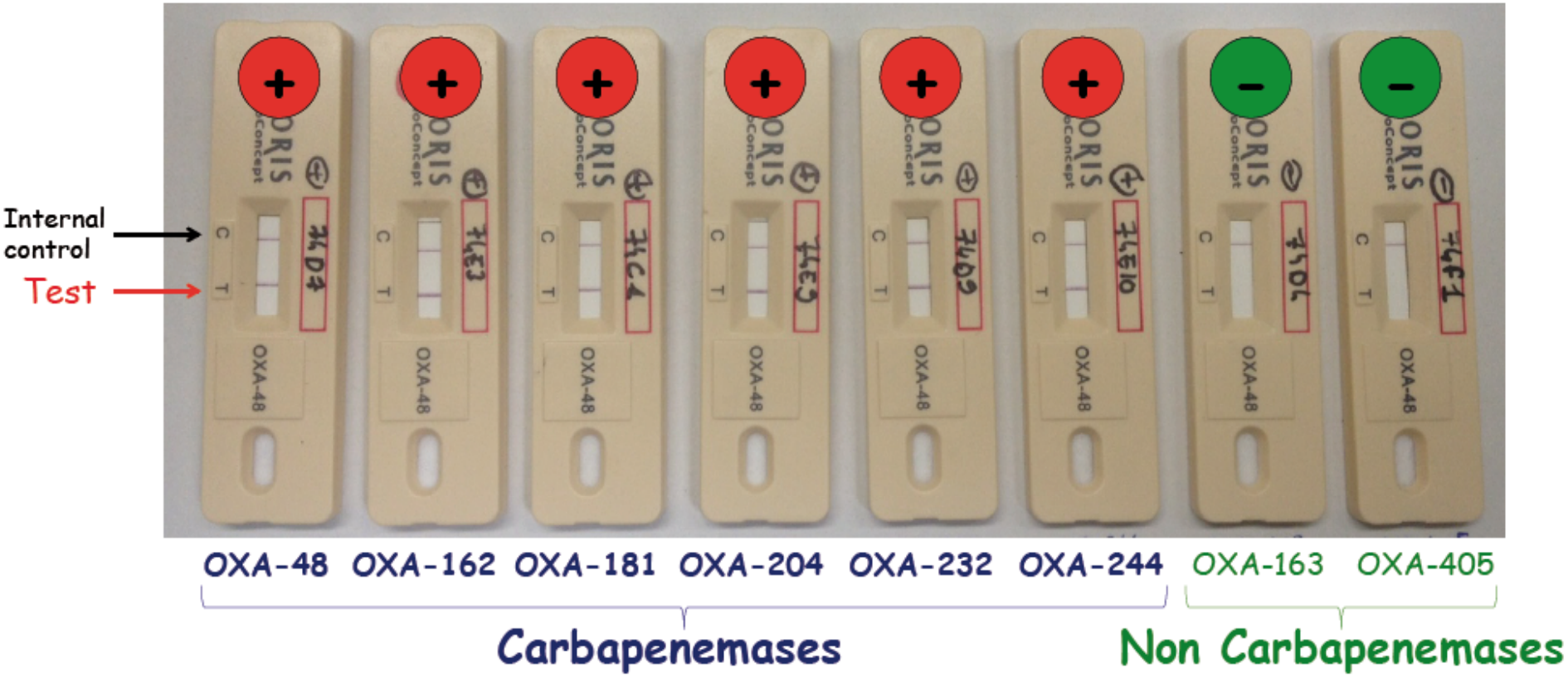


Wait for max 15 min

OXA-48 K-SeT

Lecture à 15 minutes

Bonne différentiation des variants d'OXA-48 avec ou sans activité carbapénèmase



J 0

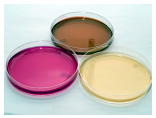
Infections

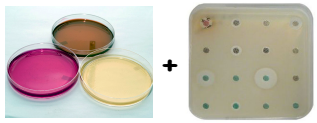
Urine

Autres prélèvements

Hémoculture → Carba NP test

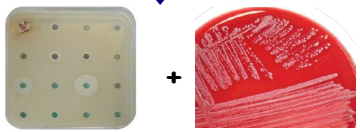
J 1





Carba NP test
BYG test
MALDI-TOF
Détection par biologie moléculaire (PCR, RT-PCR)
K-SeT OXA-48

J 2



Carba NP test
BYG test
MALDI-TOF
Détection par biologie moléculaire (PCR, RT-PCR)
K-seT OXA-48

J 3

Hydrolyse des carbapénèmes (Spectrophotométrie)

J 0

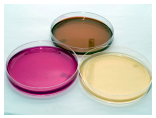
Infections

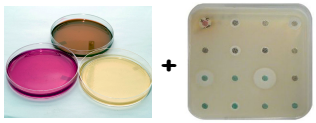
Urine

Autres prélèvements

Hémoculture → Carba NP test

J 1





Carba NP test
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Détection par biologie moléculaire (PCR, RT-PCR)
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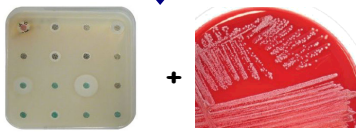
J 2



Carba NP test
BYG test
MALDI-TOF
Détection par biologie moléculaire (PCR, RT-PCR)
K-seT OXA-48

J 3

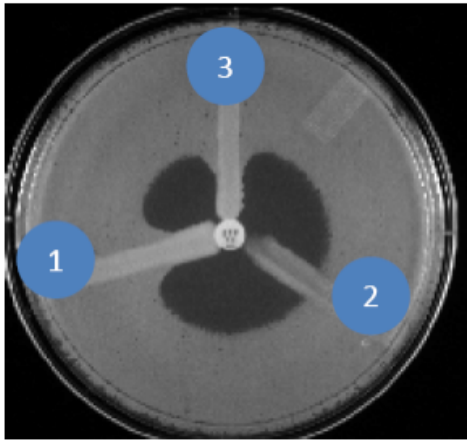
Hydrolyse des carbapénèmes (Spectrophotométrie)

Tests phenotypiques de confirmation (Hodge test, tests d'inhibition)

Test de Hodge modifié

Principe :

- Inoculum: MacFarland 0.5
- Ensemencer une gélose MH avec une souche sensible aux carbapénèmes
- Déposer au centre de la gélose un disque de carbapénème
- A partir du disque faire une inoculation en trait de la souche à tester et 2 souches de référence: carbapénémase + et carbapénémase -
- Incuber à 37° C 12-24h



- 1:T+: carbapénémase
- 2:T-: R carbapénèmes sans carbapénémase
- 3: Souche testée

Avantages :

- KPC, OXA-48 ++
- Simple
- Peu cher

Inconvénients :

- **Faux + : Hyper-expression AmpC + imperméabilité**
- **Métallo-ß-lactamases : +/-**

Gots, J. S. 1945. Science

Test de Hodge modifié

Principe :

- Inoculum: MacFarland 0.5
- Ensemencer une gélose MH avec une souche sensible aux carbapénèmes
- Déposer au centre de la gélose un disque de carbapénème
- A partir du disque faire une inoculation en trait de la souche à tester et 2 souches de
- Incuber à

Avantages :

- KPC, OXA
- Simple
- Peu cher

A ABANDONNER

Inconvénients :

- **Faux + : Hyper-expression AmpC + imperméabilité**
- **Métallo-ß-lactamases : +/-**

- 1:T+: carbapénémase
- 2:T-: R carbapénèmes sans carbapénémase
- 3: Souche testée

Gots, J. S. 1945. Science

Tests phénotypiques d'inhibition

Principe

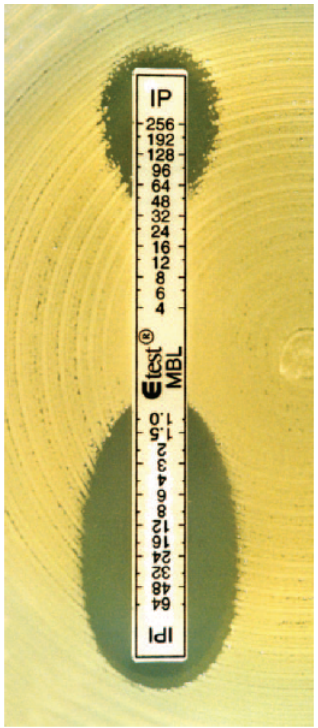
- KPC inhibé par acide boronique ou acide clavulanique
- MBL inhibée par EDTA ou acide dipicolinique
- Microcolonies autour du faropénème si OXA-48, « contact » si carbapénèmase

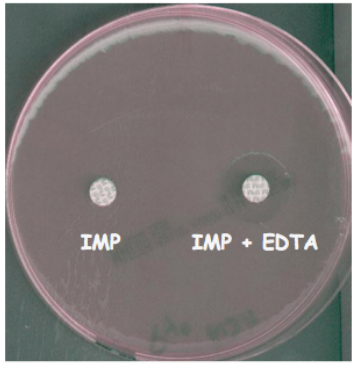
Tests disponibles

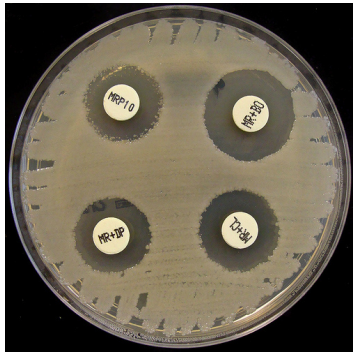
- Tests combinés (ROSCO / MAST) : méropénème +/- cloxacilline ou ac. dicolinique ou ac. boronique +/- disque de faropénème (MAST)
- E-test MBL
- Inhibition par EDTA (« technique maison »)

Inconvénients

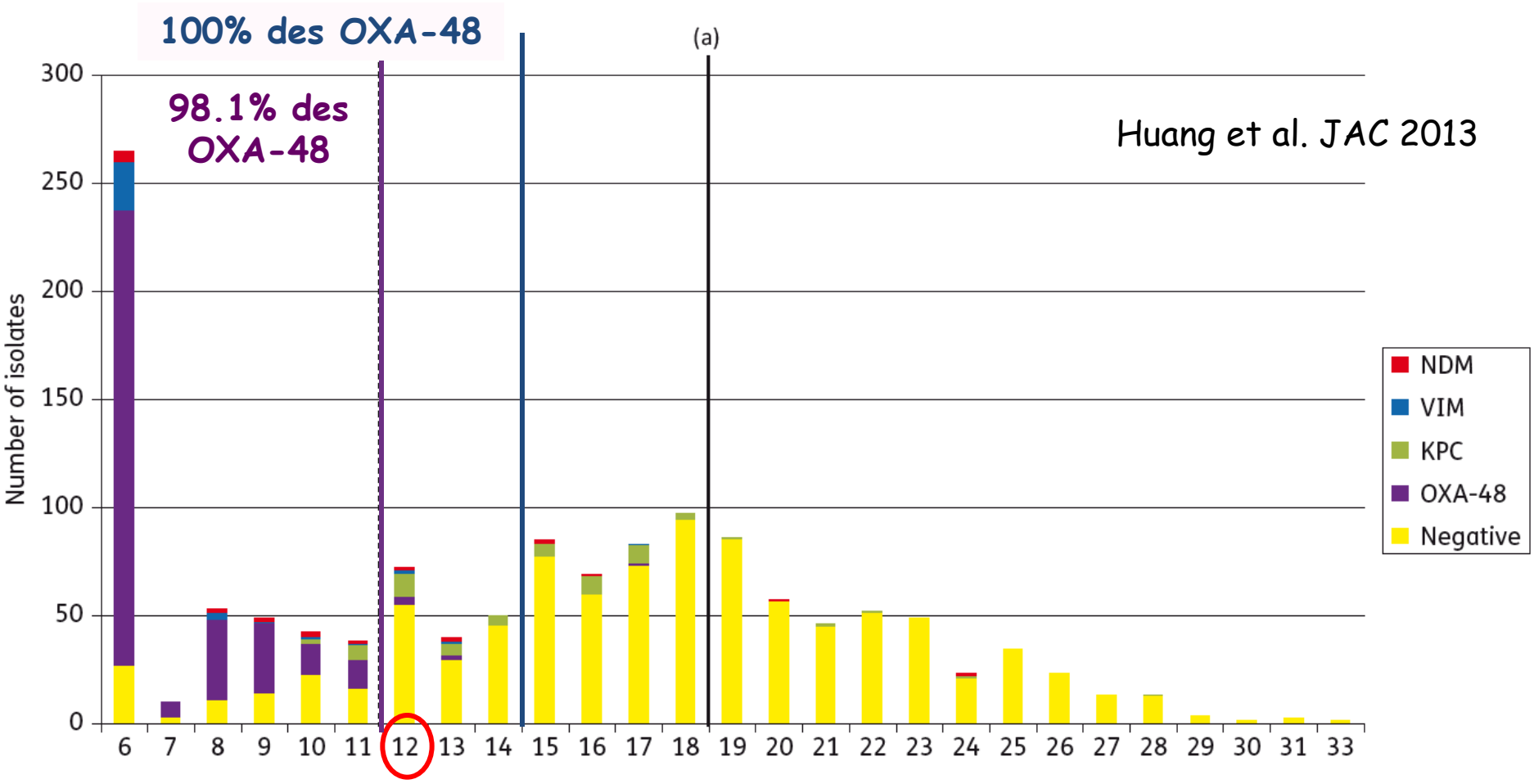
- 24h supplémentaires d'incubation
- Mauvaise spécificité (notamment pour le faropénème)





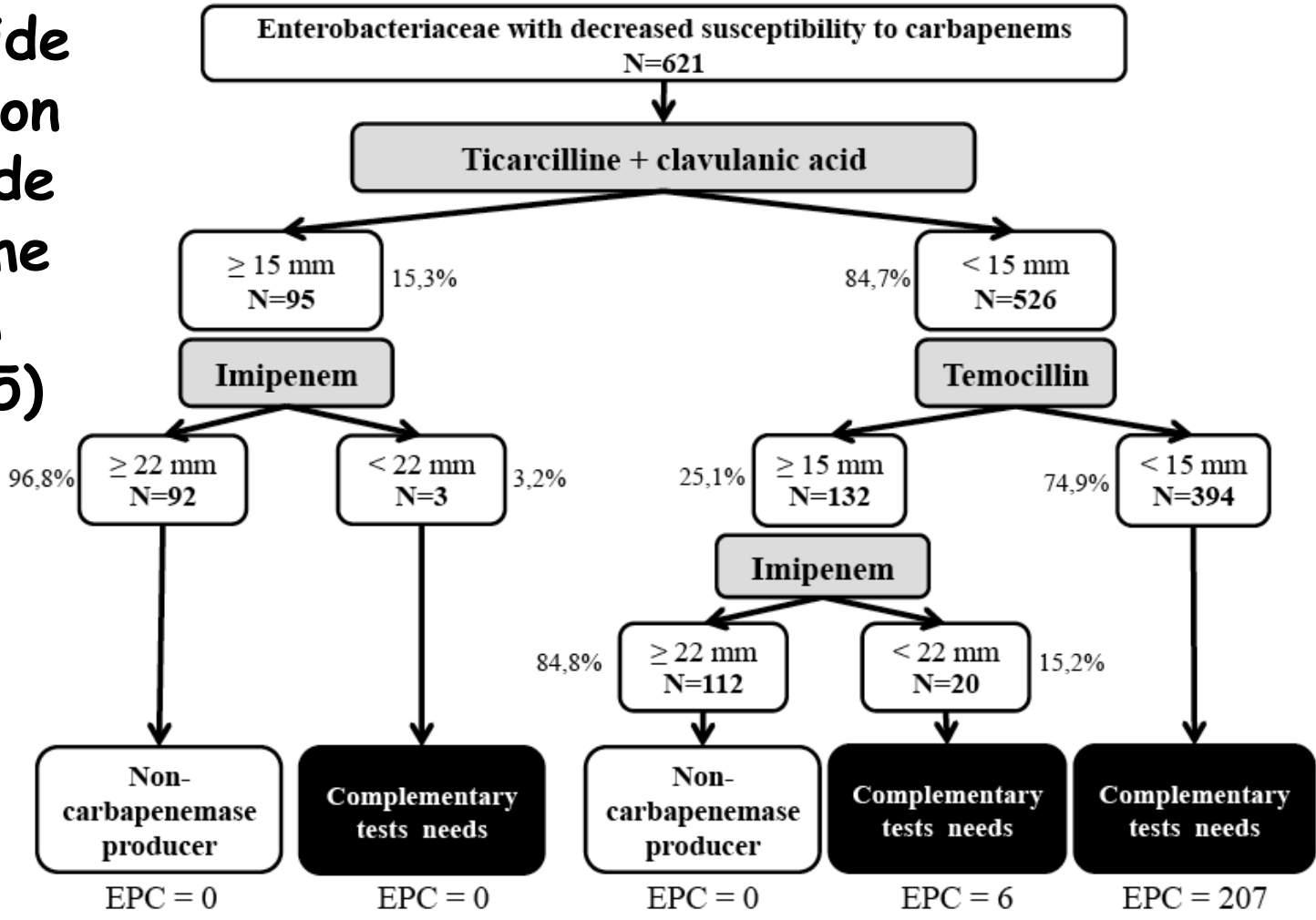


Témocilline : Bon marqueur phénotypique d'OXA-48



Diamètres d' inhibition (mm) autour du disque de témocilline 30 µg

Screening rapide des souches non EPC à partir de l'antibiogramme en diffusion (CASFM 2015)



Non EPC = 32,8%

Tests complémentaire = 67,2%

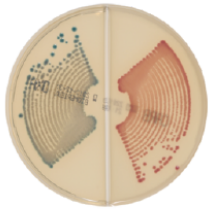
Journal of Antimicrobial Chemotherapy

Prospective evaluation of an algorithm for the phenotypic screening of carbapenemase-producing Enterobacteriaceae

Laurent Dortet[1–3]*, Gaelle Cuzon[1–3], Patrick Plésiat[4] and Thierry Naas[1–3]

CNR
RÉSISTANCE AUX ANTIBIOTIQUES

Fiche résumée globale: Recommandations pour la détection des EPC à partir d'une colonies suspecte (d'après l'épidémiologie française des EPC)



Dépistage
Pousse sur milieu de screening EPC

Antibiogramme
Diminution de sensibilité à au moins un carbapénème

***K-Set* OXA-48**

(+)

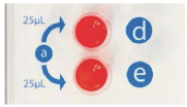
(-)

Carbapénèmase de type OXA-48

RAPIDEC CARBA NP

(+)

(-)



Envoi de la souche au CNR pour typage définitif

Carbapénèmase de type NDM, KPC, VIM, IMI, ou IMP

Absence de carbapénèmase

http://www.cnr-resistance-antibiotiques.fr/exp-des-souches-1.html

PLAN

Epidémiologie et dissémination des entérobactéries productrices de carbapénèmases

Méthodes de détection des entérobactéries productrices de carbapénèmases

1) A partir d'un prélèvement clinique (infection)

2) Dépistage des patients porteurs

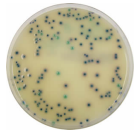
J 0

Recherche de porteurs de bactéries résistantes

Selles, écouvillon rectal

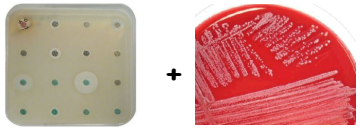
J 1

Milieux sélectifs Lequel ???



Carba NP test
BYG test
MALDI-TOF
Détection par biologie moléculaire (PCR, RT-PCR)
K-SeT OXA-48

J 2



Carba NP test
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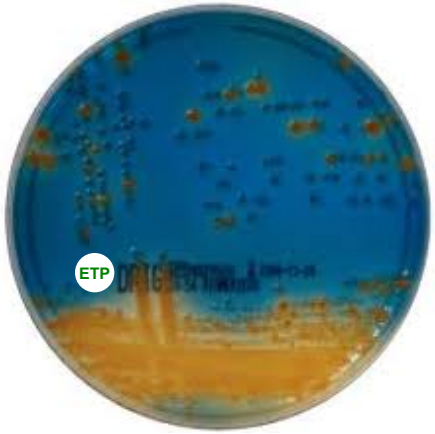
MALDI-TOF
Détection par biologie moléculaire (PCR, RT-PCR)
K-seT OXA-48

J 3

Hydrolyse des carbapénèmes (Spectrophotométrie)
Tests phenotypiques de confirmation (Hodge test, tests d'inhibition)
Identification moléculaire des carbapénèmases (séquençage, hydridation)

Milieux sélectifs de screening

Drigalski + disque ertapénème

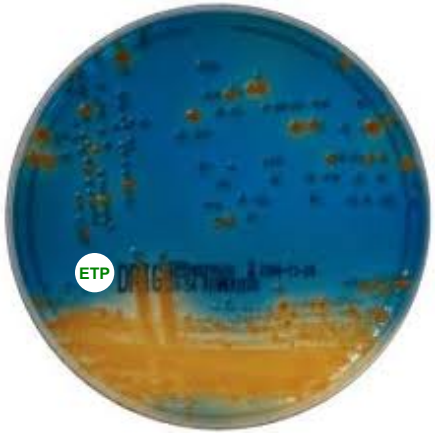


Avantages : Simple, Faible coût

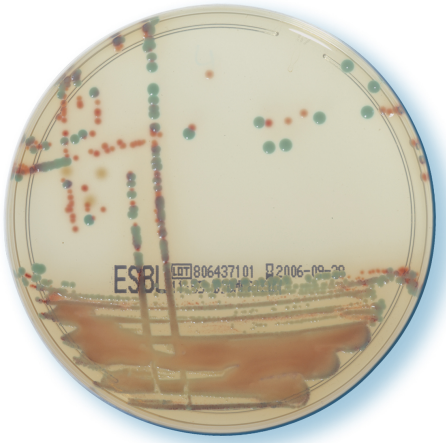
Inconvénients : Milieu non recommandé pour Carba NP test
Faible inoculum

Milieux sélectifs de screening

Drigalski + disque ertapénème



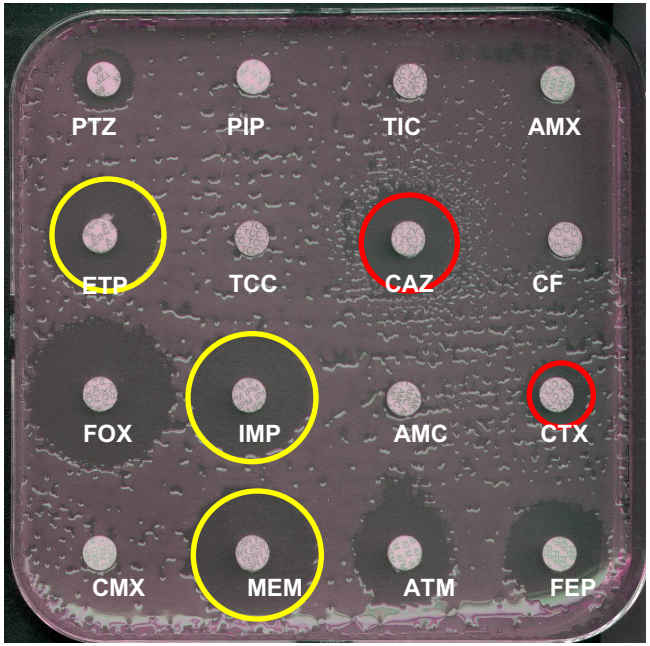
Milieux contenant des C3G



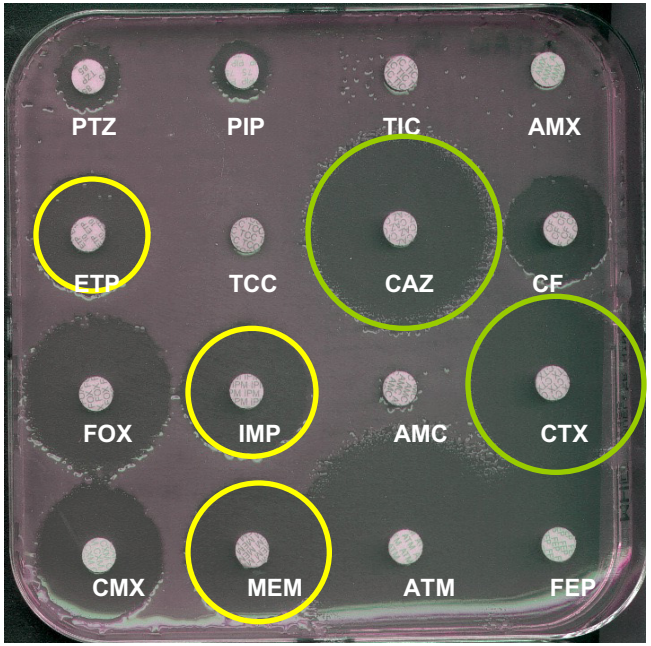
Ex : ChomID ESBL

Milieux selectifs contenant des céphalosporines

Absence de détection des souches OXA-48 sans BLSE



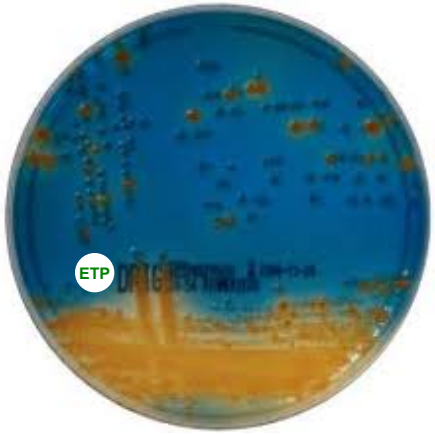
K. pneumoniae OXA-48
BLSE +



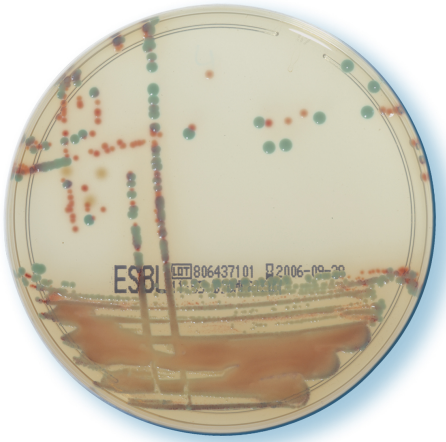
K. pneumoniae OXA-48
BLSE -

Milieux sélectifs de screening

Drigalski + disque ertapénème



Milieux contenant des C3G



Milieux contenant un carbapénème

CHROMAGAR KPC
ChromID Carba
Brillance CRE
SUPERCARBA

Milieux selectifs contenant un carbapénème

- **CHROMAGAR KPC** (Chromagar) : Méropénème + chromogènes **NON**
- **ChromID Carba** (Biomérieux) : Carbapénème (?) + chromogènes **OK sauf OXA-48**
- **Brillance CRE agar** (Oxoid) : Carbapénème (?) + chromogènes **OK sauf OXA-48**
- **SUPERCARBA medium** (made in Bicêtre) : Etapénème + cloxacillne + Zinc **OK pour tout**

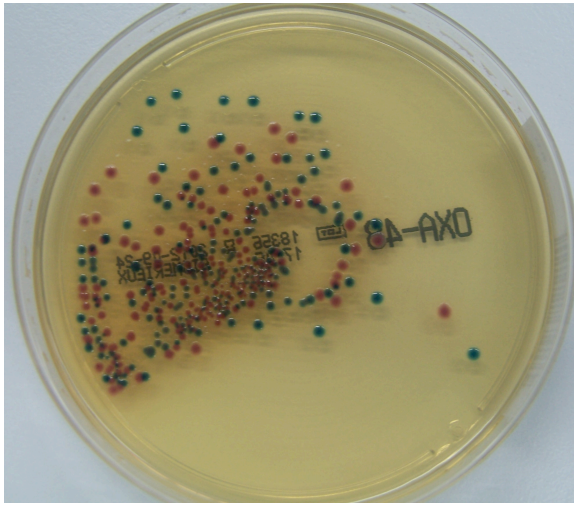
	SUPERCARBA	Brillance CRE	CHROMagar KPC
Sensibilité (%)	**96.5**	76.3	43
Spécificité (%)	60.7	57.1	67.8
Sensibilité classe A	**100**	85	70
Sensibilité classe B	**92**	78.4	58.8
Sensibilité classe D	**100**	69.8	11.6

Girlich, Poirel and Nordmann. Diag Microb Infect Dis. 2012

Milieux sélectifs de screening pour OXA-48

Contient de la témocilline ???

Présence de chromogènes

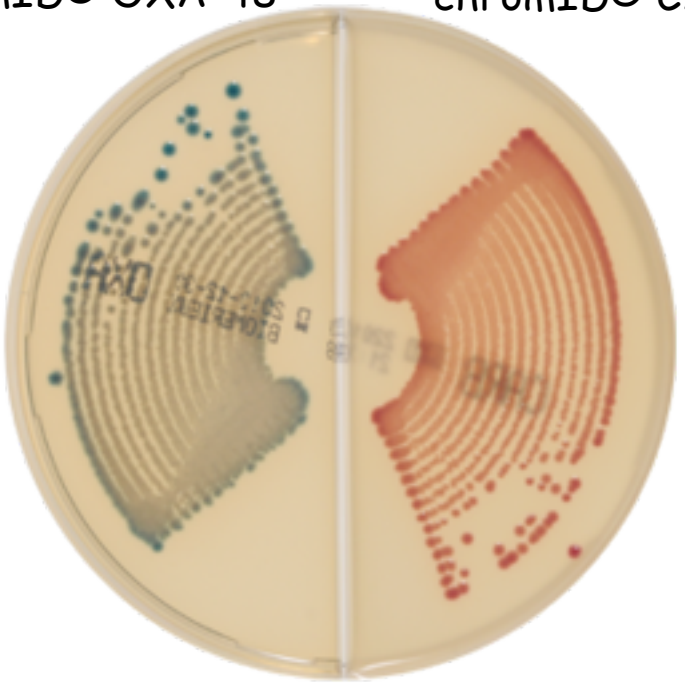


Avantages :
Simple, Milieu commercial, Bonne détection des souches OXA-48

Inconvénients :
Mauvaise mais pas des autres carbapénèmases

Milieux sélectifs de screening global bi-plate

chromID® OXA-48 chromID® CARBA



chromID® CARBA SMART

Avantages :

Simple, Milieu commercial

Bonne détection de toutes les carbapénèmases

CNR
RÉSISTANCE AUX ANTIBIOTIQUES

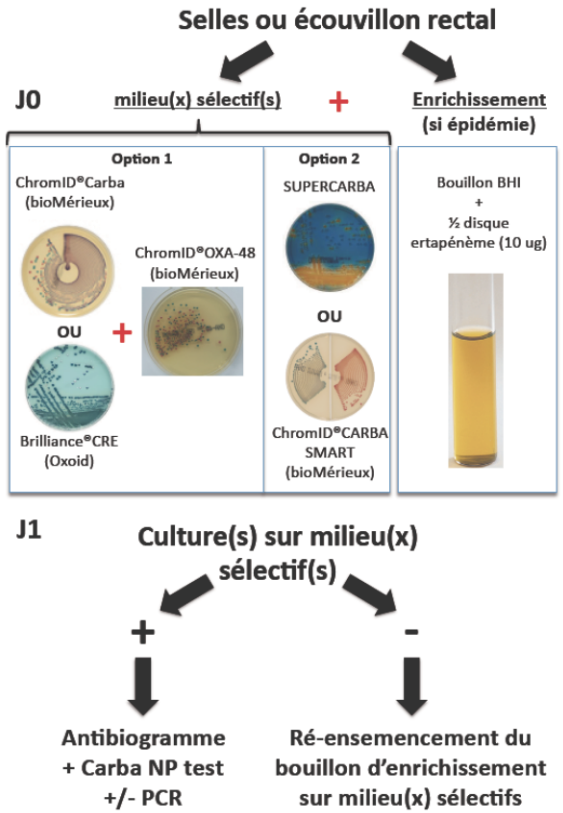
Fiche résumée : Recommandations pour le dépistage des patients porteurs d'une souche d'EPC (patients colonisés)

1) Patient ayant eu dans les 12 derniers mois une hospitalisation de plus de 24 h quel que soit le secteur ou de prise en charge dans une filière de soins spécifique (dialyse) à l'étranger.

2) Types de prélèvements : **selles** ou **écouvillonnages rectaux.** il est important de **vérifier visuellement la présence de matières fécales sur l'écouvillon.**

3) Il est conseillé de **répéter les prélèvements** en cas de forte suspicion de colonisation par une EPC (3 prélèvements à 3-4 jours d'intervalle). Ne pas hésiter à réaliser un nouveau dépistage après la mise sous antibiothérapie.

4) Méthodologie recommandée pour le dépistage des patients porteur d'une EPC :

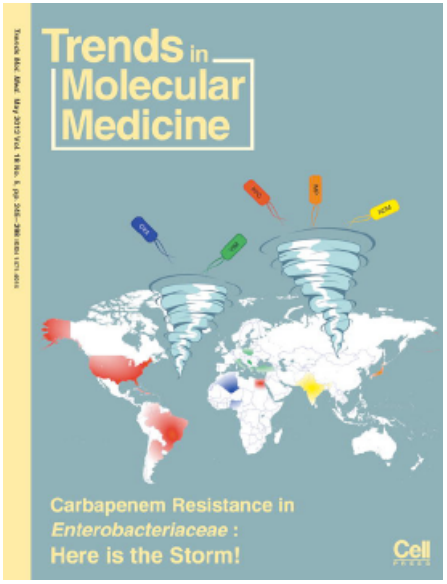


5) **La détection moléculaire de EPC directement à partir du prélèvement** permet de gagner une journée sur la détection des EPC. Etant donné la non détection de certaines carbapénèmases par biologie moléculaire il est conseillé de **réserver ce type de technique au dépistage des patients contact lors d'épidémies**. Il conviendra alors de vérifier que le kit de biologie moléculaire est capable de détecter efficacement la souche épidémique avant utilisation directe sur les prélèvements cliniques.

http://www.cnr-resistance-antibiotiques.fr/exp-des-souches-1.html

CNR
RÉSISTANCE AUX ANTIBIOTIQUES

http://www.cnr-resistance-antibiotiques.fr



Merci pour votre attention

Conclusions

2005…

CLINICAL MICROBIOLOGY REVIEWS, Apr. 2005, p. 306–325 Vol. 18, No. 2
0893-8512/05/$08.00+0 doi:10.1128/CMR.18.2.306–325.2005

Metallo-β-Lactamases: the Quiet before the Storm?

Timothy R. Walsh,[1]* Mark A. Toleman,[1] Laurent Poirel,[2] and Patrice Nordmann[2]

Department of Pathology and Microbiology, University of Bristol, Bristol, United Kingdom,[1] and Service de Bactériologie-Virologie, Hôpital de Bicêtre, Assistance Publique/Hôpitaux de Paris, Faculté de Médecine Paris-Sud, Le Kremlin-Bicêtre, France[2]

2012…

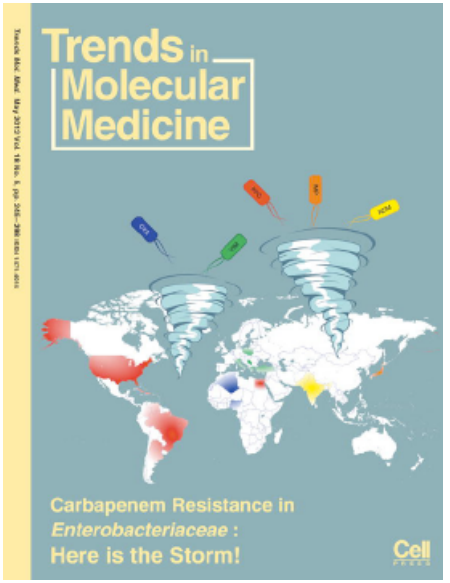
Review

Cell PRESS

Carbapenem resistance in *Enterobacteriaceae*: here is the storm!

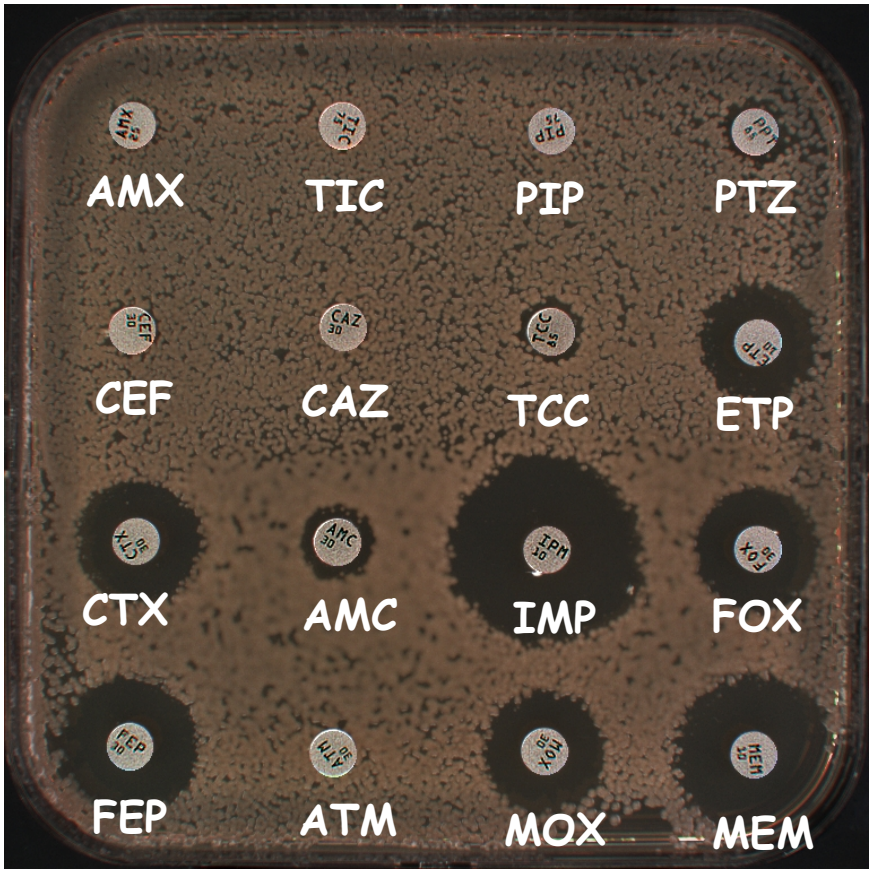
Patrice Nordmann, Laurent Dortet and Laurent Poirel

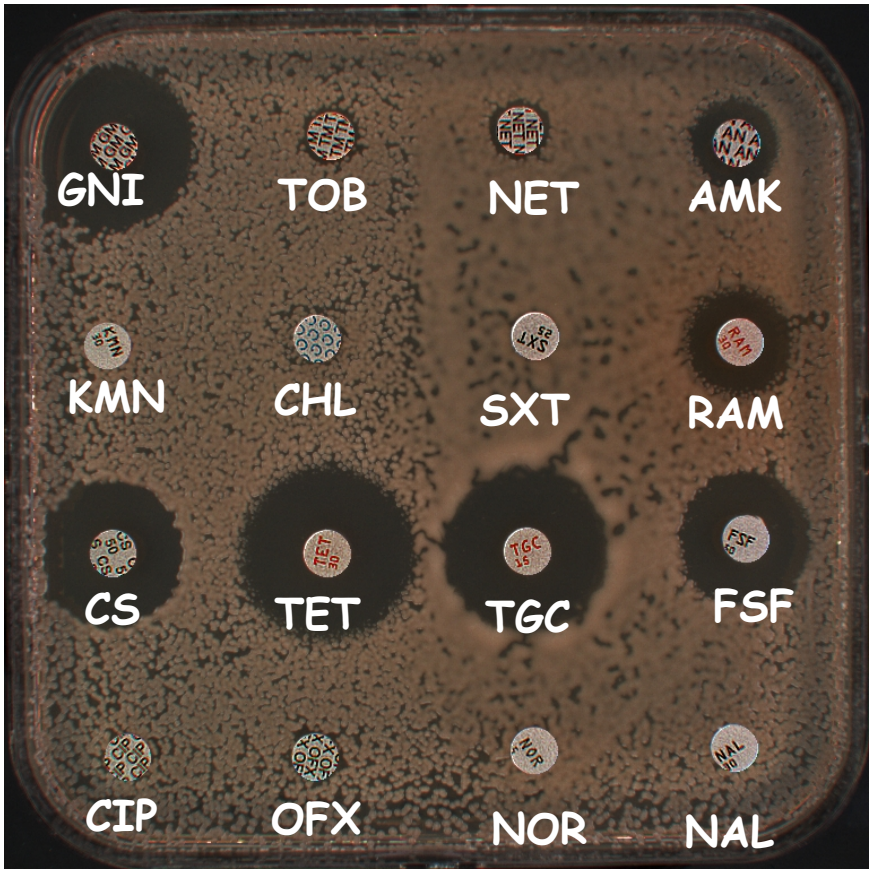
Service de Bactériologie-Virologie, INSERM U914 'Emerging Resistance to Antibiotics', Hôpital de Bicêtre, Assistance Publique/Hôpitaux de Paris, Faculté de Médecine Paris Sud, K.-Bicêtre, 78 rue du Général Leclerc, 94275 Le Kremlin-Bicêtre Cedex, France



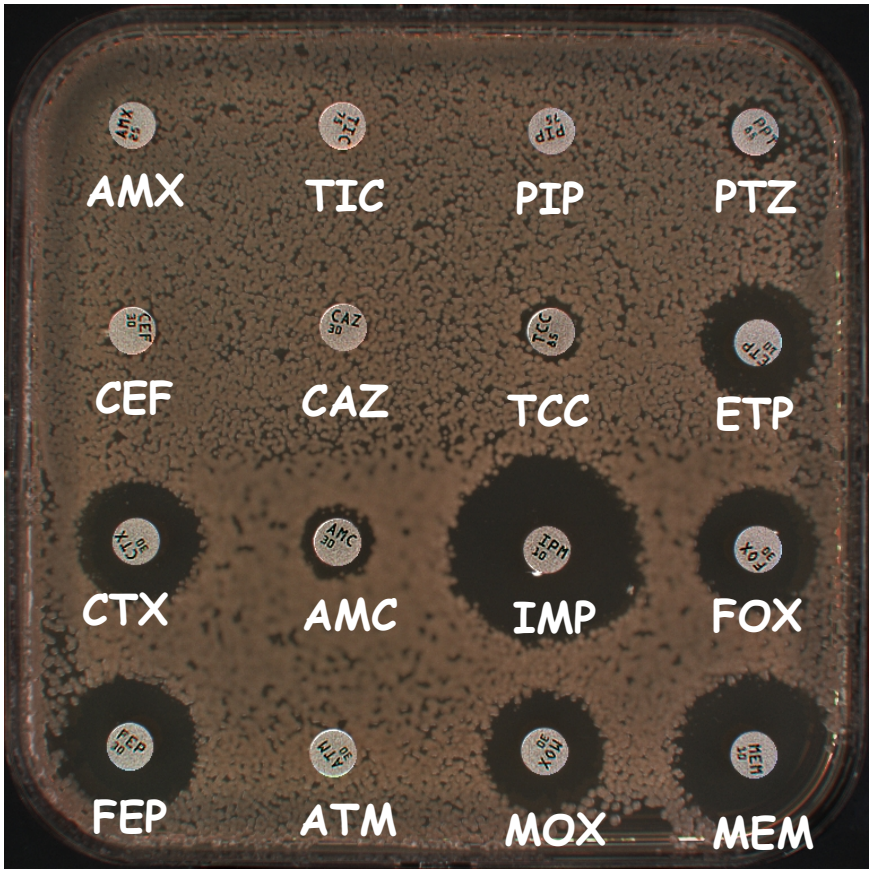
QUIZZ

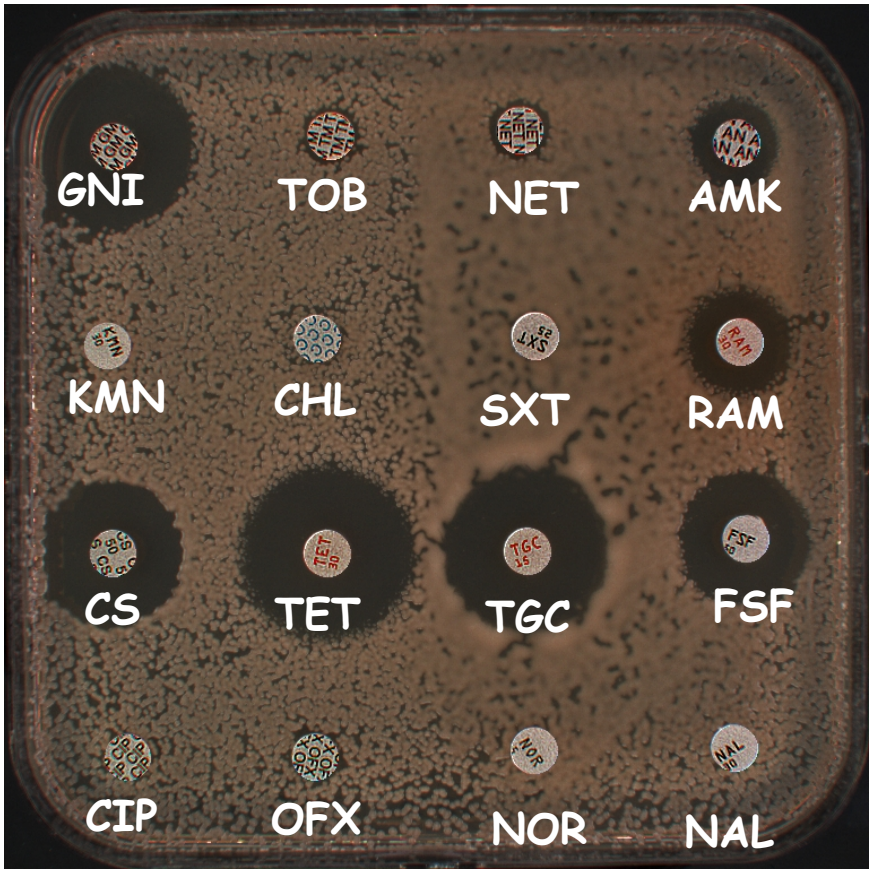
Carbapénèmase ?



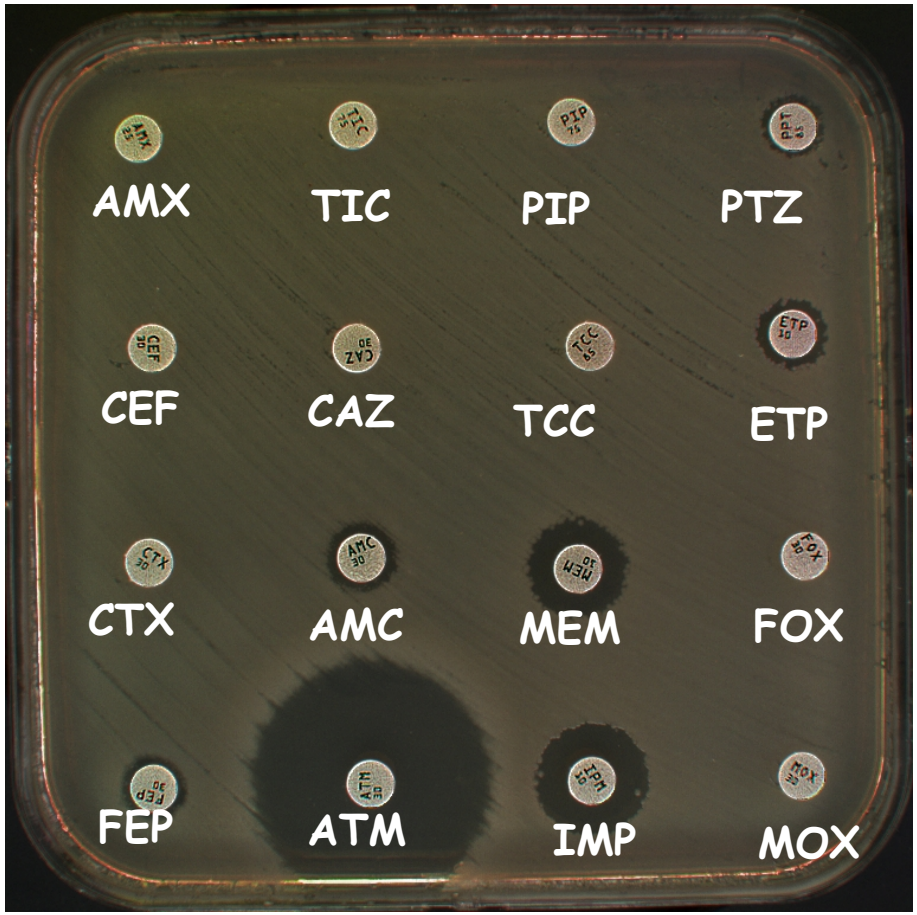


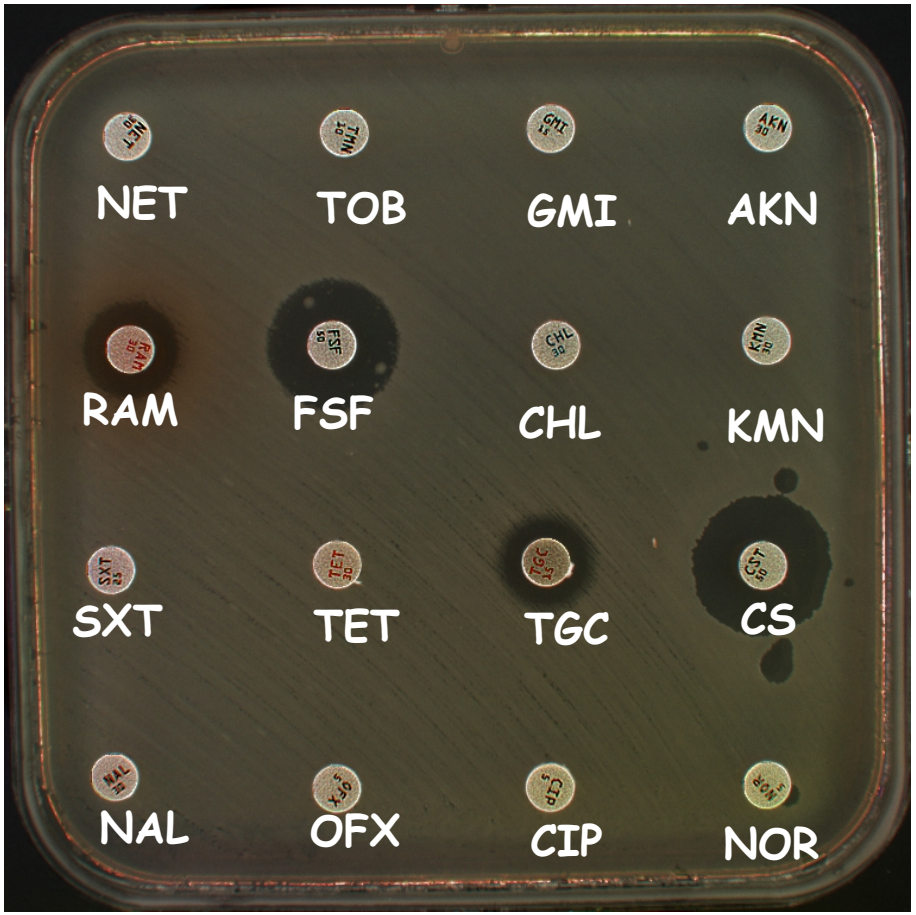
K.pneumoniae KPC-2



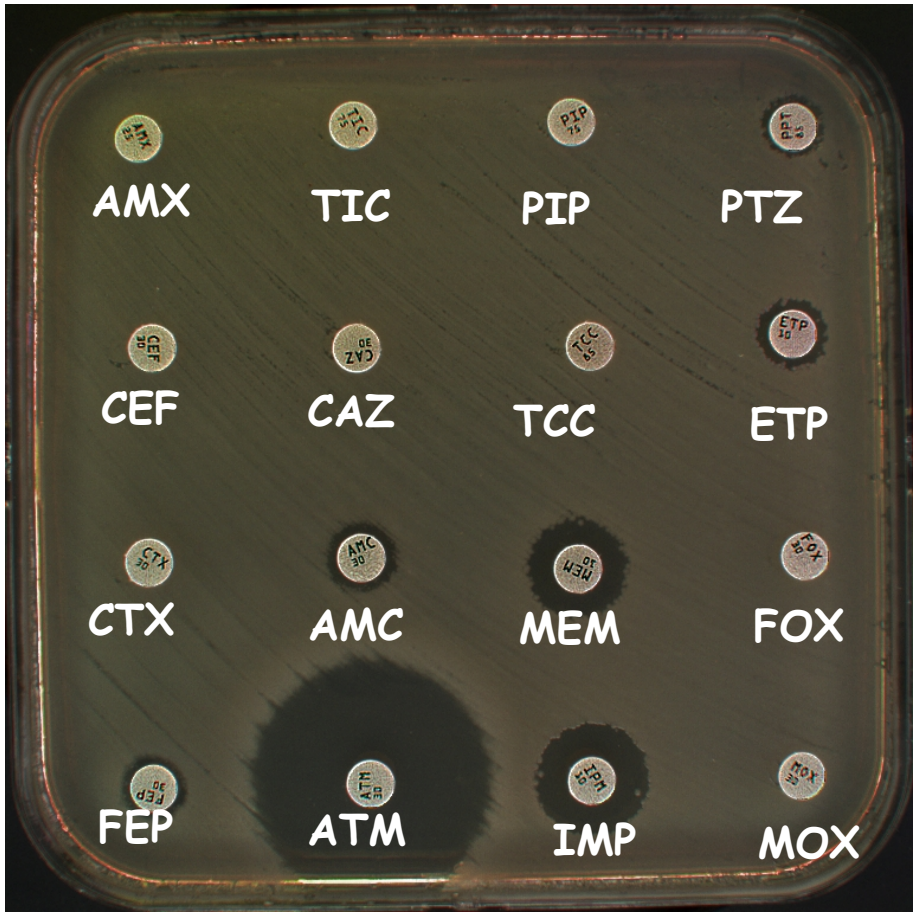


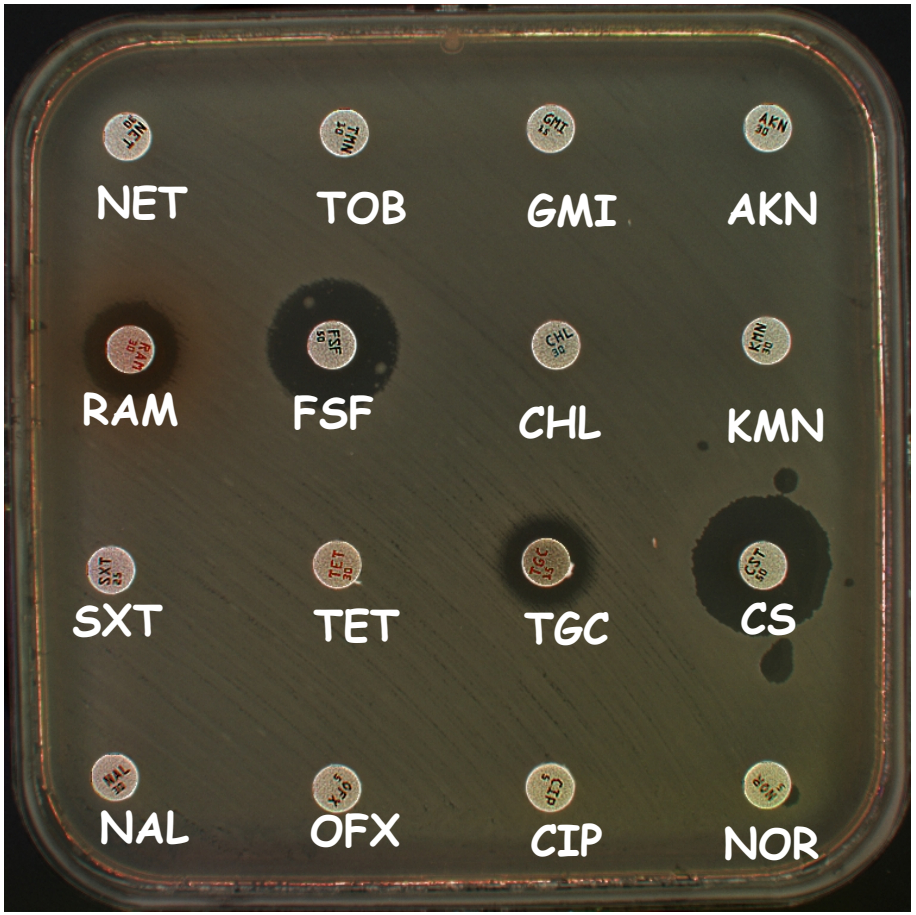
Carbapénèmase ?



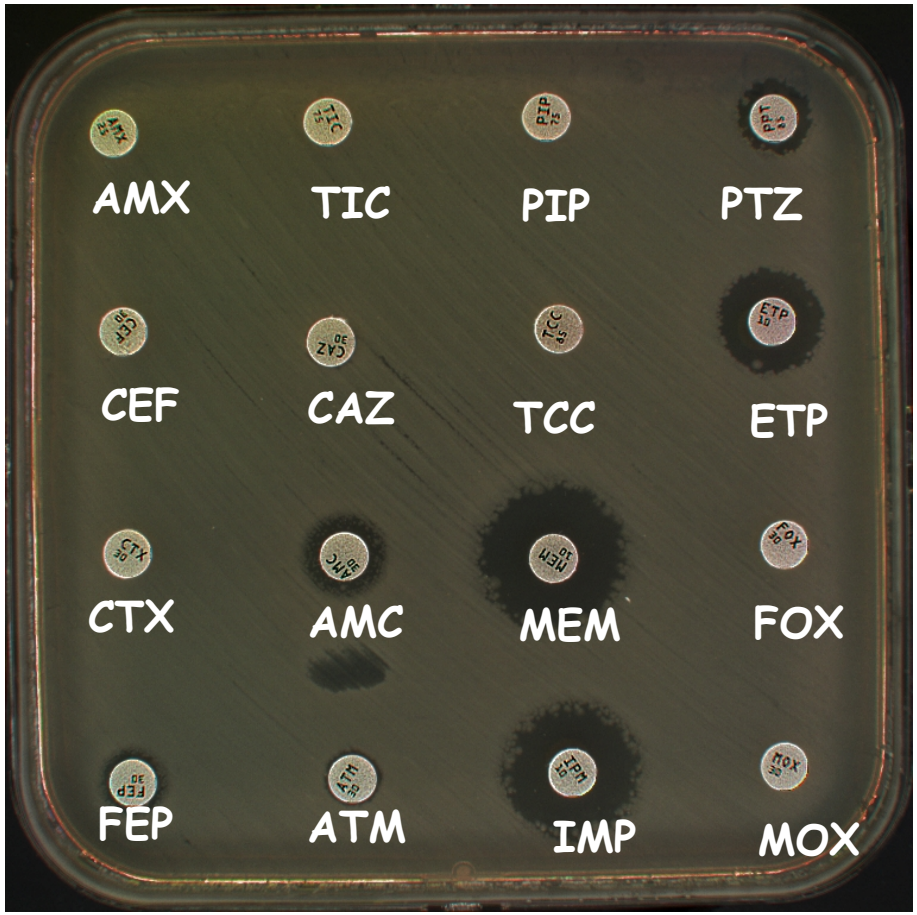


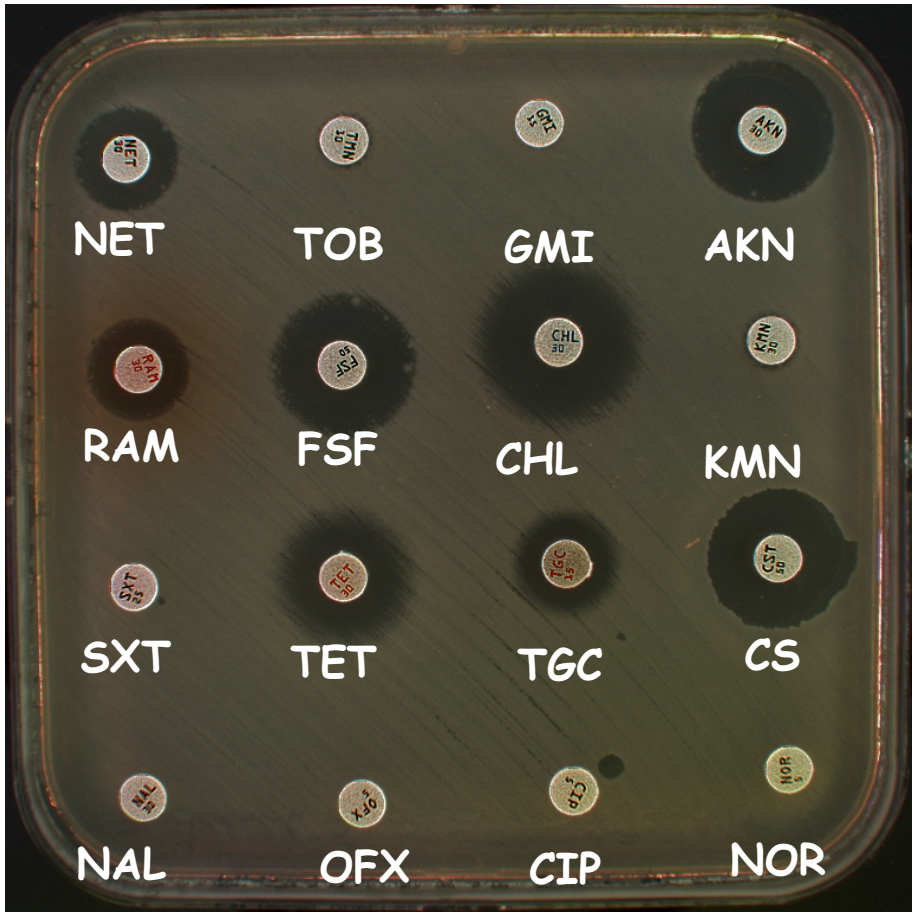
E. coli NDM-1


AMX
TIC
PIP
PTZ
CEF
CAZ
TCC
ETP
CTX
AMC
MEM
FOX
FEP
ATM
IMP
MOX

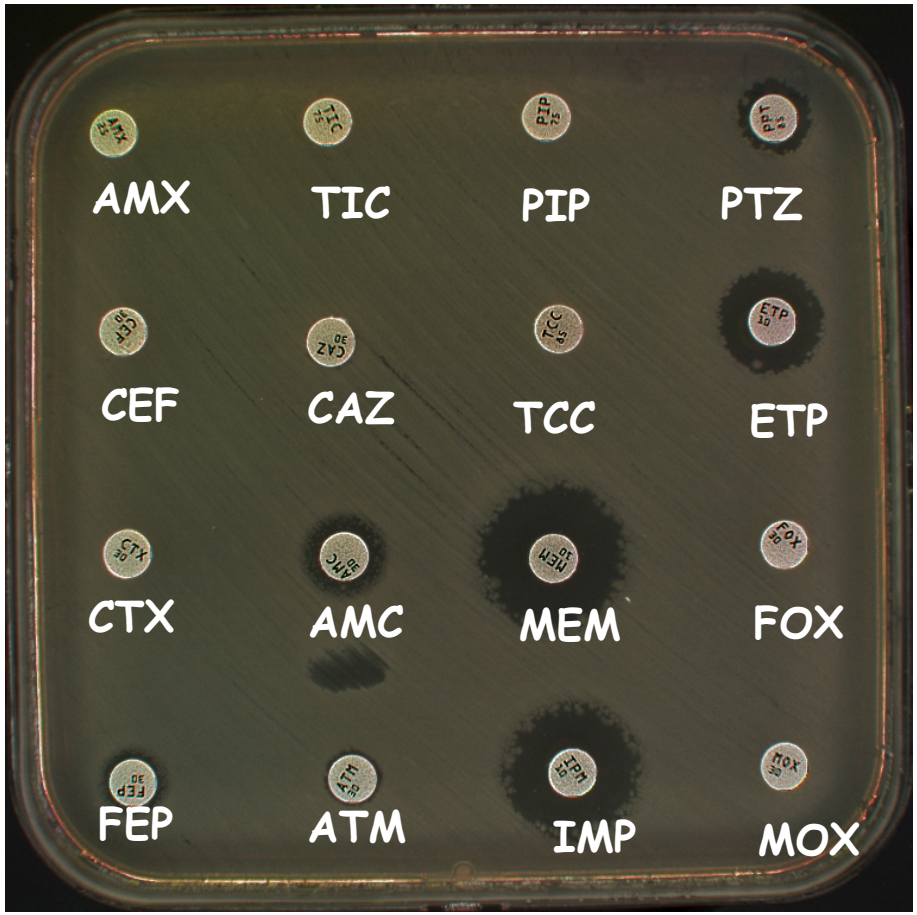

NET
TOB
GMI
AKN
RAM
FSF
CHL
KMN
SXT
TET
TGC
CS
NAL
OFX
CIP
NOR

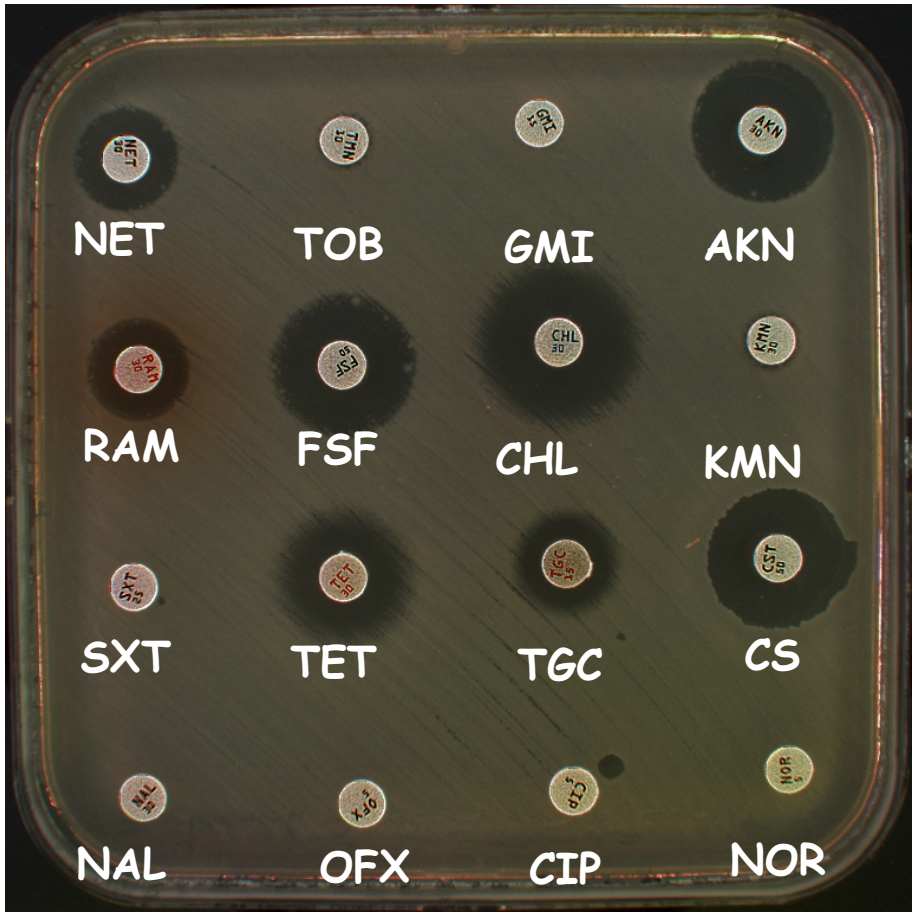
Carbapénèmase ?



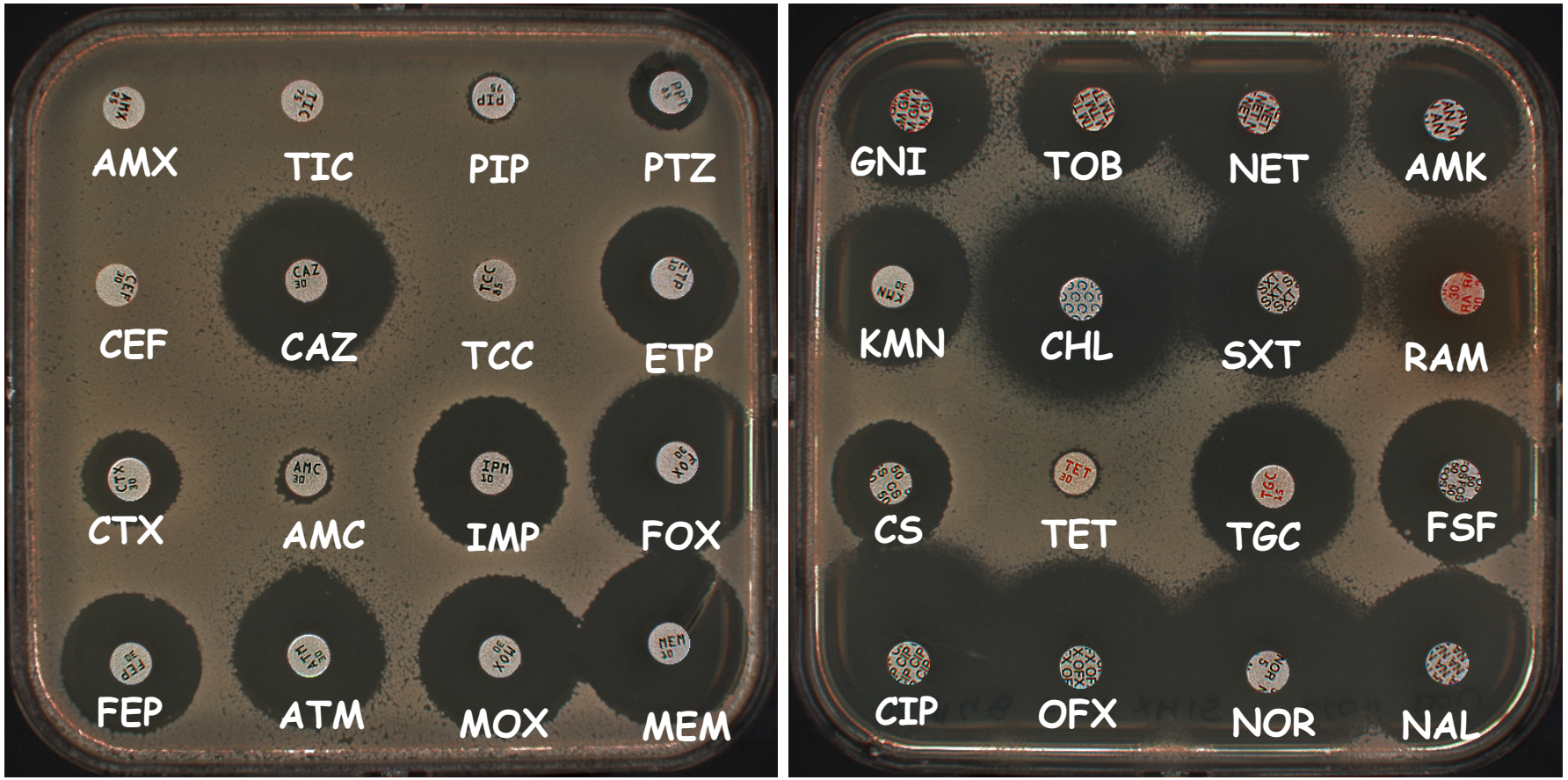


E. coli NDM-1 + CTX-M-15

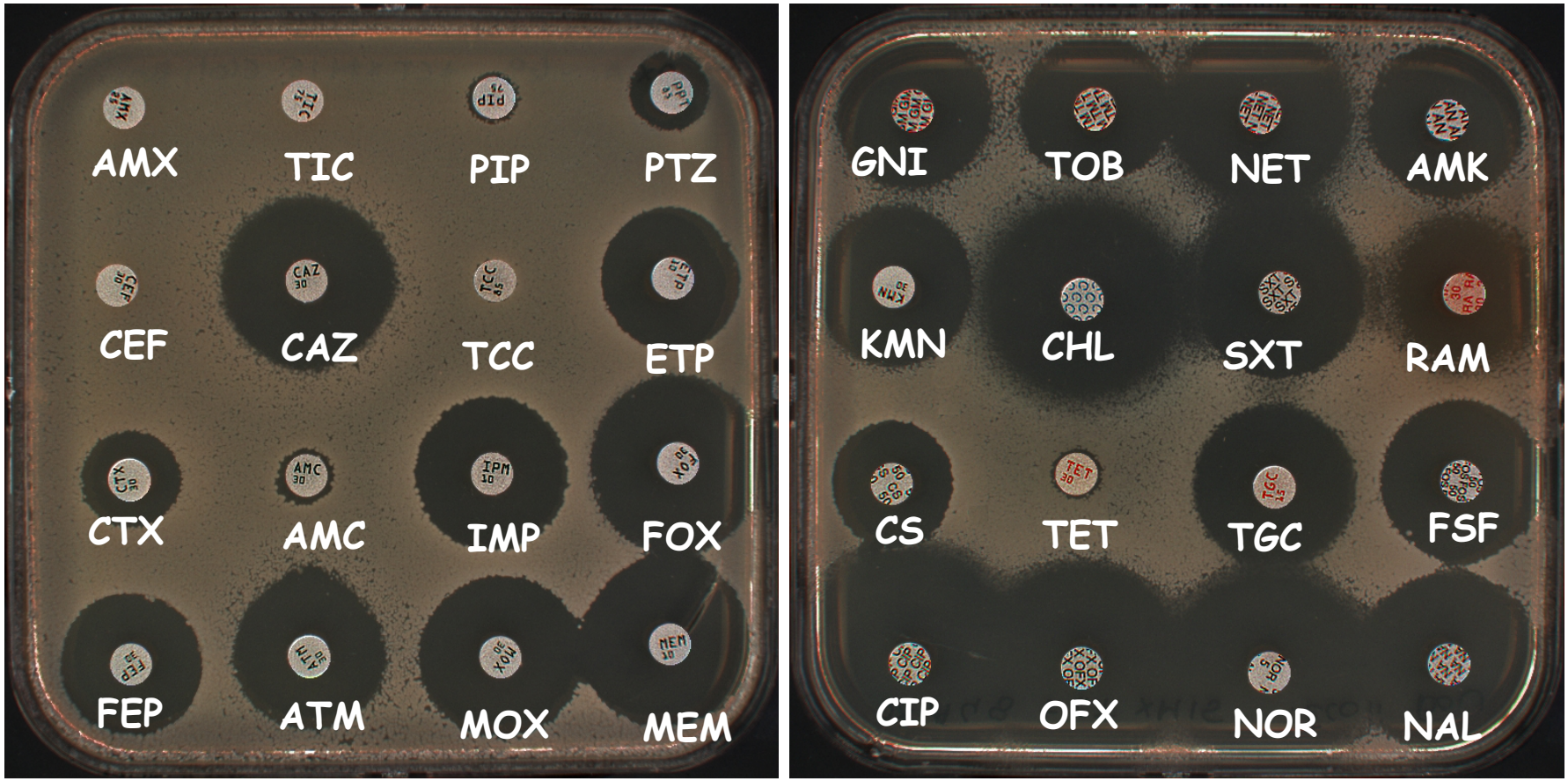




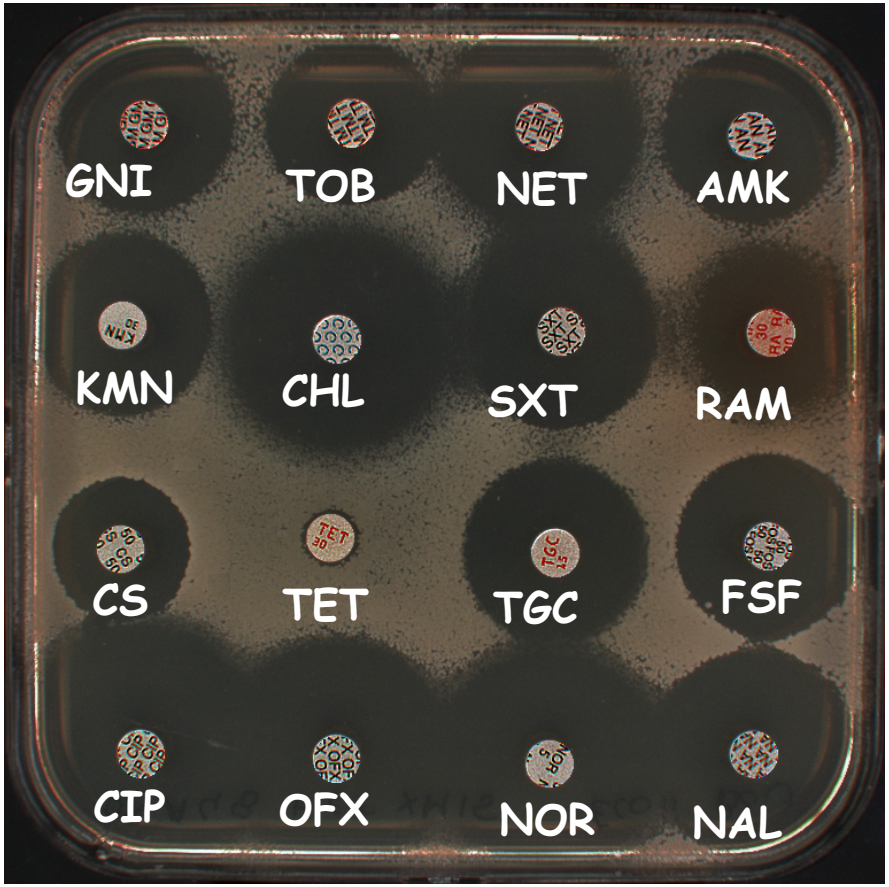
Carbapénèmase ?



E. coli OXA-48 + CTX-M-15

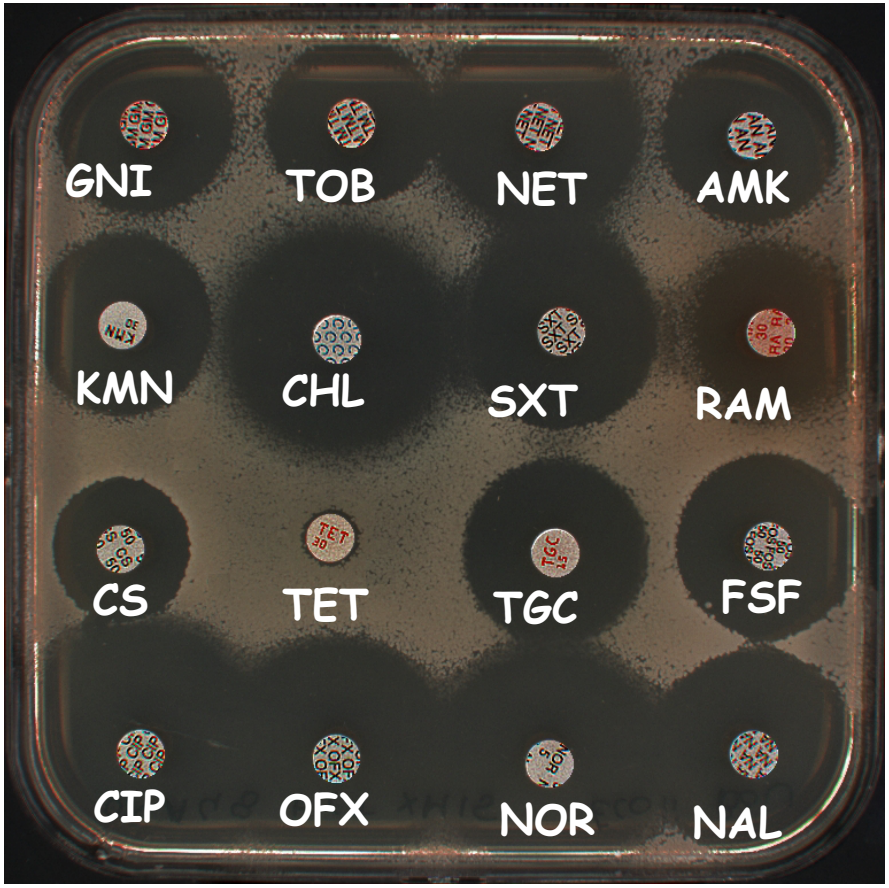


Carbapénèmase ?

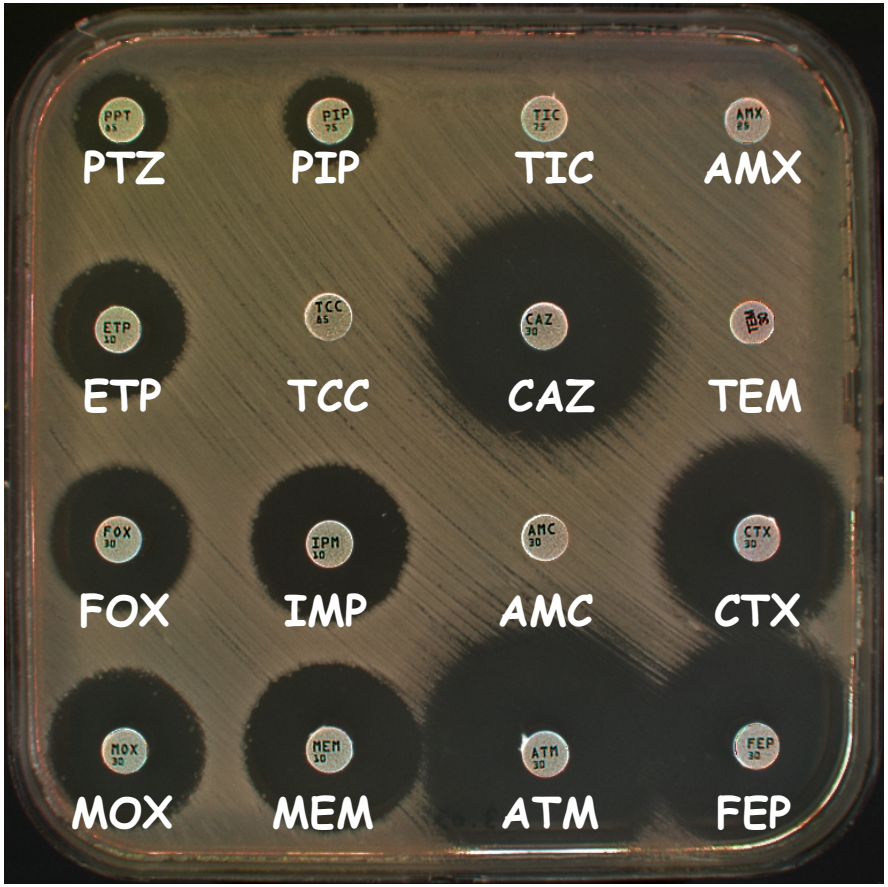


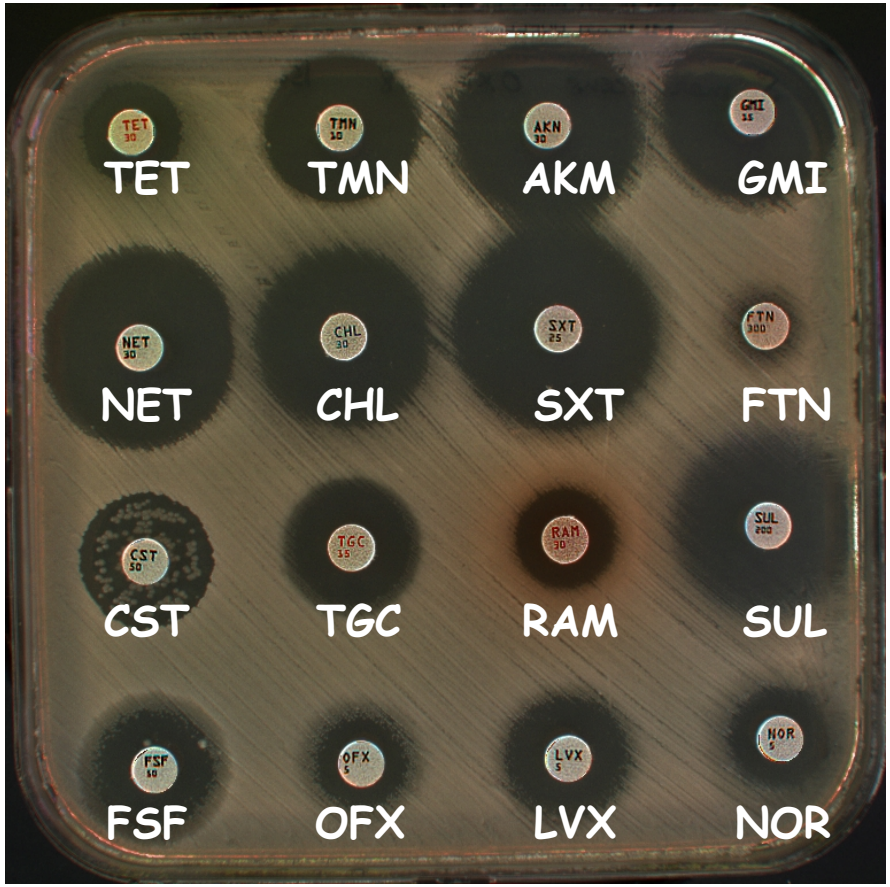
E. coli OXA-48


AMX
TIC
PIP
PTZ
CEF
CAZ
TCC
ETP
CTX
AMC
IMP
FOX
FEP
ATM
MOX
MEM

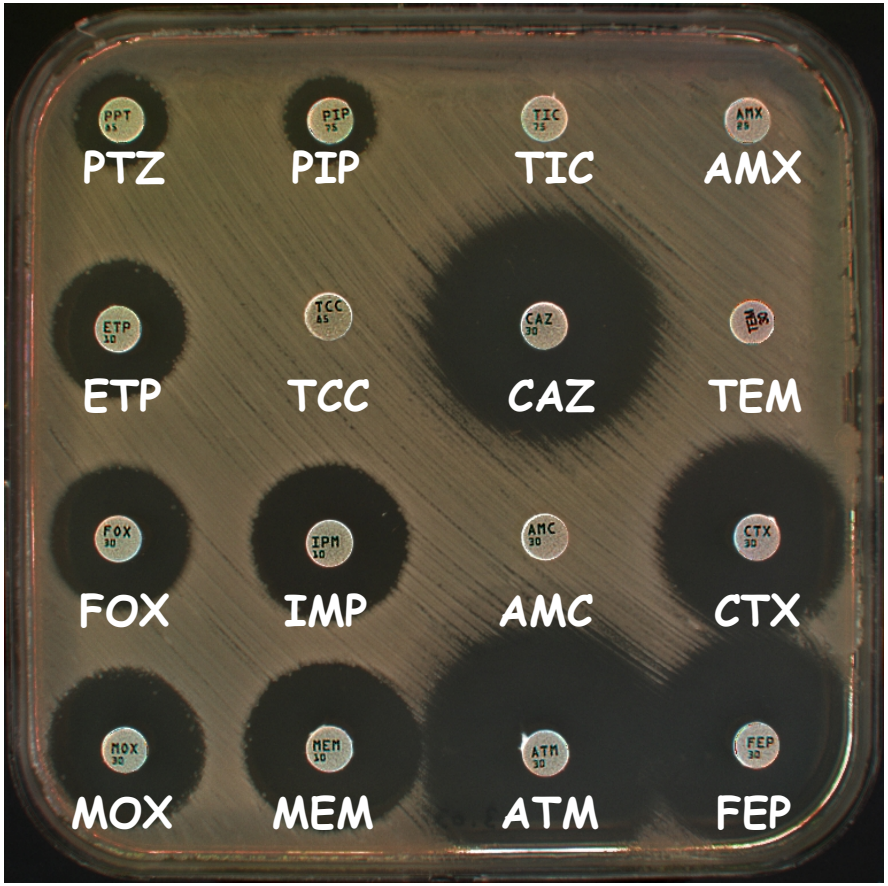

GNI
TOB
NET
AMK
KMN
CHL
SXT
RAM
CS
TET
TGC
FSF
CIP
OFX
NOR
NAL

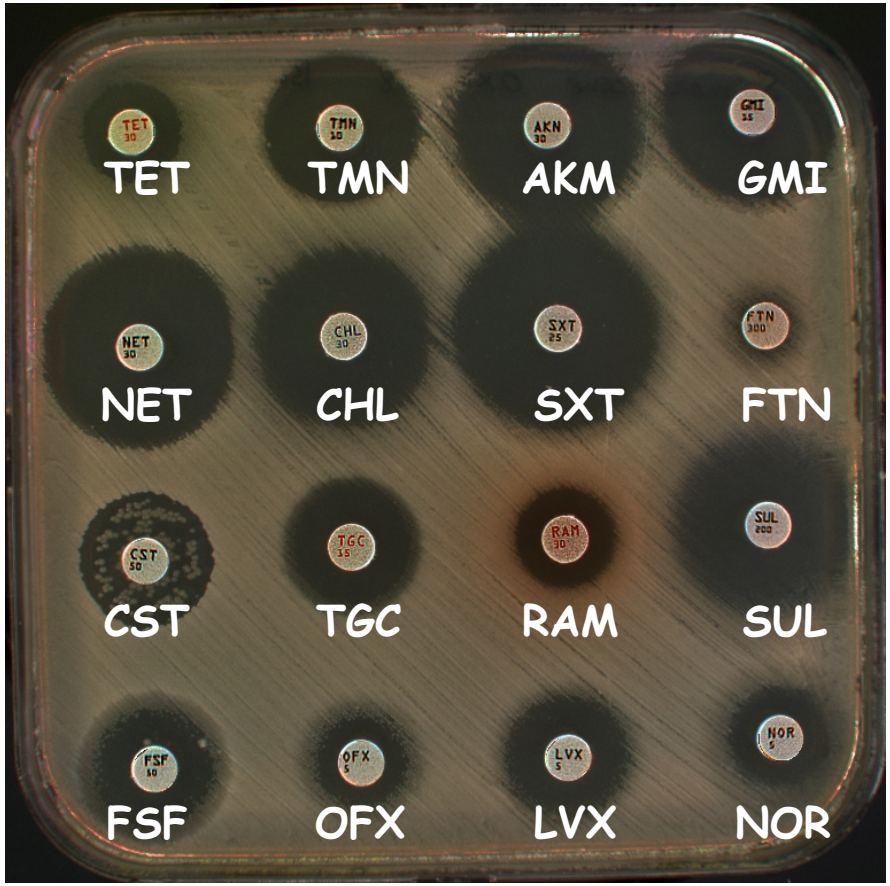
Carbapénèmase ?



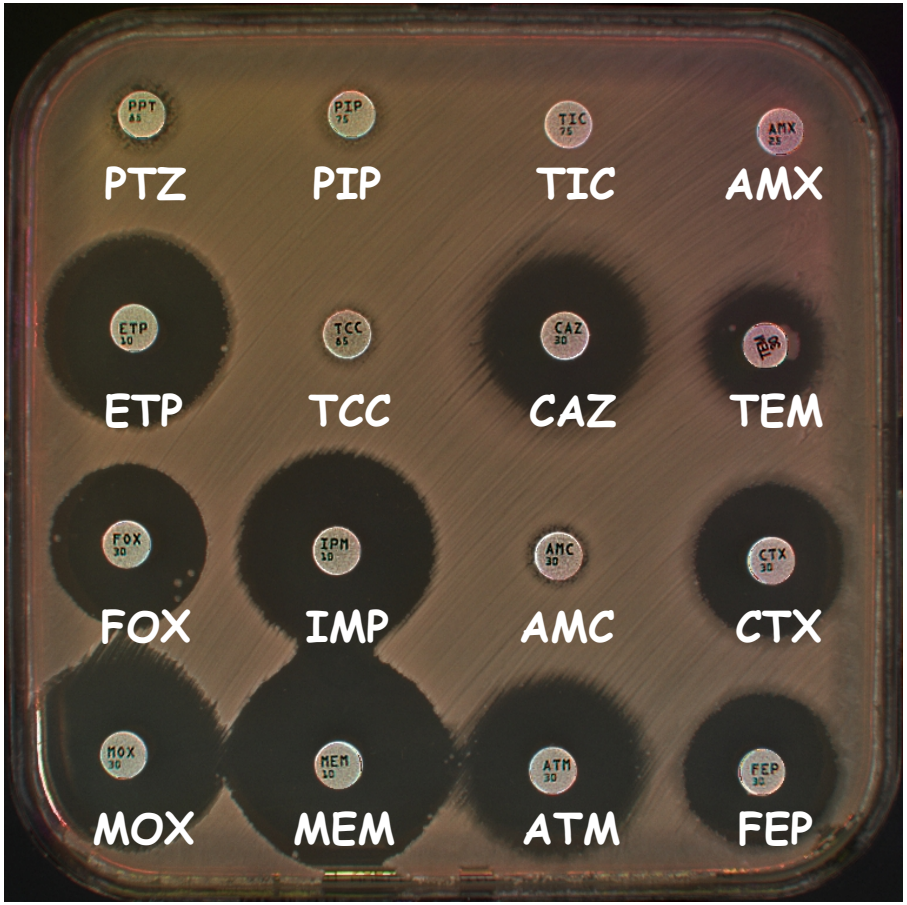


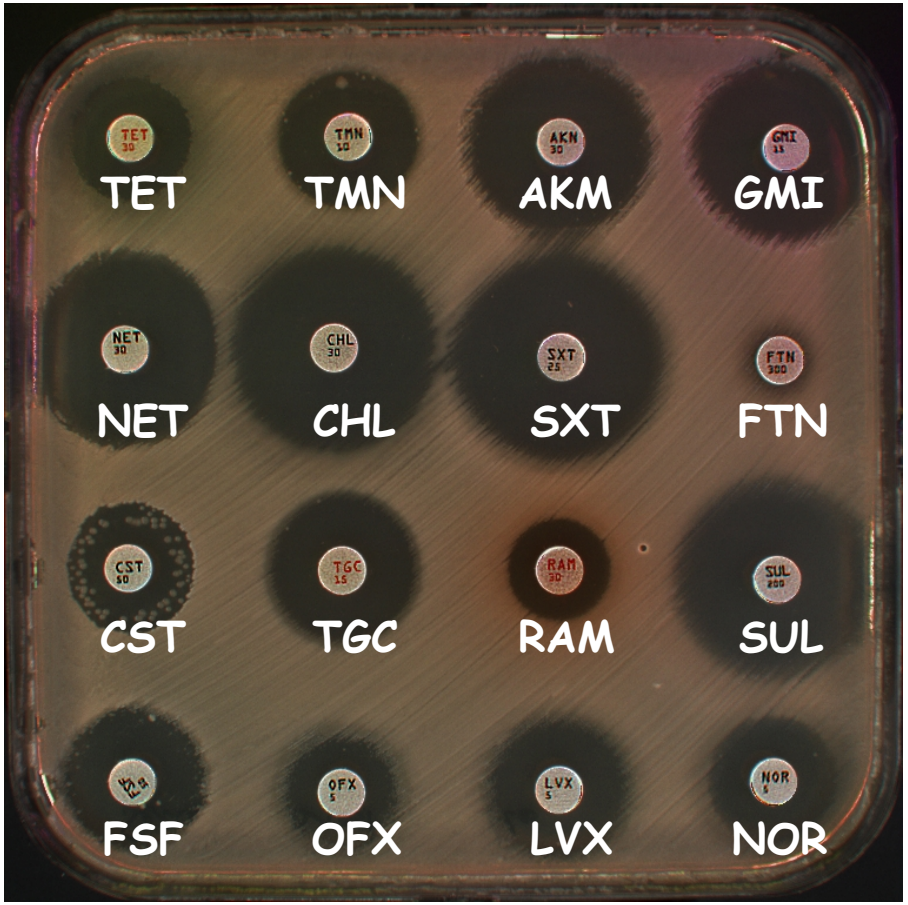
S.marcescens OXA-48



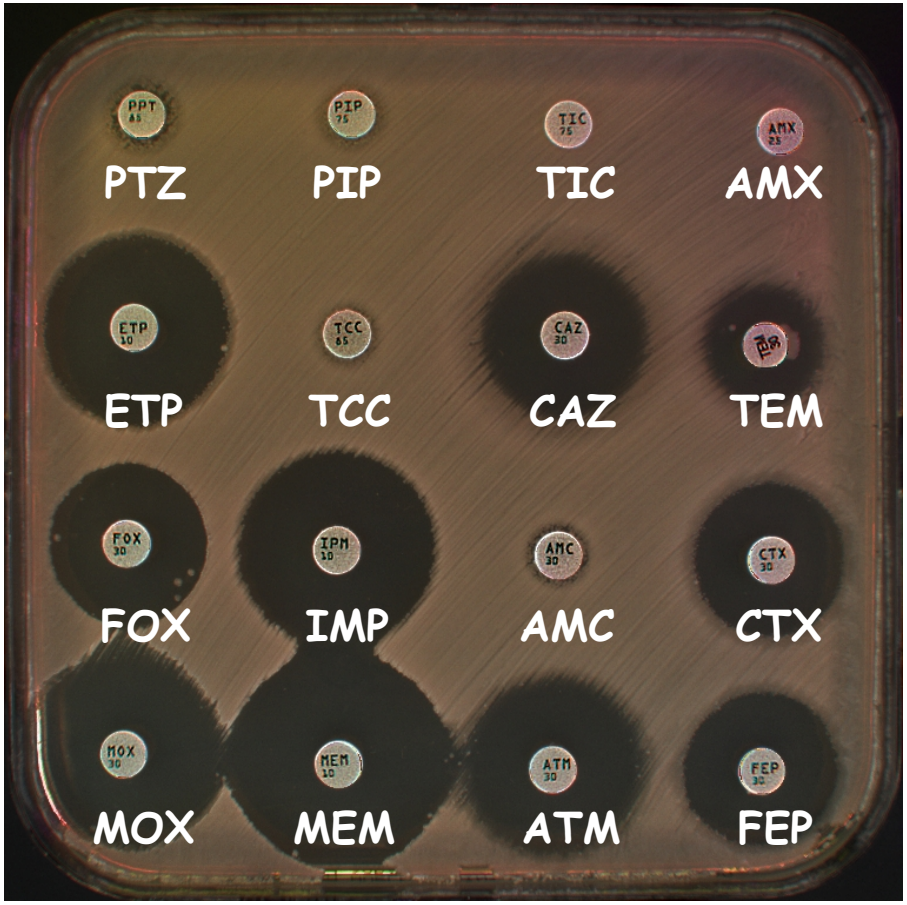


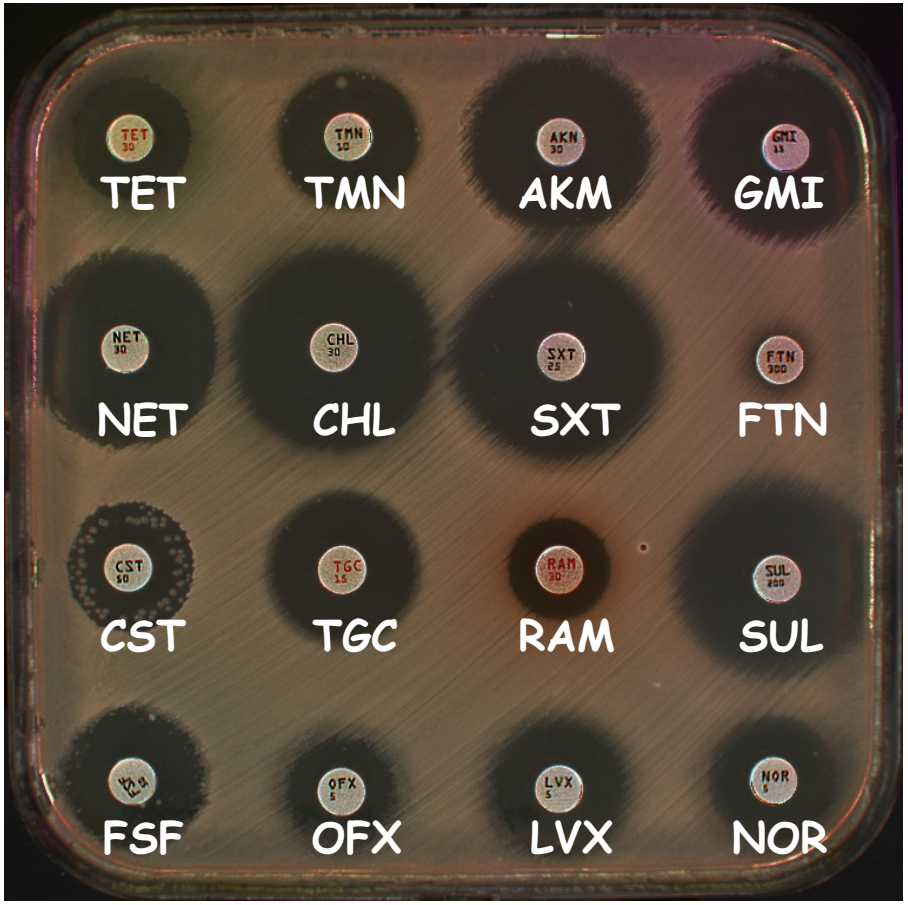
Carbapénèmase ?



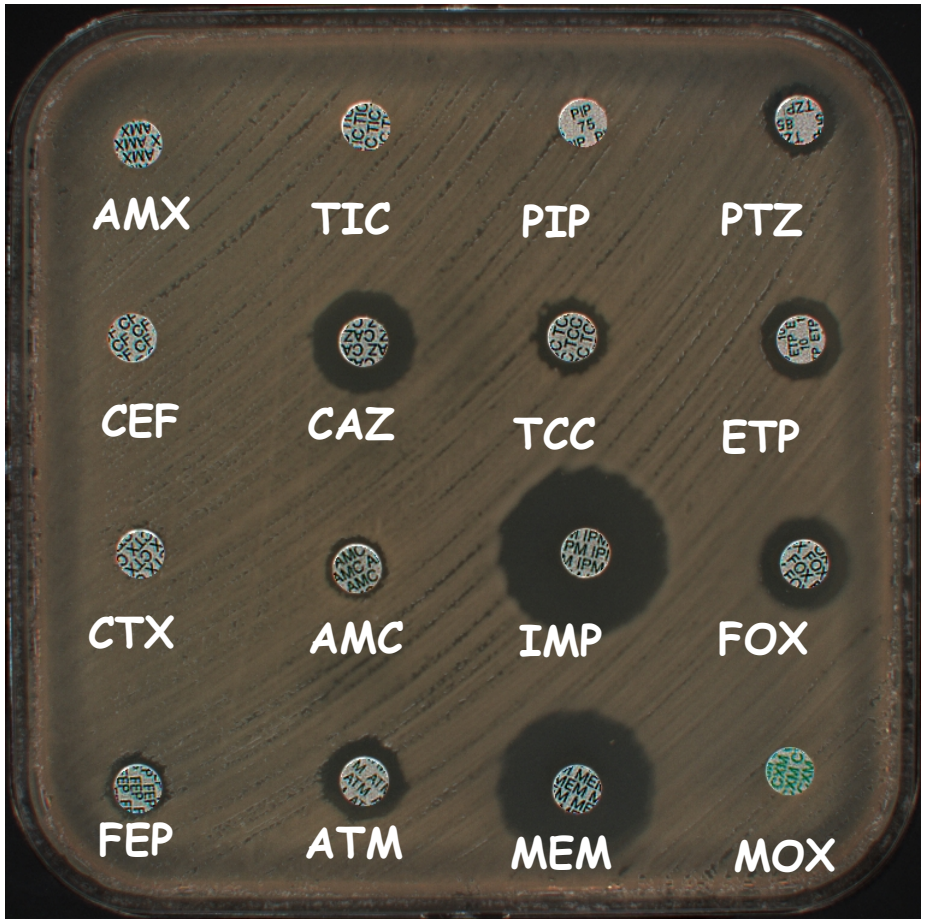


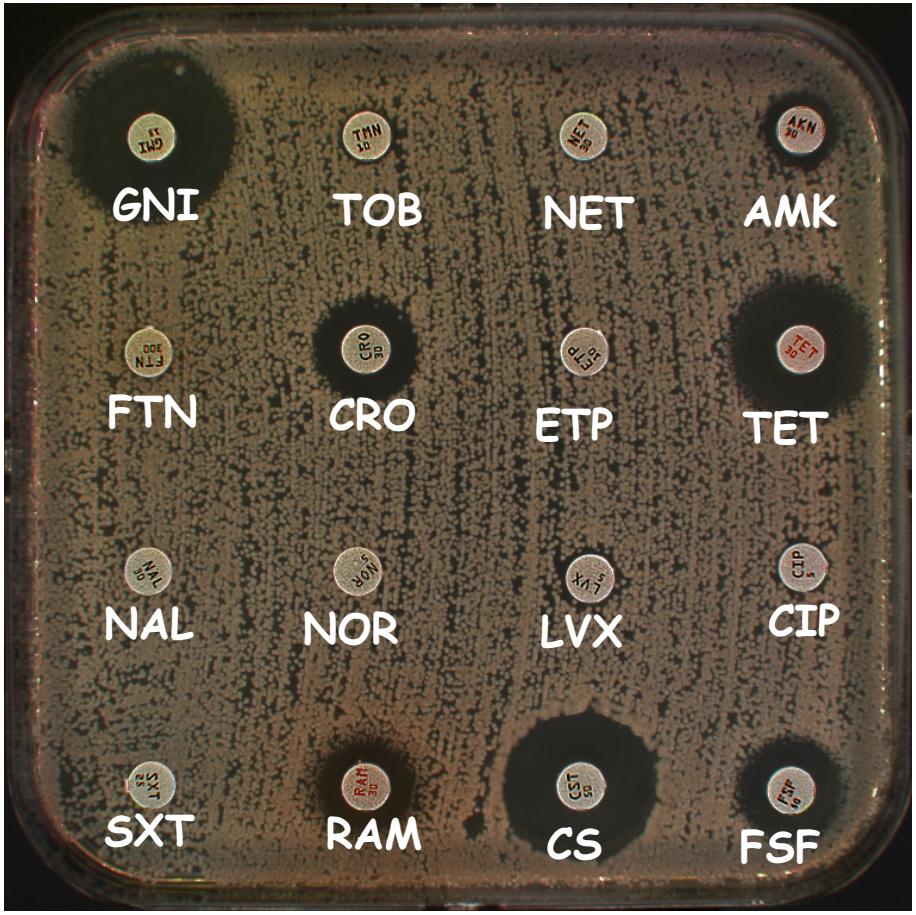
S. marcescens OXA-405





Carbapénèmase ?





K. pneumoniae CTX-M-15 + imperméabilité