Carbapenemases in *Enterobacteriaceae*: 2012

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Bicêtre hospital, South-Paris Med School

March 21, 2012

i

The essential daily briefing

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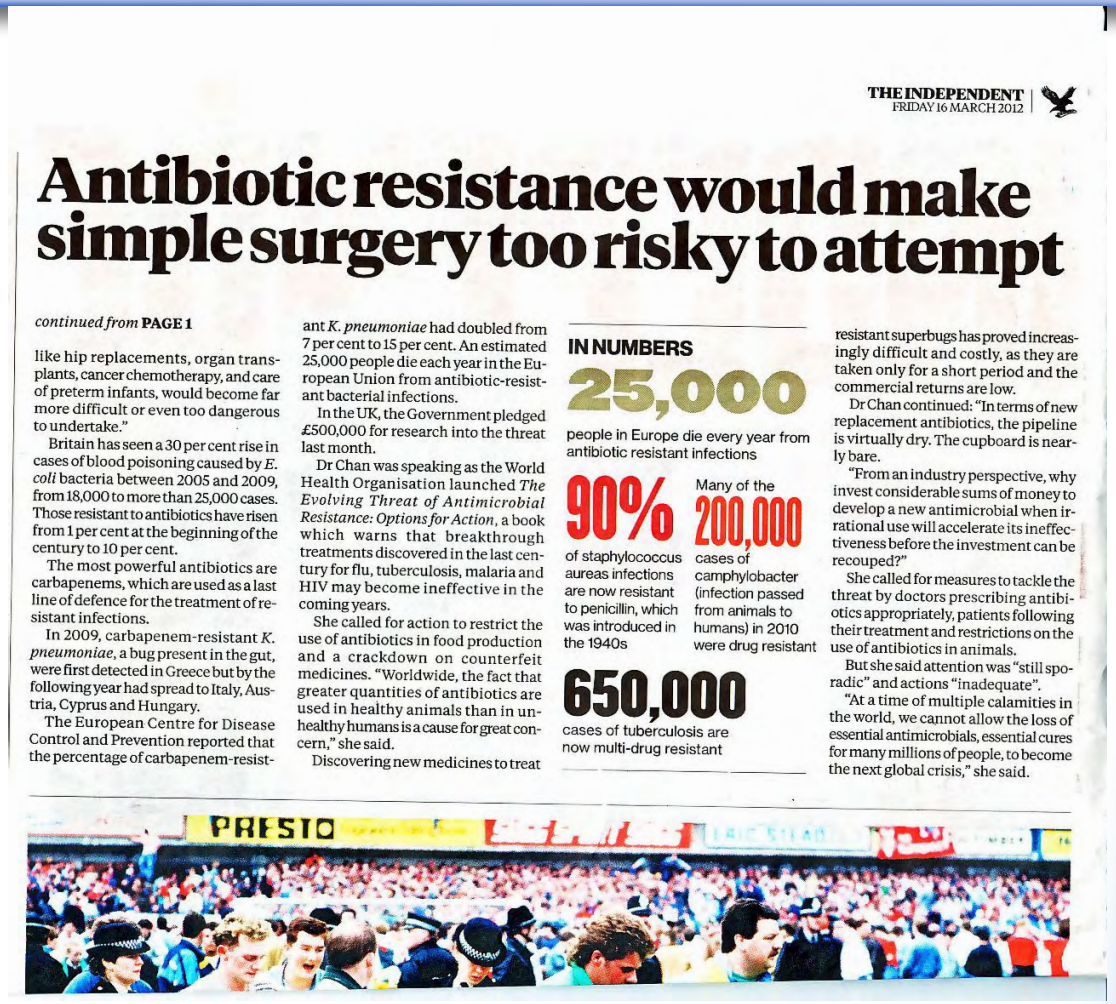
FRIDAY
16 MARCH 2012
Number 407

INSIDE TODAY
Daily Codeword
Daily Crosswords

'An end to modern medicine as we know it'

Margaret Chan
Director-General
World Health Organisation,
speaking in Copenhagen

- WHO chief's stark warning about danger of resistance to antibiotics
- 'Growing crisis' may 'turn common infections into untreatable disease
- Calls for restrictions on use in animals to halt the spread of E.coli



THE INDEPENDENT
FRIDAY 16 MARCH 2012

Antibiotic resistance would make simple surgery too risky to attempt

continued from **PAGE 1**

like hip replacements, organ transplants, cancer chemotherapy, and care of preterm infants, would become far more difficult or even too dangerous to undertake."

Britain has seen a 30 per cent rise in cases of blood poisoning caused by *E. coli* bacteria between 2005 and 2009, from 18,000 to more than 25,000 cases. Those resistant to antibiotics have risen from 1 per cent at the beginning of the century to 10 per cent.

The most powerful antibiotics are carbapenems, which are used as a last line of defence for the treatment of resistant infections.

In 2009, carbapenem-resistant *K. pneumoniae*, a bug present in the gut, were first detected in Greece but by the following year had spread to Italy, Austria, Cyprus and Hungary.

The European Centre for Disease Control and Prevention reported that the percentage of carbapenem-resistant *K. pneumoniae* had doubled from 7 per cent to 15 per cent. An estimated 25,000 people die each year in the European Union from antibiotic-resistant bacterial infections.

In the UK, the Government pledged £500,000 for research into the threat last month.

Dr Chan was speaking as the World Health Organisation launched *The Evolving Threat of Antimicrobial Resistance: Options for Action*, a book which warns that breakthrough treatments discovered in the last century for flu, tuberculosis, malaria and HIV may become ineffective in the coming years.

She called for action to restrict the use of antibiotics in food production and a crackdown on counterfeit medicines. "Worldwide, the fact that greater quantities of antibiotics are used in healthy animals than in unhealthy humans is a cause for great concern," she said.

Discovering new medicines to treat resistant superbugs has proved increasingly difficult and costly, as they are taken only for a short period and the commercial returns are low.

Dr Chan continued: "In terms of new replacement antibiotics, the pipeline is virtually dry. The cupboard is nearly bare.

"From an industry perspective, why invest considerable sums of money to develop a new antimicrobial when irrational use will accelerate its ineffectiveness before the investment can be recouped?"

She called for measures to tackle the threat by doctors prescribing antibiotics appropriately, patients following their treatment and restrictions on the use of antibiotics in animals.

But she said attention was "still sporadic" and actions "inadequate".

"At a time of multiple calamities in the world, we cannot allow the loss of essential antimicrobials, essential cures for many millions of people, to become the next global crisis," she said.

IN NUMBERS

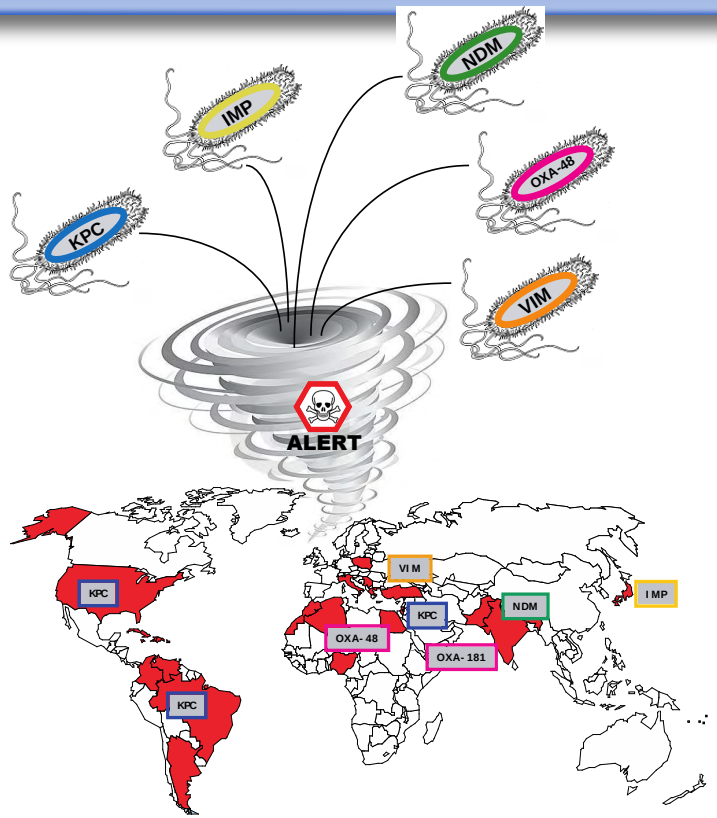
25,000
people in Europe die every year from antibiotic resistant infections

90%
of staphylococcus aureas infections are now resistant to penicillin, which was introduced in the 1940s

Many of the **200,000**
cases of camphylobacter (infection passed from animals to humans) in 2010 were drug resistant

650,000
cases of tuberculosis are now multi-drug resistant

Trends in Molecular Medecine

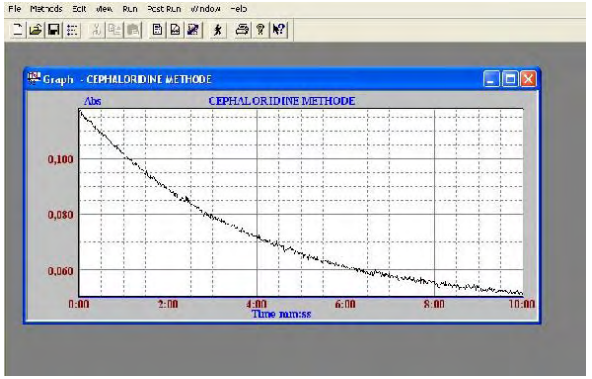


Carbapenemase producing *Enterobacteriaceae* :
Here is the storm !

April, 2012, Volume XX, Issue YY

Nordmann, Dortet , Poirel

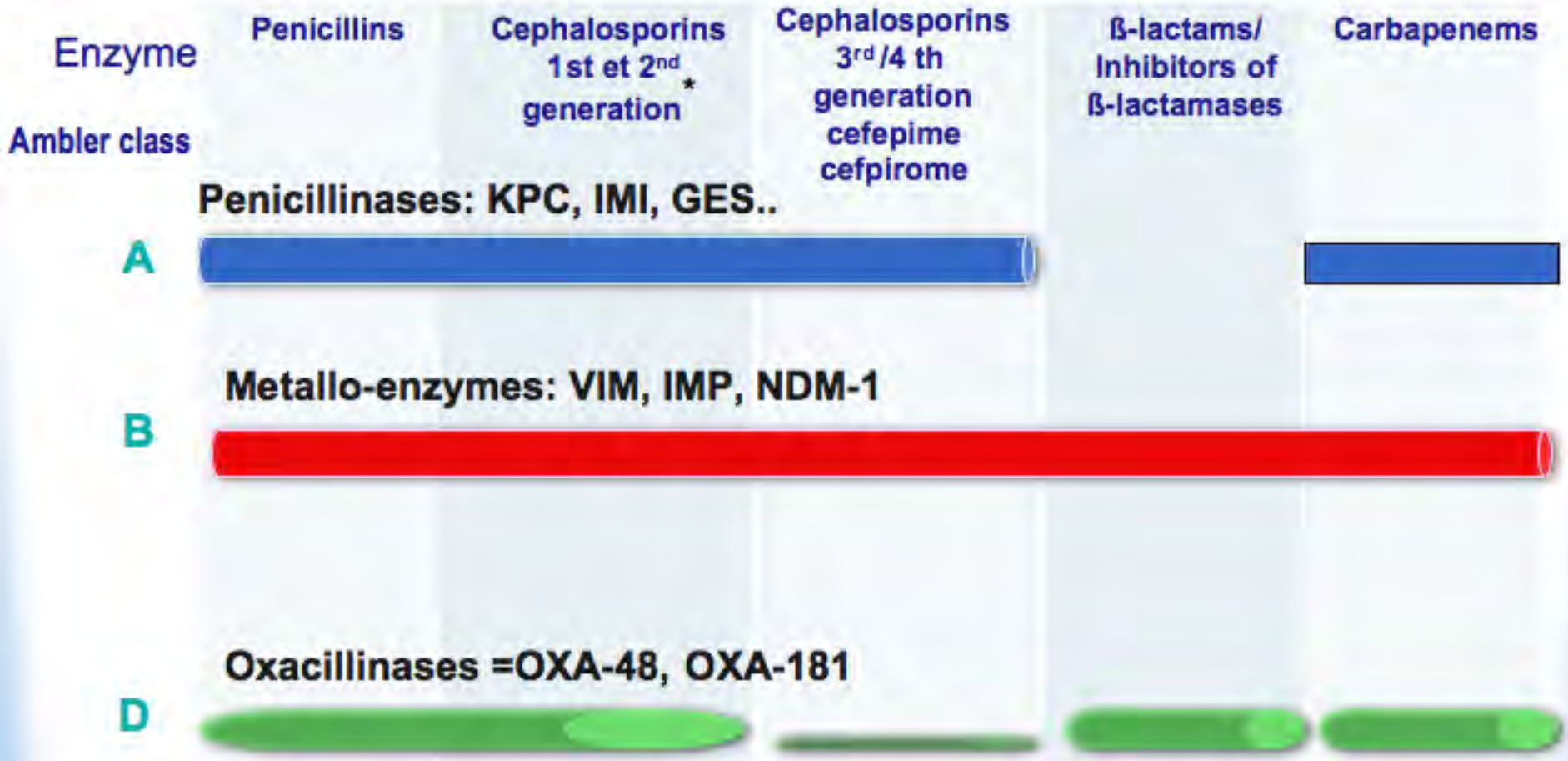
Defining a "Carbapenemase"



- Definition debated…….

  - β-lactamases able to hydrolyse carbapenems; imipenem, meropenem, ertapenem….
  - Enzymes with imipenemase activity;
  - Most, but not all, hydrolyse many β-lactams – i.e cephalosporins
  - Not all 'carbapenemases' confer clinically significant carbapenem resistance…….

The carbapenemases in *Enterobacteriaceae*



* Cephamycins excluded for most class As

KPCs; Klebsiella Pneumoniae Carbapenemase

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2001, p. 1151–1161
0066-4804/01/$04.00+0 DOI: 10.1128/AAC.45.4.1151–1161.2001
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,[1] 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

The KPC enzymes

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

Background: Carbapenem antibiotics are used to treat serious infections caused by extended-spectrum β-lactamase–carrying pathogens. Carbapenem resistance has been unusual in isolates of *Klebsiella pneumoniae*. In this study, the prevalence and molecular epidemiologic characteristics of carbapenem-resistant *K pneumoniae* are analyzed, and the experience involving 2 hospital outbreaks is described.

Methods: A citywide surveillance study was conducted in hospitals in Brooklyn. An observational study involving subsequent outbreaks at 2 hospitals was undertaken. Isolates were genetically fingerprinted by ribotyping and were examined for the presence of KPC-type carbapenem-hydrolyzing β-lactamases.

Results: Of 602 isolates of *K pneumoniae* collected during the citywide surveillance study, 45% had extended-spectrum β-lactamases. Of the extended-spectrum β-lactamase–producing isolates, 3.3% carried the carbapenem-hydrolyzing β-lactamase KPC-2. Several isolates were reported by the clinical microbiology laboratories as being susceptible to imipenem. Although all the isolates were resistant using agar diffusion methods, minimal inhibitory concentrations of imipenem were substantially lower for several isolates using standard broth microdilution tests and were highly dependent on the inoculum used. Two hospitals experienced the rapid spread of carbapenem-resistant isolates involving 5[illegible]. 14-day mortality for bacteremic patie[illegible] isolates belonged to a single ribotype.

Conclusions: Carbapenem-resistant[illegible] lates are rapidly emerging in New Yor[illegible] of a strain that possesses a carbapenem[illegible] tamase has occurred in regional hospt[illegible] isolates are resistant to virtually all o[illegible] tibiotics, control of their spread is cru[illegible] tomated systems used for susceptibil[illegible] accurately identify all these isolates, w[illegible] hamper control efforts.

Arch Intern Med. 2005;165:1430-1435

K. pneumoniae KPC+: 33%: ST-type 258

Journal of Antimicrobial Chemotherapy (2007) **60**, 78–82
doi:10.1093/jac/dkm129
Advance Access publication 9 May 2007

JAC

Evolution of antimicrobial resistance among *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae* in Brooklyn, NY

David Landman[1], Simona Bratu[1], Sandeep Kochar[1], Monica Panwar[1], Manoj Trehan[1], Mehmet Doymaz[2] and John Quale[1]*

[1]*State University of New York – Downstate, Brooklyn, NY, USA;* [2]*Beth Israel Medical Center, New York, NY, USA*

Received 16 February 2007; returned 22 March 2007; revised 2 April 2007; accepted 5 April 2007

Objectives: To document resistance patterns of three important nosocomial pathogens, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae*, present in hospitals in Brooklyn, NY.

Methods: Susceptibility profiles of pathogens gathered during a surveillance study in 2006 were analysed and compared with similar surveys performed in 1999 and 2001. MICs were determined according to CLSI standards, and selected isolates were screened by PCR for the presence of VIM, IMP and KPC β-lactamases.

Results: For *P. aeruginosa*, susceptibility to most antimicrobials fell in 2001 and then reached a plateau. However, there was a progressive decrease in the number of patients with *P. aeruginosa* during the three surveys. While the total number of isolates of *A. baumannii* remained steady, there was a progressive decrease in susceptibility to most classes of antimicrobial agents, and approximately one-third had combined resistance to carbapenems, fluoroquinolones and aminoglycosides. There was a noticeable rise in the number of isolates of *K. pneumoniae* over the surveillance periods, suggesting that this has become the predominant pathogen in many medical centres. Over one-third of *K. pneumoniae* collected in 2006 carried the carbapenemase KPC, and 22% were resistant to all three classes of antimicrobial agents.

Conclusions: Hospitals in our region have been beset with antimicrobial-resistant Gram-negative bacteria. *K. pneumoniae* has rapidly emerged as the most common multidrug-resistant pathogen. Improved therapeutic agents and methods of detection are needed to reduce transmission of these bacteria.

ORIGINAL INVESTIGATION

Rapid Spread of Carbapenem-R… *Klebsiella pneumoniae* in New Y…

A New Threat to Our Antibiotic Armamentarium

Simor… …man, MD; Robin Haag, RN; Rose Recco, MD; Anton… …Alam, MD; John Quale, MD

Arch Intern Med. 2005;165:1430-1…

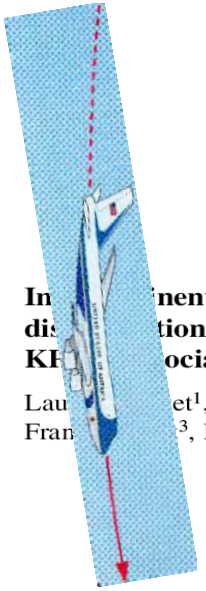
E. Cloacae KPC-4 (Ecosse)

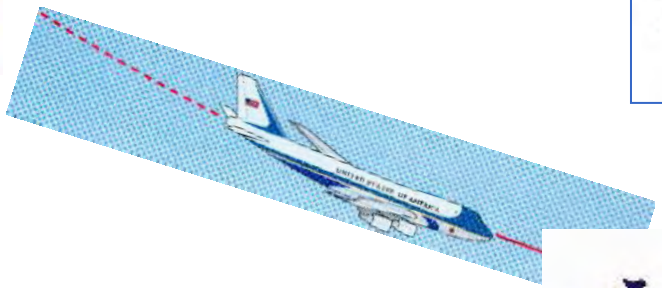
Plasmid-Mediated Imipenem-Hydrolyzing Enzyme KPC-2 among Multiple Carbapenem-Resistant *Escherichia coli* Clones in Israel

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

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





In… …nental travels of patients and dis… …tion of plasmid-mediated carbape… KP… …ociated with OXA-9 and TEM-1

Lau… …et[1], Irina Radu[1], Valérie Gautier[2], Fran… …[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

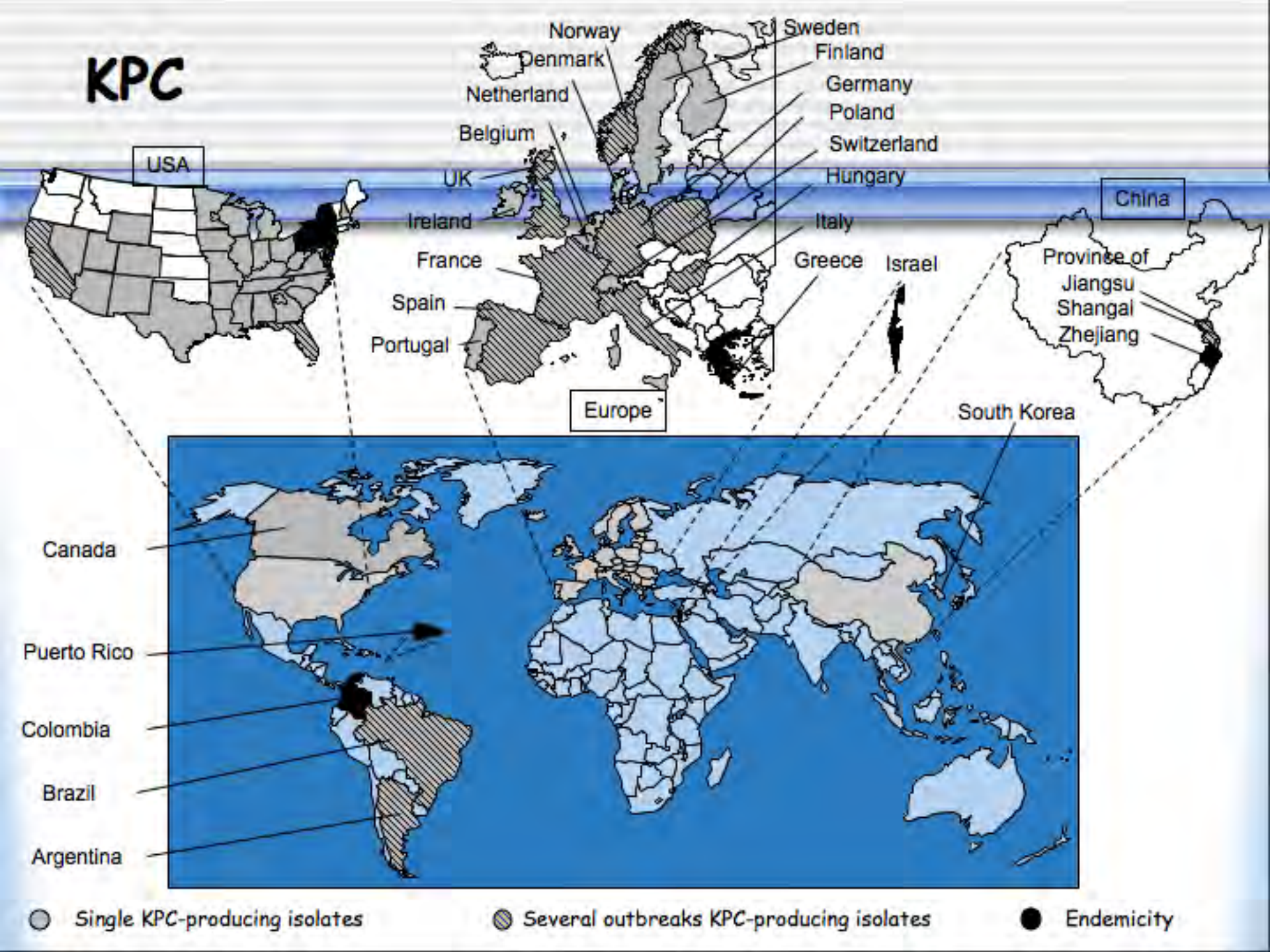
Naas, Nordmann, Vedel, Poyart AAC 2005, 49 ; 4423-4

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

Cuzon, Naas, Demachy, Nordmann (AAC 2007)

K. pneumoniae KPC-2

KPC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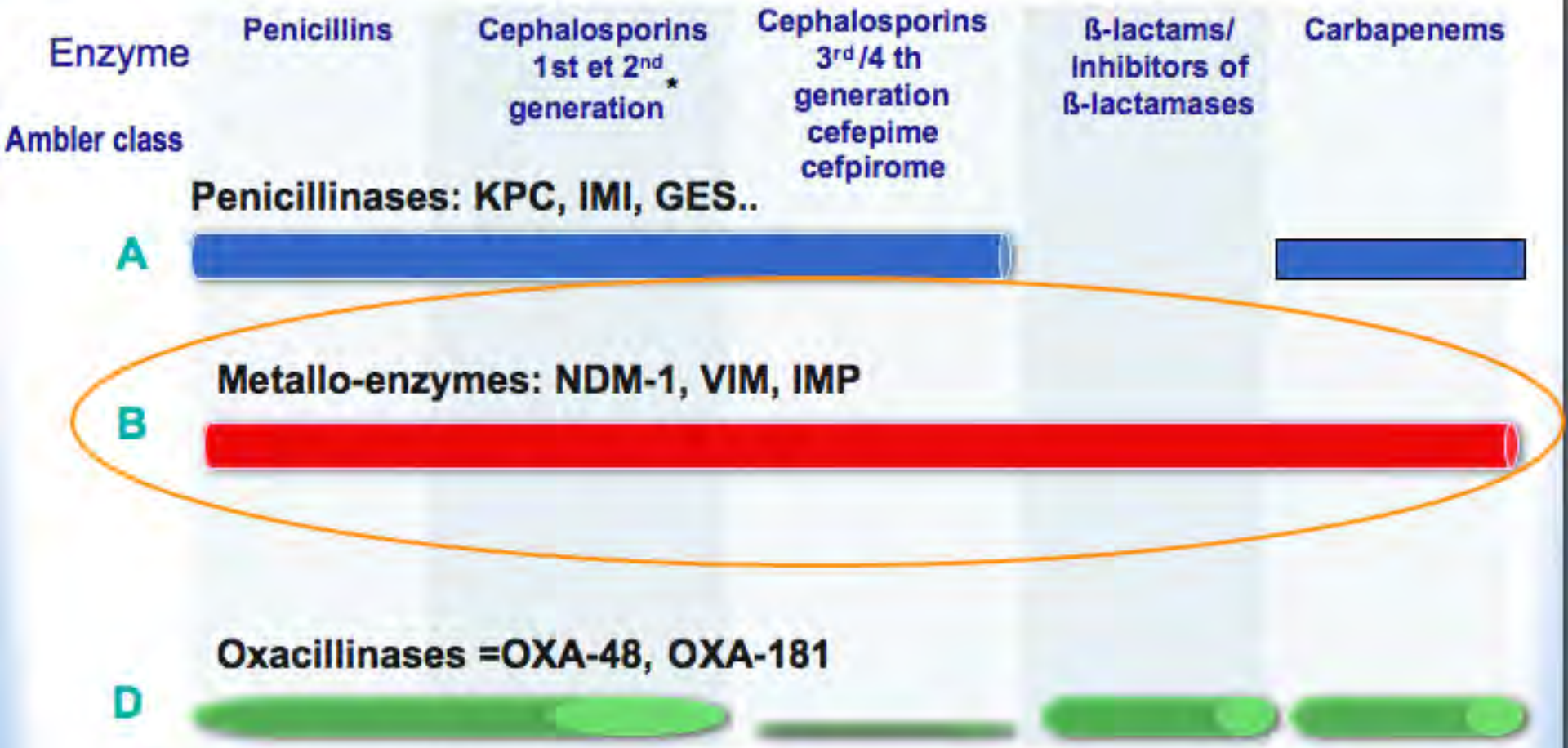
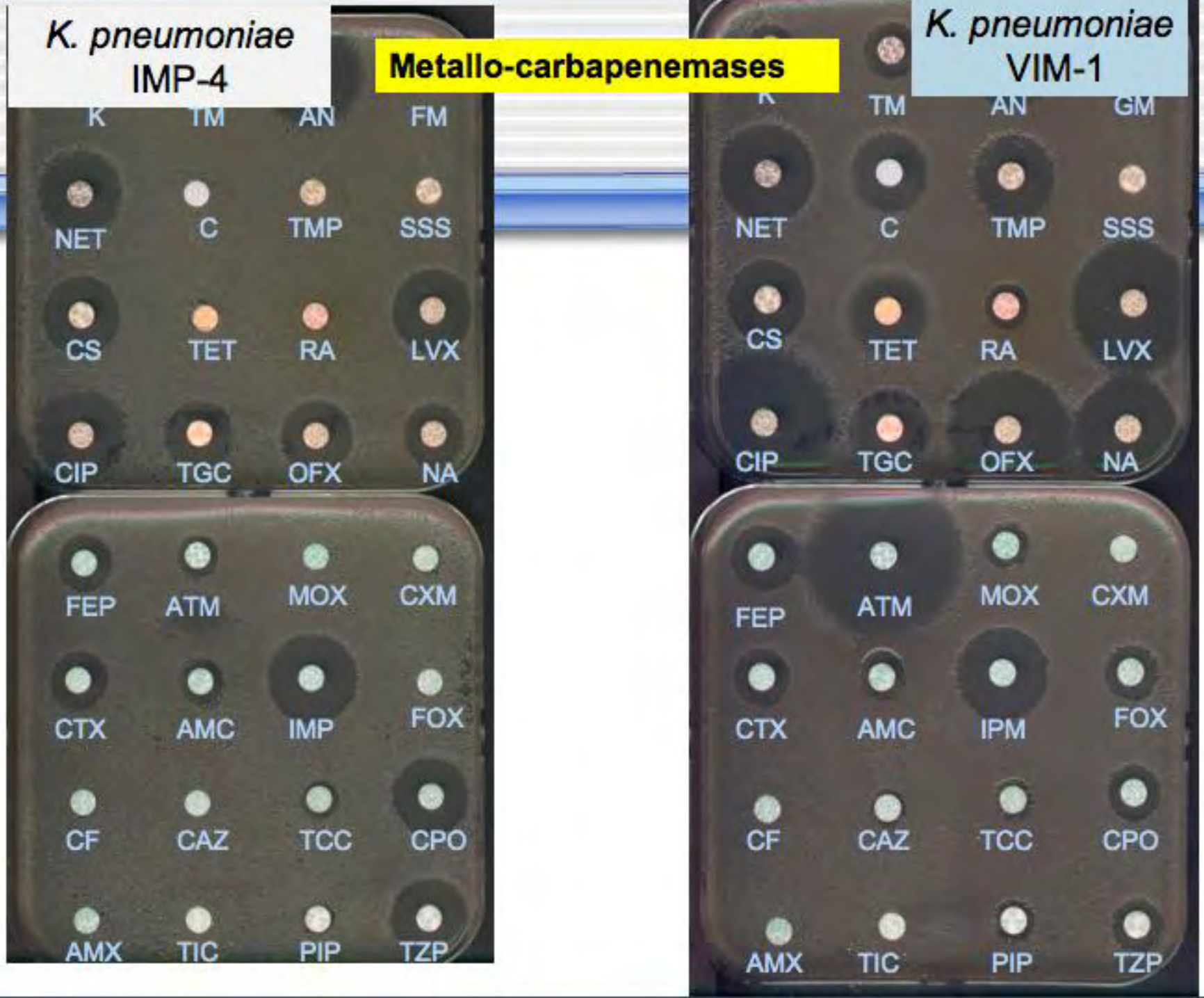
Portugal
Europe
China
Province of
Jiangsu
Shangai
Zhejiang
South Korea
Canada
Puerto Rico
Colombia
Brazil
Argentina
Single KPC-producing isolates
Several outbreaks KPC-producing isolates
Endemicity

The carbapenemases in *Enterobacteriaceae*



* Cephamycins excluded for most class As


K. pneumoniae
IMP-4
Metallo-carbapenemases
K. pneumoniae
VIM-1
K
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FM
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C
TMP
SSS
CS
TET
RA
LVX
CIP
TGC
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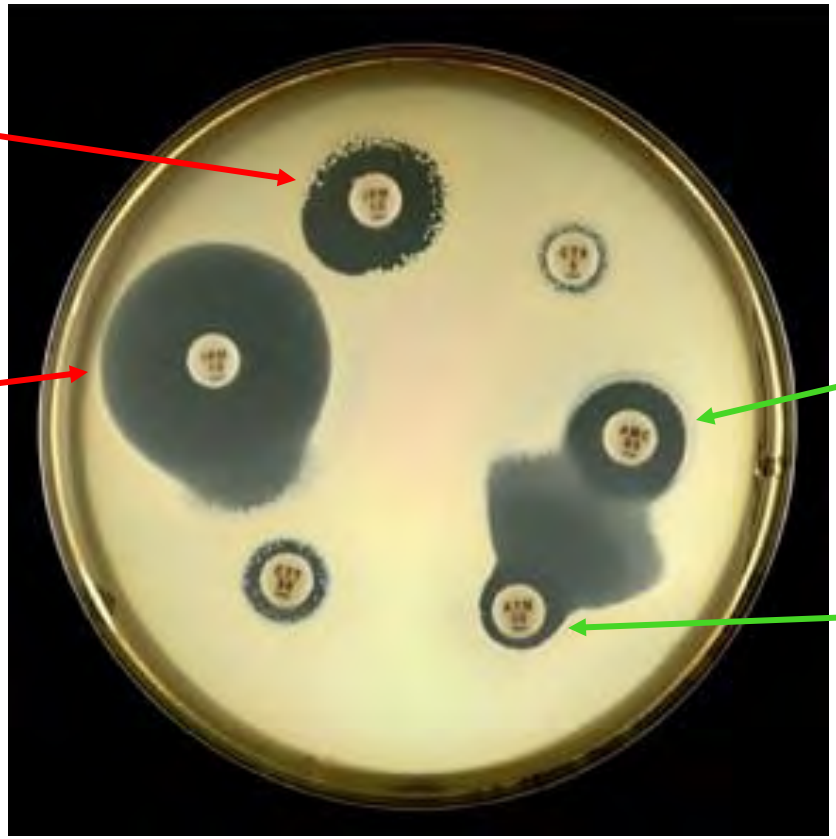
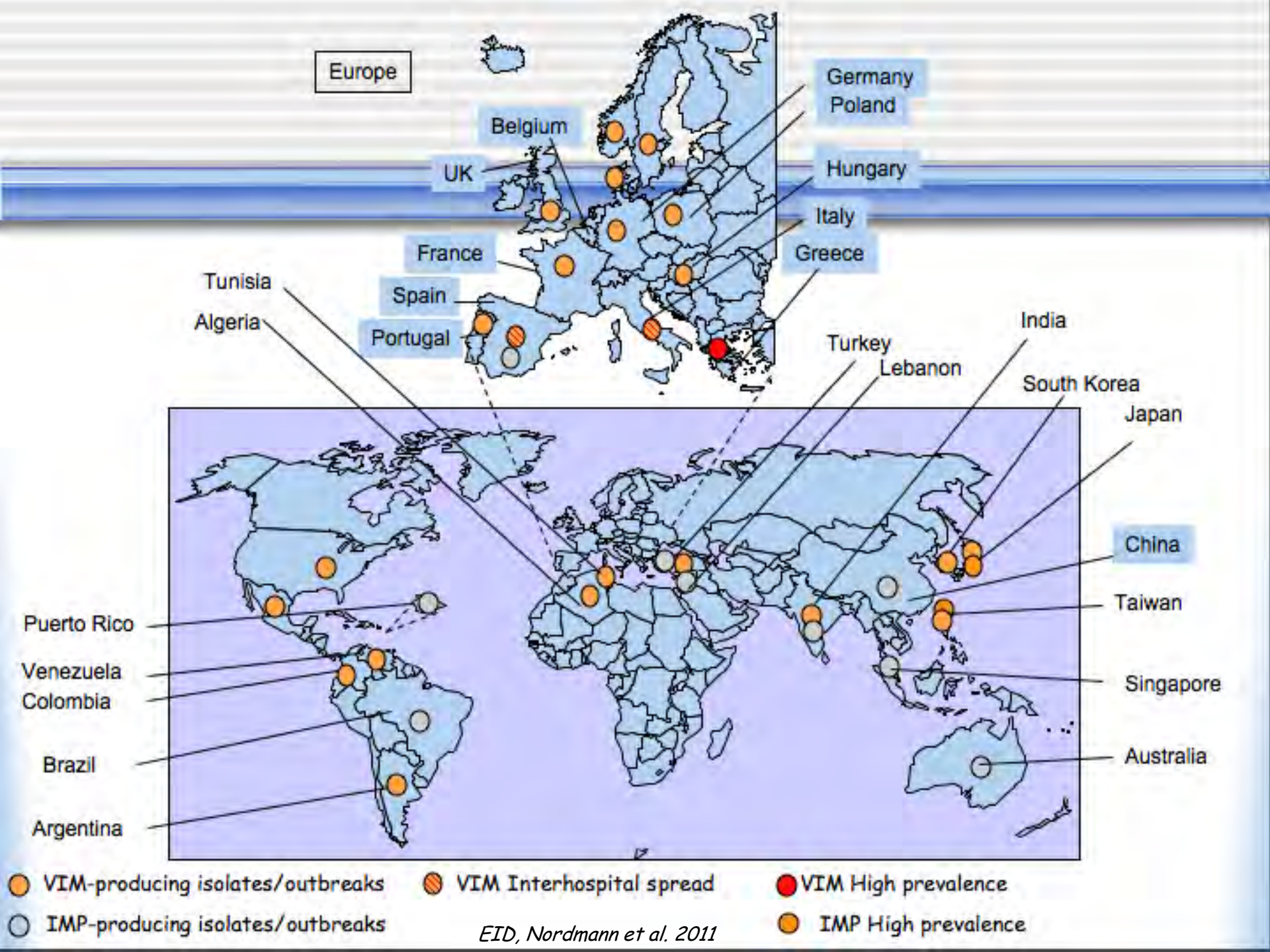
Combined Mechanisms of Resistance



ESBL (SHV-12) and metallo-ß-lactamase (IMP-4) Poirel et al., Pathology, 2004, 36, 366-8



EID, Nordmann et al. 2011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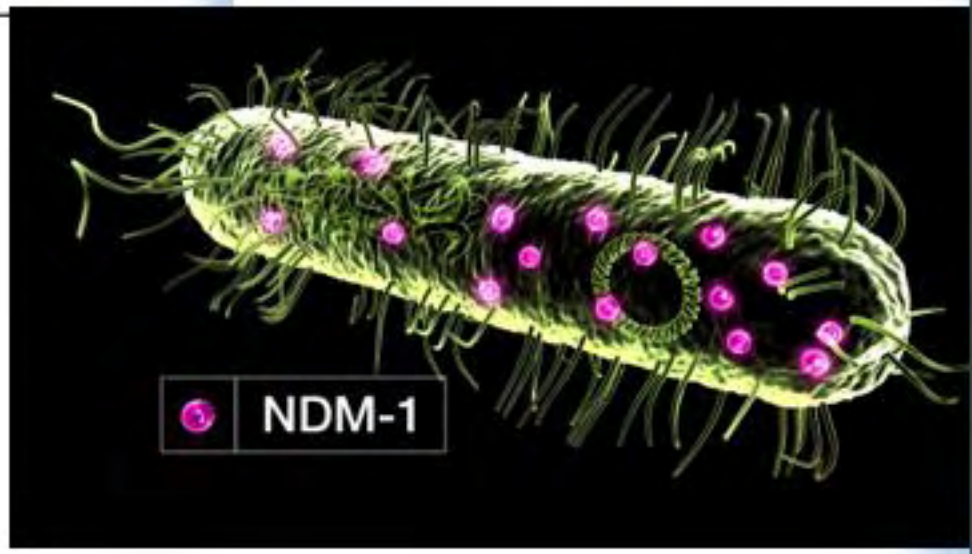

NDM-1

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]

Spread of NDM-1 from India/Pakistan to the UK

bla$_{NDM-1}$-positive bacterial clones?

MDR plasmids?

Courtesy N. Woodford

Multidrug resistance patterns of NDM-1 producers

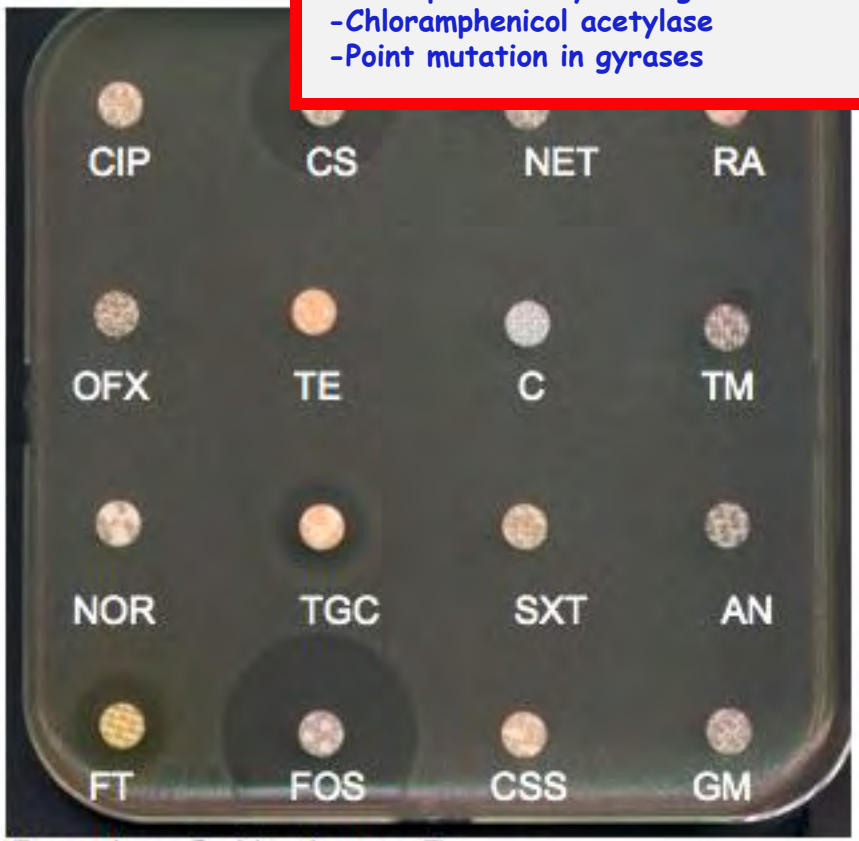
	UK (n=37)		Chennai (n=44)		Haryana (n=26)	
	MIC_{50}; MIC_{90} (mg/L)	Proportion susceptible*	MIC_{50}; MIC_{90} (mg/L)	Proportion susceptible*	MIC_{50}; MIC_{90} (mg/L)	Proportion susceptible*
Imipenem	32; 128	0%	64; 128	0%	32; 128	0%
Meropenem	32; 32	3%	32; >32	3%	>32; >32	3%
Piperacillin-tazobactam	>64; >64	0%	>64; >64	0%	>64; >64	0%
Cefotaxime	>256; >256	0%	>256; >256	0%	>256; >256	0%
Ceftazidime	>256; >256	0%	>256; >256	0%	>256; >256	0%
Cefpirome	>64; >64	0%	>64; >64	0%	>64; >64	0%
Aztreonam	>64; >64	11%	>64; >64	0%	>64; >64	8%
Ciprofloxacin	>8; >8	8%	>8; >8	8%	>8; >8	8%
Gentamicin	>32; >32	3%	>32; >32	3%	>32; >32	3%
Tobramycin	>32; >32	0%	>32; >32	0%	>32; >32	0%
Amikacin	>64; >64	0%	>64; >64	0%	>64; >64	0%
Minocycline	16; >32	0%	32; >32	0%	8; 16	0%
Tigecycline	1; 4	64%	4; 8	56%	1; 2	67%
Colistin	0·5; 8	89%†	1; 32	94%†	1; 2	100%†

MIC=minimum inhibitory concentration. *Susceptibility defined by British Society for Antimicrobial Chemotherapy and European Committee on Antimicrobial Susceptibility Testing breakpoints; doxycycline breakpoints were used for minocycline. †Colistin-resistant UK isolates were one isolate of *Morganella morganii* and one *Providencia* sp (both intrinsically-resistant species), also one *Klebsiella pneumoniae* and one *Enterobacter* sp.

Table: Antibiotic susceptibilities for NDM-1-positive Enterobacteriaceae isolated in the UK and north (Chennai) and south India (Haryana)

C. freundii NDM-1, France

Resistance genes including
-9 ß-lactamase genes including -3 carbapenemase gene and 1 ESBL gene
-16S RNA methylase gene
-Rifampicin ribosylation gene
-Chloramphenicol acetylase
-Point mutation in gyrases



Poirel L, Ros L, Carricajo A, Berthelot P, Pozetto B, , Bernabeu S,,Nordmann P
Extremely drug-resistant C. freundii in a patient returning from India and producing NDM-1 and other Carbapenemases. Antimicrob. Agents Chemother, 2010,

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

Summary

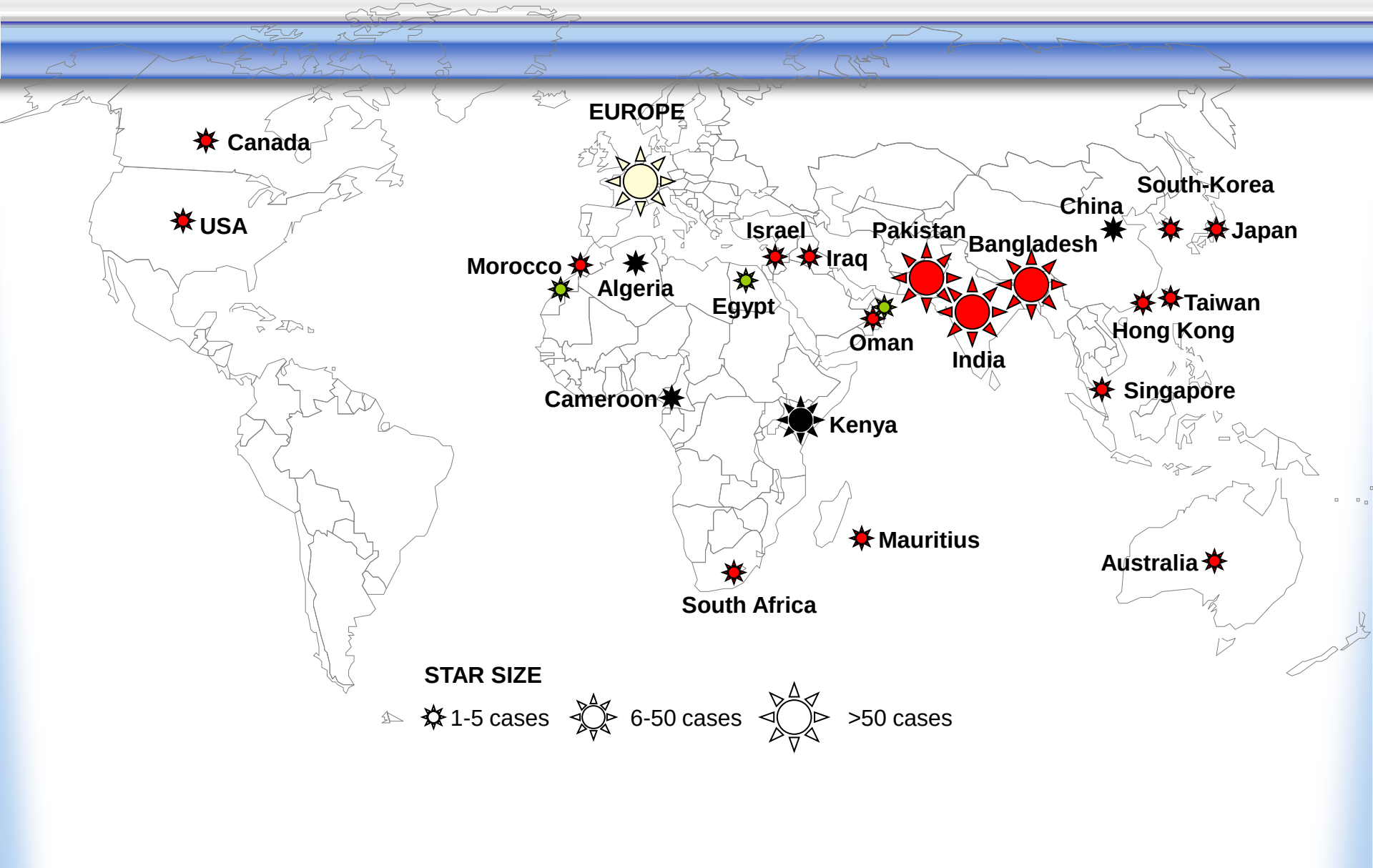
Background Not all patients infected with NDM-1-positive bacteria have a history of hospital admission in India, and extended-spectrum β-lactamases are known to be circulating in the Indian community. We therefore measured the prevalence of the NDM-1 gene in drinking water and seepage samples in New Delhi.

Methods Swabs absorbing about 100 µL of seepage water (ie, water pools in streets or rivulets) and 15 mL samples of public tap water were collected from sites within a 12 km radius of central New Delhi, with each site photographed and documented. Samples were transported to the UK and tested for the presence of the NDM-1 gene, bla_{NDM-1}, by PCR and DNA probing. As a control group, 100 µL sewage effluent samples were taken from the Cardiff Wastewater Treatment Works, Tremorfa, Wales. Bacteria from all samples were recovered and examined for bla_{NDM-1} by PCR and sequencing. We identified NDM-1-positive isolates, undertook susceptibility testing, and, where appropriate, typed the isolates. We undertook Inc typing on bla_{NDM-1}-positive plasmids. Transconjugants were created to assess plasmid transfer frequency and its relation to temperature.

Findings From Sept 26 to Oct 10, 2010, 171 seepage samples and 50 tap water samples from New Delhi and 70 sewage effluent samples from Cardiff Wastewater Treatment Works were collected. We detected bla_{NDM-1} in two of 50 drinking-water samples and 51 of 171 seepage samples from New Delhi; the gene was not found in any sample from Cardiff. Bacteria with bla_{NDM-1} were grown from 12 of 171 seepage samples and two of 50 water samples, and included 11 species in which NDM-1 has not previously been reported, including *Shigella boydii* and *Vibrio cholerae*. Carriage by enterobacteria, aeromonads, and *V cholera* was stable, generally transmissible, and associated with resistance patterns typical for NDM-1; carriage by non-fermenters was unstable in many cases and not associated with typical resistance. 20 strains of bacteria were found in the samples, 12 of which carried bla_{NDM-1} on plasmids, which ranged in size from 140 to 400 kb. Isolates of *Aeromonas caviae* and *V cholerae* carried bla_{NDM-1} on chromosomes. Conjugative transfer was more common at 30°C than at 25°C or 37°C.

Interpretation The presence of NDM-1 β-lactamase-producing bacteria in environmental samples in New Delhi has important implications for people living in the city who are reliant on public water and sanitation facilities. International surveillance of resistance, incorporating environmental sampling as well as examination of clinical isolates, needs to be established as a priority.

NDM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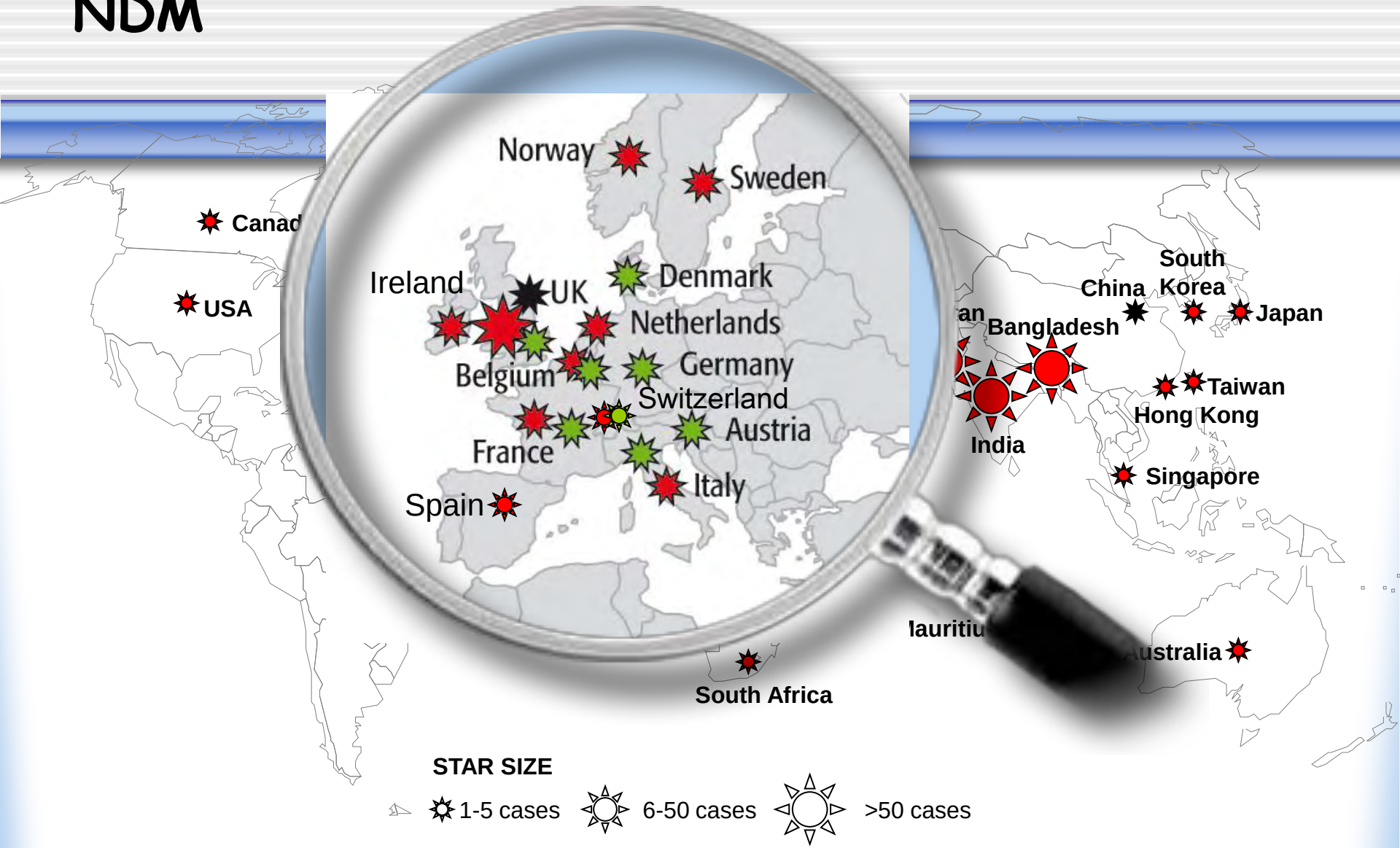
STAR SIZE
1-5 cases
6-50 cases
>50 cases

NDM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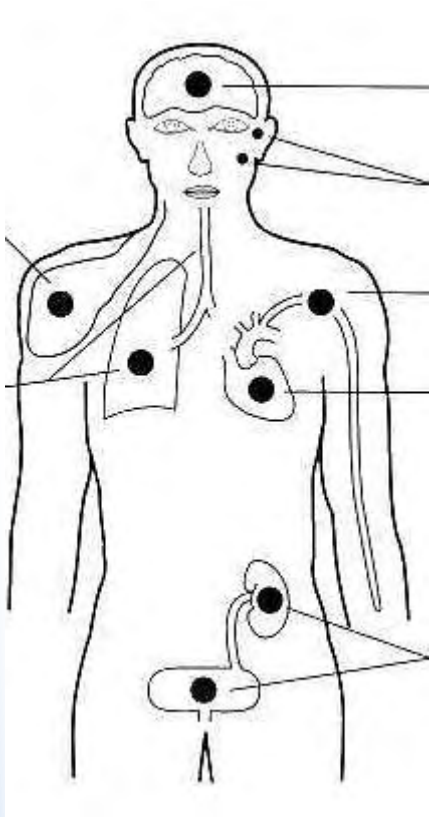
South Korea
Japan
Bangladesh
Taiwan
Hong Kong
India
Singapore
Australia
STAR SIZE
1-5 cases
6-50 cases
>50 cases

Infections with NDM producers

***E. coli, Klebsiella**, Enterobacter, Serratia, Citrobacter, Pseudomonas, Acinetobacter*



Asymptomatic colonisation

Wound infection / Diabetic foot

Lower urinary tract infection

Upper urinary tract infection

Nosocomial pneumonia / VAP

Intra-abdominal / pelvic infection

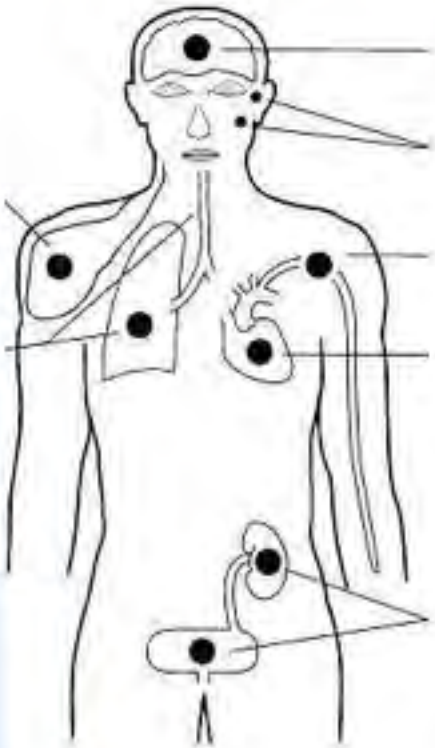
Bacteraemia / septicaemia

Neurosurgical meningitis

SEVERITY

Infections with NDM producers

E. coli, Klebsiella, *Enterobacter, Serratia, Citrobacter, Pseudomonas, Acinetobacter*



Asymptomatic colonisation

Wound infection / Diabetic foot

Lower urinary tract infection

Upper urinary tract infection

Nosocomial pneumonia / VAP

Intra-abdominal / pelvic infection

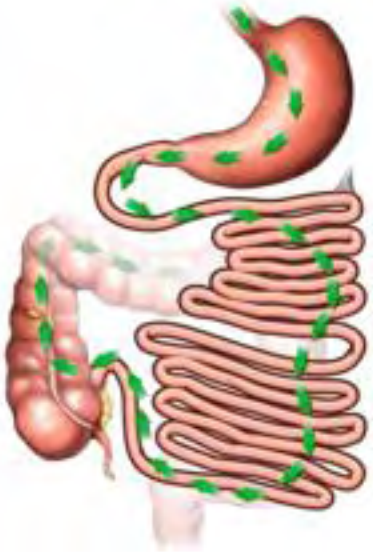
Bacteraemia / septicaemia

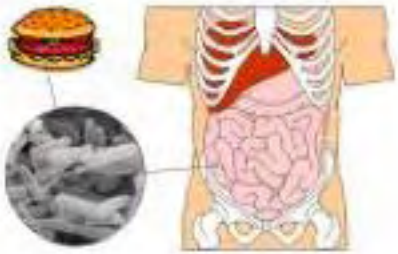
Neurosurgical meningitis

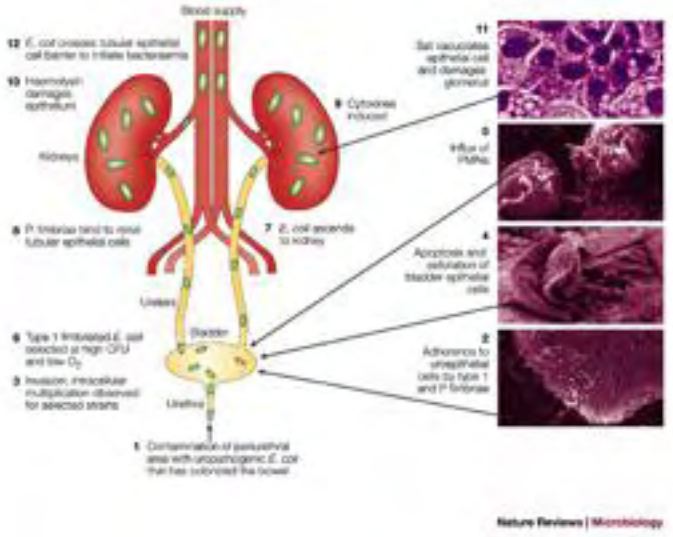
- No difference between NDM and non-NDM producers
- No known virulence factors for NDM producers
- NDM producers will not respond to conventional antibiotics !!!!

Escherichia coli

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







A successful story

Hygiena

Diarrhea

Population; overcrowded

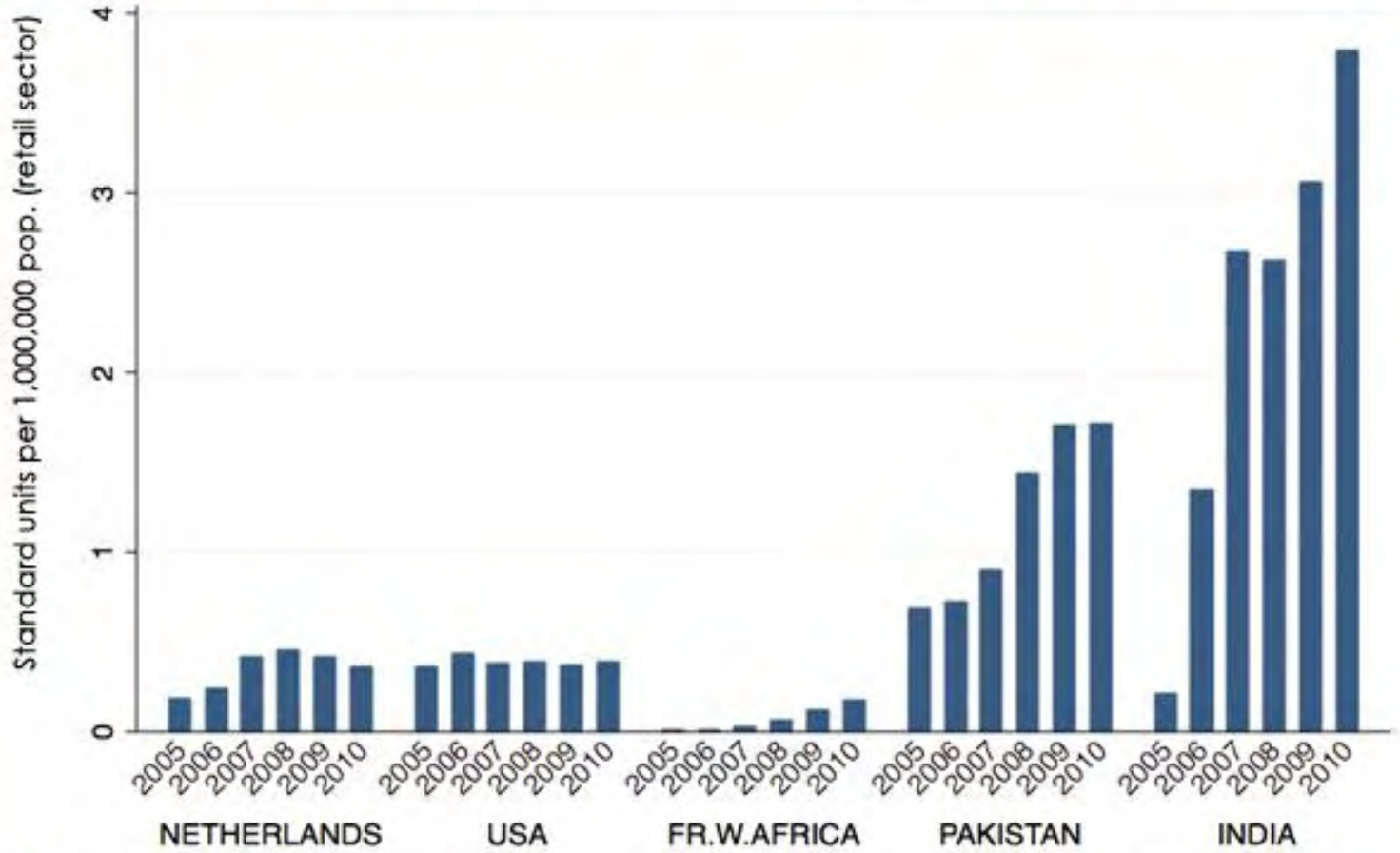
Antibiotics; misuse and overuse, over-the-counter sale

Spread of NDM-1 producers in *E. coli*, *K. pneumoniae*...

Subtropical continent

...and then higher mortality rate and length of hospitalization, overuse of broad-spectrum of antibiotics....

Retail sales of carbapenem antibiotics to treat Gram-negative bacteria are increasing rapidly in India and Pakistan



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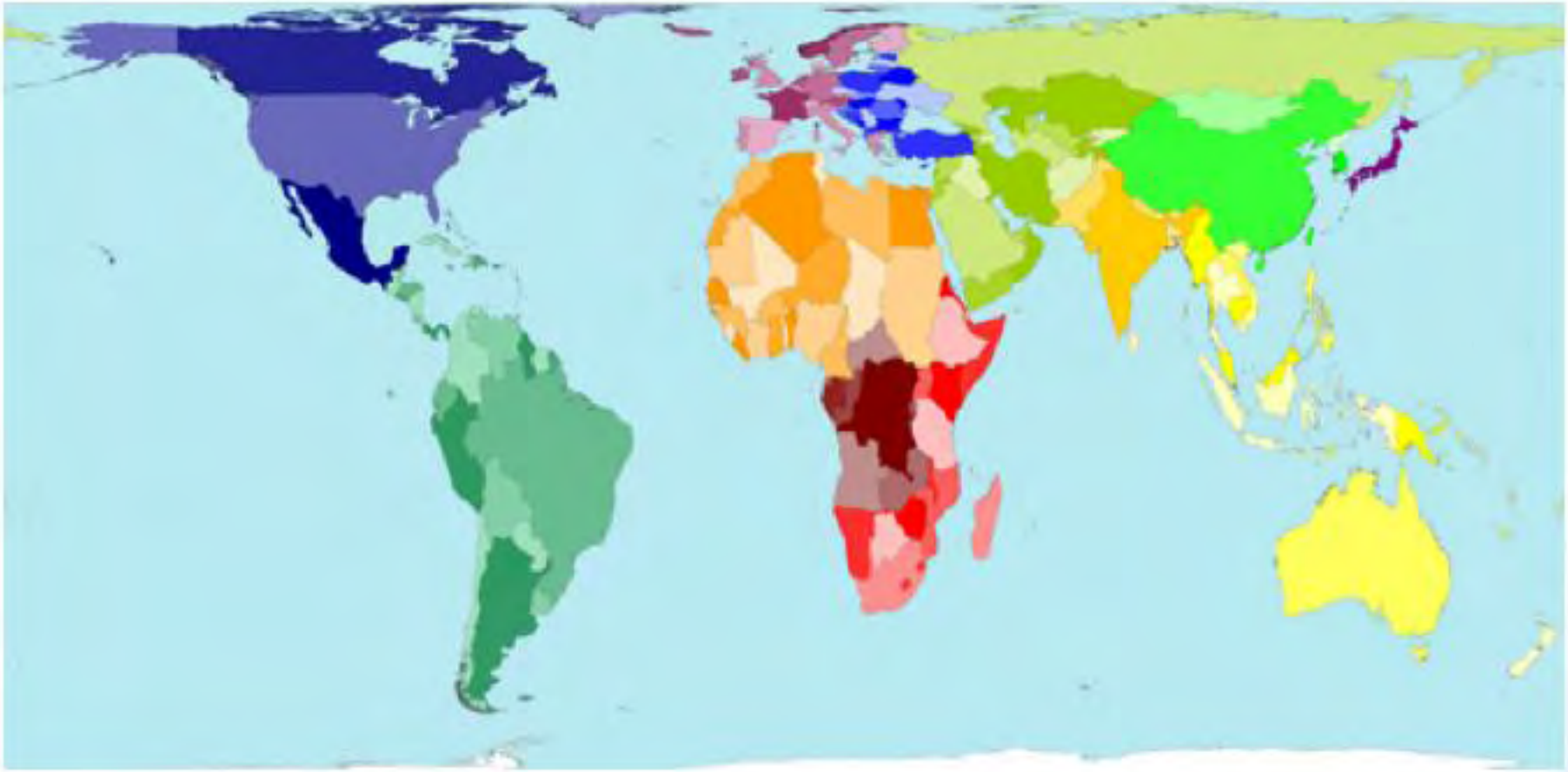
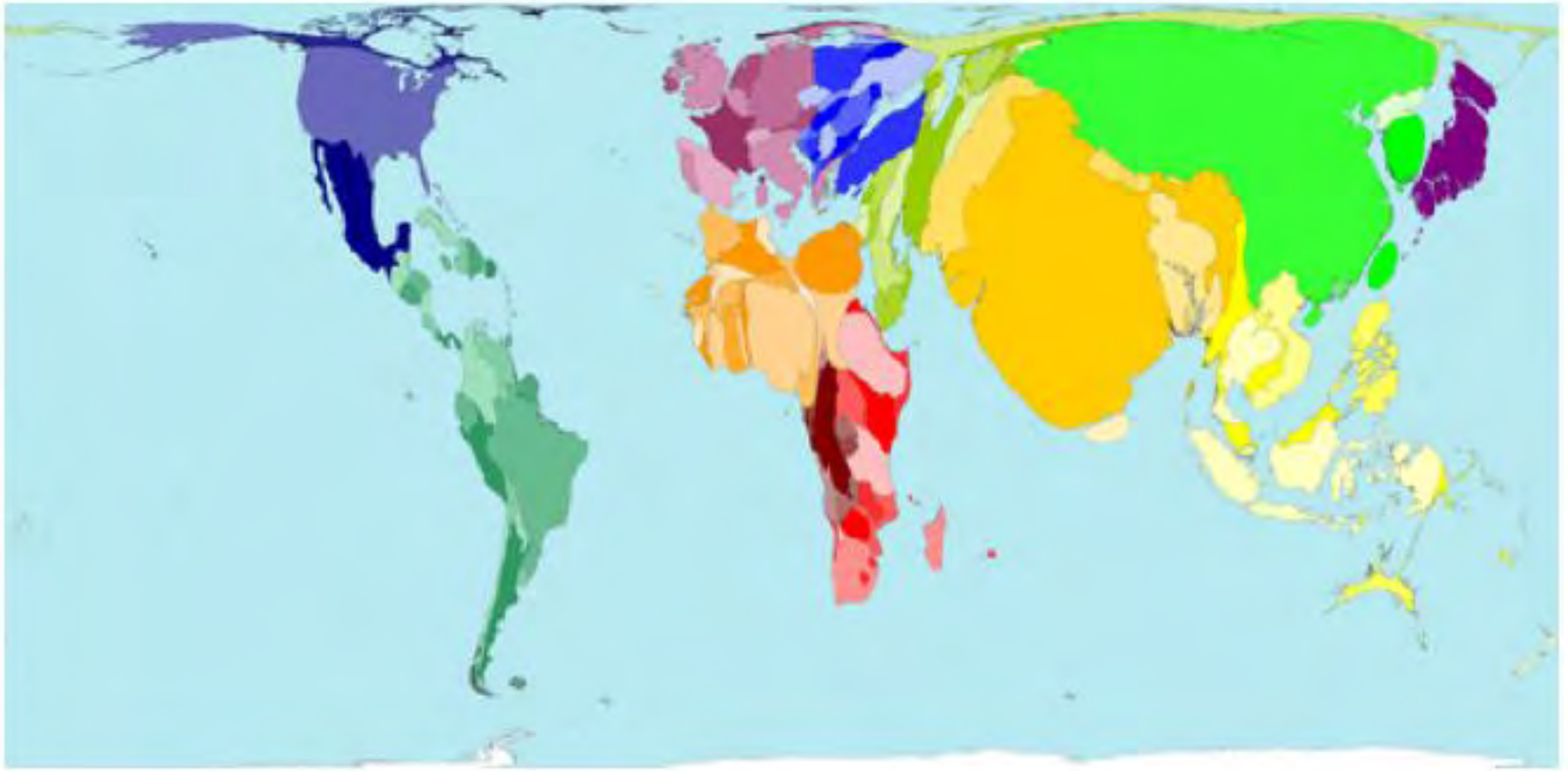
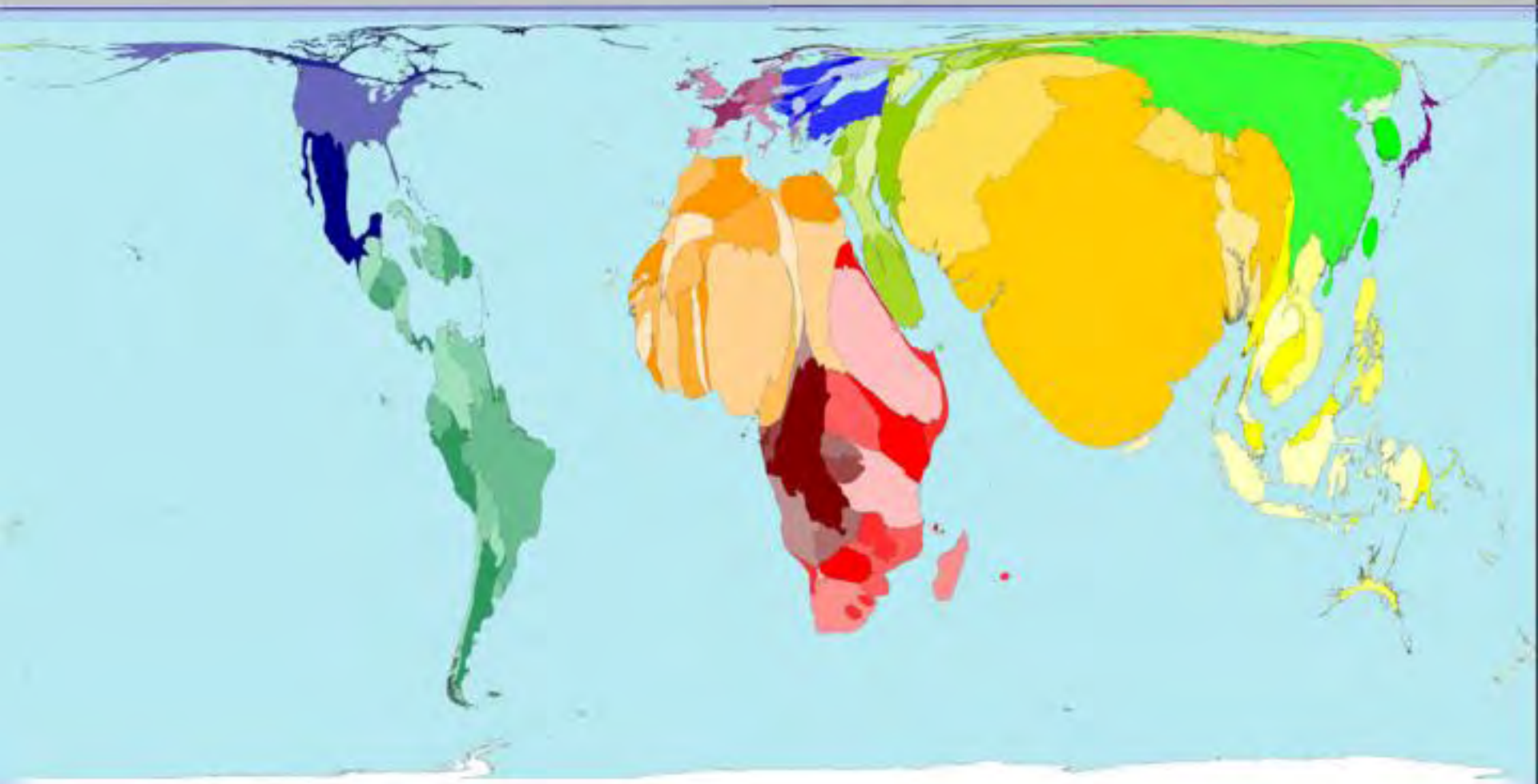
World map according to land size



World map according to population size



World map according to diarrhea



Children deaths below 10 years old

Journal of Antimicrobial Chemotherapy Advance Access published July 25, 2011

J Antimicrob Chemother
doi:10.1093/jac/dkr299

Journal of Antimicrobial Chemotherapy

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

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Objectives: To determine the prevalence and antimicrobial susceptibility of carbapenemase-producing Enterobacteriaceae among hospitalized patients and outpatients attending two military hospitals in Rawalpindi, Pakistan, and to compare the performance of two chromogenic culture media for the isolation of these organisms.

Methods: Stool samples from 200 distinct patients were cultured on MacConkey agar and subsequently on two chromogenic media—Colorex KPC and a prototype chromogenic medium, ID Carba—designed for the isolation of carbapenemase-producing Enterobacteriaceae. All Gram-negative isolates growing on either chromogenic medium were investigated for carbapenemases by phenotypic and molecular methods. Producers were subjected to susceptibility testing with 40 antimicrobials by VITEK 2 or agar dilution.

Results: In total, 64 NDM-1-positive isolates of Enterobacteriaceae, belonging to seven distinct species, were recovered from 37 (18.5%) of the stool samples. No other carbapenemase types were confirmed. Nineteen positive samples were identified among 70 from inpatients (prevalence 27.1%), and there were 18 positive samples among 130 from outpatients (prevalence 13.8%). Fifty-six isolates (87.5%) harbouring the NDM-1 enzyme were recovered on ID Carba compared with 41 isolates (64.1%) on Colorex KPC ($P = 0.012$). Multidrug resistance was prevalent, but no pan-resistant isolates were found, with most isolates susceptible *in vitro* to colistin (97%), mecillinam (95%), fosfomycin (94%), tigecycline (89%) and nitrofurantoin (78%).

Conclusions: This study shows a high prevalence of multidrug-resistant Enterobacteriaceae with the NDM-1 enzyme in Rawalpindi. The new chromogenic medium, ID Carba, was more sensitive than Colorex KPC and has potential as a screening medium for isolation of Enterobacteriaceae harbouring the NDM-1 enzyme.

Keywords: β-lactamases, antimicrobial resistance mechanisms, *Escherichia coli*

J Antimicrob Chemother
doi:10.1093/jac/dkr580

No NDM-1 carriage in healthy persons from Mumbai: reassuring for now

Payal Deshpande, Viral Vadwai, Anjali Shetty, Reeta Dalal, Rajeev Soman and Camilla Rodrigues*

P. D. Hinduja National Hospital and Medical Research Centre, Mahim, Mumbai, India

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E-mail: dr_crodrigues@hindujahospital.com

Keywords: ESBLs, carbapenems, ertapenem

E. coli NDM-1: community-acquired ! in India

3 Institut Scientifique de la Santé Publique. Guidelines for control of infections in case of cross-border transfer of patients hospitalized in countries with high endemicity of carbapenemase-producing Enterobacteriaceae. Surveillance de germes multi-résistants dans les hôpitaux belges. Sept 21, 2010. http://www.nsih.be/download/MDR/NewDelhi_fiche_alert_VS_FR.pdf (in French) (accessed Nov 8, 2010).

The plasmid-mediated bla_{NDM-1} gene that encodes a powerful carbapenemase was first identified in *Escherichia coli* and in *Klebsiella pneumoniae* in Sweden from a patient who was transferred from India.[1] It was then identified from many patients in the UK, India, and Pakistan in different enterobacterial species.[2] Here we report a woman aged 60 years who was admitted to hospital in April, 2009, for treatment of a breast cancer.

The patient came from Darjeeling, India, where she had lived for several years and had never been hospitalised. Upon her admission in France, bacterial cultures from the surface of her breast tumour were grown. The cultures were of the *E coli* isolate GUE that was resistant to most β-lactams (remaining susceptible to aztreonam) and that had reduced susceptibility to carbapenems (minimum inhibitory concentrations of imipenem 3 µg/mL, ertapenem 3 µg/mL, and meropenem 2 µg/mL).[3] This isolate was also resistant to gentamicin, kanamycin, tobramycin, sulfonamides, tetracycline, and fluoroquinolones, but remained susceptible to amikacin, chloramphenicol, rifampicin, and colistin. PCR and sequencing revealed that *E coli* GUE harboured the bla_{NDM-1} gene. Mating-out assays[4] allowed the bla_{NDM-1} gene to be identified on a 110 kb plasmid, with markers for kanamycin, gentamicin, tobramycin, trimethoprim, and sulfonamide resistance. Multilocus sequence typing[5] identified *E coli* GUE as an ST131-type strain, which corresponds to a genetic background that is also responsible for the worldwide diffusion of another common resistance determinant, CTX-M-15.

This case is the first identification of an NDM-1-producing *E coli* isolate in France, and corresponds again to an imported case from India. This example confirms the recent data suggesting that the Indian subcontinent might represent an important reservoir, and therefore a source, of NDM-producing isolates. The patient had not been hospitalised in India; therefore, the multidrug-resistant isolate had likely been community acquired. Worringly, this resistance gene has been identified here in an *E coli* strain belonging to a genotype that has proved its ability to disseminate widely in the community.

We declare that we have no conflicts of interest. This study was mostly funded by the INSERM (U914), France, and by grants from the Ministère de l'Education Nationale et de la Recherche (UPRES-EA3539), Université Paris XI, France, and from the European Community (TEMPOtest-QC, HEALTH-2009-241742).

*Laurent Poirel, Cécile Hombrouck-Alet, Claire Freneaux, Sandrine Bernabeu, *Patrice Nordmann*
nordmann.patrice@bct.aphp.fr
Hôpital de Bicêtre, Department of Bacteriology-Virology, Le Kremlin Bicêtre, Paris 94275, France

1 Yong D, Toleman MA, Giske CG, et al. 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. *Antimicrob Agents Chemother* 2009; 53: 5046–54.
2 Kumarasamy KK, Toleman MA, Walsh TR, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *Lancet Infect Dis* 2010; 10: 597–602.
3 Clinical and Laboratory Standards Institute. 2010. Performance standards for antimicrobial susceptibility testing; twentieth informational supplement. Jan, 2010. http://www.clsi.org/source/orders/free/m100-s20.pdf (accessed Nov 6, 2010).
4 Rodriguez-Martinez JM, Nordmann P, Fortineau N, Poirel L. VIM-19, a metallo-β-lactamase with increased carbapenemase activity from *Escherichia coli* and *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 2010; 54: 471–76.
5 Tartof SY, Solberg OD, Manges AR, Riley LW. Analysis of a uropathogenic *Escherichia coli* clonal group by multilocus sequence typing. *J Clin Microbiol* 2005; 43: 5860–64.

Clinical Infectious Diseases Advance Access published September 29, 2011

0 MONTH

Correspondence

Emergence of an Autochthonous and Community-Acquired NDM-1–Producing *Klebsiella pneumoniae* in Europe

To the Editor—The recently identified carbapenemase New Dehli metallo-β-lactamase (NDM-1) inactivates all β-lactams except aztreonam [1]. The corresponding gene that is usually plasmid-borne has spread mostly in *Escherichia coli* and *Klebsiella pneumoniae* [1, 2]. NDM-1 producers are multidrug resistant or even resistant to all antibiotics [1, 2]. Whereas contamination with NDM-1 producers is mostly hospital associated, rare cases of community acquisition are known and have been traced to the Indian subcontinent [2].

Here, we report a woman aged 83 years who had cystitis due to a multidrug-resistant *K. pneumoniae* in June 2011. She had a history of multiple and recurrent episodes of urinary tract infections caused by diverse Enterobacteriaceae that were always treated with narrow-spectrum antibiotics. Because the patient's symptoms tended to to disappear spontaneously and rapidly, the latest cystitis episode had not been treated.

K. pneumoniae EDU was resistant to all β-lactams, including carbapenems, as detected with a Vitek-2 automated suscep-

Polymerase chain reaction, sequencing, and plasmid analysis, performed as described elsewhere [5], revealed that *K. pneumoniae* EDU harbored the bla_{NDM-1} carbapenemase gene and the $bla_{CTX-M-15}$ extended-spectrum ß-lactamase gene, which were located on 2 different plasmids (both being approximately 150 kb in size). The isolate coexpressed the CMY-2 cephalosporinase gene, which was located on the bla_{NDM-1} plasmid. In addition, it possessed the *qnrB* gene encoding resistance to quinolones and the bla_{OXA-1} gene encoding a restricted-spectrum oxacillinase, both genes being located on the $bla_{CTX-M-15}$ plasmid. Both plasmids were self-transferable by conjugation, and the bla_{NDM-1} plasmid was found to be of the IncA/C broad-host range type [6]. Multilocus sequence typing [7] results showed that *K. pneumoniae* EDU belonged to the sequence type 1, whereas previously reported NDM-1–positive *K. pneumoniae* isolates were of other sequence types (eg, ST14 and ST147) [6].

Neither this patient nor her husband had traveled to any country in the previous 3 years, including countries with a high prevalence of NDM-1 producers (India, Pakistan, Bangladesh, United Kingdom, Balkan states, and Middle Eastern nations)

of NDM-1 producers outside its main reservoir (Indian subcontinent). The source of contamination remains unknown but may be difficult to find, because persistence of NDM-1 producers in human flora has been evidenced to be >1 year [9].

This present report may indicate the ongoing spread of NDM producers in the community worldwide. A nightmare perspective could be its spread similar to that reported for extended-spectrum β-lactamases of the CTX-M-type, which are now uncontrolled.

Notes

Financial support. This work was supported by INSERM (U914), France, and by grants from the Ministère de l'Education Nationale et de la Recherche (UPRES-EA3539), Université Paris XI, France, and from the European Community (TEMPOtest-QC, HEALTH-2009-241742).

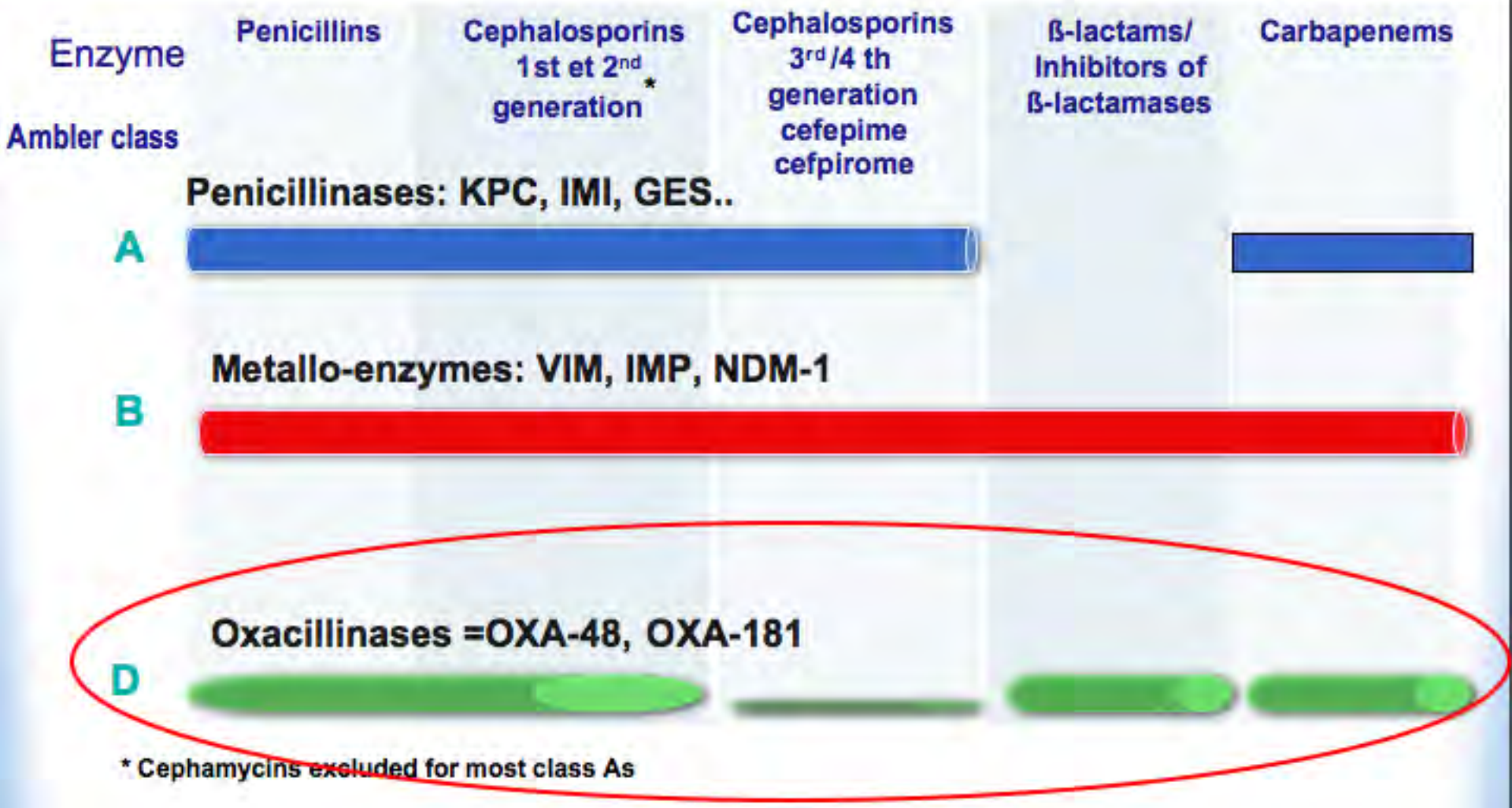
Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Patrice Nordmann,[1] Jean-Pierre Couard,[2] Dominique Sansot,[3] and Laurent Poirel[1]

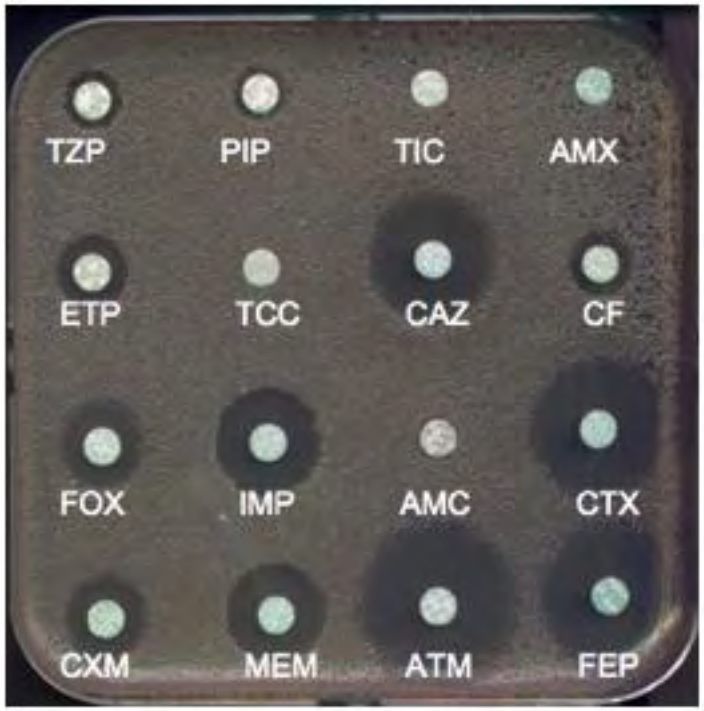
[1]Department of Microbiology, Hôpital de Bicêtre, INSERM U914, Le Kremlin-Bicêtre, [2]Laboratoire Symbiose, Cuers, and [3]Laboratoire de Biologie, Hôpital Font-Pré, Toulon, France

The carbapenemases in *Enterobacteriaceae*



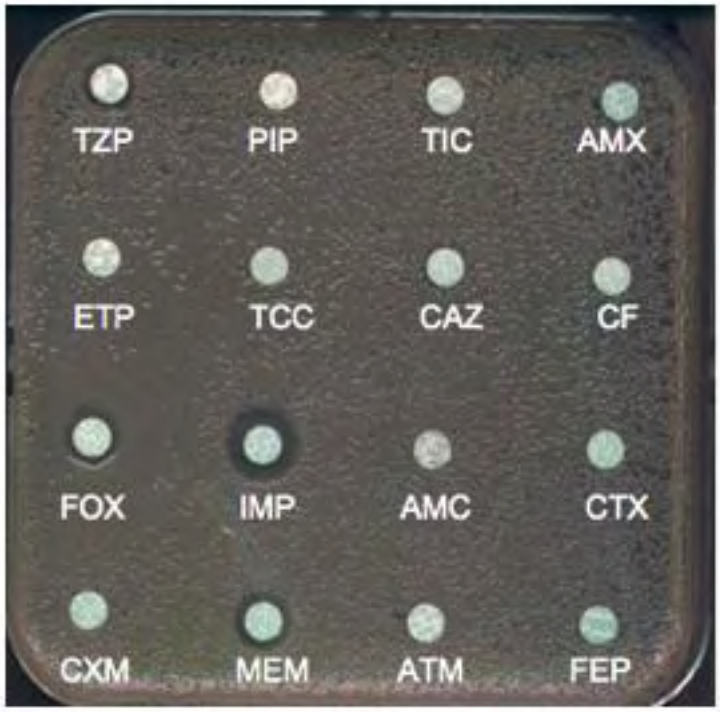
* Cephamycins excluded for most class As

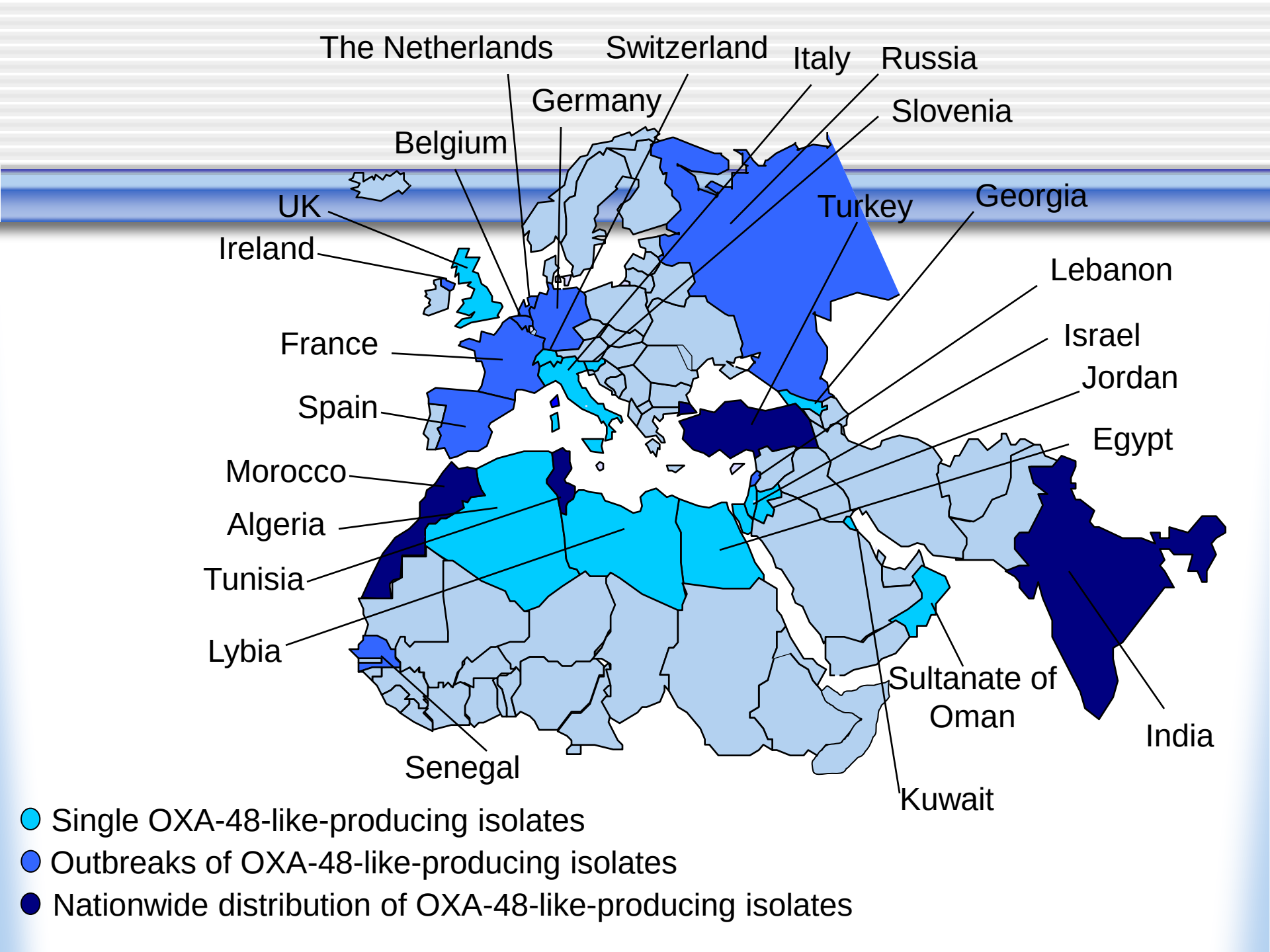
OXA-48



Emergence of oxacillinase-mediated resistance to Imipenem in Klebsiella pneumoniae
Poirel L, Héritier , Nordmann P. Tolün, AAC 2004

OXA-48 + CTX-M-15




The Netherlands
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Slovenia
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UK
Turkey
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Lebanon
France
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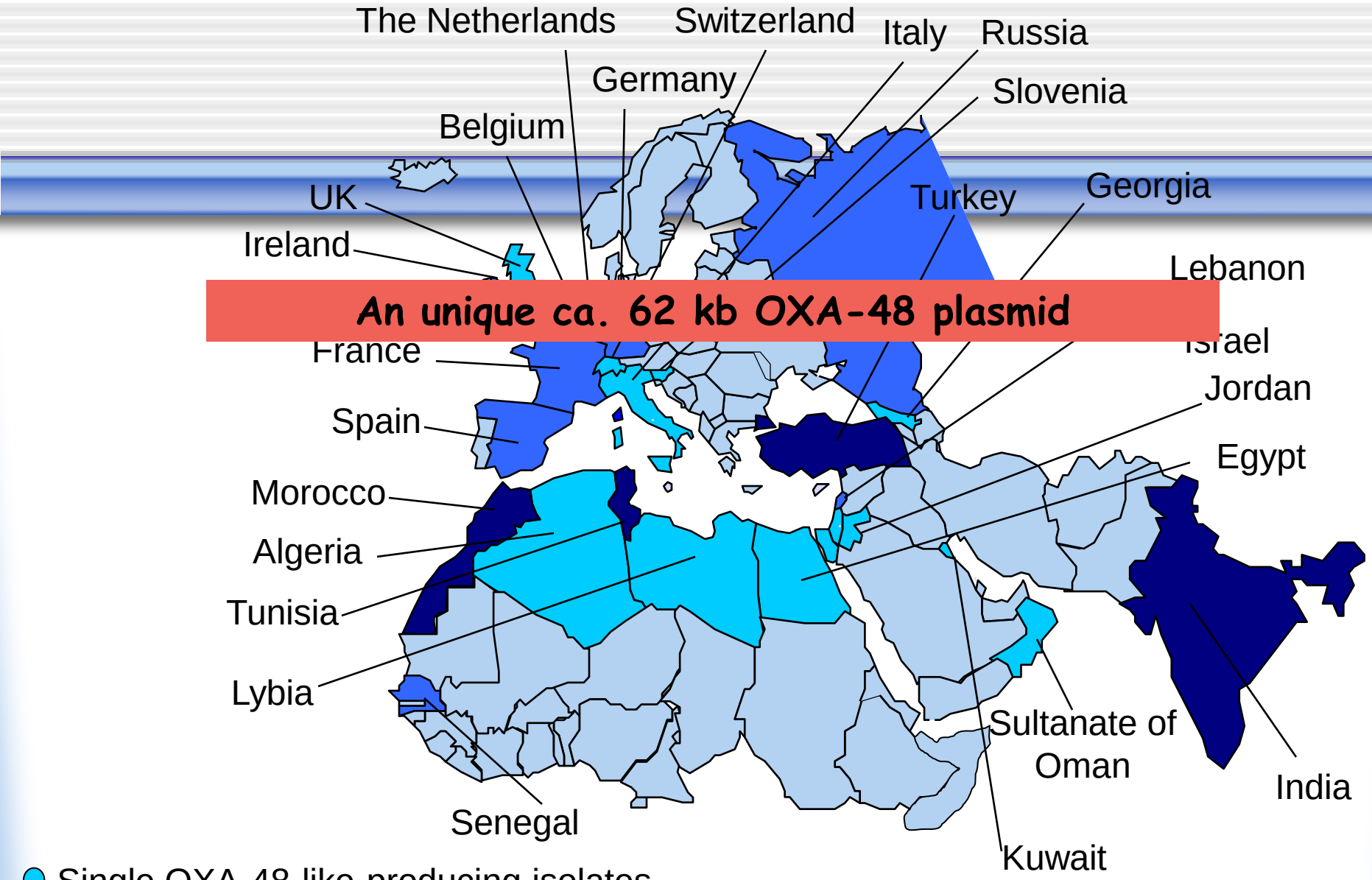
Jordan
Spain
Egypt
Morocco
Algeria
Tunisia
Lybia
Sultanate of Oman
India
Senegal
Kuwait
Single OXA-48-like-producing isolates
Outbreaks of OXA-48-like-producing isolates
Nationwide distribution of OXA-48-like-producing isolates


The Netherlands
Switzerland
Italy
Russia
Germany
Slovenia
Belgium
UK
Turkey
Georgia
Ireland
Lebanon
An unique ca. 62 kb OXA-48 plasmid
France
Israel
Jordan
Spain
Egypt
Morocco
Algeria
Tunisia
Lybia
Sultanate of Oman
India
Senegal
Kuwait
Single OXA-48-like-producing isolates
Outbreaks of OXA-48-like-producing isolates
Nationwide distribution of OXA-48-like-producing isolates

European dissemination of a single OXA-48-producing *Klebsiella pneumoniae* clone

A. Potron[1], J. Kalpoe[2], L. Poirel[1] and P. Nordmann[1]

1) *Service de Bactériologie-Virologie, INSERM U914 «Emerging Resistance to Antibiotics», Hôpital de Bicêtre, Assistance Publique/Hôpitaux de*

ulté de Médecine et Université Paris-Sud, K. Bicêt

rtment of Medical Microbiology and Infection Pre

pital, Amsterdam, the Netherlands

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2011, p. 2420–2423 Vol. 55, No. 5
0066-4804/11/$12.00 doi:10.1128/AAC.01452-10

Outbreak of OXA-48-Positive Carbapenem-Resistant *Klebsiella pneumoniae* Isolates in France[▽]

Gaelle Cuzon,[1] Jocelyne Ouanich,[2] Remy Gondret,[3] Thierry Naas,[1] and Patrice Nordmann[1]*

Service de Bactériologie-Virologie, INSERM U914: Emerging Resistance to Antibiotics, Hôpital de Bicêtre, Assistance Publique-Hôpitaux de Paris, 94275 Le Kremlin-Bicêtre, Faculté de Médecine, Université Paris-Sud, France[1]; Laboratoire de Microbiologie, Centre Hospitalier Intercommunal de Villeneuve-St. Georges, Villeneuve-St. Georges, France[2]; and Service d'Anesthésie-Réanimation, Centre Hospitalier Intercommunal de Villeneuve-St. Georges, Villeneuve-St. Georges, France[3]

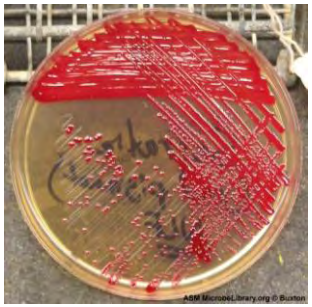
Received 20 October 2010/Returned for modification 2 January 2011/Accepted 13 February 2011

Seventeen *Klebsiella pneumoniae* isolates producing the OXA-48 carbapenemase, obtained from 10 patients hospitalized from April to June 2010, mostly in the medical intensive care unit of the Villeneuve-Saint-Georges Hospital in a suburb of Paris, France, were analyzed. Seven patients were infected, of whom five were treated at least with a carbapenem, and five patients died. Molecular analysis showed that the isolates belonged to a single clone that harbored a 70-kb plasmid carrying the bla_{OXA-48} gene and coproduced CTX-M-15 and TEM-1 β-lactamases. This is the first reported outbreak of OXA-48-producing *K. pneumoniae* isolates in France.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2011, p. 000 Vol. 55, No. 11
0066-4804/11/$12.00 doi:10.1128/AAC.05120-11

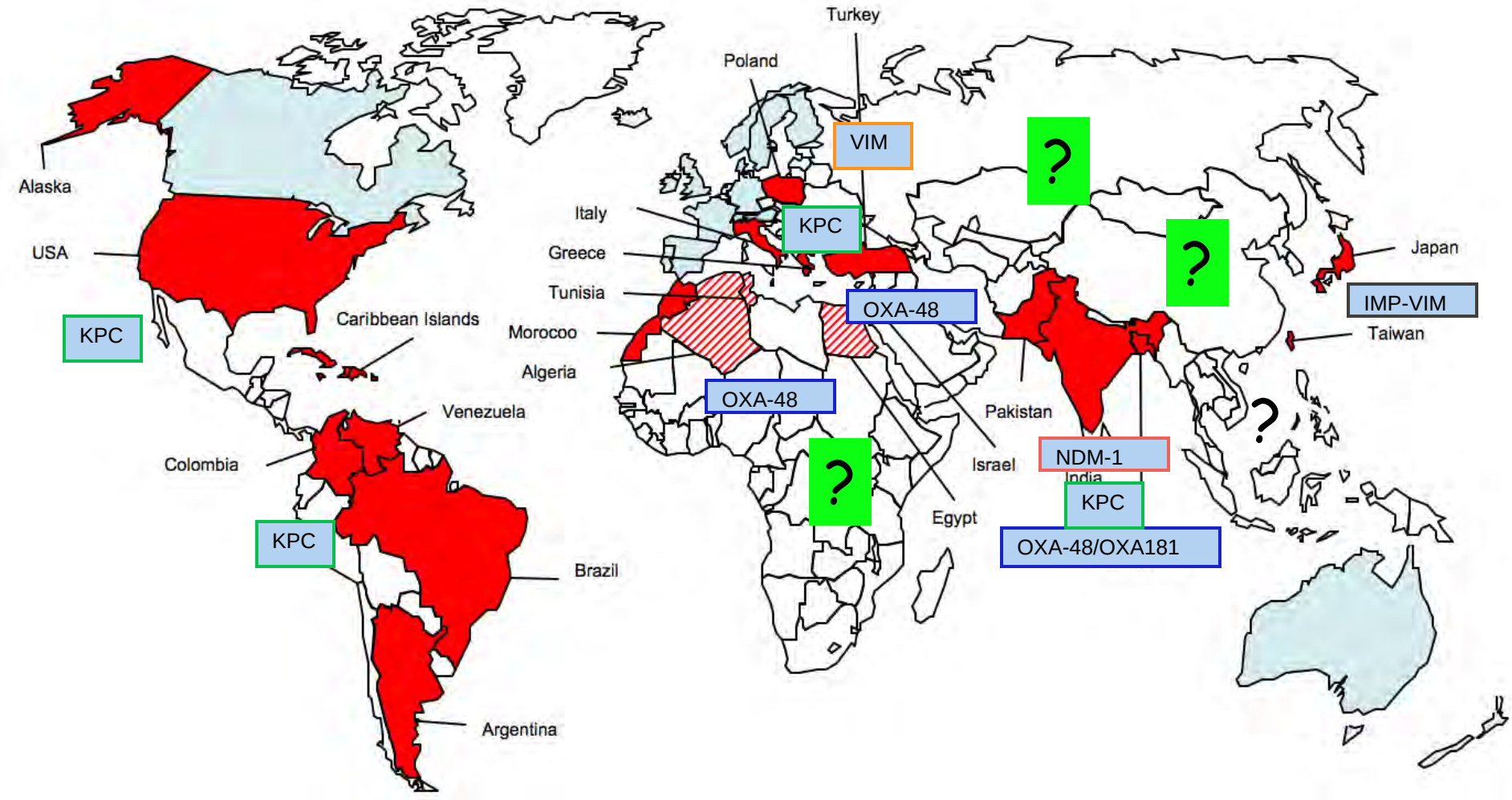
Letter to the Editor

Occurrence of the Carbapenem-Hydrolyzing β-Lactamase Gene *bla*$_{OXA-48}$ in the Environment in Morocco$^{\nabla}$

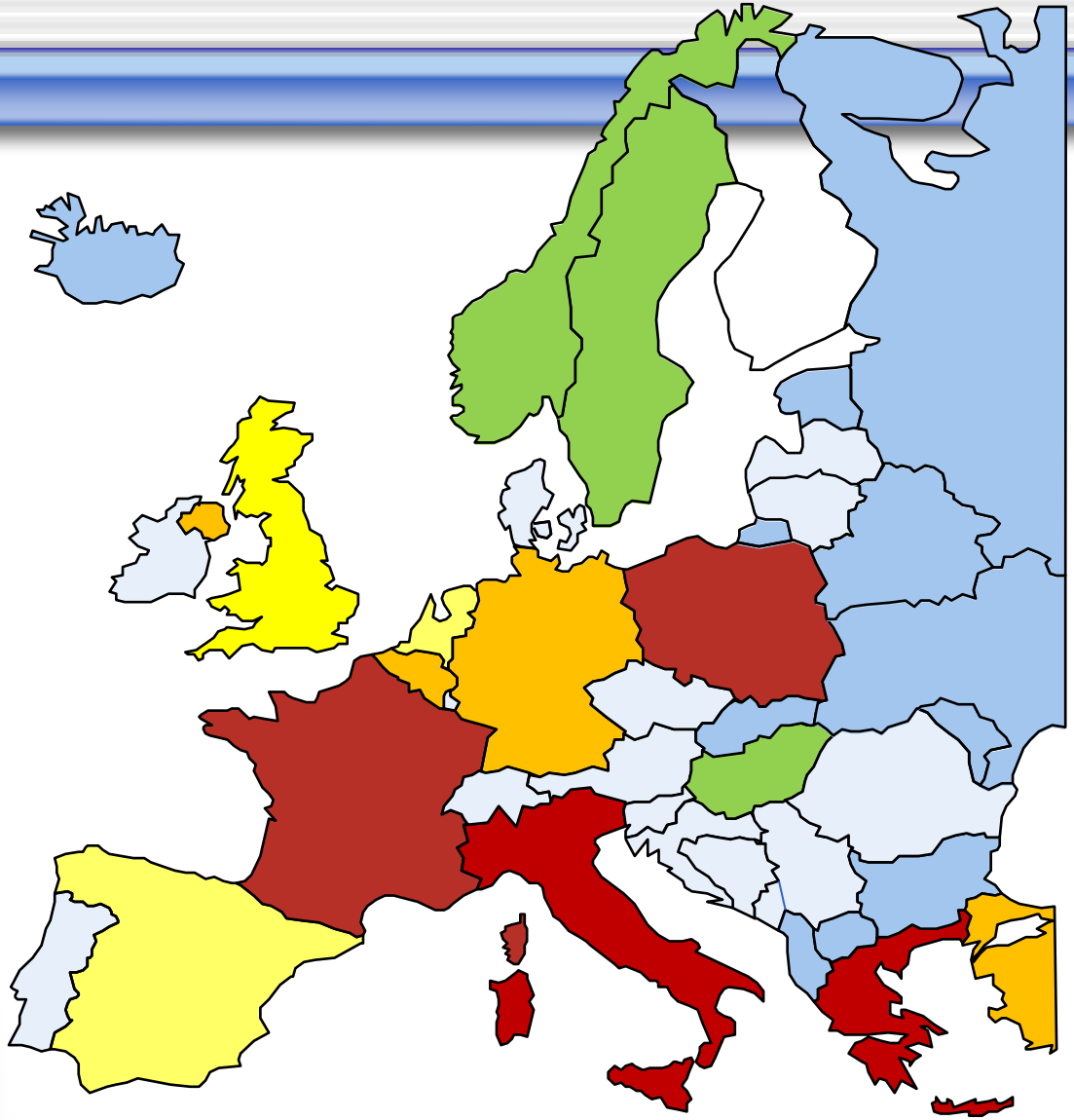


Anaïs Potron
Laurent Poirel
Florence Bussy
Patrice Nordmann*
Service de Bactériologie-Virologie
INSERM U914, Emerging Resistance to Antibiotics
Hôpital de Bicêtre

Carbapenemases- Enterobactericeae reservoirs



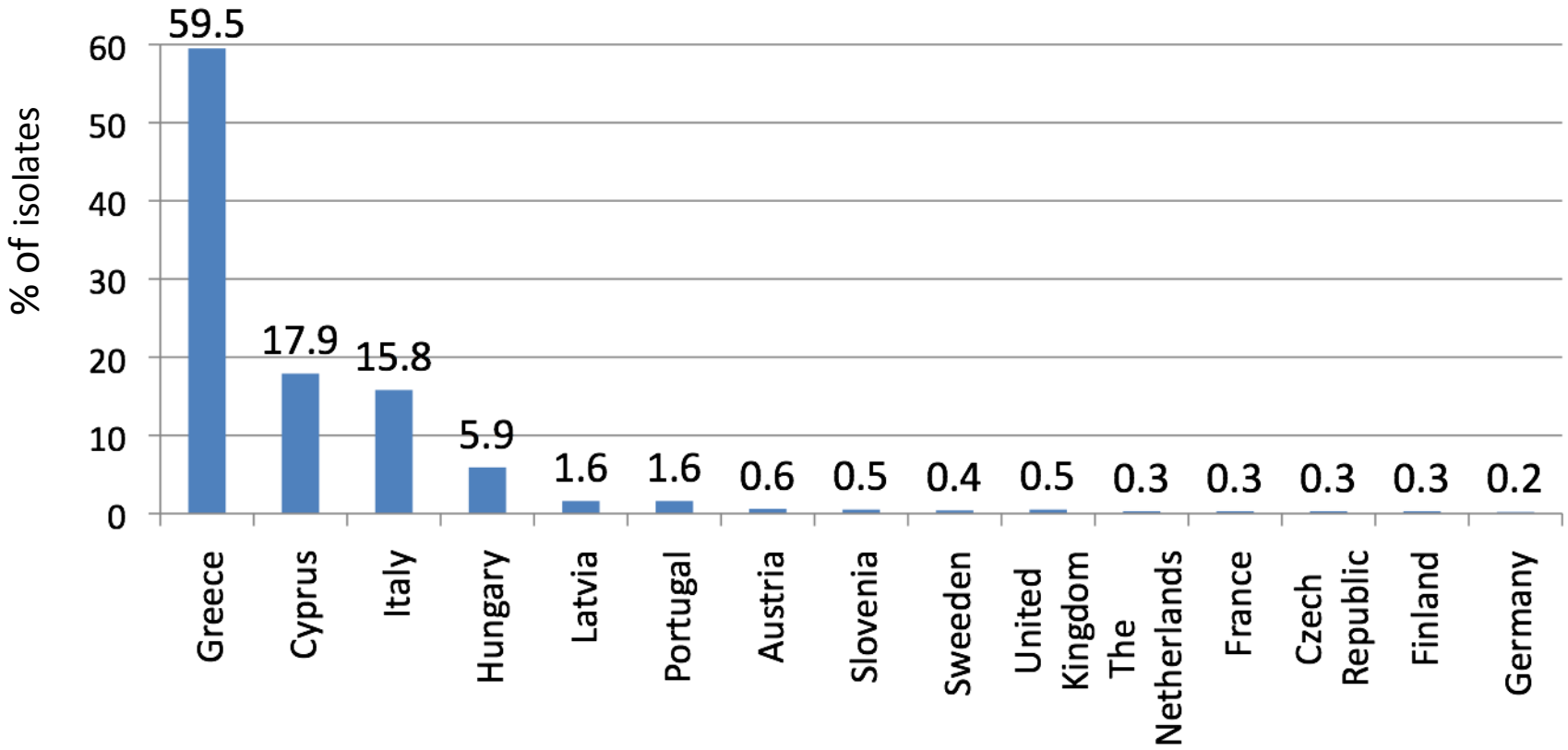
Spread of carbapenemase producers in *Enterobacteriacae* in Europe



- Endemic
- Interregional spread
- Regional spread
- Independent hospital outbreaks
- Single hospital outbreaks
- Sporadic occurrence
- Not reported / no data

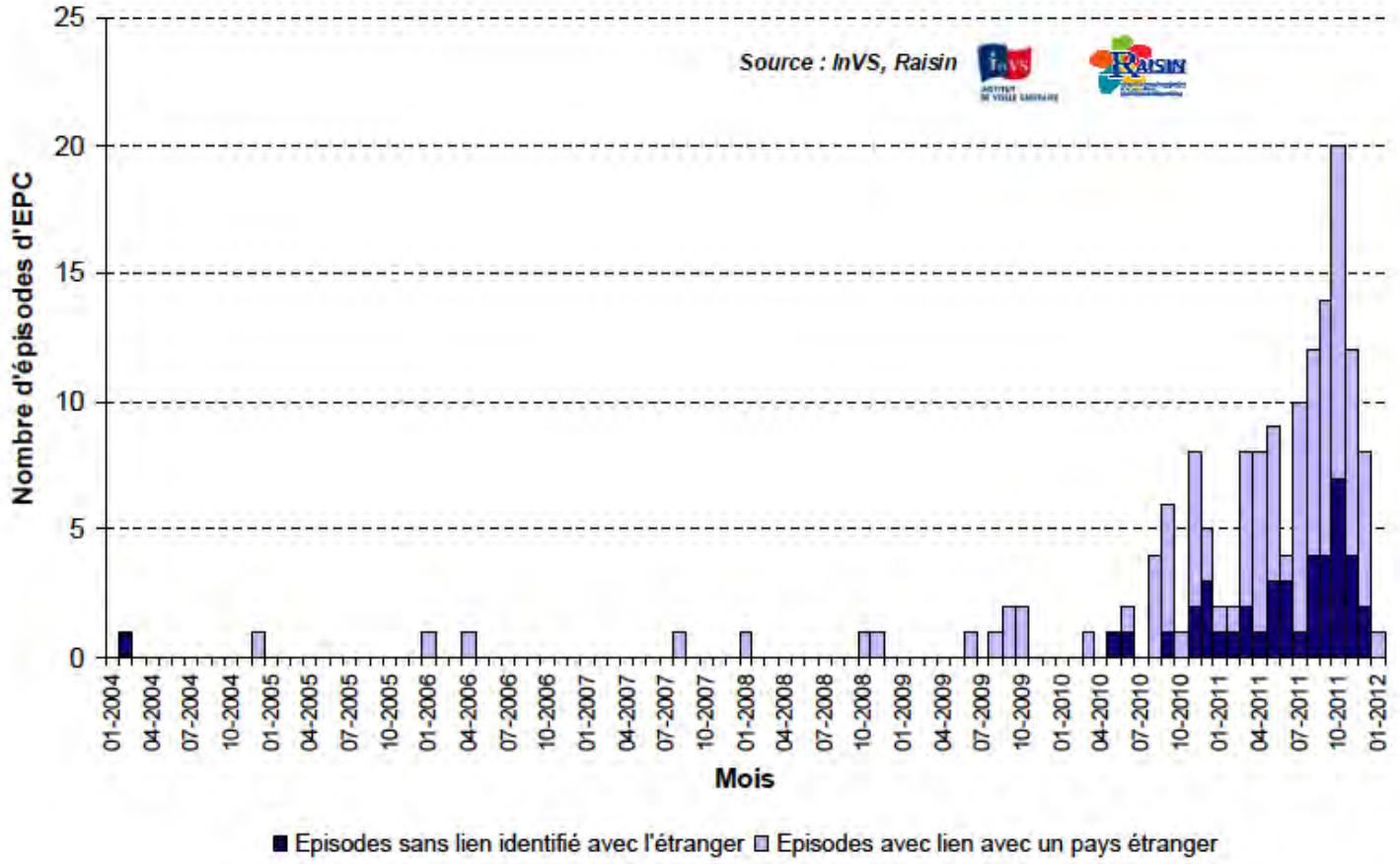
Canton R et al. CMI in press

Non-susceptibility rates of *Klebsiella pneumoniae* in Europe- 2010



Canton R et al. CMI in press

Case number (single case + outbreaks) of carbapenemases reported in France since 2004



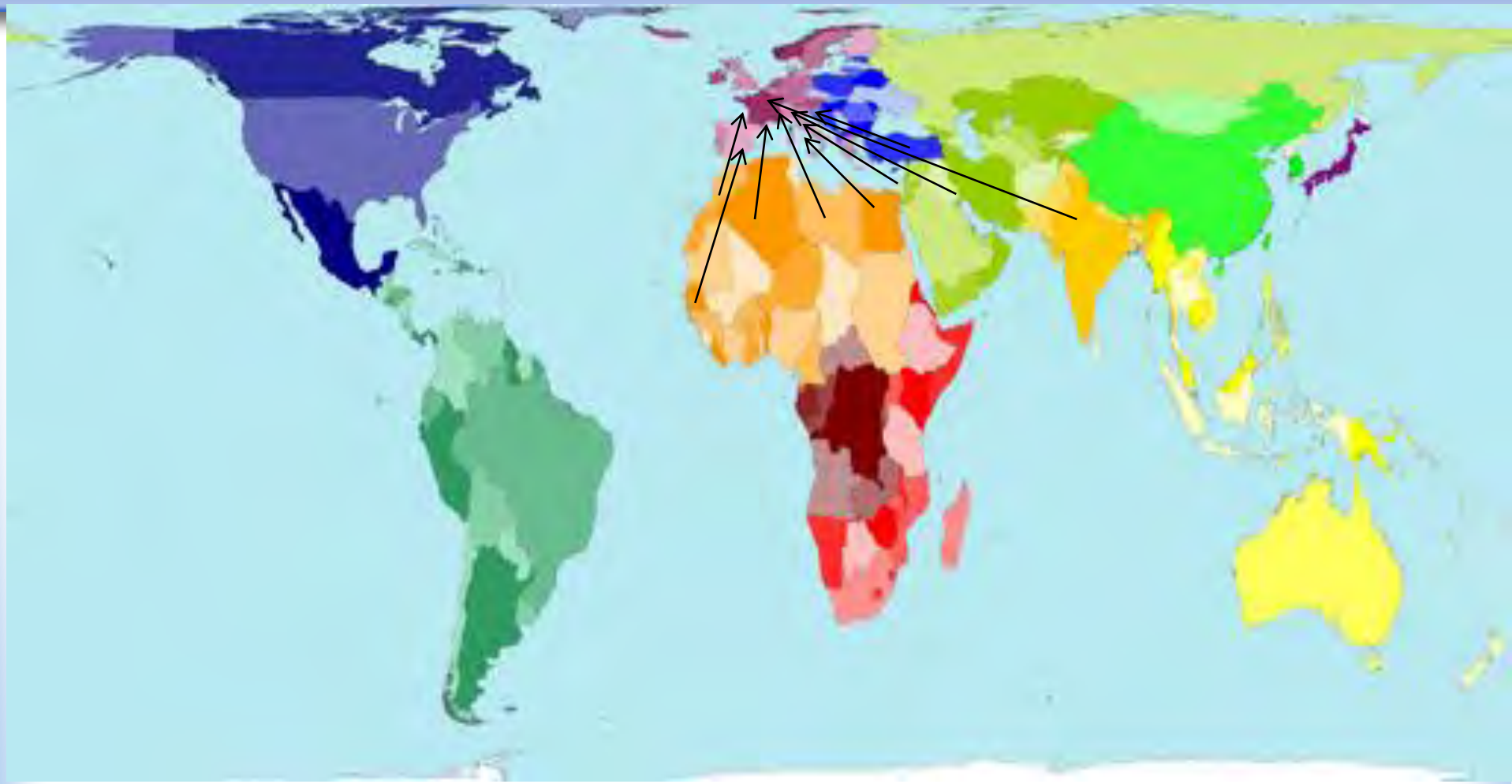
152 épisodes au total

2009 : 6 2010 : 28 2011 : 109

Carbapenemase producers according to carbapenemase type and origin - France

Pays	OXA-48	KPC	NDM	VIM	OXA-181	Total
Maroc	24 (2010)	2 (2011)				26
Grèce		18 (2007)		5 (2004)		22[a]
Inde		1 (2011)	9 (2010)		1 (2011)	10[a]
Algérie	7 (2010)	1 (2010)		1 (2008)		9
Italie		5 (2010)		3 (2008)		8
Egypte	3 (2009)	1 (2011)		1 (2010)		5
Lybie	5 (2011)					5
Tunisie	5 (2011)					5
Turquie	4 (2010)					4
Sénégal	3 (2011)					3
Koweit	2 (2011)					2
Israël	1 (2011)	1 (2011)				2
Serbie			2 (2011)			2
Irak			1 (2010)			1
Etats-Unis		1 (2006)				1
Espagne	1 (2011)					1
Afrique du Nord	1 (2011)					1
Vietnam			1 (2011)			1
Ile Maurice			1 (2011)			1
Cameroun			1 (2011)			1

Transfer of OXA-48-like producers to France



A nightmare ?


WARNING
PIT BULL
WITH AIDS
NO TRESPASSING
HUNTING OR FISHING
NOTICE!!
FunnySign.com

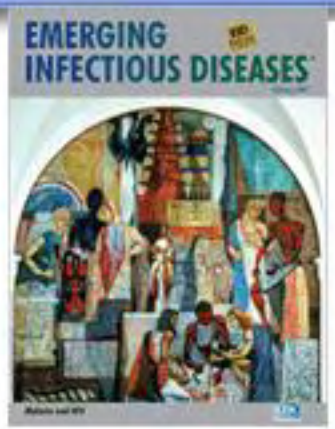
However…

- Carbapenem non-susceptible isolates do not necessary produce carbapenemases

  ⇒ ESBL production + permeability defects may lead to resistance, in particular to ertapenem

  ⇒ AmpC production + permeability defects may lead to resistance, including to imipenem

ESBL + decreased outer membrane permeability

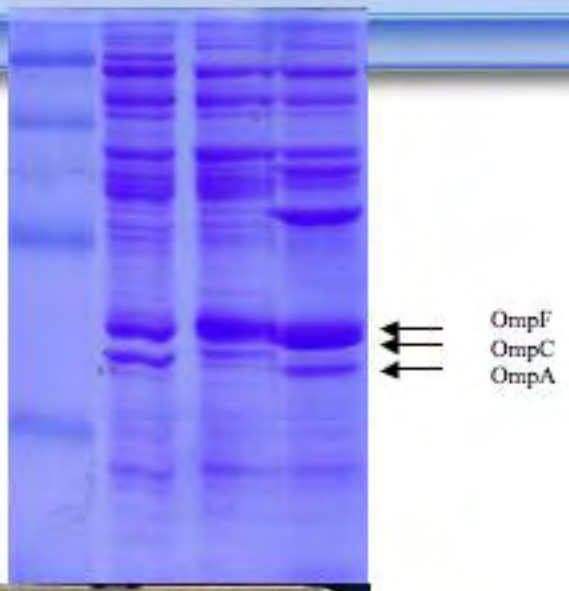


Ertapenem Resistance of *Escherichia coli*

Marie-Frédérique Lartigue,* Laurent Poirel,* Claire Poyart,† Hélène Réglier-Poupet,† and Patrice Nordmann*

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 13, No. 2, February 2007

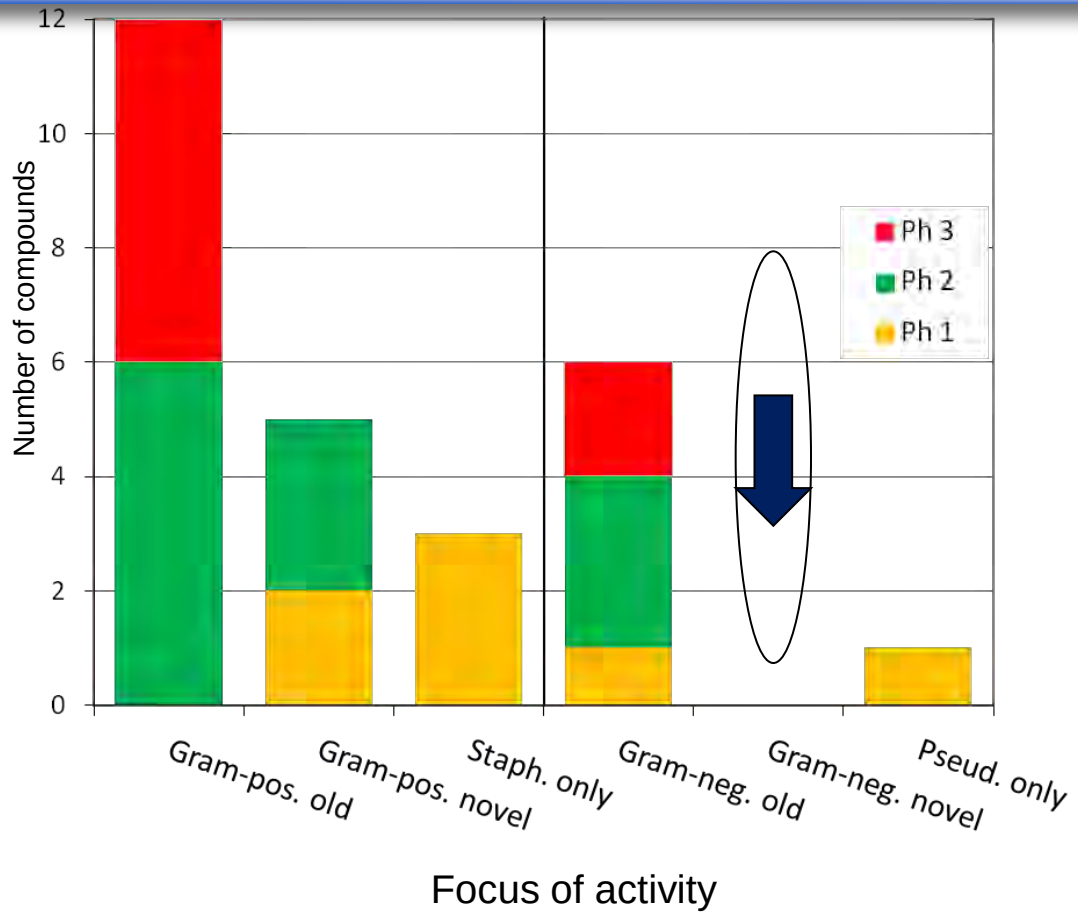
An ertapenem-resistant *Escherichia coli* isolate was recovered from peritoneal fluid in a patient who had been treated with imipenem/cilastatin for 10 days. Ertapenem resistance may be explained by a defect in the outer membrane protein and production of extended-spectrum β-lactamase CTX-M-2.



Conclusion

- Increase prevalence of carbapenemase producers worldwide
- Carbapenemase producers; multiplicity of clones and of genetic vectors
- Spread of carbapenemase producers (NDM, OXA-48) in the community (++ *E. coli*) is an important source of concern
- Difficult detection; a need for rapid identification techniques
- Multidrug resistance and pandrug resistance: reversion of multidrug resistance in Gram negatives is rare

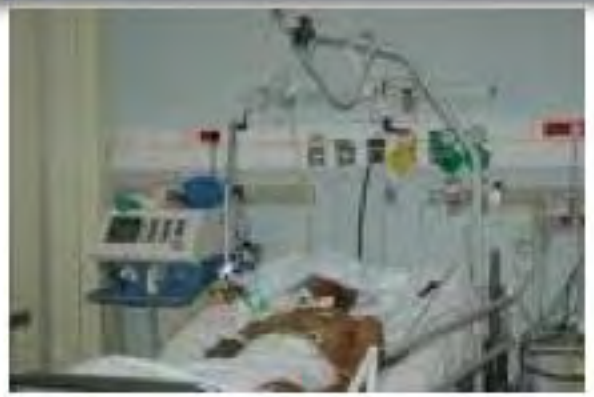
Antibiotics in the pipeline



U. Theuretzbacher: IJAA, Feb. 2012

Our medical duty in 2012; preventing the SPREAD of carbapenemase producers in *Enterobacteriacae*

Carriage detection



Hospitalized patients abroad

Secrétariat d'état à la santé

Direction générale de la santé
Personnes chargées du dossier :
Sous-direction de la prévention des risques infectieux
Dr Philippe GARNIER
tel : 01 40 56 50 06
mail : philippe.garnier@sante.gouv.fr

Département des urgences sanitaires
Dr Jacques CHEMARDIN
Tél / 01.40.56.50.91
Mail : jacques.chemardin@sante.gouv.fr

Direction générale de l'offre de soins
Sous-direction de la qualité et du fonctionnement des établissements de santé

Le directeur général de la santé

La directrice générale de l'offre de soins

à

Mesdames et Messieurs les directeurs généraux des agences régionales de santé (pour attribution)

Mesdames et Messieurs les directeurs des établissements de santé (pour attribution)

Mesdames et Messieurs les directeurs des laboratoires de microbiologie (pour attribution)

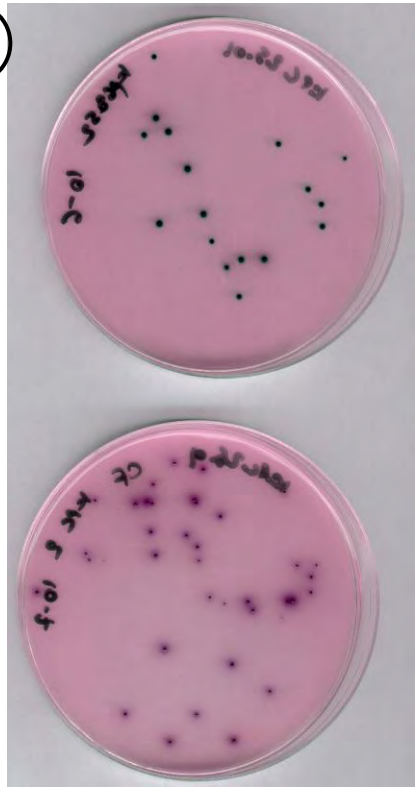
CIRCULAIRE N°DGS/RI/DGOS/PF/2010/413 du 6 décembre 2010 relative à la mise en oeuvre de mesure de contrôles des cas importés d'entérobactéries productrices de carbapénémases (EPC)

Date d'application : immédiate
NOR : ETSP1031198C
Grille de classement :
Validée par le CNP le 3 décembre 2010 - Visa CNP 2010-284

Résumé : Contrôle des cas importés d'EPC.
Mots-clés : prévention, bactéries multi résistantes
Textes de référence : article 6111-17 du Code de la santé publique, circulaire interministérielle N°DGS/DHOS/DGAS2009/264 du 19 août 2009, circulaire DHOS/E2 - DGS/SD6C N° 21 du 22 janvier 2004, circulaire DHOS/E 2 - DGS/SD5A n° 2002-272 du 2 mai 2002
Textes abrogés : Aucun

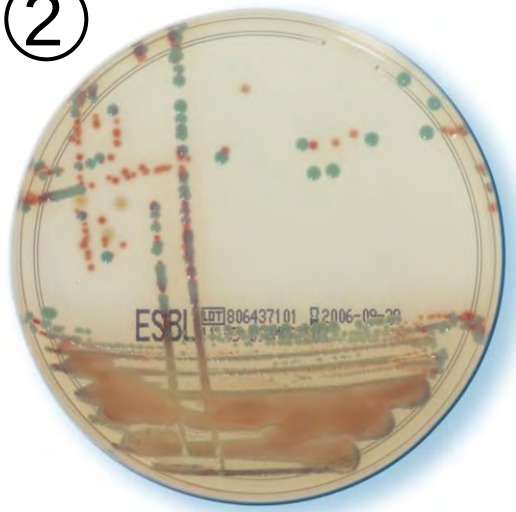
Detection of carbapenemase producers
as colonizers of the intestinal flora

①



CHROMagar KPC
(carbapenemase producers)
contains a carbapenem

②



ESBL ID bioMérieux
(Carbapenemase and ESBL producers)
contains a cephalosporin

③

Oxoid Brillance CRE agar

(Thermo Fisher)
contains a carbapenem

A novel screening medium (SUPER CARBA medium©)

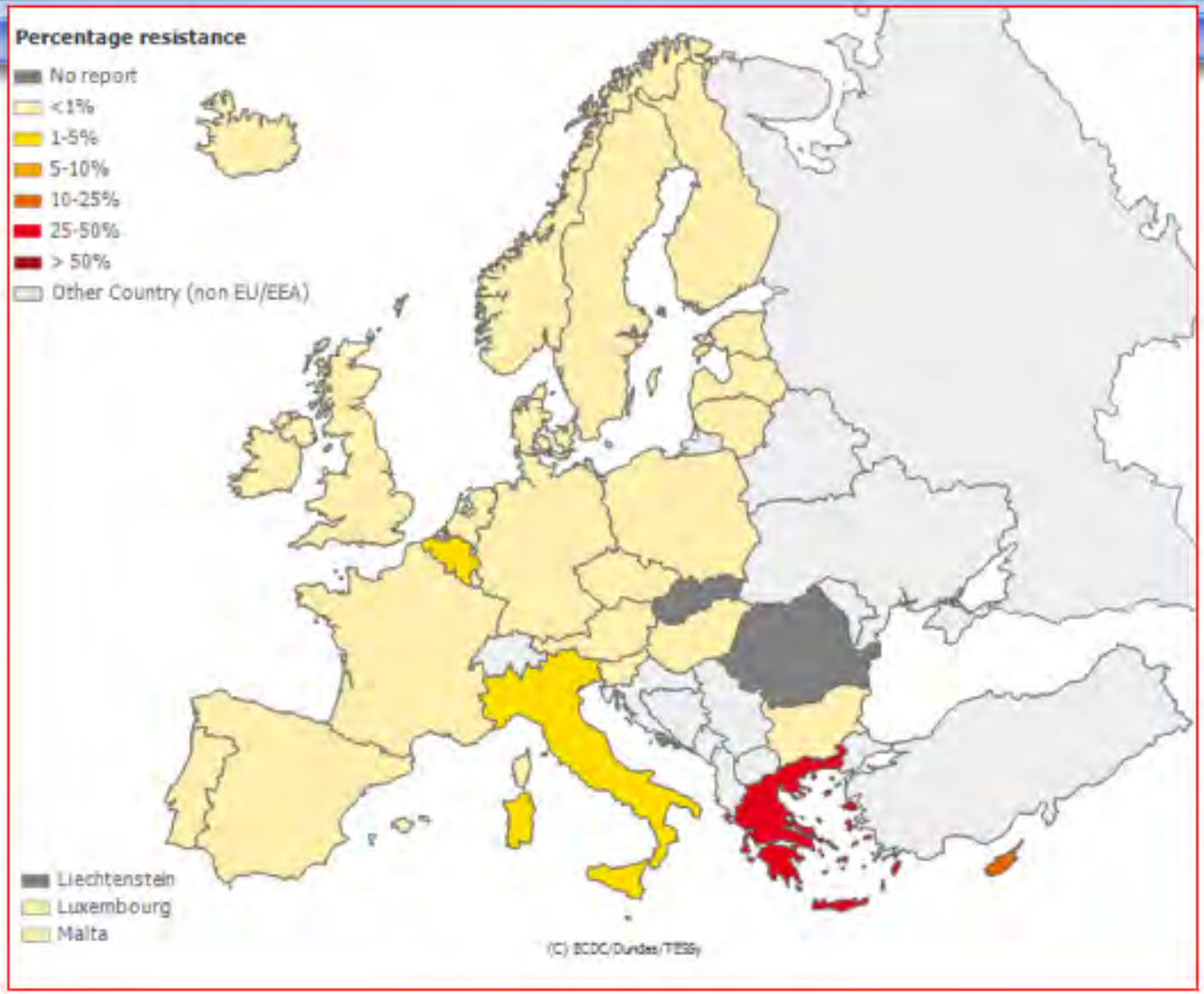
Combines many advantages

- Excellent sensitivity
  - for OXA-48 producers thanks to a low concentration of the carbapenem
  - for MBL producers (especially NDM) thanks to the addition of zinc ions

- Excellent specificity
  - supplemented with a carbapenem, not a cephalosporin (no growth of an ESBL+ and carbapenem susceptible strain)
  - supplemented with cloxacillin (no growth of an AmpC-mediated carbapenem non-susceptible strain)

Nordmann, Girlich, and Poirel, J. Clin Microbiol. 2012, in press

Carbapenem-resistance; *K. pneumoniae*: Europe, 2009



Le destin exemplaire de FLEMING (1881-1955)

Fils de modestes fermiers écossais, Victor FLEMING doit quitter sa famille pour gagner sa vie. Mais il se sent attiré vers la science et veut s'y consacrer.

Un petit héritage lui permet de reprendre ses études au Collège Ste Mary's où il deviendra plus tard le collaborateur du Docteur Wright, dans son laboratoire.

En 1928, il remarque qu'autour de moisissures sur l'une de ses cultures, les microbes se décomposent et meurent.

L'étude de ce phénomène conduit FLEMING à la découverte de la Pénicilline qui sauvera d'innombrables malades et blessés.

La fabrication de la Pénicilline se développe alors dans tous les pays. La plupart des maladies infectieuses sont vaincues.

„Sir" FLEMING est reçu à l'Académie de Médecine. Il fait sienne la parole de PASTEUR. „ La chance favorise les intelligences qui sont prêtes ".

Ce grand savant était sobre. C'est pourquoi il a pu mettre au service de la science la grande clarté de son esprit.

DESSINS EXEMPLAIRES BUVARD N° 4
EDITÉ PAR LE HAUT COMITÉ D'ÉTUDE
ET D'INFORMATION SUR L'ALCOOLISME
"SANTÉ SOBRIÉTÉ"

196

OGEP

TOI AUSSI, TU SERAS SOBRE !