JNI 16es Journées Nationales d'Infectiologie
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Antibiotic Resistance in *Enterobacteriaceae*

Prof. P. Nordmann


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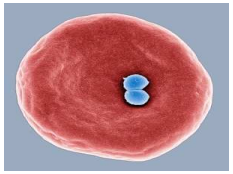
For Immediate Release — September 18, 2014

FACT SHEET: Obama Administration Takes Actions to Combat Antibiotic-Resistant Bacteria



NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

MARCH 2015

International Monetary Fund

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FINANCE and DEVELOPMENT

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Global Health Threats of the 21st Century

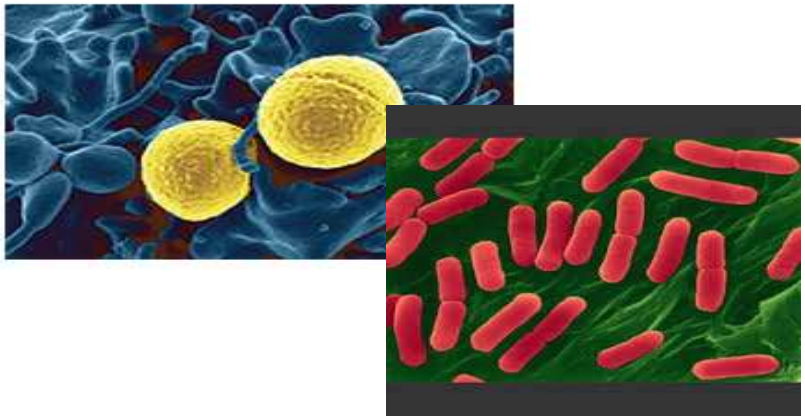
FINANCE & DEVELOPMENT, December 2014, Vol. 51, No. 4

PDF version

Antibiotic Resistance

Ramanan Laxminarayan

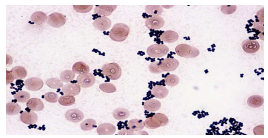
Antibiotics have transformed the practice of medicine. However, a massive scale-up in their use has resulted in an increase in drug-resistant strains of disease-causing bacteria and a global decline in antibiotic effectiveness. Rising incomes in low- and middle-income countries have generated huge demand for antibiotics, but high



Main microbial pathogens for humans

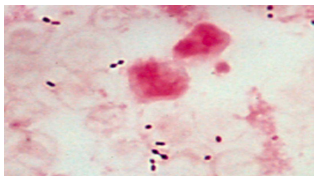
Gram positives

Staphylococcus



Enterococcus,

Streptococcus

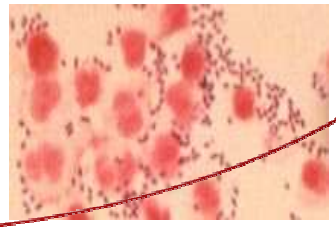


Gram negatives

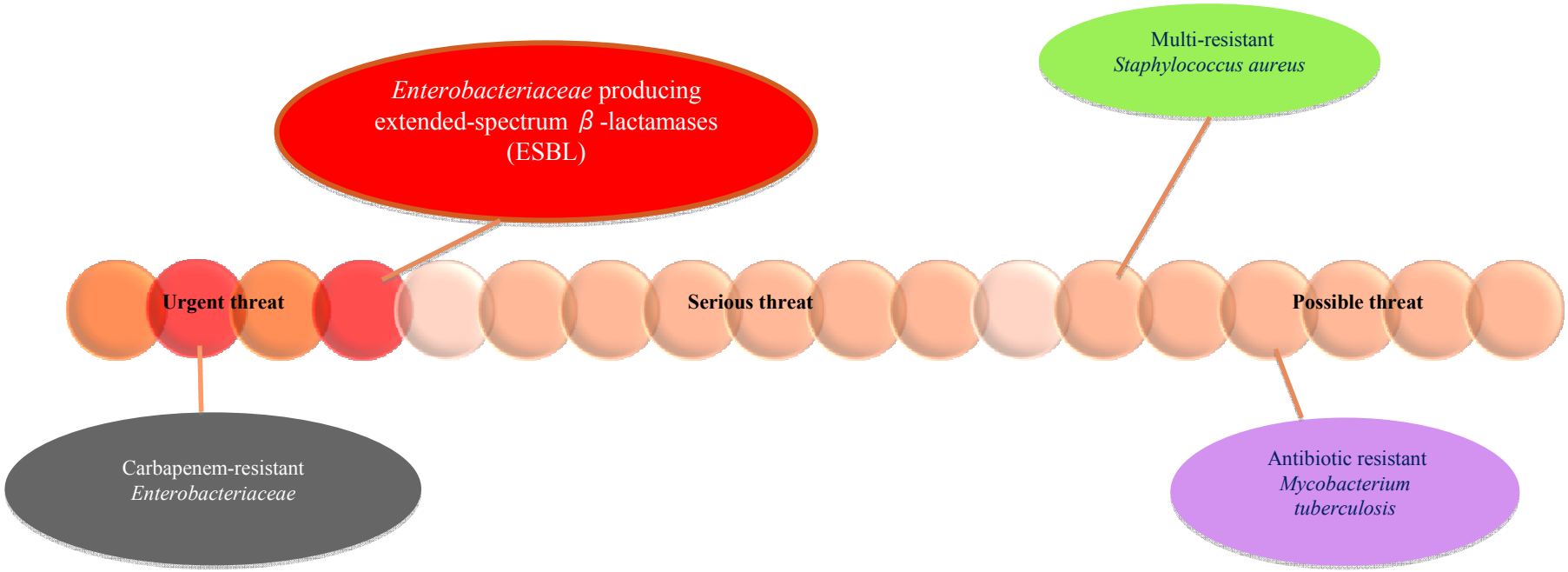
Enterobacteriaceae (E. coli, K.pneumoniae…)

Pseudomonas aeruginosa

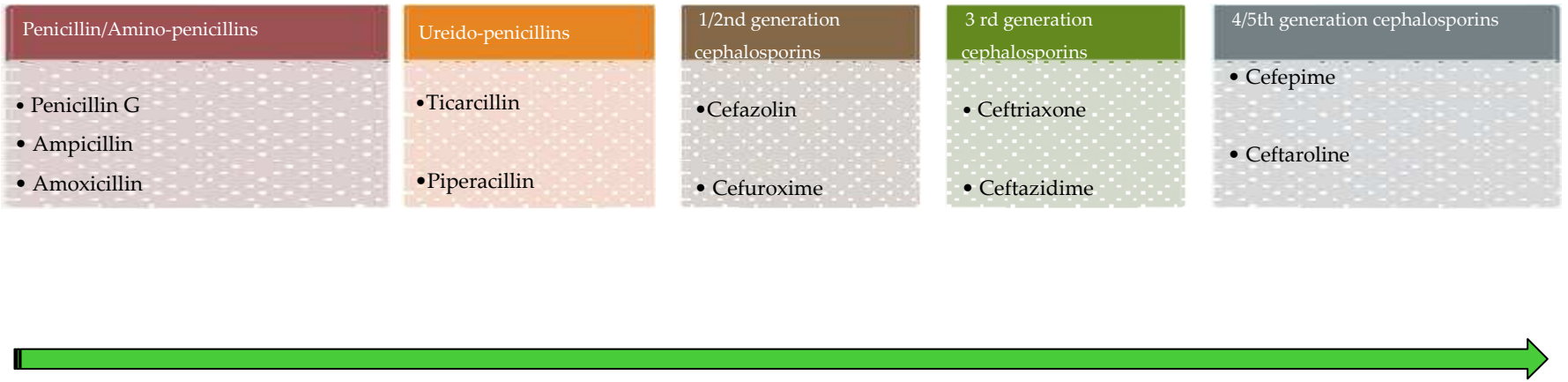
Acinetobacter baumannii



Emerging resistance threats, CDC–USA-2014

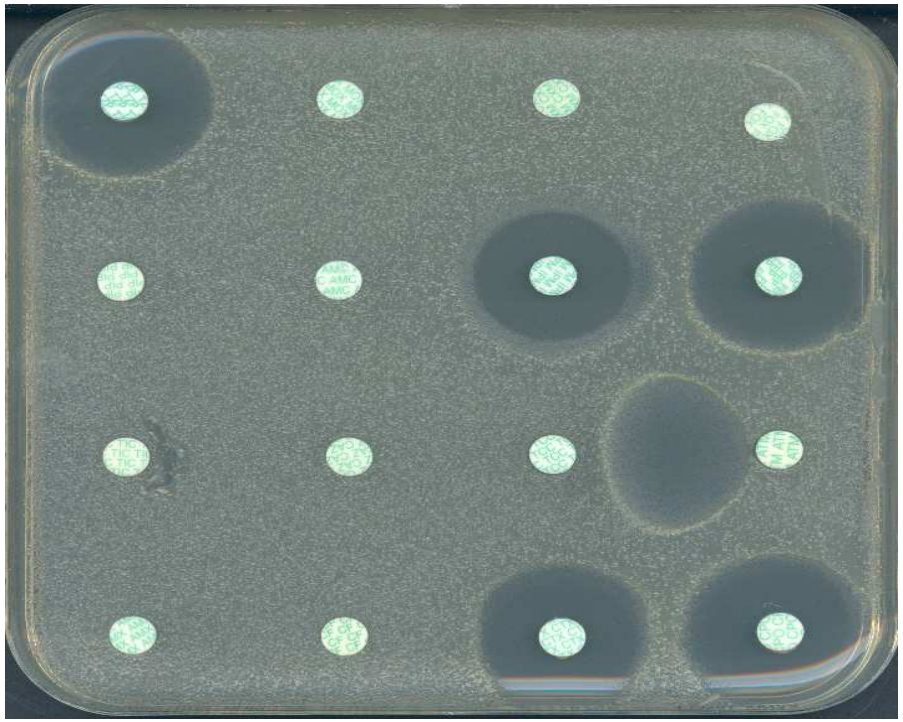


Extended-spectrum ß-lactamases (ESBL)

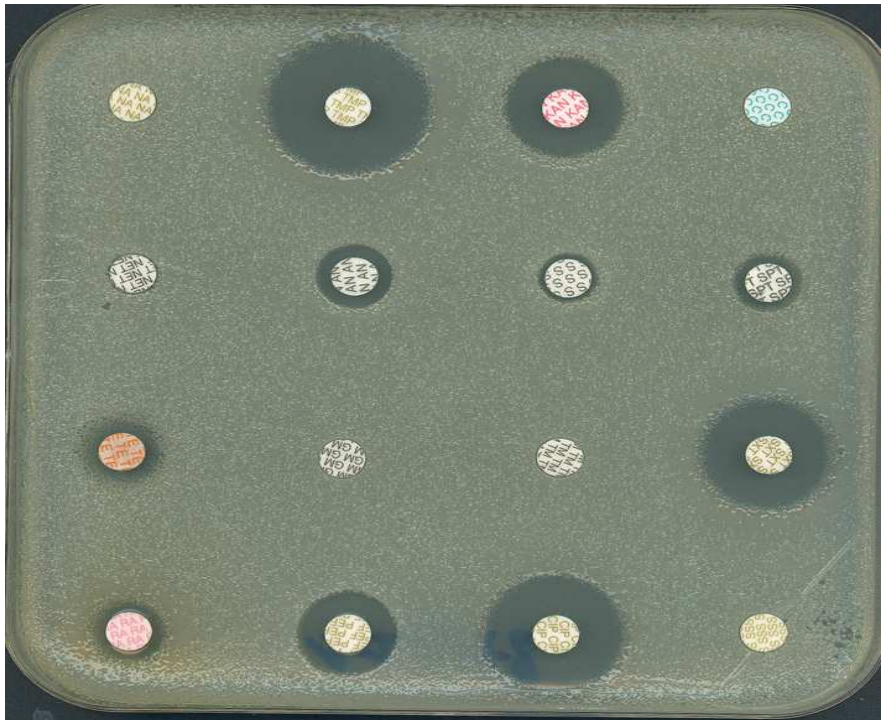


ESBL: increasing resistance towards beta-lactam antibiotics

Multidrug resistance of ESBL-producing *Escherichia coli*

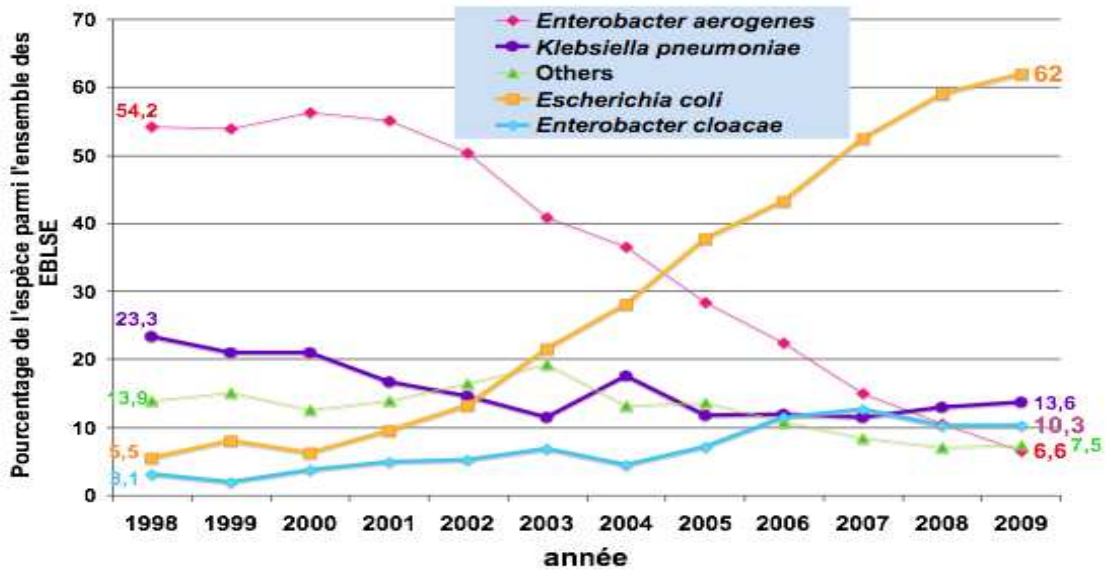


ß-Lactams

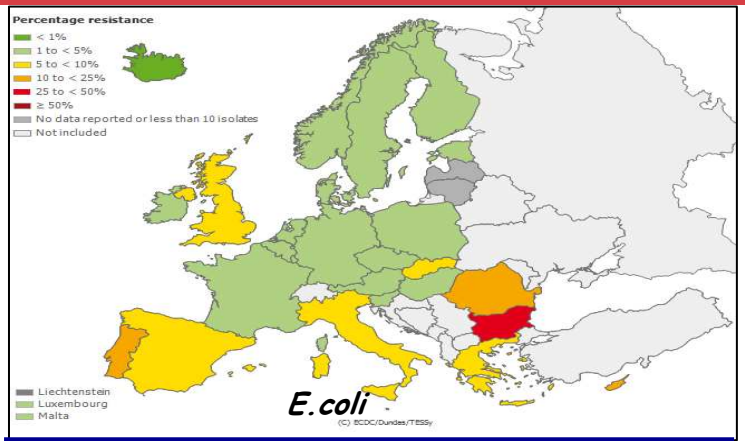


Non- ß-lactams

ESBLs in *Enterobacteriaceae*

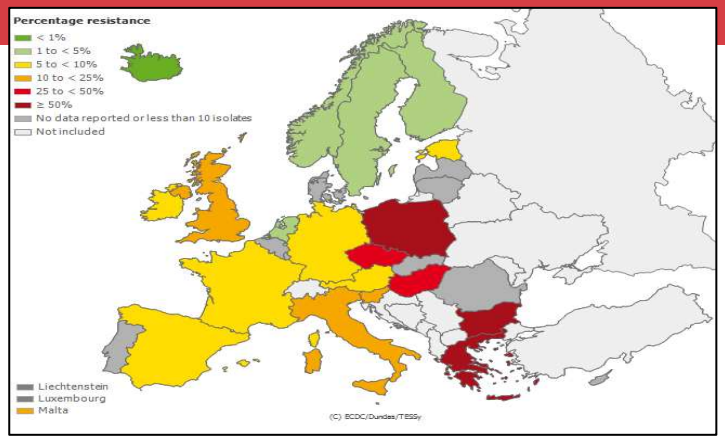


Resistance to expanded-spectrum cephalosporins. Infections. *Enterobacteriaceae* in Europe

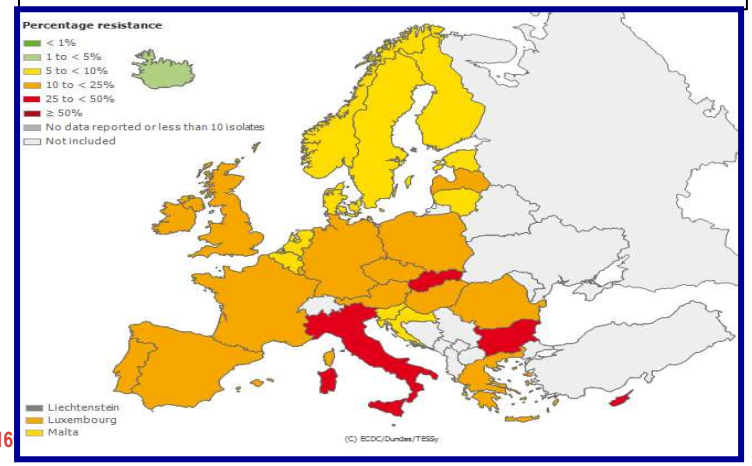


E.coli

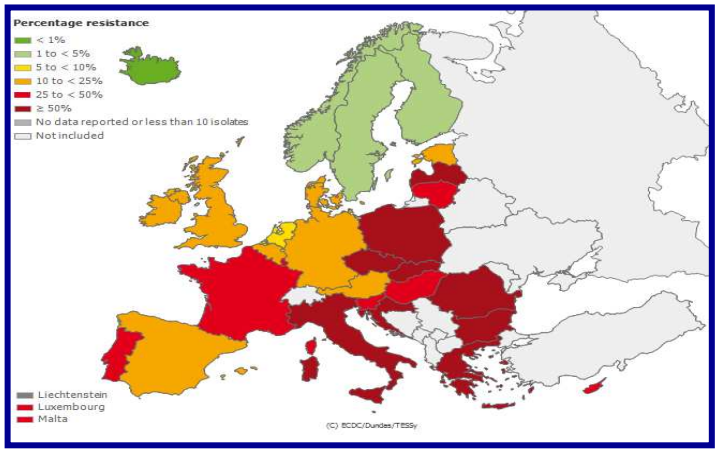
2005



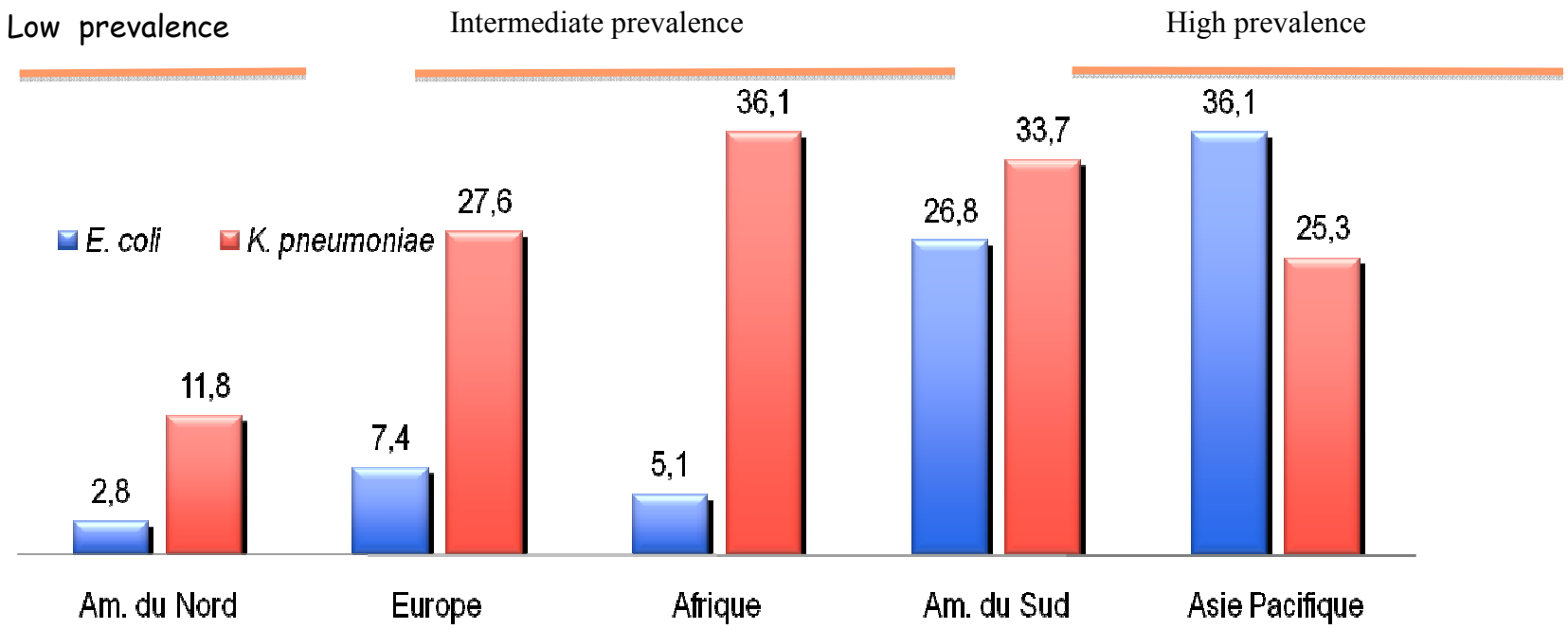
K. pneumoniae



2013



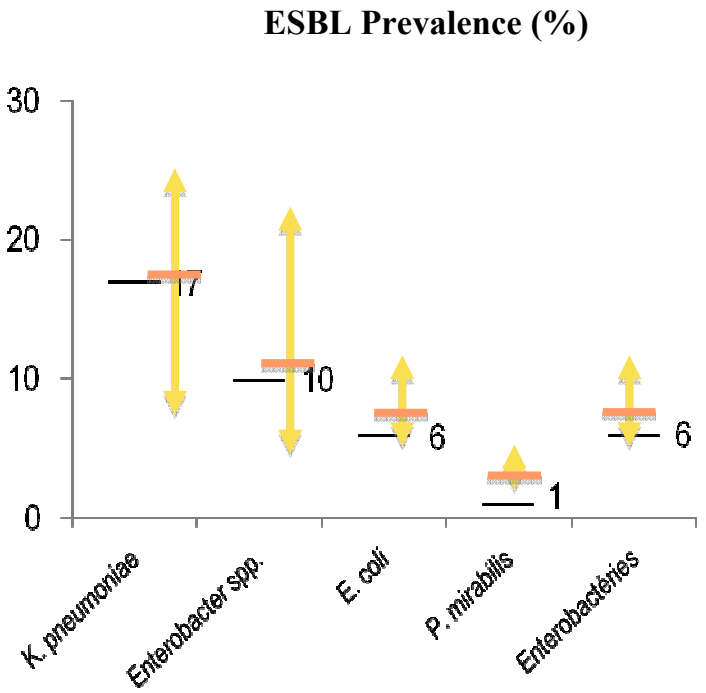
ESBL prevalence in *E. coli* and *K. pneumoniae*



Hawser et al. 2008 ; Rhomberg et al. 2009 ; Bell et al. 2002 ; Gagliotti et al. 2011

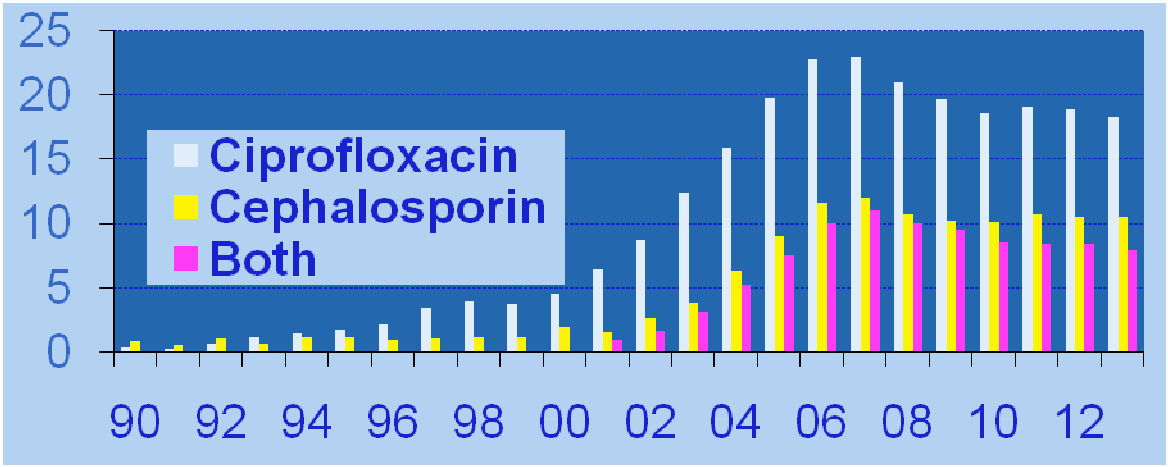
Enterobactericeae ESBL (+) in France in 2012 (n=50,378)

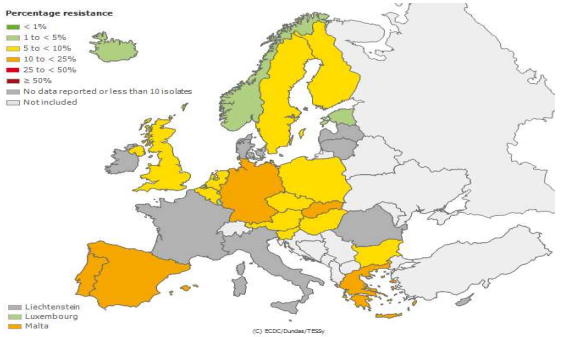
APHP Kremlin Bicêtre
APHP Pompidou
APHP St Antoine
CH Aix en Provence
CH Bayonne
CH Orléans
CHU Besançon
CHU Bordeaux
CHU Caen
CHU Clermont-Fd
CHU Dijon
CHU Grenoble
CHU Lille
CHU Limoges
CHU Nancy
CHU Nice
CHU St Etienne
CHU Tours

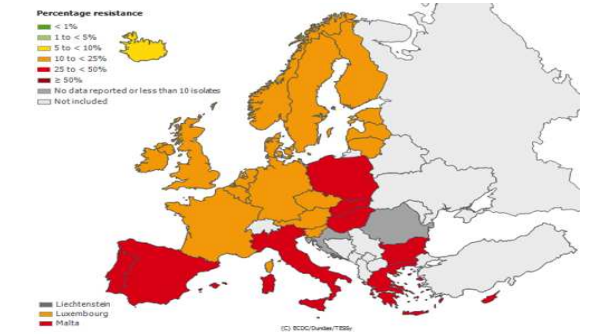


Courtesy R. Bonnet

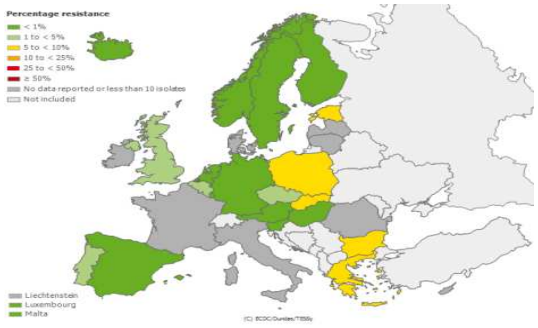
E. coli from bloodstream infections: turning nasty

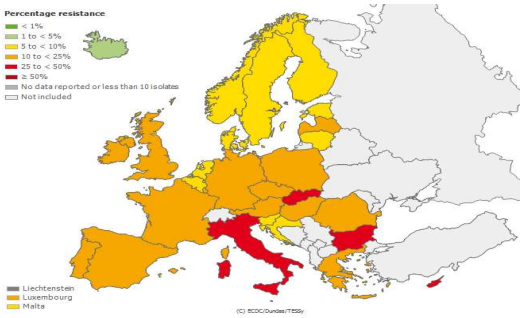






Fluoroquinolones: 2001/13





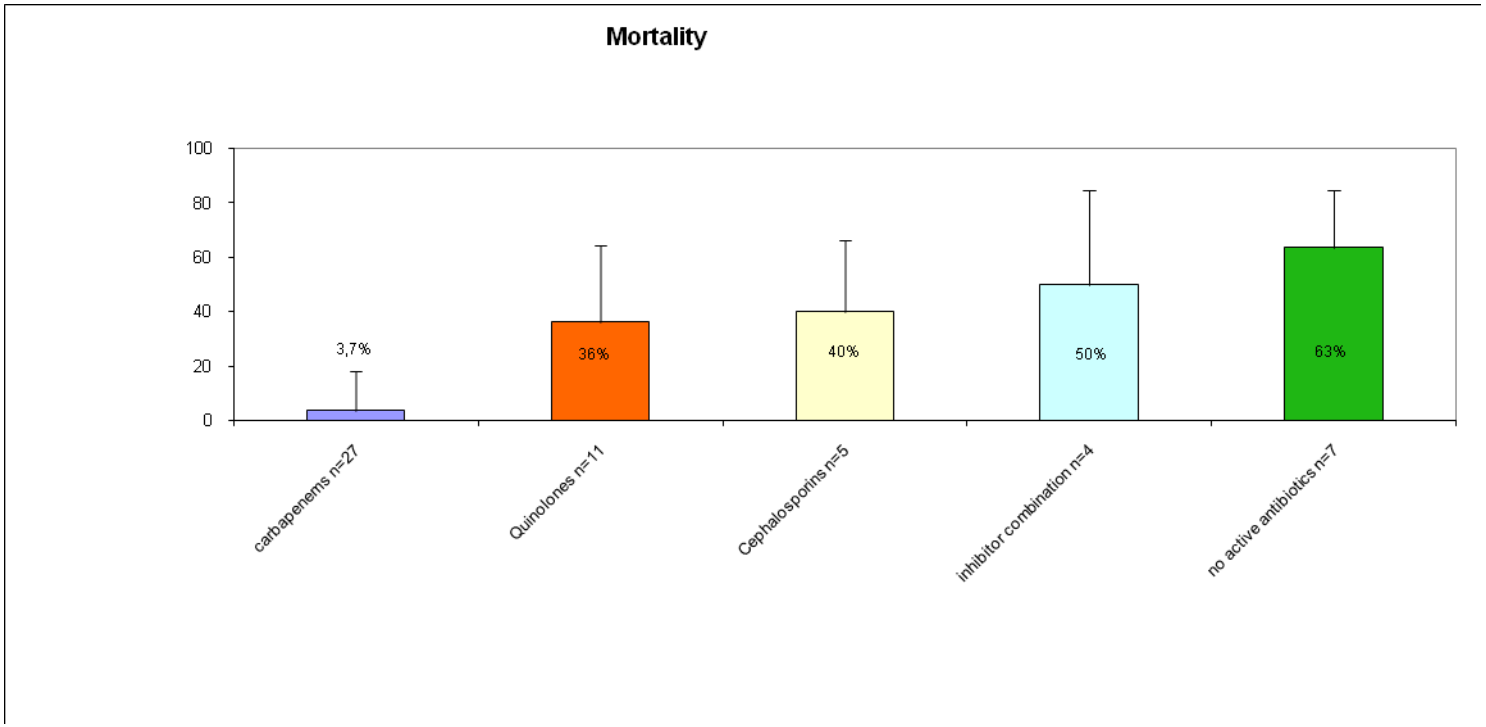
3rd Generation cephalosporins: 2001/13

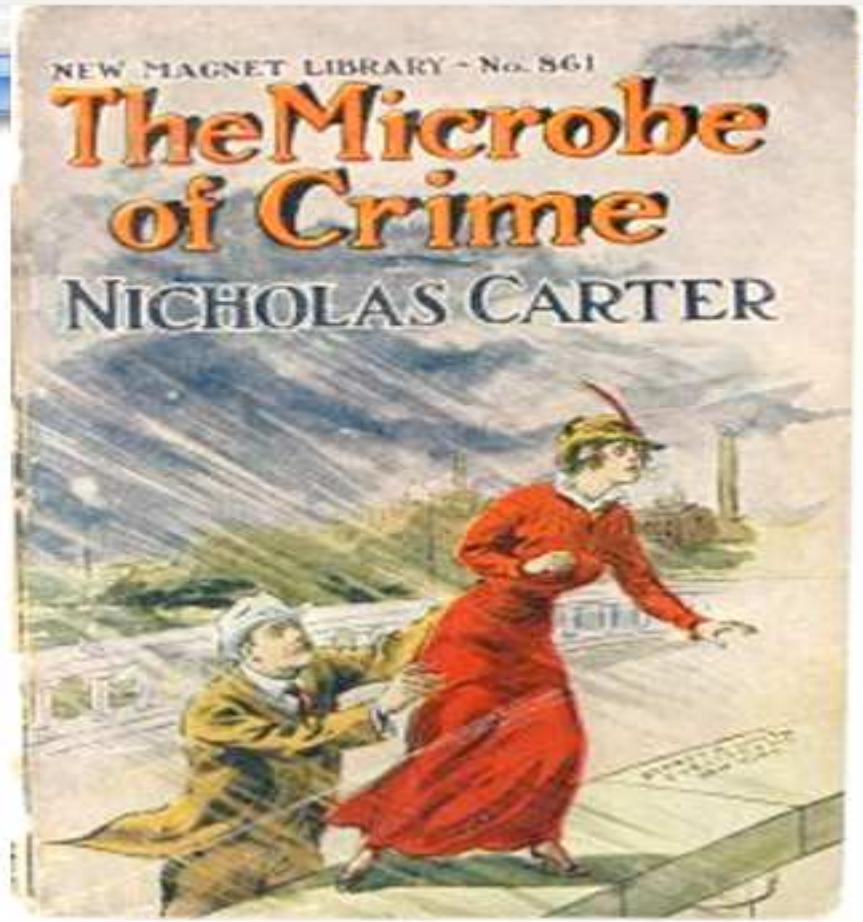
Treatment of infections due to ESBL producers

Activity spectrum + in-vitro activity spectrum+ co-resistances

	Urinary infections (per os)	Sepsis)IV)
Amino, ureidopencillins		
Amoxicillin/clav		
Piperacilline/Tazobactam		
Cephalosporines 3/4 th generations		
Carbapenem		
Aminoglycosides		
Quinolones/Fluoroquinolones		
Trimethoprim/Sulfamethoxazole		
Colistin		
Tigecycline		
Fosfomycin/Nitrofuarantoine		

Day 14 mortality per antibiotic class for bloostream infections due to ESBL producers

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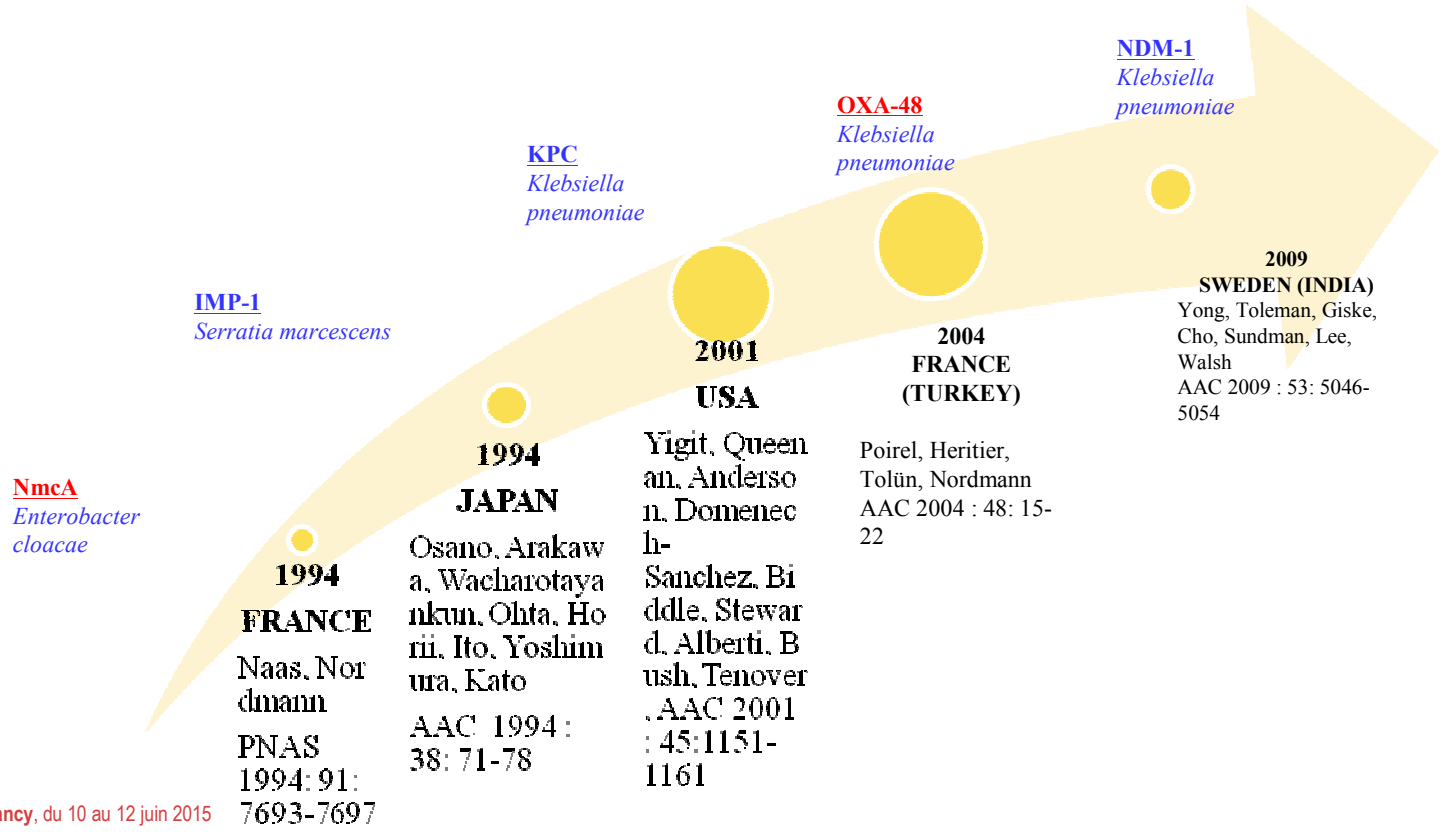
Broad-spectrum ß-lactamases in gram negatives

Penicillins	Cephalosporins	Carbapenems

Extended-spectrum ß-lactamases (ESBL); CTX-M

Carbapenemases: NDM, KPC, OXA-48

Emergence of carbapenemases in *Enterobacteriaceae*



KPCs; Klebsiella Pneumoniae Carbapenemase

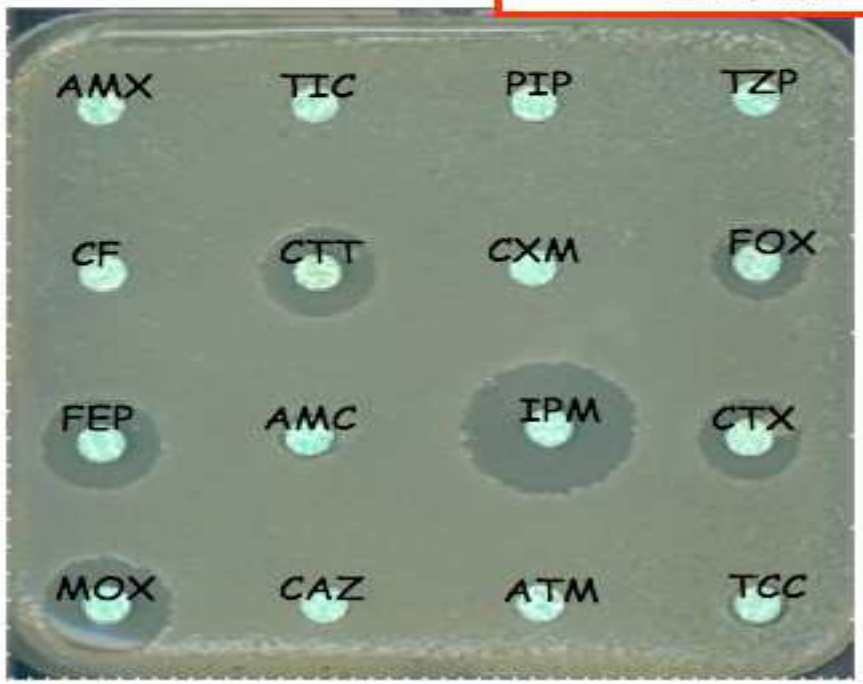
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2001, p. 1151–1161 Vol. 45, No. 4
0066-4804/01/$04.00+0 DOI: 10.1128/AAC.45.4.1151–1161.2001

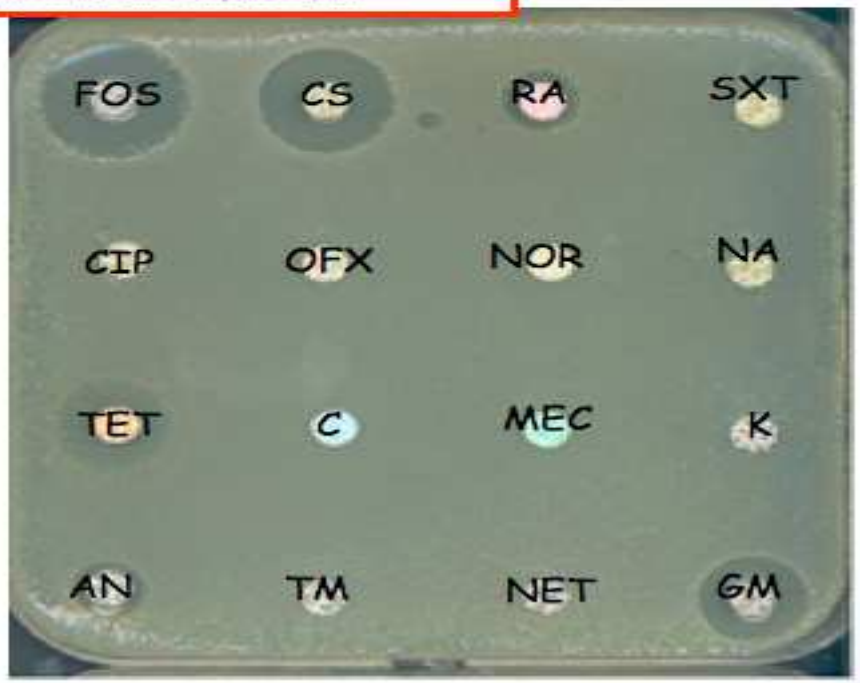
Novel Carbapenem-Hydrolyzing β-Lactamase, KPC-1, from a Carbapenem-Resistant Strain of *Klebsiella pneumoniae*

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, Andreu Doria, Palma de Mallorca, 07014,[4] and Area de Microbiologia, Universidad de las Islas Baleares, Cra. Valldemosa, Palma de Mallorca, 07071,[3] Spain

Received 19 September 2000/Returned for modification 21 November 2000/Accepted 23 January 2001





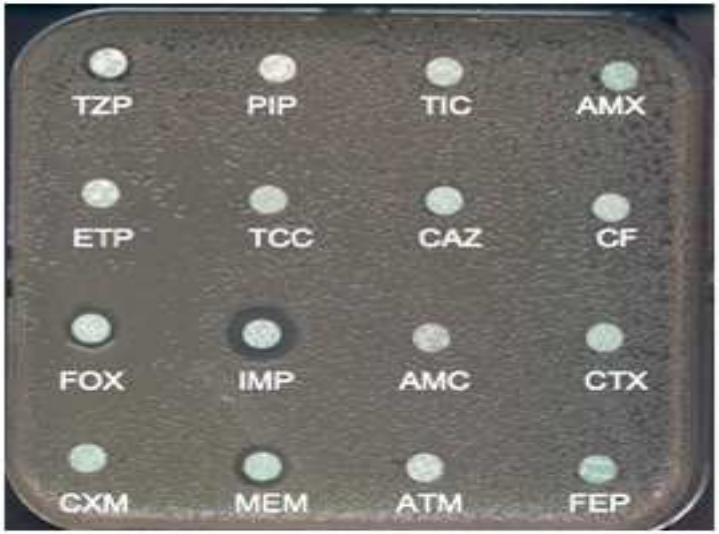
AAC,2009; 53 5046-5054

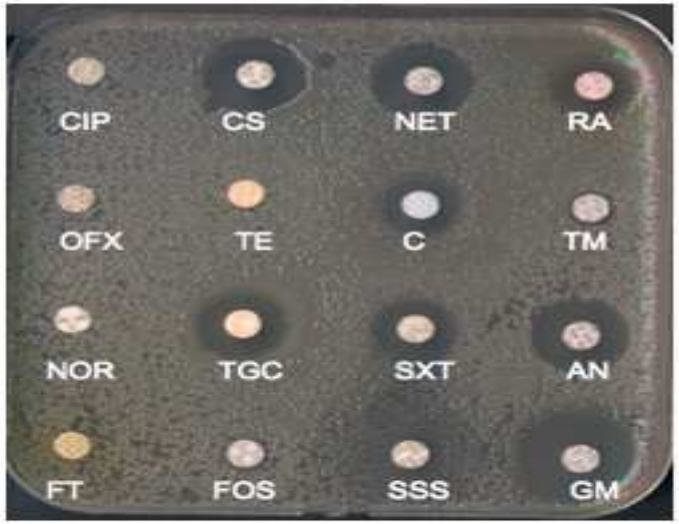
Characterization of a New Metallo-β-Lactamase Gene, *bla*$_{NDM-1}$, and a Novel Erythromycin Esterase Gene Carried on a Unique Genetic Structure in *Klebsiella pneumoniae* Sequence Type 14 from India[▽]

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]*

Yonsei University College of Medicine, Research Institute of Antimicrobial Resistance, Seoul, Republic of Korea[1]; Department of Medical Microbiology, Cardiff University, Cardiff, United Kingdom[2]; Clinical Microbiology, MTC—Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden[3]; Yonsei University College of Life Science and Biotechnology, Seoul, Republic of Korea[4]; and Department of Clinical Microbiology, Örebro University Hospital, Örebro, Sweden[5]

OXA-48 + CTX-M-15





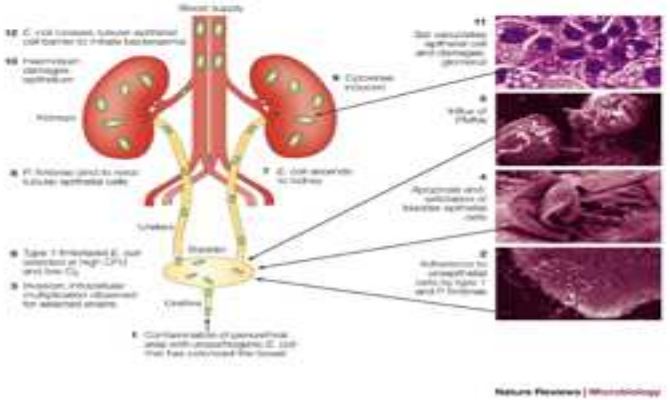
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2004, p. 15–22 Vol. 48, No. 1
0066-4804/04/$08.00+0 DOI: 10.1128/AAC.48.1.15–22.2004

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

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

The importance of *E.coli*

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



J Antimicrob Chemother 2014; **69**: 2706–2712
doi:10.1093/jac/dku208 Advance Access publication 16 June 2014

Journal of Antimicrobial Chemotherapy

Incidence rates of carbapenemase-producing Enterobacteriaceae clinical isolates in France: a prospective nationwide study in 2011–12

Jérôme Robert[1–3]*, Alix Pantel[4,5], Audrey Mérens[6], Jean-Philippe Lavigne[4,5] and Marie-Hélène Nicolas-Chanoine[7–9] on behalf of ONERBA's Carbapenem Resistance Study Group†

[1]Sorbonne Universités, UPMC Univ Paris 06, U1135, Centre d'Immunologie et des Maladies Infectieuses (CIMI), Eq 13, F-75013 Paris, France; [2]INSERM, U1135, Centre d'Immunologie et des Maladies Infectieuses (CIMI), Eq 13, F-75013 Paris, France; [3]Bactériologie-Hygiène, Hôpitaux Universitaires Pitié Salpêtrière—Charles Foix, APHP, F-75013 Paris, France; [4]INSERM U1047, UFR de Médecine, Université Montpellier 1, Nîmes, France; [5]Service de Microbiologie, CHU Carémeau, Nîmes, France; [6]Laboratoire de Biologie, Hôpital d'Instruction des Armées Bégin, Saint-Mandé, France; [7]Service de Microbiologie, Hôpital Beaujon AP-HP, Clichy, France; [8]Faculté de Médecine D. Diderot—Paris 7, Paris, France; [9]INSERM UMR 1149, Université Paris 7, Paris, France

*Corresponding author. Laboratoire de Bactériologie-Hygiène, Faculté de Médecine Pierre et Marie Curie (UPMC Paris 6), 91 Boulevard de l'Hôpital, 75634 Paris cedex 13, France. Tel: +33-1-40-77-97-49; Fax: +33-1-45-82-75-77; E-mail: jerome.robert@psl.aphp.fr
†Members are listed in the Acknowledgements.

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Objectives: To determine proportions and incidence rates of Enterobacteriaceae producing carbapenemase among those non-susceptible (NS) to carbapenems in France.

Methods: From November 2011 to April 2012, 71 laboratories recorded non-duplicate Enterobacteriaceae clinical isolates NS to at least one carbapenem and the total number of isolates of the different species. Carbapenem MICs were determined by broth microdilution and the β-lactamase content by DNA microarray.

Results: During the study period, the 71 laboratories identified 133 244 Enterobacteriaceae isolates, of which 846 (0.63%) were NS to at least one carbapenem. Carbapenem-NS isolates accounted for 0.07% (61/90 148) among *Escherichia coli* isolates, 1.1% (111/10 436) among *Klebsiella pneumoniae*, 8.2% (492/5971) among *Enterobacter cloacae* and 4.0% (84/2104) among *Enterobacter aerogenes*. Among the 541 available carbapenem-NS isolates, 222 (including 63 randomly selected *E. cloacae*) were further analysed after confirmation of carbapenem non-susceptibility. None of the *Enterobacter* spp. isolates produced carbapenemase. Among the other species, 28 isolates produced carbapenemases (22 OXA-48, 4 KPC and 2 NDM), accounting for an estimated proportion of carbapenemase-producing isolates of 0.08% for all species, 0.01% for *E. coli* and 0.27% for *K. pneumoniae*. The incidence-density rate in the participating hospitals was 0.0041 per 1000 hospital-days and the incidence rate was 0.0027 per 100 admissions.

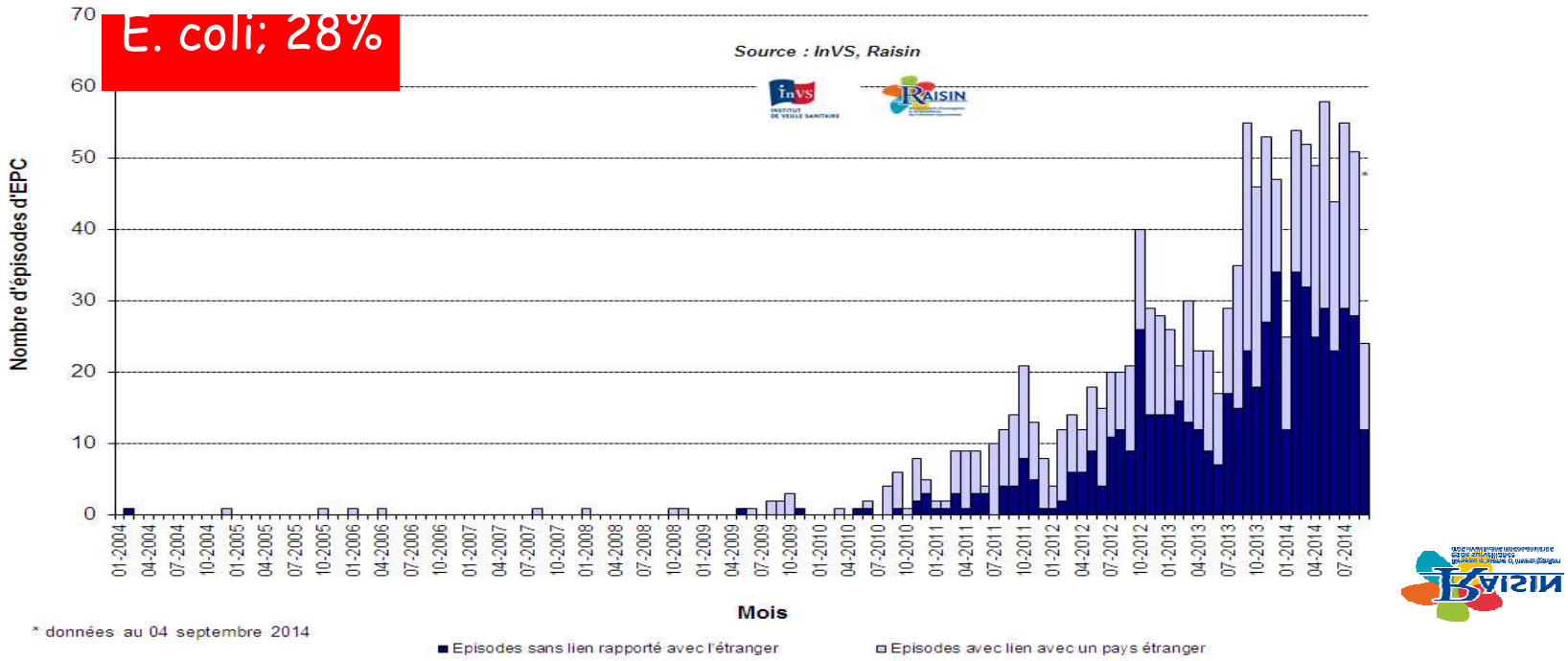
Conclusions: The incidence-density rate of carbapenemase-producing isolates per 1000 hospital-days was low and 30-fold lower than that of carbapenem-NS isolates (0.125) and almost 300-fold lower than that of ESBL-producing isolates (1.104) in these French hospitals.

Carbapenemase producers in France

Species	Total isolates	NS to ESC [*n* (%)]	ESBL+ [*n* (%)]	NS to CARB [*n* (%)]	CARBase+/no. tested (%)	Estimated proportion of isolates CARBase+ (%)
E. coli	90148	5660 (6.3)	4632 (5.1)	61 (0.07)	4/28 (14.3)	0.01
K. pneumoniae	10436	1561 (15.0)	1564 (15.0)	111 (1.1)	17/68 (25.0)	0.27
P. mirabilis	8641	111 (1.3)	70 (0.8)	1 (0.01)	1/1 (100)	0.01
E. cloacae[a]	5971	1842 (30.8)	713 (11.9)	492 (8.2)	0/63 (0)	—
K. oxytoca	3482	281 (8.1)	92 (2.6)	6 (0.2)	2/4 (50.0)	0.09
C. koseri	2509	77 (3.1)	70 (2.8)	1 (0.04)	0	—
M. morganii	2573	428 (16.6)	31 (1.2)	0 (0)	0	—
E. aerogenes	2104	650 (30.9)	164 (7.8)	84 (4.0)	0	—
Serratia spp.	1888	193 (10.2)	24 (1.3)	16 (0.9)	1/8 (12.5)	0.11
C. freundii	1451	445 (30.6)	84 (5.8)	52 (3.6)	1/10 (10.0)	0.36
P. vulgaris	1050	28 (2.7)	7 (0.7)	1 (0.1)	0/1 (0)	—
Salmonella spp.	590	6 (1.0)	6 (1.0)	1 (0.2)	1/1 (100)	0.17
Providencia spp.	523	17 (3.3)	8 (1.5)	0 (0)	0	—
Shigella spp.	60	1 (1.7)	1 (1.7)	0 (0)	0	—
Others	1821	173 (9.5)	26 (1.4)	20 (1.1)	1/10 (10.0)	0.11
Total	133244	11 471 (8.6)	7492 (5.6)	846 (0.6)	28 (12.6)	0.08

Selection criteria ; ertapenem ≥1 mg/L
imipenem
meropenem ≥ 4mg/L
ertapenem

Episodes d'EPC, France, 2004 – 2014, par mois de signalement Bilan au 04 septembre 2014 (N= 1210 épisodes)



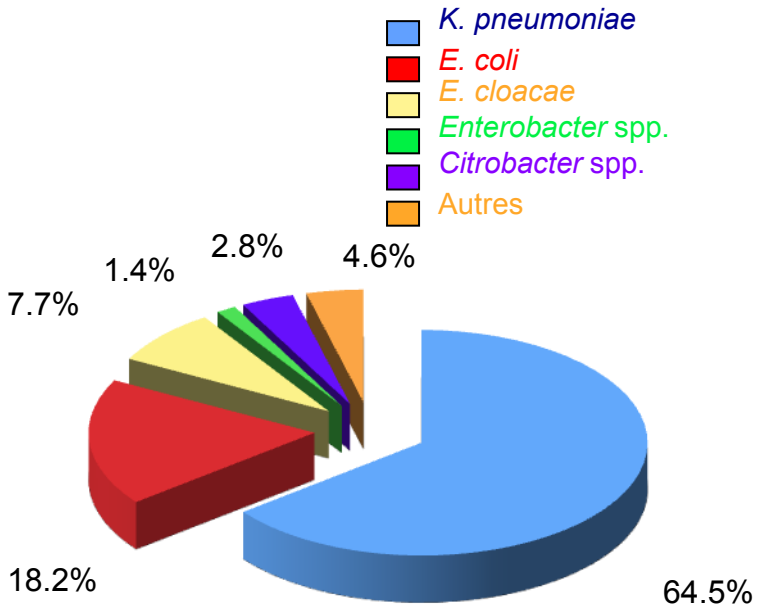
1210 épisodes au total

2009 : **10** , 2010 : **28** , 2011 : **113** , 2012 : **233** , 2013 : **405** , 2014 : **412**

Carbapenemase producers in *Enterobacteriaceae*- France- Antibiotic Resistance Reference Center- 2013

Species	n
K. pneumoniae	410
E. coli	116
E. cloacae	51
Enterobacter spp.	9
Citrobacter spp.	24
Autres	26
Total	**636**

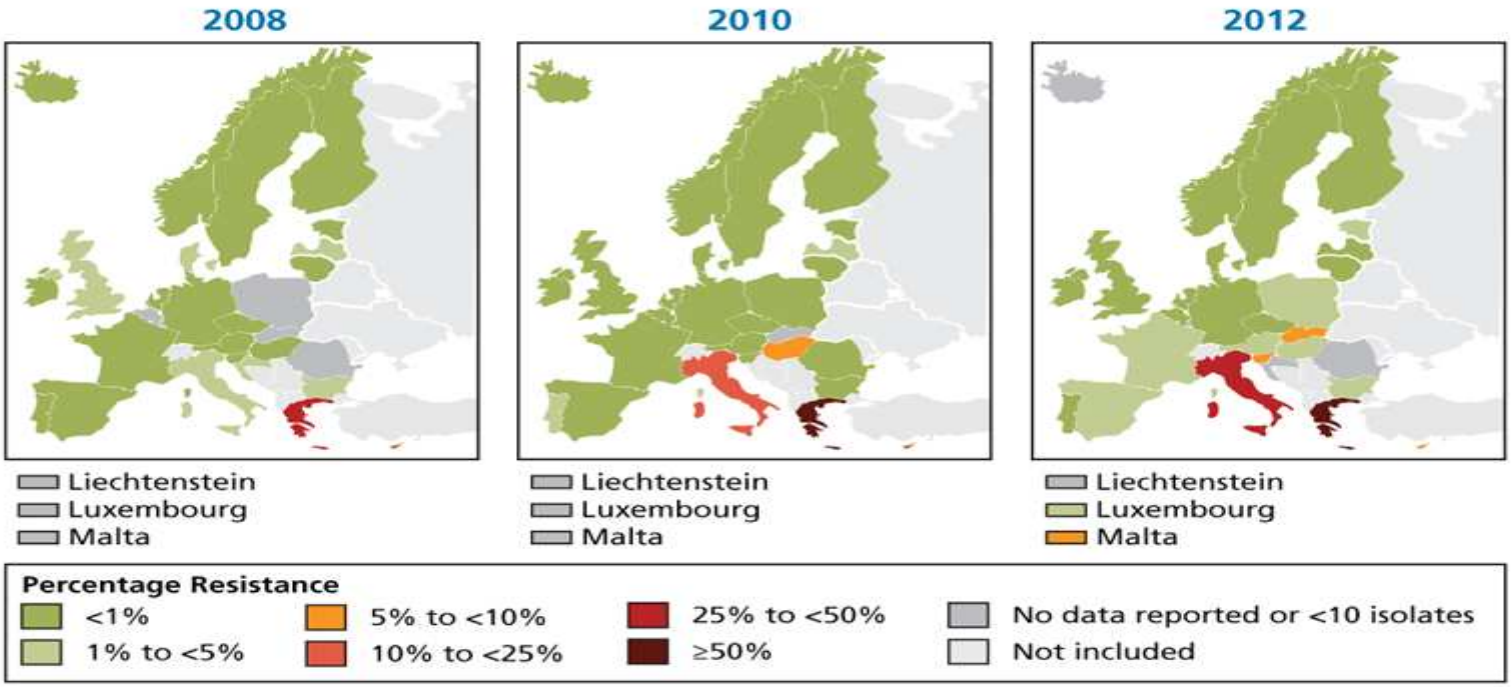
X 3 in 2 years of time



P. Nordmann, personal and unpublished data

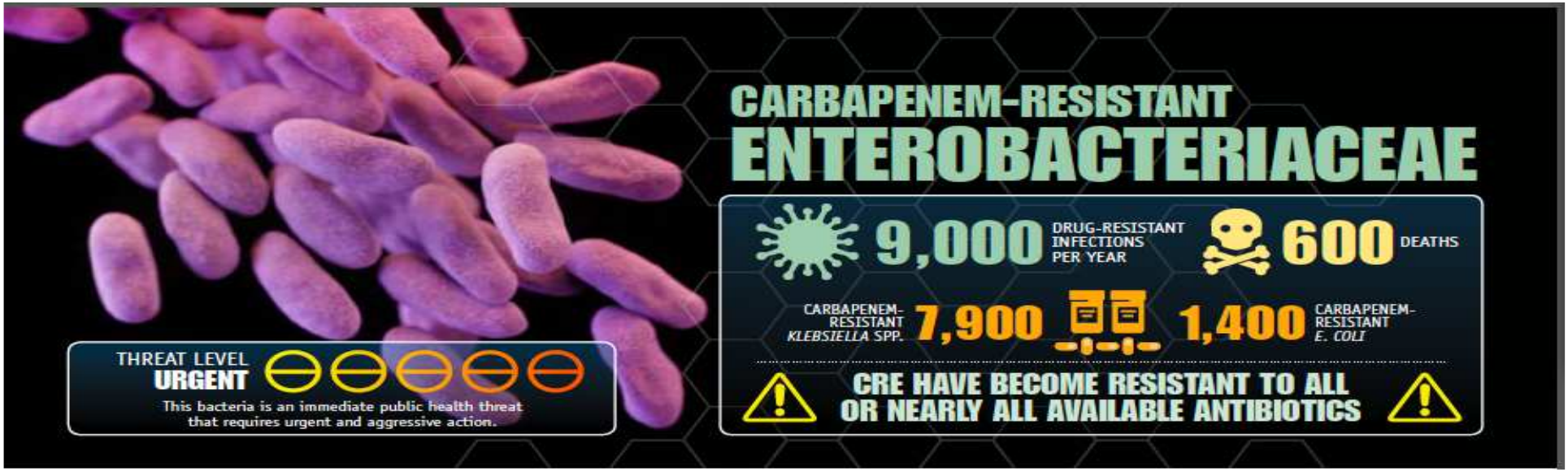
Carbapenemases in the community

Falling Dominoes: Carbapenem-Resistant *K. pneumoniae*



Carbapenemase producers, France: the future

The impact of carbapenemase producers in the USA



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LETTER TO THE EDITOR

Emergence of the 16S rRNA Methylase RmtG in an Extended-Spectrum-β-Lactamase-Producing and Colistin-Resistant *Klebsiella pneumoniae* Isolate in Chile

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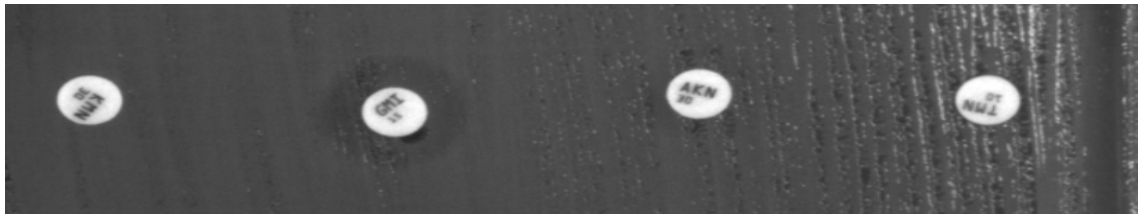

RAPID COMMUNICATIONS

Colistin resistance superimposed to endemic carbapenem-resistant *Klebsiella pneumoniae*: a rapidly evolving problem in Italy, November 2013 to April 2014

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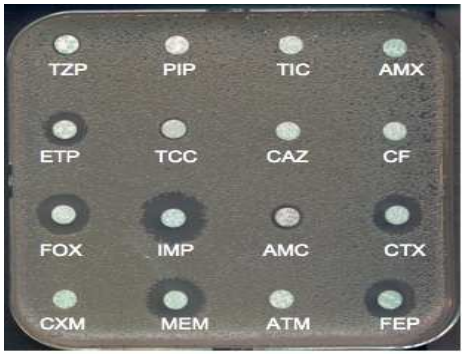
Consecutive non-replicate clinical isolates (n=191) of carbapenem non-susceptible Enterobacteriaceae were collected from 21 hospital laboratories across Italy from November 2013 to April 2014 as part of the European Survey on Carbapenemase-producing Enterobacteriaceae (EuSCAPE) project. *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* (KPC-KP) represented 178 (93%) isolates with 76 (43%) respectively resistant to colistin, a key drug for treating carbapenamase-producing Enterobacteriaceae. KPC-KP colistin-resistant isolates were detected in all participating laboratories. This underscores a concerning evolution of colistin resistance in a setting of high KPC-KP endemicity.

mortality rates are high due to limited treatment options, and some strains have the potential for rapid dissemination in healthcare settings [1,2]. In Europe, CRE have been reported from virtually all countries, but in some countries, namely Greece and Italy, they have spread rapidly and are presently endemic in many hospitals [3,4]. Resistance to carbapenems in Enterbacteriaceae is largely due to production of enzymes (carbapenemases) inactivating these antibiotics, hence the definition of carbapenemase-producing Enterobacteriaceae (CPE).

In Italy, the dramatic increase of carbapenem-resistant *Klebsiella pneumoniae* has been documented by the European Antimicrobial Resistance Surveillance

***Kp* KPC-2**

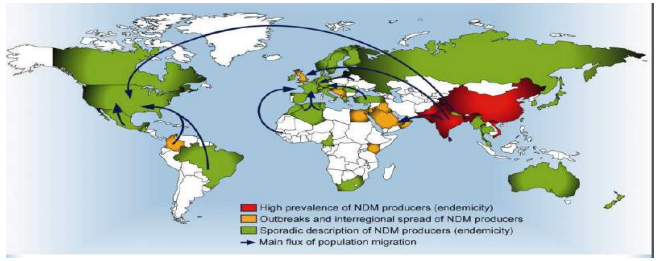


Fighting back against antibiotic resistance

Four Core Actions to Prevent Antibiotic Resistance

1. Preventing infections, preventing the spread of resistance

2. Tracking



3. Improving antibiotic prescription/stewardship

4.Developing novel diagnostic tests and new drugs