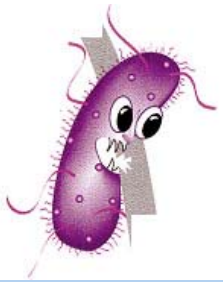
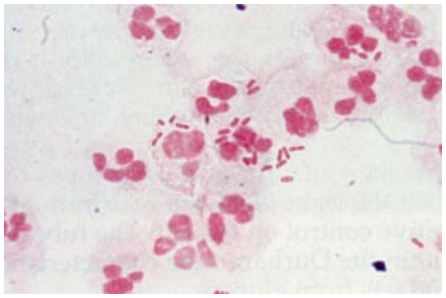
Inserm U914
Résistances Emergentes aux Antibiotiques

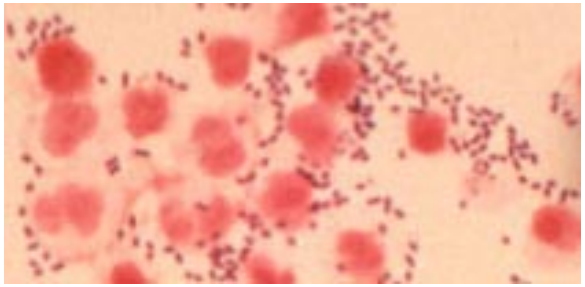
Bactéries hautement résistantes aux antibiotiques: Epidémiologie mondiale



Enterobacteriaceae



A. baumannii



P. aeruginosa

XXII^{ème} Congrès National de la Société Française d'Hygiène Hospitalière
Lille 2012

UNIVERSITE PARIS-SUD XI

T. Naas,
Hôpital de Bicêtre, INSERM 914
CNR Résistance aux carbapénèmes
Faculté de Médecine Paris-Sud

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Les ß-Lactamases qui menacent les traitements des infections à bactéries G-?

AmpC plasmidique

bla_{CMY}, bla_{DHA}

BLSEs

bla_{CTX-M}, bla_{SHV} and bla_{TEM}
bla_{VEB}, bla_{PER}, bla_{GES}, bla_{TLA}, bla_{BES}….

Résistance aux C3G
=> S aux Carbapénèmes,

MAIS

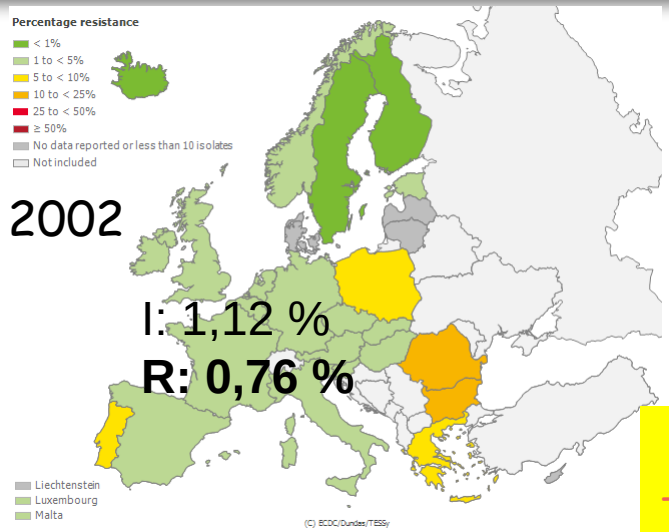
Diminution de la perméabilité peut conduire à une R additionnelle aux carbapénèmes

Carbapénèmases

- Metallo-enzymes **(bla_{VIM}, bla_{IMP}), bla_{NDM}**
- Oxacillinases ($bla_{OXA-23,-40,-58}$) and **bla_{OXA-48}**
- Class A (bla_{NMCA}, bla_{IMI}, bla_{SME}), bla_{GES}, and **bla_{KPC}**

La résistance aux C3G en Europe: Entérobactéries

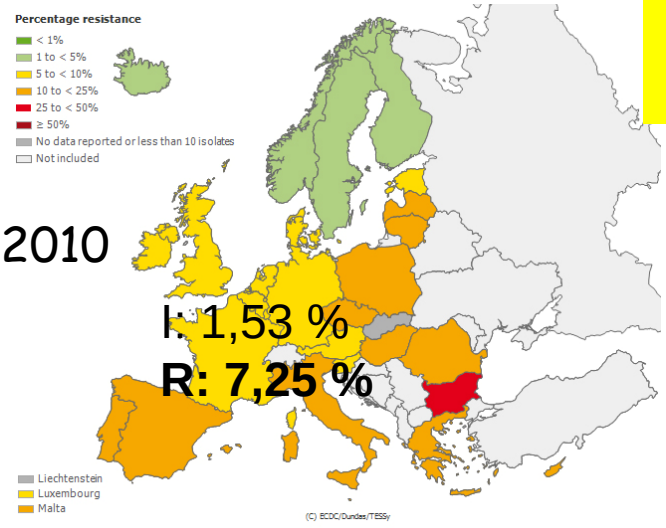
E. coli



2002

I: 1,12 %

R: 0,76 %



2010

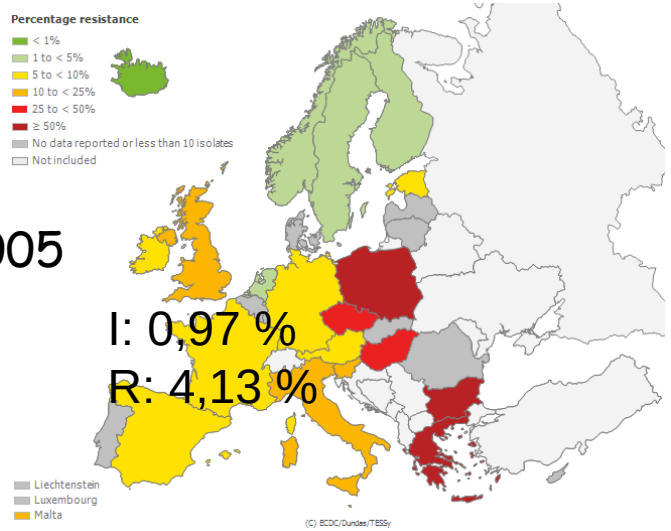
I: 1,53 %

R: 7,25 %

Explications

- AmpC plasmidique
- **BLSE**
- (Carbapénèmases)

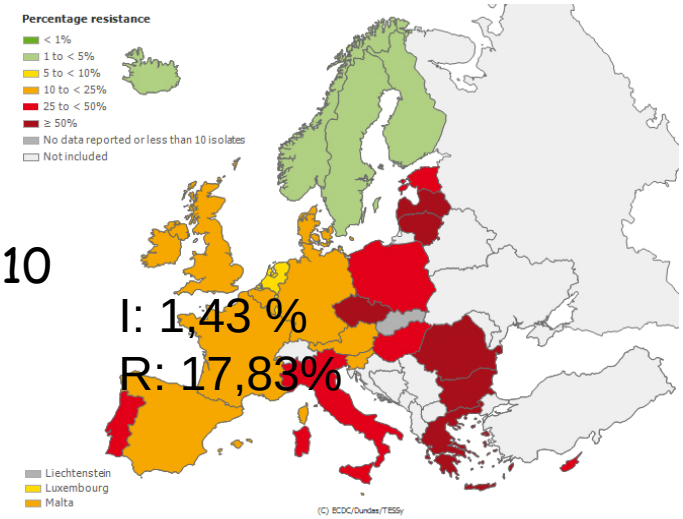
K. pneumoniae



2005

I: 0,97 %

R: 4,13 %



2010

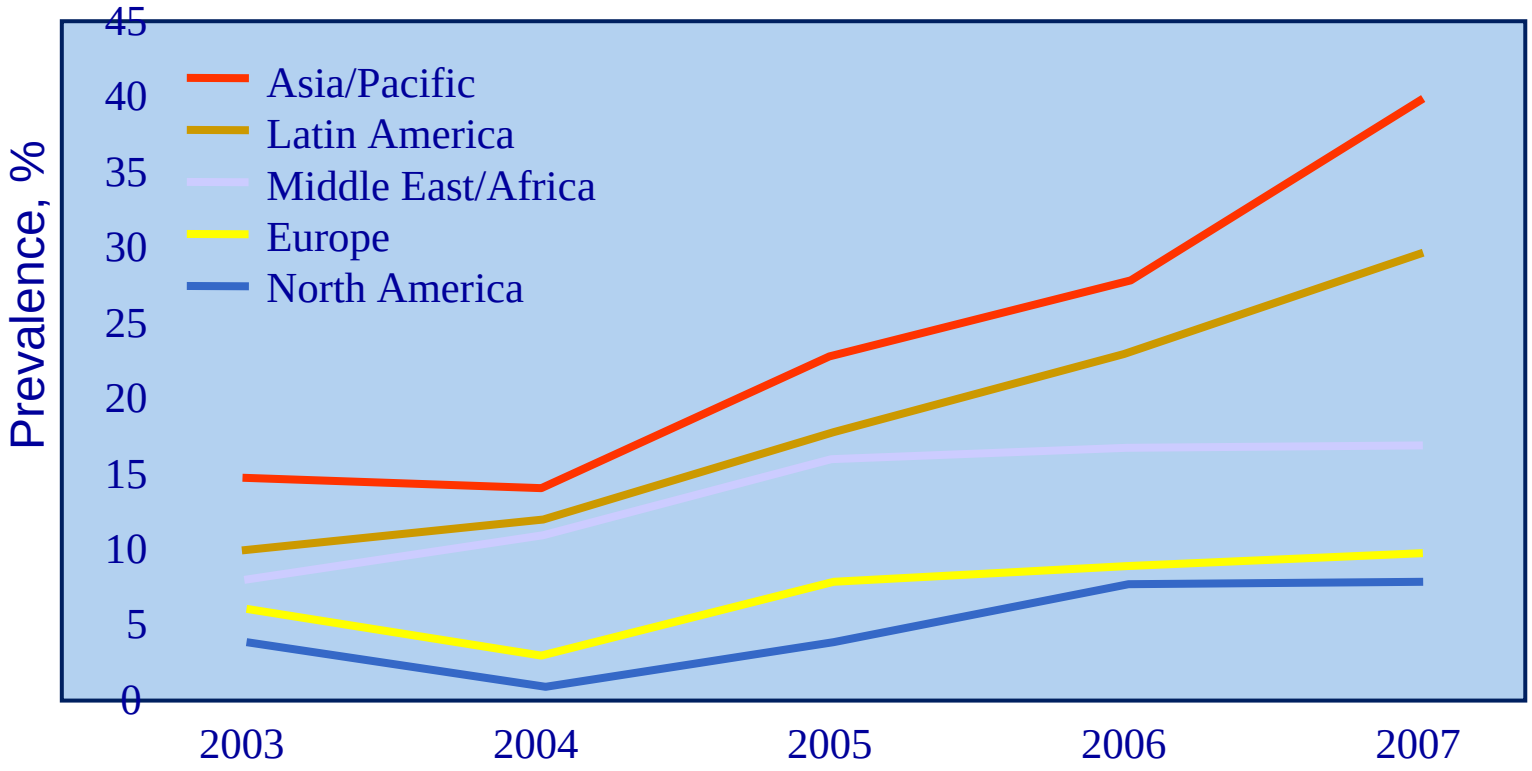
I: 1,43 %

R: 17,83%

Entérobactéries productrices de BLSE

Prévalence des souches productrices de BLSE parmi 18,845 isolats de *E. coli, K. pneumoniae* and *K. oxytoca*

(Etude SMART, 2003-2007)



Adapted from Badal R, et al. Poster presented at: 48th Annual ICAAC; Oct 2008

ESBL et tourisme

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2010, p. 3564–3568 Vol. 54, No. 9
0066-4804/10/$12.00 doi:10.1128/AAC.00220-10

Foreign Travel Is a Major Risk Factor for Colonization with *Escherichia coli* Producing CTX-M-Type Extended-Spectrum β-Lactamases: a Prospective Study with Swedish Volunteers[▽]

Thomas Tängdén,[1]* Otto Cars,[1] Åsa Melhus,[2]† and Elisabeth Löwdin[1]†

Sections of Infectious Diseases[1] and Clinical Bacteriology,[2] Department of Medical Sciences, Uppsala University, Uppsala, Sweden

Received 15 February 2010/Returned for modification 17 April 2010/Accepted 8 June 2010

TABLE 3. Travel destinations of travelers who were negative for ESBL-producing strains before the trip and rate of fecal colonization with ESBL-producing *E. coli* strains upon return[a]

Continent or region	No. of travelers	No. (%) of travelers positive for ESBL-producing isolates
Africa	25	1 (4)
Asia (India excluded)	31	10 (32)
Central America	6	0 (0)
India	8	7 (88)
Middle East	14	4 (29)
North America	2	0 (0)
South America	1	0 (0)
Southern Europe	16	2 (13)

[a] The rate of acquisition of ESBL-producing strains was highest for travelers visiting India ($P < 0.001$). Three participants visited more than one continent, and therefore, the sum of travelers in this table exceeds the actual number of 100.

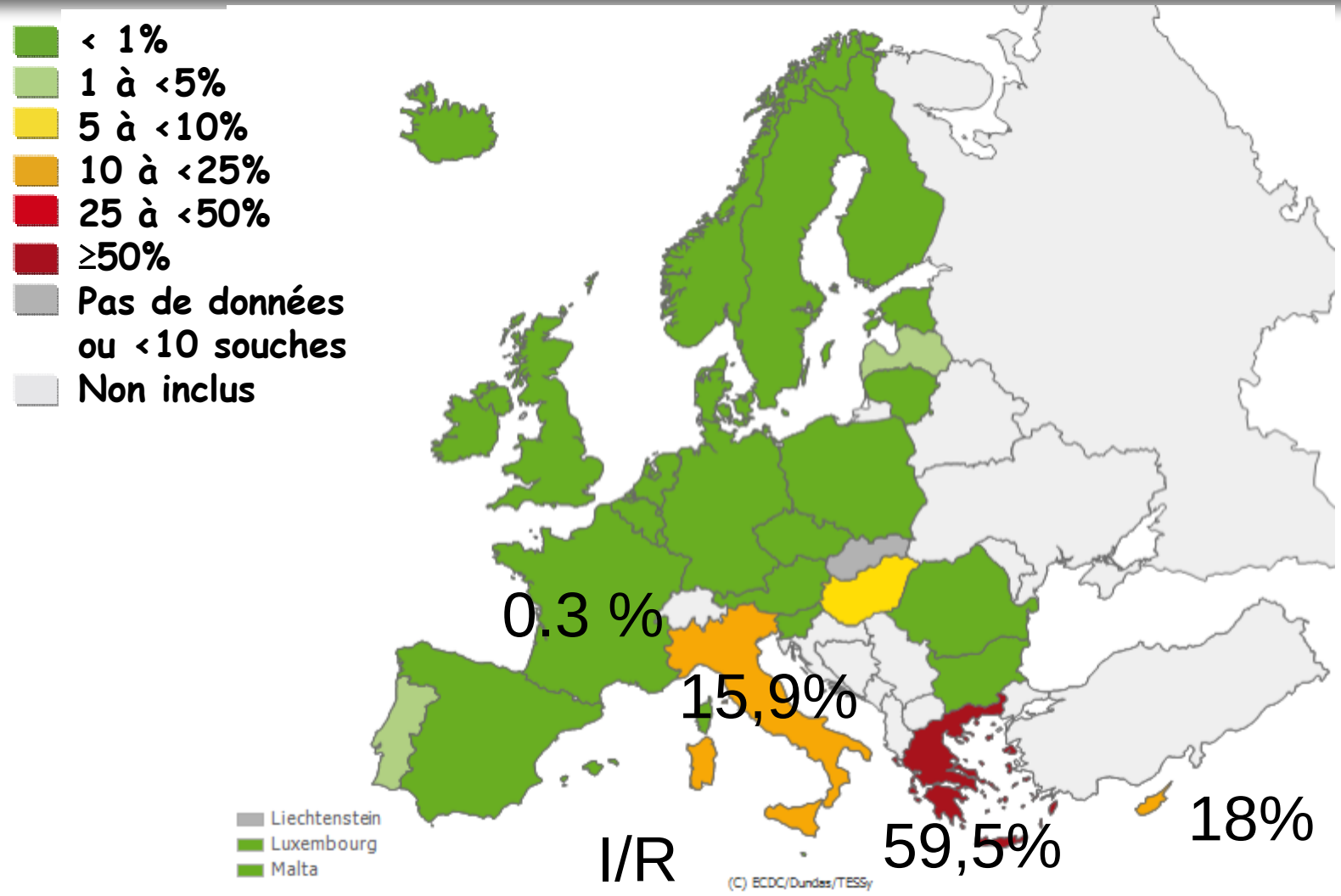
TABLE 4. Descriptive statistics on 100 Swedish travelers with negative pretravel rectal swabs for ESBL-producing *Enterobacteriaceae*[a]

Parameter	Value for group	
	ESBL negative ($n = 76$)	ESBL positive ($n = 24$)
No. (%) of male travelers	35 (46)	10 (42)
Median age (yr)	42	47
No. (%) of vegetarians	2 (3)	0 (0)
Median length of stay (wk) (%)	2.0	2.0
No. (%) of travelers on vacation	67 (88)	22 (92)
No. (%) of business travelers	10 (13)	2 (8)
No. (%) of travelers visiting friends or relatives	10 (13)	1 (4)
No. (%) of travelers staying at a hotel	61 (80)	20 (83)
No. (%) of backpacking travelers	6 (8)	4 (17)
No. (%) of travelers staying with friends or relatives	9 (12)	5 (21)
No. (%) of travelers with gastroenteritis	17 (22)	13 (54)
No. (%) of travelers on antibiotic treatment	7 (9)	3 (12)

[a] Seventy-six travelers were negative for ESBL-producing strains after their trip, whereas 24 carried ESBL-producing *Escherichia coli*. The only statistically significant difference between the groups was gastroenteritis during travel ($P = 0.003$).

25% sont revenus avec un souvenir

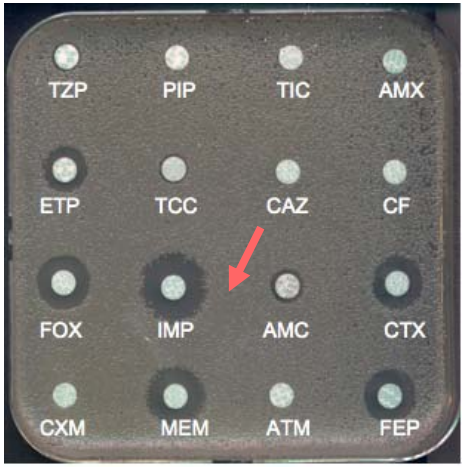
Résistance aux carbapénèmes en Europe
K. pneumoniae (2010)

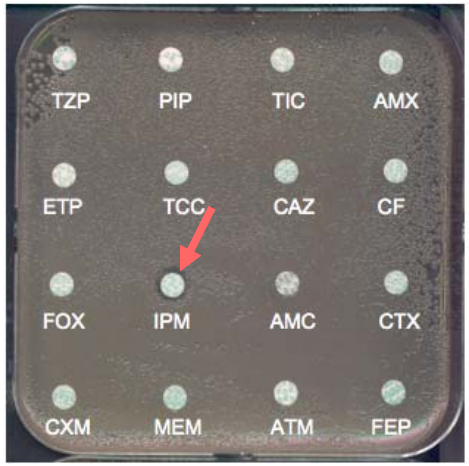


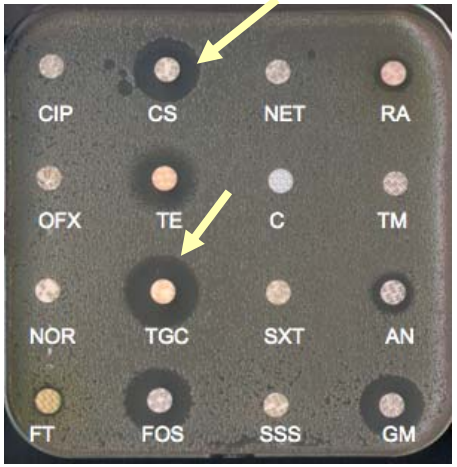
Pourquoi faut-il être vigilant ?

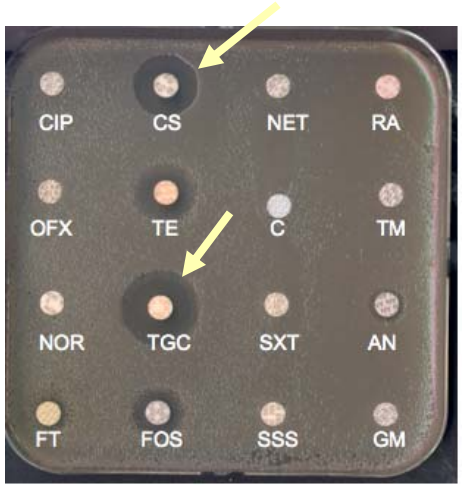
Les producteurs de carbapénèmases sont multi résistants

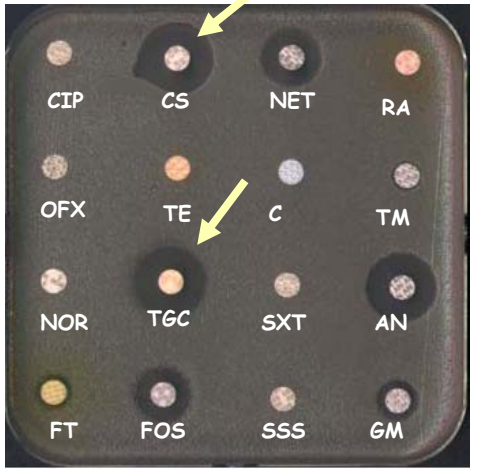
Kp KPC-2	Kp NDM-1	Kp OXA-48











Pourquoi faut-il être vigilant ?

Identification de producteur de carbapenemases difficile

Global Spread of Carbapenemase-producing *Enterobacteriaceae*

Patrice Nordmann, Thierry Naas, and Laurent Poirel

ging Infectious Diseases • www.cdc.gov/eid • Vol. 17, No. 10, October 2011

Table 1. MIC range of carbapenems for *Enterobacteriaceae* that produce several types of carbapenemases*

	MIC, mg/L		
Carbapenemase	Imipenem	Meropenem	Ertapenem
KPC	0.5–>64	1–>64	0.5–>64
Metallo β-lactamases†	0.5–>64	0.25–>64	0.5–>64
OXA-48 type	1–>64	0.5–>64	0.25–>64

*KPC, *Klebsiella pneumoniae* carbapenemase; OXA-48, oxacillinase-48.
†Including New Delhi metallo-β-lactamase-1.

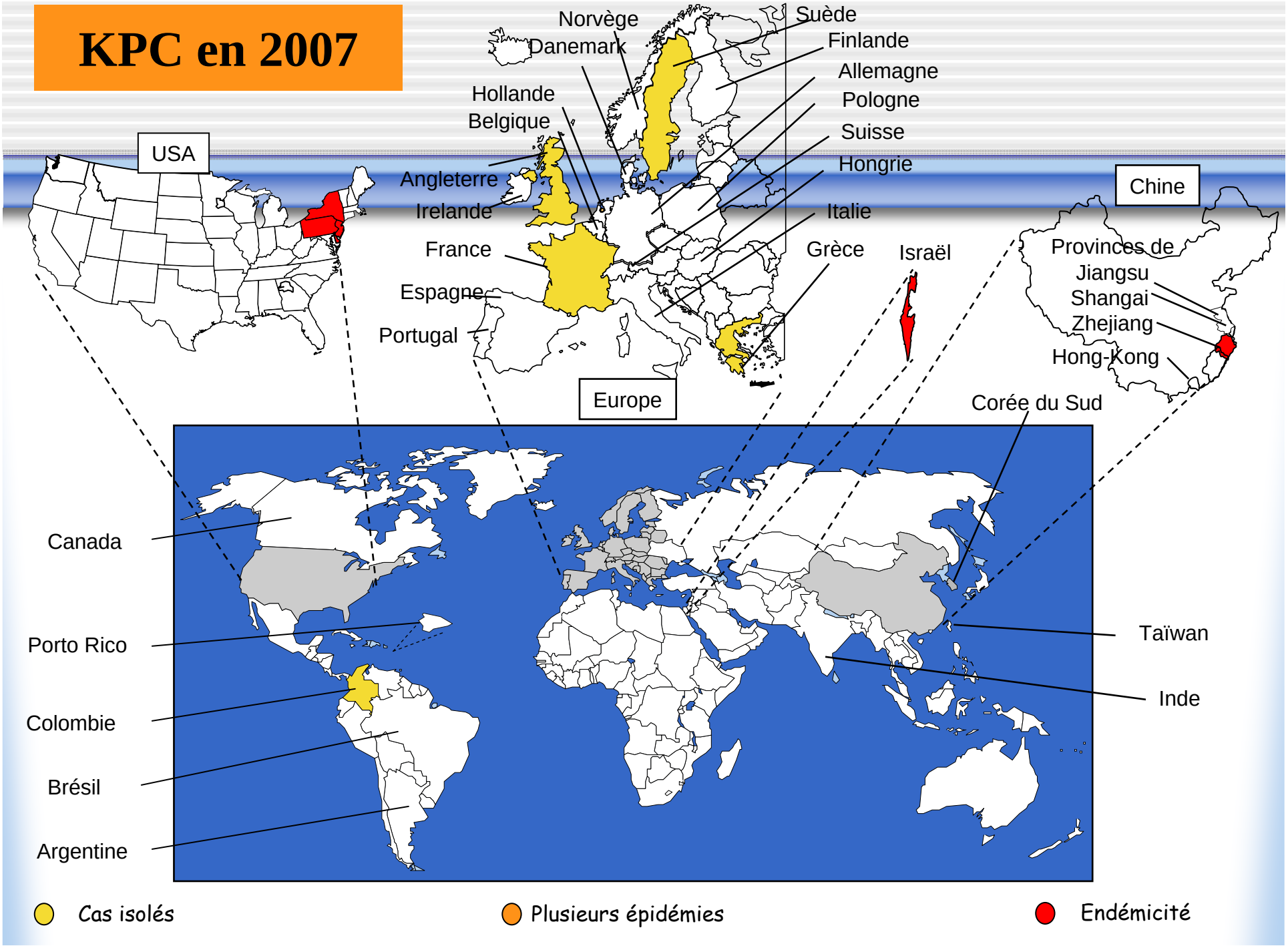
Difficult detection

Table 2. Breakpoint values (MIC, mg/L) for carbapenems according to guidelines in Europe (EUCAST) and the United States (CLSI), September 2010*

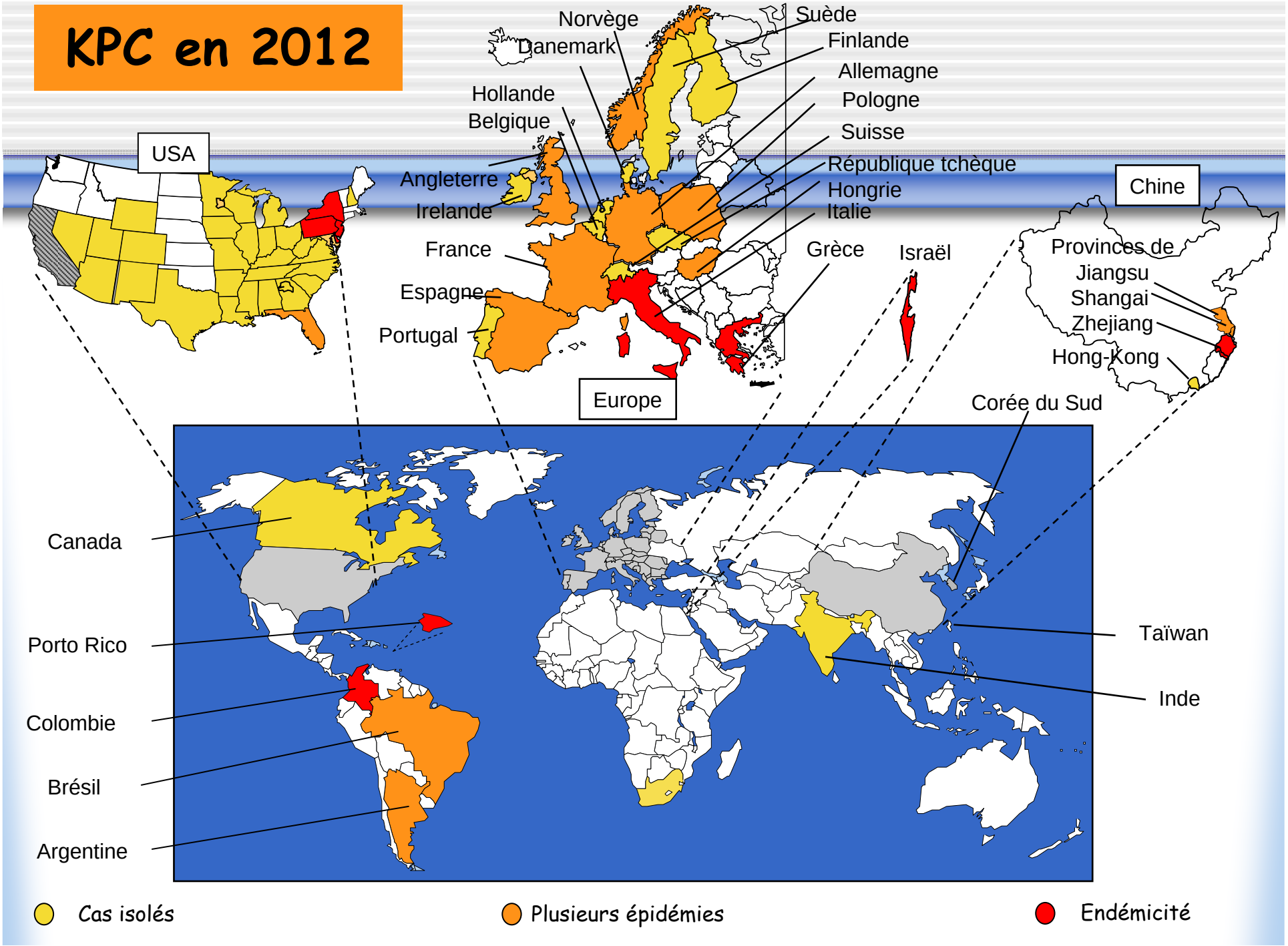
	EUCAST		CLSI	
Carbapenem	S	R	S	R
Ertapenem	≤0.5	>1	≤0.25	≥1
Imipenem	≤2	>8	≤1	≥4
Meropenem	≤2	>8	≤1	≥4
Doripenem	≤1	>4	≤1	≥4

*EUCAST, European Committee on Antimicrobial Susceptibility Testing (www.eucast.org/clinical_breakpoints); CLSI, Clinical and Laboratory Standards Institute; S, sensitive; R, resistant.

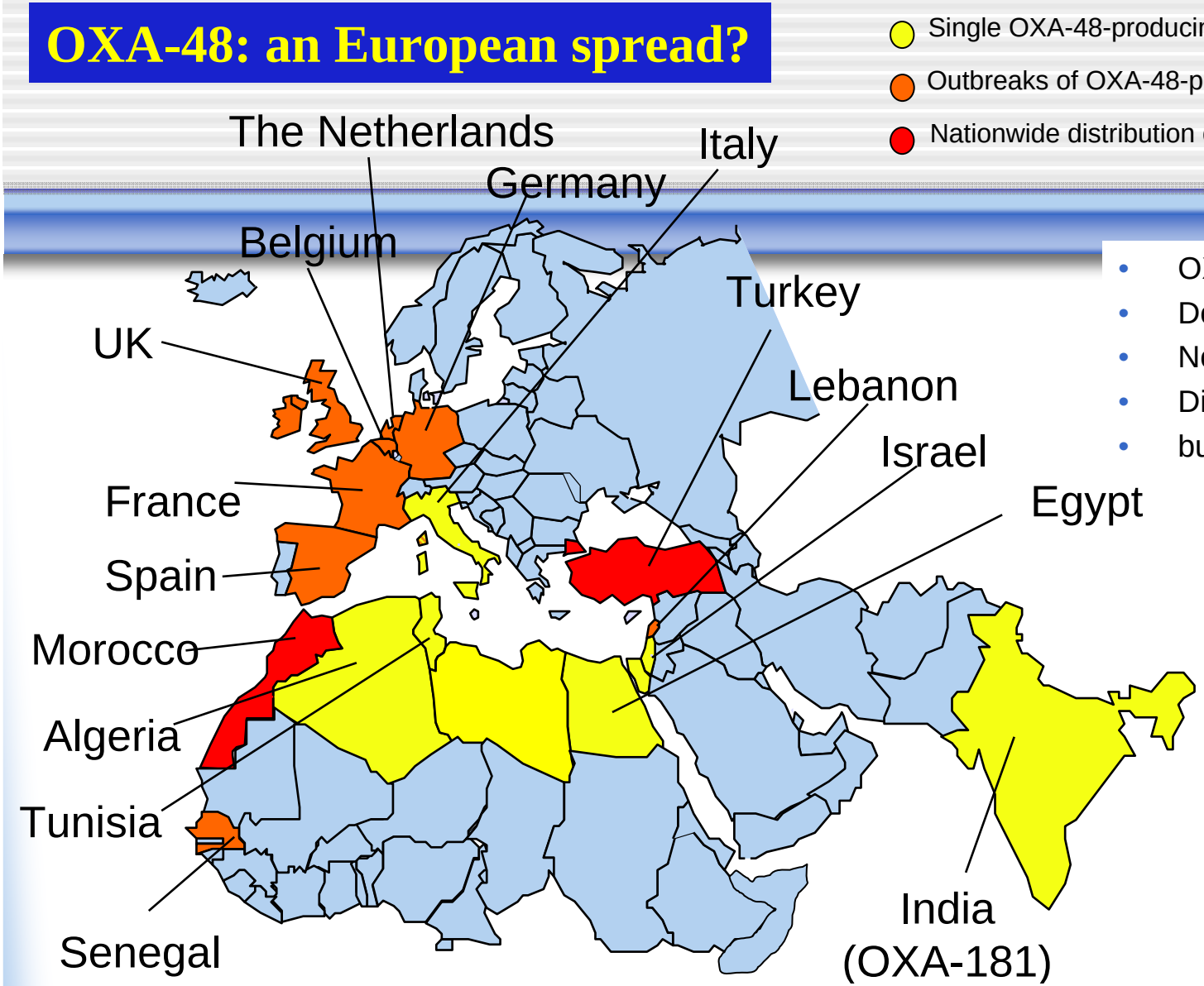
KPC en 2007


Norvège
Suède
Danemark
Finlande
Allemagne
Hollande
Pologne
Belgique
Suisse
USA
Hongrie
Angleterre
Chine
Irelande
Italie
France
Grèce
Israël
Provinces de
Jiangsu
Espagne
Shangai
Zhejiang
Portugal
Hong-Kong
Europe
Corée du Sud
Canada
Taïwan
Porto Rico
Inde
Colombie
Brésil
Argentine
Cas isolés
Plusieurs épidémies
Endémicité

KPC en 2012


Norvège
Suède
Danemark
Finlande
Allemagne
Hollande
Pologne
Belgique
Suisse
USA
Angleterre
République tchèque
Hongrie
Irelande
Italie
France
Grèce
Israël
Chine
Espagne
Provinces de
Jiangsu
Shangai
Zhejiang
Portugal
Hong-Kong
Europe
Corée du Sud
Canada
Taïwan
Porto Rico
Inde
Colombie
Brésil
Argentine
Cas isolés
Plusieurs épidémies
Endémicité

OXA-48: an European spread?



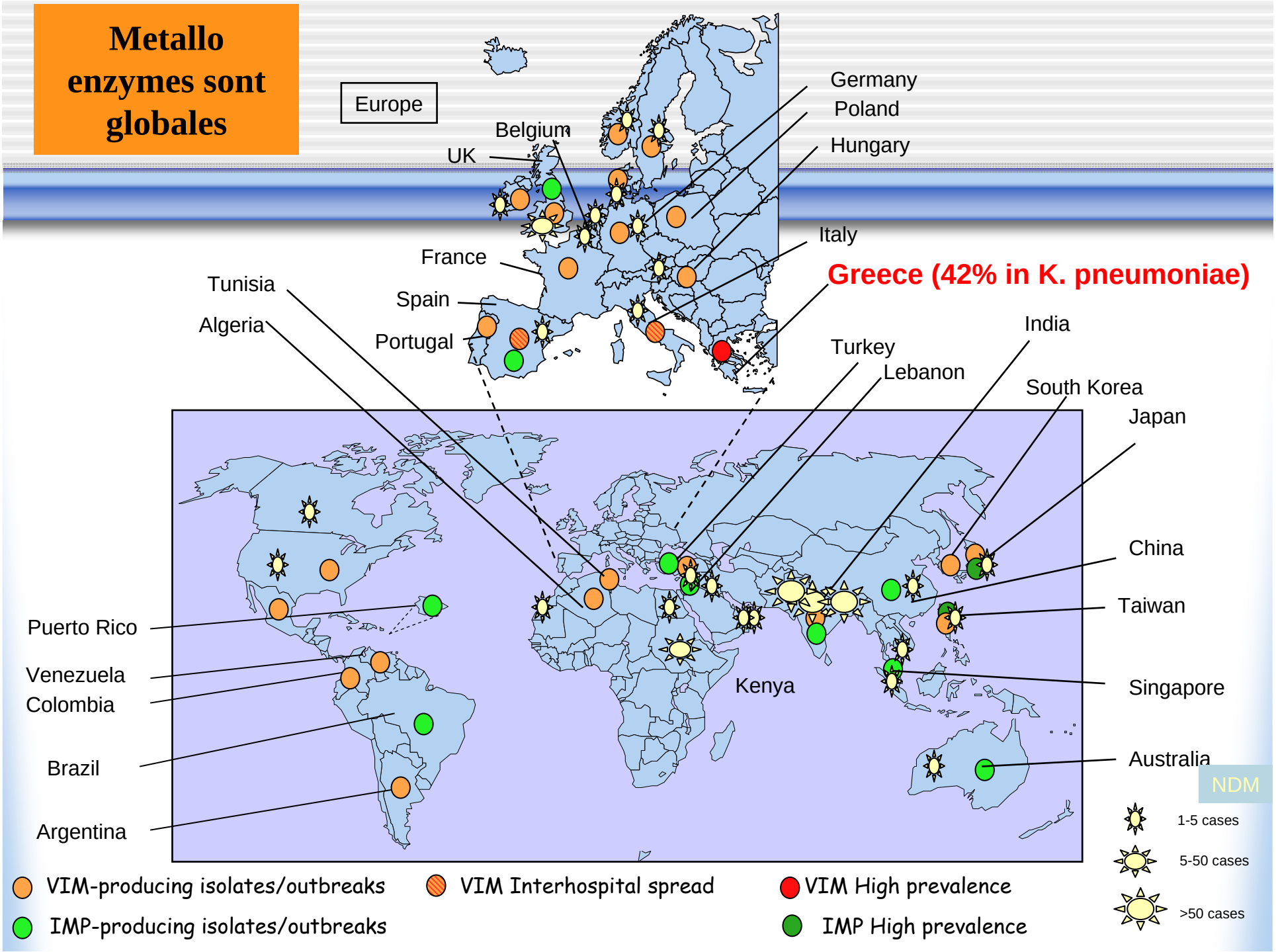
- OXA-48
- Do not hydrolyse 3GC
- No inhibitor
- Different strains
- but same plasmid

Global Spread of Carbapenemase-producing *Enterobacteriaceae*

Patrice Nordmann, Thierry Naas, and Laurent Poirel

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 17, No. 10, October 2011

Metallo enzymes sont globales



Pourquoi faut-il être vigilant ?
« Association de malfaiteurs »

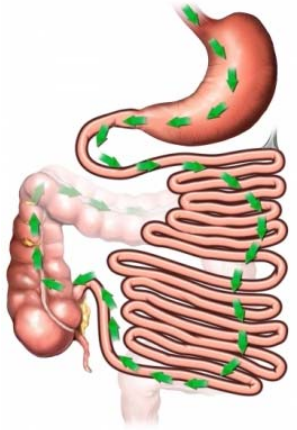
=> KPC: *K. pneumoniae* ST258

=> OXA-48: *K. pneumoniae* different clones, but emergence of ST395 clone (Cuzon et al. JCM, 2011, Potron, CMI, 2011), emergence also in *E. coli*

=> VIM, IMP: *K. pneumoniae*

=> NDM: *E. coli* et tous les autres

- **1st human bacterial pathogen**
- **1st community-acquired pathogen**
- **1st cause of urinary tract infections and diarrhea**



Infections à EPC: Taux de mortalité élevé (3x)

KPC, VIM, NDM and *E.coli* ST131

Antimicrob. Agents Chemother. October 2011 vol. 55 no. 10

Production of KPC-2 Carbapenemase by an Escherichia coli Clinical Isolate Belonging to the International ST131 Clone

Dearbháile Morris*, Fiona Boyle, Catherine Ludden, Iris Condon, James Hale, Nuala O'Connell, Lorraine Power, Teck Wee Boo, Hiran Dhanji, Christian Lavallee, Neil Woodford and Martin Cormican

- F, 84 ans
- Maison de retraite, Irlande
- Pas de voyage
- Infection urinaire

When Carbapenem-Hydrolyzing β-Lactamase KPC Meets Escherichia coli ST131 in France

Thierry Naas*, Gaelle Cuzon, Olivier Gaillot, René Courcol and Patrice Nordmann

- F, 64 ans
- Gérontologie, Lille
- Pas de voyage
- Infection urinaire

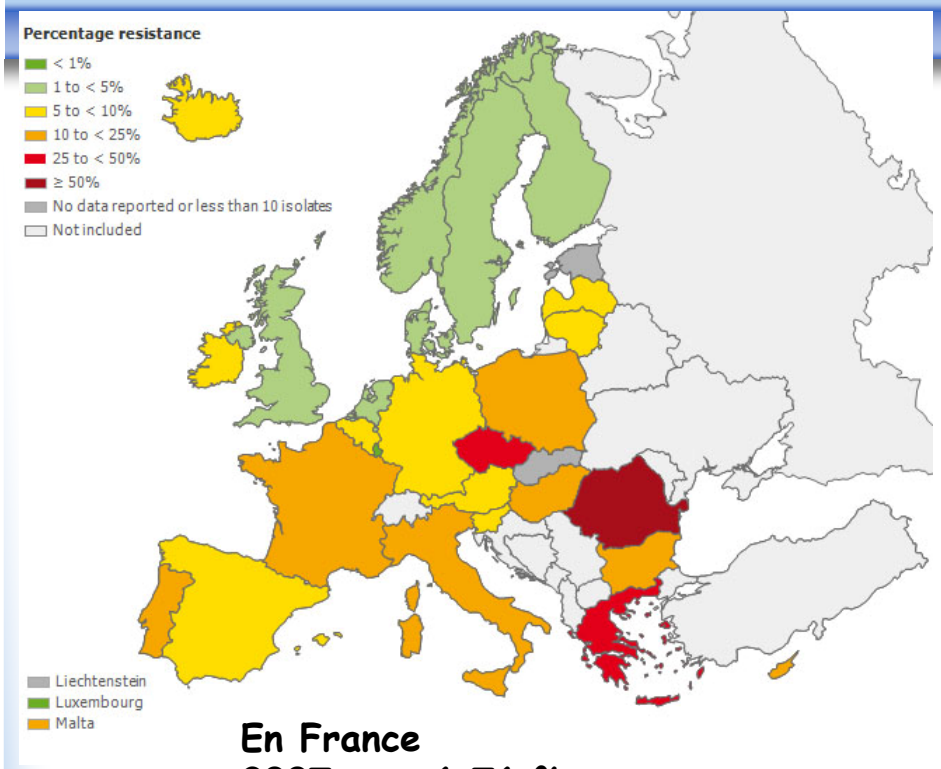
***Escherichia coli* O25b:H4-ST131**

Mais aussi VIM et NDM……

- Mantengoli E., et al. 2011. Escherichia coli ST131 producing extended-spectrum beta-lactamases plus VIM-1 carbapenemase: further narrowing of treatment options. Clin. Infect. Dis. 52:690–691.
- Peirano G., Schreckenberger P. C., Pitout J. D.. 2011. The characteristics of NDM-1-producing Escherichia coli that belong to the successful and virulent clone ST131. Antimicrob. Agents Chemother. 55:2986–2988.

P. aeruginosa (EARSS 2010)

Résistance à la Ceftazidime



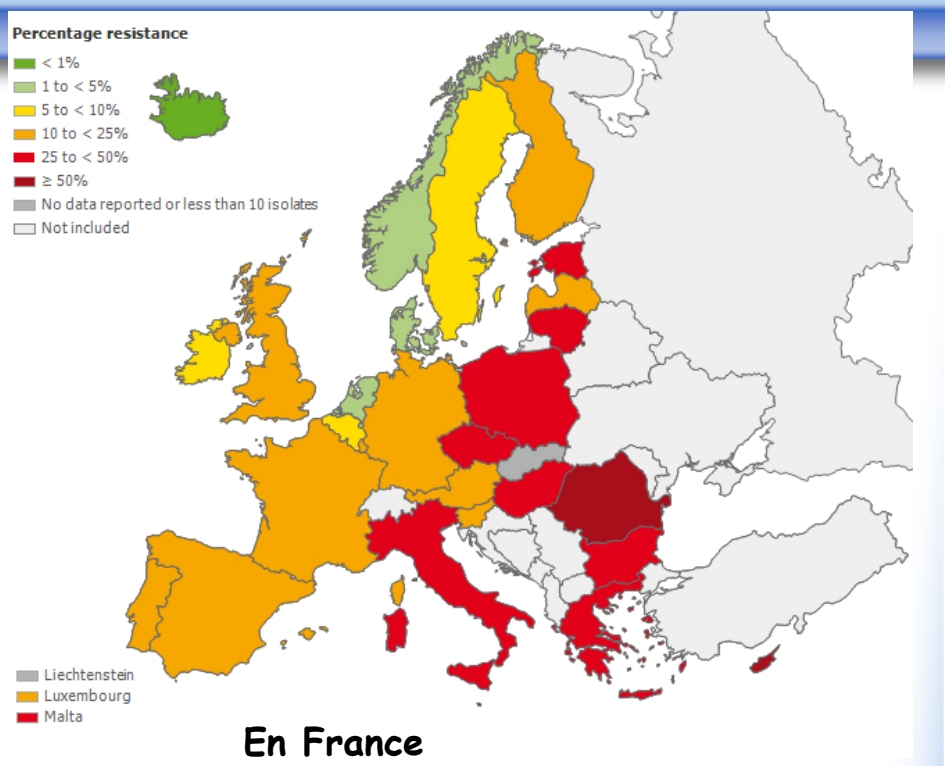
En France

2007	6.76 %
2008	8.02 %
2009	16.77 %
2010	12.69 %

AmpC hyper-produite

Mais aussi BLSE

Résistance à la l'imipénème



En France

2007	14.13 %
2008	14.23 %
2009	17.39 %
2010	17.79 %

Défaut de la porine D2

Mais aussi MBL

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

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

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

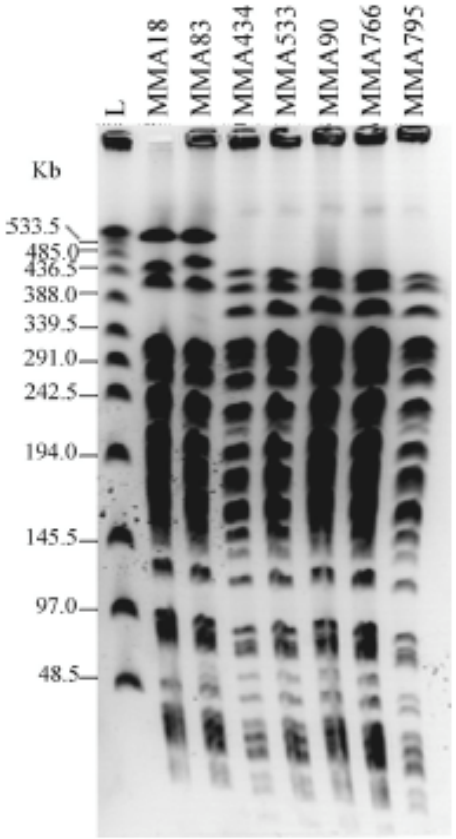


FIG. 1. PFGE profiles of *P. aeruginosa* isolates carrying the bla_{NDM-1} gene (MMA18, MMA83, MMA434, MMA533, MMA90, MMA766, and MMA795). L, λ concatemers (New England Biolabs).

P. aeruginosa et KPC

KPC-2, KPC-3, KPC-5

Colombie

(Villegas, AAC, 2007)

Porto Rico

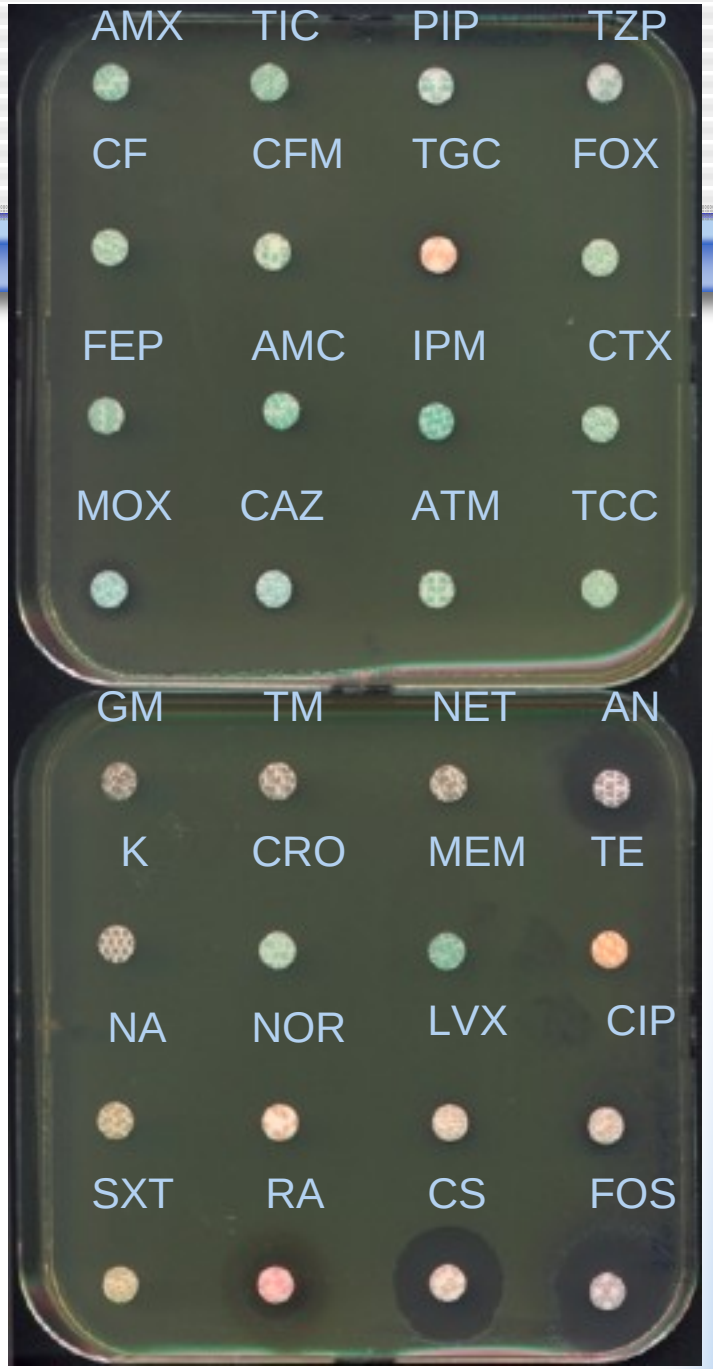
(Cai, AAC, 2008)

Trinidad et Tobago

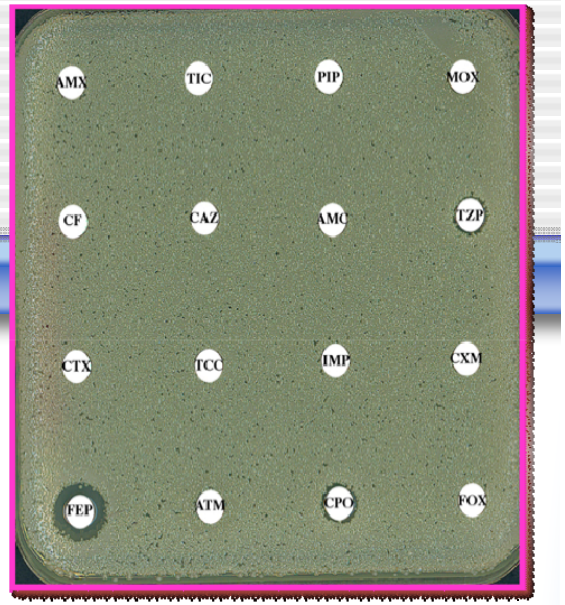
(Akpaka, JCM, 2009)

USA

(Poirel, AAC, 2010)



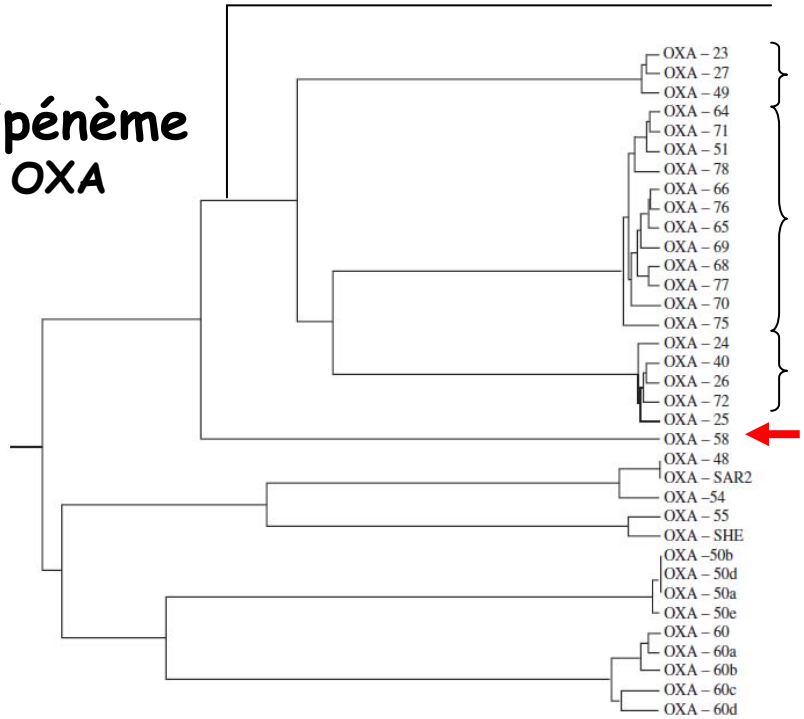
Résistance aux carbapénèmes chez *A. baumannii*



Cette résistance peut être le résultat de:

- Carbapénèmases de classe B
- Carbapénèmases de classe D (oxa)
- impermeability
- ou combination de ces mécanismes

Résistance à l'imipénème
Par production d' OXA



OXA-143

OXA-23 subgroup

OXA-51 subgroup

OXA-40 subgroup

OXA-58

POIREL, NAAS, NORDMANN, AAC 2010

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

CURRENT CONCEPTS

Acinetobacter Infection

L. Silvia Munoz-Price, M.D., and Robert A. Weinstein, M.D.

ACINETOBACTER IS A GRAM-NEGATIVE COCCOBACILLUS (FIG. 1)[1,2] THAT during the past three decades has emerged from an organism of questionable pathogenicity to an infectious agent of importance to hospitals worldwide.[3,4] Approximately one quarter of the PubMed citations for "nosocomial acinetobacter" in the past 20 years appeared in 2005 and 2006. Acinetobacter infections have long been clinically prominent in tropical countries, have been a recurrent problem during wars and natural disasters, and have recently caused multihospital outbreaks in temperate climates. Most alarming are the organism's ability to accumulate diverse mechanisms of resistance, the emergence of strains that are resistant to all commercially available antibiotics,[5] and the lack of new antimicrobial agents in development.[6] At more than 300 U.S. hospitals surveyed by the Centers for Disease Control and Prevention (CDC), rates of carbapenem resistance in 3601 isolates of *Acinetobacter baumannii*, clinically the most important of 25 acinetobacter genospecies,[1] increased from 9% in 1995 to 40% in 2004.[7]

From Medical Specialists, Dyer, IN (L.S.M.-P.); and the Division of Infectious Diseases, Stroger (Cook County) Hospital, Ruth M. Rothstein CORE Center, and Rush Medical College — all in Chicago (R.A.W.). Address reprint requests to Dr. Munoz-Price at Medical Specialists, 919 Main St., Ste. 202, Dyer, IN 46311, or at simunozprice@gmail.com.

N Engl J Med 2008;358:1271-81.

Evolution of antimicrobial resistance

Table 1. Patterns of resistance (MIC in mg/l) of *A. baumannii*.

Antimicrobial agent	Study year and ref.							
	1993 [4]	**1993** [5]	**1996** [6]	**2003** [7]	**2003** [8]	**2004** [9]	**2007** [10]	**2007** [11]
Ampicillin	98	91	88	–	–	98	–	–
Piperacillin	67	36	72	–	–	95	–	–
Ampicillin/sulbactam	48	–	34	21	–	54	–	49
Ceftazidime	45	32	42	45	27	85	97	88
Imipenem	0	0	2	5	3	48	38	71
Tobramycin	50	98	–	25	–	79	–	–
Amikacin	28	64	28	13	15	66	22	86
Ciprofloxacin	30	94	4	57	49	90	97*	93
Minocycline/doxycycline	2	–	–	–	–	35	7	–

*Levofloxacin instead of ciprofloxacin.

Vila J. and Pachón J. (2008) Expert Opin. Pharmacother. 9:587-599

Falagas M, et al: Trends in antimicrobial resistance of *Acinetobacter baumannii* clinical isolates from hospitalised patients in Greece and treatment implications
Clin Microbiol Infect 2007; 13:816

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

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

[a]Data available for the first semester of 2006.
[b]Multidrug-resistant (resistance to ceftazidime, ciprofloxacin, and amikacin).

Metallo-ß-lactamases et *A. baumannii* (très rares en France)

- VIMs
- IMPs

Metallo-ß-lactamases et *A. baumannii* (étaient rares en France?)

Coexistence of bla_{OXA-23} with bla_{NDM-1} and *armA* in clinical isolates of *Acinetobacter baumannii* from India

Kumarasamy Karthikeyan[1]*, M. A. Thirunarayan[2] and Padma Krishnan[1]

[1]Department of Microbiology, Dr. ALM PG IBMS, University of Madras, Taramani, Chennai-600113, India; [2]Department of Microbiology, Apollo Hospitals, 21 Greams Lane, Off Greams Road, Chennai-600006, India

*Corresponding author. Tel: +91-9994751555; Fax: +91-4424540709; E-mail: skk.microbes@gmail.com

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Mais aussi en France:

NDM-1-producing- *Acinetobacter baumannii* from Algeria. A Boulanger, T Naas, N Fortineau, S Figueiredo, and P Nordmann (AAC sous presse)

Et Chine, Egypt, Allemagne, Maroc, Israel …..

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Detection of the KPC Gene in *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* during a PCR-Based Nosocomial Surveillance Study in Puerto Rico▽

Iraida E. Robledo, Edna E. Aquino, and Guillermo J. Vázquez*

University of Puerto Rico, School of Medicine, Department of Microbiology and Medical Zoology, San Juan, Puerto Rico

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A 6-month, PCR-based, island-wide hospital surveillance study of beta-lactam resistance in *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* was conducted in Puerto Rico. Of 10,507 isolates, 1,239 (12%) unique, multi-beta-lactam-resistant isolates from all geographical regions were identified. The KPC gene was detected in 61 *E. coli*, 333 *K. pneumoniae*, 99 *P. aeruginosa*, and 41 *A. baumannii* isolates, indicating the widespread dissemination of the KPC gene in clinically significant nosocomial isolates.

TABLE 1. Numbers of KPC-positive *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii* isolates among the total number of isolates and the multi-beta-lactam-resistant isolates

Organism	No. of isolates			No. of KPC producers/ total (%)	
	Total	MβLR	KPC producers	All isolates	MβLR isolates
E. coli	4,329	219	61	61/4,329 (1.4)	61/219 (33)
K. pneumoniae[a]	2,805	457	333	333/2,805 (12)	333/457 (73)
P. aeruginosa	2,415	272	99	99/2,415 (4.1)	99/272 (44)
A. baumannii	958	291	41	41/958 (4.3)	41/291 (14)
Total	10,507	1,239	534	534/10,507 (5)	534/1,239 (43)

[a] $P \leq 0.05$.

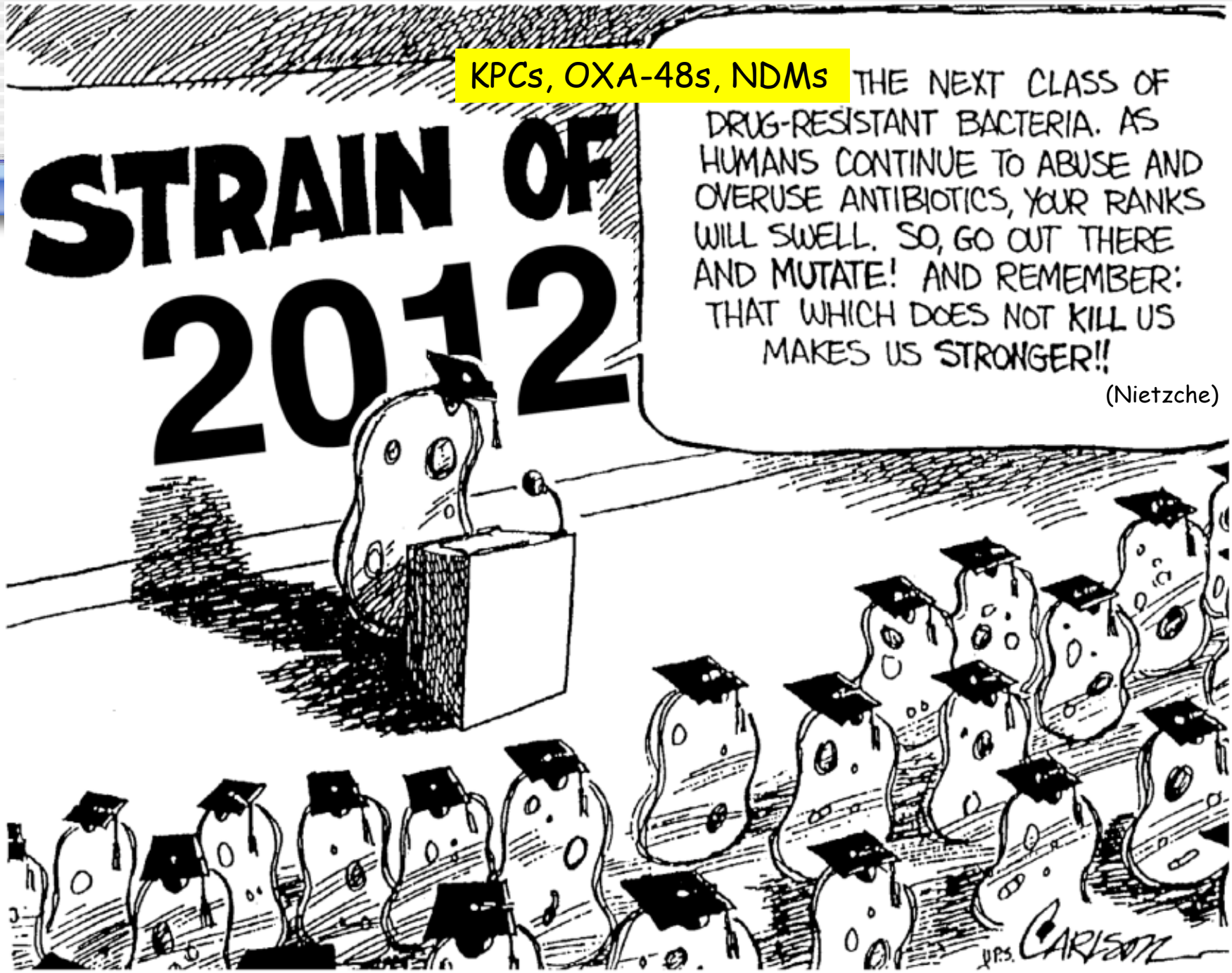
10.507 souches
1.239, Multi ß-lactam R (12%)
534 souches KPC+ (43%)

Conclusion: Les nouvelles ne sont pas bonnes

- De nombreux pays plus ou moins loin de la France avec forte prévalence de souches productrices de carbapénèmases

- La diffusion rapide des EPC constitue une urgence de Santé Publique et de maîtrise de leur diffusion.

- Pour combatre ces EPC, il faudra:
  - **Détection rapide des patients infectés et porteurs**
  - **et biensur**
    - **réduire la consommation des antibiotiques**
    - **Stricte compliance aux pratiques standard d'hygiène**
    - **Nouvelles molécules (rève?)**


KPCs, OXA-48s, NDMs
STRAIN OF 2012
THE NEXT CLASS OF DRUG-RESISTANT BACTERIA. AS HUMANS CONTINUE TO ABUSE AND OVERUSE ANTIBIOTICS, YOUR RANKS WILL SWELL. SO, GO OUT THERE AND MUTATE! AND REMEMBER: THAT WHICH DOES NOT KILL US MAKES US STRONGER!!
(Nietzche)
J.P.S. CARLSON